

ESMO 2014 Congress Scientific Meeting Report

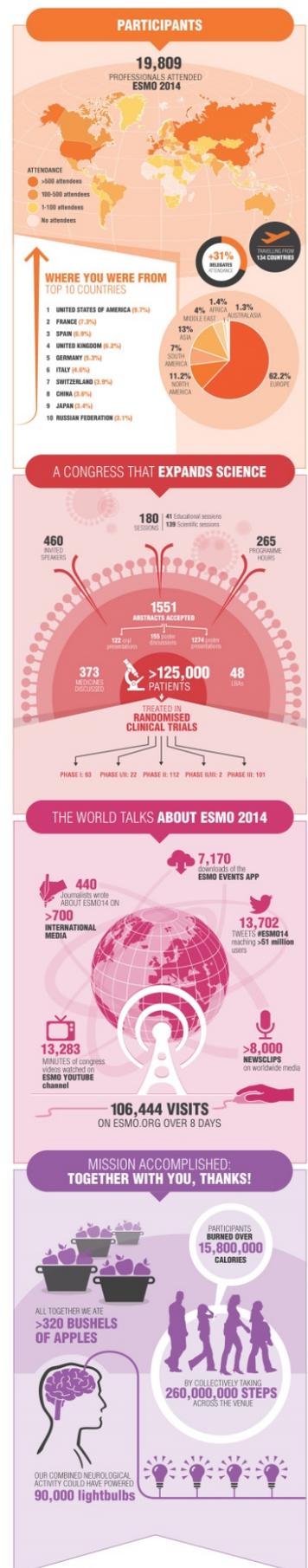
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Madrid, Spain

Summary

The European Society for Medical Oncology (ESMO) Congress, held September 26 to 30 in Madrid, Spain, was a record-breaker on nearly all levels. It was resounding success and in a dedicated infographic you can find the congress statistics. A primary emphasis in the scientific programme was placed on precision medicine and how it will change the future treatment landscape in oncology. In addition, a number of scientific presentations were dedicated to cancer immunology and immunotherapy across multiple tumour types. This report is an overview of key scientific presentations made during the congress by leading international investigators. It attempts to represent the diversity and depth of the ESMO 2014 scientific programme, as well as advances in oncology.

Infographic (right): ESMO 2014 record breaking Congress



Contents

Precision Medicine in Cancer Care.....	6
Breast Cancer.....	8
Randomised phase II, three armed, EORTC study of neoadjuvant treatment with docetaxel plus lapatinib/trastuzumab/or both, followed by an anthracycline based chemotherapy in HER2-positive breast cancer	8
Activity of neoadjuvant lapatinib plus trastuzumab for early breast cancer according to PIK3CA mutations: pCR rate in the CherLOB study and pooled analysis of randomised trials.....	9
Dual blockade with afatinib and trastuzumab as neoadjuvant treatment for patients with locally advanced or operable breast cancer receiving taxane-anthracycline containing chemotherapy	11
Final OS analysis from the CLEOPATRA study in patients with HER2-positive metastatic breast cancer.....	12
IMELDA: Efficacy and safety of maintenance bevacizumab with or without capecitabine after initial first-line bevacizumab plus docetaxel.....	14
TANIA: Efficacy and safety of continued or reintroduced bevacizumab after first-line bevacizumab for HER2-negative locally recurrent/metastatic breast cancer.....	17
CNS Malignancies	21
Randomised phase II trial AVAREG (ML25739) with bevacizumab or fotemustine in recurrent glioblastoma	21
Developmental Therapeutics	23
Pimasertib and SAR245409, a MEK and PI3K/mTOR inhibitors combination: A phase Ib trial with expansions in selected genotype-defined solid tumours.....	23
Phase Ib trial trial of RG7116, a glycoengineered monoclonal antibody targeting HER3, in combination with cetuximab or erlotinib in patients with advanced/metastatic tumours of epithelial cell origin expressing HER3 protein	24
Dose-escalation study of sonidegib (LDE225) plus buparlisib (BKM120) in patients with advanced solid tumours.....	25
Endocrine Cancers	27
Comprehensive analysis of serum biomarker and tumour gene mutation associated with clinical outcomes in the phase III study of lenvatinib in differentiated thyroid cancer.....	27
Gastrointestinal Cancers.....	29
A phase IB study of pembroluzumab in patients with advanced gastric cancer	29
REACH: Ramucirumab as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib	29
Axitinib plus best supportive care in patients with advanced hepatocellular carcinoma following prior antiangiogenic therapy	32
Optimal treatment strategy with anti-EGFR or anti-VEGF treatments in first-line RAS wild type metastatic CRC patients.....	35

CALGB/SWOG 80405: Phase III trial of FOLFIRI or mFOLFOX6 with bevacizumab or cetuximab for patients with expanded RAS analyses in untreated metastatic adenocarcinoma of the colon or rectum	35
Independent radiological evaluation of ORR, early tumour shrinkage, and depth of response in the FIRE-3 study: Analysis in the final RAS evaluable population	37
Data interpretation	39
TAS-102 improves OS and PFS in patients with metastatic CRC refractory to standard therapies	40
Bevacizumab/erlotinib as maintenance therapy in metastatic CRC: Final results of the GERCOR DREAM study	42
Final results from QUASAR2, a multicentre, international randomised phase III trial of capecitabine plus/minus bevacizumab in the adjuvant setting of stage II/III CRC	43
Genitourinary Cancers	45
A phase IB study of pembrolizumab in patients with advanced urothelial tract cancer.....	45
Gynaecologic Cancers.....	46
Activity of second-line dovitinib in advanced and/or metastatic endometrial cancer.....	46
Final OS analysis of the phase III randomised trial of chemotherapy with and without bevacizumab for advanced cervical cancer.....	49
Head and Neck Cancer.....	53
Afatinib vs. methotrexate in second-line treatment of recurrent and/or metastatic head and neck squamous cell carcinoma: Primary efficacy results of a phase III LUX-Head and Neck 1 trial...	53
Randomised phase II study of MEHD7945A vs. cetuximab in at least second-line recurrent/metastatic squamous cell carcinoma of the head and neck progressive on/after platinum-based chemotherapy	54
A phase IB study of pembrolizumab in patients with human papillomavirus (HPV)-positive and -negative head and neck cancer.....	56
Haematological Malignancies	57
Brentuximab vedotin in combination with CHP in patients with newly-diagnosed CD30-positive peripheral T-cell lymphomas	57
Carfilzomib vs. low-dose corticosteroids and optional cyclophosphamide in patients with relapsed and refractory multiple myeloma.....	58
Lung Cancer	60
Final results of the SAKK 16/00 trial: A randomised phase III trial comparing neoadjuvant chemoradiation to chemotherapy alone in stage IIIA/N2 NSCLC	60
Adjuvant treatment with MAGE-A3 cancer immunotherapeutic in patients with resected NSCLC does not increase DFS: Results of the MAGRIT, a double-blind, randomised, placebo-controlled phase III study	61

TARGET: A phase II trial with vintafolide in second-line treatment of folate-receptor-positive NSCLC	63
BRF113928: A phase II study with dabrafenib in patients with BRAF V600E-mutant advanced NSCLC	64
A phase II study of neratinib with or without temsirolimus in patients with NSCLC carrying HER2 somatic mutations	65
IMPRESS: Continuation of gefitinib plus pemetrexed/cisplatin of no clinical benefit in NSCLC patients with acquired resistance to gefitinib	67
New data on first- and second-line ALK inhibition in NSCLC patients.....	69
Overall and intracranial efficacy results and time to symptom deterioration in the PROFILE 1014 study	69
Antitumour activity of alectinib in crizotinib pre-treated ALK-rearranged NSCLC.....	71
Defining and refining the ALK treatment paradigm in NSCLC	71
Results of LUX-Lung 8, the largest prospective trial to compare EGFR TKIs in patients with relapsed/refractory squamous cell carcinoma of the lung	72
Antitumour activity of pembrolizumab and correlation with PD-L1 expression in a pooled analysis of patients with advanced NSCLC	74
How to guide the selection of chemotherapy regimen for non-squamous NSCLC	75
Docetaxel plus cisplatin vs. pemetrexed plus cisplatin in first line non-squamous NSCLC.....	76
Pemetrexed plus cisplatin vs. gemcitabine plus cisplatin according to thymidylate synthase expression in non-squamous NSCLC	77
Prospective molecular evaluation of small cell lung cancer utilising the comprehensive mutation analysis programme at Memorial Sloan Kettering Cancer Center	78
Melanoma and Other Skin Tumours	81
Results of the COMBI-v randomised, open-label, phase III study in the first-line treatment of patients with unresectable or metastatic cutaneous melanoma	81
Results of a phase III study of cobimetinib in combination with vemurafenib in previously untreated patients with BRAFV600 mutation-positive melanoma.....	83
Results of a phase III randomised study of nivolumab in patients with advanced melanoma after prior anti-CTLA4 therapy	86
Randomised, double-blind study of sonidegib (LDE225) in patients with advanced basal cell carcinoma.....	88
Neuroendocrine Cancers	90
Everolimus for the treatment of advanced pNET: Final OS results of a randomised, double-blind, placebo-controlled, multicenter phase III trial	90
Public Health and Health Economics	92
Risk of incremental toxicities and associated costs of new anticancer drugs.....	92

Author financial conflicts of interest in clinical practice guidelines for systemic anti-cancer drugs	93
Cross-comparison of cancer drug approvals among international regulatory bodies	94
Sarcoma.....	96
Pazopanib improves PFS in phase II study in patients with advanced GIST.....	96
Phase II study of imatinib in RECIST progressive desmoid tumours not amenable to surgical resection or accompanied by unacceptable function loss	99
Outcome of first-line treatment of elderly advanced soft tissue sarcoma patients.....	100
Supportive and Palliative Care.....	101
Rolapitant plus granisetron/dexamethasone in prevention of chemotherapy-induced nausea and vomiting	101
Oral rivaroxaban for the treatment of symptomatic venous thromboembolism in patients with cancer.....	102
Anamorelin for the treatment of cancer anorexia-cachexia in NSCLC: Results from the phase III studies ROMANA 1 and 2	104
Satisfying Career Needs of Young Oncologists	105
RELATED INFORMATION	106
Save the date	106
Affiliations and Disclosure	106
Acknowledgment	106

Precision Medicine in Cancer Care

The theme for ESMO 2014: 'Precision Medicine in Cancer Care' was chosen to drive improvements in research, and patient treatment and outcomes through dynamic discussions and knowledge exchange. Each Congress track hosted a special session that highlighted the subject in more detail.

The special symposium in CNS tumours: current concepts and future avenues in meningioma, was designed to enhance understanding of the challenges and morbidity of this non-malignant disease providing biological insight into novel and targeted treatments, and indications, and the limitations of the current standards of care for meningioma subtypes.

The special symposium in developmental therapeutics: challenges and perspectives of molecular profiling, highlighted the missing link between the basic science/translational research sessions and the organ-oriented sessions. It also emphasised the extent to which molecular profiling has impacted current clinical reality and the potential problems faced when integrating precision medicine into oncology management.

The special symposium on advances in precision medicine of metastatic colorectal cancer (mCRC) provided insight into the future molecular understanding of mCRC, leading to a potential new classification and the consecutive development of therapeutics. In particular the lectures focused on biomarkers and methodologies employed to identify tumour subtypes and how do they might correlate with treatment sensitivity. However, large scale retrospective and prospective studies are needed for data validation. In addition, tumour heterogeneity/plasticity should be addressed and followed upon disease progression. Gene signatures might be replaced by proteomics in the future. The Symposium also provided an excellent update on new classes of anticancer treatments in this disease.

The special symposium entitled 'Towards personalised medicine in gastric, pancreatic and liver cancer – from "omics" research to treatment', offered attendees the possibility to get a clear picture of how new developments in "omics" may potentially translate into clinical actions for patients with gastric, pancreatic and liver cancers.

The special symposium on precision medicine in prostate cancer provided insight into prostate cancer biology and heterogeneity, the rationale and link current therapy/drug development to the impetus for disease biology, and informed on biomarker development and on current precision medicine perspectives specific to prostate cancer.

The special symposium entitled 'Beyond tumour heterogeneity – new pathways in kidney cancer' presented the latest molecular classification of kidney cancer and discussed its relevance for practising clinicians. It also highlighted major clinical problems such as drug resistance and lack of predictive biomarkers for drug therapies. There was a focus on new targets and drugs, particularly immunotherapies such as anti-PD1 agents.

The special symposium on personalised medicine in head and neck cancer discussed therapeutic perspectives for squamous cell carcinoma, including immunotherapy, according to novel targets and better individual patient selection, identification of therapeutic targets for salivary gland cancers, and integration of innovative technology for next generation trials based on biological tumour characteristics.

The special symposium on the impact on health services from personalised targeted therapies discussed the budgetary impact of the cost of new diagnostic procedures and therapies and the changes in health services associated with them, and integration of all aspects of cancer care – ranging from health promotion to rehabilitation, reintegration and palliation.

The special symposium on targeting precision medicine toxicity provided an excellent tool to learn about the completely different side effects from all the new therapies available over the past years. More precisely it covered next spectrum of toxicities from novel agents: cardiac, pulmonary, skin, endocrine, osteoarticular, and gastrointestinal (GI).

Breast Cancer

Randomised phase II, three armed, EORTC study of neoadjuvant treatment with docetaxel plus lapatinib/trastuzumab/ or both, followed by an anthracycline based chemotherapy in HER2-positive breast cancer

Prof. Herve Bonnefoi of the Institute Bergonié, Bordeaux, France, presented results of a phase II study that demonstrated a numerically higher pathological complete response (pCR) rate with double anti-HER2 blockade (lapatinib-trastuzumab) plus chemotherapy, but the use of docetaxel rather than paclitaxel may not reduce toxicity. From a clinical perspective the modest increase in pCR comes with additional toxicity.

Neoadjuvant trials with a double HER2-blockade with lapatinib and trastuzumab, combined with different paclitaxel-containing chemotherapy regimens, have shown high pCR rates, but at the cost of important toxicity. The European Organisation for Research and Treatments of Cancer (EORTC) researchers hypothesised that this toxicity might be due to a specific interaction between paclitaxel and lapatinib.

Patients with stage IIA to IIIC HER2-positive breast cancer received 6 cycles of chemotherapy every 3 weeks (3 cycles of docetaxel followed by 3 cycles of fluorouracil, epirubicin, and cyclophosphamide). They were randomised to receive, during the first 3 cycles, either lapatinib in arm A, trastuzumab in arm B, or trastuzumab and lapatinib in arm C. The primary endpoint was pCR rate in the breast (ductal carcinoma in situ was allowed). Secondary endpoints included safety and toxicity, response rate, rate of breast conserving surgery and translational research. Exploratory analysis allowed pCR rates assessment in the breast and lymph nodes and its assessment by hormone receptors status.

For a null hypothesis of a 40% pCR rate and an alternative hypothesis of a 60% pCR rate, 50 eligible patients needed to be treated in each arm to have a 92.5% power. An experimental arm was deemed interesting for further research if at least 25 pCR out of 50 treated eligible patients are observed. This decision rule corresponded to rejecting the null hypothesis.

In June 2012, arm A was closed for futility based on the results from other studies. When the lapatinib monotherapy arm was closed prematurely, the statistical plan was not altered for the 2 remaining arms.

From October 2010 to January 2013, 128 patients were included in 14 centres, 6 patients were ineligible. The pCR rate in breast in arm A was 45.5%, 51.9% in arm B, and 60.4% in the C. The pCR rate in breast and lymph nodes in arm A was 36.4%, 51.9% in arm B, and 56.3% in arm C. The pCR rate in breast and lymph nodes in hormone receptor positive tumours was 51.9% in arm B and 47.8% in arm C. In hormone receptor negative tumours, it was 52% in arm B and 64% in arm C. Lapatinib group results were not presented since the numbers are small.

Frequency of most frequent grade 3-4 toxicities in arms A/B/C were: febrile neutropaenia 23/15/10%; diarrhoea 9/2/18%; other infection 9/4/8%; and liver enzyme alteration 0/4/10%. A dose reduction for any of the neoadjuvant drugs was required in 36/13/48% of patients.

Prof. Bonnefoi concluded that using the definition of pCR in both, breast and lymph nodes, the pCR rates for the lapatinib, trastuzumab and combination groups respectively are similar in the EORTC trial and in the 3 trials with a “pragmatic” design reported (CHERLOB, LPT, NSABP-B41). A meta-analysis of neoadjuvant trials with double HER2 blockade may be useful to better take into consideration the heterogeneity of HER2 positive breast cancer and to understand the differences in pCR rates between treatment groups and long-term outcomes.

Prof. Joseph Gligorov of the Tenon University Hospital, Paris, France, who discussed the study results, said that lapatinib-trastuzumab combination increases the pCR rate in neoadjuvant setting compared to lapatinib or trastuzumab alone. The study is not strictly comparable with other according to tumour characteristics (N0; hormone receptors status, chemotherapy partner). The comparison to other anti-HER2 doublet strategies is important because of toxicity and treatment discontinuation concerns. If pCR is the endpoint in the neoadjuvant strategies, then anti-HER2 doublets with chemotherapy do better. In metastatic setting, the best anti-HER2 doublet is actually pertuzumab-trastuzumab. However, Dr Gligorov questioned if there are new interesting doublets, could we better select the population to be treated with treatments according to pCR endpoint, and is pCR relevant from a clinical point of view in early stage HER2 positive breast cancers.

The sponsor of the study was EORTC. GlaxoSmithKline was the study collaborator.

Reference

[2530: Neoadjuvant treatment with docetaxel plus lapatinib \(L\), trastuzumab \(T\), or both followed by an anthracycline based chemotherapy in HER2-positive breast cancer: Results of the randomised phase II EORTC 10054 study](#)

Activity of neoadjuvant lapatinib plus trastuzumab for early breast cancer according to PIK3CA mutations: pCR rate in the CherLOB study and pooled analysis of randomised trials

Prof. Valentina Guarneri of the Oncology Institute, University of Padova, Padova, Italy reported that increased activity of the dual anti-HER2 blockade with trastuzumab plus lapatinib in the neoadjuvant breast cancer setting seems to be limited to tumours not harbouring PIK3CA mutations.

PIK3CA mutations are common in breast cancer. PIK3CA is mutated in 20 to 25% of HER2-positive breast cancer. Preclinical data have shown mutated PIK3CA to be associated with resistance to lapatinib and trastuzumab. PIK3CA mutations are associated with poor prognosis in advanced HER2-positive breast cancer patients treated with chemotherapy and trastuzumab +/- pertuzumab or chemotherapy +/- lapatinib.

The aim of this study was to evaluate the correlation of PIK3CA mutational status with pCR in patients with HER2-positive early breast cancer treated with neoadjuvant chemotherapy plus trastuzumab, lapatinib or combined trastuzumab and lapatinib.

PIK3CA mutations were evaluated in 121 patients randomised to neoadjuvant anthracyclines/taxane-based chemotherapy plus trastuzumab, lapatinib, or both. Exon 9 and exon 20 PIK3CA mutations were evaluated on formalin-fixed, paraffin-embedded core biopsies by

pyrosequencing. An event-based pooled analysis of trials reporting pCR events according to PI3KCA mutation status was performed.

PIK3CA status was available for 108 of the 121 patients: 22 presented a PIK3CA mutation. In the whole population, pCR rates are similar in PIK3CA wild type and PIK3CA mutated patients (33.7% vs. 22.7%; $p = 0.32$). However, for 41 patients receiving trastuzumab plus lapatinib the probability of achieving a pCR is higher in case of PIK3CA wild type (48.4% vs. 12.5%; $p = 0.06$).

An event-based pooled analysis was accomplished by extracting activity events (pCR as reported by trialists) and deriving 95% CIs. Inclusion criteria considered trials in which HER2-positive breast cancer patients who were candidates for neoadjuvant chemotherapy were assigned to receive chemotherapy plus trastuzumab, lapatinib or the combination. The pCR was reported according to PIK3CA status (mutated and wild-type). In addition, a cumulative Odds Ratio of single versus dual HER2 inhibition was conducted (for randomised trials only), with a random effect model considering the known heterogeneity. Interaction according to PIK3CA status (mutated vs. wild-type) was calculated as well.

The accumulated data, including those deriving from the NeoALTTO and GeparSixto trials, in 702 patients. The pCR rates in PIK3CA mutated patients receiving lapatinib is 16.2%, 22.2% in those who received trastuzumab, and 21.4% in those who received lapatinib plus trastuzumab. In PIK3CA wild type patients who received lapatinib, the pCR was 21.3%, 26.9% in those who received trastuzumab, and 43.6% in those who received lapatinib plus trastuzumab.

The non-overlapping 95% CIs, between pCR in patients receiving lapatinib plus trastuzumab and those undergoing trastuzumab or lapatinib may suggest a higher activity of the dual HER2 inhibition in patients without PI3KCA mutation. Conversely, no difference in pCR according to PIK3CA status seems to emerge among patients treated with single anti-HER2 agents.

The strengths were that PIK3CA analysis was prospectively planned in all trials, effective sample collection and analysis (78%-89% of patients), consistent results regardless of the adopted technique, and similar effects across studies. The limitations are relatively limited sample size, too few studies for definitive conclusions, unknown surrogacy of pCR in PIK3CA wild type vs. mutated tumours, potential imbalance of HR status in wild-type vs. mutated tumours, no uniform pCR definition across studies, and chemotherapy as a confounder.

The authors concluded that PIK3CA wild-type status is related to a higher pCR rate following chemotherapy plus dual HER2 blockade with trastuzumab and lapatinib. PIK3CA mutational status does not predict any differential sensitivity to chemotherapy plus either trastuzumab or lapatinib. These data warrant further prospective validation testing of the interaction according to the PIK3CA mutation in the adjuvant setting. If confirmed, the wild-type PIK3CA status might be a marker to select patients to be treated with trastuzumab and lapatinib.

Prof. Joseph Gligorov of the Tenon University Hospital, Paris, France, who discussed the study results, said that PIK3CA mutation is a bad prognostic factor in early stage HER2 positive disease treated with trastuzumab. It is still not known clearly if all the mutations have the same value. Prognostic and predictive value of PIK3CA status might be confounding factors. Better pCR might not be clearly correlated with better disease-free survival (DFS) or overall survival (OS) in the adjuvant setting particularly if the patient receives trastuzumab. Until now, there is no even clinical

argument that PIK3CA mutated populations are more sensitive to PI3K inhibitors. PIK3CA mutation might be stratification factor for further studies, but not yet a decision factor for choosing optimal treatment.

The study was sponsored by GlaxoSmithKline.

Reference

[2540: Activity of neoadjuvant lapatinib \(L\) plus trastuzumab \(T\) for early breast cancer \(EBC\) according to PIK3CA mutations: Pathological complete response \(pCR\) rate in the CherLOB study and pooled analysis of randomized trials](#)

Dual blockade with afatinib and trastuzumab as neoadjuvant treatment for patients with locally advanced or operable breast cancer receiving taxane-anthracycline containing chemotherapy

Dr Claus Hanusch of the Rotkreuzklinikum, Munich, Germany presented results from the efficacy and safety analysis of the (DAFNE)-GBG70 study. Despite a tolerable safety profile of the dual blockade with afatinib, the pCR was lower than the challenging 70% expected rate. A subsequent phase III study therefore cannot be supported.

Neoadjuvant chemotherapy of anthracycline/taxane based combinations of at least 18 weeks is considered a standard treatment. Concurrent administration of trastuzumab in HER2-positive disease achieves a pCR rate of approximately 40%. Dual anti-HER2 blockade can increase the rate by another 20%.

The DAFNE is a multicenter, prospective, open-label phase II study evaluating efficacy and safety of afatinib, an irreversible ErbB-family inhibitor in combination with weekly paclitaxel plus trastuzumab, followed by epirubicin/cyclophosphamide/trastuzumab (ECH) as neoadjuvant therapy in untreated, centrally assessed HER2-positive, operable or locally-advanced breast cancer patients.

All patients were treated for 30 weeks: 6 weeks with afatinib and trastuzumab; 12 weeks with additional weekly paclitaxel; and 12 weeks with ECH. Afatinib was given every other day for the first 2 weeks to reduce the risk of diarrhoea and skin toxicities. Primary prophylaxis with loperamide was mandatory for the first 4 weeks of afatinib/trastuzumab and the first 2 weeks of paclitaxel.

Primary objective was pCR rate (ypT0/is ypN0). Secondary objectives were efficacy using other pCR definitions (ypT0 ypN0, ypT0 ypN0/+, ypTany ypN0), clinical response rates, rate and type of surgery, compliance and toxicity, correlation of skin toxicity and diarrhoea and pre-specified molecular markers with pCR. Assuming a pCR rate of 70%, a sample size of 65 patients was needed to exclude a pCR of $\leq 55\%$.

In total 74 patients were recruited from May 2012 to July 2013 in 11 German centers, with 65 intent-to-treat (ITT) patients. Median age was 50 years. cT2 had 76.6% of patients, 51.6% had cN0 disease, 89.2% ductal invasive, 60% grade 3 and 70.8% hormone receptors positive tumours.

Of the 22 serious adverse events in 16 patients, 27.3% were GI, 18.2% haematologic, 13.6% infections and 9.1% related to the nervous system. Afatinib and trastuzumab in combination with anthracycline-taxane-based chemotherapy as given in the DAFNE study showed no new safety signals.

The study didn't meet the primary objective with a pCR (ypT0/is ypN0) rate of 49.2%.

The pCR by other definitions was 33.9% for ypT0, ypN0; 55.4% for ypT0/is, ypN0/+; 83.1% for ypTany, ypN0. The pCR ypT0/is, ypN0 was 43.5% in patients with oestrogen receptor positive and 63.2% in those with oestrogen receptor negative tumours.

The pCR according to PIK3CA status was 54.2% in wild-type tumours and 38.5% in those with PIK3CA mutated tumours. The pCR according to lymphocyte predominant breast cancer (LPBC) status was 26.8% in those without LPBC and 77.8% in those with LPBC (p=0.0053). The authors stated that their results provide further support for the predictive value of LPBC and PIK3CA mutations in this treatment setting. There was no association between the pCR and skin toxicity or diarrhoea.

Clinical objective response rate at surgery was 96.3%. Complete/partial response after 6 weeks of dual HER2 blockade was 5.3 and 36.8%. Clinical signs of tumour progression after 6 weeks of dual HER2 blockade was recorded in 14% of evaluable patients. Breast-conserving surgery rate was 60%.

Prof. Joseph Gligorov of the Tenon University Hospital, Paris, France, who discussed the study results, said that dual HER2 blockade, afatinib-trastuzumab did not meet the primary endpoint, and the regimen is too toxic. However, the results of ExteNET trial, not yet presented, demonstrate that one year treatment with neratinib after one year treatment with trastuzumab result in 33% improvement in DFS vs. placebo (HR 0.67; p = 0.0046), suggesting that maybe independently of the drug difference, neoadjuvant and adjuvant situation are different for drug evaluation.

The study was organised by the German Breast Group. The study was supported by Boehringer Ingelheim.

Reference

[255O: Dual blockade with afatinib and trastuzumab as neoadjuvant treatment for patients with locally advanced or operable breast cancer receiving taxane-anthracycline containing chemotherapy \(DAFNE\)-GBG70 - efficacy and safety analysis](#)

Final OS analysis from the CLEOPATRA study in patients with HER2-positive metastatic breast cancer

In the CLEOPATRA study, first-line treatment with pertuzumab/trastuzumab/docetaxel significantly improved OS for patients with HER2-positive metastatic breast cancer compared with placebo/trastuzumab/docetaxel, providing a 15.7 month increase in the median values. The median OS of 56.5 months is unprecedented in first-line and this substantial improvement confirms the pertuzumab containing regimen as standard of care in this setting, reported Prof. Sandra Swain of the Medstar Washington Hospital Center, Washington Cancer Institute, Washington, USA.

In the CLEOPATRA study, 808 patients from 25 countries with HER2-positive metastatic breast cancer were randomised to receive first-line placebo/trastuzumab/docetaxel or pertuzumab/trastuzumab/docetaxel. Randomisation was stratified by geographic region and neo/adjuvant chemotherapy.

The patients were eligible for the study if they had HER2-positive (centrally confirmed), metastatic, locally recurrent, or unresectable breast cancer, measurable or non-measurable disease; had received ≤ 1 hormonal regimen for metastatic breast cancer prior to randomisation, disease-free interval at least 12 months since prior neo/adjuvant treatment, and left ventricular ejection rate (LVEF) $\geq 50\%$ at baseline.

The study primary endpoint was progression-free survival (PFS) independently assessed. Secondary endpoints included investigator-assessed PFS, objective response rate (ORR), safety, and OS. Final analysis was planned at 385 deaths, with two interim analyses at 165 and 267 deaths.

At the primary analysis in May 2011, pertuzumab was shown to increase PFS significantly, with a strong trend to OS benefit. At a second interim analysis in May 2012, the OS was improved to a degree which was both statistically significant and clinically meaningful with hazard ratio (HR) 0.66 ($p = 0.0008$), but the median OS in patients who received pertuzumab was not reached.

In July 2012, the patients still on placebo were offered crossover to pertuzumab.

At ESMO 2014 the CLEOPATRA researchers reported results of a final prespecified OS analysis (February 2014). This OS analysis was planned when ≥ 385 deaths were reported. The log-rank test, stratified by prior treatment status and geographic region, was used to compare OS between the arms, applying the threshold of $p \leq 0.0456$. Subgroup analyses of OS were performed for stratification factors and other key baseline characteristics.

At median follow-up of 50 months (range 0 to 70 months), the statistically significant improvement in OS in favour of the pertuzumab/trastuzumab/docetaxel arm was maintained (HR = 0.68, $p = 0.0002$). Median OS was 40.8 months in the placebo arm and 56.5 months in the pertuzumab arm, with difference of 15.7 months.

The OS benefit in predefined subgroups was consistent with previous observations. It is to be noted that following the previous report of OS benefit, 48 patients in the placebo arm crossed over to the pertuzumab arm.

The PFS in the pertuzumab arm was 18.7 vs. 12.4 months in the placebo arm, HR 0.68 ($p < 0.0001$).

Median time on study treatment was 17.4 months in the pertuzumab arm vs. 11.4 months in the placebo group.

The safety profile of pertuzumab/trastuzumab/docetaxel in the overall population and in patients who crossed over to the pertuzumab arm was consistent with the known safety profile of pertuzumab with more pronounced diarrhoea, rash, mucosal inflammation, pruritus, dry skin, and muscle spasm. No new safety concerns were seen with longer follow-up. There was no evidence of cumulative or late toxicity. The long-term cardiac safety profile was maintained.

Dr Luca Gianni of the IRCCS San Raffaele Hospital, Milan, Italy, who discussed the study results, said that CLEOPATRA is an unquestionable therapeutic success with an unquestionable clinical implication: docetaxel/trastuzumab/pertuzumab is the new standard, not an option for first-line treatment of HER2-positive metastatic breast cancer. However, adjuvant trastuzumab was administered in only 10% of the study population. Dr Gianni said that the therapeutic role and wide applicability of dual HER2-blockade with monoclonal antibodies is established but new therapeutic

approaches to improve the overall results of CLEOPATRA should address the different biology and different drug sensitivity of subsets of HER2-positive tumours.

Improvements can be expected by addressing key features of HER2-positive breast cancer linked to different sensitivity in term of hormone receptor status (positive vs. negative), PIK3CA status (wild type vs. mutant), and immune environment.

The CLEOPATRA study did not allow endocrine therapy of patients with ER-positive tumours. Dual blockade of HER2 with pertuzumab/trastuzumab and concomitant endocrine therapy is feasible as shown by APHINITY study in the adjuvant setting. Dr Gianni wondered if the addition of endocrine therapy after the end of chemotherapy would increase the already large benefit observed in women with HER2-positive/ER-positive metastatic breast cancer patients enrolled in the CLEOPATRA study.

The PIK3CA status can be easily assessed on tumour biopsies or liquid biopsies. Many PI3K inhibitors are available and being tested in combination with standard HER2-directed therapy. T-DM1 is effective in HER2-positive breast cancer regardless of whether or not the tumours carry a mutation in the PIK3CA. Therapies tailored according to PIK3CA mutational status of HER2-positive metastatic breast cancer should be tested.

Immune mechanisms and tumour lymphocyte infiltration are involved in the probability of pCR in HER2-positive breast cancer. There is a high expression of PDL1 and CTLA4 linked to residual disease in ER-negative tumours. Dr Gianni concluded that tests should be carried out to see if blocking of CTLA4 and/or PD1/PDL1 will be useful for some patients treated per the CLEOPATRA protocol.

The CLEOPATRA study was sponsored by F.Hoffmann-La Roche

Reference

[3500 PR: Final overall survival \(OS\) analysis from the CLEOPATRA study of first-line \(1L\) pertuzumab \(Ptz\), trastuzumab \(T\), and docetaxel \(D\) in patients \(pts\) with HER2-positive metastatic breast cancer \(MBC\)](#)

IMELDA: Efficacy and safety of maintenance bevacizumab with or without capecitabine after initial first-line bevacizumab plus docetaxel

In IMELDA study, adding capecitabine to maintenance bevacizumab provided statistically significant and clinically meaningful improvements in PFS and OS. The rationale for the study was observation that prolonging first-line chemotherapy results with maintenance treatment may influence OS.

In HER2-negative patients with locally recurrent/metastatic breast cancer, combining bevacizumab with first-line chemotherapy significantly improves PFS. Bevacizumab benefit is most pronounced when combined with a taxane. Cumulative toxicity prevents taxane continuation until disease progression. Until regulatory withdrawal of bevacizumab/docetaxel in 2011, this combination was considered as a valid first-line option for HER2-negative metastatic breast cancer based on results of a phase III trial. The PFS and response rate (RR) with maximum 9 cycles of first-line docetaxel were significantly improved by adding bevacizumab continued until disease progression.

The open-label randomised phase III IMELDA trial tested whether switching to a more tolerable chemotherapy with a different mechanism of action while continuing VEGF inhibition may be more

effective. It was meant that by adding capecitabine to maintenance bevacizumab was continued until disease progression after initial bevacizumab/docetaxel which improved PFS. The study findings were presented by Prof. Joseph Gligorov of the Tenon University Hospital, Paris, France.

Patients with HER2-negative measurable metastatic breast cancer, ECOG performance status (PS) <2 and no prior chemotherapy were eligible for study inclusion.

After 3–6 cycles of bevacizumab/docetaxel, patients without disease progression were randomised to bevacizumab alone or bevacizumab/capecitabine until disease progression. Stratification factors were oestrogen receptor (ER) status, presence of visceral metastases, response status and LDH concentration.

The primary endpoint was PFS from randomisation to progression/death; secondary endpoints included RR, clinical benefit rate, time to disease progression, OS from randomisation, safety and quality of life (QoL). The sample size was calculated based on a PFS HR of 0.70 with median PFS improvement from 5.8 to 8.3 months. In total 360 enrolled patients were required for 290 randomised patients. It was planned that 244 PFS events provide 80% power at 5% 2-sided α . The study was not designed for formal OS comparison.

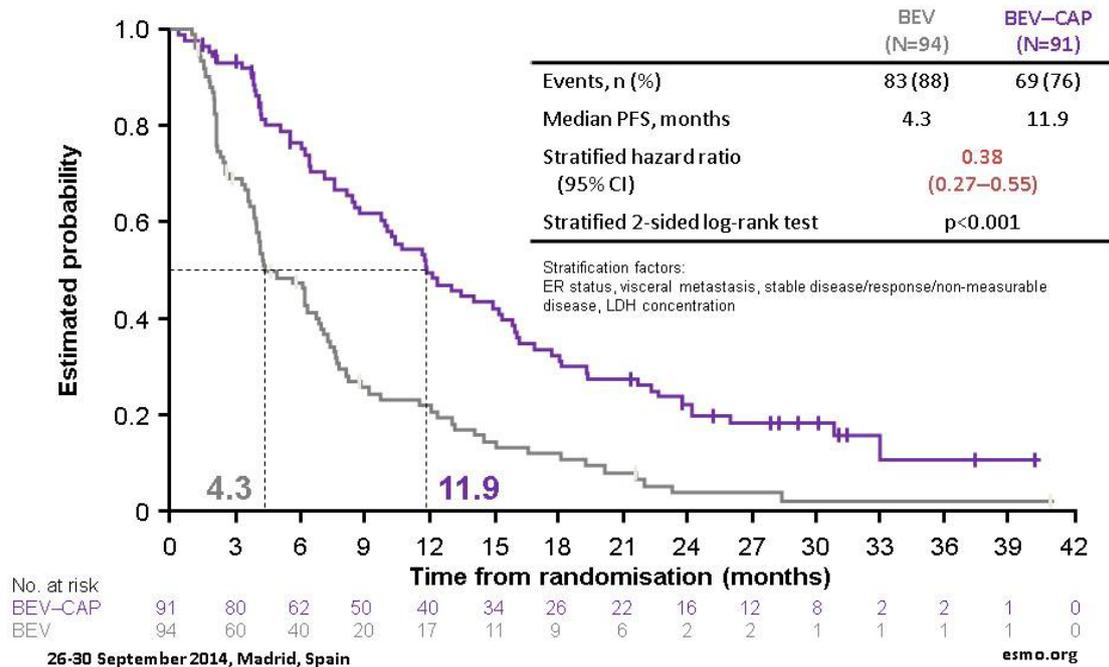
Between June 2009 and March 2011 when enrolment was prematurely terminated, 287 patients were enrolled and 284 of them treated with 185 (65%) who completed initial treatment and subsequently randomised to maintenance treatment. The protocol was amended to continue follow-up for 2 years after last randomisation.

