ONCOLOGY PRO
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ESMO Congress 2012

28 September - 2 October, 2012
Vienna, Austria

SUMMARY

The European Society for Medical Oncology (ESMO) Congress, held September 28 to October 2 in Vienna, Austria, was a record-breaker on nearly all levels. There were 16,394 participants: many were international delegates, including 1116 from the US, 539 from Japan, 292 from China and 550 from Argentina and Brazil.

The strong scientific program benefited from the submission of approximately 2200 abstracts - an increase of more than 30% since the previous ESMO Congress in 2010 - of which 1240 were presented. There were just over 50 late breaking abstracts submitted and data from 110 phase III trials were reported. The five day event was comprised of two Presidential Symposia, several Joint Symposia with other societies, several special sessions, proffered paper sessions, and 7 Young Oncologist sessions, together with 37 industry-sponsored symposia.

A primary emphasis was placed on personalized medicine and how it will change the future treatment landscape in oncology.

A new feature this year was the Society Village, where information was available from 28 non-profit societies and a number of medical societies, including an ESMO booth dedicated to membership. ESMO acquired approximately 300 new members who signed up during the Congress.

The congress also featured 68 companies that exhibited state of the art and novel therapeutic agents and devices vital to cancer treatment and research.

INTRODUCTION

The key message delivered by Josep Tabernero, MD, chair of the ESMO 2012 Scientific Committee was that personalized cancer medicine is becoming a reality in clinical work. Many of the

presentations contained new information on biomarkers and several presented studies that used biomarker data to stratify patient treatment. Some of the results presented were practice changing and many others suggested new or alternative treatment options for patients.

The special symposium focused on the impact of genetic information on clinical practice. According to Judith Balmaña, MD, who co-chaired the session, approximately 10% of the most prevalent cancers are related to a genetic mutation. Moreover, there is a growing fount of data that provides information on mutations that are clinically relevant and targetable by novel agents.

The ESMO Scientific Committee has turned a watchful eye to the economic crisis and included topics such as the economic burden, both direct and indirect, of cancer in Europe, health economics, drug costs and the unsustainability of cancer care, which were presented and discussed by experts.

During the Opening Ceremony the 2012 ESMO Awards were presented to Professors Ian Tannock, Jean Yves Blay and to the European Organisation for Research and Treatment of Cancer (EORTC). Dr. Ian Tannock was recognized for his "contributions in improving methodology for undertaking clinical trials with emphasis on endpoints of clinical benefit and, at a laboratory level, unmasking aspects of solid tumor biology as well as improving outcomes of treatment with chemotherapy," according to Dr. Tabernero, chair of the ESMO Fellowship and Awards Committee. Professor Jean Yves Blay was the recipient of the 2012 ESMO Hamilton Fairley Award, for his contribution to translational cancer research. The 2012 ESMO Lifetime Achievement Award was presented to the European Organisation for Research and Treatment of Cancer (EORTC) for 50 years commitment in the organization of clinical trials. It continues to be the largest organization which carries out independent clinical studies at the European level in all types of cancer. The award was accepted by Professor Françoise Meunier, the EORTC Director General for over 20 years.

This report is an overview of representative expert scientific presentations made during the congress by premier international investigators. It attempts to represent the diversity and depth of the ESMO 2012 scientific program.

BASIC SCIENCE AND TRANSLATIONAL RESEARCH

Prevalence of ALK gene rearrangement in Europe: Preliminary results from the Lungscape Project

The Lungscape Project, a pan-European collaboration, is currently evaluating ALK gene expression in patients with resected non-small cell lung cancer (NSCLC) from 13 sites in 11 European countries in an effort to establish the prevalence of ALK gene rearrangement within Europe. Cases of NSCLC

are being retrospectively identified at these sites, with accompanying clinical, demographic and outcome data being recorded. Patient tissue is being collected according to predefined protocol criteria and entered, together with clinical outcomes, into a central, secure database. ALK expression is being determined by immunohistochemistry (IHC) using antibody clone 5A4 (Novocastra) and an H-score modified after publication of Ruschoff *et al*. and all cases were analyzed using the same protocol, control tissue microarray. Immunohistochemistry results are available from 743 (74%) of the 998 cases of adenocarcinoma that have been entered into the database. Preliminary results from this cohort of 38% women and 62% men demonstrate a prevalence of ALK of 7.3%, determined by positive IHC staining in 54 cases (7.3%) with IHC 3+ present in 17 cases (2.3%). Positive IHC for ALK was seen more frequently in females and never smokers, with 11% of women, 5.6% of men, 13% of never-smokers, 5.3% of former smokers and 9.3% of current smokers being IHC+. Disease stage I, II and III was reported in 55, 23 and 22% of patients, respectively. Sixteen percent are never-smokers. The cohort is 99% Caucasian with a median age of 65 years (range 23-86). The median age of patients with IHC+ results is 63.2 years. The median immunohistochemistry score (H-score) is 45 with a range of from 1 to 300. Homo- and heterogeneous staining in was seen in 30% and in at least 70% of cases. Correlation of IHC scores with fluorescent in situ hybridization, clinical demographics and outcomes is ongoing. Blackhall, *et al.* Abstract 167O

Practice point and future research opportunities

A database of ALK gene expression is being created from a large multicenter European cohort of patients with resected NSCLC to establish the prevalence of ALK mutation in Europe, as well as other pertinent information.

LACE-BIO study finds prognostic and predictive value for KRAS combined with p53 in non-small cell lung cancer

Janne *et al.* have found two genetic mutations that may signal which patients with non-small cell lung cancer (NSCLC) will benefit from adjuvant chemotherapy. Findings from this group, previously reported by Shepherd at ASCO 2012, eliminated KRAS as a prognostic or predictive marker; the group then evaluated p53 and EGFR, also seen in NSCLC, as markers for adjuvant chemotherapy benefit. Since p53 mutations often are seen with KRAS, analysis of KRAS in EGFR wild-type (wt) adenocarcinoma patients and KRAS plus p53 were also undertaken using combined data from the IALT, JBR10, CALGB-9633 and ANITA trials. Among 1543 patients with documented KRAS genotype, 605 patients had adenocarcinoma and 938 were non-adenocarcinoma; EGFR was available in 485 of 605 patients and p53 in 1181 of 1543 patients, representing 12 and 36% of mutations, respectively. Genetic analysis was done in blinded fashion in 3 laboratories by direct sequencing. KRAS mutation was detected in 426 (40%) of EGFR-wt patients with adenocarcinoma and was neither predictive nor prognostic in the observation group. In patients with KRAS and p53

status, 16% had only KRAS, 32% had only p53 and 4% had both mutations; overall survival was decreased in patients receiving adjuvant chemotherapy who displayed both KRAS/p53 mutations compared with the observation group hazard ratio (HR) 2.49 (p = 0.03) but not in patients with either single mutation: KRASmut/p53wt (HR 0.73), KRASwt/p53mut (HR 0.97) and wt/wt (HR 0.82). No significant heterogeneity was seen in these four HRs (p = 0.06); however, a significant difference was observed in comparison between only wt/wt and mut/mut groups (p = 0.01). The prognostic value of the KRAS/p53 combination was not significant in the observation group (p = 0.57). Results for disease-free survival in these patients were similar. Janne, *et al.* Abstract 170O

Practice point and future research opportunities

Patients whose tumors express mutations in both KRAS and P53 may have a poorer outcome following adjuvant chemotherapy than patients with wt/wt tumors. Further studies are needed to understand the underlying biological basis.

BREAST CANCER

BREAST CANCER, EARLY STAGE

HERA TRIAL: Results of an 8 year median follow-up of 2 years versus 1 year of trastuzumab after adjuvant chemotherapy in women with HER2-positive early breast cancer

HERA was an international, multicenter, phase III randomized trial that evaluated whether longer term trastuzumab treatment would improve outcome of patients with HER2-positive early breast cancer. A total of 5102 women were randomized following completion of primary therapy consisting of surgery, chemotherapy and radiotherapy, as indicated, to observation only or trastuzumab every 3 weeks for one year or two years. This efficacy analysis compares the outcome of 1703 women receiving trastuzumab for one year and 1701 women receiving trastuzumab for two years who were disease-free at one year post randomization. The primary endpoint was disease-free survival (DFS) and secondary endpoints included overall survival (OS) and time to distant recurrence. Updated efficacy analyses of the trastuzumab arms compared with the observation arm after 8 years of median follow-up were also presented. On 12 April 2012 HERA reached the target number of 725 DFS events required to detect a true hazard ratio (HR) at 80% power of 0.80 for the comparison of two years versus one of trastuzumab; the unadjusted HR for an event in the treatment arms was 0.99; p = 0.86. At 8 years of follow-up, DFS and OS in the two arms were comparable, with no significant difference between treatment duration; however, trastuzumab treatment for either one or two years showed a significant benefit compared to observation, despite selective crossover. The primary cardiac endpoint (cardiac death or severe congestive heart failure defined as a NYHA class III or IV,

confirmed by a cardiologist, and a significant left ventricular ejection rate - LVEF decrease) was comparable at 0.96% vs. 0.83% but the secondary cardiac endpoint (defines as an absolute decline 10% points from baseline LVEF and to <50%) was 7.17% vs. 4.10% for the two years and one year arms, respectively. The durable benefit in DFS and OS for the trastuzumab arms compared with observation remained stable at 8 years of median follow-up. Goldhirsch, *et al.* Abstract LBA6_PR

Practice point and future research opportunities

One year of adjuvant trastuzumab remains the standard of adjuvant care for patients with HER2-positive early breast cancer with evidence of increased benefit with prolonged treatment. The response is durable and the incidence of cardiac events remained low at a median follow-up of 8 years.

PHARE: Comparison of 6 to 12 months of adjuvant trastuzumab in early breast cancer

Adjuvant trastuzumab in patients with early breast cancer and HER2 over-expression has been carried out for one year as a standard adjuvant treatment; however, the optimal duration of trastuzumab has not been fixed and results for the recent FinHer trial showed that a similar magnitude of benefit was obtained with 9 weeks of trastuzumab as with one year. Concerns of overtreatment and cardiac toxicity associated with trastuzumab led the French National Cancer Institute to initiate an academic, randomized, non-inferiority comparison of trastuzumab exposure of 6 months to the standard 12 month course. The PHARE (Protocol for Herceptin® as Adjuvant therapy with Reduced Exposure') trial enrolled 3382 patients with HER2-positive early breast cancer who had previously received at least 4 cycles of (neo)-adjuvant chemotherapy. The patients were randomized 1:1 using a minimization algorithm stratified by concomitant or sequential trastuzumab administration with chemotherapy, estrogen receptor status and center to receive trastuzumab for 6 or 12 months. The primary endpoint was disease free survival (DFS), and overall survival (OS) and cardiac toxicity were investigated as secondary aims. An absolute loss of 2% in DFS in the experimental arm was defined as the non-inferiority margin (1.15 in relative terms) and required a minimum 3400 patients with alpha = 0.05 and 80% power. Disease and treatment characteristics were well balanced between the arms. Patients had a median age of 55 years, median tumor size of 20 mm, node involvement was seen in 45% of patients, 56% of patients had **Scarff-Bloom-Richardson** grade III disease and 58% were ER-positive. In all, 88%, 58% and 73% of patients had received prior radiotherapy, concomitant trastuzumab administration and anthracycline and taxane containing chemotherapy, respectively. The median follow-up was 47.2 months. No significant difference was shown in DFS between 6 and 12 months of treatment, the hazard ratio was 1.28 (p = 0.29). The lower boundary of the 95% confidence interval crosses the prespecified non-inferiority margin of 1.15. Pivot, *et al.* Abstract LBA5_PR

Practice point and future research opportunities

Adjuvant trastuzumab treatment for 12 months remains the standard for patients with HER2-positive early breast cancer. Non-inferiority results were inconclusive and non-inferiority of a six month regimen could not be demonstrated.

Whole expression genome array can be used in daily practice for selecting neo-adjuvant treatment

A French team explored whether DNA array could be used to increase the efficacy of neoadjuvant chemotherapy in the Remagus04 Trial, a prospective randomized phase III trial that enrolled 303 patients with HER2 negative breast carcinoma who were not candidates for conserving surgery. Of these patients, 64 (21%) were not included in the main trial; only samples with more than 30% cancer cells, a RNA integrity number (RIN) > 6 and a test array positive were eligible. Affymetrix U133Av2 DNA array could be performed within 15 days in 59% of the patients, leaving 142 patients who were randomized to either a "genomic-driven" chemotherapy arm or a standard chemotherapy control. In the array arm, 39% of the patients had an ER-negative or high grade tumor compared to 57% of control patients. Patients in the genomic-driven chemotherapy arm received paclitaxel for 12 weeks. Afterwards, patients with DLD30+ received 4 weeks of FEC100 (flourouracil, epirubicin, cyclophosphamide) and patients who were TOP2A+/DLD30- were given 4 weeks of FEC followed by 4 weeks of docetaxel and patients with DLD30-/TOP2A- status received 6 weeks of docetaxel/capecitabine. Patients in the control arm received 4 cycles of FEC followed by 4 cycles of docetaxel. The trial was halted after a preplanned interim showed fewer than 2 pathological complete responses (pCR) in the docetaxel group. Of the 142 patients in the clinical decision trial, 39% presented an ER-negative and 57% a high grade tumor. The overall pCR rate was 22%, with no difference observed between the genomic driven and standard arms (pCR rates: 22 % and 21% respectively). The DLD30+ prediction score associated with a 36% likelihood of achieving pCR compared to 3% for DLD30-. DLD30+ associated with odds ratio for pCR at 4.7 (p = 0.09) by multivariate analysis. Pierga, *et al.* Abstract 245O

Practice point and future research opportunities

This is the first prospective trial demonstrating the utility of genome array and validating the predictive value of DLD30+ of pathological complete response and immune signatures. It demonstrated the feasibility of using whole expression genome array within the context of daily practice to generate immune signatures. The authors anticipate future use of genome array as a basis for therapeutic decision making in personalized medicine.

Analysis of NEOALTTO trial data shows discrepancy between high pathological complete

response rate following neoadjuvant therapy and breast conserving surgery

As reported at the European Multidisciplinary Cancer Congress 2011, patients with HER2+ breast cancer who received paclitaxel plus lapatinib and trastuzumab prior to surgery in the NeoALTTO trial achieved a greater pathological complete response (pCR) rate of 52.3% compared to that seen in patients receiving paclitaxel plus either lapatinib or trastuzumab alone, 29.5% and 24.7%, respectively. Although pCR was defined as the absence of invasive cancer in the breast at the time of surgery, achieving pCR did not correspond to an improved breast conserving surgery rate, which was similar, approximately 40%, between arms. Criscitiello *et al*. evaluated the factors, including pCR which was achieved by 160 (37%) patients, affected the type of surgery. Following exclusion of NeoALTTO participants who did not undergo surgery, the data from 429 women were analyzed; 242 (57%) underwent mastectomy and 187 (43%) patients had breast conserving surgery. Mastectomy was done in all 17 patients diagnosed with lobular cancer regardless of pCR and in 36 (53%) of 68 patients who demonstrated radiological complete response, including the 25 (70%) of these patients who also achieved a pCR. Factors that influenced the decision for mastectomy were age (< 50 years), whether treatment was carried out in a developing country, tumor multicentricity, size (>5 cm) and ER- status. Breast conserving surgery was initially considered in 128 women but carried out in just 95 (74%) patients. The decision for breast conserving surgery was largely not impacted by pCR status; 79% of patients who underwent breast conserving surgery had achieved pCR and 72% had not. However, initial diagnosis was modified to allow breast conserving surgery in 30% of the patients who were evaluated at diagnosis as inoperable or requiring mastectomy. Criscitiello, et *al.* Abstract 247O

Practice point and future research opportunities

Initial tumor characteristics rather than response to neoadjuvant therapy appeared to play a larger role in deciding the type of surgery. Breast conserving surgery was less likely to be considered in cases where the tumors were multicentric and/or ER-. These results call for clarification on the role of breast conserving surgery; progress in neoadjuvant therapies resulting in radiological and pathological complete response should be considered when deciding between types of surgery and will translate into improved breast conservation rates.

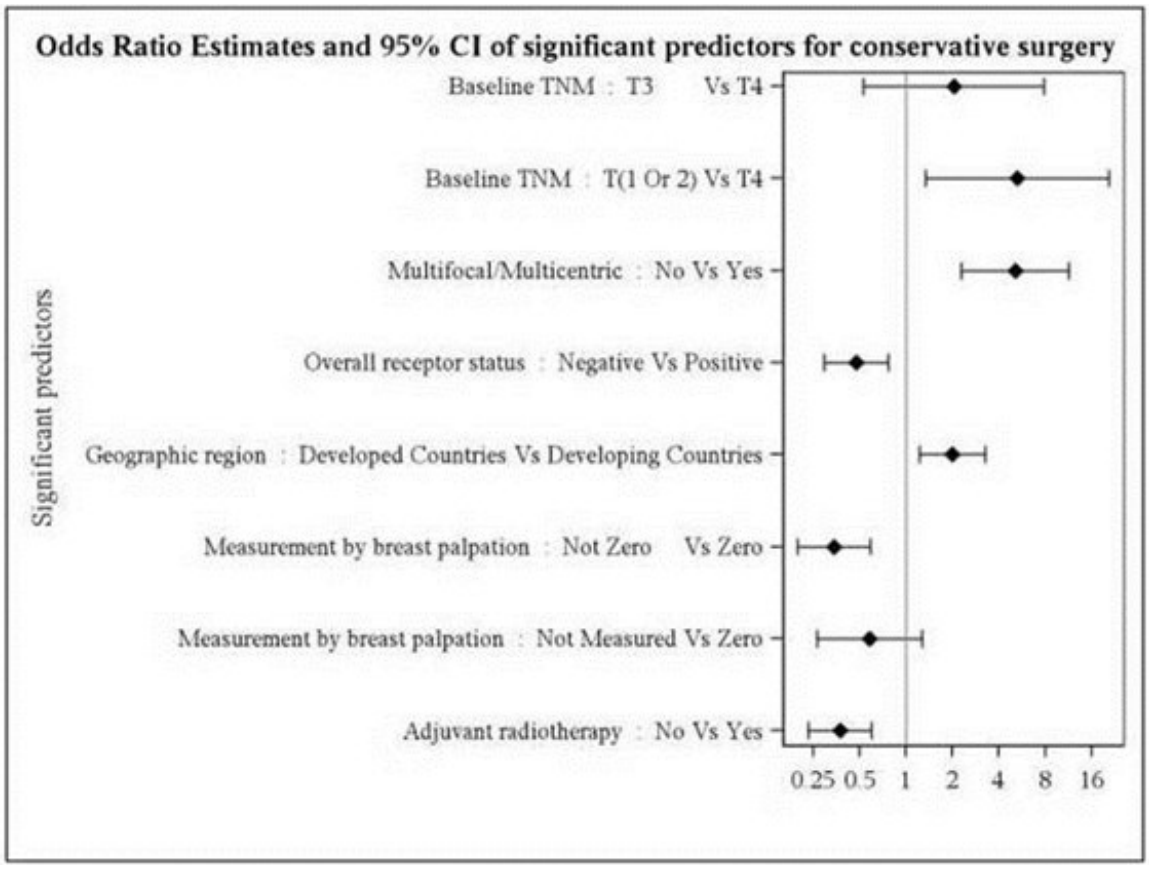

Figure 1. Odds ratio estimates and 95% CI of significant predictors for conservative surgery

Detection of CTCs in patients with primary HER2+ breast cancer following treatment with chemotherapy plus anti-HER2 agents

Azim *et al.* reported on a subanalysis of data for the NeoALTTO phase III trial to determine whether circulating tumor cells could be detected in women with primary HER2+ breast cancer following preoperative chemotherapy plus anti-HER2 agents. In NeoALTTO, 455 patients with primary HER2+ breast cancer were randomized to receive either trastuzumab, lapatinib or a combination of the two for 6 weeks followed by paclitaxel for 12 weeks prior to surgery. The circulating tumor cells (CTCs) sub-study involved blood samples taken at baseline, after two weeks of treatment and just prior to surgery from 51 (11%) patients in this cohort. Following isolation of CTCs, determination of HER2 expression was planned and associations between CTC detection and patient outcome, primary tumor characteristics, pathological complete response (pCR) and PET/CT response at weeks two and six were evaluated using the chi-square test. Of the 51 subset patients, 5 of 46 (11%), 4 of 41 (10%) and 5 of 31 (16%) patients had one or more CTC per 22.5 ml of blood at baseline, week two and at surgery, respectively. HER2+ CTCs were still detectable after 18 weeks of treatment with anti-HER2 agents plus paclitaxel in 3 of 31 (10%) patients. However, CTC detection at any time point did not significantly associate with clinico-pathologic characteristics, pCR or PET/CT response at either week 2 or week 6. Azim, *et al.* Abstract 255PD

Practice point and future research opportunities

This sub-study was hindered by small sample size and did not show an association between the presence of CTCs and pathologic complete response in women receiving preoperative chemotherapy plus anti-HER2 agents.

BREAST CANCER, METASTATIC DISEASE

UNICANCER SAFIR-01: Array CGH and DNA sequencing to personalize therapy for metastatic breast cancer

The ongoing SAFIR01 trial is analyzing DNA from the entire genome of individual breast cancers by **Array Comparative Genomic Hybridization** (aCGH) and Sanger sequencing to find actionable genomic alterations to be used in directing patients to specific targeted agents. The prospective trial enrolled 423 patients with metastatic breast cancer from 18 centers. The metastatic site was biopsied in all patients and DNA extracted from all tumor samples containing more than 50% cancer cells. DNA was sent to one of the 5 genomic platforms where aCGH (Agilent 8*60K or Affy6.0) and Sanger sequencing of PIK3CA (exon 10/21) and AKT1 (exon 3) were done. . As of 23 September 2012, biopsies had been performed in samples from 402 breast cancer patients, including 26 patients for whom analyses are ongoing. Results were obtained for 276 patients, including whole genome analysis for 248. A genomic alteration that could be targeted by an anticancer drug was found in 172 of those patients. Approximately 20% of the patients' samples presented rare genomic alteration, which highlighted the utility of whole genome approaches. An actionable alteration was found in 140 patients involving PIK3CA mutation, AKT1 mutation, FGFR1 amplification and CCND1. Thirty-three additional genomic actionable genomic alterations occurred rarely (<3% for each), including 6 each of EGFR and MDM2, 3 each of FGFR2 and PIK3CA and 2 each of IGF1R, PIK3CB and ALK. Thus far, 26 patients have received a targeted agent matched to the genomic alteration. Preliminary results from analysis of pooled data from the SAFIR01 trial and the pilot phase showed antitumor activity in 18 out of 48 patients treated according to whole genome analysis. André *et al.* Abstract LBA13_PR

Practice point and future research opportunities

This large, prospective trial is first to show that whole genome approaches are feasible in the context of daily practice, and can provide the first genomic landscape of breast cancer metastases that may direct patient therapy. In the future, whole-genome approaches to cancer testing of cancer could become the standard of care since they provide a broad picture of genomic alterations.