Median age in the bevacizumab arm was 54 years and 49 years in the bevacizumab/capecitabine arm. Triple-negative disease was recorded in 22% of patients included in the bevacizumab arm and 27% of patients in the bevacizumab/capecitabine arm. Visceral metastases were nearly identical in both group (69% vs. 68%), however their presence in ≥ 3 organs was higher in bevacizumab arm at enrolment to the initial phase (57% vs. 47%).

In the maintenance arm, median treatment duration was longer in bevacizumab/capecitabine group (8.3 vs. 3.5 months). Adding capecitabine to maintenance bevacizumab provided statistically significant and clinically meaningful improvements in PFS from time of randomisation (HR 0.38, $p < 0.001$; median 11.9 vs. 4.3 months) and exploratory analysis (PFS from start of first-line therapy), as well as improvement in median OS from time of randomisation (HR 0.42, $p < 0.001$; 39 vs. 23.3 months), despite the smaller than planned sample size because of early termination of accrual.

MADRID 2014 ESMO congress

Primary endpoint: PFS from time of randomisation

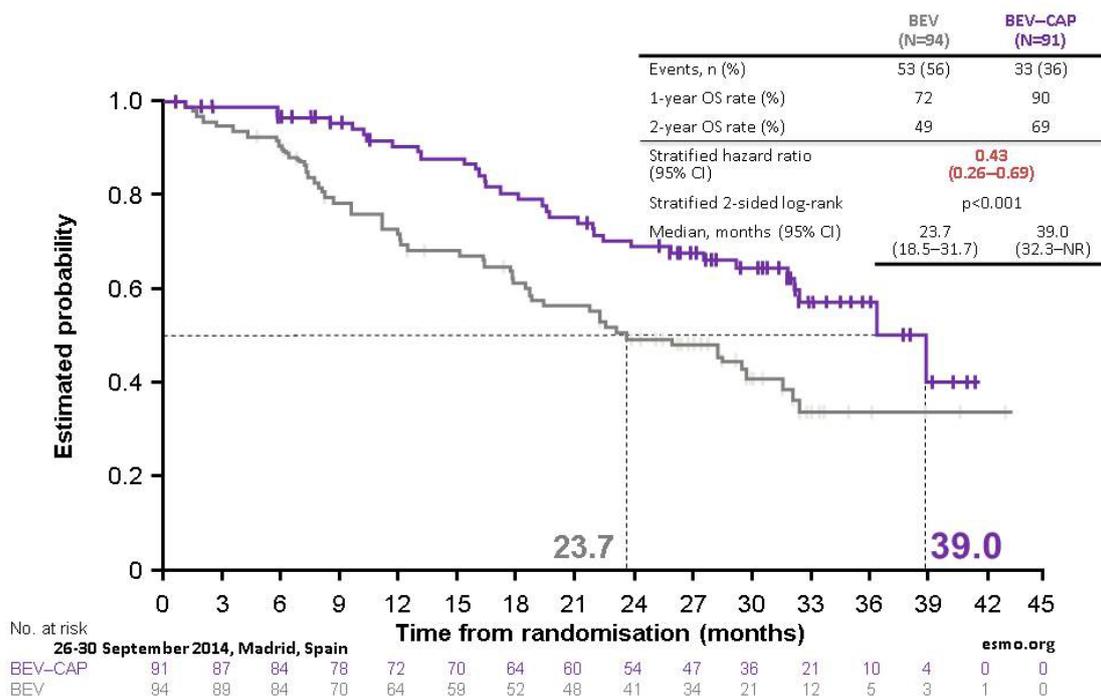


Caption: PFS from time of randomisation. © Joseph Gligorov

However, at the time of report there was insufficient duration of OS follow-up with the low event rate.

MADRID 2014 ESMO congress

Secondary endpoint: OS from time of randomisation



Caption: OS from time of randomisation. © Joseph Gligorov

There was a manageable increase in adverse events mainly due to hand-foot syndrome experienced in 33% of patients in bevacizumab/capecitabine arm. Hypertension was recorded in 9% of patients in the combined arm and 3% of patients in the bevacizumab only arm. The rate of proteinuria was same (4%) in both groups. Gastroenteritis occurred in 3 patients in the bevacizumab single agent arm.

Prof. Gligorov concluded that in patients benefiting from first-line bevacizumab-containing therapy, continued bevacizumab with capecitabine improves efficacy. Ongoing evaluation considers collection of data on anti-cancer treatment after study therapy and patient-reported outcomes.

Dr Hope Rugo of the UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, USA, who discussed the study results, said that the IMELDA trial tried to answer the question: does continuing bevacizumab post progression have an impact on outcome? Dr Rugo questioned if bevacizumab is an adequate maintenance therapy after response to first-line chemotherapy. In the study, there was a longer duration of treatment with capecitabine/bevacizumab vs. bevacizumab (twice the number of cycles), markedly longer PFS, and the PFS from start of first-line was doubled, OS was significantly longer, but there were also almost double the grade > 3 toxicity (mainly hand-foot syndrome, hypertension, but also thromboembolism). Hand-foot syndrome resulted in discontinuation of capecitabine in 10% of patients.

Upon the presentation at ESMO 2014, the study results were published in the Lancet Oncology.

The study was sponsored by F. Hoffmann-La Roche.

Reference

[352O: Efficacy and safety of maintenance bevacizumab \(BEV\) with or without capecitabine \(CAP\) after initial first-line BEV plus docetaxel \(DOC\) for HER2-negative metastatic breast cancer \(mBC\): IMELDA randomised phase III trial](#)

[TANIA: Efficacy and safety of continued or reintroduced bevacizumab after first-line bevacizumab for HER2-negative locally recurrent/metastatic breast cancer](#)

The primary objective of open-label randomised phase III TANIA study was met, showing statistically significantly improvement in PFS with bevacizumab after progression on first-line bevacizumab-containing therapy in bevacizumab-pretreated patients with HER2-negative locally recurrent/metastatic breast cancer. The study results were presented by Gunther von Minckwitz, Managing Director of the German Breast Group and University Women's Hospital, Neu-Isenburg, Germany.

Combining bevacizumab with first- or second-line chemotherapy in randomised phase III trials showed significantly improved PFS in HER2-negative locally recurrent/metastatic breast cancer. Sustained VEGF blockade may be important for long-term disease control. Patients with HER2-negative locally recurrent/metastatic breast cancer who had progressed during/after ≥12 weeks of first-line bevacizumab plus chemotherapy were randomised 1:1 to second-line single-agent chemotherapy either alone or with bevacizumab (15 mg/kg q3w or 10 mg/kg q2w).

Stratification factors were: hormone receptor status; time to first-line progression (<6 vs. ≥6 months); chemotherapy choice (taxane vs. non-taxane vs. vinorelbine); and LDH concentration (≤1.5 vs. >1.5 x upper normal limit).

Second-line therapy was continued until disease progression, unacceptable toxicity or consent withdrawal. At disease progression, patients in the chemotherapy arm received third-line chemotherapy without bevacizumab (no crossover); patients initially randomised to chemotherapy plus bevacizumab received third-line chemotherapy plus bevacizumab.

Chemotherapy options were based on investigator's choice, but doublets were not allowed: paclitaxel, nab-paclitaxel, docetaxel, capecitabine, gemcitabine, pegylated liposomal doxorubicin, non-pegylated liposomal doxorubicin, doxorubicin, epirubicin, vinorelbine, cyclophosphamide, ixabepilone and in third line only eribulin.

The primary endpoint was PFS from randomisation to second disease progression/death. Additional endpoints included second-line PFS in prespecified subgroups, second- and third-line PFS calculated from randomisation to third disease progression/death, second-line ORR, OS, safety, QoL and biomarkers.

Sample size was calculated based on assuming prolonging median PFS from 7 to 9.3 months and a HR of 0.75. PFS events were required in 384 of 488 patients for 80% power at 2-sided $\alpha=0.05$.

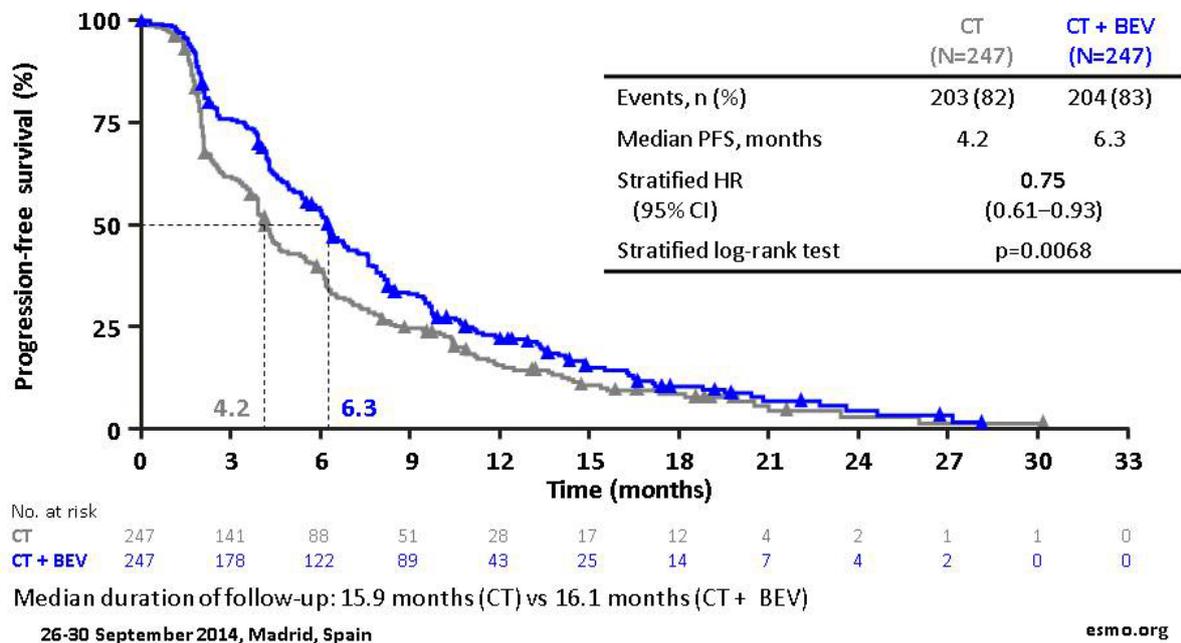
At ESMO 2014, the investigators presented the mature pre-specified second-line PFS analysis. Endpoints relating to third-line therapy will be presented at the final analysis.

From January 2011 to April 2013, 494 patients were enrolled (247 in chemotherapy arm and 247 in chemotherapy plus bevacizumab arm). Baseline characteristics were similar in chemotherapy vs. chemotherapy plus bevacizumab groups: median age 54 vs. 56 years; triple negative disease 23.1% vs. 19.8%; disease-free interval ≤ 12 months 9.7% vs. 7.3%.

The most frequently chosen second-line chemotherapy was capecitabine, 59.7% in chemotherapy group and 60.4% in the chemotherapy plus bevacizumab group.

Median follow-up was similar in both groups. At data cut-off on 20 December 2013, median second-line PFS was 4.2 months in chemotherapy vs. 6.3 months in chemotherapy/bevacizumab groups (stratified HR 0.75, $p = 0.0068$). Subgroup analysis for PFS by stratification factor was also more favourable for the bevacizumab/chemotherapy group.

Primary endpoint: Second-line PFS



Caption: Primary endpoint – Second-line PFS. © Gunter von Minckwitz

The best ORR was not statistically different in two groups (16.8% vs. 20.9%). However, the stable disease (SD) was recorded in 33.5% patients in the chemotherapy arm and 48.9% in the bevacizumab/chemotherapy arm.

Median duration of response (DoR) was 10.6 vs. 8.3 months for chemotherapy and bevacizumab/chemotherapy patients.

The rate of side effects was slightly higher in the chemotherapy/bevacizumab arm: hypertension (7.1% vs. 13.5%), proteinuria (0.4% vs. 6.9%), venous thromboembolic event (2.1% vs. 3.3%), febrile neutropaenia (1.7% vs. 3.3%), congestive heart failure (0.4% vs. 2.0%), bleeding (1.7% vs. 0.4%), arterial thromboembolic event (1.3% vs. 0%), wound-healing complication (0% vs. 0.8%), GI perforation (0% vs. 0.4%), and fistula/abscess (0% in both groups).

The authors concluded that the primary objective of the study was met, showing statistically significantly improved PFS with bevacizumab after disease progression on first-line bevacizumab-containing therapy. Second-line safety results were as expected from previous bevacizumab trials in locally recurrent/metastatic breast cancer. Final OS, PFS from randomisation to third-line progression/death and third-line safety results are anticipated in mid 2015.

Dr Hope Rugo of the UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, USA, who discussed the results from this study as well, said that the TANIA trial tried to see the impact of chemotherapy vs. targeted therapy alone as maintenance therapy after response. Almost 85% of patients received first-line taxane (73% paclitaxel). There was an unusually long PFS in first-line. Almost 60% received second-line capecitabine. The PFS increased with continued bevacizumab; there was an increase in SD but not ORR and, as in prior studies, the

greater benefit was in triple-negative breast cancer. Furthermore, there was more toxicity with bevacizumab (hypertension, proteinuria, neutropenia).

Maintenance chemotherapy improves PFS and OS after response to first-line chemotherapy. Unclear additional benefit from bevacizumab must be balanced against cost and toxicity. Bevacizumab alone should not be used as maintenance therapy in this setting. Almost 75% had hormone receptor-positive disease and there might be a role of maintenance hormone therapy.

Dr Rugo concluded that at present the role of bevacizumab is unclear in breast cancer.

Upon the presentation at ESMO 2014, the study results were published in the Lancet Oncology.

The study was sponsored by F. Hoffmann-La Roche.

Reference

[353O: Efficacy and safety in TANIA, a randomised phase III trial of continued or reintroduced bevacizumab \(BEV\) after 1st-line BEV for HER2-negative locally recurrent/metastatic breast cancer \(LR/mBC\)](#)

CNS Malignancies

Randomised phase II trial AVAREG (ML25739) with bevacizumab or fotemustine in recurrent glioblastoma

Dr Alba Brandes of the Bellaria Hospital, Bologna, Italy presented final results from the randomised phase II AVAREG (ML25739) trial in which bevacizumab showed no better outcome in patients with recurrent glioblastoma when compared with fotemustin.

In glioblastoma, global functioning worsens every time the disease relapses. Recurrent glioblastoma is determined by change in personality, neurocognitive decline, PS decline, and needs for corticosteroids associated with side effects.

The role of bevacizumab in glioblastoma treatment has been largely debated since only a few data compared this agent with standard therapy. Fotemustine is a third generation chloroethylnitrosourea with limited lung toxicity. It is the most used nitrosourea in Italy.

A multicenter, open label, randomised (2:1), non-comparative phase II study with bevacizumab every 2 weeks or fotemustin on days 1, 8, 15 followed, after a 35 days interval, by fotemustin every 3 weeks had as a primary endpoint OS at 6 months (OS6). Secondary endpoints were OS-9 and OS-12, median OS, PFS6, response rate, toxicity profile, and QoL.

Stratification factors were age (<55 years or >55 years) and resection for recurrent disease (yes vs. no).

Central imaging review was pre-planned using RANO criteria and Macdonald's criteria. Central pathology review was also pre-planned.

The initially planned sample size of 75 patients was increased according to the expected dropout rate of about 17%. In total 91 ITT patients with recurrent glioblastoma were enrolled among 10 Italian centers between November 2011 and September 2012. Median age was 57 years (range: 28-78), ECOG PS was 0/1/2 in 42/35/14 patients. All patients received radiotherapy/temozolomide according to the EORTC 26981-22981/NCIC CE3 protocol.

Time from diagnosis to first recurrence was 331 days in the bevacizumab arm and 460 days in the fotemustin arm. At the time of recurrence, 21 patients (23.1%) underwent re-resection before the inclusion into the study (13 patients in the bevacizumab arm and 8 patients in the fotemustin arm, respectively). Fifty-nine patients were enrolled in the bevacizumab arm and 32 patients in the fotemustin arm.

OS6 was 62.1% and 73.3%, OS9 was 37.9% and 46.7% in the bevacizumab and fotemustin arms, respectively. Median OS was 7.3 months in the bevacizumab arm and 8.7 months in the fotemustin arm. Median PFS in the bevacizumab arm was 3.38 months and 3.45 months in the fotemustin arm.

In the bevacizumab arm, OS6 and OS9 were 77.8% and 59.3% in patients ≤55 years, and 48.4% and 19.3% in patients >55 years. The HR for OS in the bevacizumab group for patients >55 years compared with patients ≤55 years was 2.0 (p = 0.05).

Concordance between local and central assessments was 72.5% using RANO criteria and 71.1% with Macdonald's criteria.

Grade 3-4 toxicities in the bevacizumab and fotemustin arms were neutropaenia (1.7% vs. 12.5%), thrombocytopaenia (0 vs. 21.9%), intestinal perforation (3.4% vs. 0), cerebral ischaemia/haemorrhage (3.4% vs. 0), pulmonary embolism (1.7% vs. 0), and acute myocardial infarction (1.7% vs. 0).

Dr Brandes concluded that bevacizumab and fotemustine had differing toxicity profiles in this trial. Both bevacizumab and fotemustine are highly active in the treatment of recurrent glioblastoma. Bevacizumab activity seen is in line with all reported series.

Limitations of phase II studies are that they are non-comparative, underpowered for face-to-face comparison, limited sample size may not protect from biases, and ambitious endpoints (such as mOS and OS rates) may be hampered by known and unknown factors.

Prof. Evanthia Galanis of the Mayo Clinic, Rochester, USA, who discussed the study results, said that AVAREG was well conducted, randomised, non-comparative trial in recurrent glioblastoma. Bevacizumab and nitrosourea arms performed similarly but final information on crossover is pending. There is a different, but acceptable side effects profile. The data support the use of bevacizumab in recurrent glioblastoma if take into consideration clinical characteristics, symptom status, and comorbidities.

The study was sponsored by F. Hoffmann-La Roche.

Reference

[414O: Randomized phase II trial AVAREG \(ML25739\) with bevacizumab \(BEV\) or fotemustine \(FTM\) in recurrent GBM: Final results from the randomized phase II trial](#)

Developmental Therapeutics

Pimasertib and SAR245409, a MEK and PI3K/mTOR inhibitors combination: A phase Ib trial with expansions in selected genotype-defined solid tumours

Dr Rebecca Heist of the Massachusetts General Hospital Cancer Center, Boston, USA reported that dual inhibition of the MAPK and PI3K pathways using a combination of pimasertib and SAR245409 given once daily is feasible. Combination therapy is generally well tolerated. Pimasertib and SAR245409 combination therapy demonstrated clinical activity in patients with solid tumours; however, the response rate was limited. Further investigations are required, including pharmacokinetic analyses, to better understand these preliminary outcomes.

In preclinical studies, simultaneous inhibition of the MAPK and PI3K/PTEN signalling pathways led to enhanced antitumour activity compared with inhibition of either pathway alone. Pimasertib (MEK1/2 inhibitor) combined with SAR245409 (PI3K and mTOR inhibitor) is being evaluated in patients with solid tumours. Initial dose-escalation investigations determined the maximum tolerated dose (MTD) for pimasertib/SAR245409 and based on this, expansion into disease-specific patient populations has occurred. Patient populations to be investigated were chosen based on activity signals from the dose-escalation phase of this study and published evidence from ongoing trials with similar combinations, scientific rationale and supportive non-clinical data, as well as unmet medical needs.

Inclusion criteria considered patients with ECOG PS 0-1. Prior MEK and/or PI3K inhibitor therapy was not allowed. Safety and efficacy were analysed using standard criteria (NCI CTCAE v4.0 and RECIST v1.1).

At the recommended phase 2 dose (RP2D), 4 disease- and genotype-specific cohorts were recruited: RAS mutated non-small cell lung cancer (NSCLC) - 24 patients, triple-negative breast cancer (TNBC, 26 patients), BRAF inhibitor resistant melanoma (15 patients) and dual KRAS and PIK3CA mutated CRC (18 patients).

The most frequent ($\geq 20\%$) all grade treatment-emergent adverse events were: diarrhoea (77.1%), fatigue (54.2%), nausea (50.6%), vomiting (47.0%), dermatitis acneiform (37.3%), maculo-papular rash (30.1%), decreased appetite (30.1%), peripheral edema (25.3%), pyrexia (25.3%), stomatitis (24.1%), dizziness (24.1%), dyspnea (21.7%), skin rash (21.7%), increased creatinine phosphokinase levels (21.7%), abdominal pain (20.5%) and pruritus (20.5%). Serous retinal detachment, which is a class effect of MEK inhibitors, was reported in 34.9% of patients and all cases were resolved without serious damage to the eyesight.

Confirmed responses were observed in 2 of 18 evaluable NSCLC patients and in 1 of 13 evaluable melanoma patients.

Dr Elizabeth Eiesenhauer of the Queen's University, Kingston, Canada, who discussed the study results, said that dual pathway inhibition in this study represents one of many combination of MEK and PI3K (mTOR) inhibitors. Tumour and biomarker in the study are defined based on relevant pathway mutations (KRAS, PIK3CA, BRAF mutations). The both drugs have limited activity in solid tumours. Approximately 80% of patients experienced > grade 3 adverse events, but they were considered tolerable. Doses of both drugs were lower than if applied as a single agent. Antitumour activity of combination is low, similar to other PI3k/mTOR combinations.

The study was sponsored by Merck KGaA and Sanofi.

Reference

443O: Pimasertib (PIM) and SAR245409 (SAR) - a MEK and PI3K/MTOR inhibitor combination: A phase Ib trial with expansions in selected genotype-defined solid tumors

Phase Ib trial of RG7116, a glycoengineered monoclonal antibody targeting HER3, in combination with cetuximab or erlotinib in patients with advanced/metastatic tumours of epithelial cell origin expressing HER3 protein

Dr Ulrik Lassen of the Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark reported that RG7116 combination with cetuximab or erlotinib in a phase Ib study was well tolerated, and demonstrated preliminary signs of clinical activity.

RG7116 locks HER3 in its closed, inactive conformation. It shows a strong inhibition of HER3 signalling. It is glycoengineered for enhanced immune effector recruitment and showed antitumour activity in numerous xenograft models.

Patients with ECOG PS ≤2, advanced or metastatic solid tumours of epithelial origin, and centrally confirmed HER3 protein expression were included. RG7116 plus cetuximab and RG7116 plus erlotinib combinations were evaluated in a dose escalation study with “3 + 3” design.

Twenty-seven patients were enrolled in 5 cohorts in the cetuximab arm. One dose-limiting toxicity (DLT) of grade 3 dehydration was reported in the 800 mg cohort.

Twenty-seven patients were enrolled in 4 cohorts in the erlotinib arm. One DLT was reported in the 1600 mg cohort (grade 3 diarrhoea and grade 3 hypokalaemia) and one DLT was reported in the 2000 mg cohort (grade 3 blood bilirubin increase).

No maximum tolerated dose was reached.

The most frequently reported adverse events of any grade were EGFR inhibitor related: diarrhoea (78%) and rash (59%) for the cetuximab arm and diarrhoea (82%) and decreased appetite (48%) for the erlotinib arm. In the erlotinib arm treatment-related grade 3 diarrhoea was observed more frequently at higher doses of RG7116. Overall, infusion-related reactions related to RG7116 occurred in 11% of patients. Two of these were grade 3 (4%).

The pharmacokinetic profile of RG7116 in combination with cetuximab and erlotinib was comparable to that in the monotherapy setting.

HER3 membranous protein down-regulation was observed from 400 mg onwards in on-treatment tumour and skin tissue.

In the cetuximab arm, two patients with colorectal carcinoma had confirmed partial response (PR). In the erlotinib arm, one patient with ovarian carcinoma had a confirmed PR. Metabolic PR on FDG-PET occurred in 42% of patients in the cetuximab arm and in 28% of patients in the erlotinib arm.

Dr Elizabeth Eiesenhauer of the Queen’s University, Kingston, Canada, who discussed the study results, said that in this study two drugs were investigated of different MOA affecting same target/pathway to maximise inhibition of the pathway. Their combination was studied in any epithelial solid tumour that must be HER3-positive. However, it is unclear if prior epidermal growth factor receptor (EGFR) inhibitor was allowed. RG7116 (HER3 inhibitor) is not evaluated yet in

solid tumours, while cetuximab and erlotinib were but data in HER3 selected patients are unknown. Full doses of erlotinib and cetuximab were foreseen by design. Toxicity was not limiting. Activity of combination is low. Higher response was seen when using PET, but meaning of this finding is unclear.

The study was sponsored by F. Hoffmann La-Roche.

Reference

444O: Phase Ib trial of RG7116, a glycoengineered monoclonal antibody targeting HER3, in combination with cetuximab or erlotinib in patients with advanced/metastatic tumors of epithelial cell origin expressing HER3 protein

Dose-escalation study of sonidegib (LDE225) plus buparlisib (BKM120) in patients with advanced solid tumours

Dr Quincy Siu-chung Chu of the University of Alberta Cross Cancer Institute, Edmonton, Canada reported that LDE225 and BKM120 combination is tolerable, with expected DLTs, consistent with phase I studies. Pharmacokinetics of each agent in combination appear similar to pharmacokinetics observed in single-agent studies. Based on these data, further study of the combination is warranted.

Aberrant hedgehog (Hh) signaling has been observed in tumours with dysregulated PI3K signalling. Sonidegib (LDE225; smoothed inhibitor that blocks Hh activity) and buparlisib (BKM120; pan class I PI3K inhibitor) show antitumour activity in phase I studies and combined, enhanced activity in xenograft models.

In this phase Ib study, the MTD and/or recommended dose for expansion (RDE), pharmacokinetic interaction, and preliminary antitumour activity of LDE225 plus BKM120 were assessed in patients with metastatic breast cancer, pancreatic adenocarcinoma, metastatic CRC, or recurrent glioblastoma.

Adult patients received different daily doses (followed by Bayesian logistic regression model) of LDE225 and BKM120. Safety, tolerability, pharmacokinetic, antitumour activity, and biomarkers PIK3CA/PTEN were assessed. The researchers reported at ESMO 2014 safety and pharmacokinetic results.

In total 46 patients (7 with metastatic breast cancer, 9 with pancreatic adenocarcinoma, 19 with mCRC, and 11 with glioblastoma) were enrolled into 5 cohorts. As of 12 December, 2013, 44 patients (95.7%) discontinued, primarily due to disease progression (29 cases) and adverse events (7 cases).

Grade 3/4 adverse events (> 5%) regardless of study drug included increased alanine and aspartate aminotransferase (21.7% each), increased blood creatine phosphokinase (17.4%), hyperglycaemia (8.7%), and increased blood alkaline phosphatase, aphasia, nausea, fatigue (6.5% each).

The team reported DLTs in each cohort; however MTD was not reached. At the RDE (LDE225 400 mg/BKM120 80 mg), no drug-drug interaction was observed, the interindividual variability of LDE225 and BKM120 pharmacokinetic (cycle 1, day 1) was approximately 67% and 30%, respectively, and trough levels over time aligned with single-agent exposure. No obvious drug-

drug interactions between sonidegib and buparlisib were observed. The pharmacokinetics of each agent in combination appear similar to those observed in single-agent studies.

Dr Elizabeth Eiesenhauer of the Queen's University, Kingston, Canada, who discussed the study results, said that a dual pathway inhibition in this study was tested in tumours associated with aberrant Hh and/or PI3K signalling. Sonidegib shows activity in basal cell cancer, but not in tumours tested. Buparlisib has limited activity in solid tumours reported to date. Approximately 74% patients had > grade 3 adverse events, but they were considered tolerable. Doses of both drugs were lower than for single agent use. Activity of combination was not reported.

The study was sponsored by Novartis.

For all three above targeted drugs combination studies, Dr Eisenhauer said that it is unlikely these combinations will have dramatic effects in randomised clinical trials.

Reference

[445O: Dose-escalation study of sonidegib \(LDE225\) plus buparlisib \(BKM120\) in patients \(pts\) with advanced solid tumors](#)

Endocrine Cancers

Comprehensive analysis of serum biomarker and tumour gene mutation associated with clinical outcomes in the phase III study of lenvatinib in differentiated thyroid cancer

Dr Makoto Tahara of the National Cancer Center Hospital East, Kashiwa, Japan reported results from the comprehensive analysis of serum biomarker and tumour gene mutations in the SELECT study. Lenvatinib vs. placebo benefit in PFS was maintained regardless of baseline circulating cytokine/angiogenic factors (CAFs) or BRAF/RAS mutational status. Baseline angiopoietin-2 (Ang2) was predictive of tumour shrinkage and PFS in a subset of patients (lowest quartile, 0-25%) with lenvatinib, indicating that Ang2 may play a predictive role in defining sensitivity to lenvatinib. Additionally, BRAF mutation may be a positive prognostic factor in papillary thyroid cancer.

Lenvatinib—an oral multikinase inhibitor of VEGFR1–3, FGFR1–4, PDGFR α , RET, and KIT—significantly prolonged PFS by 14.7 months vs. placebo in patients with 131I-refractory differentiated thyroid cancer in the phase III SELECT study. This analysis investigated potential lenvatinib efficacy biomarkers from the SELECT study.

Blood samples were collected at baseline, cycle 1/day 15, day 1 of subsequent cycles, and at treatment end. Circulating CAFs were measured by ELISA. Tumour tissues were analysed for mutations of BRAF, NRAS, KRAS and HRAS. For prognostic and predictive biomarker analyses (p for interaction) of baseline CAFs, patients were dichotomised: low (first quartile) vs. high (others).

CAF and tissue samples were analysed from 387 (99%) and 183 (47%) of all randomised patients (in total 392), respectively. PFS HR was similar between these groups and the overall study; lenvatinib PFS benefit was maintained in all assessments.

Low baseline Ang2 was significantly associated with tumour shrinkage in lenvatinib ($p = 0.017$), but not placebo. PFS HR of lenvatinib to placebo for low Ang2 (0.08; $p < 0.001$) was lower than for high Ang2 (0.24; $p < 0.001$); low Ang2 was a positive predictive factor for lenvatinib PFS ($p = 0.018$).

High baseline thyroglobulin (Tg) was a negative prognostic factor for PFS ($p = 0.023$); PFS HR of lenvatinib to placebo for high Tg (0.14; $p < 0.001$) was lower than for low Tg (0.32; $p < 0.001$). With lenvatinib, Tg rapidly decreased by cycle 1/day 15; a large change correlated to better objective response (cycle 1/day 15 and later).

In mutation analyses, no significant differences in clinical outcomes were observed; BRAF mutation was an independent positive prognostic factor for PFS in papillary thyroid cancer ($p = 0.019$). BRAF mutation and NRAS mutation have significantly low and high baseline Tg, respectively, compared with wild type.

Dr Sandrine Faivre of the Beaujon University Hospital, Clichy, France, who discussed the study results, said that a large set of biological data (47% of tumours, 99% of serum) from this phase III study explored the multikinase inhibitor lenvatinib in patients with differentiated thyroid cancers. Tumour mutations (BRAF, RAS) do not impact on lenvatinib effects but on prognosis of certain histological subgroups (BRAFV600 in papillary thyroid cancer). In contrast, low level of Ang2 serum biomarker might be predictive of lenvatinib treatment benefit (associated with tumour size

reduction and favorable PFS). Other angiogenesis-related biomarkers (VEGF, sTie2) were not predictive of lenvatinib effect. Tg remains an important biomarker of monitoring to follow response to lenvatinib.

The study was sponsored by Eisai Inc.

Reference

[LBA30: Comprehensive analysis of serum biomarker and tumor gene mutation associated with clinical outcomes in the phase 3 study of \(E7080\) lenvatinib in differentiated cancer of the thyroid \(SELECT\)](#)

Gastrointestinal Cancers

A phase IB study of pembrolizumab in patients with advanced gastric cancer

In a phase Ib study the researchers assessed the safety, tolerability, and antitumour activity of pembrolizumab in gastric cancer patients. The results were presented by Dr Kei Muro of the Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan. Pembrolizumab was generally well tolerated and provided antitumour activity in patients with advanced gastric cancer that expressed PD-L1.

Using a prototype immunohistochemistry (IHC) assay, PD-L1 expression was assessed in archival tumour samples from patients with recurrent/metastatic adenocarcinoma of the stomach or gastroesophageal junction. Eligible patients with PD-L1 staining in stroma or $\geq 1\%$ of tumour cells were enrolled and treated with pembrolizumab every 2 weeks for up to 24 months or until complete response (CR), disease progression, or unacceptable toxicity.

Enrolment was designed to include an equal number of patients from Asia Pacific and the rest of the world. Adverse events were monitored and graded per the NCI CTCAE v4.0. Radiographic imaging was performed every 8 weeks. Primary efficacy endpoint was ORR assessed by RECIST v1.1.

Of the 162 patients screened, 65 (40%) were PD-L1-positive of which 39 enrolled: 19 from Asia Pacific, 20 from rest of world. Median age was 63 years, and 72% of patients were men. Patients from Asia Pacific were more heavily pretreated than patients from rest of world (≥ 2 prior therapies in 79% vs. 55%). Median follow-up duration was approximately 6 months.

The most common adverse events deemed treatment-related by investigators were hypothyroidism and fatigue. Grade ≥ 3 adverse events deemed treatment-related occurred in 3 patients (1 each for hypoxia, peripheral neuropathy, and pneumonitis).

The ORR (confirmed and unconfirmed) was 31.6% in Asia Pacific and 30% in the rest of world. Responses were ongoing for 6 of 6 Asia Pacific patients and 5 of 6 patients from the rest of world (median response duration not reached; range 8+ to 20+ weeks).

Evidence of an association between PD-L1 expression and PFS ($p = 0.032$) and ORR ($p = 0.071$) was observed. Preliminary data correlating PD-L1 expression with clinical outcomes will be further explored.

The robust antitumour activity observed supports the further development of pembrolizumab in advanced gastric cancer.

The study was supported by Merck Sharp & Dohme Corp.

Reference

[LBA15: A phase 1b study of pembrolizumab \(Pembro; MK-3475\) in patients \(Pts\) with advanced gastric cancer](#)

REACH: Ramucirumab as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib

The results of the REACH randomised, phase III study were presented by Prof. Andrew Zhu of the Massachusetts General Hospital Cancer Center, Boston, USA. The study primary endpoint was not met, but in a selected population of patients with an elevated baseline α -fetoprotein (AFP), a

meaningful OS improvement in the ramucirumab arm was observed. The treatment was well tolerated and demonstrated an acceptable safety profile. Given the high unmet medical need for second-line treatment in hepatocellular carcinoma, further investigation of ramucirumab might be warranted.

Sorafenib is the only approved first-line treatment in hepatocellular carcinoma. No treatment has demonstrated a survival benefit in the second-line setting. Vascular endothelial growth factor (VEGF) and VEGF-receptor 2-mediated signalling and angiogenesis likely contribute to pathogenesis of hepatocellular carcinoma.

Ramucirumab is a fully human IgG1 monoclonal antibody that binds to extracellular domain of VEGFR-2, preventing ligand binding and receptor activation. Preliminary evidence of ramucirumab anticancer activity in treatment-naïve hepatocellular carcinoma was demonstrated in a single-arm phase II study.

The REACH study evaluated the safety and efficacy of ramucirumab in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib.

It was required that patients eligible for the study have advanced hepatocellular carcinoma (histological or radiographical imaging confirmation) in stage BCLC C or B, who are refractory or not amenable to loco-regional therapy, have Child-Pugh A, ECOG PS 0 or 1, intolerance to sorafenib despite dose reduction, or disease progression during or following sorafenib, and adequate haematologic and biochemical parameters.

Patients were randomised 1:1 to receive ramucirumab i.v. plus best supportive care or placebo plus best supportive care every 2 weeks until disease progression, unacceptable toxicity, or death.