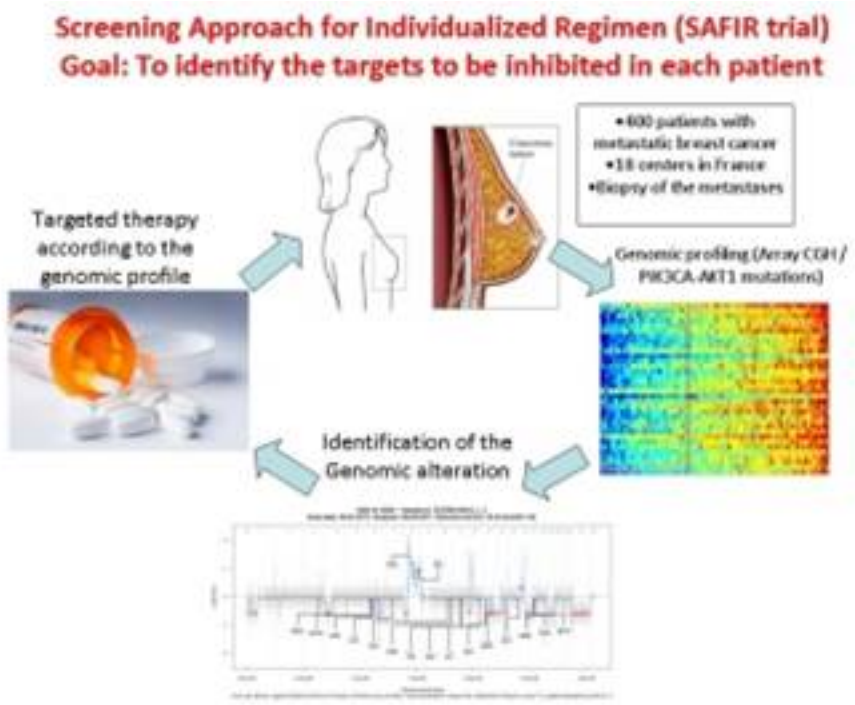

Figure 2. Screening approach for individualized treatment regimens in the SAFIR study

Docetaxel plus cancer vaccine, PANVAC shows greater benefit than docetaxel alone

PANVAC, a poxviral based cancer vaccine, showed promising clinical efficacy and suggested immunologic activity in patients with breast and ovarian cancer in a phase I/II trial. Based upon preclinical data showing that docetaxel can modify tumor phenotype making it more susceptible to T-cell mediated killing, this open-label, phase II randomized, multicenter trial tested whether docetaxel and PANVAC could act synergistically to improve clinical outcomes over docetaxel alone. A total of 48 patients with metastatic breast cancer were randomized to receive docetaxel plus PANVAC (arm A) or docetaxel alone (arm B). Cross-over to arm A was allowed upon progression. Patients had ECOG performance status 1, normal organ and immune function and unlimited previous lines of therapy, but not with docetaxel. HER2-positive patients receiving trastuzumab were allowed to continue. All patients received docetaxel but 25 arm A patients were "primed" with recombinant vaccinia-PANVAC on study day one and three weeks later began 28-day cycles of docetaxel with a "boost" of recombinant fowlpox-PANVAC given on day one per cycle until progression. A total of 23 patients received sole docetaxel. Computed tomography (CT) and bone scans were performed after 3 cycles and then every 2 cycles. The primary endpoint was progression-free survival (PFS) with secondary endpoints of overall survival and immunologic correlative studies. Patient and tumor characteristics were well matched between 25 patients in arm A and 23 patients in arm B. Two patients on arm A and 3 on arm B remain on treatment. Analysis done at median follow-up of 5.1 months showed improved PFS of 6.6 months with PANVAC (arm A) compared to 3.8 months with docetaxel alone, hazard ratio 0.67, p = 0.12. Though not significant, this p-value indicates improved

PFS in a sample of this small size. Toxicity was similar in both arms. Immune analysis and correlation to patient clinical outcomes is ongoing. Heery, *et al.* Abstract LBA 14

Practice point and future research opportunities

Adding docetaxel to PANVAC prolonged progression-free survival in patients with metastatic breast cancer and may provide increased clinical benefit over docetaxel alone. The potential benefit was not statistically significant, likely due to the small sample size. This was a hypothesis generating study and may provide both rationale and statistical assumptions for a larger definitive randomized trial.

EMILIA: Increased benefit from trastuzumab emtansine over capecitabine/lapatinib in HER2-positive locally advanced or metastatic breast cancer

Results from the phase III EMILIA trial showed that trastuzumab emtansine improved outcome in patients with confirmed HER2-positive locally advanced or metastatic breast cancer. Emtansine is an antibody-drug conjugate incorporating the HER2-targeted antitumor properties of trastuzumab with cytotoxic activity from the microtubule inhibitor DM1. EMILIA compared trastuzumab emtansine to capecitabine/lapatinib in patients who were previously treated with trastuzumab and a taxane. The trial enrolled 991 patients and randomized 495 to receive trastuzumab and 496 to the capecitabine/lapatinib arm. Both arms were balanced for baseline demographics, prior therapy, and disease characteristics. Updated results presented at ESMO 2012 showed that progression-free survival (PFS) was significantly improved with trastuzumab emtansine; median PFS was 9.6 months with trastuzumab emtansine versus 6.4 months with capecitabine/lapatinib hazard ratio (HR) 0.60, $p < 0.0001$. Median overall survival was 30.9 months in the trastuzumab emtansine arm compared to 25.1 months with capecitabine/lapatinib, HR 0.683, $p = 0.0006$. Progression-free survival benefit was observed in most subgroups, including the number of lines of prior therapy, type of prior treatment, patients' menopausal or hormone receptor status, the number of disease sites and race that favoured trastuzumab emtansine. Benefit was also observed in older patients but the subgroup of patients 75 years and older was too small to be confirmed. Secondary end points, including objective response rate and clinical benefit rate were 43.6% versus 30.8% and 58.2% versus 44.2%, respectively, favouring trastuzumab emtansine. The time to treatment failure was 7.9 with trastuzumab emtansine compared to 5.8 months with capecitabine/lapatinib, HR 0.703. Trastuzumab emtansine was well tolerated with 1.6% of patients reporting diarrhea grade 3 compared to 20.7% of patients in the capecitabine/lapatinib arm; hand/foot syndrome was reported by 16.4%, of capecitabine/lapatinib patients. Both arms had similar low incidence rates of cardiac adverse events and left ventricular dysfunction. Verma, *et al.* Abstract LBA12

Practice point and future research opportunities

Significant and clinically meaningful improvement in progression-free survival was demonstrated by trastuzumab emtansine compared to capecitabine/lapatinib, which may be considered as a potential new therapy for patients with HER2-positive metastatic breast cancer who received previous trastuzumab and a taxane.

CEREBEL: Incidence of metastases to the central nervous system in patients with HER2-positive metastatic breast cancer receiving lapatinib/capecitabine or trastuzumab/capecitabine therapy

Metastases to the central nervous system (CNS) occur in 28 to 43% of HER2-positive breast cancer and lapatinib is reported to have activity in CNS metastases, leading the CEREBEL investigative team to evaluate the prophylactic impact of lapatinib plus capecitabine compared to trastuzumab/capecitabine on the incidence of CNS metastasis. CEREBEL was an open-label, phase III, multicenter study in patients with HER2-positive metastatic breast cancer who did not have CNS metastases at baseline, confirmed centrally by MRI, and were randomized to lapatinib/capecitabine or trastuzumab/capecitabine. Prior treatment must have included anthracyclines or taxanes in (neo-)adjuvant or metastatic setting. The primary endpoint was incidence of CNS as first site of relapse. Secondary endpoints were progression free survival (PFS), overall survival (OS), CNS progression at any time, overall response rate (ORR), clinical benefit response rate, duration of response and safety. A pre-specified interim analysis that included 475 patients was performed by an independent monitoring committee (IDMC). A total of 43% versus 46% of patients had not received prior treatment for metastatic breast cancer and 38% versus 40% of patients had not received prior trastuzumab, in the lapatinib/capecitabine and trastuzumab/capecitabine arms, respectively. In the modified intent to treat population with 218 patients per arm, the incidence of CNS metastasis as site of first relapse was 3% for lapatinib/capecitabine versus 4% for trastuzumab/capecitabine; incidence of brain metastases were similar in both arms, at 6% and 7%. Median PFS was 6.6 months with lapatinib/capecitabine and 8.0 months with trastuzumab/capecitabine, hazard ratio (HR) 1.3; and median OS was 22.4 and 27.3 month, respectively, HR 1.58. Adverse events were similar in both arms with the exception of diarrhea, nausea and rash which were higher with lapatinib/capecitabine. Based on these results, the study was halted by IDMC recommendation. Pivot, *et al.* Abstract LBA11

Practice point and future research opportunities

Adding lapatinib to capecitabine showed no benefit over trastuzumab and capecitabine and did not decrease the incidence of metastasis to the central nervous system in patients with breast cancer, but a trend towards better progression-free and overall survival was seen with trastuzumab.

Comparing two bevacizumab-containing regimens as first-line therapy for HER2 negative metastatic breast cancer

The first efficacy results from the phase III study run by the Central European Cooperative Oncology Group (CECOG) were presented. The study was entitled the 'capeciTabine and bevacizUmab Randomised Against avastiN anD taxOl Trial' (TURANDOT). The study compared two bevacizumab-containing regimens as first-line therapy for HER2 negative metastatic breast cancer. Prof. Zielinski reported results from a preplanned analysis of data at 19 months from this phase III trial of bevacizumab plus either paclitaxel or capecitabine as first-line therapy for patients with HER2 negative breast cancer. The primary objective was to demonstrate non-inferiority in overall survival with bevacizumab/capecitabine vs. bevacizumab/paclitaxel. Interim and final overall survival analyses were planned after 175 and 389 deaths, respectively, in the per-protocol population to reject the null hypothesis of inferiority hazard ratio (HR) 1.33 with 80% power and overall = 0.025. Secondary endpoints included response rate, progression-free survival, safety and quality of life. In this study, chemotherapy naive patients were randomized to placebo or one of two bevacizumab regimens; 10 mg/kg d1 bevacizumab plus 90 mg/m2 d1 paclitaxel four times weekly or 15 mg/kg d1 bevacizumab plus 1000 mg/m2 bid capecitabine three times per week until disease progression or unacceptable toxicity occurred. Patients' baseline characteristics were similar in both arms. The trial's primary endpoint, non-inferiority in overall survival was not met at the level of statistical significance. The pre-planned interim analysis done at a median of 19 months post-treatment showed one year overall survival rates of 81% in 285 patients treated with bevacizumab plus paclitaxel and 79% in 279 patients receiving the bevacizumab/capecitabine combination hazard ratio 1.04 (to 1.69); p = 0.0593. The response rate was 44% and 27%, in the two arms, respectively (p = 0.0001). Progression-free survival in the bevacizumab/paclitaxel and bevacizumab/capecitabine arms was median 11 months and 8.1 months, respectively (p = 0.0052). No safety issues were raised; adverse events were consistent with the known safety profiles of all three drugs. The most common adverse events of grade 3 were neutropenia (18%), peripheral neuropathy (14%) and leucopenia (7%) in patients receiving bevacizumab plus paclitaxel while hand-foot syndrome (16%), hypertension (6%) and diarrhea (5%) occurred with bevacizumab/capecitabine. Final results from this trial are anticipated in 2014. Zielinski, *et al.* Abstract 317O

Practice point and future research opportunities

Although non-inferiority criteria were not met in this planned interim analysis, the combination of bevacizumab plus capecitabine yielded overall survival similar to bevacizumab and paclitaxel when administered as first line treatment of patients with HER2 negative metastatic breast cancer. However, a significantly better progression-free survival and overall response rate were seen with paclitaxel plus bevacizumab regimens in this randomized controlled trial.

BKM120 plus trastuzumab in patients with trastuzumab-resistant HER2+ advanced breast cancer

Since upregulation of the PI3K/AKT/mTOR pathway is thought to play a role in resistance to trastuzumab, this phase IB/II study evaluated whether pathway inhibition using BKM120, an oral pan-class I PI3K inhibitor, could restore sensitivity. Fifty-three patients with HER2+ locally advanced/metastatic breast cancer who were resistant to trastuzumab and had progressed on or following treatment, received the recommended phase II dose of BKM120 (100 mg) daily plus the standard weekly dose of trastuzumab. To be eligible patients had one or more measurable lesion, between 1 and 4 prior anti-HER2 treatments, including at least once cycle of trastuzumab, and fewer than 3 prior lines of chemotherapy for metastatic disease. Of the 53 enrolled patients, 49 were evaluable for response; their median age was 52 years with a median of 4 prior antineoplastic regimens. Five patients had a baseline central nervous system (CNS) lesion; of these 2 patients achieved stable disease (SD) in the CNS at study withdrawal, 2 patients had overall SD for 90 and 106 day each before progression in the CNS and 1 patient was not evaluated in the CNS after study entry. Partial responses (PR) by RECIST were seen in 4 (8%) and stable disease (SD) was seen in 20 (41%) patients, yielding a disease control rate of 49%. At data cut-off, 9 patients were still on study. The majority of patients (55%) discontinued treatment due to disease progression and 8 patients (16%) withdrew due to adverse events. The mean duration of BKM120 exposure was 11 weeks (range 0.1 to 41). The most common grade 3/4 adverse events thought to be related to study drug were increased ALT in 5 patients, rash in 5, increased AST in 4 patients and asthenia in 3 patients. Two patients each experienced nausea, anxiety, skin photosensitivity and hyperglycemia. Pistilli, *et al.* Abstract 318O

Practice point and future research opportunities

Preliminary results suggest that BKM120 combined with trastuzumab has activity in heavily pretreated HER2+ metastatic patients with trastuzumab resistance, including patients with brain metastasis.