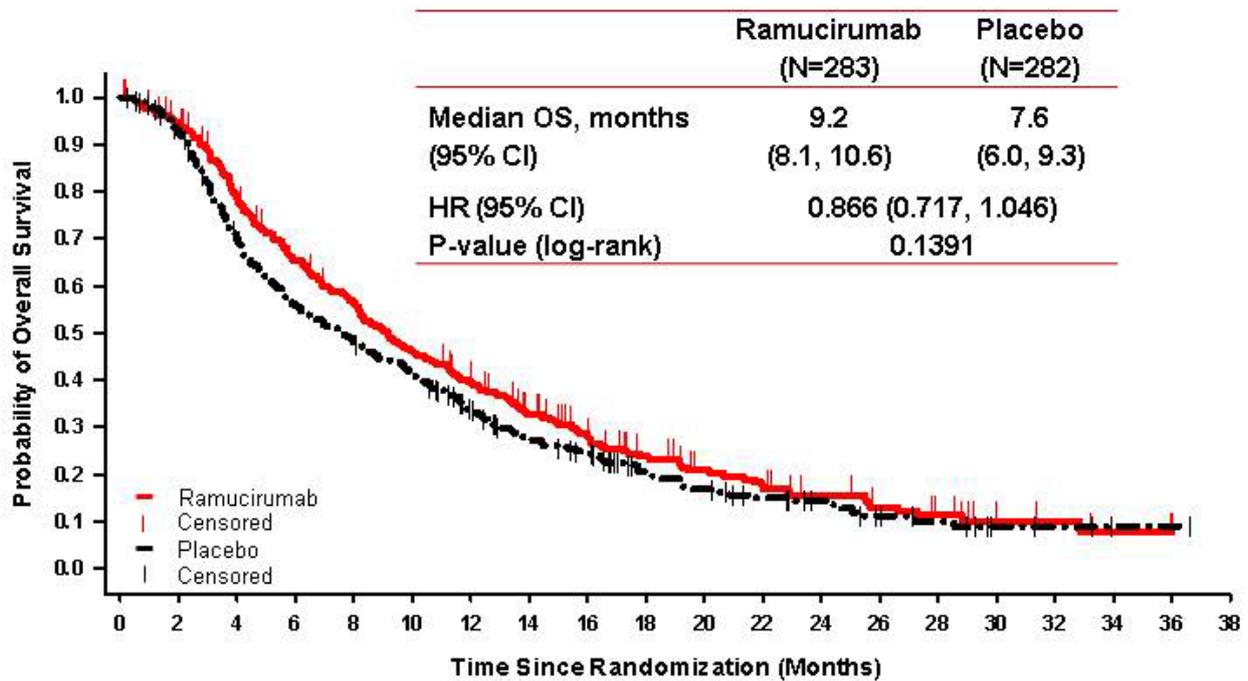
The primary endpoint was OS. Secondary endpoints included PFS, time to progression, ORR, safety and patient reported outcomes.

The sample size of 544 patients was calculated to enable 85% power to demonstrate statistical significance at an overall two-sided α of 0.05, assuming a HR of 0.75 and OS improvement from 8 to 10.67 months in the ramucirumab arm.

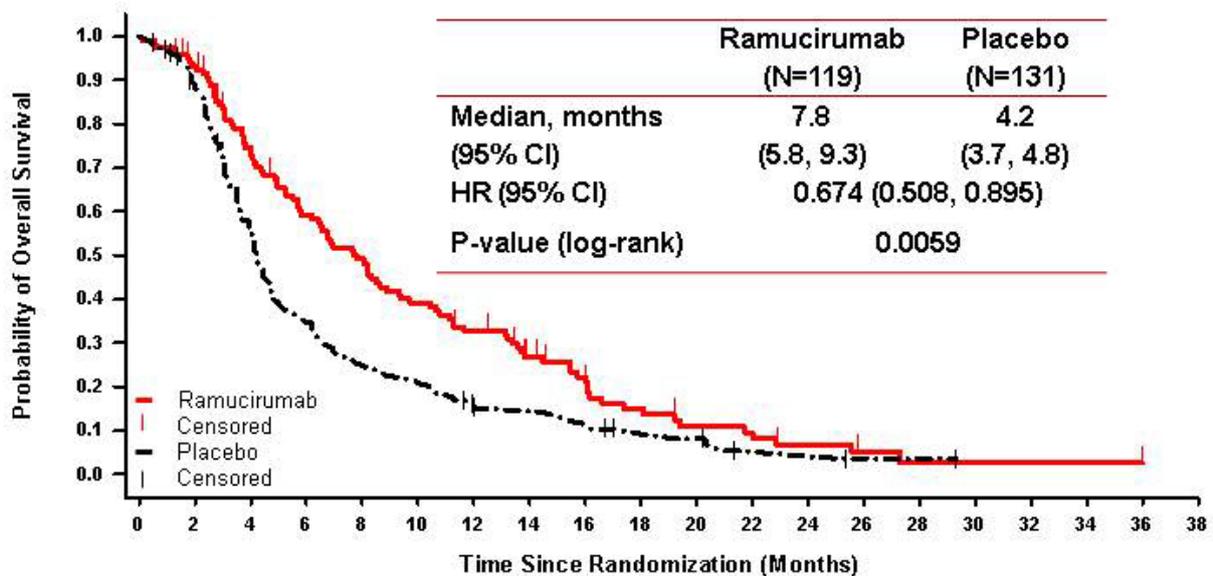
Between November 2010 and April 2013, 565 ITT patients were randomised: 283 in the ramucirumab arm and 282 in the placebo arm. Baseline patient characteristics were balanced between the two arms.

In the ITT population, the OS HR was 0.866 ($p = 0.1391$); median OS was 9.2 months for the ramucirumab arm vs. 7.6 months for the placebo arm. Forest plot of OS by subgroup favoured ramucirumab.

Overall Survival in Hepatocellular Cancer Patients ITT Population



Overall Survival in Hepatocellular Cancer Patients Baseline Alpha-fetoprotein ≥ 400 ng/mL



Caption: OS in the study ITT population and in patients with baseline α -fetoprotein ≥ 400 ng/mL. © Andrew Zhu

Median PFS in the ITT population with ramucirumab was 2.8 months and 2.1 months with placebo, respectively (HR 0.63, $p < 0.0001$) with forest plot by subgroup in favour of ramucirumab.

Median time to progression was 3.48 months in the ramucirumab arm vs. 2.63 months in the placebo arm ($p < 0.0001$). The ORR was 7.1% in the ramucirumab arm and 0.7% in the placebo arm ($p < 0.0001$).

In 250 patients with baseline α -fetoprotein (AFP) ≥ 400 ng/mL which was pre-specified, OS HR was 0.67 ($p = 0.0059$) with median OS of 7.8 months for ramucirumab vs. 4.2 months for placebo.

The safety population comprised 553 patients (277 patients in the ramucirumab arm and 276 patients in the placebo arm). No new safety signals were observed. However, grade ≥ 3 adverse events occurring in $> 5\%$ of treated ramucirumab patients included: hypertension (12.3% in the ramucirumab arm vs. 3.6% in the placebo arm), asthenia (5.1% vs. 1.8%), aspartate aminotransferase increase (5.4% vs. 8.3%), and malignant neoplasm progression (6.5% vs. 4.0%).

The study was sponsored by Eli Lilly.

Reference

[LBA16: Ramucirumab \(RAM\) as second-line treatment in patients \(pts\) with advanced hepatocellular carcinoma \(HCC\) following first-line therapy with sorafenib: Results from the randomized phase III REACH study](#)

Axitinib plus best supportive care in patients with advanced hepatocellular carcinoma following prior antiangiogenic therapy

Prof. Yoon-Koo Kang of the Department of Oncology, Asan Medical Center, Seoul, Korea presented results of a study with axitinib plus best supportive care vs. placebo plus best supportive care in patients with advanced hepatocellular carcinoma following prior antiangiogenic therapy.

Sorafenib, multi-targeted tyrosine kinase inhibitor (TKI) is the current standard treatment for advanced hepatocellular carcinoma. It prolonged OS over placebo in patients with advanced disease. However, other molecular targeted agents failed to show survival benefit in first- or second-line hepatocellular carcinoma. Therefore, an unmet need exists for treatment of patients who progressed on or are intolerant to sorafenib.

The efficacy and safety of axitinib, a potent and selective inhibitor of VEGF receptors 1-3, was evaluated in this global, randomised, double-blind phase II clinical trial in patients with locally-advanced or metastatic hepatocellular carcinoma.

Eligible patients who progressed on or were intolerant to one prior antiangiogenic therapy, Child-Pugh Class A or B (score 7 only) and ECOG PS 0 or 1 were randomised 2:1 to receive axitinib plus best supportive care or placebo plus best supportive care. They were stratified by tumour invasion defined as a presence vs. absence of extrahepatic spread and/or vascular invasion, and geographic region (Asia vs. non-Asia).

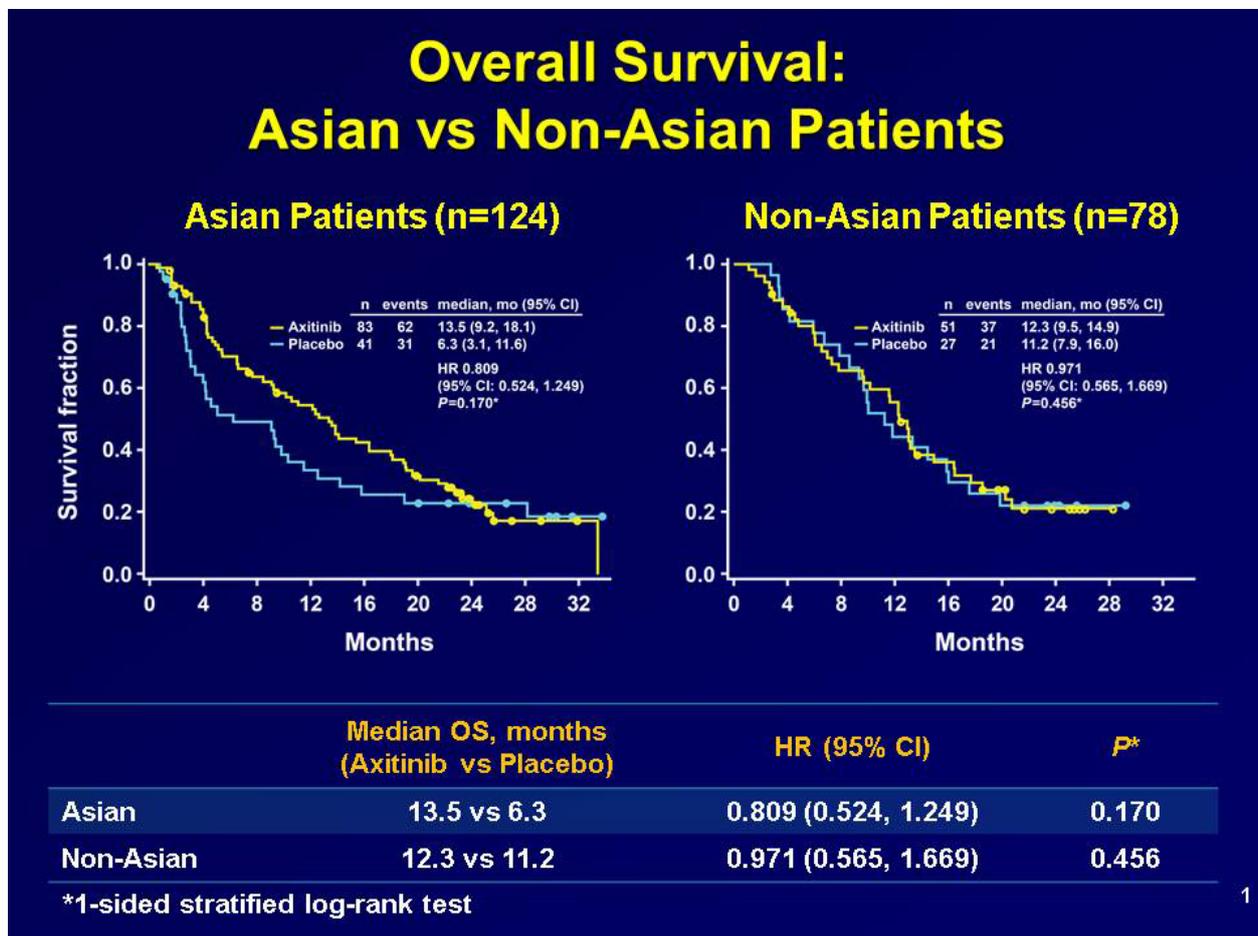
The primary endpoint was OS and secondary endpoints included PFS, time to progression, ORR, DoR, disease control rate (DCR), safety, health related QoL and biomarkers.

The study had 80% power to detect an improvement in median OS from 5.0 to 8.3 months with axitinib plus best supportive care, corresponding to a HR 0.60 (1-sided $\alpha = 0.025$).

To achieve the targeted number of 150 events (deaths) for final analysis, 198 patients had to be enrolled. From December 2010 to July 2012, 202 patients were randomised. An interim analysis was performed after approximately 50% of OS events occurred. The Independent Data Monitoring Committee recommended to proceed as per plan. As of the data cut-off for primary analysis (3 March 2014) 151 events were reported with 29 patients alive, 8 on treatment (axitinib 7 vs. placebo 1).

Two hundred two patients were randomised (134 in the axitinib arm and 68 in the placebo arm). They were predominantly of Asian origin (63% vs. 62%). Baseline patient characteristics and stratification factors were well balanced between the axitinib vs. placebo arms. All patients had Child-Pugh A category and 76% of patients in both arms had tumour invasion.

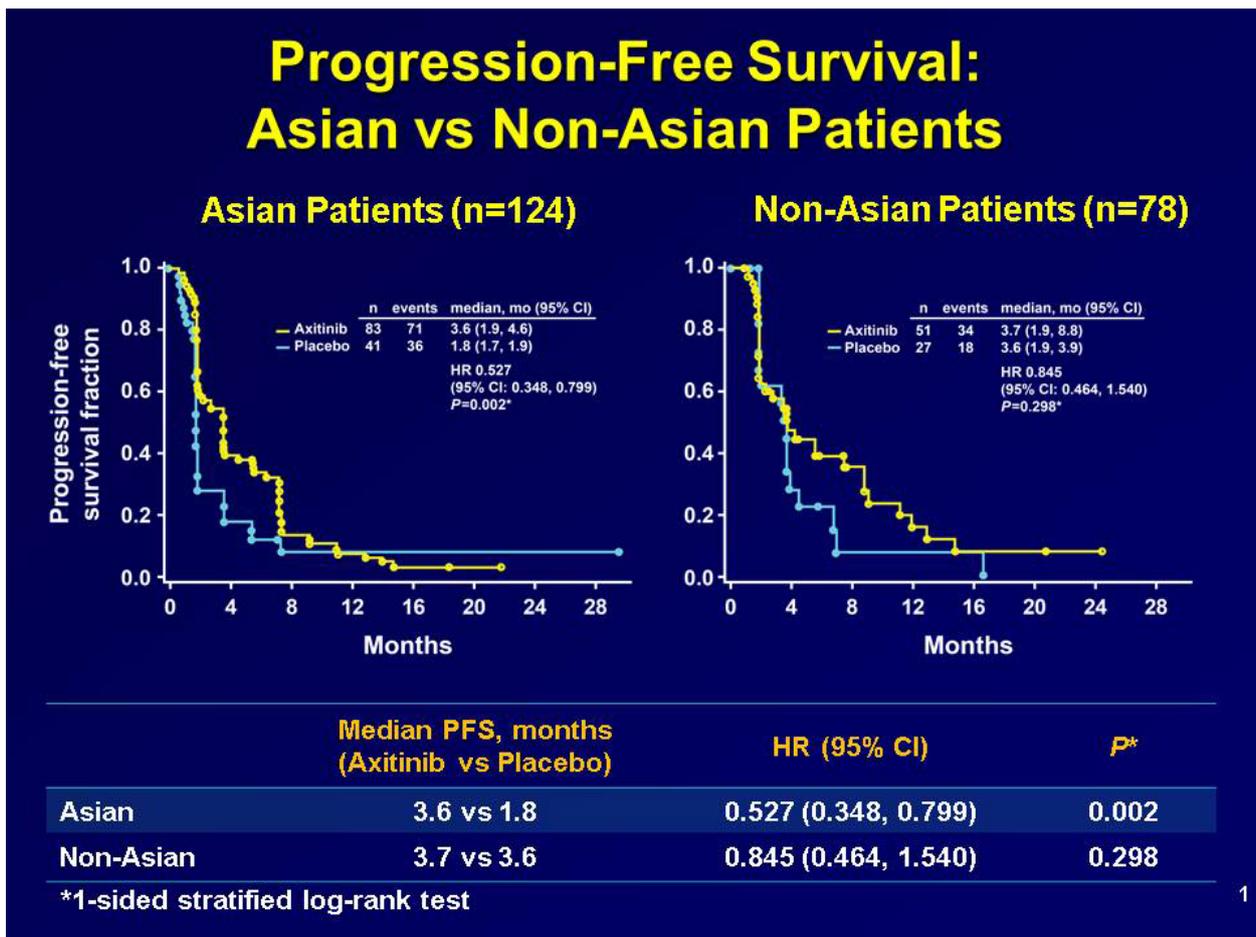
Median OS with axitinib was 12.7 months vs. 9.7 months with placebo, a difference that was not statistically significant (HR 0.870; $p = 0.211$). In Asian patients median OS was 13.5 months vs. 6.3 months in non-Asian, but this difference was not statistically significant either.



Caption: OS in Asian vs. non-Asian patients. © Yoon-Koo Kang

Investigator-assessed median PFS in all randomised patients was 3.6 months with axitinib vs. 1.9 months with placebo and was statistically significant (HR 0.618; $p = 0.004$). The difference between PFS in Asian patients vs. non-Asian was statistically significant too, 3.6 vs. 1.8 month (HR 0.527, $p = 0.002$).

Progression-Free Survival: Asian vs Non-Asian Patients



Caption: PFS in Asian vs. non-Asian patients. © Yoon-Koo Kang

The ORR was 9.7% with axitinib vs. 2.9% with placebo (p = 0.083).

Overall DCR was 31.1% vs. 11.8% in favour of axitinib treated patients (p = 0.002).

Safety profile with axitinib was consistent with earlier clinical trials and no new safety signal was detected. However, more patients discontinued treatment due to adverse events with axitinib vs. placebo.

Most common all cause adverse events in axitinib vs. placebo group were: diarrhoea (54% vs. 12%), hypertension (54% vs. 13%), decreased appetite (47% vs. 21%), fatigue (35% vs. 26%), abdominal pain (34% vs. 21%), hand-foot syndrome (34% vs. 6%), weight decrease (27% vs. 3%), nausea (26% vs. 10%), dysphonia and hypothyroidism (25% vs. 0% each).

Grade ≥ 3 adverse events were higher in the axitinib group: diarrhoea (20% vs. 0%), hypertension (26% vs. 1%), and hand and foot syndrome reaction (15% vs. 0%).

The authors concluded that axitinib plus best supportive care did not demonstrate statistically significant improvement in median OS but improved median PFS when compared with placebo plus best supportive care in patients with advanced hepatocellular carcinoma who received prior antiangiogenic therapy. Regional differences in the efficacy were noticeable.

The study was sponsored by Pfizer Inc.

Dr Michel Ducreux of the Institut Gustave Roussy, Villejuif, France, who discussed the results from two above studies, said that there is something there but the researchers were unable to

demonstrate it because hepatocellular carcinoma is an entity of different diseases with different biological pathways and different clinical features.

Reference

[LBA17: Randomised study of axitinib \(Axi\) plus best supportive care \(BSC\) versus placebo \(Pbo\) plus BSC in patients with advanced hepatocellular carcinoma \(HCC\) following prior antiangiogenic therapy](#)

Optimal treatment strategy with anti-EGFR or anti-VEGF treatments in first-line RAS wild type metastatic CRC patients

During the special session at ESMO 2014 on defining the optimal treatment strategy with anti-EGFR or anti-VEGF treatments in first-line RAS wild type metastatic CRC patients, the CALGB/SWOG 80405 researchers presented long awaited results of OS in all RAS wild type population, while FIRE-3 study researchers presented independent radiological evaluation of ORR, early tumour shrinkage, and depth of response in the final RAS evaluable population.

The session was moderated by Dr Dirk Arnold and the data were discussed by doctors Andres Cervantes, Alberto Sobrero, and Fortunato Ciardiello.

CALGB/SWOG 80405: Phase III trial of FOLFIRI or mFOLFOX6 with bevacizumab or cetuximab for patients with expanded RAS analyses in untreated metastatic adenocarcinoma of the colon or rectum

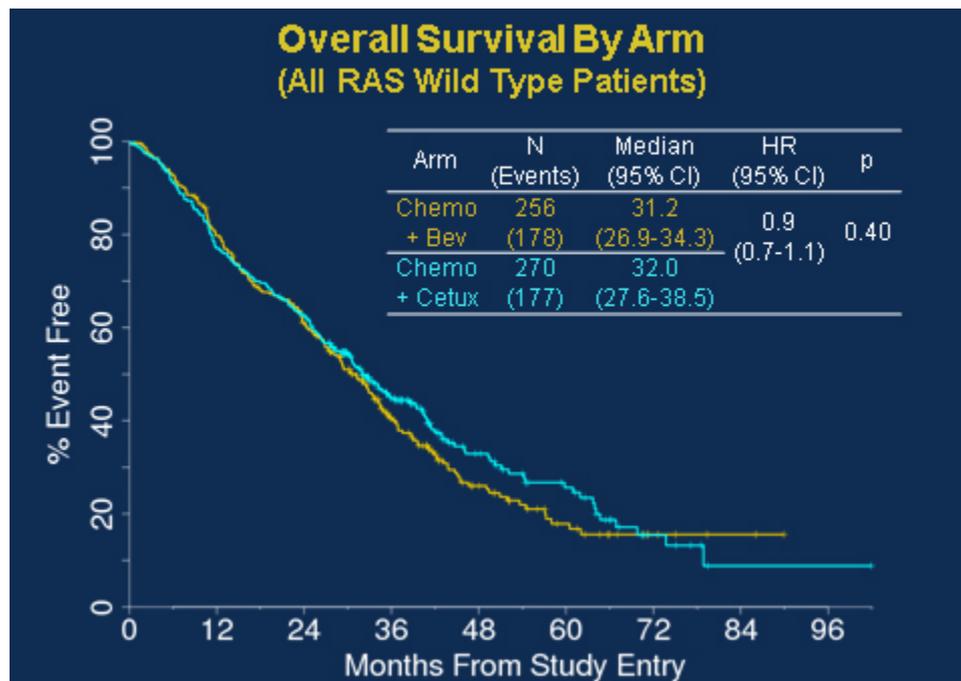
Dr Heinz-Josef Lenz of the Division of Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, USA presented results of expanded RAS analysis in the CALGB/SWOG 80405 study. Earlier this year, the study researchers presented the findings concluding that FOLFIRI/cetuximab and mFOLFOX6/bevacizumab are equivalent in terms of OS in patients with previously untreated KRAS wild type (codons 12 and 13) metastatic CRC and that either regimen is appropriate in first-line treatment. The OS of longer than 29 months and 8% of long-term survivors confirmed the progress in this setting. However, the oncology community expected that expanded RAS and other molecular and clinical analyses could identify subsets of patients who get more or less benefit from specific regimens.

The original CALGB/SWOG 80405 study included unselected patients with metastatic CRC who received treatment according to physician-selected chemotherapy (FOLFIRI or mFOLFOX6) and were randomised to cetuximab, bevacizumab or both (the third arm was subsequently closed). After 1420 patients were accrued the study was amended as following: only patients with wild type KRAS tumours (codon 12 and 13) were included. Accrual goal was 1142 patients.

Between November 2005 and March 2012, 3058 unselected patients were enrolled and 2334 KRAS wild type patients randomised. The final number included 1137 patients (333 pre-amend eligible retrospective KRAS test, and 804 post-amend).

Expanded RAS was tested in all wild type RAS exon 2 using beaming technology including KRAS exon 3,4 and NRAS exon 2, 3 and 4 with a detection sensitivity of 0.01%. The primary endpoint was OS.

In expanded the RAS wild type population, the median OS was pushed beyond 30 months. However, there was no significant difference between the cetuximab and bevacizumab in combination with chemotherapy (32 months vs. 31.2 months).



Caption: OS in all RAS wild type patients in CALGB/SWOG 80405 study. © Heinz-Josef Lenz

There was no difference in the PFS either. However, there was higher response achieved in the cetuximab arm in the expanded RAS population, 68.6% vs. 53.6% ($p < 0.01$).

In a separate analysis from the study of KRAS wild type patients undergoing surgery as a part of treatment strategy, the goal of which was to determine the characteristics and the long-term outcome of patients enrolled in the trial, Dr Alan Venook of the Division Of Medical Oncology, University of California, San Francisco, USA reported that 130 patients enrolled reached a stage of non evidence of disease (NED) after chemotherapy and surgery. The median OS in these patients was 60 months although many have recurred.

However, at the time of the abstract submission, the study researchers anticipated evaluation of all RAS status and planned an analysis in the subset of patients who underwent surgery to identify possible predictive characteristics but also to determine if there is an explanation for the fact that more patients on cetuximab went to surgery than patients on bevacizumab. During the session, Dr Venook reported that patients were likelier to reach NED stage on cetuximab but the ultimate outcome seems to be similar.

The trial lead organizations/sponsors were the Cancer and Leukemia Group B (CALGB), USA National Cancer Institute, and Southwest Oncology Group (SWOG).

Reference

[5010: CALGB/SWOG 80405: PHASE III trial of irinotecan/5-FU/leucovorin \(FOLFIRI\) or oxaliplatin/5-FU/leucovorin \(mFOLFOX6\) with bevacizumab \(BV\) or cetuximab \(CET\) for patients \(pts\) with expanded ras analyses untreated metastatic adenocarcinoma of the colon or rectum \(mCRC\)](#)

Independent radiological evaluation of ORR, early tumour shrinkage, and depth of response in the FIRE-3 study: Analysis in the final RAS evaluable population

Based on an independent radiological review, FOLFIRI plus cetuximab induced a significantly higher ORR, a greater rate of early tumour shrinkage (ETS), and an increased depth of response (DpR) compared to FOLFIRI plus bevacizumab. These response-related outcomes may in part explain the significant OS advantage of FOLFIRI plus cetuximab treatment observed in the extended RAS wild type study population. The findings were reported by Dr Sebastian Stintzing of the University of Munich, Department of Hematology and Oncology.

The FIRE-3 study, performed in 150 centres in Germany and Austria, compared first-line therapy with FOLFIRI plus either cetuximab or bevacizumab (1:1) and was amended in October 2008 to include only KRAS wild-type patients. The study was conducted in 592 KRAS exon 2 wild-type metastatic CRC patients. Extended RAS analysis was carried out in KRAS and NRAS exon 2, 3 and 4 (codons 12, 13, 59, 61, 117 and 146) using pyro-sequencing technique.

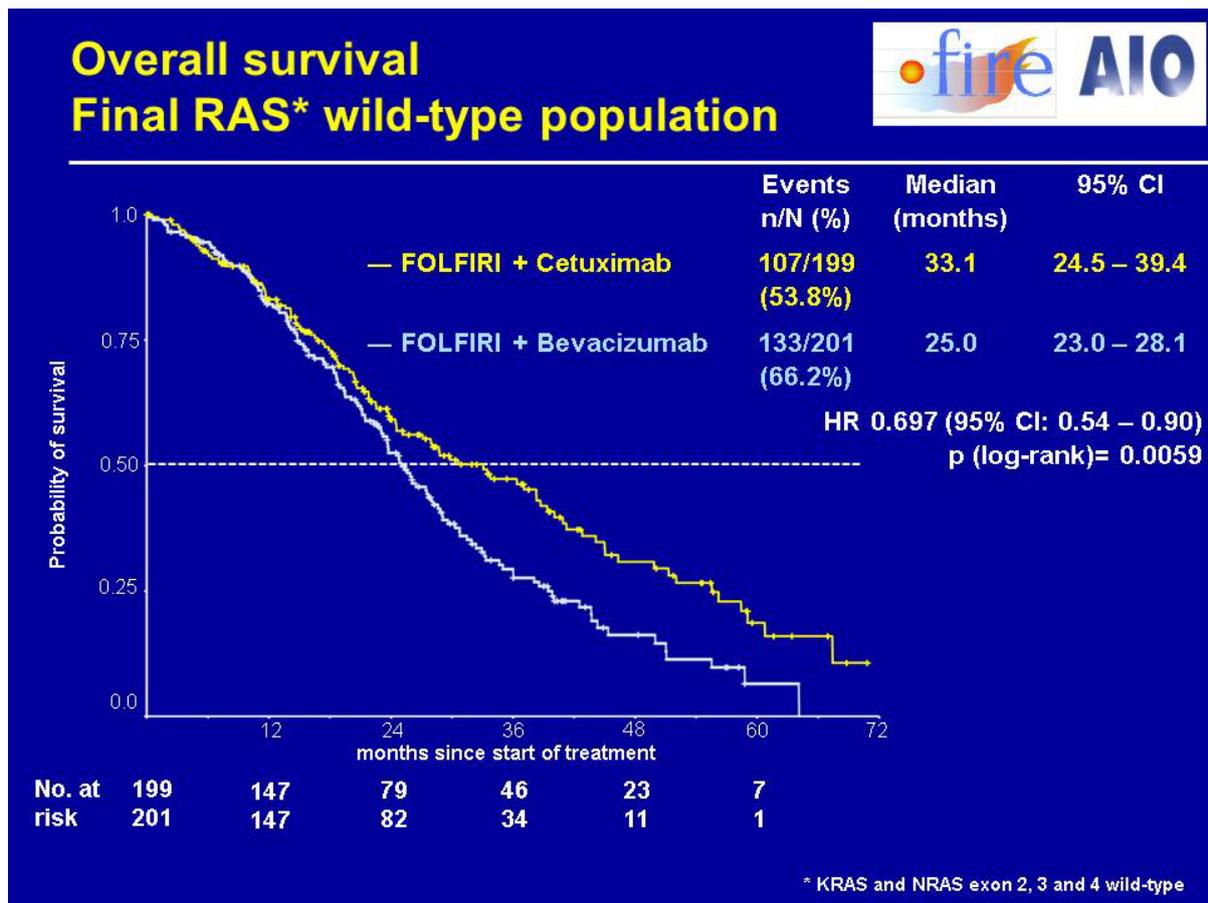
An independent radiological review was performed to evaluate tumour response according to RECIST v1.1 and to define ETS and DpR. Reviewers were blinded to patient data.

ETS was defined as a reduction in tumour diameter of more than 20% at first-tumour assessment after baseline (week 6). DpR was defined as the maximal tumour shrinkage observed at the nadir compared with baseline.

Calculations were done for both the ITT and the extended RAS wild-type population. At ESMO 2014, Dr Stintzing presented data from the analysis in final RAS evaluable patients.

Independent evaluation in KRAS exon 2 wild type population showed an ORR of 66.5% in the cetuximab arm and 55.6% in the bevacizumab arm ($p = 0.016$). In the final RAS wild type population, the ORR was 72% in the cetuximab arm vs. 56.1% in the bevacizumab arm ($p = 0.003$).

The OS favoured the cetuximab arm, 33.1 months vs. 25.0 months (HR 0.697, $p = 0.0059$).



Caption: OS in the final RAS wild type population in the FIRE-3 study. © Sebastian Stintzing

In the final RAS wild type population, PFS in patients with ETS in the cetuximab arm was 9.7 months vs. 5.8 months in patients with no-ETS. In the bevacizumab arm the PFS in ETS patients was 11.7 months vs. 8.3 months in non-ETS patients.

DoR correlated significantly with OS and PFS (p = 0.0003 in KRAS exon 2 wild-type patients and p < 0.0001 in the final RAS wild type population).

Median time to tumour nadir in the cetuximab arm was 15.0 weeks and 15.7 weeks in the bevacizumab arm.

Dr Stintzing said that extended RAS testing was possible in > 80% of FIRE-3 ITT population. He concluded that median OS was markedly superior in all-RAS wild type patients receiving first-line therapy with cetuximab. The independent radiology review demonstrated a significantly higher ORR in FOLFIRI plus cetuximab treated patients compared to those receiving FOLFIRI plus bevacizumab. The ETS was significantly more frequent in the cetuximab arm, and it was significantly associated with prolonged survival independent of the treatment arm. Median DoR was significantly greater in the cetuximab arm and correlated with survival.

FIRE-3 was an investigator sponsored study. The study collaborator was Merck KGaA.

Reference

[LBA11: Independent radiological evaluation of objective response, early tumor shrinkage, and depth of response in FIRE-3 \(AIO KRK-0306\) in the final RAS evaluable population](#)

Data interpretation

Prof. Andres Cervantes of the University Hospital, Valencia, Spain addressed the following two important questions:

Why are the OS results discordant in these two trials?

A detailed information on second- and further line therapies is needed. In particular, the proportion of patients randomised to chemotherapy plus bevacizumab who never got cetuximab could be of importance to interpret these results. In a setting where more than 80% of patients get second-line therapy, it could imply that the sequence of treatments would not be relevant for OS. However, if the proportion of patients missing cetuximab in second-line is higher, the sequence of treatments could be very relevant.

What is the relevance of having a higher response rate in cetuximab containing regimens?

Chemotherapy plus bevacizumab or plus cetuximab are two potential options to start treatment in all RAS wild type advanced CRC patients. But, how does the fact that a higher response rate with cetuximab containing regimens influence decisions in selecting initial therapeutic approach? The CALGB 80405 data on response rate has to be further analysed in respect to depth of response and early tumour shrinkage. This could be an important point to communicate with patients when taking therapeutic decisions.

Dr Alberto Sobrero of the IRCCS AOU San Martino - IST-Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy, said that the FIRE-3 study shows internal consistency and strengthened plausibility while the CALGB researchers presented early data analysis from a trial performed over 10 years. Therefore, he would wait for complete data before conclusion.

Prof. Dirk Arnold of the Clinic for Tumour Biology, Freiburg, Germany, said that patients with RAS wild type do (slightly) better with anti-EGFR therapies. However, many open questions remain: why is this so, will further information of treatment characteristics (e.g. duration and second-line treatments) really change clinical view on the data?

RAS is important, but taken alone it is not a great positive predictive biomarker. Any of the combinations used is an excellent option and should be part of the first-line treatment as OS is longer than 31 months. Presumably, the first-line choice is not that important for most patients (maybe except need for early tumour shrinkage and depth of response).

According to Prof. Fortunato Ciardiello of the Seconda Università Studi di Napoli Policlinico Federico II, Naples, Italy, who was one of discussants in the session, metastatic CRC is a heterogenous disease. A subset of metastatic CRC is highly dependent on EGFR signalling. KRAS and NRAS testing are the first step to identifying those patients that could benefit from anti-EGFR monoclonal antibodies treatment.

All metastatic CRC patients should have extended RAS testing before first-line treatment choice to offer them all available therapeutic opportunities.

Patients with RAS wild type cancer have two good therapeutic options that should be offered sequentially in first- and second-lines (FOLFOX or FOLFIRI plus either anti-EGFR monoclonal antibodies or bevacizumab).

In his opinion, FOLFIRI or FOLFOX with an anti-EGFR antibody is the preferred first-line choice if tumour shrinkage is a relevant therapeutic goal (high tumour burden, symptomatic disease, potential conversion to surgical resection of liver metastases or, possibly, of the primary tumour).

Tolerability, side effects and informed discussion with the patient could be important aspects for first-line choices.

For Prof. Ciardiello, open issues for clinical and translational research on how to optimise therapeutic management of metastatic CRC patients with RAS wild type tumours are:

- Role of maintenance; chemotherapy depotentiation; reintroduction of chemotherapy.
- Role of appropriate sequencing of bevacizumab and anti-EGFR monoclonal antibodies.
- Strategies to prevent/overcome acquired resistance to anti-EGFR monoclonal antibodies and to bevacizumab.

TAS-102 improves OS and PFS in patients with metastatic CRC refractory to standard therapies

A final analysis of primary endpoints from the phase III RECOURSE study in patients with metastatic CRC refractory to standard therapies showed a statistically significant OS and PFS benefit with TAS-102 in all prospectively defined subgroup analyses, including prior therapy with regorafenib. The results were presented by Prof. Eric Van Cutsem of the Digestive Oncology Unit, University Hospital Leuven, Leuven, Belgium.

The data from the RECOURSE study was first reported at the ESMO World Congress in GI Cancer earlier this year in Barcelona, Spain. At ESMO 2014, Prof. Van Cutsem presented new data, in particular subgroup analyses of OS and PFS by KRAS status, stratification factors and patient characteristics, and time to worsening of ECOG PS to 2 or more.