E-3810 has antitumor activity in patients with FGFR1 amplified breast cancer

Amplification of the FGFR1 gene is seen in subsets of tumors, including breast cancer, resulting in an altered FGF pathway that may be clinically relevant. E-3810, a kinase inhibitor that targets FGFR1 and VEGFR1, 2 and 3 was assessed in patients with solid tumors and FGFR1 amplification in an open label non-comparative extension of the first in man dose-escalation trial. The study enrolled 46 patients with diverse tumor types, including 13 FGFR1+ tumors, 4 with non-FGFR1+ and 4 with FGFR1+ tumors, and 12 women with breast cancer, of whom 9 were hormone receptor positive (HR+), 1 was HER2+/HR+, 2 women had triple negative disease; in the breast cancer cohort, 8 patients were FGFR1+ and 2 had 11q amplification. These women had received a median of five prior chemotherapy lines; 9, 10 and 5 patients also received one or more endocrine, antiangiogenic

and experimental therapies, respectively. Following treatment with E-3810 at either 15 or 20 mg, a subgroup of 24 patients who were antiangiogenic sensitive demonstrated 3 partial responses (PRs), 14 patients had stable disease (SD) and 7 patients had progressive disease (PD). Of the 11 patients with amplified FGFR1 cohort, 4 patients achieved PR, 4 had SD and 3 had PD. This cohort contained 9 women with breast cancer of whom 7 had a response to E-3810 and 2 had progressive disease. The partial response was maintained over 4 to 6 treatment cycles and 3 of these responding patients remain on treatment. No patients in the FGFR1+ cohort withdrew due to toxicity. Grade 3 proteinuria was experienced by 5 patients, headache and vomiting by 2 and one patient showed an increase in pancreatic enzymes. All patients recovered. Hypertension grade 2-3, proteinuria grade 2, gastrointestinal intolerance, asthenia and weight loss led to dose reduction in 20 patients and frequently occurring TSH increases required supplementation. The FGFR1+ cohort had less prior antiangiogenic exposure and tolerated treatment better. No major cardiovascular signals were raised. Dienstmann, et *al.* Abstract 319O

Practice point and future research opportunities

E-3810 showed promising activity in heavily pretreated patients with breast cancer. A durable response was seen in patients with altered FGF pathway activity and further studies are planned in this population.

CANCER IN ADOLESCENTS AND YOUNG ADULTS

Program detects cancer early in high risk patients

The High Risk and Cancer Prevention Unit (HRCPU) at Hospital Vall d'Hebron began a proactive program in 2009 to monitor adolescent and adult patients with Fanconi anemia who have an increased risk of developing secondary malignancies during subsequent years. Patients visit the unit annually to undergo a complete anamnesis and the multidisciplinary surveillance program which includes hemograms and bone marrow aspiration, detailed examinations to detect head and neck lesions done by an otolaryngologist and of the oral cavity by a maxillofacial specialist. Women undergo semestral gynecologic examinations with annual cervical cytology testing and breast examination. All patients receive health education and HPV vaccination is encouraged. Fourteen patients with Fanconi anemia have participated in the program; 50% were women, aged from 14 to 32 years with a median age of 22 years (range 14-32). The mean age at Fanconi anemia diagnosis was 6.5 years; 57% of patients belonged to FANCA group and 57% underwent bone marrow transplantation. Follow up has ranged from 1 month to 3 years. Compliance is high with 70% of patients continuing the program and 83% of women have received HPV vaccination. Malignant tumors have been detected in 4 (29%) patients; two were head and neck tumors, the third was a

lingual squamous cell carcinoma and the fourth was a squamous cell carcinoma of the epiglottis. These last 2 patients have developed several basal cell carcinomas in the jaw and back. The third patient underwent bone marrow transplantation at age 8 and died at age 30 years. Premalignant lesions were found in two (14.5%) patients, one was in the oral cavity and one was gynecological; the latter was diagnosed at age 24 years, recurred at 4 years and the patient died at age 30. Balmana, et *al.* Abstract 1024PD

Practice point and future research opportunities

Head and neck tumors are frequent neoplasms in young adults with Fanconi anemia. The High Risk and Cancer Prevention Unit at Hospital Vall d'Hebron provides an example of how surveillance and prevention programs can monitor known high risk patients to lower this risk, identify cancer at an early stage and provide treatment and demonstrates the need for surveillance programs.

CANCER IN THE ELDERLY

How does co-morbidity in elderly myeloma patients affect on clinical outcomes

Kim reported results from a retrospective analysis of 132 patients aged 65 years and older who were newly diagnosed with symptomatic myeloma and were not eligible for undergoing autologous stem transplantation. Co-morbidity at the time of diagnosis was assessed by the Charlson Comorbidity Index. The patients were between 65-92 years with median age of 71. At a follow-up at median of 20 months, it was found that nearly half (48.5%) of the patients had comorbidities. Diabetes mellitus was the most frequent disorder and was reported in 22 (16.7%) patients. The Charlson Comorbidity Index scores ranged from 0 to 6 and these scores were used to stratify the patients into three groups of comorbidities: 0, 1-2, 3-6. No significant difference in overall survival among the groups was observed: the median survival was 42.6, 34.1, and 25.3 months in patients with 0, 1-2 and 3-6 co-morbidities, respectively. Other comparisons were also non significant suggesting that co-morbidities do not affect survival and complications in elderly myeloma patients. Kim *et al.* Abstract 1065O

Practice point and future research opportunities

The presence of co-morbidities in elderly patients did not significantly affect overall survival and should not deter clinicians from using standard treatments for elderly patients with multiple myeloma.

LV5FU2 +/- irinotecan in the first-line treatment of elderly patients with metastatic colorectal cancer

Paradoxically, metastatic colorectal cancer (mCRC) most frequently occurs in elderly patients who

are less likely to be given chemotherapy than younger patients. Mitry reported the final results of the first phase III study where 5FU-based chemotherapy (5-flouracil) was administered to previously untreated elderly patients with mCRC. Patients aged 75 and older were randomly assigned to receive 5FU-based chemotherapy, either alone or in combination with irinotecan (FU arms: LV5FU2 or simplified LV5FU2, irinotecan arms: LV5FU2-CPT11 or FOLFIRI, reduced dosage for cycles 1 and 2) and stratified according to center, Charlson index, Karnofsky index, previous adjuvant chemotherapy, sex, age and prior treatment with alkaline phosphatases. Patient characteristics, including age, were well-balanced in the 142 patients in the 5-FU and 140 irinotecan groups. Median duration of treatment was 3.5 months with 5-FU and 4.5 moths with the irinotecan combination. At least one chemotherapy dose reduction was observed for 30.9% patients receiving 5-FU and 52.6% patients receiving irinotecan. Although a trend favoring chemotherapy plus irinotecan was shown, no significant difference was observed in median progression-free survival (PFS) between the groups, which was 5.2 compared to 7.3 months with 5-FU and irinotecan, respectively, hazard ratio (HR) = 0.84 (p = 0.15); 240 events (282 patients) were required to demonstrate an improvement of median PFS from 5.5 to 7.9 months in the irinotecan arm. Median overall survival was also similar, 14.2 months with 5-FU compared to 13.3 months with irinotecan (HR 0.96). However the overall response rate favoured irinotecan, 27.4% with 5-FU and 46.3% with irinotecan (p = 0.002). Complete response was achieved by 5 patients receiving 5-FU and by 7 patients receiving irinotecan. Partial response and stable disease were achieved by 32 and 62 patients in the 5-FU arm and by 55 and 43 irinotecan patients, respectively. More patients receiving irinotecan presented grade 3-4 toxicities, 76.3% compared to 52.2% of patients in the 5-FU arm. The toxicities, mainly neutropenia, diarrhea and febrile neutropenia, respectively, were seen in 38.5%, 22.2% and 6.7% of patients in the irinotecan arm compared to 5.2%, 5.2% 0.7% of patients receiving 5-FU. Toxic deaths occurred in two patients per arm. Mitry, et *al.* Abstract 529PD

Practice point and future research opportunities

The addition of irinotecan to infusional 5FU-based chemotherapy improved the overall response rate and seemed to increase progression-free survival but did not enhance overall survival and was associated with higher toxicity in the elderly population.

CNS MALIGNANCIES

TEMAVIR ANOCEF: Final results of irinotecan plus bevacizumab as neo-adjuvant and adjuvant to temozolomide-based chemoradiation versus chemoradiation for unresectable glioblastoma

A French team of investigators evaluated whether irinotecan and bevacizumab added to

temozolomide-based chemoradiation would improve the prognosis of patients with unresectable glioblastoma. The phase II, randomized trial enrolled 120 patients, aged 18 to 70 years with *de novo* unresectable glioblastoma, Karnofsky performance status > 50 and recursive partitioning analysis (RPA) class 5. Patients were randomized, 60 patients per arm, to receive four cycles of neo-adjuvant bevacizumab plus irinotecan prior to radiotherapy with concurrent temozolomide and bevacizumab or to receive control treatment of concomitant temozolomide plus radiotherapy for 6 months. Clinical factors were well balanced between arms and cross-over was allowed upon progression. An evaluation done at 16 months after the treatment showed longer progression-free survival (PFS) in the treatment over the control arm; six and twelve months PFS were achieved by 65% and 31% of patients in the treatment arm compared with 41% and 18% of control patients. However, overall survival (OS) was similar between groups; six and twelve month OS were achieved by 75% and 48% compared with 72% and 50% of patients in the treatment and control arms, respectively. Treatment-related serious adverse events of fatal brain hemorrhages occurred in 3 patients, 3 cases (one fatal) of biliary or digestive perforation/infection and 4 non-fatal thrombo-embolisms were seen in the treatment arm. In the control arm, two non-fatal cases of biliary or digestive perforation/infection, 1 non-fatal pulmonary infection, 2 non-fatal cases of thrombo-embolism and 4 non-fatal cases of thrombo- and/or neutropenia. Chauffert, *et al.* Abstract LBA15

Practice point and future research opportunities

The addition of irinotecan plus bevacizumab as neo-adjuvant and adjuvant to temozolomide-based chemoradiation showed a trend towards improved progression-free survival but did not improve six and twelve month overall survival compared to chemoradiation**.**

DEVELOPMENTAL THERAPEUTICS

Four new pharmacological interventions show promise in crizotinib naive patients or in overcoming resistance to ALK and tyrosine kinase inhibitors

Translocations of the anaplastic lymphoma kinase (ALK) gene are present in 3 to 8% of non-small cell lung cancer (NSCLC) cases. Resistance to tyrosine kinase inhibitors (TKIs) due to activating EGFR mutations (EGFR-mut) is seen in 10-20% of NSCLCs. Four ongoing, early stage trials are evaluating four new agents that show considerable clinical benefit with acceptable toxicity.

AUY922 blocks HSP90 chaperone activity of ALK+ and EGFR-mut and is therefore active against both mutations. AUY922 is being tested in a phase II trial in patients with ALK-rearranged (ALK+) or EGFR-mut advanced NSCLC who progressed following at least one line of chemotherapy; most (61%) patients had received three or more prior treatments. At the April 6, 2012 cutoff, 121 patients

had received once-weekly 70 mg/m2 AUY922. Partial response was seen in 6 of 22 (29%) ALK+ patients and 7 of 35 (20%) EGFR-mut patients. Of the 6 ALK+ responders, four were crizotinib-naive and 2 had received crizotinib. No partial response was seen in 28 patients with KRAS-mutation, 33 EGFR/KRAS/ALK wild-type and 3 mutation undetermined patients. Median progression-free survival rates at 18 weeks were 42% in ALK+ and 34% in EGFR-mut patients. Median progression-free survival (PFS) rate at 18 weeks was greatest in EGFR-mut patients who had progressed after EGFR tyrosine kinase inhibitor therapy compared to tyrosine kinase inhibitor-naive patients; 45% versus 21%, respectively. The most frequent adverse events were grades 1/2, with higher grade adverse events occurring in 10% of patients that included eye disorders, diarrhea and nausea (46%), which were reported in 77%, 74% and 46% of patients, respectively. Felip, *et al.* Abstract 438O

Gettinger reported results from a first-in-human phase I/II dose-finding study of AP26113, a new, orally-active, dual inhibitor of ALK+ and EGFR-mut activity. AP26113 is a tyrosine kinase that inhibits ALK+ and EGFR-mut and is also active against other tyrosine kinase inhibitor resistant forms, including L1196M (ALK) and T790M (EGFR), but does not affect wild type EGFR. AP26113 was administered daily to 15 patients with advanced malignancies; 11 with NSCLC, and one patient each with pancreatic, colon, cholangiocarcinoma and adenocarcinoma of unknown primary. Ten patients were documented ALK+ and 5 were EGFR-mut. All patients had been heavily pretreated; 4 ALK+ NSCLC patients failed prior crizotinib and 4 EGFR-mut patients had failed prior EGFR targeted therapy. Three, 5 and 4 patients received AP26113 at 30, 90 mg and 120 mg, respectively and achieved measurable blood levels. All 4 ALK+ patients achieved partial responses, one patient at 60 mg and the remaining 3 at the 90 mg dose. Anti-tumor activity and safety at 120 mg remains to be evaluated. The trial was discontinued by 8 patients due to disease progression, and by one patient due to investigator discretion; however, no treatment related serious events were observed. The most commonly reported adverse events were fatigue and nausea. No dose-limiting toxicity was recorded. A phase II expansion is planned that will test AP26113 in four cohorts; two groups of patients with ALK+ NSCLC who are naive or resistant to prior ALK-targeted therapy; patients with EGFR-mut NSCLC resistant to EGFR-targeted therapy and a fourth group of patients with other cancers with abnormalities in ALK or other AP26113 targets. Gettinger, *et al.* Abstract 439O

Fifty-one percent of patients showed a response to LDK378, a small molecule ALK inhibitor that had shown activity in ALK+ NSCLC xenografts. This ongoing trial enrolled patients with ALK+ advanced solid tumors; 50 patients with primary NSCLC, 4 with primary breast cancer and two patients with other ALK+ cancers, of whom 88% were ECOG performance status 0/1. Of the 50 lung cancer patients, 37 had been refractory to prior crizotinib. All patients received LDK378 at doses of 50 to 750 mg/day. Response was seen in 42 of 47 patients with ALK+ NSCLC (FISH positive in 15%) evaluable for response (per investigator). A stronger response was seen in patients with NSCLC who had progressed following crizotinib and were treated at 400 mg/day with LDK378, where 21 of 23 (81%) patients responded. Dose limiting toxicities of diarrhea, vomiting, nausea, dehydration, and ALT

elevation were recorded in 2 of the 14 patients who received LDK378 at 400 mg/day, 2 of 9 patients at 600 mg/day, and in 1 of the 9 patients dosed at 750 mg/day. The maximum tolerated dose was 750 mg/day. At the 25 April, 2012 cutoff date, 36 (64%) patients continued treatment. One (2%) patient left the study due to adverse events and 19 (34%) patients discontinued because of disease progression. The most frequent adverse events (all grades) were nausea, vomiting, and diarrhea, which were reported by 59%, 54% and 48% of patients, respectively. Grade 3/4 adverse events diarrhea occurred in 5 (9%) patients. Oral LDK378 was quickly absorbed with a half-life of about 36 hours. Shaw, *et al.* Abstract 440O

Nishio reported interim safety and efficacy results from the phase II portion of a phase I/II trial of CH5424802, an oral ALK inhibitor, in patients with ALK+ NSCLC. Phase I results that showed promising efficacy and acceptable safety with CH5424802 were previously reported at ASCO 2012. As of March 23, 2012, 34 patients with ALK-positive NSCLC, measurable disease, and no prior ALK inhibitor therapy were enrolled and treated with CH5424802 at 300 mg bid until progressive disease or intolerable toxicity. The majority (62%) of patients were never-smokers with ECOG performance score 0/1. Patients had received up to four prior chemotherapies. Among the first 15 patients receiving CH5424802, one patient achieved complete response and 10 patients showed partial responses, with a response rate of 73.3%. At the time of abstract submission, 30 patients remain on study (range 1-8 months). Most treatment-related adverse events were grade 1, with two cases of grade 3 neutropenia reported; no dose reductions were made. Just one case of treatment-related eye disorder, blurred vision, was reported, in contrast to the number of eye disorders frequently reported with crizotinib. Nishio, *et al.* Abstract 441O

Practice point and future research opportunities

Four new therapeutic agents currently being tested show considerable clinical benefit with acceptable toxicity in patient populations that were distinct, either regarding mutations or prior treatments. Further study is required to bring these agents to market for treatment of patients who are refractory to ALK and tyrosine kinase inhibitors.

AUY922 showed activity in both ALK+ and EGFR-mut patients, especially in EGFR-mut patients who progressed following treatment with TKIs. The response was seen in all treated patients with ALK+ NSCLC, whether they had failed or never received crizotinib.

Remarkable activity was observed with two ALK specific agents in patients with ALK+ NSCLC. Just over half of the patients receiving LDK378 showed a response and an 81% response rate was seen in patients who had failed crizotinib, while CH5424802 demonstrated clinically meaningful antitumor activity in a cohort of patients who had not received prior ALK inhibitor therapy.

Clinical activity of PI3K kinase inhibitor GSK458 in selected patient populations defined by predictive markers

GSK458 is an oral, potent inhibitor of PI3K (, , , and), mTORC1, and mTORC2. That has shown activity in cell lines with activated PI3K pathways. Munster reported study results of GSK458 in 170 patients with advanced solid tumors who received GSK458 at once (QD) and twice daily dosing (BID).The trial evaluated pharmacodynamics in unselected populations and clinical activity in specific mutation defined populations, including patients with PIK3CA-mutant and wild-type (wt) bladder cancer, renal cell carcinoma, PIK3CA-mutant metastatic breast cancer, and KRAS-wt metastatic endometrial cancer. Nearly half (49%) of patients were female; with a mean age of 57 years. Patients were administered GSK458 in doses that ranged from 0.1 to 3 mg and the maximum tolerated dose for both QD and BID was determined to be 2.5 mg. Longer median time above the target plasma concentration (20 ng/mL) was achieved with BID versus QD dosing of 21 hours compared with 8 hours in 6 and 18 patients, respectively. The pharmacodynamic effects suggest that activity of GSK458 is by on-target inhibition of PI3K. Most frequent drug related adverse events were diarrhea which occurred in 28%, fatigue in 24% and nausea in 23% of patients. Dose reduction occurred in two patients with grade 3 diarrhea. A dose response relationship was seen between GSK458 plasma concentrations and increases in serum insulin levels. Nine patients had pre/post-dose FDG-PET. Thirteen paired pre-/post-dose tumor biopsies were obtained and analysis of pre- and post-dose biopsy tissue for pAKT is ongoing. No responses were reported per RECIST, although one patient had a mean SUV value decrease by 30% post-dose. Objective responses were reported by one patient with PIK3CA mutant bladder cancer, in 2 patients with wild-type bladder cancer and 2 patients with renal cell; one patient had a complete response lasting more than 25 months, and one patient had partial response. No responses were seen in patients with PIK3CA-mutant breast cancer or KRAS-wt endometrial cancer. Munster *et al.* Abstract 442O

Practice point and future research opportunities

GSK458 showed promising activity in PIK3CA mutant bladder cancer and renal cell carcinoma, but not in other solid tumors. The maximum tolerated dose of GSK458 daily is 2.5 mg; diarrhea is a dose-limiting toxicity. Insulin levels may be a surrogate pharmacodynamic marker indicating target activity.

Phase I study of afatinib/nintedanib combination therapy of patients with advanced solid tumors

Results from a phase I trial that combined an irreversible ErbB family blocker, afatinib plus nintedanib, a triple angiokinase inhibitor of VEGFR, PDGFR and FGFR, showed activity from the combination in 45 heavily pre-treated patients with diverse tumor types. The trial determined the maximum tolerated dose (MTD) of afatinib within a 28 day cycle by escalating the dose from 10 to 40 mg once daily (QD)

given either continuously or intermittently, every two weeks; nintedanib was given at a fixed-dose of 200 mg twice daily (BID) that was lowered to 150 mg BID after protocol amendment. Secondary endpoints were safety, efficacy, pharmacokinetics (PK), and analysis of circulating tumor cells (CTCs). Treatment continued until disease progression or intolerability. The study included 26 men and 19 women with a median age of 56 years with heavily pretreated non-small cell lung cancer, colorectal, breast, melanoma and ovarian cancer. Two MTDs were established: afatinib given continuously at 40 mg QD or given intermittently at 30 mg QD, plus nintedanib 150 mg BID. Evidence of antitumor activity was demonstrated by 2 patients, one with HER2-negative breast cancer and one with head and neck squamous cell carcinoma who achieved partial responses (RECIST) and by 27 patients who achieved stable disease, which lasted more than 3 months in 8 patients. No drug-drug interaction was seen. Soria *et al.* Abstract 446PD

Practice point and future research opportunities---

Afatinib plus nintedanib at the maximum tolerated dose showed a manageable safety profile. Anti-tumor activity was demonstrated by inhibiting multiple signaling pathways using the given on either a continuous or intermittent schedule in patients with diverse advanced solid tumors.

GASTROINTESTINAL TUMORS

COLORECTAL CANCER

PETACC8: No gain from adding cetuximab to FOLFOX4 in patients with resected stage III colon cancer, but benefit observed in some subgroups

Final results of the PETACC8 Intergroup phase III trial showed that adding cetuximab to FOLFOX4 does not improve overall survival in patients with resected stage III colon cancer whose tumors express KRAS-wild type (-wt) and KRAS/BRAF-wt. Patients with colon cancer were randomized between 28 to 56 days following resection to receive either 12 biweekly cycles of FOLFOX4 alone (arm A) or together with weekly cetuximab (arm B) at 250 mg/m2 following the initial dose of 400 mg/m2. The primary endpoint was disease free survival (DFS). The trial enrolled 1,602 KRAS-wt patients; arm A had 811 patients and 791 patients were randomly assigned to arm B. BRAF status was determined in 1134 (71%) KRAS-wt patients. Analysis done at a median follow-up of approximately 40 months showed no difference between arms for either DFS (HR 1.047; p = 0.66) or overall survival (OS) (HR 1.09; p = 0.55) in KRAS-wt patients. No differences were observed in 984 KRAS/BRAF-wt patients in DFS (HR 0.985; p = 0.91) or OS (HR 0.98; p = 0.92). Poorer DFS outcomes were seen with cetuximab in 149 patients older than 70 years (HR 1.97; p = 0.051), in 666 females (HR 1.45; p = 0.03) and in 570 patients with right-sided colon cancer (HR 1.40; p = 0.04).

The trial was discontinued by 42.7% of patients over 70 years in the cetuximab group versus 26.4% of patients receiving only FOLFOX4. A trend towards better outcome was seen in patients with poor prognosis, high grade, T4N2 tumors, perforation/obstruction or VELI+ tumors that was significant in 146 patients who were pT4N2 at diagnosis HR 0.55; p = 0.01. Taieb, *et al.* Abstract LBA4

Practice point and future research opportunities

Adding cetuximab to FOLFOX4 did not improve disease-free survival in patients with colon cancer and the primary endpoint of the study was not met, but benefit was seen in patients with pT4N2 tumors. Patients who were elderly, female or had right-sided tumors had poorer outcomes with cetuximab and MSI analysis is ongoing to understand these results.

CORRECT: Overall survival update of regorafenib in metastatic colorectal cancer

Updated overall survival (OS) results from the CORRECT trial presented at ESMO 2012 confirmed results previously reported at ASCO 2012. The CORRECT study evaluated the oral multikinase inhibitor regorafenib in patients with documented metastatic colorectal cancer whose disease had progressed during treatment or within three months of receiving standard therapy. A total of 760 enrolled patients who were randomized 2:1 to receive best supportive care plus either regorafenib (n=505) or placebo (n=255) on a 3 weeks on/1 week off schedule. The primary endpoint of OS was met at a pre-planned interim analysis. A descriptive updated analysis of OS was performed based on a database cut-off of November 13, 2011, that showed hazard ratio (HR) for regorafenib versus placebo of 0.76, p = 0.0038. Median OS with regorafenib was 6.4 months compared to 5.6 months with placebo. Overall survival rates at 6 and 12 months were 52.2% and 24.1% with regorafenib compared to 43.1% and 17.0% with placebo, respectively. These data are updates from the previously reported OS data from an earlier interim analysis that was based on 432 (74%) events, which showed a HR of 0.77, p = 0.0052. An average of 78.9% and 90.2% of the planned doses of regorafenib and placebo, respectively, were administered. The mean treatment duration was 12.1±9.7 weeks with regorafenib and 7.8±5.2 weeks with placebo. Incidence of treatment-emergent, adverse events associated with regorafenib was similar across age, sex, renal function and hepatic function subgroups; however, incidence of 98.6% in Asian patients compared with 92.3% in Caucasian was observed and the incidence of treatment related adverse events was also higher in patients with a baseline ECOG performance status (PS) of 0 (97.0%) compared with patients with ECOG PS 1 (88.6%). Van Cutsem, *et al.* Abstract LBA18

Practice point and future research opportunities

The robust benefit seen with first-line regorafenib compared to placebo was confirmed in an updated analysis in patients with metastatic colorectal cancer.