TAS-102 is a combination of a novel oral nucleoside, trifluridine (FTD) with the thymidine phosphorylase inhibitor, tipiracil hydrochloride (TPI), which prevents the degradation of FTD, enabling sustained and effective FTD levels.

RECOURSE was conducted to evaluate the efficacy and safety of TAS-102 in patients with mCRC refractory to standard therapies. Patients with ECOG PS 0-1 who had failed two or more prior treatments with fluoropyrimidines, irinotecan, oxaliplatin, bevacizumab and cetuximab/panitumumab (in case of KRAS wild-type disease) were eligible for the study.

Treatment continuation was foreseen until progression, intolerant toxicity or patient refusal. It was a multicenter, randomised, double-blind, placebo-controlled, phase III study with stratification by KRAS status, time from diagnosis to metastatic disease, and geographical region. It was performed in 13 countries around the world. Enrollment started in June 2012 and finished in October 2013.

The study primary endpoint was OS and the key secondary efficacy endpoint was PFS. Other secondary endpoints included safety, tolerability, time to treatment failure (TTF), ORR, DCR, DoR, OS and PFS in subgroups determined by KRAS status.

The OS and PFS were evaluated by using univariate and multivariate analyses for prospectively defined subgroups and a retrospectively defined subgroup of patients with prior treatment with regorafenib.

In total 800 patients were randomised to TAS-102 (534 patients) or placebo (266 patients). In the ITT population, patient demographics and characteristics were balanced between the two arms with one third of Asian patients in each group.

The HRs for OS and PFS were 0.68 ($p < 0.0001$) and 0.48 ($p < 0.0001$), respectively, both favouring TAS-102. The OS in TAS-102 group was 7.1 month vs. 5.3 month in placebo group. Median PFS was 2.0 months in TAS-102 treated patients and 1.7 month in the placebo arm.

The OS and PFS benefit with TAS-102 was consistent across all subgroups. In particular, the HRs for OS in subgroups were 0.58 in patients with KRAS wild-type tumours and 0.80 in KRAS mutated tumours; 0.64 in Western population and 0.75 in Asian patients; 0.73 in patients with PS 0 and 0.61 in patients with PS 1; and 0.69 for patients who have already received or not regorafenib.

In patients with time from diagnosis to first metastasis shorter than 18 months, the HR for OS was 0.84 and 0.64 in those with ≥ 18 months. In patients younger than 65, this HR was 0.74 and 0.62 in the group ≥ 65 years old. In patients who received three prior treatments, the HR was 0.74 and 0.59 in those who received ≥ 4 treatment lines.

The OS treatment effect remained the same in the multivariate model. No predictive factors were identified. Statistically significant prognostic factors ($p < 0.05$) in final model based on stepwise selection were:

- time since diagnosis of first metastasis,
- ECOG PS,
- and number of metastatic sites.

Time to worsening of ECOG PS status to 2 or more was significantly delayed with TAS-102 vs. placebo with medians of 5.7 vs. 4.0 months (HR 0.66, $p < 0.0001$). Post-study treatment was similar between the arms (41.2% in TAS-102, 42.5% in placebo).

Safety results were previously presented at the ESMO World Congress on GI Cancer 2014. The most frequently observed toxicities were GI and haematologic. Serious adverse events were observed in 29.6% patients in TAS-102 and 33.6% patients in placebo group. Primary reason for treatment discontinuation due to adverse events was 3.6% in TAS-102 and 1.5% in the placebo group. One treatment-related death was observed in TAS-102 group. The rate of febrile neutropenia was 3.8% and frequency of G-CSF usage 9.4% in TAS-102 and 0% in placebo group.

Prof. Van Cutsem concluded that TAS-102 demonstrated a clinically relevant improvement in OS and PFS compared with placebo in patients with mCRC refractory/intolerant to standard therapies. Improved OS benefit was statistically significant or trended favorably for TAS-102 across all stratification factors and predefined subgroups. Consistent with OS results, PFS improvement for TAS-102 was statistically significant across all stratification factors and predefined subgroups. The OS benefit was maintained irrespective of regorafenib use.

Discussant Prof. Christophe Tournigand of the Hôpital Henri Mondor, Créteil, France, said that in the RECURSE study TAS-102 significantly improved OS and PFS in patients with metastatic CRC, refractory or intolerant to standard therapies. However, questions for the future would be: identifying biomarkers, addressing the question of QoL improvement, and seeing efficacy/tolerance in combination therapy, and efficacy in earlier lines of therapy.

The sponsor of the study was Taiho Oncology Inc./Taiho Pharmaceutical Co. Ltd.

Reference

[LBA13: Phase III RECOURSE trial of TAS-102 vs. placebo, with best supportive care \(BSC\), in patients \(pts\) with metastatic colorectal cancer \(mCRC\) refractory to standard therapies](#)

Bevacizumab/erlotinib as maintenance therapy in metastatic CRC: Final results of the GERCOR DREAM study

Dr Benoist Chibudel of the Institut Hospitalier Franco-Britannique, Levallois-Perret, France reported that combination of erlotinib and bevacizumab as maintenance therapy significantly prolonged PFS and OS in patients with unresectable metastatic CRC. The combination of anti-VEGF monoclonal antibody and EGFR TKI is active, even in mutated KRAS patients.

VEGF or EGFR targeted monoclonal antibodies with chemotherapy demonstrated clinical activity in metastatic CRC. Yet, combining these monoclonal antibodies in mCRC achieved adverse outcomes. However, erlotinib, an EGFR TKI, combined with bevacizumab as maintenance therapy after bevacizumab-based induction therapy improved PFS according to results presented at 2012 Congress of the American Society of Clinical Oncology (ASCO). At ESMO 2014, the researchers reported the final results of the DREAM study.

VEGF inhibition with bevacizumab or aflibercept increases survival in combination with oxaliplatin- or irinotecan-based chemotherapy in first- or second-line. EGFR inhibition (panitumumab or cetuximab) increases survival in patients with RAS wild-type tumours. Crosstalk between EGFR pathway and VEGF is involved in tumour growth and survival. Bevacizumab and erlotinib are more active than bevacizumab alone in three xenograft models. Quantitative IHC analysis showed that bevacizumab activated EGFR in the tumour cells and in the tumour-associated endothelial cells which was attenuated by erlotinib.

DREAM is a phase III trial in patients with unresectable metastatic CRC. Patients without progression or surgery after a bevacizumab-based induction therapy were randomised to bevacizumab or bevacizumab plus erlotinib as maintenance therapy until progression after stratification by centre, baseline ECOG PS, ALP, LDH, induction chemotherapy (XELOX2/bevacizumab vs. mFOLFOX7/bevacizumab or FOLFIRI/bevacizumab), KRAS status, age, number of metastatic sites and tumour response.

Primary endpoint was maintenance PFS from randomisation. Secondary endpoints were OS, PFS from registration, response according to KRAS status, adverse events, curative resection, chemotherapy-free interval, and QoL.

Among 701 registered patients, 452 were randomised for maintenance (228 in the bevacizumab arm; 224 in the bevacizumab/erlotinib arm). Median follow-up was 50 months.

In the bevacizumab arm vs. bevacizumab/erlotinib arm, medians were for maintenance PFS 4.9 vs. 5.9 months (HR 0.77; $p = 0.012$), PFS from registration 9.3 vs. 10.2 months (HR 0.76; $p = 0.007$), maintenance OS 22.1 vs. 24.9 months (HR 0.80; $p = 0.035$), OS from registration 26.9 vs. 30.5 months (HR 0.80; $p = 0.040$). All subgroups, including KRAS, had a benefit in OS.

Response rate from baseline maintenance were in the bevacizumab vs. bevacizumab/erlotinib arm: all patients 11.5% vs. 22.5% ($p = 0.003$), KRAS wild-type 15.4% vs. 24% ($p = 0.133$), KRAS mutated 8.3% vs. 19.7% ($p = 0.041$).

Patients in the bevacizumab arm vs. bevacizumab/erlotinib arm experienced less grade 3/4 diarrhoea (0.9% vs. 9.3%) and skin rash (0% vs. 21.4%).

Dr Axel Grothey of the Mayo Clinic, Rochester, USA who discussed the study results, said that he was skeptical at first of whether the trial design is scientifically valid, but the results validate it. There is heterogeneity of induction chemotherapy and bevacizumab alone is not the optimal control arm in maintenance. The results are not as expected, and they are still a bit puzzling (no effect of KRAS status, short duration of erlotinib, PFS HR is similar to OS HR). There is a need for confirmatory/additional studies. The results don't have implications for clinical practice, as there is a need for confirmatory results. The results also don't have yet implications for future clinical trials. This was investigator led study. The study sponsor was GERCOR.

Reference

[4970: Bevacizumab-erlotinib as maintenance therapy in metastatic colorectal cancer. Final results of the GERCOR DREAM study](#)

Final results from QUASAR2, a multicentre, international randomised phase III trial of capecitabine plus/minus bevacizumab in the adjuvant setting of stage II/III CRC

Dr Rachel Midgley of the University of Oxford, Oxford, UK reported that final results from the QUASAR2 study support data from two other trials suggesting no role for bevacizumab in the adjuvant CRC setting. The QUASAR2 biobank and linked database allows further collaborative biomarker hypotheses to be tested. According to QUASAR2 investigators there is a rationale for meta-analysis of all bevacizumab adjuvant CRC studies to more fully explore the putative temporal effect of bevacizumab administration on DFS.

The aims of QUASAR2 were to assess whether the addition of bevacizumab to single agent capecitabine increases DFS and OS in CRC patients after resection of the primary tumour; and to validate suggested, or discover new, biomarkers of bevacizumab efficacy and toxicity.

It was a phase III international randomised controlled trial, coordinated by the UK and recruiting in 6 countries. In addition to the collection of data on toxicity, DFS and OS, a biobank comprising 1350 FFPE blocks and 1000 germline DNA samples was established. Hypothesis-driven biomarkers, as MSI status, epithelial/stromal ratio, chromosomal instability, RAS, RAF, POLE and an 80-gene ion torrent panel, were analysed to assess their prognostic and predictive bevacizumab utility.

In total, 1941 patients were randomised in a 1:1 ratio and demographics and disease characteristics were well balanced between the two arms. The DFS in the whole trial population demonstrates that bevacizumab does not improve outcome in this setting (3-year DFS 75.4% for capecitabine/bevacizumab vs. 78.4% for capecitabine; HR 1.06; p = 0.5). Similarly OS was not improved (3-year OS 87.5% for capecitabine/bevacizumab vs. 89.4% for capecitabine; HR 1.11, p = 0.3). There may be a temporal trend in HRs (HRs: 1-year 0.83, 2-year 0.87, 3-year 1.32).

Subgroup analysis did not reveal a specific subpopulation (defined by stage/subsite/gender/age) that benefits from bevacizumab therapy.

Biomarker analyses confirm that high tumour stromal content confers a worse prognosis (3-year DFS HR 1.58; p = 0.001). However, there was no evidence this marker determined responsiveness to bevacizumab. MSS positivity was associated with a worse DFS in patients

treated with capecitabine/bevacizumab compared to those treated with capecitabine alone (in 840 patients HR 1.43; $p = 0.005$) suggesting a negative predictive effect for bevacizumab. For MSI positive patients, there was no significant difference in DFS between the two arms (in 135 patients HR 0.74; $p = 0.42$).

Dr Axel Grothey of the Mayo Clinic, Rochester, USA who discussed the study results, said that regarding the trial's design scientific validity, it was worth investigating given the clinical synergism between fluoropyrimidines and bevacizumab in the advanced CRC setting. However, omission of oxaliplatin for stage III cancers is of some concern. Sample size and statistical assumptions were adequate. The results are as expected with the exception of the MSI story. The MSI interaction might need preclinical studies. There is no need for confirmatory/additional studies. The results don't have implications for clinical practice, actually they confirm what we knew. In addition, the results don't have implications for future clinical trials, as well.

The unrestricted educational grant for this study was provided by F.Hoffmann-La Roche.

Reference

[LBA12: Final results from QUASAR2, a multicentre, international randomised phase III trial of capecitabine \(CAP\) +/- bevacizumab \(BEV\) in the adjuvant setting of stage II/III colorectal cancer \(CRC\)](#)

Genitourinary Cancers

A phase 1B study of pembrolizumab in patients with advanced urothelial tract cancer

Dr Elizabeth Plimack of the Fox Chase Cancer Center, Philadelphia, USA and colleagues assessed the safety, tolerability, and antitumour activity of pembrolizumab in patients with recurrent or metastatic urothelial cancer in the KEYNOTE-012 study.

The KEYNOTE-012 study was a phase 1b multi-cohort study of pembrolizumab in patients with PD-L1-positive advanced solid tumours: TNBC, head and neck cancer, urothelial cancer, and gastric cancer.

Archival or newly obtained tumour samples from patients with advanced carcinoma of the renal pelvis, ureter, bladder, or urethra were screened for PD-L1 expression using a prototype IHC assay. PD-L1 expression in stroma or $\geq 1\%$ of tumour cells was required for study entry. Patients received pembrolizumab every 2 weeks until CR, progression, or unacceptable toxicity. Patients deriving benefit could remain on pembrolizumab beyond initial progression. Response was assessed every 8 weeks per RECIST v1.1 by an independent central review (primary efficacy endpoint).

In total 33 patients were enrolled, including 30 with transitional cell histology and 3 with non-transitional cell or mixed histology. Median age was 70 years (range 44-85), 70% had ECOG PS 1, 52% received ≥ 2 prior therapies for advanced disease, 21% had liver metastases; and 22 patients (67%) received ≥ 3 pembrolizumab doses.

Median follow-up duration was 11 months (range 10-13), and 7 patients (21%) remain on therapy. Adverse events were reported in 61% of patients (≥ 1 drug-related), most commonly fatigue, peripheral oedema, and nausea; 4 patients (12%) reported grade 3-4 drug-related adverse events, with only rash seen in more than 1 patient. In total 29 patients received ≥ 1 dose of pembrolizumab, had a baseline scan with measurable disease, and were evaluable for response.

The ORR by central review was 24.1%, with 10.3% CRs. Response duration is 16 to 40+ weeks (median not reached), with 6 of 7 responses ongoing. In the patients evaluable for response, median PFS is 8.6 weeks. In all patients, median OS is 9.3 months (6 months OS rate, 58%). Analysis of the relationship between PD-L1 expression and pembrolizumab efficacy is ongoing.

Pembrolizumab shows acceptable safety and tolerability and provides promising antitumour activity in patients with advanced urothelial cancer. These data support the continued development of pembrolizumab in advanced urothelial cancer.

The study was supported by Merck Sharp & Dohme Corp.

Reference

[LBA23: A phase 1b study of pembrolizumab \(Pembro; MK-3475\) in patients \(Pts\) with advanced urothelial tract cancer](#)

Gynaecologic Cancers

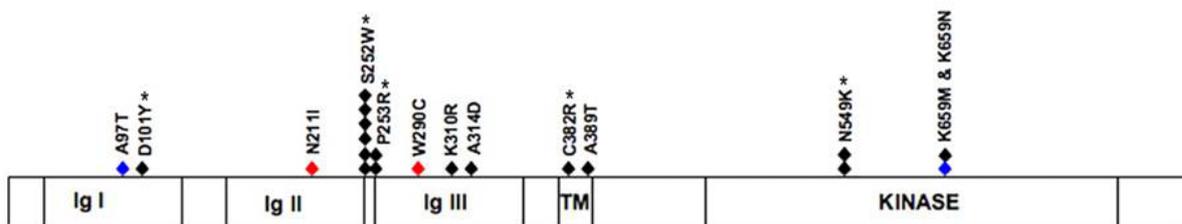
Activity of second-line dovitinib in advanced and/or metastatic endometrial cancer

The single-agent dovitinib demonstrated clinically meaningful activity in second-line treatment of patients with fibroblast growth factor receptor 2 (FGFR2)-mutated or -non-mutated advanced and/or metastatic endometrial cancer and a trend toward greater median PFS and OS in the FGFR2-mutated group. The results of a phase II study were presented by Prof. Gottfried Konecny of the Gynecologic Oncology Unit, UCLA Westwood Oncology Hematology, Los Angeles, USA.

Activating mutations in FGFR2, identified in 10%-15% of primary endometrial cancers, are associated with disease progression and poor outcome.

The molecular screening assay FGFR2 mutation analysis

- FGFR2 mutations in endometrial cancer:



Dutt A et al. PNAS 2008;105:8713-8717

- ◆ Squamous lung
- ◆ Cervical
- ◆ Endometrial

- Direct sequencing of 5 codons will be performed on each molecular screening sample to determine mutation status

Caption: FGFR2 mutation analysis in endometrial cancer. © Gottfried Konecny

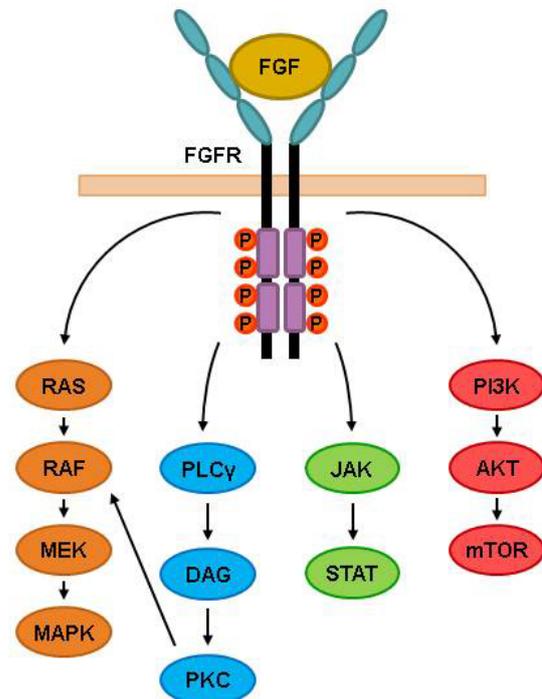
Dovitinib (TKI258) is a potent TKI that targets FGFR, vascular endothelial growth factor receptor (VEGFR) and platelet derived growth factor receptor (PDGFR) and other kinases. Dovitinib demonstrated dose-dependent growth inhibition of FGFR2-mutated and FGFR2-non-mutated xenografts.

In this phase II study, researchers evaluated dovitinib as a second-line therapy in patients with FGFR2-mutated or –non-mutated disease. Women who progressed after first-line chemotherapy for advanced and/or metastatic endometrial cancer underwent molecular prescreening for FGFR2 status and then clinical screening if eligible for the study (ECOG PS ≤ 2). Then they were treated with oral dovitinib on a 5-days-on/2-days-off schedule.

The primary endpoint was percentage of patients who are progression-free by investigator assessment after 18 weeks. The trial used a 2-stage design for each group; stage 2 could proceed if ≥ 8 of the first 20 treated patients (40%) met the primary endpoint. Secondary endpoints

included ORR, DCR, DoR, PFS, OS, safety, tolerability, pharmacokinetics, and pharmacodynamics.

- FGF/FGFR system
 - Receptors: 4 FGFRs
 - Ligands: 22 FGFs
 - Each FGFR has specificity for particular FGFs
- Context-dependent signaling through various intracellular pathways
- Regulates normal biological processes
 - Protein synthesis
 - Cell growth and proliferation
 - Cell motility, migration, invasion
 - Cell differentiation
 - Resistance to cell death
 - Angiogenesis



Turner N, et al. *Nat Rev Cancer*. 2010;10(2):116-129.
Itoh N, Ornitz DM. *J Biochem*. 2011;149(2):121-130.

Caption: The fibroblast growth factor (FGF) pathway. © Gottfried Konecny

A key eligibility criterion was progressive disease after first-line antineoplastic treatment for advanced and/or metastatic endometrial cancer. Eligible histologies were endometrioid, serous, clear cell, mucinous, adenosquamous, and mixed types. Prior antineoplastic treatment should have included at least one cytotoxic agent and prior hormonal therapy was not considered as a line of treatment.

Response was assessed by local investigator every 6 plus/minus 1 weeks according to RECIST v1.1 criteria. Adverse events were assessed according to CTCAE v4.03.

FGFR2 analysis was performed on archival tumour blocks or fresh fixed tumour biopsies. FGFR2-mutated status was identified by Sanger sequencing of the 5 main hotspot mutation sites reported for endometrial cancer.

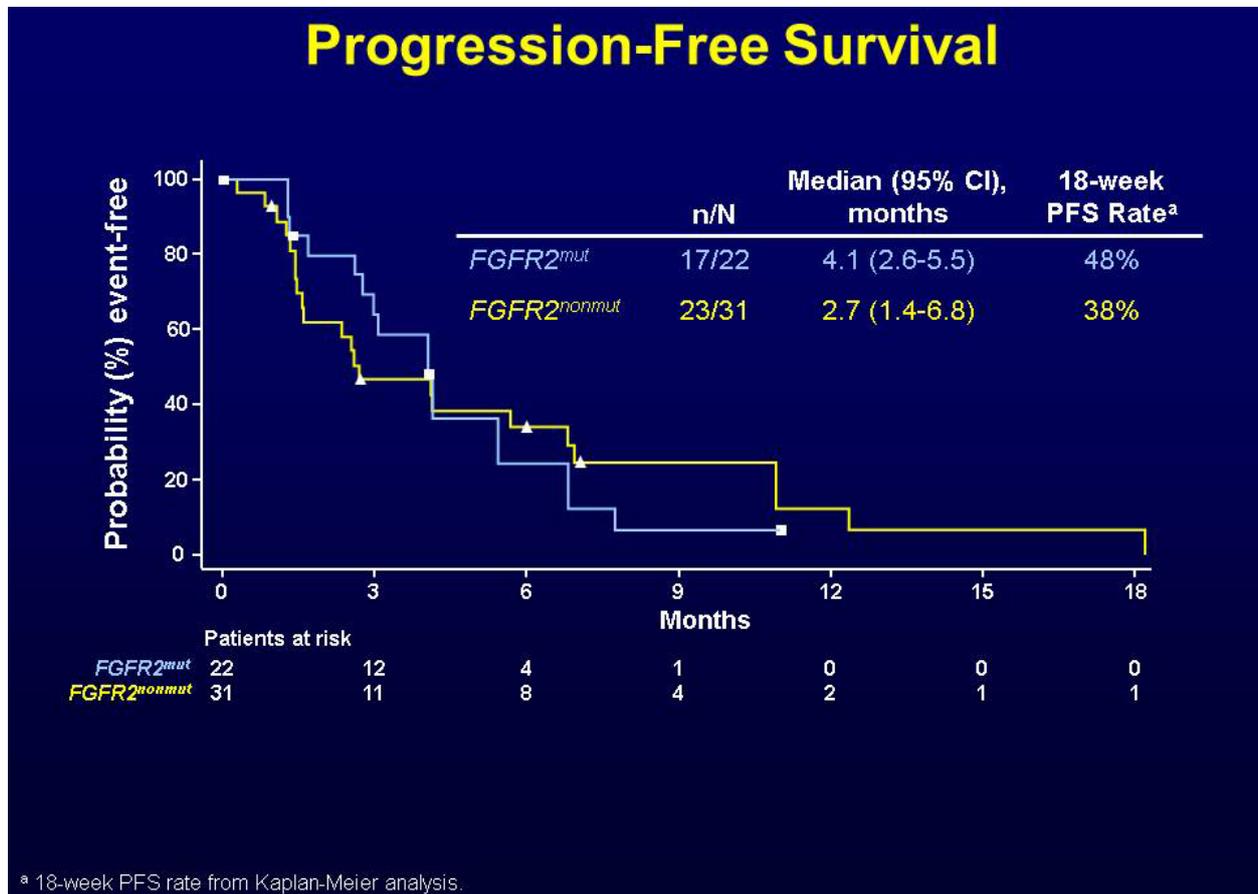
Of 248 pre-screened patients, 27 had FGFR2-mutated tumours (11%). The study enrolled 53 patients, of which 22 had FGFR2-mutated disease and 31 FGFR2-non-mutated.

Among patients with FGFR2-non-mutated tumours, 17 had ECOG PS 1 vs. 7 patients with mutated tumours. In the same group there were also slightly more patients with serous and clear cell adenocarcinoma histology and poorly differentiated tumours. Median relative dose intensity was similar.

All patients discontinued the treatment mostly due to progressive disease (66%) or adverse events (26%). Most frequent adverse events leading to discontinuation were deep vein thrombosis, pulmonary embolism, and small intestinal obstruction.

The observed 18-week PFS rates were 32% in patients with FGFR2-mutated tumours and 29% in patients with FGFR2-non-mutated. The 18-week PFS rate in the first 20 patients was 35% and 25% in the FGFR2-mutated and FGFR2-non-mutated groups, respectively. However, the study did not proceed to stage 2 based on the predefined criteria.

The 18-week PFS rates from a Kaplan Meier analysis were 48% in FGFR2-mutated and 38% in FGFR2-non-mutated group.



Caption: PFS in study patients with endometrial cancer (FGFR2-mutated and FGFR2–non-mutated). © Gottfried Konecny

The DCR (≥ SD) was 64% (59% SD, 5% PR) in the FGFR-2 mutated group and 51% (35% SD, 16% PR) in the FGFR2-non-mutated groups, respectively.

Median PFS (4.1 vs. 2.7 months) and OS (20.2 vs. 9.3 months) trended to be higher in the FGFR2-mutated group.

Adverse events suspected to be study drug related were similar between the groups. The most common grade 3/4 adverse events were hypertension (17%) and diarrhoea (9%). Of the 5 on-treatment deaths, 4 were due to endometrial cancer and 1 was due to cardiac arrest. The safety profile was similar to that observed in other dovitinib trials.

Prof. Konecny concluded that single-agent dovitinib demonstrated clinically meaningful activity in both groups. There was a trend toward greater median PFS and survival in the FGFR2-mutated group. The overall safety profile was similar to that observed in other dovitinib trials. However, the incidence of thrombosis appeared more common in this patient population.

Dr Michael Bookman of the University of Arizona Cancer Center, Tucson, USA, who discussed the study results, said that accrual was biased toward high-grade and advanced-stage tumours with increased risk of recurrence. 40-50% of patients have already received pelvic radiation, with impact on haematologic reserve. Recurrent disease within the pelvis is less responsive to many treatments, due to prior surgery and/or radiation. Historical controls are necessary to define the primary study hypothesis, but the reference population may not have the same molecular profile as the enrolled population.

According to Dr Bookman, the investigators have provided a well-designed and carefully-conducted phase II experiment with dovitinib in endometrial cancer. Patients were allowed one prior treatment, plus/minus pelvic radiotherapy, and appear similar to patients enrolled on GOG 229 phase II trials, contributing to a broader experience. As a multi-targeted tyrosine kinase inhibitor, dovitinib also inhibits VEGFR2. Without randomised combinations or stratification for prior anti-VEGF therapy, it is uncertain which pathway(s) accounted for the observed outcomes.

FGFR2 is mutated in 10% of early-stage endometrioid (type I) tumours, and associated with risk of recurrence. The prognostic significance of mutations in recurrent or metastatic disease is uncertain. However, in this trial, patients with FGFR2-mutated tumours had an improved prognosis, compared to non-endometrioid (type II) tumours.

Type I endometrial cancer is associated with frequent (non-overlapping) mutations in KRAS, CTNNB1, FGFR2, and PIKC3A, with associated pathway activation. In recurrent disease, targeting VEGF (with bevacizumab) demonstrates activity that appears equal or superior to multi-targeted TKIs, including anti-FGFR2. Some TKIs may not be effective in the setting of common activating mutations within the kinase domain of FGFR2. Understanding, and optimising, the net contribution of each pathway awaits randomised trials that incorporate stratification based on prior treatment and analysis of biospecimens.

The study sponsor was Novartis Pharmaceuticals.

Reference

[LBA27: Phase 2 study of second-line dovitinib \(TKI258\) in patients with fibroblast growth factor receptor 2 \(FGFR2\)-mutated or -nonmutated advanced and/or metastatic endometrial cancer](#)

Final OS analysis of the phase III randomised trial of chemotherapy with and without bevacizumab for advanced cervical cancer

Final OS data from the NRG Oncology - Gynecologic Oncology Group (GOG) study of chemotherapy with and without bevacizumab for advanced cervical cancer has showed that the benefit conferred by the incorporation of bevacizumab is sustained beyond 50 months as evidenced by the survival curves remaining separated. The results were reported during the ESMO 2014 by Prof. Krishnansu Tewari of the Department of Obstetrics & Gynaecology, University of California, Irvine Medical Center, Orange, USA.

On 14 August, 2014, the USA Food and Drug Administration approved bevacizumab with chemotherapy for women with recurrent, persistent, or metastatic cervical cancer. This regulatory milestone was due to GOG protocol 240 that met its primary endpoint with the arm administering chemotherapy plus bevacizumab resulting in significantly improved OS compared to

chemotherapy alone. These results were publicly announced following a data freeze on 12 December, 2012 when 271 deaths had occurred.

At ESMO 2014, the study investigators reported planned final analysis of OS and a detailed updated toxicity analysis based on the protocol-specified 346 events. The study results that were previously presented during the ASCO 2013 were from the second analysis. These results were also published in the New England Journal of Medicine on 20 February 2014.

The GOG 240 is a phase III randomised clinical trial using a 2x2 factorial design to determine whether chemotherapy plus bevacizumab and/or the non-platinum chemotherapy doublet (topotecan plus paclitaxel) improves OS in women with recurrent/persistent and metastatic cervical cancer.

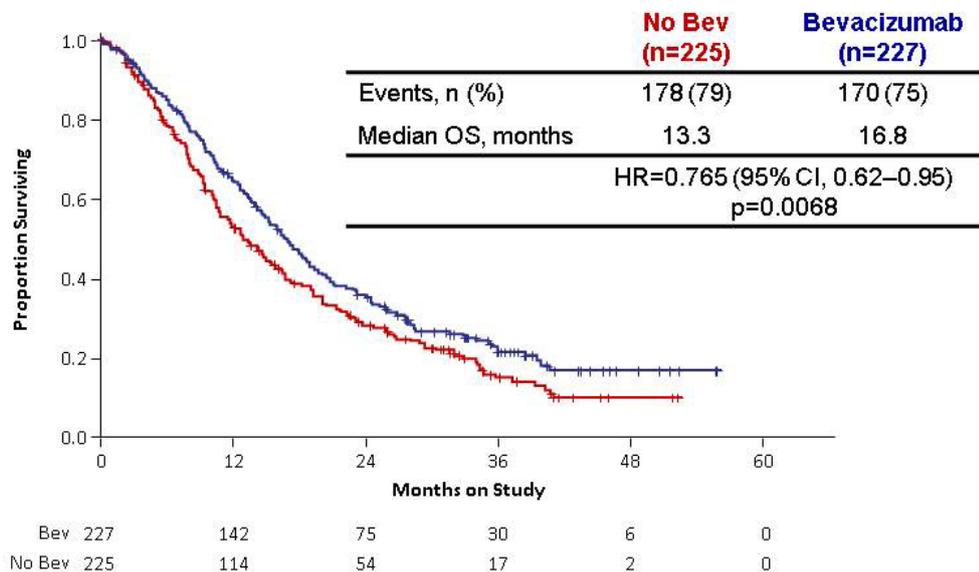
The primary endpoints were OS and toxicity and secondary endpoints PFS and response.

The study investigators calculated that they would have to enrol approximately 450 patients with approximately 346 deaths expected to provide the study with 90% power to detect a reduction in the risk of death of at least 30% with either experimental treatment, with the one-sided type I error rate limited to 2.5% for each regimen.

The median age was 49 years and groups were well-balanced for disease status (70-73% recurrent), prior chemoradiation (74-75%), and in-field pelvic recurrence (53-54%).

When 348 events had occurred (2 more than the pre-specified number estimated for final analysis), the regimens administering bevacizumab continued to demonstrate a significant improvement in OS over chemotherapy alone: 16.8 vs. 13.3 months (HR 0.765; p=0.0068). The benefit conferred by the incorporation of bevacizumab is sustained beyond 50 months as evidenced continued separation of the survival curves.

FINAL OS chemo vs chemo plus bev



bev, bevacizumab; chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; OS, overall survival.

26-30 September 2014, Madrid, Spain

esmo.org

KS Tewari (study chair). www.ClinicalTrials.gov Identifier: NCT00803062.

Caption: Final OS analysis in the GOG240 study shows significant improvement in the bevacizumab/chemotherapy arm vs. chemotherapy alone. © Krishnansu S. Tewari

GI perforations were reported in 3.2% of patients receiving bevacizumab, all of whom had prior radiotherapy. GI-vaginal fistula occurred in 8.2% of patients treated with bevacizumab vs. 0.9% of those treated with chemotherapy alone. Grade 3 plus venous thromboembolic events were reported in 10.6% in the chemotherapy plus bevacizumab arm vs. 5.4% in the chemotherapy alone arm.

Bevacizumab is the first targeted agent to be granted regulatory approval in the USA for treatment of cervical cancer.

Dr Sandro Pignata of the Istituto Nazionale Tumori – I.R.C.C.S - Fondazione Pascale, Naples, Italy, who discussed the study results, said that strengths of the study are the first improvement in OS after several years in this setting, first biological drug approved for cervical cancer, and clear demonstration that targeting angiogenesis is important in this disease.

However, there was a significant toxicity rate in the study with GI fistula in 8.6%, GI perforations in 3.2%, thromboembolism > grade 3 in 8.2% of patients, bleeding > grade 3 in 4.5% and death in 3.3% of patients. There was no analysis reported for risk factors related to toxicity and it is urgently needed in term of disease in the pelvis, previous radiotherapy, PS, etc. Dr Pignata said that the use of the drug in patients unselected for clinical trials may require special attention.

Bevacizumab is a significant advance in the therapy of metastatic cervical cancer, but management of toxic events is still an open issue. The question is if the results could be

generalizable in high incidence, but poor resource countries. According to Dr Pignata, resources still need to be directed with priority on screening and prevention of cervical cancer.

The GOG 240 was sponsored by the USA National Cancer Institute (NCI). Genentech, the drug manufacturer, provided support for the trial under the Cooperative Research and Development Agreement with the NCI for the clinical development of bevacizumab.

Reference

[LBA26: Final overall survival analysis of the phase III randomized trial of chemotherapy with and without bevacizumab for advanced cervical cancer: A NRG Oncology - Gynecologic Oncology Group Study](#)

Head and Neck Cancer

Afatinib vs. methotrexate in second-line treatment of recurrent and/or metastatic head and neck squamous cell carcinoma: Primary efficacy results of a phase III LUX-Head and Neck 1 trial

Primary efficacy data from the LUX-Head and Neck, phase III trial of second-line treatment with afatinib vs. methotrexate showed improvement in the study's primary endpoint PFS and delayed deterioration of patient-reported outcomes with a manageable safety profile in patients with head and neck squamous cell carcinoma (HNSCC) after failure of platinum-based therapy. The results were presented by Prof. Jean-Pascal Machiels of the Medical Oncology Department, Cliniques Universitaires St. Luc, Brussels, Belgium.

Patients with recurrent/metastatic HNSCC who progress after first-line platinum-based therapy have a dismal prognosis with median OS of approximately 3–6 months.

EGFR is overexpressed in approximately 90% of HNSCC and is associated with poor prognosis. Afatinib, an orally available, irreversible ErbB family blocker, showed promising anti-tumour activity in a phase II trial in patients with recurrent/metastatic HNSCC.

In this phase III trial, patients with recurrent/metastatic HNSCC after progression on/after platinum-based therapy were randomised 2:1 to oral treatment with afatinib (322 patients) or intravenous methotrexate (161 patients). They were stratified by ECOG PS (0 vs. 1) and prior use of anti-EGFR antibody therapy in the recurrent/metastatic setting.

The primary endpoint was PFS; secondary endpoints included OS, ORR, patient reported outcomes and safety.

The study used RECIST v1.1 criteria and the primary analysis was based on independent radiology review. It was required 364 independent events to detect HR of 0.70 (increase in median PFS from 2.1 to 3.0 months) at 90% power with one-sided type-I error of $\alpha=0.025$. For OS analysis it was required 343 deaths to detect HR of 0.73 (increase in median OS from 6.5 to 8.9 months) at 80% power with one-sided type-I error of $\alpha=0.025$.

The study recruitment in 19 countries around the world started in January 2012 and finished in December 2013 with a median follow-up of 6.7 months. Patient characteristics were well balanced in both groups.

Afatinib improved at a statistically significant level the primary study endpoint of PFS (median 2.6 vs. 1.7 months; $p = 0.03$). The PFS was more favourable with afatinib in subgroup analysis as well. However, afatinib did not improve OS in comparison with methotrexate (median 6.8 vs. 6.0 months).

The DCR was higher with afatinib vs. methotrexate (49.1% vs. 38.5%; $p=0.035$); the ORR was 10.2% vs. 5.6% ($p=0.10$).

Tumour shrinkage from baseline was observed in 34.8% afatinib-treated patients compared with 22.4% of methotrexate-treated patients.

Assessed by EORTC questionnaire QLQ-C30 and Head and Neck cancer-specific module (QLQ-H&N35) for pain and swallowing, afatinib showed delay in deterioration of global health status, pain and swallowing (all $p \leq 0.03$), and provided improvement in pain.

The most frequent grade 3/4 drug-related adverse events were rash/acne (9.7%) and diarrhoea (9.4%) with afatinib, and leukopaenia (15.6%) and stomatitis (8.1%) with methotrexate.

Prof. Machiels concluded that afatinib significantly improved PFS vs. methotrexate. Tumour shrinkage was greater, RR higher and DCR significantly higher compared to methotrexate. Patient-reported outcomes favoured afatinib over methotrexate. Fewer treatment-related dose reductions, discontinuations and fatal events were recorded with afatinib compared with methotrexate.

Afatinib is the first oral TKI to demonstrate efficacy and improved patient-reported outcomes in a phase III trial in this setting. Investigations with adjuvant afatinib in locally-advanced HNSCC following chemoradiotherapy are ongoing.

At the beginning of the session, the participants were alerted to the fact that the last approved therapy in Head & Neck cancer was cetixumab, 10 years ago, and that there is a desperate need for progress. Cetixumab is the only approved targeted therapy but there are no predictive biomarkers.

LUX-1 trial is the second positive study for recurrent/metastatic Head and Neck cancer since the EXTREME study. Afatinib was shown to be an active agent in this disease and the first oral targeted agent to show benefit, QoL and functional outcome improvements.

Discussing the study results, Dr Tanguy Seiwert of the University of Chicago, Chicago, USA, said that the difference of 0.9 months in PFS is of unclear clinical benefit and uncertain to lead to the drug approval. However, he suggested that there are two potential ways to lead to progress in this setting, one being more passive, waiting for the results of the LUX-2 study results and the second one, active search of predictive biomarkers to identify population with larger effect size.

The subgroup analysis showed that most benefit seemed to be found in the patients who did not receive prior EGFR therapies (suggesting a degree of cross-resistance) and in patients with p16 positive status (HPV negative disease) but this finding should be cautiously interpreted.

The study was sponsored by Boehringer Ingelheim.

Reference

[LBA29 PR: Afatinib versus methotrexate \(MTX\) as second-line treatment for patients with recurrent and/or metastatic \(R/M\) head and neck squamous cell carcinoma \(HNSCC\) who progressed after platinum-based therapy: primary efficacy results of LUX-Head & Neck 1, a phase III trial](#)

Randomised phase II study of MEHD7945A vs. cetuximab in at least second-line recurrent/metastatic squamous cell carcinoma of the head and neck progressive on/after platinum-based chemotherapy

Dr Jérôme Fayette of the Léon Bérard Center, University of Lyon, Lyon, France reported that MEHD7945A did not improve outcomes of patients with recurrent/metastatic squamous cell carcinoma of the head and neck when compared with cetuximab.

MEHD7945A, a novel dual-action humanised IgG1 antibody that blocks ligand binding to EGFR and HER3, inhibits signalling from all ligand-dependent HER dimers, and can elicit antibody dependent cell mediated cytotoxicity. MEHD7945A is active in multiple tumour models, including

models resistant to anti-EGFR or anti-HER3 targeting. Preclinical and early clinical data suggest that high expression of neuregulin 1 (NRG1) in tumours may enhance sensitivity to MEHD7945A.

This multicenter, open-label, randomised phase II study evaluated efficacy in recurrent/metastatic squamous cell carcinoma of the head and neck patients progressive on/after platinum-based chemotherapy, and in those whose tumours express high NRG1. Primary endpoint was PFS according to RECIST v1.1, secondary endpoints were ORR, DoR, OS and safety according to CTCAE v4.0.

Patients received MEHD7945 or cetuximab until progression or intolerable toxicity. Upon central confirmation of progression on cetuximab, patients could crossover to MEHD7945A. Mandatory tumour samples were assayed for biomarkers related to mechanism of action and squamous cell carcinoma of the head and neck, including NRG1 expression and HPV status.

In total 121 patients were randomised, 59 in the MEHD7945A arm and 62 in the cetuximab arm. Median age was 62 years, all patients had ECOG PS 0-2. There no differences between the treatment arms; median PFS was 4.1 month in the MEHD7945A arm and 4.0 month in the cetuximab arm; median OS was 7.2 month in the MEHD7945A arm and 8.5 month in the cetuximab arm; ORR was 11.9% in the MEHD7945A arm and 14.5% in the cetuximab arm.

Grade ≥ 3 adverse events that were more frequent with MEHD7945A (61%) compared to cetuximab (51%) included infections (22.0% vs. 11.5%) and GI disorders (13.6% vs. 6.6%) contributing to higher rates of serious adverse events (40.7% vs. 29.5%); metabolic disorders were less experienced with MEHD7945A (10.2% vs. 14.8%). Any grade skin toxicity was lower with MEHD7945A (45.8% vs. 59.7%).

High NRG1 expression in tumour (primary biomarker hypothesis) did not enhance for MEHD7945 efficacy. Responses to both MEHD7945 and cetuximab associated with higher amphiregulin expression.

Dr Tanguy Seiwert of the University of Chicago, Chicago, USA, who discussed the study results, said that MEHD7945A showed comparable activity to cetuximab. Following the lead of afatinib further development is feasible, however it appears unclear at this point whether MEHD7945A is an improvement upon treatment with cetuximab. Further development in a biomarker defined population may be promising. In this study, outstanding biomarker work was done. HPV-positive tumours have less or no benefit from EGFR targeting agents. HER ligands amphiregulin/hereregulin correlate (moderately) with benefit from EGFR/HER agents and can potentially be used for enrichment. Further validation is required, and we still need reliable assays. Prior studies that used p16 should be re-analysed for HPV. The p16 use in the setting of both de-escalation and EGFR targeting is not sufficiently accurate, and accurate HPV testing is necessary.

The study was sponsored by Genentech, Inc.

Reference

[986O: Randomized phase II study of MEHD7945A \(MEHD\) vs cetuximab \(Cet\) in \$\geq\$ 2nd-line recurrent/metastatic squamous cell Carcinoma of the head & neck \(RMSCHN\) progressive on/after platinum-based chemotherapy \(PtCT\)](#)

A phase IB study of pembrolizumab in patients with human papillomavirus (HPV)-positive and -negative head and neck cancer

Dr Laura Chow of the Medical Oncology, University of Washington, Seattle, USA presented updated safety, tolerability, and antitumour activity of pembrolizumab for recurrent/metastatic head and neck cancer. Data from this cohort were previously reported at the ASCO 2014, but the data presented at ESMO 2014 are updated and expanded.

During screening, PD-L1 expression in archival or newly obtained tumour samples was assessed using a prototype IHC assay; PD-L1 expression in stroma or $\geq 1\%$ of tumour cells was required for study entry.

Pembrolizumab was given every 2 weeks until CR, progression, unacceptable toxicity, physician decision, or consent withdrawal. Adverse events were recorded throughout the study. Response was assessed every 8 weeks. Primary endpoint was ORR per RECIST v1.1.

Out of 104 head and neck cancer patients screened, 81 (78%) were PD-L1-positive of which 61 enrolled, and 60 received ≥ 1 pembrolizumab dose: 23 HPV-positive, 37 HPV-negative. After a median follow-up of 10.2 months, 15 patients (25%) remain on pembrolizumab.

The ORR (confirmed and unconfirmed) per RECIST v1.1 by investigator review was 20%, and response duration ranged from 8+ to 41+ weeks (median not reached). Nine of 11 responders had a smaller target lesion burden at baseline. The ORR was similar in HPV-positive and HPV-negative patients, whereas PFS and OS were longer in HPV-positive patients. PD-L1 expression was positively correlated with ORR ($p = 0.018$) and PFS ($p = 0.024$). The ORR was 50% in the 12 patients with high PD-L1 expression.

Drug-related adverse events of any grade occurred in 58% of patients (grade ≥ 3 in 17%). The most common drug-related adverse events were fatigue (18%), pruritus (10%), and nausea (8%). There were no drug-related deaths.

The study researchers concluded that pembrolizumab is safe and tolerable and shows antitumour activity in both HPV-positive and HPV-negative advanced head and neck cancer. These findings support further development of pembrolizumab in advanced head and neck cancer.

The study was supported by Merck Sharp & Dohme Corp.

Reference

[LBA31: A phase Ib study of pembrolizumab \(Pembro; MK-3475\) in patients \(Pts\) with human papilloma virus \(HPV\)-positive and negative head and neck cancer \(HNC\)](#)

Haematological Malignancies

Brentuximab vedotin in combination with CHP in patients with newly-diagnosed CD30-positive peripheral T-cell lymphomas

Prof. Michelle Fanale of the University of Texas MD Anderson Cancer Center, Houston, USA reported that brentuximab vedotin in combination with CHP chemotherapy delivered durable remissions in newly-diagnosed patients with peripheral T-cell lymphomas, with a 2 year PFS rate of 54%.

Peripheral T-cell lymphomas comprise a subset of aggressive non-Hodgkin lymphomas. Outcomes of frontline treatment are poor, with CR rates of 39%–53% and 5 year OS rates of 12%–49%, depending on subtype.

Brentuximab vedotin has shown clinical activity in a phase I trial of treatment in sequence with CHOP or in combination with CHP in patients with newly-diagnosed peripheral T-cell lymphomas.

This phase I, open-label study conducted in USA and Europe, assessed the safety and efficacy of brentuximab vedotin administered sequentially with standard-dose CHOP or in combination with CHP for the frontline therapy of peripheral T-cell lymphomas. ALK-positive systemic anaplastic large cell lymphoma patients must have had IPI score ≥ 2 . Combination therapy included a cohort to determine the recommended dose of brentuximab vedotin to be evaluated in an expansion cohort. Responders could receive single-agent brentuximab vedotin for up to 10 additional cycles. Updated PFS and OS data from combination therapy were presented.

The median age of patients was 56 years. Diagnoses included systemic anaplastic large cell lymphoma in 19 cases from whom 16 were ALK-negative, peripheral T-cell lymphoma in 2 cases, angioimmunoblastic T-cell lymphoma in 2 cases, adult T-cell leukaemia/lymphoma in 2 cases, and enteropathy-associated T-cell lymphoma in 1 case.

The maximum tolerated dose of brentuximab vedotin in combination with chemotherapy was not exceeded at 1.8 mg/kg i.v., based on 1 DLT (grade 3 rash). Six cycles of combination therapy were completed in 23 of 26 patients.

Treatment-emergent adverse events ($\geq 40\%$) included peripheral sensory neuropathy, nausea, fatigue, alopecia, diarrhoea, and dyspnoea.

At the end of combination therapy, the ORR was 100% and CR rate was 88%. After a median observation time of 27.1 months, the 2 year PFS rate was 54%. Ten of 19 patients with anaplastic large cell lymphoma and 5 of 7 patients with other entities remain free of disease progression or death. The estimated median PFS was not reached. No patients went on to receive a consolidative stem cell transplant. The 2 year OS rate was 80%. Four patients received subsequent brentuximab vedotin treatment after progression. After progression, 3 patients received stem cell transplants (2 allogeneic, 1 autologous).

ECHELON-2, a phase III study comparing brentuximab vedotin plus CHP to CHOP regimen in the frontline therapy of peripheral T-cell lymphomas is underway.

Dr Enrico Derenzini of the Institute of Hematology and Medical Oncology L.A. Seragnoli, Bologna, Italy, who discussed the study results, said that the question addressed in the presentation was feasibility and activity of a combination strategy including brentuximab vedotin and chemotherapy

in newly diagnosed CD30-positive peripheral T-cell lymphoma, in particular an update focusing on combination arm. The combination of brentuximab vedotin and chemotherapy has manageable toxicity, increased peripheral neuropathy, mainly grade 2, and transient. Efficacy of the combination therapy is impressive with durable remissions seen in poor prognosis non-Hodgkin lymphoma subtype. However, the question is if standard CH(O)P represents the best partner for brentuximab vedotin.

The study was sponsored by Seattle Genetics.

Reference

[944O: Brentuximab vedotin in combination with CHP in patients \(Pts\) with newly-diagnosed CD30+ peripheral T-cell lymphomas \(PTCL\): 2-year follow-up](#)

Carfilzomib vs. low-dose corticosteroids and optional cyclophosphamide in patients with relapsed and refractory multiple myeloma

Prof. Heinz Ludwig of the Wilhelminenspital, Vienna, Austria reported results from a phase III FOCUS study in heavily pretreated patients with relapsed and refractory multiple myeloma. Median OS for single-agent carfilzomib was similar to the active control arm.

Carfilzomib is a second generation proteasome inhibitor. It irreversibly binds to the constitutive proteasome and the immunoproteasome. It is able to overcome bortezomib resistance and shows less off target activity than bortezomib.

The study aim was to compare carfilzomib with low-dose corticosteroids and optional cyclophosphamide. Patients were randomised 1:1. The primary endpoint was OS with 80% power to detect a HR of 0.7 (median OS assumptions were for the carfilzomib arm 8.6 months and 6 months in the control arm). Secondary endpoints included PFS, ORR and safety.

Between September 2010 and October 2012, 315 patients were randomised, 157 in the carfilzomib arm and 158 in the control group. Baseline characteristics were balanced between the groups. Median age was 65 years. Patients received 5 (median) prior regimens in each group; median time since diagnosis was 6.0 years in the carfilzomib group and 5.4 years in the control group.

Median treatment duration was 16.3 weeks in the carfilzomib group and 10.7 weeks in the control; 92% of patients in the control group received cyclophosphamide. Median relative dose intensity was 99.9% in each group. The study did not meet the primary endpoint for OS (HR 0.975; $p = 0.4172$). Median OS was 10.2 month in the carfilzomib group and 10.0 month in the control group. Median follow-up for OS was 27.8 month in the carfilzomib group and 29.8 month in the control group. Median PFS was 3.7 month in the carfilzomib group and 3.3 month in the control group. The ORR was 19.1% in the carfilzomib group and 11.4% in the control group.

Treatment discontinuation due to an adverse event occurred in 14.6% (carfilzomib group) and 20.3% of patients in the control group; 10.2% in the carfilzomib group and 12.4% of patients in the control group died on study due to an adverse event. Grade ≥ 3 treatment-emergent adverse events ($\geq 5\%$) included anaemia (25.5% in the carfilzomib group vs. 30.7% in the control group), thrombocytopaenia (24.2% in the carfilzomib group vs. 22.2% in the control group), neutropaenia (7.6% in the carfilzomib group vs. 12.4% in the control group), acute renal failure (7.6% in the carfilzomib group vs. 3.3% in the control group), pneumonia (6.4% in the carfilzomib group vs.

12.4% in the control group), and renal failure (5.1% in the carfilzomib group vs. 1.3% in the control group).

Prof. Faith Davies of the University of Arkansas for Medical Sciences, USA, who discussed the study results, said that carfilzomib is an effective treatment with a good safety profile. The discussion covered difficulties in developing a drug in the relapsed refractory myeloma setting. It is difficult to design a study that meets regulatory, commercial, patient and scientific needs with an open question what should the control arm be. Regarding use of single agent carfilzomib, Dr Davies said that we never use single agent – always use a combination of a doublet or a triplet.

The study was sponsored by Onyx Therapeutics, Inc.

Reference

[LBA28: Carfilzomib \(K\) vs low-dose corticosteroids and optional cyclophosphamide \(Cy\) in patients \(pts\) with relapsed and refractory multiple myeloma \(RRMM\): Results from a phase 3 study \(FOCUS\)](#)

Lung Cancer

Final results of the SAKK 16/00 trial: A randomised phase III trial comparing neoadjuvant chemoradiation to chemotherapy alone in stage IIIA/N2 NSCLC

Prof. Miklos Pless of the Kantonsspital Winterthur, Winterthur, Switzerland reported results from the first completed phase III trial that evaluated the role of induction chemoradiotherapy and surgery, in comparison to neoadjuvant chemotherapy alone followed by surgery in patients with stage IIIA/N2 NSCLC. Radiotherapy was active; it increased response, complete resection and pCR rates. However, this failed to translate into an improvement of local control, EFS or OS. Notably, surgery after induction treatment was safe, including pneumonectomy. The OS rates of the neoadjuvant regimen in the study are very encouraging, especially for a multicenter setting.

One standard option in the treatment of stage IIIA/N2 NSCLC is neoadjuvant chemotherapy followed by surgery. Swiss researchers investigated in a randomised trial whether the addition of neoadjuvant radiotherapy would improve the outcome. At ESMO 2014, they presented the final results of the study.

Patients with pathologically proven, resectable stage IIIA/N2 NSCLC, PS 0-1, and adequate organ function were randomised 1:1 to chemoradiation with 3 cycles of neoadjuvant chemotherapy (cisplatin/docetaxel) followed by accelerated concomitant boost radiotherapy with 44 Gy in 22 fractions in 3 weeks, or neoadjuvant chemotherapy alone, with subsequent surgery for all patients. The primary endpoint was EFS (from randomisation to either relapse, progression, second tumour or death).

In total 232 patients were randomised, the median follow-up was 53 months. Two thirds were men, median age was 60 years. Histology was squamous cell in 33%, and adenocarcinoma in 43%.

Response rate to chemoradiotherapy was 61% vs. 44% with chemotherapy. Among all patients 85% underwent surgery, 30-day postoperative mortality was 1%. The rate of complete resection was 91% in chemoradiotherapy patients vs. 81% in chemotherapy patients and the pCR rate was 16% vs. 12%.

The median EFS was 13.1 months for the chemoradiotherapy group vs. 11.8 months in the chemotherapy arm ($p = 0.665$). The median OS in chemoradiotherapy group was 37.1 months, and with chemotherapy 26.2 months ($p = 0.938$). The local failure rate was 23% in both arms.

In the chemotherapy arm, 12 patients were given postoperative radiotherapy for R1 resection, 6 patients received postoperative radiotherapy in violation of the protocol. Patients with a pCR, mediastinal downstaging to ypN0/1 and complete resection had a better outcome. Toxicity of chemotherapy was substantial, especially febrile neutropaenia was common, whereas radiotherapy was well tolerated.

Dr Rafal Dziadziuszko of the Medical University of Gdańsk, Gdańsk, Poland, who discussed the study results, said that the study hypothesis was that addition of sequential radiotherapy to induction chemotherapy followed by surgery improved event-free survival in potentially resectable stage IIIA/N2 NSCLC. He said that chemotherapy plus one local treatment remains the standard of care. Concurrent chemoradiation is most often used. Chemotherapy/surgery is still a valid option in selected patients (based on MDT, patient preference, comorbidities and surgical risk-assessment).

This was an investigator-led study. It was supported by the Swiss State Secretariat for Education, Research and Innovation, Swiss Cancer League (Grant KLS-2745-02-2011), and Sanofi.

Reference

[1195O: Final results of the SAKK 16/00 trial: a randomized phase III trial comparing neoadjuvant chemoradiation to chemotherapy alone in stage IIIA/N2 non-small cell lung cancer \(NSCLC\)](#)

Adjuvant treatment with MAGE-A3 cancer immunotherapeutic in patients with resected NSCLC does not increase DFS: Results of the MAGRIT, a double-blind, randomised, placebo-controlled phase III study

The MAGRIT global trial assessed the efficacy of the recMAGE-A3 + AS15 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive NSCLC. In this study, treatment with MAGE-A3 cancer immunotherapeutic did not increase DFS compared to placebo in either the overall population or in patients who did not receive adjuvant chemotherapy. The results were presented by Prof. Johann Vansteenkiste of the Respiratory Oncology Unit, University Hospitals Leuven - Campus Gasthuisberg, Leuven, Belgium.

Adjuvant chemotherapy is the standard of care for stage II and IIIA NSCLC, and for high risk stage IB NSCLC. However, the 5-year DFS rate remains poor (35-50%) and about half of the patients will not receive adjuvant chemotherapy for various reasons. Tolerability of adjuvant cisplatin-based chemotherapy is suboptimal.

MAGE-A3 is a tumour-specific antigen. It is expressed in several tumour types, including NSCLC. MAGE-A3 cancer immunotherapeutic is delivered as a recombinant protein, combined with immunostimulants.

MAGE-A3 cancer immunotherapeutic showed activity in metastatic melanoma. The double-blind, placebo-controlled, phase II trial in completely resected MAGE-A3-positive stage IB-II NSCLC showed, at 44 months follow-up, a 25% reduction in the relative risk of cancer recurrence with HR 0.75. It was very well tolerated. Predictive gene signature was discovered in metastatic melanoma and reproduced in NSCLC.

MAGRIT was a randomised, double-blind, placebo-controlled trial that investigated whether the recMAGE-A3+AS15 cancer immunotherapeutic as adjuvant therapy improves DFS in patients with completely resected (R0), anatomically resected, MAGE-A3-positive NSCLC (stages IB, II, and IIIA according to TNM classification version 6) who did or did not receive adjuvant chemotherapy (up to 4 cycles of platinum-based regimen), ECOG PS 0, 1 or 2, adequate bone-marrow reserve, renal function and hepatic function and no auto-immune disease.

MAGE-A3 status was assessed in primary tumour by RT-PCR test on formalin-fixed paraffin embedded tissue.

Patients were randomly assigned (2:1) to receive 13 intramuscular injections of MAGE-A3 cancer immunotherapeutic or placebo over a 27 month treatment period.

The three co-primary endpoints were DFS in the overall and in the no-adjuvant chemotherapy population and DFS in patients with a potentially predictive gene signature.

Secondary endpoints included OS, lung cancer specific survival, DFS, immunogenicity, safety, and health-related QoL.

In total 13,849 patients were screened and 4,210 of them had a MAGE-A3 positive tumour sample. However, 2,272 patients were randomised and treated.

One interim analysis was done which concluded that the study may continue as pre-specified boundary was not met and the treatment was well tolerated.

Overall, 52% of the patients received adjuvant chemotherapy. Stage IB disease was recorded in 47%, stage II in 36% and 17% were stage IIIA. Median age was 63 years and 24% of patients were female.

Mean relative dose intensity was above 98% in both groups throughout the treatment period.

Common adverse events present in more than 10% of patients treated with MAGE-A3 cancer immunotherapeutic vs. placebo were: pyrexia (35% vs. 5%), injection site pain (31% vs. 5%), injection site reaction (18% vs. 14%), fatigue (16% vs. 7%), pain (16% vs. 2%), influenza-like illness (13% vs. 3%), and myalgia (12% vs. 2%), respectively.

However, the rate of grade ≥ 3 adverse events did not differ between treatment groups and was below 1%.

Median follow-up at the time of final analysis was 38.8 months. In the overall study population, median DFS was 60.5 months and 57.9 months respectively for MAGE-A3 cancer immunotherapeutic and placebo (HR 1.024, $p = 0.7379$). In patients who did not receive adjuvant chemotherapy, median DFS was 58.0 months and 56.9 months for MAGE-A3 cancer immunotherapeutic and placebo groups, respectively (HR 0.970, $p = 0.7572$).

The OS in the overall population was not reached, but it might be expected to exceed median value of 5 years.

Due to the absence of treatment effect, a gene signature predictive of clinical benefit to MAGE-A3 cancer immunotherapeutic could not be identified.

The authors concluded that MAGRIT is the largest clinical trial in NSCLC and the first one to investigate immunotherapy in the adjuvant setting of early stage NSCLC. Adjuvant treatment with the MAGE-A3 cancer immunotherapeutic did not increase DFS compared to placebo in the overall population nor in patients who did not receive adjuvant chemotherapy. No benefit was observed in any subset analyses. MAGE-A3 cancer immunotherapeutic was generally well tolerated with mainly mild toxicities and no detectable increase in immune-mediated disorders. No predictive gene signature was identified in the training set. The study database is a source for further analysis on global contemporary approach to early stage NSCLC.

Prof. George Coukos of the Centre Hospitalier Universitaire Vaudois - CHUV, Lausanne, Switzerland, who discussed the study results, said that the advantages of vaccine therapy in NSCLC are low toxicity, easiness of administration, and ability to induce anti-tumour protective memory. The disadvantages are low impact at present time. Clinical indication might be in the maintenance/consolidation setting.

The normal function of MAGE-A3 is unknown, but its presence on tumour cells has been associated with a worse prognosis. The MAGE-A3 antigen is expressed in a variety of tumour cells, but not in normal tissues (except for the testes). In NSCLC, expression can be demonstrated

in 35% of early-stage tumours. The 'MAGE-A3 vaccine' is an example of a recombinant protein antigen-based vaccine.

Possible reasons for study failure, according to Prof. Coukos, are retrospective subset analysis that may be deceiving, monovalent molecularly defined vaccines might be too weak to make an impact, metastatic or progressive tumours may be immune escape variants, and/or it could be due to epigenetic mechanisms (association between methylation and lung cancer recurrence).

Prof. Coukos discussed future of vaccines in NSCLC, in particular awaiting the results from other monovalent molecularly defined vaccines and developing polyvalent molecularly defined vaccines.

High mutational rates may contribute to increased immunogenicity. Melanomas and lung tumours display many more mutations than average, with approximately 200 non-synonymous mutations per tumour. These larger numbers reflect the involvement of potent mutagens. Lung cancers in smokers have 10 times as many somatic mutations as those from non-smokers.

Therefore, the future opportunities for vaccines in NSCLC, according to Prof. Coukos, are personalised molecular vaccines based on mutanome analysis and autologous whole tumour antigen vaccines designed to address specific mutations.

GlaxoSmithKline Biologicals SA was the funding source in all stages of the study/project conduct and analysis.

Reference

[11730: MAGRIT, a double-blind, randomized, placebo-controlled Phase III study to assess the efficacy of the recMAGE-A3 + AS15 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive non-small cell lung cancer \(NSCLC\)](#)

TARGET: A phase II trial with vintafolide in second-line treatment of folate-receptor-positive NSCLC

A randomised, phase II trial comparing vintafolide vs. vintafolide plus docetaxel vs. docetaxel alone in second-line treatment of folate-receptor-positive NSCLC showed clinically meaningful improvement across all efficacy endpoints (ORR, PFS, and OS) with vintafolide/docetaxel over single-agent docetaxel treatment. The largest benefit was observed in the adenocarcinoma subgroup. The results were presented by Dr Nasser Hanna of the Department Of Medicine, Indiana University, Indianapolis, USA.

The folate receptor is expressed in many epithelial cancers, including NSCLC, and may be a useful biomarker for therapy selection.

Vintafolide, a folate-vinca alkaloid drug conjugate, is a folate receptor-targeted drug. Its companion imaging agent, ^{99m}Tc-etarfolatide, enables non-invasive imaging of folate receptor expression.

The TARGET study assessed the benefit of folate receptor-targeted therapy in 199 second-line NSCLC patients with all target lesions expressing folate receptor (100%).

Patients were randomised 1:1:1 to vintafolide, vintafolide plus docetaxel, or docetaxel alone.

Vintafolide was administered on day 1, 4, 8, and 11 and docetaxel on day 1 of a 3-week cycle.

The primary endpoint was PFS; secondary endpoints included OS and ORR. The significance level of each PFS and OS analysis was one-sided $\alpha = 0.10$ with no multiple testing adjustments.

The ORR in the vintafolide/docetaxel arm was 22% in the overall study population; HR for PFS was 0.75 ($p = 0.0696$); and median OS 11.5 months. In the adenocarcinoma subgroup, the ORR was 21%, the HR for PFS 0.73 ($p = 0.0899$) and median OS 12.5 months.

With the pre-specified stratified analysis adjusting for baseline factors (time since last chemotherapy, best response and stage), the OS HR for vintafolide/docetaxel vs. docetaxel were 0.75 (1-sided $p=0.1066$) for all patients, and 0.51 (1-sided $p=0.0147$) for the predefined adenocarcinoma patient subgroup.

Prof. Giorgio Scagliotti of the University of Torino at San Luigi Gonzaga Hospital Regione Gonzole 10, Orbassano, Italy, who discussed the study results, spoke about real-time identification of tumour lesions and response to vintafolide treatment. He said that there was no assessment of any genomic alteration in patients with adenocarcinoma. In addition, there was no information on post-study therapy. In second-line therapy there is still a huge room for improvements in terms of selecting candidate patients and treatments, he concluded.

The study was sponsored by Endocyte, Inc.

Reference

LBA40 PR: TARGET: A randomized, phase II trial comparing vintafolide versus vintafolide plus docetaxel, versus docetaxel alone in second-line treatment of folate-receptor-positive non-small cell lung cancer (NSCLC) patients

BRF113928: A phase II study with dabrafenib in patients with BRAF V600E-mutant advanced NSCLC

Dabrafenib is the first drug of its class to show activity in a prospective trial of NSCLC with BRAF mutations. Treatment of BRAF V600E mutated advanced NSCLC patients with dabrafenib demonstrated significant anti-tumour activity with durable objective responses and an acceptable safety profile in a multicenter, open-label, phase II trial. The findings were reported by Dr David Planchard of the Medical Oncology Department, Institut Gustave Roussy, Villejuif, France.

Activating BRAF V600E mutations in NSCLC are present in approximately 1.5% of tumours, primarily adenocarcinomas, offering an opportunity to test targeted therapy in this subset of patients.

This single-arm, 2-stage design, phase II study enrolled stage IV BRAF V600E-mutant NSCLC patients determined by local laboratory testing.

The primary endpoint was investigator-assessed ORR per RECIST v1.1 criteria.

As of 30 April 2014, 84 patients (female 52%, median age 66, ECOG PS 0–1 86%, Asian 21%, never-smoker 37%, adenocarcinoma histology 96%) were enrolled in the study since August 2011.

Median duration of treatment was 4.3 months (range, 0.3–25.2) with 21 (25%) patients still on treatment.

Six patients had not received any prior regimen for metastatic disease (first-line), 40 patients had one line and 38 patients had received ≥ 2 lines (range 2–9).

The ORR for 78 patients with more than one line of prior therapy (second-line plus patients) was 32%. All of these 25 patients experienced PR. The DCR longer than 12 weeks was 56%. Median DoR was 11.8 months (95% CI 5.4–not reached) with 48% of responders progressed.

Based on assessment by independent review committee, 64 second-line plus patients had measurable disease; ORR and DCR were 28% and 52% respectively, and median DoR has not been reached.

Among the six first-line patients, four patients had measurable disease based on independent review committee with three PRs.

Most common (>25%) adverse events were pyrexia (36%), asthenia (30%), hyperkeratosis (30%), decreased appetite (29%), nausea (27%), cough (26%), fatigue (26%) and skin papilloma (26%). Cutaneous squamous-cell carcinomas, including keratoacanthoma, were reported in 18%.

Grade ≥ 3 adverse events occurred in 45% with one event of grade 5 intracranial haemorrhage.

Dr Enriqueta Felip of the Vall d'Hebron University Hospital Institut d'Oncologia, Barcelona, Spain, who discussed the study results, said that BRAF V600E mutations are present in 1.5% of NSCLC and are mutually exclusive to other driver alterations. BRAF mutations identified in NSCLC are V600E (50%), G469A (40%), D594G (10%). In this study, dabrafenib showed clinically meaningful anti-tumour activity in BRAF V600E mutated NSCLC.

Dr Felip highlighted the recommendation from the 2nd ESMO Consensus Conference on Lung Cancer about optimal treatment for patients with ROS1, RET, BRAF or HER2 genomic alterations after standard treatment: Specific targeted treatments should be discussed with the patients and may be considered in individual patients based on expected risk-benefit, biological plausibility, preclinical data, and limited clinical efficacy data for authorised therapies in different indications.

Dr Felip questioned if in patients with uncommon alterations there is a need for randomised trials if there are good results from single arm phase II trials.

Next steps for researchers would be identification of acquired resistance mechanisms to BRAF inhibitors, testing anti-PD1 and anti-PDL1 strategies and combination of targeted therapies. In the latest one, there is a trial in which a cohort B with dabrafenib/trametinib is actively recruiting.

The study was sponsored by GlaxoSmithKline.

Reference

[LBA38 PR: Dabrafenib in patients with BRAF V600E-mutant advanced non-small cell lung cancer \(NSCLC\): A multicenter, open-label, phase II trial \(BRF113928\)](#)

A phase II study of neratinib with or without temsirolimus in patients with NSCLC carrying HER2 somatic mutations

In a phase II international randomised study of neratinib with or without temsirolimus in patients with NSCLC and tumours carrying HER2 somatic mutations, the combination therapy with neratinib/temsirolimus met the efficacy criteria in stage 1 study and has been subsequently expanded into stage 2. The results were presented by Dr Benjamin Besse of the Department of Cancer Medicine, Institut Gustave Roussy, Villejuif, France.

Somatic HER2 mutations occur in approximately 2-4% of patients with NSCLC.

In vivo data suggest that combined HER2/mTOR inhibition have synergistic effects in HER2-driven lung tumours. In a phase I study, 5 of 7 HER2-mutated NSCLC patients showed tumour regression (PR/SD) after treatment with neratinib, an irreversible pan-HER TKI and mTOR inhibitor, temsirolimus. However, the effects of neratinib alone are unknown.

This randomised 2-stage phase II study compared neratinib with or without temsirolimus in patients with stage IIIB/IV NSCLC and HER2 somatic mutations.

Patients whose tumours had a documented HER2 mutation were randomised 1:1 to receive oral neratinib 240 mg once daily continuously with or without temsirolimus i.v. 8 mg/week, escalated to 15 mg/week after one 3-week cycle if tolerated.

Addition of temsirolimus was permitted in patients assigned to neratinib alone after progression.

High-dose loperamide prophylaxis for diarrhoea was mandatory throughout cycle 1.

The primary endpoint was ORR. Secondary endpoints included: clinical benefit rate, PFS, and safety.

It was foreseen if ≥ 2 of 13 patients in each arm have a response at 12 weeks in stage 1, a further 26 patients per arm will be enrolled in stage 2.

In stage 1, 27 patients were enrolled (13 in the neratinib arm and 14 in the combined neratinib/temsirolimus arm) with approximately 12 weeks between randomisation of last patient and data cut-off.

Baseline characteristics of these 27 patients included in stage 1 were: male/female 52%/48%; median age 65 year; never smokers 63%. Two patients, both in the neratinib/temsirolimus arm, had not received prior anticancer medications.

In stage 1, ORR was 21% in the neratinib/temsirolimus arm vs. 0% in the neratinib arm. PR was observed in 3 patients in the combined arm and none in the neratinib arm alone. SD was recorded in 6 patients in the combined arm and 4 patients in the neratinib arm.

Median PFS was 4.0 months in the neratinib/temsirolimus arm and 2.9 months in the neratinib arm.

In all 27 patients, the most common all-grade adverse events were diarrhoea, constipation, nausea, dyspnoea, asthenia, and vomiting. Most common grade 3/4 adverse events were dyspnoea, diarrhoea (grade 3 only), vomiting, and nausea.

Grade 3 diarrhoea was recorded in 2 patients in the neratinib/temsirolimus arm and 1 patient in the neratinib arm. It was not a limiting toxicity with aggressive upfront management.

Dr Enriqueta Felip of the Vall d'Hebron University Hospital Institut d'Oncologia, Barcelona, Spain, who discussed the study results, said that NSCLC is divided into subsets by the presence of molecular alterations (EGFR, ALK, KRAS, ROS1, RET, HER2, BRAF, NTRK1, FGFR, among others). Challenges are reflected in genotyping, some molecularly defined subsets are rare and a clear effort is required to identify these patients. There are few trials in these uncommon molecular alterations and directing patients to targeted trials requires collaboration.

HER2 mutations are present in 2% of NSCLC. They are mutually exclusive with other driver alterations. Potential synergistic effect of combined HER2 and mTOR inhibition has been

observed in preclinical models of HER2 mutated NSCLC. In this study encouraging results were seen with the inhibition of both the HER2 and the PI3K pathway. She concluded that neratinib/temsirolimus combination deserves further development in HER2 mutated NSCLC.

The study sponsor was Puma Biotechnology, Inc.

Reference

LBA39 PR: Neratinib (N) with or without temsirolimus (TEM) in patients (pts) with non-small cell lung cancer (NSCLC) carrying HER2 somatic mutations: An international randomized phase II study

IMPRESS: Continuation of gefitinib plus pemetrexed/cisplatin of no clinical benefit in NSCLC patients with acquired resistance to gefitinib

The IMPRESS study is the first and only randomised phase III trial to confirm that continuation of gefitinib in addition to pemetrexed/cisplatin would be of no clinical benefit for patients with NSCLC and acquired resistance to gefitinib. The results were reported by Prof. Tony Mok of the Clinical Oncology Department, The Chinese University of Hong Kong, Hong Kong, China.