BEBYP: Continuation of bevacizumab beyond progression improves survival in patients with metastatic colorectal cancer

A phase III study conducted by the Gruppo Oncologico Nord Ovest (Italy) evaluated whether continuing bevacizumab with second line chemotherapy beyond progression would improve survival in patients with unresectable metastatic colorectal cancer (mCRC), as suggested by retrospective data. The trial randomized patients with mCRC who had received bevacizumab plus first line chemotherapy with fluoropyrimidine, FOLFIRI, FOLFOX or FOLFOXIRI to receive a second line of chemotherapy using either FOLFOX or FOLFIRI alone (arm A) or together with bevacizumab (arm B). Patients were stratified according to center, performance status (PS 0 vs. 1-2), disease free interval from the last administration of first line chemotherapy (3 months vs. >3 months) and the second line regimen. The primary endpoint was progression-free survival (PFS). The trial was designed to randomize 262 patients but accrual was halted on May 11th 2012 when it was noted that the similarly designed AIO/AMG ML18147 trial showed improved overall survival (OS) with bevacizumab beyond progression. Prior to the early end, the trial had randomized 185 patients; 184 patients were included in the intent to treat analysis since one patient had been randomized in error. Arm A comprised 92 patients who were 75% male with a median age of 66 years; 82% of patients had PS 0 and 76% had disease at multiple sites; liver only disease was seen in 15% of patients. Patients in arm B were slightly younger with a median age of 62 but other characteristics were the same or similar to arm A. The study met the primary endpoint; at median follow up of 18 months there were 172 (93%) events for PFS and median PFS was 4.97 months for arm A chemotherapy alone patients compared to 6.77 months for arm B plus bevacizumab patients, hazard ratio (HR) 0.65, p = 0.0062. A PFS analysis that adjusted for stratification factors, age and sex confirmed that bevacizumab added to chemotherapy improved PFS over chemotherapy alone, HR 0.70, p = 0.032. An increased response was also demonstrated in arm B with response rates of 18% for chemotherapy alone and 21% for chemotherapy plus bevacizumab, but the difference was not statistically significant. Overall survival data are not yet mature with arm A having 52 events and arm B having 46 events thus far. The adverse event profile was consistent with previously reported data for bevacizumab plus chemotherapy. Masi, *et al.* Abstract LBA17

Practice point and future research opportunities

This is the second randomized, controlled trial to show continued bevacizumab plus second-line chemotherapy after progression improves progression-free survival in patients with metastatic colorectal cancer and may represent a new treatment option.

Maintenance treatment with MGN1703 following standard first line treatment prolongs progression-free survival in patients with metastatic colorectal cancer

Results of maintenance therapy with MGN1703 following successful standard first line treatment in patients with metastatic colorectal cancer (mCRC) was reported by Arnold. MGN1703 is a synthetic DNA-based immunomodulator with TLR-9 agonist activity. The phase II/III IMPACT study evaluated the clinical efficacy, immunogenicity and safety of MGN1703 compared to placebo in patients with mCRC who achieved complete response (CR), partial response (PR) or stable disease (SD) following 4.5 to 6 months of first-line standard therapy with FOLFOX/XELOX or FOLFIRI, both with and without bevacizumab (investigator´s choice). Randomization following enrollment was halted after interim analysis of unblinded data demonstrated a strong therapeutic effect with MGN1703; the hazard ratio (HR) was 0.53 (p = 0.062) in 55 patients comprising the intent to treat population. In the per-protocol population, which excluded screening failures and contained 50 patients the HR was 0.43 (p = 0.015), again favoring MGN1703. Progression-free survival (PFS) in the pre-defined target population of 46 patients (2 out of 3 factors: CEA <30 x ULN, GGT <2 x ULN, AP <2 x ULN) was 5.8 months with MGN1703 compared to 2.7 months with placebo, HR 0.39; p = 0.013. Following three months of treatment, PFS rates were 43% with MGN1703 and 8% with placebo (p < 0.001); after six months rates were 34% compared to 8% (p = 0.011) and at nine months PFS rates were 22% compared to 0% (p = 0.010) for MGN1703 and placebo, respectively. The treatment was well tolerated with low toxicity. Drug-related adverse events included fever, atypical pneumonia, muscle aching, arthralgia, fatigue, paresthesia, rash, pruritus on injection sites, and increased ANA. Arnold, *et al.* Abstract 518O

Practice point and future research opportunities

A clinical study in patients with mCRC is being initiated to confirm the results of significantly prolonged progression-free survival associated with MGN1703 compared to placebo in patients successfully completing standard chemotherapy with or without bevacizumab and is accompanied by low toxicity. A confirmatory clinical study in patients with mCRC is currently being planned.

Switch to raltitrexed lessens fluoropyrimidine induced cardiac toxicity

Treatment management of patients who experienced cardiac toxicity, a rare but potentially fatal side effect of fluoropyrimidine therapy, was investigated in the ARCTIC trial. A clinical audit was done of 42 patients who were switched to raltitrexed after being identified with fluoropyrimidine-associated cardiac toxicities, including 42 patients who experienced angina, 5 with myocardial infarct and two with arrhythmia (some patients experienced more than one event); 8 patients experienced two separate cardiac toxicity events, and two patients had three events prior to the switch. The majority, 39 patients had been treated for colorectal cancer, two for esophageal and one patient for ampullary carcinoma. The median number of fluoropyrimidine cycles given before the switch to raltitrexed was 2, and ranged from 1 to 11 cycles of regimens that included FOLFOX, CAPOX, continuous infusion 5-fluorouracil, ECF or sole capecitabine. After the switch, 9 patients received only raltitrexed, 32

patients were given raltitrexed plus other agents or radiotherapy and one patient received a sequence of raltitrexed followed by a combination for a median number of six raltitrexed cycles (range 1-21). The rate of cardiac toxicity was 2.4% (p = 0.004) following the switch to raltitrexed, a much lower rate than the 20% reported previously by Jensen *et al*. for continued fluoropyrimidine treatment of patients with diverse cancers; one patient experienced a potentially related cardiac event of acute arrhythmia after five months of raltitrexed treatment. Price *et al.* Abstract 5190O

Practice point and future research opportunities

Raltitrexed may be considered as a treatment option for patients who show benefit, but experience cardiac toxicity, following treatment with fluoropyrimidines.

Meta-analysis of data from the CAIRO, CAIRO2, COIN and FOCUS studies evaluates effect of deficient mismatch repair and BRAF mutation status on survival in patients with metastatic colorectal cancer

Venderbosch provided data on the prognostic value of BRAF mutation in combination with deficient mismatch repair (dMMR) from a large series of patients with metastatic colorectal cancer (mCRC) in a meta-analysis of four trials: CAIRO, CAIRO2, COIN and FOCUS. A higher incidence of BRAF mutation was seen in patients with dMMR in this cohort of patients with advanced disease than previously reported for patients with early-stage CRC. They determined hazard ratios (HR) for progression free survival (PFS) and overall survival (OS) in relation to both BRAF and MMR status using Cox regression analysis. Data from 3064 patients reveal that 151 (4.9%) patients exhibited dMMR, and 263 (8.6%) patients displayed BRAF mutation, which was seen in 211 (7.2%) patients with a proficient mismatch repair system (pMMR) and 52 (34.4%) patients with dMMR. Progression-free survival, but not OS, was significantly worse for patients with dMMR compared to those with pMMR, HR 1.2 and HR 1.13, respectively. Both PFS and OS were significantly worse for BRAF mutation compared to BRAF wild type (wt) (PFS, HR=1.28 and OS, HR=1.81). Among patients with pMMR, patients with BRAF mutation showed significantly worse PFS and OS compared to BRAF wt patients: HR 1.32 and HR 1.88, respectively. Patients with dMMR showed no significant differences in PFS and OS between patients with BRAF mutation. In patients with BRAF mutation, PFS and OS did not differ significantly between patients with pMMR and those with dMMR. In patients with BRAF wt, PFS and OS also did not differ significantly between patients with pMMR and dMMR. Venderbosch et *al.* Abstract 521O

Practice point and future research opportunities

In this meta-analysis of patients with metastatic colorectal cancer, deficient mismatch repair associates with poorer progression-free survival compared to patients with pMMR. BRAF mutation is

prognostic for overall survival and progression-free survival only in patients with pMMR. This study confirms that BRAF mutation is prognostic for poorer outcome compared to patients with BRAF wt mCRC.

A GEMCAD STUDY: Pharmacogenetic predictors of severe chronic peripheral neuropathy in stage II-III colon cancer patients following oxaliplatin-based adjuvant chemotherapy

Oxaliplatin-based chemotherapy is the standard adjuvant therapy given after resection of stage III and selected high-risk stage II colon cancer even though patients often develop cumulative peripheral neuropathy. Custodio *et al.* sought to identify genetic differences that could identify patients at risk for developing severe neuropathy. In GEMCAD, DNA was extracted from formalin-fixed-paraffin-embedded samples of 202 surgically treated high-risk patients with colon cancer who were treated with adjuvant oxaliplatin and fluoropyrimidines chemotherapy (25.24% FOLFOX and 74.75% CAPOX) over a four year period. Stage II disease was reported in 29.7% and stage III in 70.3% of patients. Single nucleotide polymorphisms (SNPs) in genes involved in oxaliplatin sensitivity were identified to predict severe, grade 2-3, oxaliplatin-induced chronic peripheral neuropathy. Genotyping was performed for 35 SNPs in 18 genes involved in oxaliplatin metabolism (ERCC and XRCC groups) and in cell cycle and drug transport using MassARRAY (SEQUENOM) technology. A total of 177 stage II-III patients with colon cancer who had also received oxaliplatin-based chemotherapy were enrolled as a validation set. At follow-up done at median 51.4 months, range 7-96 months, 48 (23.8%) patients in the first group experienced grade 2-3 oxaliplatin-induced chronic peripheral neuropathy. The cyclin H (CCNH) (rs2230641) C/C genotype associated with a higher risk of severe oxaliplatin-induced chronic peripheral neuropathy. It was seen in 57.1% of patients with C/C genotype, 24.2% C/T and 21.3% of patients with T/T ($p = 0.041$). In addition, patients harboring the CCNH (rs2230641) C/C and/or ATP-binding cassette subfamily G member (ABCG2) (rs3114018) A/A haplotype had a higher risk of 36.5% of grade 2-3 oxaliplatin-induced chronic peripheral neuropathy compared to 19.6% seen with CCNH (rs2230641) any T and ABCG2 (rs3114018) any C haplotype ($p = 0.022$). Validation in the second cohort showed a significant association between high risk haplotypes and oxaliplatin-induced chronic peripheral neuropathy ($p = 0.003$). Custodio *et al.* Abstract 527PD

Practice point and future research opportunities

An array of single nucleotide polymorphism in CCNH and ABCG2 genes predicts the risk of patients with stage II-III colon cancer developing severe oxaliplatin-induced chronic peripheral neuropathy and may be useful in deciding on alternative adjuvant treatment for risk patients.

The effect of chemotherapy holiday on overall survival in patients with advanced colorectal cancer

The controversy surrounding whether continuous or interrupted chemotherapy strategies have more benefit was addressed in a meta-analysis of four randomized controlled trials comparing the impact on overall survival of continuously administered chemotherapy versus interrupted chemotherapy in patients with metastatic colorectal cancer (mCRC). A systematical search was done of PubMed, Cochrane Library and ASCO/ESMO abstracts up to February 2012 for all clinical trials randomizing patients with mCRC to receive either continuous or interrupted chemotherapy until progression or discontinuation either after maximal response or a fixed number of cycles. Hazard ratios (HR) were calculated for the meta-analysis; statistical heterogeneity of data was evaluated by the chi-square test and expressed using the I2 index. The search retrieved 42 randomized clinical trials; four were ultimately considered eligible that included 1776 patients. Progression-free survival (PFS) was not analyzed due to differences in PFS definitions across trials. The median chemotherapy free interval (treatment holiday) in the discontinuation group was 3.9 months. The meta-analysis of overall survival favored continuous therapy over chemotherapy holiday; a statistically significant survival benefit was demonstrated with continuously given chemotherapy, HR 0.90, p = 0.03 over chemotherapy that employed a holiday strategy. Pereira *et al.* Abstract 528PD

Practice point and future research opportunities

Modest but significantly prolonged overall survival was observed in patients with advanced colorectal cancer receiving continuous chemotherapy until tumor progression over those given chemotherapy that was interrupted after a fixed number of cycles or a response was observed. Continued therapy may be considered for selected patients with more aggressive disease.