The study design was previously presented at the 10th Annual Meeting of the Japanese Society of Medical Oncology, 26–28 July 2012, Osaka, Japan. The latest findings presented as a late breaking abstract at ESMO 2014 report on previously unpublished primary and secondary analysis data.

Most patients with EGFR mutation-positive NSCLC respond to first-line EGFR tyrosine kinase inhibitors (TKIs), but later acquire resistance. Optimal management for patients with acquired resistance has yet to be defined, and options include:

- Discontinuing EGFR TKI therapy and commencing platinum-based doublet chemotherapy
- Continuing EGFR TKI therapy in combination with platinum-based doublet chemotherapy.

The second option is suggested to be beneficial because of the potential tumour heterogeneity at the time of EGFR TKI resistance, and it is also supported by retrospective clinical studies.

The phase III, double-blind IRESSA Mutation Positive Multicentre Treatment Beyond ProgRESSion Study (IMPRESS) evaluated the efficacy and safety of continuing gefitinib plus pemetrexed/cisplatin vs. placebo plus pemetrexed/cisplatin in patients with acquired resistance to first-line gefitinib.

Patients ≥ 18 years (in Japan ≥ 20 years) who were chemotherapy-naive, and who had cytological or histological confirmation of locally advanced/metastatic NSCLC other than predominantly squamous cell histology with an activating EGFR mutation as determined locally, and in whom a prior disease progression was recorded on first-line treatment with gefitinib, were eligible for the study.

Exclusion criteria included prior chemotherapy or other systemic anti-cancer treatment (excluding gefitinib); palliative bone radiotherapy had to be completed at least 2 weeks before start of study treatment with no persistent radiation toxicity; past medical history of interstitial lung disease, drug-induced interstitial disease, radiation pneumonitis which required steroid treatment or any evidence of clinically active interstitial lung disease; other co-existing malignancies or malignancies diagnosed within the last 5 years, with the exception of basal cell carcinoma or

cervical cancer in situ or completely resected intramucosal gastric cancer; any evidence of severe or uncontrolled systemic disease; and treatment with an investigational drug within 4 weeks before randomisation.

Patients from 71 centres in Europe and Asia Pacific were randomised to gefitinib or placebo. The primary endpoint was PFS. Secondary endpoints included OS, ORR, DCR, safety/tolerability, health-related QoL. Exploratory analysis of biomarkers is not yet completed and will be reported separately.

The study researchers estimated that 250 patients would need to be randomised to achieve 190 PFS events (75% PFS maturity); 90% power to demonstrate superiority of gefitinib in combination with chemotherapy vs. chemotherapy alone; and 2-sided 5% significance for assuming a HR of 0.63 for median PFS of 9.5 months vs. 6.0 months.

Randomisation did not include stratification factors, but the analysis was adjusted for two covariates: age (<65 vs. ≥65 years) and prior response to gefitinib (SD vs. PR plus CR).

From March 2014 to December 2013, 265 patients were randomised, 133 in the gefitinib arm and 132 in the placebo arm. Median follow-up in the study was 11.2 months.

The patient demographics in the two arms were well balanced. However, there were more patients ≥65 years in the gefitinib arm and more patients with baseline brain metastases in the chemotherapy arm.

There was no statistically significant improvement in PFS for gefitinib vs. placebo; HR 0.86; $p = 0.273$. Median PFS was 5.4 months in each arm.

The OS was immature (33% of patients had died), with better OS for placebo vs. gefitinib (HR 1.62; $p = 0.029$).

Ad hoc PFS and OS analyses included the addition of brain metastases at baseline as a covariate (brain metastases vs. no brain metastases), but there was no difference in term of PFS.

No treatment differences were found in ORR and DCR.

The safety profile for gefitinib plus pemetrexed/cisplatin was in line with what is already known.

The most common adverse events in the safety population (132 patients in each arm) were nausea recorded in 64% in the gefitinib group and 61% in the placebo group and decreased appetite (49% in the gefitinib treated patients vs. 34% in the placebo arm). No interstitial lung disease was noted. Gefitinib was associated with increased grade 1/2 gastrointestinal toxicities.

Adverse events with outcome of death were reported, in particular 2 casually-related in the gefitinib/chemotherapy arm and 1 casually-related in placebo/chemotherapy group.

Post-discontinuation therapy in ITT population was higher in the placebo arm, where 17% of patients received platinum based regimens in comparison to 5% in the gefitinib arm, and 44% received EGFR TKI vs. 30% of patients in the gefitinib arm.

Prof. Mok concluded that continuation of gefitinib in addition to pemetrexed/cisplatin would be of no clinical benefit for patients with acquired resistance to gefitinib. The IMPRESS study showed no statistically significant improvement in PFS with continuation of gefitinib in addition to chemotherapy beyond RECIST progression to first-line EGFR TKI for patients with EGFR

mutation-positive NSCLC. The OS was immature and not conclusive. There were imbalances in post study treatment in favour of the placebo arm (more doublet platinum chemotherapies and more EGFR TKI rechallenge).

Prof. Solange Peters of the Centre Hospitalier Universitaire Vaudois - CHUV, Lausanne, Switzerland, who discussed the study results, said that there are multiple mechanisms of resistance to EGFR TKIs reported in pre-clinical and clinical trials (MET amplification, HGF overexpression, PIK3CA mutations, PTEN loss, FGFR1/2/3 overexpression, AXL overexpression, CRKL amplification, NFκB activation, BRAF mutation, anti-apoptotic pathway (BIM deletion), loss of EGFR mutant gene, HER2 amplification, PDGFRb expression, and EMT). T790M mutation causes drug resistance by increasing the affinity for ATP. Dynamics of resistance evolution and the question of heterogeneity add to complexity of the problem.

Upon discussing treatment options of EGFR TKI resistance (chemotherapy, immunotherapy, EGFR TKI beyond progression, second generation TKI, third generation TKI, targeting bypass tracks, and chemotherapy plus EGFR TKI - which was tested in the IMPRESS study), she concluded that the IMPRESS study confirms that doublet chemotherapy should continue to be the standard of care for patients who develop resistance to first-line gefitinib. According to her, first-line EGFR TKI should be continued as long as possible and EGFR TKI should be subsequently rechallenged in the course of the disease.

The study was sponsored by AstraZeneca.

Reference

[LBA2 PR: Gefitinib/chemotherapy vs chemotherapy in epidermal growth factor receptor \(EGFR\) mutation-positive non-small-cell lung cancer \(NSCLC\) after progression on first-line gefitinib: The phase III, randomised IMPRESS study](#)

New data on first- and second-line ALK inhibition in NSCLC patients

Two presentations on metastatic NSCLC discussed the use of crizotinib in the first-line setting and efficacy of a second-generation ALK inhibitor, alectinib, in patients with crizotinib-resistant disease. Patients with NSCLC and ALK gene rearranged tumours show dramatic and sustained responses to treatment with ALK inhibitors, with crizotinib being the first-in-class ALK inhibitor. Unfortunately, resistance to crizotinib invariably develops and the researchers are trying to address it with next generation ALK inhibitors.

Overall and intracranial efficacy results and time to symptom deterioration in the PROFILE 1014 study

The efficacy of first-line crizotinib in improving PFS compared with standard pemetrexed/platinum chemotherapy in patients with advanced ALK-positive NSCLC was established in the phase III PROFILE 1014 study which included 343 patients. The results were presented earlier this year during ASCO 2014. Dr Benjamin Solomon from the Peter MacCallum Cancer Centre, Melbourne, Australia, reported additional data from this study during the ESMO 2014.

Crizotinib is an oral small-molecule TKI that targets ALK, ROS1, and MET. It is approved for advanced ALK-positive NSCLC. PROFILE 1014 is the first prospective, randomised phase III trial to compare the efficacy and safety of ALK-targeted therapy with standard chemotherapy for advanced ALK-positive NSCLC in the first-line setting.

Clinical outcomes (overall and intracranial efficacy, lung cancer symptoms) with crizotinib vs. standard chemotherapy as first-line treatment were compared in this ongoing multicentre study in the whole patient population and in patient subgroups.

Patients with previously untreated advanced non-squamous ALK-positive NSCLC were randomised 1:1 to crizotinib (172 patients) or pemetrexed plus cisplatin or carboplatin (171 patients). Continuation of/crossover to crizotinib after progression of disease per independent radiology review was allowed for patients randomised to both arms.

The primary endpoint was PFS per independent radiology review. Secondary endpoints included OS, intracranial time to progression, time to deterioration in symptoms of chest pain, dyspnoea, or cough, and safety.

The study met its primary objective: crizotinib was superior to chemotherapy in prolonging PFS (median 10.9 vs. 7.0 months; HR 0.45, $p < 0.0001$). The PFS benefit with crizotinib was observed in most patient subgroups analysed. Median PFS was 6.9 months with pemetrexed/cisplatin (HR 0.49, $p < 0.0001$) and 7.0 months with pemetrexed/carboplatin (HR 0.44, $p < 0.0001$).

Objective responses with crizotinib were rapid and durable when compared with chemotherapy (74% vs. 45%). With 68% of patients still in follow-up, median OS was not reached in either arm. There was a numerical improvement in OS in the crizotinib arm (HR 0.82, $p = 0.361$).

The analysis was not adjusted for the potentially confounding effects of crossover; 70% of patients in the chemotherapy arm received crizotinib after progression.

The intracranial time to progression HR for crizotinib vs. chemotherapy was 0.60 (non-significant difference; only around 15% of patients had intracranial events). In patients with baseline brain metastases, first-line crizotinib showed a numerical improvement in intracranial time to progression and demonstrated a statistically significant improvement in intracranial DCR at 12 ($p = 0.0003$) and 24 weeks ($p = 0.006$).

The time to deterioration in symptoms was around four times longer in the crizotinib arm than in the chemotherapy arm (median 2.1 months vs. 0.5 months; HR 0.62; $p = 0.0004$).

The most common adverse events of any cause with crizotinib were vision disorder and GI symptoms. Adverse events with pemetrexed/platinum chemotherapy were consistent with those previously reported in unselected NSCLC.

The authors concluded that crizotinib showed significant improvements in PFS and the time to deterioration in symptoms vs. pemetrexed/platinum chemotherapy, a numerical improvement in intracranial time to progression, and an acceptable safety profile, establishing crizotinib as the standard of care for patients with treatment-naive advanced ALK-positive non-squamous NSCLC.

The study was sponsored by Pfizer.

Reference

[1225O: Overall and intracranial \(IC\) efficacy results and time to symptom deterioration in PROFILE 1014: 1st-line crizotinib vs pemetrexed - platinum chemotherapy \(PPC\) in patients \(pts\) with advanced ALK-positive non-squamous non-small cell lung cancer \(NSCLC\)](#)

Antitumour activity of alectinib in crizotinib pre-treated ALK-rearranged NSCLC

Alectinib showed promising a response, including patients with brain metastases, and good tolerability in crizotinib pre-treated NSCLC patients, according to the updated efficacy and safety data from the JP28927 study. The results were presented by Dr Takashi Seto from the National Kyushu Cancer Center, Fukuoka, Japan.

Alectinib is a CNS-penetrant, highly selective ALK inhibitor. It has been approved in Japan since 7 April 2014 and is designated by FDA as a breakthrough therapy. ALEX is a global randomised, phase III, first-line study of alectinib vs. crizotinib that currently recruits treatment-naïve patients with ALK-positive advanced NSCLC.

The JP28927 was a clinical pharmacological study to evaluate the bioequivalence of alectinib in ALK-rearranged NSCLC patients with or without previous treatment with ALK inhibitor. The results for bioequivalence, food effect, efficacy and safety were reported earlier this year at ASCO 2014.

The study included ALK-rearranged NSCLC patients who had to discontinue treatment from crizotinib, a first generation ALK inhibitor, because of drug resistance or intolerance. During the ESMO 2014, the investigators presented updated efficacy and safety data for alectinib in 28 crizotinib pre-treated NSCLC patients included in this study.

As of 11 January, 2014, median follow-up duration was 141 days and 21 patients continued treatment with alectinib without progressive disease. Among 24 patients with target lesions, tumour shrinkage of more than 30% was observed in 18 patients. Confirmed RR was 58.3% and DCR was 83.3 % as assessed by study investigators.

From 19 patients who had brain metastases at baseline, 13 (including 4 patients without prior brain irradiation) were still on study treatment without disease progression.

The safety profile was favourable and continued the same trend previously reported. No patients discontinued study treatment for safety reasons. GI and visual disorders, characteristic for crizotinib treatment, were mild and not so frequent with alectinib.

The authors concluded that their findings suggest that alectinib is a novel therapeutic option for crizotinib pre-treated ALK-rearranged NSCLC.

The study was sponsored by Chugai Pharmaceutical Co., Ltd.

Reference

[1224O: Anti-tumor activity of alectinib in crizotinib pre-treated ALK-rearranged NSCLC in JP28927 study](#)

Defining and refining the ALK treatment paradigm in NSCLC

Dr Alice Shaw of the Massachusetts General Hospital, Boston, USA, who discussed the results of both studies, said that for patients with advanced ALK-positive NSCLC crizotinib represents a standard first-line therapy. However, it has modest activity in the CNS. Next generation ALK inhibitors, like alectinib and ceritinib, are active in patients who relapse on crizotinib, and represent a new standard of care.

Further studies are needed to determine the optimal sequencing of ALK inhibitors. The open questions, according to Dr Shaw, are:

- should a next generation ALK inhibitor be used as first-line therapy;
- which ALK inhibitor should be used in the second-line setting in term of CNS efficacy, tolerability, and resistance mechanism;
- is there a role for a third-line ALK inhibitor in terms of CNS disease and resistance mechanism.

Results of LUX-Lung 8, the largest prospective trial to compare EGFR TKIs in patients with relapsed/refractory squamous cell carcinoma of the lung

In the LUX-Lung 8, a global, randomised, phase III study the PFS and DCR were significantly better in patients with relapsed/refractory squamous cell carcinoma of the lung treated with afatinib than in those treated with erlotinib. The study was presented by Prof. Glenwood Goss of the Division of Medical Oncology, University of Ottawa, Ottawa, Canada.

Squamous histology represents approximately 30% of NSCLC cases. Limited progress and therapeutic options exist for these patients in second-line setting. Targetable oncogenic alterations are limited and have not yet translated to a therapeutic paradigm. In addition, patients often have extensive comorbidities.

Erlotinib is the last drug approved (in 2005) based on efficacy vs. placebo in second-/third-line setting. Survival benefit was confirmed in subset analysis of male, ever-smokers with squamous cell carcinoma.

Afatinib is an irreversible ErbB-family blocker that inhibits all kinase-active members (EGFR, HER2 and HER4). Proof of concept in squamous histology was observed in various trials in lung and head and neck cancer. It was approved in the major International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use regions of USA, EU and Japan for the treatment of patients with NSCLC harbouring distinct types of EGFR-activating mutations.

The LUX-Lung 8 study is a randomised, open-label, prospective phase III trial in patients with squamous cell carcinoma of the lung following failure of first-line chemotherapy. It compared afatinib with erlotinib, an EGFR inhibitor.

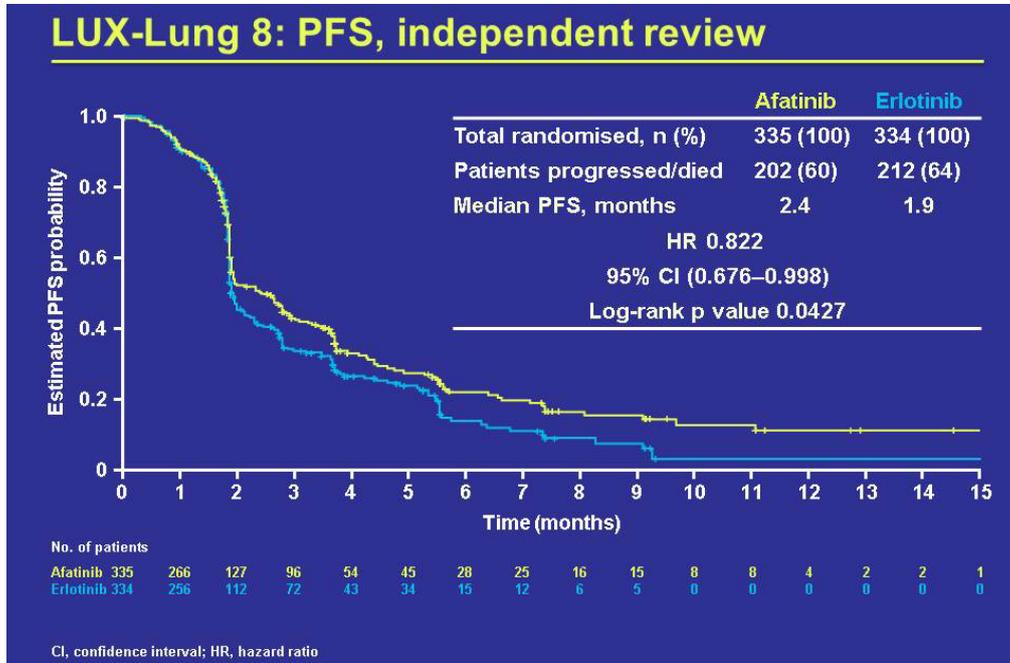
Eligible patients with stage IIIB/IV squamous cell carcinoma of the lung and ECOG PS 0 and 1 were randomised 1:1 to receive afatinib or erlotinib until disease progression. All patients had progressed after ≥ 4 cycles of platinum-based doublet chemotherapy and had not received prior EGFR TKIs. Patients were stratified based on race (East Asian vs. other).

The trial was powered for PFS and OS. The primary endpoint was PFS according to RECIST v1.1 criteria as assessed by independent radiological review (IRR). Secondary endpoints included OS planned at 632 events, ORR, DCR, safety and health-related QoL.

An interim futility analysis was performed by an independent data monitoring committee and the trial was allowed to accrue to the planned 800 patients. Overall 795 patients were recruited between March 2012 and January 2014. Planned primary analysis was based on 414 PFS events by IRR in the first 669 patients randomised (afatinib 335, erlotinib 334) while recruitment was ongoing.

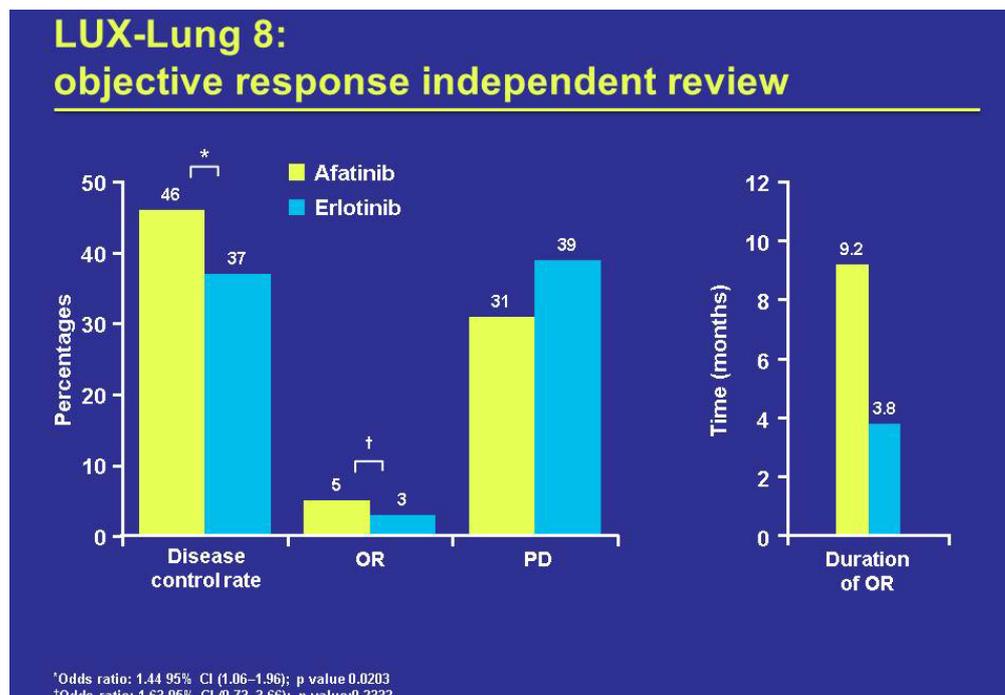
Baseline characteristics were well balanced between the arms. Median age was 65 years, 85% of patients were male, East Asians accounted of 22% of the study population, and never smokers 5%.

Median PFS was significantly higher for afatinib than erlotinib, both by IRR (2.4 vs. 1.9 months; $p=0.0427$) and investigator review (2.7 vs. 1.9 months; $p=0.0053$), respectively.



Caption: PFS by independent review in the LUX-Lung 8 study. © Glenwood Goss

The ORR was 4.8% vs. 3.0% ($p=0.233$), but DCR 45.7% vs. 36.8% ($p=0.020$) was significantly higher with afatinib vs. erlotinib.



Caption: The ORR was 4.8% vs. 3.0% ($p=0.233$), but DCR (45.7% vs. 36.8%; $p=0.020$) was significantly higher with afatinib vs. erlotinib.

The overall adverse event profile was comparable and consistent with the mechanistic profile of EGFR inhibition (patients with \geq grade 3 adverse events: 50.2% and 49.1% for afatinib and erlotinib with higher incidence of drug-related \geq grade 3 diarrhoea (9.7% vs. 2.4%) and grade 3 stomatitis (3.3% vs. 0.0%) with afatinib and higher incidence of grade 3 rash/acne with erlotinib (5.5% vs. 9.0%).

The authors concluded that LUX-Lung 8 is the largest prospective trial to compare EGFR TKIs in patients with relapsed/refractory squamous cell carcinoma of the lung. The PFS was statistically significantly increased with afatinib than erlotinib. Tumour shrinkage was greater, response rate higher, and DCR significantly higher in the afatinib arm compared to the erlotinib arm. Overall adverse event profile was consistent with mechanistic profile of EGFR inhibition and was manageable. Patient-reported outcomes favoured afatinib versus erlotinib. The OS data are awaited.

Dr Pasi Janne of the Dana-Farber Cancer Institute, Boston, USA, in his discussion entitled “Who should be treated with EGFR TKI”, said that the clinical implications of LUX-Lung 8 study are marginal benefit of afatinib over erlotinib and increased toxicity. EGFR-inhibitors are used less (if at all) in squamous cell lung cancer, chemotherapy is generally more effective in this disease and more than 99% of EGFR mutations actually occur in adenocarcinoma. New therapies are emerging for squamous cell cancer in particular anti-PD 1, anti-PD-L1 and anti-PD-L2 inhibitors.

The study was sponsored by Boehringer Ingelheim.

Reference

[1222O: A randomized, open-label, phase III trial of afatinib \(A\) vs erlotinib \(E\) as second-line treatment of patients \(pts\) with advanced squamous cell carcinoma \(SCC\) of the lung following first-line platinum-based chemotherapy: LUX-Lung 8 \(LL8\)](#)

Antitumour activity of pembrolizumab and correlation with PD-L1 expression in a pooled analysis of patients with advanced NSCLC

The anti-PD-1 antibody pembrolizumab has shown durable antitumour activity and acceptable toxicity in treatment-naïve and previously treated advanced NSCLC patients. Correlation between tumour PD-L1 expression and improved pembrolizumab antitumour activity has been observed. Prof. Edward Garon of the David Geffen School of Medicine at UCLA, Santa Monica, USA presented analysis in 282 patients with treatment-naïve or previously treated advanced NSCLC enrolled in randomised and non-randomised cohorts of the phase I KEYNOTE-001.

PD-1 is a negative co-stimulatory receptor expressed primarily on activated T cells. Binding of PD-1 to its ligands inhibits effector T-cell function. Expression of PD-L1 on tumour cells and macrophages can suppress immune surveillance and permit neoplastic growth. Pembrolizumab is able to achieve a dual blockade (PD-L1 and PD-L2). It shows no cytotoxic (ADCC/CDC) activity.

In this study, tumour PD-L1 expression was determined prospectively by a prototype IHC assay in all patients. Samples were independently reanalysed using a clinical trial IHC assay.

Pembrolizumab was given at 2 mg/kg every 3 weeks (Q3W), 10 mg/kg Q3W, or 10 mg/kg Q2W until progression, death, or unacceptable toxicity.

The ORR was assessed per RECIST v1.1 by central review and per immune-related response criteria (irRC) by investigator review.

Mature data are available for 262 patients with 5.4 months of median follow-up.

Grade 3-5 drug-related adverse events occurred in 24 (9%) patients, most commonly pneumonitis.

The ORR in patients with measurable disease at baseline was 21% according to RECIST v1.1 and 23% according to irRC in overall study population (26%/47% in treatment naive, 20%/18% in previously treated, respectively) and was 18% in patients with squamous and 23% in patients with non-squamous histology. The ORR was 33%/67% at 2 mg/kg Q3W, 21%/22% at 10 mg/kg Q3W, and 21%/22% at 10 mg/kg Q2W. The ORR was 23%/25% in patients with $\geq 1\%$ PD-L1 staining and 9%/13% in patients with negative PD-L1 staining.

In all treatment-naive patients, responses are still ongoing, in 77% of previously treated patients.

In treatment-naive patients the PFS is 27 weeks with a 24-week PFS rate of 51%. In the same group, median OS has not yet been reached and the 6 month OS rate is 86%. In previously treated patients the median PFS is 10 weeks, and 24 week PFS rate is 26%. The median OS is 8.2 months and 6 month OS rate is 59%.

In the pooled population, median PFS is 13 weeks and 24 week PFS rate 30%. The median OS is 8.2 months with a 6 month OS rate of 64%.

The data for PD-L1 staining using the clinical trial IHC assay are available for nearly half of the patients. In these patients, the ORR was higher in patients with strong PD-L1 expression ($\geq 50\%$ staining) than in patients with weak/negative PD-L1 expression.

The PFS was longer in patients with PD-L1 strong-positive vs. PD-L1 weak-positive/negative tumours (HR, 0.52). The OS was longer in patients with PD-L1 strong-positive v. PD-L1 weak-positive/negative tumours (HR 0.59).

Prof. Garon concluded that pembrolizumab is tolerable and provides antitumour activity in treatment-naive or previously treated advanced NSCLC, regardless of dose/schedule. Patients with strong PD-L1 tumour expression may derive particular benefit from pembrolizumab. Validation of the prospective PD-L1 cut point will be performed in an additional 300 patients enrolled in KEYNOTE-001. Ongoing studies with pembrolizumab in NSCLC are KEYNOTE-010, -024, and -042.

The study was supported by Merck Sharp & Dohme Corp.

Reference

[LBA43: Antitumor activity of pembrolizumab \(Pembro; MK-3475\) and correlation with programmed death ligand 1 \(PD-L1\) expression in a pooled analysis of patients \(pts\) with advanced non-small cell lung carcinoma \(NSCLC\)](#)

How to guide the selection of chemotherapy regimen for non-squamous NSCLC

Although docetaxel plus cisplatin vs. pemetrexed plus cisplatin showed similar PFS and RR in a phase III study of first-line treatment for non-squamous NSCLC, more frequent adverse events and higher toxicities were observed in the docetaxel arm. In another Korean, biomarker-stratified, randomised phase II study, RR and PFS with pemetrexed/cisplatin regimen compared to gemcitabine/cisplatin chemotherapy were more prominent in the thymidylate synthase (TS)-negative group than in TS-positive group, suggesting that TS can be used as a predictive biomarker.

Docetaxel plus cisplatin vs. pemetrexed plus cisplatin in first line non-squamous NSCLC

For patients with non-squamous-NSCLC, pemetrexed plus cisplatin is superior to gemcitabine plus cisplatin in terms of efficacy and toxicity. Docetaxel/cisplatin is an active regimen for first-line NSCLC. Median PFS of pemetrexed/cisplatin is 6.4 months in East Asians compared with 5.3 months in all ethnic patients. However, there was no prospective phase III trial that directly compared the efficacy of the two regimens. The objective of the study presented by Prof. Young-Chul Kim of the Pulmonology Unit, Chonnam National University Hwasun Hospital Lung Cancer Clinic, Hwasun Gun, Korea was to prove the non-inferiority of PFS of docetaxel/cisplatin compared with pemetrexed/cisplatin.

The researchers performed an open-label phase III trial. The study recruitment was between August 2011 and December 2013 at 14 centers in Korea. Patients with chemotherapy-naive non-squamous-NSCLC were randomised into 3 weekly cisplatin-based chemotherapies, with either docetaxel or pemetrexed, for up to 4 cycles with stratification by PS and sex. Thereafter, the patients continued treatment with either pemetrexed, EGFR TKI or docetaxel.

The primary objective was to assess PFS and the secondary endpoints were RR assessed by RECIST v1.1 criteria, OS and safety.

In total, 156 patients were randomised, but after 149 patients had been enrolled - pemetrexed/cisplatin (77) and docetaxel/cisplatin (72) - the study team finished enrolment due to the approval and popular use of maintenance treatment with pemetrexed in Korea.

Clinical characteristics including sex, age, and performance status were well balanced between the arms. The number of cycles and relative dose intensity were not significantly different between the arms.

In ITT population, PR was observed in 24 (31.2%) and 24 (33.3%) patients in pemetrexed/cisplatin and docetaxel/cisplatin group, respectively.

Median PFS was 4.7 months in the pemetrexed/cisplatin arm and 4.6 months in the docetaxel/cisplatin arm. Median OS was 19.7 month in the pemetrexed/cisplatin arm and 28.0 month in the docetaxel/cisplatin arm.

Rate of grade 3 or 4 neutropaenia and febrile neutropaenia, number of serious adverse events were significantly higher in the docetaxel arm.

Prof. Kim concluded that in non-squamous NSCLC without driver mutations, both regimens showed similar PFS and RR. However, more frequent adverse events and higher toxicities were observed in the docetaxel/cisplatin arm. Numerically shorter PFS were seen in both arms in this trial in comparison to the East Asian and overall population in other trials which suggests that maintenance treatment should be considered unless disease progression is noted.

Dr Giorgio Scagliotti of the University of Torino at San Luigi Gonzaga Hospital Regione Gonzole 10, Orbassano, Italy, who discussed the study results, said that it was planned as a non-inferiority study with a margin of 1.5 months. The original sample size was 562 patients, however, it was stopped after enrollment of 159 patients (28%) and for him this is just a randomised phase 2 study, therefore no meaningful conclusion could be drawn because of the limited number of patients. The PFS data are comparable to Caucasian patients, longer OS data in both arms are typical for data seen in Asian patients. As expected lung toxicity is higher with the

docetaxel/cisplatin treatment. Pemetrexed-based chemotherapy remains the preferred doublet in non-oncogene addicted non-squamous NSCLC.

Reference

[LBA41 PR: A randomized phase III study of docetaxel plus cisplatin versus pemetrexed plus cisplatin in first line non-squamous non-small cell lung cancer \(NSq-NSCLC\)](#)

Pemetrexed plus cisplatin vs. gemcitabine plus cisplatin according to thymidylate synthase expression in non-squamous NSCLC

Prof. Myung-Ju Ahn of the Department Of Internal Medicine, Hematology, Oncology, Sungkyunkwan University, School of Medicine, Seoul, Korea presented results of a biomarker-stratified randomised phase II trial. The primary endpoint was to determine the predictive value of TS in non-squamous NSCLC in term of ORR by testing the interaction between treatment arms and TS positivity.

As background, the Korean researchers explained that pemetrexed/cisplatin showed superior outcomes in non-squamous NSCLC compared with gemcitabine/cisplatin; however a phase III trial showed it was inferior in squamous NSCLC. One of culprits for this phenomenon is the different expression level of TS according to histotypes where TS expression is higher in squamous NSCLC than in non-squamous NSCLC.

TS is an important enzyme in de novo DNA synthesis and one of target proteins of pemetrexed. Many retrospective analyses showed better clinical outcomes of pemetrexed-based therapy in NSCLC patients with low TS-expressing tumours. This study was conducted to evaluate whether TS expression is a predictive factor for pemetrexed/cisplatin compared with gemcitabine/cisplatin in non-squamous NSCLC patients.

The main inclusion criteria were patients ≥ 18 years with histologically or cytologically confirmed advanced stage (IIIB or IV, or recurrent disease at least 6 months after complete resection), non-squamous NSCLC except large cell neuroendocrine carcinoma, at least one measurable lesions, ECOG PS 0 or 1, adequate organ function, and no prior chemotherapy for advanced disease. Written consent was obtained from eligible patients.

TS expression was measured by IHC. The patients with more than 10% of tumour cells expressing TS were grouped as a TS-positive and those with 10% or less were grouped as a TS-negative. In a retrospective study by the same investigators, the median H score of 15 as the cut-off value for TS-positive or TS-negative tumours was identical to the expression in 10% of tumour cells irrespective of staining intensity.

After being stratified as TS-positive or TS-negative, patients were randomised to either pemetrexed/cisplatin or gemcitabine/cisplatin arms in a 1:1 fashion.

The study primary endpoint was interaction between TS and treatment allocation as assessed by response rate. Secondary endpoints included interaction between TS and treatment allocation in terms of PFS or OS, and safety of treatment.

This trial was designed to provide 90% power to detect an interaction term of $b=1.294$ based on the response rate of each group as estimated from the investigators' previous study. One-sided α of 0.1 was used for the analysis of interaction term, whereas two-sided α of 0.05 was used for other endpoints.

Chemotherapy in both arms was administered until disease progression or unacceptable toxicity with maximum 6 cycles. Response evaluation by RECIST v1.1 was done every 2 cycles during treatment and every 2 months after completion of study chemotherapy.

For 315 evaluable patients, the RR calculated by investigators in pemetrexed/cisplatin and gemcitabine/cisplatin was 47.0% and 21.1% in the TS-negative group, and 40.3% and 39.2% in the TS-positive group ($p = 0.008$), respectively. The RR in the pemetrexed/cisplatin and gemcitabine/cisplatin arms as evaluated by independent reviewers were 38.6% and 21.1% in TS-negative group, and 40.3% and 48.1% in TS-positive group ($p = 0.007$), respectively.

The median PFS in the pemetrexed/cisplatin and gemcitabine/cisplatin arms were 6.4 and 5.5 months in TS-negative group ($p = 0.013$), and 5.9 and 5.3 months in TS-positive group ($p = 0.64$) (interaction $p = 0.07$), respectively.

Out of 88 patients with tumours harboring EGFR mutations, 74 received gefitinib or erlotinib, while 9 had not commenced post-discontinuation therapy because their disease had not yet progressed at the time of data cut-off.

The median OS in the pemetrexed/cisplatin and gemcitabine/cisplatin arms were not different in TS-negative group (not reached vs. 28.3 months, $p = 0.86$), or the TS-positive group (19.0 vs. 14.4 months, $p = 0.36$) (interaction $p = 0.31$). However, in multivariate analyses, TS-negative expression was significantly associated with longer survival (HR 0.64), along with younger age (HR 0.62) and EGFR mutation (HR 0.45).

The authors concluded that in terms of RR and PFS, clinical benefits with pemetrexed/cisplatin chemotherapy compared with gemcitabine/cisplatin were more prominent in the TS-negative group than in the TS-positive group, suggesting that TS can be used as a predictive biomarker. Furthermore, given that low TS expression was associated with prolonged OS irrespective of chemotherapeutic regimens, the authors noted that TS expression can also serve as a prognostic biomarker.

Dr Giorgio Scagliotti of the University of Torino at San Luigi Gonzaga Hospital Regione Gonzole 10, Orbassano, Italy, who discussed the study results said that it was a reasonably well designed study, however, prognostic/predictive role of TS remains unsolved. IHC, according to Dr Scagliotti, should not be used, while a role of RT-PCR detection would be more appropriate.

Pharmacogenomic markers are still restricted to clinical research settings and no data support their use in clinical practice to select patients.

Reference

[LBA42 PR: Cisplatin plus pemetrexed \(CP\) versus cisplatin plus gemcitabine \(CG\) according to thymidylate synthase expression in non-squamous NSCLC: A biomarker-stratified randomized phase II trial](#)

Prospective molecular evaluation of small cell lung cancer utilising the comprehensive mutation analysis programme at Memorial Sloan Kettering Cancer Center

Dr Lee Krug of the Memorial Sloan Kettering Cancer Center (MSKCC), New York, USA reported that comprehensive molecular evaluation of small-cell lung cancer (SCLC) is feasible on clinical specimens. Prospective collection of SCLC tumour samples and mutational analyses in the study

continue. Such analyses will allow characterisation of SCLC molecular diversity and identification of patients who may be candidates for targeted therapies.

Recent studies using next generation sequencing (NGS) on resected SCLC specimens have led to insights into the molecular heterogeneity of this disease. However, comprehensive, prospective molecular profiling of patients with advanced SCLC using the biopsy specimens available in clinical practice has not been performed, the authors explained in study background.