UPPER GASTROINTESTINAL TUMORS

START trial update: Docetaxel added to S-1 improves outcome for patients with advanced gastric cancer (JACCRO and KCSG study group)

Asian patients with unresectable or recurrent gastric cancer showed improved progression-free survival when docetaxel was added to S-1, according to a new analysis of a randomized phase III trial. S-1 is an oral fluoropyrimidine that is widely used as a standard treatment for advanced and recurrent gastric cancer in East Asia. Results from a multicenter study done in Japan and Korea that evaluated S-1 plus docetaxel in patients with advanced gastric cancer were reported at ASCO 2011 Gastrointestinal Symposium (Kim, *et al.)* where an independent biostatistician pointed out that the large number of censored cases led to an insufficient number of events for proper analysis. The analysis was redone according to the biostatistician's recommendations, including further follow-up of survival status, and the corrected analysis was presented at ESMO 2012. In the phase III START trial, previously untreated patients with advanced gastric cancer were randomly assigned to docetaxel plus S-1 or S-1 alone, respectively. The data from 635 patients were analyzed and showed median

overall survival, the primary endpoint, of 12.48 months in the docetaxel/S-1 arm compared to10.78 months in the S-1 arm, p = 0.0319. The secondary endpoints also showed improved outcome with combination treatment; progression-free survival was 5.29 months and 4.17 months in the docetaxel/S-1 and S-1 groups, respectively (p = 0.001). A significantly higher response rate of 38.8% was seen in the docetaxel/S-1 patients compared to 26.8% in those receiving S-1 group, p = 0.0048; complete response was achieved by 3 patients receiving combination compared to 5 patients in the sole S-1 arm, PR was achieved by 89 versus 60 of patients docetaxel and S-1 patients, respectively. Stable disease was seen in 82 versus 92 and progressive disease was seen in 45 versus 68 patients receiving S-1/docetaxel and S-1, respectively. Neutropenia was the most frequent adverse event in the docetaxel/S-1 arm with one death occurring from grade 4 thrombocytopenia. Yoshida, *et al.* Abstract LBA19_PR

Practice point and future research opportunities

Adjunct docetaxel with S-1 significantly improved outcome over S-1 alone in untreated patients with advanced gastric cancer that provides a new treatment option despite the occurrence of serious hematological toxicities.

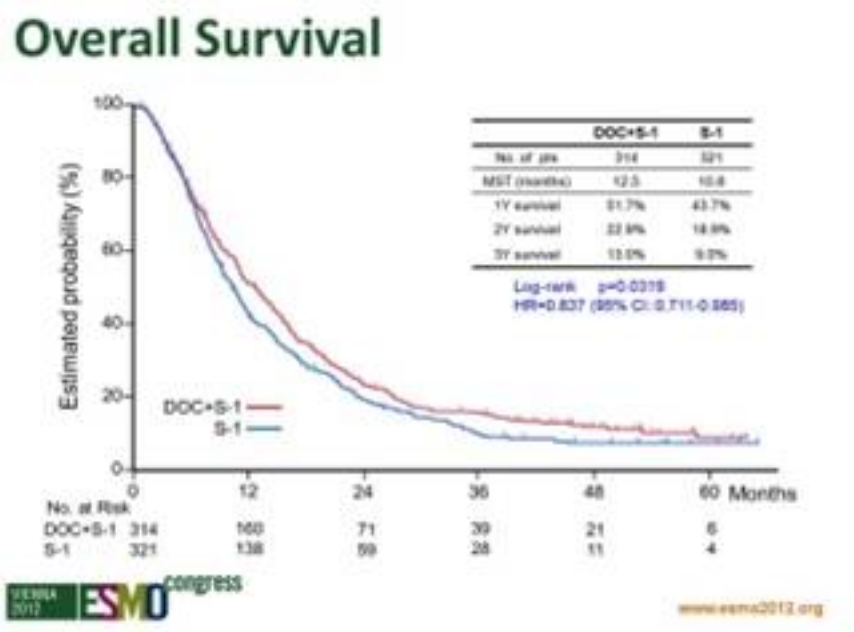

Figure 3. Overall survival curve in the START trial

EXPAND: Cetuximab in combination with capecitabine and cisplatin as first-line treatment in advanced gastric cancer

EXPAND was a large open-label, randomized, controlled, phase III trial of cetuximab plus

capecitabine and cisplatin in patients with advanced gastric cancer, which has a poor prognosis and no established standard treatment. The current trial compared capecitabine and cisplatin with and without anti-EGFR agent cetuximab in patients with gastric and gastroesophageal junction cancer. Between June 2008 and December 2010, 904 patients from 25 countries were enrolled and randomized; 455 patients received capecitabine and cisplatin plus cetuximab and 449 received only capecitabine and cisplatin. Overall, patients were 74% male and 83% had stomach cancer; 97% of the patients had metastatic disease. Patient outcome was similar between treatment groups and the primary and secondary endpoints were not met; progression-free survival was 4.4 versus 5.6 months and overall survival was 9.4 versus 10.7 months with cetuximab combination and control treatment, respectively. Overall response rates were 29% with cetuximab and 30% with control. Safety profiles were consistent with those known for each agent but more grades 3/4 and serious adverse events were reported in the cetuximab arm. Tissue was available from 97% of patients and biomarkers analysis is ongoing. Lordick *et al.* Abstract LBA3

Practice point and future research opportunities

No benefit was seen from adding cetuximab to first-line capecitabine and cisplatin for treating patients with advanced gastric cancer. No new safety signals were raised for any agent. More study is needed to find effective treatments for these patients.

Gefitinib shows benefit over placebo in patients with good performance status and esophageal cancer progressing after chemotherapy

Gefitinib is an EGFR kinase inhibitor that has shown a trend in several phase II trials toward improved survival in patients with metastatic esophageal cancer who progressed following 1st/2nd line chemotherapy. Based upon the rationale that patients with esophageal cancer and high EGFR expression have a poorer prognosis, the Cancer Research UK phase III multi-center, randomized, double-blind, placebo-controlled trial tested gefitinib against placebo in patients with esophageal cancer who progressed after chemotherapy. Patients with performance status 0-2 and measurable/evaluable metastatic esophageal or types I/II junctional adeno- or squamous cell carcinoma were randomized 1:1 to gefitinib or placebo. Increased overall survival (OS) at one year of 10 to 18% was the trial's primary endpoint with secondary endpoints of safety, progression-free survival (PFS), health-related quality of life (HRQL; EORTC QLQ-C30 and QLQ-OG25) and predictive biomarkers. The trial enrolled 450 patients from 51 centers in the UK from March, 2009 until November, 2011. The median age was 64 years and 83% of patients were male in the two well-balanced treatment arms. Adenocarcinoma and esophageal cancer was present in 76% and 78% of patients, respectively, and 25% with performance status (PS0 0, 54% PS 1, and 21% of patients had PS 2. The primary endpoint was not met, although gefitinib again showed a trend towards improved OS in these patients; median OS with gefitinib was 3.73 months compared to 3.60 months with

placebo, hazard ratio (HR) 0.90; p = 0.285. Median PFS improved from 35 days with placebo to 49 days with gefitinib, p = 0.017. The disease control rate at 8 weeks was 26% with gefitinib and 16.0% with placebo, p = 0.014. No new safety signals were seen. Performance status was determined to be a highly significant prognostic factor for both PFS and OS. The median PFS was 1.8, 1.4 and 1.0 months and median OS was 6.0, 3.9 and 2.0 months, respectively, for PS 0, PS 1 and PS 2. HRQL factor of odynophagia, was improved with gefitinib, p = 0.004. The investigators are conducting a translational study to investigate the association between biomarkers and outcome in 300 patient samples. Ferry, *et al.* Abstract LBA20_PR

Practice point and future research opportunities

Gefitinib may be considered in the 2nd/3rd line setting in patients with esophageal cancer, which currently has no set standard therapy. Gefitinib demonstrated durable response, including prolonged progression-free survival and palliation of symptoms. Performance status at baseline was indicative of patient outcome.

Patients with advanced hepatocellular carcinoma show no benefit from adding erlotinib to sorafenib

Zhu and colleagues tested whether adjunct erlotinib, a direct and reversible EGFR tyrosine kinase inhibitor, could have synergistic or additive antitumor effects when used with sorafenib in patients with advanced hepatocellular carcinoma. The phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib enrolled 720 patients with advanced hepatocellular carcinoma aged 18 or more years, ECOG performance status (PS) 0-1 and Child-Pugh class A. Patients were stratified by ECOG PS of 0 or 1, macroscopic vascular invasion and/or presence of extrahepatic spread, smoking status (current, former or never) and by region: the Americas and Europe vs. South Africa and Asia-Pacific. The patients were randomized 1:1 to receive either continuous treatment with oral sorafenib 400 mg bid plus erlotinib 150 mg daily or sorafenib 400 mg bid plus placebo 150 mg daily and monitored every 6 weeks by CT scans. Median overall survival, the primary endpoint, in the 362 patients receiving the sorafenib/ erlotinib was 9.5 compared with 8.5 months in the sorafenib/placebo arm, HR 0.929, p = 0. 201. Time to progression also did not vary significantly between treatment arms and was 3.2 compared with 4.0 months, with sorafinib/erlotinib and sorafenib/palcebo, respectively. No significant regional differences in overall survival or time to progression were noted. While the overall response rate tended to be higher in the combination arm (p = 0.051), the disease control rates of 43.92% and 52.51% significantly favored the sorafenib/placebo arm, p = 0.0104. The median treatment duration of 2.8 and 4.0 months was longer with sorafenib/placebo, which reflected the percentage of patients withdrawing after completing one or fewer treatment cycles; the withdrawal rate was 34.0% in the sorafenib/erlotinib arm compared with 23.8% with sorafenib/placebo. The rates of treatment-emergent and drug-related adverse events were similar between arms; treatment-

emergent and drug-related serious adverse events were also similar (58.0% versus 54.6% and 21.0% versus 22.8% in the sorafenib/erlotinib and sorafenib/placebo arms, respectively). No new or unexpected toxicities were observed between combination treatment and sorafenib or erlotinib alone. Biomarkers analyses are ongoing. Zhu, *et al.* Abstract LBA2

Practice point and future research opportunities

Erlotinib added to sorafenib did not improve overall survival or time to progression over sole sorafenib; sole sorafenib remains the standard of care in patients with advanced hepatocellular carcinoma. Safety profiles were similar between the two treatment groups and consistent with those of each individual agent; however, toxicity and the withdrawal rate were higher in the erlotinib/sorafenib arm, with fewer patients completing one or more cycles.

GENITOURINARY TUMORS

PROSTATE CANCER

MAINSAIL: Addition of lenalidomide to docetaxel and prednisone does not benefit patients with castration-resistant prostate cancer

MAINSAIL was a phase III, multicenter, randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of lenalidomide added to docetaxel and prednisone compared to docetaxel and prednisone plus placebo as first-line treatment for patients with castration-resistant prostate cancer (CRPC). The trial enrolled 1059 chemotherapy-naive patients with progressive metastatic CRPC who were randomized to oral lenalidomide at 25 mg/day on days 1-14 of each 21-day cycle or placebo; all trial participants received docetaxel intravenously at 75 mg/m2 on day 1 of each cycle, and prednisone at 5 mg twice daily. The primary endpoint was overall survival (OS) and secondary endpoints were progression-free survival (PFS), objective response rate, and safety. The lenalidomide arm had 533 patients and 526 patients were in the placebo arm. The arms were well balanced; the overall mean age was 69 years and ECOG performance status were 0 in 48.1% and 1 in 47.5% of patients. Median number of cycles administered was 6 and 8 in the lenalidomide and placebo arms, respectively. Median OS was 77 weeks with lenalidomide and compared to median not reached with placebo, hazard ratio (HR) 1.53, p = 0.0017 and median PFS was 45 and 46 weeks with lenalidomide and placebo, respectively, HR 1.32, p = 0.0187. The most commonly reported adverse events of grade 3 with lenalidomide were neutropenia (22%), febrile neutropenia (12%), and neutropenic sepsis (3%). Vascular events of grade > 3 were reported in 7.4% of patients in the lenalidomide arm compared to 4.4% in the placebo arm. No increased mortality due to toxicity was seen. Petrylak, *et al.* Abstract LBA24

Practice point and future research opportunities

Adding lenalidomide to docetaxel/prednisone did not improve overall or progression-free survival over placebo plus docetaxel/prednisone in patients with chemotherapy-naïve, progressive metastatic castration-resistant prostate cancer. Lenalidomide was also associated with greater toxicity. Studies are underway to evaluate the lack of benefit with lenalidomide; shorter treatment duration, lower dose intensity and earlier treatment discontinuation might have contributed.