Utilising an institutional review board-approved protocol, the MSKCC researchers prospectively evaluated the SCLC tumours of patients in active treatment. The biopsies were evaluated by fluorescence in situ hybridisation (FISH) for FGFR1 and MET copy number, point mutation genotyping for known oncogenes by a mass spectrometry based assay (Sequenom), and NGS with a panel of 300 cancer-related genes. They first tested the feasibility of this approach in a series of patients with SCLC identified retrospectively, with matched tumour and normal pairs, and performed NGS, confirming the findings by FISH.

In the feasibility cohort, 21 patients with SCLC had FFPE samples available. After histologic review and DNA extraction, 10 patients had adequate material for NGS. The researchers observed recurrent mutations in RB1 (7 cases) and TP53 (8 cases) and amplifications of FGFR1 (2 cases) and MET (1 case), using as little as 15 nanograms of DNA. FISH confirmed FGFR1 and MET amplification in the identified cases.

Since February 2013, SCLC patients undergoing active treatment, with sufficient archived tissue, provided consent for the SCLC mutational analysis programme. Thus far, 43 patient samples have been tested. Sequenom in 32 patients identified an AKT1 E17 mutation in one case and a PIK3CA E542K mutation in one case. NGS in 25 patients has yielded the following: loss of RB1 (18 mutations, 4 deletions); mutations in TP53 (24), MLL3 (9), and EPHA 5 (9); and amplifications of CDKN2C (5), MYCL1 (3), SOX2 (2), and FGFR1 in one case confirmed by FISH. Four patients had insufficient material.

The findings are confirmatory of previous retrospective studies with frequent inactivation of TP53, RB1 and comparable frequency of alterations such as SOX2 and FGFR1 amplifications, and PTEN loss. Homozygous deletions are more common in refractory disease. In this series, extensive stage disease is not associated with an increased number of mutations relative to limited stage disease. When further evaluated for response, several mutations appear to be specific to sensitive disease patients. Ongoing analyses are focused on correlating SCLC gene alterations with outcomes and associating these patients with appropriate targeted therapy.

Prof. Caroline Dive of the Christie Hospital, Manchester, UK said that obtaining serial and sufficient biopsies from SCLC is possible, but difficult. There is an urgent need for better therapies, useful biomarkers for drug development and patient relevant mouse models to explore biology and test new treatments.

SCLC is not routinely resected and therefore there is a limited amount of tissue for research. SCLC cell lines were amongst the first to be developed, but the generated hypotheses have mainly not been upheld in the clinic. Patient derived explant models to explore biology and pharmacology require fresh tissue, but it remains challenging to get SCLC biopsies (small, necrotic masses). It has been done in this study and the data are pioneering. Some key issues are

if this approach is realistic for SCLC patients who don't attend large well funded comprehensive cancer centres, with what frequency should progression biopsies be obtained to study drug resistance mechanisms, how many targeted therapies are available now for patients with molecular analyses to hand, how many molecular hits were actionable and in how many patients, does a small biopsy miss important subclonal drivers, and what do we really know about intratumour heterogeneity and evolution of SCLC? The authors noted that a greater number of genes are altered in patients with sensitive disease compared to refractory disease, but these results require validation, according to Prof. Dive.

The study was funded, in part, by the Lung Cancer Research Foundation.

Reference

[1463O: Prospective molecular evaluation of small cell lung cancer \(SCLC\) utilizing the comprehensive Mutation Analysis Program \(MAP\) at Memorial Sloan Kettering Cancer Center \(MSKCC\)](#)

Melanoma and Other Skin Tumours

Results of the COMBI-v randomised, open-label, phase III study in the first-line treatment of patients with unresectable or metastatic cutaneous melanoma

First-line treatment with combination therapy dabrafenib plus trametinib improves OS in comparison with vemurafenib in patients with BRAF V600E/K mutation-positive unresectable or metastatic cutaneous melanoma. The results of a randomised, open-label, phase III, COMBI-v study were presented by Dr Caroline Robert of the Institut Gustave Roussy, Villejuif, France.

Dabrafenib, a BRAF inhibitor and trametinib, a MEK inhibitor demonstrated superior PFS vs. chemotherapy in patients with BRAF V600E/K mutation-positive metastatic melanoma. However, the emergence of disease resistance and development of cutaneous squamous cell carcinoma are associated with BRAF inhibition. Simultaneous inhibition of BRAF and MEK mitigated these effects as shown in the phase I/II study of dabrafenib/trametinib combination vs. treatment with single agent dabrafenib and in the phase III study of dabrafenib/trametinib combination vs. dabrafenib monotherapy with an improvement in ORR, PFS and reduced frequency of cutaneous squamous cell carcinoma.

The COMBI-v phase III study was conducted to establish the superiority of dabrafenib/trametinib combination over vemurafenib with respect to OS in patients with BRAF V600E/K mutation-positive metastatic melanoma.

Patients were randomised 1:1 to receive dabrafenib/trametinib vs. vemurafenib monotherapy as first-line therapy.

Eligible patients were ≥ 18 years old and had an ECOG PS ≤ 1 , with histologically confirmed, unresectable stage IIIC or IV, BRAF V600E/K mutation-positive metastatic melanoma. All patients were treatment-naïve with no brain metastasis except those treated and stable status longer than 12 weeks. Stratification was according V600E vs. V600K mutation and LDH level.

The primary endpoint was OS; secondary endpoints were PFS, ORR, DoR, and safety.

The study crossover was prohibited.

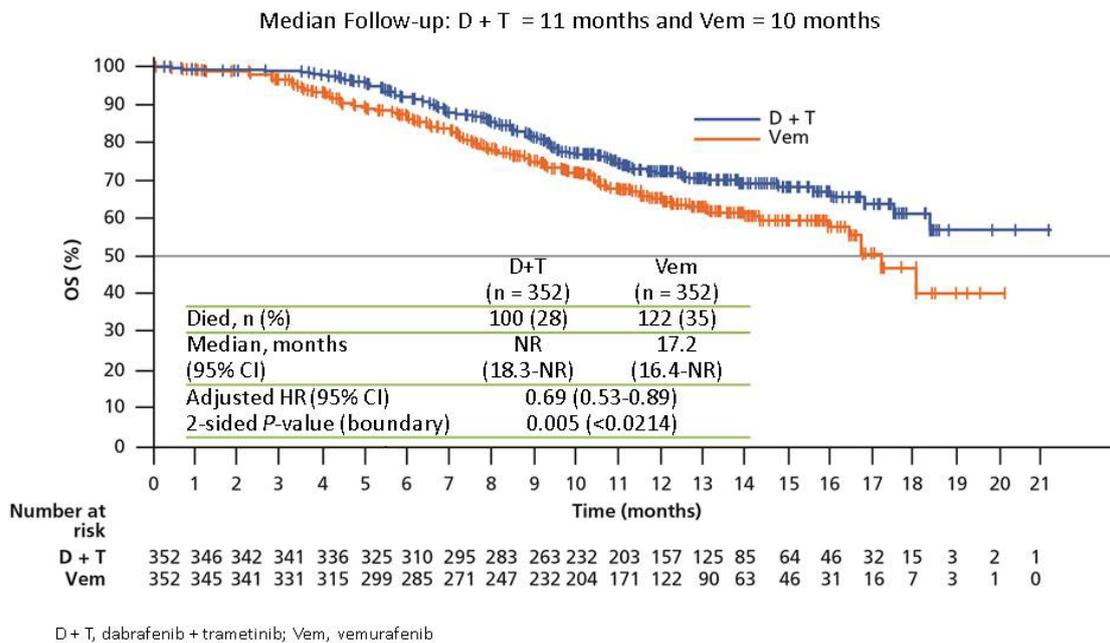
From June 2012 to October 2013, 1644 patients were screened and 704 patients were randomised (352 patients in each arm).

A pre-specified interim OS analysis was planned when 70% (202 of 288) of the total number of expected deaths, required for the protocol-specified final analysis, are observed. The study could be stopped for efficacy if the one-sided p value was < 0.0107 . However, due to data entry lag, there were 222 (77%) observed death events at data cut-off.

It was pre-specified that if the Independent Data Monitoring Committee (IDMC) recommends stopping at interim, interim analysis would become the final one.

The IDMC recommended stopping the study based on an interim analysis which demonstrated an OS benefit that crossed the pre-specified efficacy stopping boundary for dabrafenib/trametinib combination. At the time of analysis, the median OS was not reached in the dabrafenib/trametinib arm and 17.2 months in the vemurafenib arm (HR 0.69, $p = 0.002$). The OS data in subgroup analysis favoured the dabrafenib/trametinib arm.

COMBI-v: Overall Survival



Caption: First-line combination therapy dabrafenib plus trametinib improves OS compared to vemurafenib in patients with BRAF V600E/K mutation-positive melanoma. © Caroline Robert

The PFS was 11.4 vs. 7.3 months in favour of the dabrafenib/trametinib arm (HR 0.56, $p < 0.001$). Difference in best confirmed RR was 13% among the two study arms, again in favour of dabrafenib/trametinib treatment ($p < 0.001$). The DoR was 13.8 months in the dabrafenib/trametinib arm and 7.5 months in the vemurafenib arm.

Rates of adverse events were generally similar in both arms and consistent with data from previous trials. However, all grades and grade 3 of arthralgia, rash, alopecia, hyperkeratosis, photosensitivity and skin papilloma were present more among patients treated with vemurafenib. Grade 3 pyrexia was present more in the dabrafenib/trametinib arm.

Among BRAF inhibitor-related adverse events, cutaneous small-cell carcinoma and keratoacanthoma, hyperkeratosis, skin papilloma, hand-foot syndrome, alopecia, photosensitivity plus sunburn, and non-cutaneous malignancy were present more in the vemurafenib arm.

Among MEK inhibitor-related adverse events, decrease in ejection fraction was present more in the dabrafenib/trametinib arm.

Dr Robert concluded that dabrafenib/trametinib vs. vemurafenib resulted in significant improvement in OS for combination treatment with 31% reduction in the risk of death (median OS not reached for combination vs. 17.2 months in the vemurafenib arm) and significant improvement in PFS for combination treatment with 44% reduction in the risk of progression or death (median PFS of 11.4 months for combination vs. 7.3 months for vemurafenib treated patients).

Dr Christian Blank of the The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands, who discussed the study results, said that N-RAS mutation was discovered in 1985, loss of CDKN2 in 1994, PTEN loss in 1997, B-RAF mutation in 2002, CSK4 mutation in 2005, c-KIT mutation in 2006, GNAQ mutation in 2009, and erbB4 mutation in 2009.

Among these genetic changes observed in melanoma, the oncology community was excited with findings from 2009 coming from phase 1 study of BRAF inhibition in advanced melanoma and fast induced responses. After this, he spoke about the rationale for dual targeting of the MAPK pathway.

The observed response rate in the COMBI-v study was 64% with 13% CRs and 51% PRs, SD was observed in 26% of patients. Median PFS was 7.3 months and OS was 17.2 months. COMBI-v confirms improved efficacy for combinations of BRAF inhibitor and MEK inhibitor therapies as compared to single BRAF inhibition in BRAFV600 mutant melanoma. This combination leads to decreased toxicity occurring from paradoxical MAPK pathway activation in BRAF wild-type cells. Dabrafenib and trametinib toxicity is similar to the toxicity observed from single treatment. If the mature data confirm the presented observations BRAF and MEK inhibition would be the new standard targeted therapy in BRAFV600 melanoma.

Dr Blank questioned why gaining 4 months of PFS translated only into 2 months of OS benefit. In addition, he asked what kind of pricing this OS benefit will justify.

The study describes investigational use of dabrafenib/trametinib combination and was funded by GlaxoSmithKline.

Reference

[LBA4 PR: COMBI-v: A randomised, open-label, phase III study comparing the combination of dabrafenib \(D\) and trametinib \(T\) with vemurafenib \(V\) as first-line therapy in patients \(pts\) with unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma](#)

Results of a phase III study of cobimetinib in combination with vemurafenib in previously untreated patients with BRAFV600 mutation-positive melanoma

coBRIM, a phase III, double-blind, placebo-controlled study of vemurafenib vs. vemurafenib plus cobimetinib in previously untreated patients with BRAFV600 mutation-positive unresectable locally-advanced or metastatic melanoma met its primary endpoint. Cobimetinib in combination with vemurafenib significantly improved PFS among patients with BRAFV600-mutant tumours. The results were reported by Prof. Grant McArthur of the Peter MacCallum Cancer Centre, Melbourne, Australia.

Combined inhibition of BRAF and MEK is hypothesised to improve clinical outcomes by preventing or delaying the onset of resistance observed with BRAF inhibitors alone. The most common mechanism of acquired resistance to vemurafenib is MAPK reactivation through MEK. MEK plus BRAF inhibition prevents the development of acquired resistance in preclinical models. Dabrafenib plus trametinib in phase III and vemurafenib plus cobimetinib in phase I/II study improved RRs and PFS in BRAF inhibitor-naïve melanoma patients. Reduced incidence of hyperproliferative lesions is seen by blocking paradoxical activation of the MAPK pathway from RAF inhibition.

This randomised phase III study evaluated the combination of the BRAF inhibitor vemurafenib and the MEK inhibitor cobimetinib. Cobimetinib is an oral, small molecule, highly selective, allosteric inhibitor of MEK.

Between January 2013 and January 2014, 495 patients were randomly assigned (1:1) to receive vemurafenib/cobimetinib or vemurafenib/placebo.

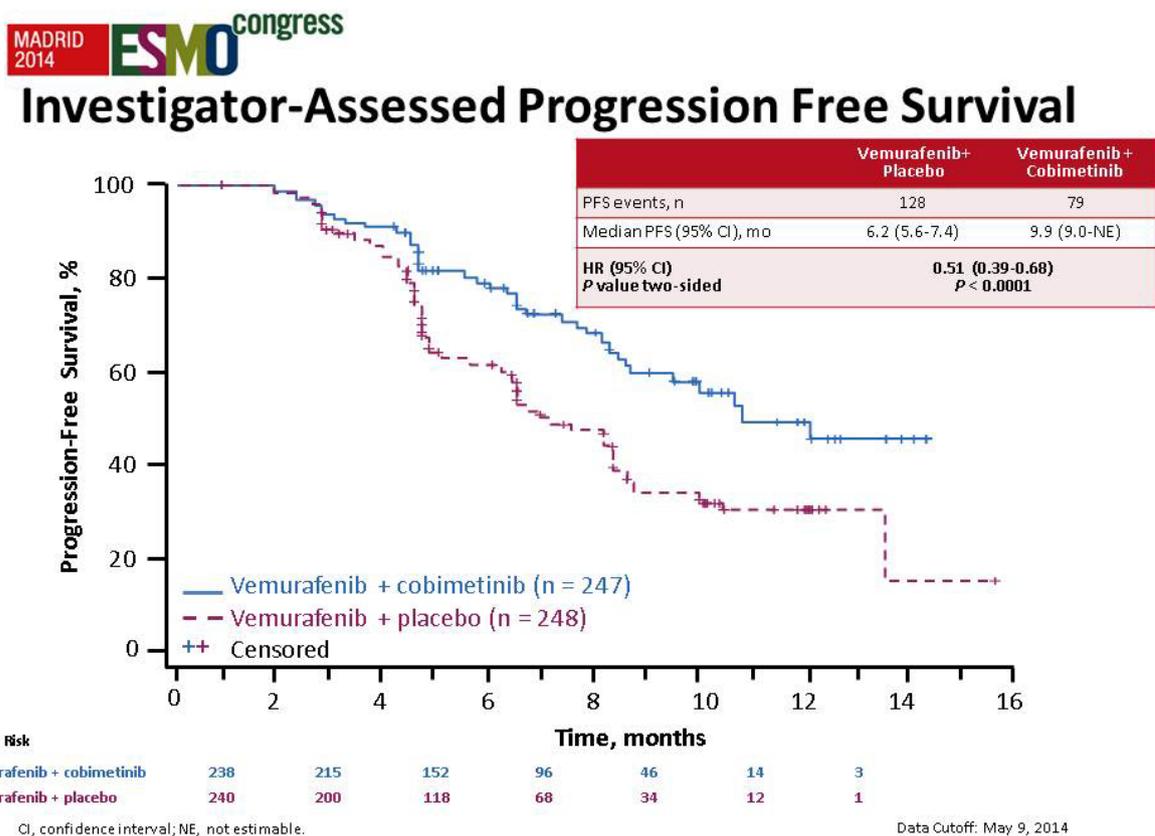
The study eligibility criteria included treatment-naïve patients with BRAFV600 mutation–positive (detected by cobas® 4800) unresectable locally-advanced or metastatic melanoma, adequate PS and organ function, and no prior therapy for advanced disease. The treatment was given until disease progression, unacceptable toxicity, or withdrawal of consent. The patients were stratified by geographic region and extent of disease (M1c vs. other).

The primary endpoint was investigator-assessed PFS. Secondary endpoints included OS, ORR, DoR, PFS assessed by Independent Radiology Committee (IRC), safety, pharmacokinetics, QoL assessed by QLQ-C30 and EQ-5.

Statistical assumptions were 95% power to detect an improvement in median PFS from 6 to 11 months (HR 0.55) and 80% power to detect an improvement in median OS from 15 to 20 months (HR 0.75).

Patient characteristics were well balanced, except PS 1 which was slightly higher in the vemurafenib plus placebo arm.

Prof. McArthur reported that median investigator-assessed PFS was 9.9 months with the combination compared with 6.2 months in the control arm (HR 0.51; $p < 0.0001$).



Caption: The MEK inhibitor cobimetinib in combination with the BRAF-inhibitor vemurafenib improves PFS compared to vemurafenib alone in patients with BRAFV600-mutated melanoma. © Grant McArthur

Investigators-assessed PFS based on key demographic and tumour characteristics were consistent with PFS in the ITT population. The PFS assessed by independent review was comparable with investigator-assessed PFS (11.3 months vs. 6.0 months, HR 0.60, $p = 0.0003$).

The rate of CR and PR was 68% in the combination arm and 45% in the vemurafenib arm ($p < 0.0001$), including CR in 10% of patients treated with the combination and 4% of patients in the vemurafenib group.

The 9 months OS rate was 81.1% in the combination arm vs. 72.5% in the vemurafenib arm (HR 0.65, $p=0.046$).

Vemurafenib/cobimetinib combination, compared with vemurafenib alone, was associated with a higher incidence of grade ≥ 3 adverse events (65% vs. 59%). However, there was no difference in the rate of adverse events leading to study drug discontinuation.

The study investigators found a decrease in the occurrence of secondary cutaneous neoplasms with the combination treatment.

The rate of grade 1 and 2 serous retinopathy (includes specific terms chorioretinopathy and retinal detachment) was higher in the cobimetinib/vemurafenib arm, but there were no cases of retinal veinocclusion reported. In the combination arm, there was also higher rate of grade 2 of decreased ejection fraction.

Prof. McArthur concluded that the coBRIM study provides clear and definitive evidence that combined BRAF and MEK inhibition results in improved clinical outcomes. The combination of vemurafenib plus cobimetinib vs. vemurafenib alone resulted in 49% reduction in risk of progression. Interim OS showed a reduction in risk of death of 35%. The study is ongoing to evaluate mature OS.

Prof. McArthur said that the study results are being published simultaneously with the presentation at the ESMO 2014 Congress in the New England Journal of Medicine.

Dr Christian Blank of the The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands, who discussed the study results, congratulated the authors and said that confirmed objective response of 68% as well as CR rate of 10%, PR rate of 58% and SD seen in 20% of patients in the coBRIM study are in line with the results from other dual-MAPK targetting. The resemblance between the arms in the coBRIM study showed a higher ECOG PS 0 rate in vemurafenib and cobimetinib treated patients. The PFS and OS were more favourable in the vemurafenib and cobimetinib arm. However, OS data were immature at the time of presentation.

coBRIM confirms improved efficacy for combinations of BRAF inhibitor and MEK inhibitor as compared to single BRAF inhibition in BRAFV600 mutant melanoma. The combination therapy leads to decreased toxicity occurring from paradoxical MAPK pathway activation in BRAF wild-type cells. Vemurafenib and cobimetinib toxicity is similar to the toxicity observed from single treatment. If the mature data confirm the presented observations, BRAF and MEK inhibition would be the new standard targeted therapy in BRAFV600 melanoma.

The coBRIM study was sponsored by F. Hoffmann-La Roche, Ltd. Cobimetinib is being developed by Genentech, Inc, a member of the Roche Group, under a collaboration agreement with Exelixis.

Reference

[LBA5 PR: Phase 3, double-Blind, placebo-controlled study of vemurafenib versus vemurafenib + cobimetinib in previously untreated BRAFV600 mutation-positive patients with unresectable locally advanced or metastatic melanoma \(NCT01689519\)](#)

Results of a phase III randomised study of nivolumab in patients with advanced melanoma after prior anti-CTLA4 therapy

In patients with metastatic melanoma who progressed on or after anti-CTLA-4 therapy and treatment with BRAF inhibitors in the case of BRAF mutation positive disease, nivolumab was well tolerated and showed a higher ORR when compared with investigator's choice chemotherapy. Durable tumour regression was observed in the majority of responders to nivolumab. The results of a phase III randomised, open-label study were presented by Prof. Jeffrey Weber of Lee Moffitt Cancer Center & Research Institute, Tampa, USA.

Effective therapies are needed for patients with melanoma who progress on or after anti-CTLA-4 therapy and a BRAF inhibitor.

Nivolumab is a fully human IgG4 monoclonal antibody that inhibits the PD-1 immune checkpoint protein. In early studies, single-agent nivolumab demonstrated meaningful clinical activity and a manageable safety profile in pretreated patients with advanced melanoma with promising OS rates of 63%, 48%, and 41% observed at 1, 2, and 3 years, respectively.

In this phase III open-label trial, patients with advanced melanoma who progressed on or after anti-CTLA-4 therapy and a BRAF inhibitor in case of BRAF V600 mutation positive disease were randomised 2:1 to receive nivolumab (268 treated patients) or investigator's choice chemotherapy (dacarbazine, or carboplatin plus paclitaxel) (102 treated patients) until progression or unacceptable toxicity. Patients receiving nivolumab may be treated beyond initial progression if considered by the investigator to be experiencing clinical benefit.

Patients were stratified by PD-1 ligand expression status (PD-L1 positive vs. PD-L1 negative/indeterminate; PD-L1 positive status was defined as $\geq 5\%$ tumour cell surface staining cut-off by IHC); BRAF status (BRAF wild-type vs. BRAF V600 mutant); and best overall response to prior anti-CTLA-4 therapy (clinical benefit defined as best overall response that included CR/PR/SD) vs. no clinical benefit (progressive disease).

Exclusion criteria were active brain metastases; prior therapy with anti-PD-1, anti-PD-L1 or anti-PD-L2 antibodies; grade 4 toxicity or use of infliximab to manage adverse events from prior ipilimumab treatment and ocular melanoma.

Co-primary endpoints were ORR by independent radiology review committee and OS. Secondary objectives included to compare PFS of nivolumab to investigator's choice chemotherapy at the time of OS analysis and to evaluate PD-L1 expression as a predictive biomarker for ORR and OS. However, OS analysis had not taken place at the time of interim ORR analysis.

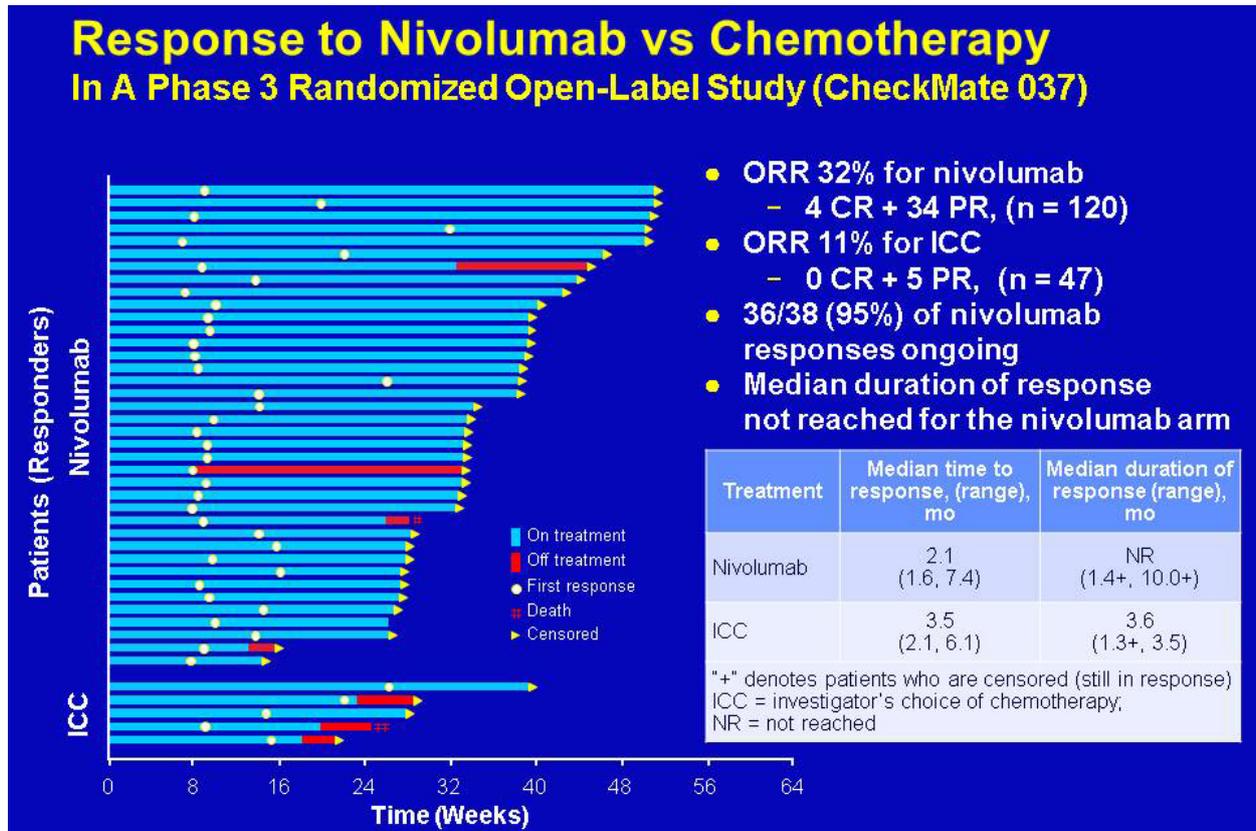
Response according to RECIST v1.1 criteria was assessed 9 weeks after randomisation, followed by 6 week assessments for the first 12 months and then by assessments every 12 weeks.

The ORR was assessed as planned in the first 120 patients treated with nivolumab and 47 patients who received investigator's choice chemotherapy with follow-up of at least 6 months.

Baseline age, sex and metastasis stage were balanced between the arms. However, there were slightly more patients with a history of brain metastasis and elevated LDH in the nivolumab arm.

Median time on therapy was 5.3 months in the nivolumab arm and 2 months in the investigator's choice chemotherapy arm. Disease progression was the most common reason for discontinuation in the nivolumab (43%) and investigator's choice chemotherapy arms (61%).

Confirmed ORR by independent radiology review committee in nivolumab and patients treated with investigator's choice chemotherapy was 32% and 11%, with a median time to response of 2.1 months (range: 1.6, 7.4) and 3.5 months (range: 2.1, 6.1), respectively.



Caption: Response to nivolumab vs. chemotherapy. © Jeffrey Weber

Median DoR for nivolumab was not reached (range: 1.4+, 10+ months) with 36 (95%) patients being still in response. Median DoR in patients treated with investigator's choice chemotherapy was 3.6 months (range: 1.3+, 3.5) with 4 (80%) patients still in response.

Consistently higher clinical activity was observed for nivolumab vs. investigator's choice chemotherapy regardless of pre-treatment PD-L1 expression status, BRAF mutation status and prior anti-CTLA-4 benefit.

Reduction of $\geq 50\%$ in target lesion burden occurred in 82% (31/38) of nivolumab responders and 60% (3/5) of responders in the investigator's choice chemotherapy arm. Among nivolumab-treated patients, an additional 10 (8%) patients had immune-related response patterns observed ($\geq 30\%$ reduction in target lesion tumour burden).

Grade 3-4 drug-related adverse events were seen in 9% and 31% of patients treated with nivolumab and investigator's choice chemotherapy, respectively. Discontinuations due to drug-related adverse events of any grade occurred in 2% and 8% of treated patients, respectively. No drug-related grade 3-4 adverse events were reported in $\geq 2\%$ of nivolumab treated patients. All grade 3-4 drug-related adverse events belonging to the select adverse event categories resolved. Corticosteroids were the most common immunosuppressive medication used.

There were no deaths related to study drug toxicity. One patient in the nivolumab group experienced grade 5 hypoxia, possibly pneumonitis, in the setting of lymphangitic spread and

possible pneumonia; this patient's cause of death was classified by the investigator as 'other' rather than 'study drug toxicity'.

The study authors concluded that in patients with advanced melanoma who have progressed despite anti-CTLA-4 therapy and BRAF inhibitors if BRAF is mutated, nivolumab monotherapy demonstrated superior efficacy to investigator's choice chemotherapy. The majority of nivolumab treatment-related adverse events were of a low grade and manageable using recommended treatment algorithms. Co-primary endpoint (OS) data was pending at the time of presentation.

Dr Ignacio Melero of the Clinica Universitaria de Navarra, Pamplona, Spain, who discussed the study results, said that immunotherapy of cancer is no longer a quixotic goal. In his talk, Dr Melero highlighted the recent approvals of nivolumab in Japan and pembrolizumab in USA for the treatment of advanced melanoma. He further said that chemotherapy might be eliminated as an option in BRAF wild-type disease but the clinical trials are important because the best is yet to come. This is particularly true for combination therapy. In terms of biomarker analysis from tumour biopsy, antigenicity, immunogenicity, immune escape, and T-cell infiltrates should be considered. PD-L1 as single parameter is not good enough, according to Dr Melero. The scenario might be going towards a multiparameter scores (including tumour PD-L1 status). The highest number of mutations in solid tumours is observed in melanoma and NSCLC with lower frequencies in other tumour type and in that regard, melanoma remains at the top of the iceberg.

The study was supported by Bristol-Myers Squibb, Ono Pharmaceutical Company, Ltd. and Dako for collaborative development of the automated PD-L1 IHC assay.

Reference

[LBA3 PR: A phase 3 randomized, open-label study of nivolumab \(anti-PD-1; BMS-936558; ONO-4538\) versus investigator's choice chemotherapy \(ICC\) in patients with advanced melanoma after prior anti-CTLA-4 therapy](#)

Randomised, double-blind study of sonidegib (LDE225) in patients with advanced basal cell carcinoma

Prof. Reinhard Dummer of the Universitätsspital Zürich, Switzerland reported that sonidegib demonstrates clinically meaningful tumour shrinkage, sustained responses, and prolonged PFS in patients with advanced basal cell carcinoma. Reduced GLI1 levels vs. baseline were seen in patients with disease control.

The BOLT phase II study, comparing two doses of sonidegib, a hedgehog (Hh) pathway inhibitor, in patients with advanced basal cell carcinoma, met its primary endpoint of ORR $\geq 30\%$ in both arms in analyses of data collected up to 6 months after randomisation of the last patient. Median follow-up was 13.9 months for data presented at ASCO 2014. Associations of GLI1 (marker of Hh pathway activation) with clinical outcome and updated 12 months efficacy and safety data were presented at ESMO 2014.

Patients with locally advanced basal cell carcinoma (194 cases) not amenable to curative surgery or radiation, or metastatic basal cell carcinoma (36 cases) were randomised 1:2 to receive sonidegib 200 or 800 mg daily. Clinical response was assessed by central review using modified RECIST for locally advanced basal cell carcinoma or RECIST v1.1 for metastatic basal cell carcinoma. Exploratory analyses in a subset of patients (137 with locally advanced basal cell

carcinoma and 13 with metastatic basal cell carcinoma) assessed GLI1 levels in tumour tissue collected at baseline, week 9, and week 17.

GLI1 levels decreased from baseline with both doses at week 9 and 17 ($p < 0.0001$) and in patients with disease control (CR, PR, SD). Median % changes with 200 mg at week 17 by response were -99.47 for CR; -90.79 for PR; -96.58 for SD; +10.19 for PD; and for unknown -94.24. With an additional 6 month follow-up, median exposure duration was 11.0 (200 mg) and 6.6 month (800 mg). Half of patients with locally advanced basal cell carcinoma in the 200 mg arm responded, and tumour responses in both arms were durable.

The safety profile of sonidegib was typical of Hh pathway inhibitors. The 200 mg dose had a better benefit-risk profile. The most common adverse events (200/800 mg) were muscle spasms in 52% of patients in the 200 mg arm and 69% patients in the 800 mg arm, alopecia in 49% patients in the 200 mg arm and 57% patients in the 800 mg arm, and dysgeusia in 41% patients in the 200 mg arm and 60% patients in the 800 mg arm.

The 200 mg dose has been selected for future use based on its more favourable benefit-risk profile.

The study was sponsored by Novartis.

Reference

[LBA33: Randomized, double-blind study of sonidegib \(LDE225\) in patients \(pts\) with advanced basal cell carcinoma \(BCC\)](#)

Neuroendocrine Cancers

Everolimus for the treatment of advanced pNET: Final OS results of a randomised, double-blind, placebo-controlled, multicenter phase III trial

Prof. James Yao of the University of Texas MD Anderson Cancer Center, Houston, USA reported that everolimus demonstrated a median OS of 44 months, the longest OS reported for progressive advanced pancreatic neuroendocrine tumors (pNET) patients in a phase III study. A clinically important improvement of 6.3 months in median OS vs. placebo was observed in RADIANT-3 study, although the difference did not reach statistical significance. Crossover of majority of patients (85%) may also have confounded OS. The safety of everolimus was consistent with previous experience.

Everolimus significantly improved median PFS vs. placebo in patients with pNET by 6.4 months in RADIANT-3 study (11.0 vs. 4.6 months; HR 0.35, $p < 0.001$). At ESMO 2014, the study researchers presented final OS results and safety findings.

Patients with progressive advanced, low- or intermediate-grade pNET were randomised to everolimus (207 patients) or placebo (203 patients), both with best supportive care. Upon disease progression during double-blind phase, crossover from placebo to open-label everolimus was allowed. At the time of unblinding, all ongoing patients transitioned into the extension phase to receive open-label everolimus. After 256 events, OS analysis was performed in the ITT patient population (410, all randomised patients).

Of 410 patients, 225 switched to open-label everolimus; including 85% of patients initially randomised to placebo (172 of 203). Median open-label everolimus exposure was 67.1 weeks in patients initially randomised to everolimus and 44.0 weeks in patients randomised to placebo.

Median OS was 44.0 months for the everolimus arm and 37.7 months for the placebo arm (HR 0.94, log rank $p = 0.30$; significance boundary 0.0249). The overall survival HR adjusted for for pre-specified baseline covariates including age, gender, region, and prior somatostatin analogue use was 0.90.

With a high crossover rate of 85%, the conventional ITT analysis approach likely underestimated the treatment effect on OS. A rank preserving structural failure time model corrected for the effect of crossover by estimating the multiplicative factor effect of each day of everolimus treatment on OS and subsequently adjusting for effect of everolimus received after crossover in the placebo arm. The rank-preserving structural failure time analysis adjusting for crossover bias showed a survival benefit with everolimus. Estimated OS rates were 82.6% vs. 74.9% at 12 months and 67.7% vs. 55.6% at 24 months.

The safety profile of everolimus observed during open label extension was similar to the known safety profile of everolimus and similar to those observed during double blind phase. The most common adverse event was stomatitis or aphthous ulceration. It occurred among 54% of patients receiving everolimus during double blind phase vs. 13% of patients receiving placebo. This was similar at 47% during the open-label extension phase. The rate of grade 3/4 stomatitis was 4.9% during double blind phase and 2.2% in the open label extension phase. Of note, in a recent meta-analysis of phase III studies with everolimus that included RADIANT3, development of stomatitis

within 8 weeks of treatment start was associated with longer PFS compared those without stomatitis.

Dr Alexandria Phan of the Methodist Cancer Center and Weill Cornell Medical College, Houston, USA, who discussed the study results, said that crossover in randomised clinical trials leads to underestimation of true clinical gain in OS, if the experimental drug has benefit over placebo/control. Even the more complex methods such as rank-preserving structural failure time have important limitations, especially with inaccurate assumptions and increasing crossover percentage. Crossover of 85% of patients from the placebo arm to open-label everolimus likely confounded OS results. However, survival benefit with everolimus is 44 months, at least 6.3 months longer than placebo and at most 23.4 months longer than placebo.

The study was funded by Novartis Pharmaceuticals Corporation.

Reference

[1132O: Everolimus \(EVE\) for the treatment of advanced pancreatic neuroendocrine tumors \(pNET\): Final overall survival \(OS\) results of a randomized, double-blind, placebo \(PBO\)-controlled, multicenter Phase III trial \(RADIANT-3\)](#)

Public Health and Health Economics

Risk of incremental toxicities and associated costs of new anticancer drugs

Dr Saroj Niraula of the CancerCare Manitoba MacCharles, Winnipeg, Canada said that newly approved anticancer drugs are associated with increased toxicity and management of toxicity leads to an increase in overall cost of treatment except when agents with a specific molecular target on cancer cells are used. Adopting policy to encourage development of biomarker-driven drugs is encouraged. Frequency of toxicity and associated costs are likely higher in less selected patients treated in general oncologic practice.

The aim of this meta-analysis was to quantify the frequency of serious toxicities caused by new anticancer drugs and incremental costs associated with their management, according to the type of anticancer drugs.

The researchers identified anticancer drugs approved by the US Food and Drug Administration (FDA) during 2000-2011, and pivotal trials supporting their registration. Twelve frequent, grade III-IV adverse events were weighted and pooled in a meta-analysis to obtain both relative and absolute excess risk in experimental groups compared to the control groups of the registration trials. Estimates of incremental drug prices and costs for management of adverse events were calculated according to types of new agents based on target-specificity of the new drugs and activity of comparator groups used in the pivotal trials. Costs were derived from pharmacy "red book" and literature, adjusted for inflation to reflect 2014 dollar value.

The study team identified 41 studies with 27,500 patients involving 19 drugs. Agents directed against a specific molecular target on cancer cells had a lower incidence of grade III-IV toxicities than the controls, median relative risk 0.7, $p = 0.2$; whereas less-specific targeted agents, including angiogenesis inhibitors (median relative risk 3.4, $p < 0.001$), and chemotherapeutic agents (median relative risk 1.6, $p < 0.01$) were more toxic. Risk was increased regardless of whether the control arm contained active treatment (relative risk 2.1, $p < 0.001$) or not (relative risk 3.0, $p < 0.001$).

Median incremental drug-price for experimental agents was 6000 dollars/patient/month. Median cost of managing adverse events was decreased in the experimental arm compared to the control for specifically targeted agents but this was persistently higher than controls across all 12 adverse events for less-specific targeted agents and chemotherapy. Sensitivity analyses performed using broader hypothetical range strengthened the findings.

However, Dr Niraula reported the study limitations: they only used published data and toxicities are underreported in published clinical trials, information on recurring adverse events are usually not clear in clinical trial reports, they did not consider low grade adverse events, sources of cost of toxicity were heterogeneous and such cost is sensitive to local healthcare market. Therefore, the data on toxicity are likely to be underestimates of the true cost.

Dr Josep Borràs of the Institut Català d'Oncologia Hospital Duran i Reynals, Barcelona, Spain, who discussed the study results, said that median incremental drug price was higher in the experimental drug than in the control group for less specific target drugs and for chemotherapy. This work allowed analysis of the question of access in a more qualitative way: relevance of safety and risk/benefit ratio of new drugs, as well as impact on health care resources utilisation and cost.

Different drugs showed a higher cost for cancer care. A relevant question is if these differences should be taken into account in the approval process. Drugs are not equal in efficacy but also not in their risk/benefit ratio and in the incremental cost of management of the adverse events associated with new drugs. There is a need for a better alignment between prescribers and regulators in order to assess the quality and contribution of a new drug more consistently.

All authors in this study have declared no conflicts of interest.

Reference

[1386O PR: Risk of incremental toxicities and associated costs of new anticancer drugs: A meta-analysis](#)

Author financial conflicts of interest in clinical practice guidelines for systemic anti-cancer drugs

Dr Ariadna Tibau of the Hospital de la Santa Creu i Sant Pau, Barcelona, Spain said that reporting of financial conflicts of interest (COIs) in clinical practice guidelines (CPGs) and consensus statements has improved in the last decade. However, published expert recommendations may still be influenced by use of medical writers or financial COIs of authors. Author financial COIs are associated with endorsement of specific drugs.

CPGs and consensus statements are used to apply evidence-based medicine or expert recommendations to routine clinical practice. In this study, the researchers explore the prevalence and transparency of self-reporting of financial COIs and their relationship with endorsement of specific drugs.

An electronic search of MEDLINE was conducted to identify CPGs and consensus statements in breast, colorectal, lung and prostate cancer published between January 2003 and October 2013. The search was restricted to English language articles evaluating systemic therapy. When more than one CPG or consensus statement from the same source was identified, the most recent version was evaluated. Particular attention was paid to collecting data on self-reporting of funding sources, author financial COIs and involvement of manuscript writers who were not listed as authors. The association between endorsement of a specific drug in the abstract of the guideline and author financial COIs with the company marketing that drug was evaluated.

In total, 142 articles were evaluated; 64% were CPGs and 36% were consensus statements. In total 41% of articles addressed breast cancer, 20% CRC, 25% lung cancer, 11% prostate cancer and 3% more than one tumour type. Only 45% of articles explicitly reported funding sources and of these, 65% disclosed partial or full industry sponsorship. Use of medical writers was declared in 13%, but among the other articles, only 17% of articles explicitly reported that authors were involved in the writing and final approval of the manuscript.

Author financial COIs were declared in 45% of articles, 23% affirmed no financial COIs and 31% did not include disclosures of financial COIs. The proportion of articles reporting financial COIs increased from 11% in 2003 to 93% in 2013. There was a significant association between financial COIs of any author and endorsement of specific drugs ($p = 0.001$). Similar results were obtained when analysis was limited to first, senior or corresponding author ($p = 0.01$).

Further research is needed to improve published standards for guideline development.

All authors have declared no conflicts of interest.

Reference

[1385O: Author financial conflicts of interest \(FCOIs\) in Clinical Practice Guidelines \(CPGs\) for systemic anti-cancer drugs](#)

Cross-comparison of cancer drug approvals among international regulatory bodies

Dr Nardin Samuel of the Sunnybrook Odette Cancer Centre, Toronto, Canada reported findings from the first study to systematically compare cancer drug approvals between three major regulatory bodies. The researchers anticipated that the differences in drug approval times can create a dialogue between clinicians and government agencies to understand the current challenges in approval processes and work jointly towards improving them.

The therapeutic care of cancer patients is significantly impacted by timely access to drugs that improve survival and overall patient outcomes. The key objective of this study was to examine the drug approval process and time to approval by three international regulatory bodies – Health Canada, US FDA and European Medicines Agency (EMA).

The publicly available Health Canada Drug Product Database was surveyed for all currently marketed anti-neoplastics approved between 1 January, 2005 and 1 June, 2013. For this set of cancer drugs, data was obtained on submission and approval dates by Health Canada, FDA and EMA and time to approval were calculated from the dates of initial drug submission filing to final approval for marketing.

Using Health Canada as a comparative benchmark, the study team identified 41 antineoplastic agents that met the study criteria. Overall, the time to approval was significantly less for the FDA when compared with the EMA (6.0 months, $p < 0.001$) and Health Canada (7.6 months, $p < 0.001$). There was no overall significant difference in time to approval between Health Canada and the EMA (3.43 months, $p = 0.446$).

Azactidine, approved for haematological malignancies, had the greatest delay (66.1 months) between FDA and Health Canada approval. The EMA approved azactidine 10.3 months earlier than Health Canada but 55.8 months following FDA approval. Among all drugs assessed cabazitaxel, approved for metastatic prostate cancer, was associated with the shortest time to approval by the FDA at only 17 days. In Canada and Europe, the time to approval for cabazitaxel was 11.63 months and 11.03 months, respectively.

Regarding drug approval timelines, on average, cancer drugs are approved by the FDA 20.6 months earlier than Health Canada. The EMA approves cancer drugs an average of 10.0 months earlier than Health Canada, while the FDA approvals are an average of 24.9 months earlier than the EMA.

Dr Samuel stated that the analysis was limited by the consideration of only initial drug approvals in Canada and not supplementary drug approvals, which constitute a large portion of cancer drug approvals. Indeed, the trends observed may be different when considering time to supplementary drug approval once the drug has initially been given regulatory approval. Approval times are not the only dimension to drug access. Cancer drug approval times may not necessarily precede swift regulation of drug costs and coverage, yet early approval times are a salient aspect of drug access.

Dr Josep Borrás of the Institut Català d'Oncologia Hospital Duran i Reynals, Barcelona, Spain, who discussed the study results, said that FDA approved drugs an average of 24.9 months earlier than EMA. Also, EMA approves cancer drugs an average of 10.0 months earlier than Health Canada. Benchmark as a method focused in this study on two variables (time to approval and timelines), but in reality there are relevant differences in other key aspects, such as health care services organisation, reimbursement systems, price negotiations between industry and regulators (also, among EU countries), societal values, and we should not forget that we are not comparing similar countries.

Access to cancer therapies is defined as a timely use of personal health services to achieve the best possible health outcomes. Relevant factors associated with access are attributes of health systems (coverage of health care, geographic access, coordination among levels of care, reimbursement), patients (perception of benefit, information available), and physicians (knowledge, expertise). Differences according to socio-economic level, residence of patient, reimbursement systems are widely found. Access to cancer drugs is an essential factor in high quality cancer care, but pressure for cost containment in health care systems runs up against ensuring affordable access to new cancer drugs.

Policy issues not considered in the study, but relevant at country level are after regulatory approval at national or EU level, price negotiation and funding evaluation for reimbursement from national health system, regional and hospital level (approval for local drug formularies) in several countries. Access to cancer drugs is an essential factor in high quality cancer care, but access should be timely to high quality cancer care, not only to cancer drugs. High quality cancer care is a multidisciplinary activity involving diagnosis, surgery, radiotherapy and chemotherapy in many cancer patients. In this study access to cancer drugs measured by time to approval showed clear differences related to health care systems.

All authors in this study have declared no conflicts of interest.

Reference

[10360 PR: Cross-comparison of cancer drug approvals among international regulatory bodies](#)

Sarcoma

Pazopanib improves PFS in phase II study in patients with advanced GIST

The results of PAZOGIST, a randomised phase II study of pazopanib plus best supportive care vs. best supportive care alone in patients with unresectable metastatic and/or locally-advanced gastrointestinal stromal tumours (GIST), who are resistant or experienced toxicity to previous treatments with standard doses of imatinib and sunitinib, show an improvement in PFS in favour of the pazopanib arm. The study was presented by Prof. Jean-Yves Blay of the University Claude Bernard Lyon I, Centre Léon Bérard, Lyon, France.

GIST is the most common mesenchymal neoplasm of the GI tract. In unresectable and metastatic or locally-advanced disease, imatinib followed by sunitinib, then regorafenib represent the standard treatments in first-, second- and third-line treatments, respectively.

Pazopanib is an active treatment in soft tissue sarcomas, but it has never been evaluated in a randomised setting in advanced GIST.

In this open-label, multicentre phase II study, eligible adult patients with adequate organ functions were randomly assigned 1:1 to receive pazopanib plus best supportive care or best supportive care alone. Randomisation was stratified by number of prior drugs (2 vs. ≥ 3). Switch to pazopanib was allowed for patients from the best supportive care arm with a progressive disease.

The primary endpoint was PFS. It was planned to include 80 patients to detect an improvement in the 4 month PFS rate from 15% in the best supportive care arm alone to 45% in the pazopanib plus best supportive care with 5% two-sided α error and 80% power. Secondary objectives included OS, ORR at 4 months, best response rate and tolerance.

It was required that patients have GIST diagnosis documented histologically, measurable disease according to RECIST criteria, ECOG PS ≤ 2 , adequate organ functions, and absence of known contraindication to pazopanib administration.

For data analysis, 42 PFS events were needed, and 80 randomised patients were planned. An interim analysis with a futility stopping rule was planned after a 4 month follow-up of 27 randomised patients.

At the interim analysis in September 2012, based on both efficacy and safety results, the IDMC recommended that study enrollment should be pursued until the targeted sample size.

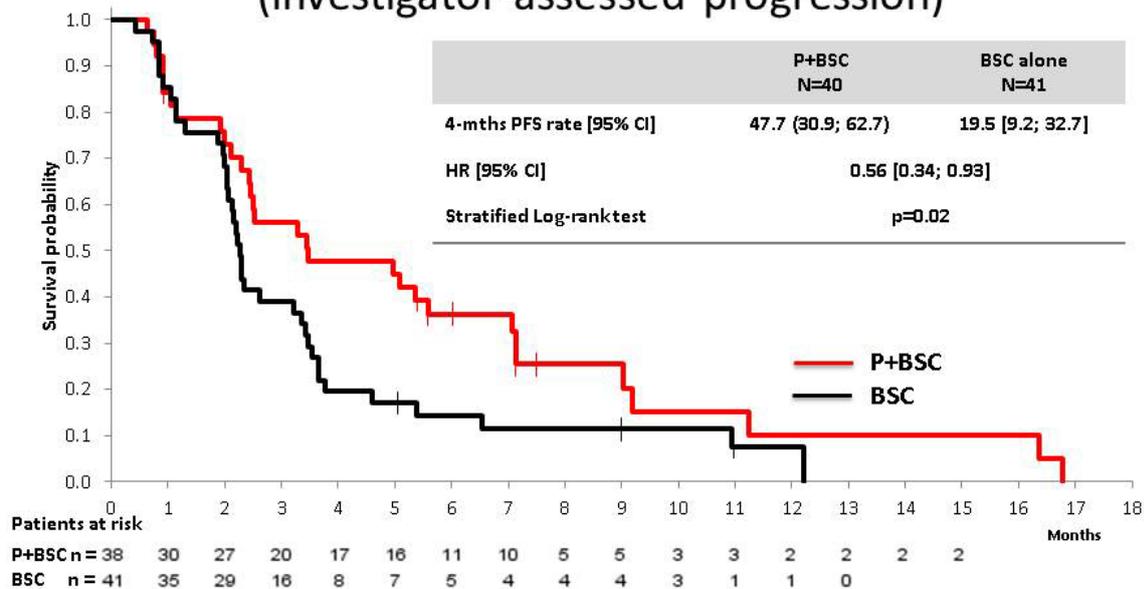
From April 2011 to December 2013, 81 patients were randomised: 40 to the pazopanib plus best supportive care and 41 to the best supportive care alone arm.

Median age was 65 years in the pazopanib plus best supportive care arm and 59 years in the best supportive care arm. The location of the primary in the pazopanib plus best supportive care vs. best supportive care arms were small intestine (35.9% vs. 43.6%), stomach (30.8% vs. 30.8%), colon/rectum (7.7% vs. 5.1%), mesentery (2.6% vs. 2.6%), oesophagus (0% vs. 2.6%) and other (23.1% vs. 15.4%). Regarding disease status at inclusion, there were 30.8% vs. 53.8% of patients with locally-advanced disease in the pazopanib plus best supportive care vs. best supportive care arms, respectively.

The ITT analysis based on investigator-assessed progression showed a significant improvement in PFS with 4 month PFS rate of 47.7% for pazopanib plus best supportive care vs. 19.5% for best supportive care (HR 0.56, stratified log-rank p = 0.02).



Progression-free survival (investigator-assessed progression)



26-30 September 2014, Madrid, Spain

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Caption: Investigator-assessed PFS. © Jean-Yves Blay.

Following progression assessed by investigators, 36 of 41 patients allocated to the best supportive care arm received pazopanib. Median duration from inclusion to switch was 2.2 months and median PFS from date of switch 3.6 months.

The best ORR assessed by central review showed PR in 0% vs. 2.4%, SD in 84.2% vs. 70.7% and progressive disease in 15.8% vs. 26.8% of patients in the pazopanib plus best supportive care and best supportive care arms.

At least one serious adverse event was experienced by 52.5% of patients receiving pazopanib plus best supportive care vs. 14.6% of patients receiving best supportive care alone. In the pazopanib plus best supportive care arm, the most frequent serious adverse events were GI disorders (17.5%), deterioration of global health status (15%) and pulmonary embolism (12.5%).

Prof. Blay concluded that pazopanib deserves further evaluation in this population of patients. When combined with best supportive care, it improves PFS in patients with advanced GIST resistant to imatinib and sunitinib. The 4 month PFS rate was 50% in the pazopanib arm. Toxicity was consistent with that reported with pazopanib in other indications. The OS data will be available at beginning of 2015.

Prof. Stefan Sleijfer of the Erasmus MC Daniel den Hoed Cancer Center, Rotterdam, The Netherlands, who discussed the study results, said that the introduction of imatinib in advanced GIST led to a RR higher than 50%, median OS of 5 years (before imatinib it was 9 months)

and >10% benefits for more than 10 years from first-line imatinib, results that made this cancer a chronic disease. Despite the great success of imatinib, the vast majority of patients develop resistance. Subsequent treatment options based on randomised phase III studies are sunitinib in second-line with a RR of 7% and median PFS of 6-7 months, and regorafenib in third-line with a RR of 5% and median PFS of 4-5 months. Pazopanib is active in non-adipocytic soft tissue sarcoma and targets VEGFR1-3, PDGFR α , and c-KIT.

Prof. Sleijfer further said that based on the results of the PAZOGIST phase II study, a further study of pazopanib is needed. An appropriate design for a subsequent study would be a phase III trial of pazopanib vs. regorafenib in GIST patients failing to imatinib and sunitinib.

He also said that imatinib-treated GIST has transformed from a homogeneous disease with one major tumour driver to a heterogeneous disease with multiple drivers differing in tyrosine kinase inhibition sensitivity. It is unlikely that one drug will induce prolonged SD in majority of patients after imatinib failure, as illustrated by short PFS and low response rate from KIT-targeting agents after failure to imatinib.

New treatment approaches would be combination treatments that are difficult due to toxicity, inhibition of KIT-signaling downstream from KIT, KIT degradation, and individualised treatment based on mutational profile of dominant clone.

For future treatment in GIST after imatinib failure it would be important to identify drugs based on the molecular characteristics of the dominant clone, to monitor molecular evolution of tumour cells during treatment, and to adjust treatment if necessary. The requirements would be to know which KIT mutations causing imatinib resistance respond to other targeting TKIs (sunitinib, regorafenib, pazopanib, sorafenib, nilotinib, masitinib), tools to assess the mutational profile of the dominant clone (ctDNA, molecular imaging), and randomised study in imatinib resistant GIST of traditional treatment (sunitinib followed by regorafenib) vs. treatment based on mutational profiles.

Prof. Sleijfer concluded by stating that it is obvious to the sarcoma community that, in order to address these challenges, global collaboration is needed.

GlaxoSmithKline provided the study drug and research funding for this investigator-sponsored study.

Reference

[LBA45: A randomized multicentre phase II study of pazopanib plus best supportive care \(BSC\) vs BSC alone in metastatic gastrointestinal stromal tumors \(GIST\) resistant to imatinib and sunitinib](#)

Phase II study of imatinib in RECIST progressive desmoid tumours not amenable to surgical resection or accompanied by unacceptable function loss

Prof. Bernd Kasper of the University of Heidelberg, Mannheim University Medical Center, Mannheim, Germany presented results from a study conducted by the German Interdisciplinary Sarcoma Group (GISG). With a 65% progression arrest rate at 6 months after start of treatment, imatinib exceeded the primary study endpoint encouraging further investigation in this histology. Follow-up will continue until the end of the two years treatment duration.

Desmoid tumours are rare monoclonal, fibroblastic proliferations characterised by a variable and often unpredictable clinical course. Surgery is the therapeutic mainstay for progressing patients, except if mutilating and associated with considerable function loss. For advanced disease different treatment approaches have been investigated and promising results could be demonstrated using imatinib.

This phase II trial was initiated with imatinib to induce tumour progression arrest in desmoid tumour patients not amenable to surgical resection with R0 intent or accompanied by unacceptable function loss. Major eligibility criteria were histologically confirmed desmoid tumour showing progressive disease according to RECIST v1.0 within 6 months. Patients were treated with imatinib daily over two years.

Primary endpoint was the non-progression rate after 6 months of treatment. Eleven out of 37 evaluable patients were needed to achieve a positive study result. Accrual started in July 2010 in five GISG centers and was finalised in September 2013.

The final analysis for the primary endpoint showed that 24 out of 37 evaluable patients were progression-free at 6 months of imatinib treatment and reached the primary endpoint. Response assessment after 6 months revealed 1 PR (3%) and 23 SDs (62%). Out of the 13 patients counted as non-successors, 10 patients had documented disease progression (27%). One patient terminated due to toxicity and there were two study withdrawals.

Prof. Stefan Sleijfer of the Erasmus MC Daniel den Hoed Cancer Center, Rotterdam, The Netherlands, who discussed the study results, said that several small studies explored imatinib in desmoids. However, the biological rationale is not that strong, the response rate between 6 and 16%, and PFS data difficult to put into perspective due to indolent growth of the disease. Imatinib is highly likely to induce growth arrest in progressive desmoids. It might have a role in selected patients, but there is a strong need for predictive markers. In this study, translational research considered therapy monitoring using FDG PET to determine early whether patients benefit from imatinib therapy or not, and analysis of mutations in the beta-catenin gene CTNNB1 and correlation with PFS. The results are pending.

The study was funded by Novartis Pharma GmbH.

Reference

[1412O: Phase II study evaluating imatinib to induce progression arrest in RECIST progressive desmoid tumors not amenable to surgical resection with R0 intent or accompanied by unacceptable function loss - a study of the German Interdisciplinary Sarcoma Group \(GISG\)](#)

Outcome of first-line treatment of elderly advanced soft tissue sarcoma patients

Prof. Winette Van der Graaf of the Radboud University Medical Centre Nijmegen, Nijmegen, The Netherlands reported that outcome of elderly patients with advanced soft tissue sarcoma is slightly worse and new strategies are urgently needed in this setting. The results from the pooled analysis of 11 EORTC Soft Tissue and Bone Sarcoma Group trials can be used as benchmark for developing new trials in this age group.

Half of patients diagnosed with soft tissue sarcoma are older than 65 years, yet little data is available about survival of elderly patients with metastatic disease receiving standard chemotherapy.

The researchers evaluated patients who had an indication for systemic treatment because of locally unresectable or metastatic disease. The EORTC database contains information on 2636 patients who did not receive prior chemotherapy and who were treated with doxorubicin, epirubicin, ifosfamide or a combination of doxorubicin and ifosfamide in the context of 11 clinical trials in advanced soft-tissue sarcoma. Of these, 274 patients were older than 65 years. The endpoints of interest for this analysis were OS, PFS and RR.

Median age of elderly patients was 68 years, with a maximum of 80 years. Almost half (49%) had PS 1, 12% had PS of 2 or more; 27% had histological grade 3. The most frequently reported histology was leiomyosarcoma (39%). For 48% of patients disease involved the primary site of origin, 47% had lung metastases, 19% liver metastases, 8% bone metastases and 26% had other metastases.

In total 91 (33%) patients were treated with doxorubicin, 43 (16%) with epirubicin, 26 (9%) with ifosfamide and 114 (42%) with doxorubicin-ifosfamide. Median OS of elderly patients was 9.8 months for doxorubicin, 9.9 months for epirubicin, 9.7 months for ifosfamide, 12 months for doxorubicin-ifosfamide. Median PFS was 2.8 months for doxorubicin, 3.8 months for epirubicin, 2.2 months for ifosfamide and 5.2 months for doxorubicin-ifosfamide. In total 42 (15.4%) patients achieved a response to treatment (CR or PR).

In comparison, median OS of the 2363 patients aged less than 65 (median age 49 years) was 11.5 months for doxorubicin, 11.2 months for epirubicin, 11.1 months for ifosfamide and 13.2 months for doxorubicin-ifosfamide, respectively. Median PFS was 3.5 months for doxorubicin, 2.9 months for epirubicin, 2.8 months for ifosfamide and 6.2 months for doxorubicin-ifosfamide, respectively.

Dr Thomas Brodowicz of the Medical University Vienna, Austria, who discussed the study results, said that it seems that elderly patients are less likely to be treated with adjuvant anthracyclines/ifosfamide. He said that open questions are if this regimen is appropriate as first-line in metastatic disease in elderly and if > 65 years is really considered elderly. Studies in elderly patients with soft-tissue sarcomas are needed with less toxic drug(s) even in first line.

All authors in this study have declared no conflicts of interest.

Reference

[1415O: Outcome of first-line treatment of elderly advanced soft tissue sarcoma \(STS\) patients: a pooled analysis of eleven EORTC Soft Tissue and Bone Sarcoma Group trials](#)

Supportive and Palliative Care

Rolapitant plus granisetron/dexamethasone in prevention of chemotherapy-induced nausea and vomiting

A phase III trial of rolapitant plus granisetron/dexamethasone in patients treated with cisplatin-based chemotherapy revealed good tolerance and superiority in preventing chemotherapy-induced nausea and vomiting (CINV) in comparison with granisetron/dexamethasone alone. The results were presented by Dr Martin Chasen from the Elizabeth Bruyere Hospital Division of Palliative Care, Ottawa, Canada.

Rolapitant is a highly selective, competitive, long acting NK-1 receptor antagonist. Its long half-time (approximately 180 hours) suggests that a single dose may be sufficient to prevent CINV during the entire 5-day (0-120 hours) at periods of risk. A dose of 200 mg achieved >90% NK-1 receptor occupancy in the brain and maintained that level for up to 5 days post a single dose. There is a reduced risk of drug interactions as it is not an inducer or inhibitor of CYP3A4.

Rolapitant demonstrated safety and efficacy of a single oral dose in large global randomised, controlled, double blind studies. It was studied in two phase III trials in patients receiving cisplatin-based highly emetogenic chemotherapy and in one phase III study in patients receiving moderately emetogenic anthracycline-based chemotherapy.

Key inclusion criteria for the study were patients ≥ 18 years of age, of either gender, and of any race, naive to cisplatin-therapy. Cisplatin-based chemotherapy was defined as a dose ≥ 60 mg/m². Key exclusion criteria were patients scheduled to receive any other chemotherapeutic agent with an emetogenicity level of ≥ 4 on Hesketh Scale from day 2 through day 6.

Events of emesis and use of rescue medication were recorded for 5 days.

In this multi-centre, randomised double-blind phase III study, 532 patients were randomised 1:1 to receive oral rolapitant plus granisetron/dexamethasone or placebo plus granisetron/dexamethasone prior to chemotherapy.

The primary endpoint was CR defined as no emesis/no rescue medication in the delayed phase (>24-120 hours post-chemotherapy). Secondary endpoints included safety and tolerability; CR rates during acute (0-24 hours) and overall (0-120 hours) phases post-chemotherapy; incidence of no emesis in the acute, delayed, and overall phases of CINV; incidence of no significant nausea in the overall phase of CINV; and time to first emesis or use of rescue medication. Tertiary endpoints were effect of rolapitant on health-related QoL assessed by the Functional Living Index-Emesis Questionnaire (FLIE); complete protection defined as no emesis, no rescue medication, and maximum nausea VAS <25 mm (scale of 0 to 100 mm) for the Nausea and Vomiting Subject Diary Question 2; and incidence of no significant nausea in acute and delayed phases of CINV.

Demographics were well balanced between rolapitant and control groups with respect to gender, age, tumour type, and CINV risk factors.

The primary objective of this study was achieved with a higher CR rate in the delayed phase compared to placebo (72.7% vs. 58.4%, $p < 0.001$). Statically significant results were also observed in key secondary endpoints of acute phase CR rate (83.7% vs. 73.7%, $p = 0.005$), and overall CR rate (70.1% vs. 56.5%, $p = 0.001$).

Protection from CINV with rolapitant compared to control was observed early and persisted throughout the delayed phase. Treatment effect was initiated in the acute phase at approximately 12 hours following administration of chemotherapy. Time to first emesis or use of rescue medication was longer in rolapitant vs. control group. By days 2–3, the rolapitant curve begins to plateau, indicating these patients are protected for up to 5 days post chemotherapy. In contrast, patients in the control group continued to experience late events of emesis and require rescue medication.

A regional CR analysis was prospectively conducted in North America, Asia/South Africa, Europe, and Central/South America. The CR with rolapitant was observed consistently across geographic regions.

Slightly more patients reported no impact on daily QoL with rolapitant but it was not statistically significant (72.8% vs. 67.8%, $p = 0.231$).

Treatment emergent adverse events were consistent across both arms (0.8% and 3.8%). Constipation and asthenia were most frequently reported treatment emergent adverse events. The majority of treatment emergent adverse events were considered by investigators to be related to chemotherapy or underlying cancer and not to rolapitant.

The authors concluded that the results of this study demonstrate the clinical benefit achieved over the entire CINV at risk period in the rolapitant group.

A new drug application was submitted to the FDA in early September 2014.

Prof. Jorn Herrstedt of the Odense University Hospital, Odense, Denmark, who discussed the study results, agreed on most of the conclusions from the study authors and added that they may have an impact on future antiemetic guidelines. However, in terms of conclusion that mean QoL (total and vomiting domain scores) improved significantly with rolapitant, he questioned if it is clinically relevant. He also said that rolapitant was well tolerated and overall incidences of treatment emergent adverse events were similar to those in the control group suggesting possibly less risk of drug-drug interactions.

The study was funded by Tesaro, Inc.

Reference

[LBA47 PR: Phase 3 \(P04832\) trial results for rolapitant, a novel NK-1 receptor antagonist, in the prevention of chemotherapy-induced nausea and vomiting \(CINV\) in patients receiving cisplatin-based chemotherapy](#)

Oral rivaroxaban for the treatment of symptomatic venous thromboembolism in patients with cancer

Prof. Martin Prins of the Maastricht University Medical Center, Maastricht, The Netherlands reported that rivaroxaban has similar efficacy to enoxaparin/vitamin K antagonist in patients with venous thromboembolism and active cancer or a history of cancer, but it was associated with a significant reduction in major bleeding in patients with active cancer.

The aim of the research was to compare the efficacy and safety of oral rivaroxaban with that of enoxaparin/vitamin K antagonist in patients with cancer among 8282 patients with acute venous thromboembolism enrolled in the EINSTEIN programme.

Patients with cancer and venous thromboembolism constitute a medical challenge for physicians because while anticoagulant treatment can prevent recurrent venous thromboembolism it is associated with a high risk of major bleeding.

EINSTEIN deep venous thrombosis and EINSTEIN pulmonary embolism were randomised, event-driven, non-inferiority, open-label phase III studies. Patients were treated for 3, 6 or 12 months with rivaroxaban or enoxaparin/vitamin K antagonist (international normalised ratio 2.0–3.0) and followed for suspected recurrent venous thromboembolism, bleeding and mortality.

Cancer patients were classified as active cancer at baseline (diagnosis or treatment within 6 months before enrolment or recurrent/metastatic cancer) or diagnosed during the study (655 patients) or a history of cancer (469 patients).

Recurrent venous thromboembolism occurred with a similar incidence in the rivaroxaban and enoxaparin/vitamin K antagonist groups in patients with active cancer (HR 0.67) and patients with a history of cancer (HR 0.98). In patients with active cancer, the risk of major bleeding was significantly reduced in the rivaroxaban group (HR 0.42), whereas it was similar between treatments in patients with a history of cancer (HR 0.23). Mortality occurred with a similar incidence between treatments in patients with active cancer (HR 0.93) and patients with a history of cancer (HR 1.12).

Prof. Prins concluded that rivaroxaban is an alternative to standard therapy when a physician decides against long-term low molecular weight heparin. A head-to-head comparison of rivaroxaban with low molecular weight heparin in patients with cancer and venous thromboembolism is warranted.

Following the presentation, the study was published in the Lancet Haematology.

Dr Florian Scotte of the Georges Pompidou European Hospital, Paris, France, who discussed the study results, said that in general physicians tend to under-report patients' subjective toxicities. In this analysis, toxicity rates reported by physicians were always lower than those reported by patients. Under-reporting by physicians was high ranging from 54.2% to 80.2% of cycles when patients reported "any severity" toxicity and ranging from 22.2% to 62.1% examining only cycles when patients reported "very much" toxicity. He questioned the assessment quality in research, toxicity assessment, high level of toxicity, subjective vs. objective toxicity, assessment inside vs. outside hospital, physicians' education in supportive care, and patients' education in supportive care.

The study was funded by Bayer HealthCare Pharmaceuticals and Janssen Research & Development.

Reference

[LBA48: Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism in patients with cancer](#)

Anamorelin for the treatment of cancer anorexia-cachexia in NSCLC: Results from the phase III studies ROMANA 1 and 2

Dr Jennifer Temel of the Massachusetts General Hospital, Boston, USA reported that in two global, large-scale phase III studies, 12 weeks of anamorelin was well tolerated, and significantly improved lean body mass, body weight, and anorexia-cachexia symptoms/concerns in advanced NSCLC patients with cachexia.

Cancer anorexia-cachexia syndrome is a common debilitating condition, characterised by decreased body weight, mainly lean body mass and negatively impacts QoL and prognosis. Anamorelin is a novel selective ghrelin receptor agonist with appetite-enhancing and anabolic activity.

ROMANA 1 and 2 were two international, double-blind, phase III trials assessing anamorelin efficacy and safety in patients with unresectable stage III/IV NSCLC, ECOG PS 0-2 and cachexia ($\geq 5\%$ weight loss within prior 6 months or body mass index < 20 kg/m²). Patients were randomised (2:1) to anamorelin or placebo, given daily orally for 12 weeks and were permitted to receive chemotherapy while on study.

Co-primary endpoints were change from baseline over 12 weeks in lean body mass and in handgrip strength. Secondary endpoints included change in body weight and in the anorexia-cachexia subdomain of the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire. Safety assessments included lab values and adverse events.

There were no within-study population differences for ROMANA 1 (484 patients) and ROMANA 2 (495 patients). Over 12 weeks, anamorelin significantly increased lean body mass vs. placebo ($p < 0.0001$) in both studies. In ROMANA 1, median change in lean body mass was 1.10 kg for anamorelin vs. -0.44 kg for placebo; similarly, changes in ROMANA 2 were for anamorelin 0.75 kg vs. -0.96 kg for placebo. Change in handgrip strength was not statistically different between the study arms.

Anamorelin increased body weight ($p < 0.0001$ in both studies) and improved FAACT subdomain scores ($p = 0.0004$ in ROMANA 1; and $p = 0.0016$ in ROMANA 2 study).

The results on OS are pending.

In the anamorelin arm, the most frequent drug-related adverse events were hyperglycemia (5.3%) and nausea (3.8%) for ROMANA 1, hyperglycemia (4.2%) and diabetes (2.1%) for ROMANA 2. Both studies had few drug-related grade ≥ 3 adverse events (0.9%, 2.7%).

Dr Florian Scotte of the Georges Pompidou European Hospital, Paris, France, who discussed the study results, said that muscle wasting is common in lung cancer patients regardless of body weight. Cancer induced wasting begins early in the course of malignancy and up to 50% of lung cancer patients have severe muscle wasting at diagnosis. In the studies, he questioned an effect on OS, effect on the tumour, methods to assess cachexia/sarcopenia, and long term follow-up.

This study was supported by Helsinn Therapeutics, Inc. (USA).

Reference

[14830 PR: Anamorelin for the treatment of cancer anorexia-cachexia in NSCLC: Results from the phase 3 studies ROMANA 1 and 2](#)

Satisfying Career Needs of Young Oncologists

The Young Oncologist (YO) Track Sessions are specially designed by young oncologists for young oncologists and initiated by the ESMO YO Committee. The sessions are educational and cover topics which are highly relevant to YOs in their daily practice and/or research activities.

The YO Masterclass was organised in collaboration with the European Association for Cancer Research, and featured four talks on exciting areas where basic science is being integrated into clinical research: functional characterisation of tumours using patient-derived models and therapeutic implications, inter- and intra-tumour genetic heterogeneity and challenges for targeted therapy, circulating biomarkers, and next generation of clinical trial design.

The Vesalius Talk is a rare opportunity for a direct discussion between young oncologists and key opinion leaders in the field of medical oncology. This year's Vesalius Talk gave YOs the opportunity to learn about how key opinion leaders carved their own paths to success, and receive frank advice from experts with the aim of inspiring them to make the right professional decisions.

The breakfast sessions were delivered in a relaxed and friendly environment with the opportunity to ask questions and enter in to discussion on how to address the media, how to find the right work-life balance, and risk and boundaries of doctor/patient relationship.

The speakers at the YO Forum gave hints and tips on how to find the perfect mentor, along with writing tricks relevant to early career cancer researchers, in particular writing a clinical trial protocol, the importance of a well written grant application and writing a scientific paper.

The fellowship session this year featured presentations by two previous ESMO fellows, who were chosen from a competition open to recent fellowship recipients. Some practical advice from a former fellow, was added to the detailed overview of available ESMO Fellowship Programme.

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Save the date

European Cancer Congress 2015 (ECC 2015), Vienna, Austria, 25-29 September 2015.

Affiliations and Disclosure

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Disclosure

No conflicts of interest to disclose.

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