ARADES trial: First-in-man study of ODM-201 in patients with progressive metastatic castration-resistant prostate cancer

The hallmark of castration-resistant prostate cancer (CRPC) is persistent, high level androgen receptor expression and resistance to conventional anti-androgens; ODM-201 is a new generation, androgen receptor antagonist that does not enter the brain in nonclinical models, unlike other anti-androgens, and inhibits androgen receptor function by blocking nuclear translocation. ODM-201 has no agonist activity when the androgen receptor is overexpressed. ARADES was a first-in-man, multi-center phase I/II dose-escalation trial in patients with progressive metastatic CRPC who were either treatment naive or had received prior chemotherapy. The study was started in March 2011 to assess safety, pharmacokinetics, and anti-tumor effects of ODM-201. The study planned to enroll three to six patients per dose-escalation cohort on the pre-planned doses of 100, 200, 300, 500, 700 and 900 mg twice daily. Once the safety of an administered dose was established, next dose level was administered, and patients at the previous dose level were allowed to continue treatment until progression or an intolerable adverse event occurred. The dose-escalation part of the study is ongoing at 900 mg dose level twice daily. To date, 21 patients have tolerated ODM-201 with no significant treatment emergent adverse events. The most common adverse events were asthenia, nausea and diarrhea. A prostate specific antigen (PSA) response, defined as a decrease of 50% or more of PSA levels, was achieved by 90% of pre-chemotherapy and 75% of post-chemotherapy patients, including all six patients who had previously received docetaxel. At 12 weeks, ODM-201 demonstrated partial response or stable disease by RECIST in soft tissue in all evaluable patients and stable disease in bone was achieved by 90% of evaluable patients. One patient who had previously received abiraterone experienced a 26% decrease in PSA levels.

The pharmacokinetics is linear in dose range 100 - 300 mg x 2 and the steady state is reached at day 8. The authors plan to assess ODM-201 in a larger phase II trial, and include CRPC patients with difficult to treat or resistant disease. Massard, *et al.* Abstract LBA25_PR

Practice point and future research opportunities

ODM-201, a novel and unique androgen receptor antagonist, showed high anti-cancer activity in

patients with metastatic castration resistant prostate cancer, including those receiving prior docetaxel. ODM-201 was also well tolerated at oral doses of 700 mg twice daily. Expansion of the phase II trial began in June 2012.

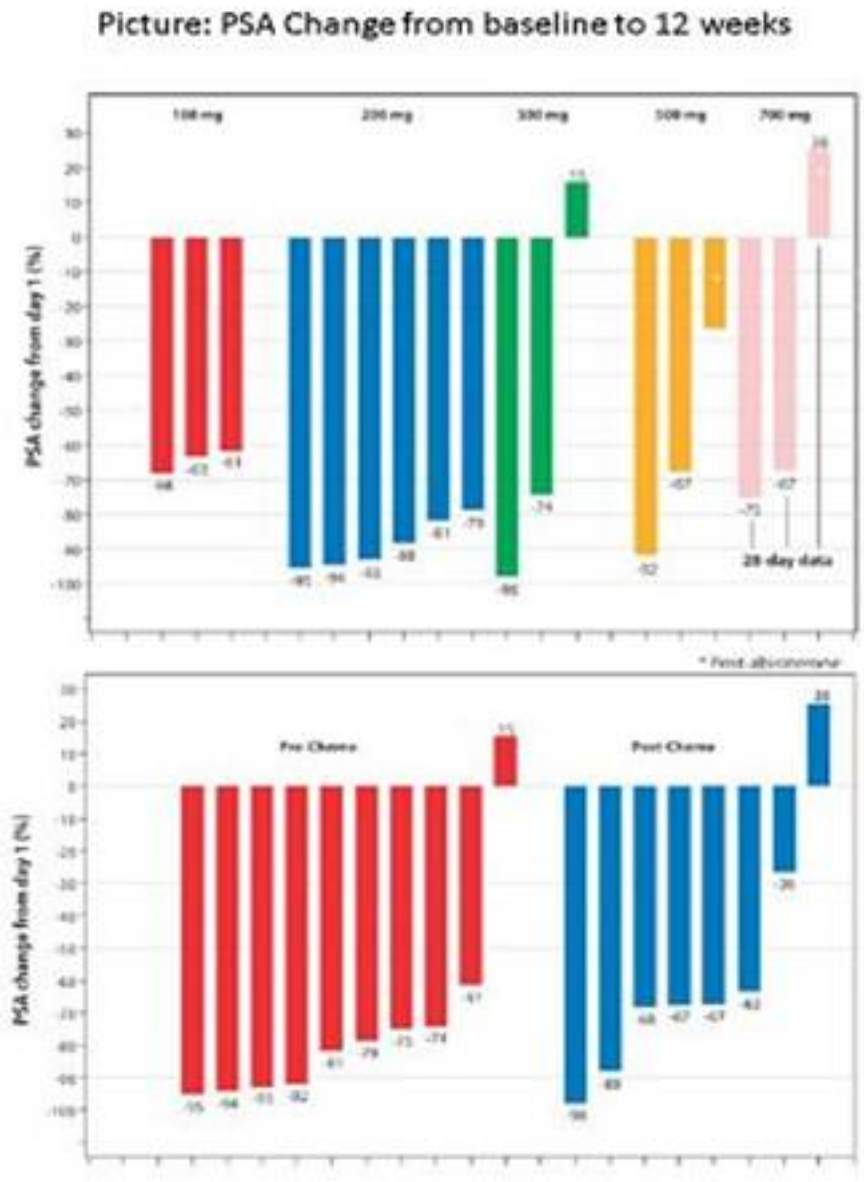

Figure 4. PSA change from baseline to 12 weeks observed in the ARADES study

RENAL CANCER

COMPARZ: A head to head comparison of pazopanib versus sunitinib as first-line treatment of patients with metastatic renal cell carcinoma

The randomized, open label, phase III COMPARZ (Comparing the Efficacy, Safety, and Tolerability of

Pazopanib vs. Sunitinib) trial was a head to head comparison of the efficacy, safety and tolerability of pazopanib versus sunitinib in 1110 treatment naive patients with clear cell metastatic renal cell carcinoma (mRCC) and measurable disease. The patients were randomized 1:1 to receive either continuous pazopanib or sunitinib in six week cycles. The primary endpoint of progression-free survival (PFS) was based on a planned 631 PFS events by independent review committee (IRC) to give the study 80% power to detect non-inferiority of pazopanib to sunitinib. Key secondary endpoints included overall survival (OS), overall response rate (ORR), adverse events, and quality of life. Patient characteristics were balanced between arms. The non-inferiority of pazopanib was demonstrated; the upper bound of the 95% confidence interval for PFS was less than 1.25. In 557 pazopanib treated patients versus 553 receiving sunitinib, the IRC and investigator determined median PFS rates were 8.4 versus 9.5 months, hazard ratio (HR) 1.0466 and 10.5 versus 10.2 months, HR 0.998, respectively. Median OS was 28.4 months with pazopanib and 29.3 with sunitinib, HR 0.93. The ORR favored pazopanib at 31% compared with 25% in the sunitinib arm. The most commonly reported adverse events reported by 40% or more patients of diarrhea, fatigue, hypertension and nausea occurred at similar frequency in both treatment arms. Hand-foot syndrome was reported by 29% of pazopanib and 50% of sunitinib patients; higher rates of dysgeusia, dyspepsia, hypothyroidism, mucositis, neutropenia, thrombocytopenia and neutropenia were also seen in the sunitinib arm. More patients in the pazopanib arm showed liver function adverse events; 33 versus 18 showed elevated ALT (HR 1.74) and 31 versus 25 showed elevated AST (HR 1.49) than with sunitinib. Differences in 11 of 14 quality of life domains, all favouring pazopanib, were reported but the minimally important difference was not met. Motzer, *et al.* Abstract LBA8_PR

Practice point and future research opportunities

Pazopanib demonstrated non-inferiority to sunitinib as first-line treatment of patients with clear cell metastatic renal cell carcinoma with a more favorable safety profile and improved patient reported quality of life domains.

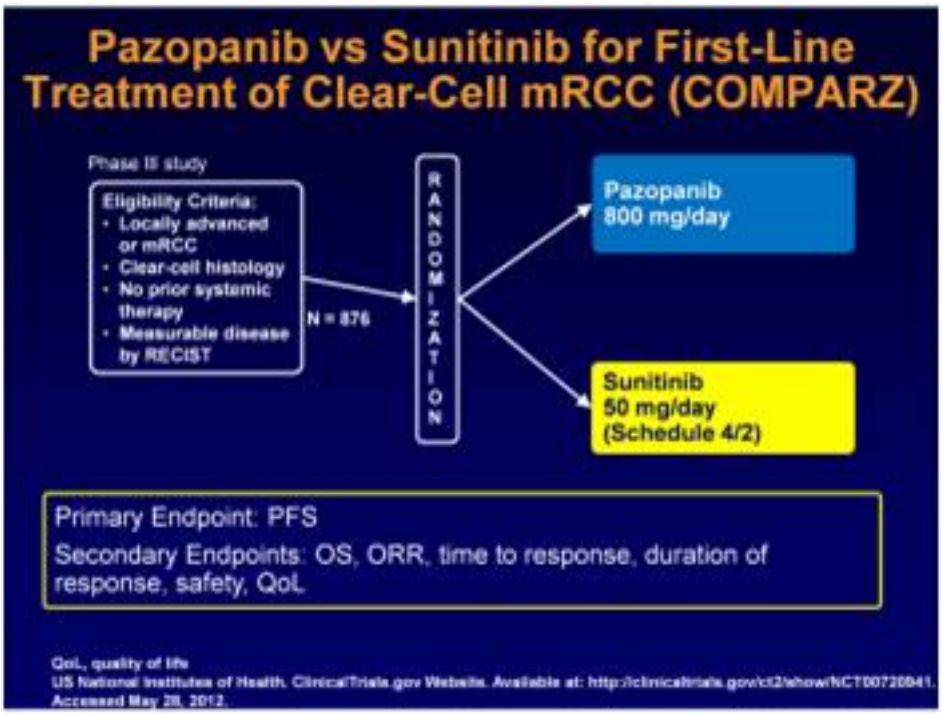

Figure 5. Design of the COMPARZ study

INTORSECT: No gain with second-line temsirolimus over sorafenib in metastatic renal cell carcinoma

The efficacy of temsirolimus following VEGF inhibitor therapy is not known but temsirolimus has shown an overall survival benefit compared to interferon- in treatment-naive patients with metastatic renal cell carcinoma. The multicenter, randomized, open-label phase III INTORSECT trial enrolled 512 patients with metastatic renal cell carcinoma from 112 sites in 20 countries. All patients were ECOG performance status 0 or 1 who progressed following first-line sunitinib therapy. Patients were stratified according to whether they had received fewer or more than six months of sunitinib therapy, prognostic risk, histology (clear cell or non-clear cell), and nephrectomy status and randomized 1:1 to receive temsirolimus 25 mg/wk intravenously or sorafenib 400 mg bid, with dose reductions allowed. Patient characteristics were well balanced between the 259 patients in the temsirolimus and 253 patients in the sorafenib arms; the median age was 60 years, 75% were male, and 67% of patients were Caucasian. Histology was predominantly clear cell in 422 patients and non-clear cell in 90 patients. The primary endpoint, 33% improvement in progression-free survival by independent central review, was not met and superiority of temsirolimus over sorafenib was not demonstrated. At data cut-off, 389 patients had independently assessed progression-free survival events and 351 patients had died. Median progression-free survival in the temsirolimus and sorafenib arms was 4.28 and 3.91 months, respectively; median overall survival was 12.27 and 16.64 months, respectively ($p = 0.0144$). The most commonly reported adverse events (all grades, all cause) with temsirolimus were rash, fatigue, diarrhea, anemia, and hyperglycemia, while diarrhea, rash, hand-foot syndrome, and

decreased appetite were reported with sorafenib. Hutson, *et al.* Abstract LBA22_PR

Practice point and future research opportunities

Temsirolimus did not show superiority over sorafenib in patients with renal cell carcinoma for progression-free survival or overall survival following first-line sunitinib, although more evaluation may define the optimal sequence after prior sunitinib therapy in patients with metastatic renal cell carcinoma.

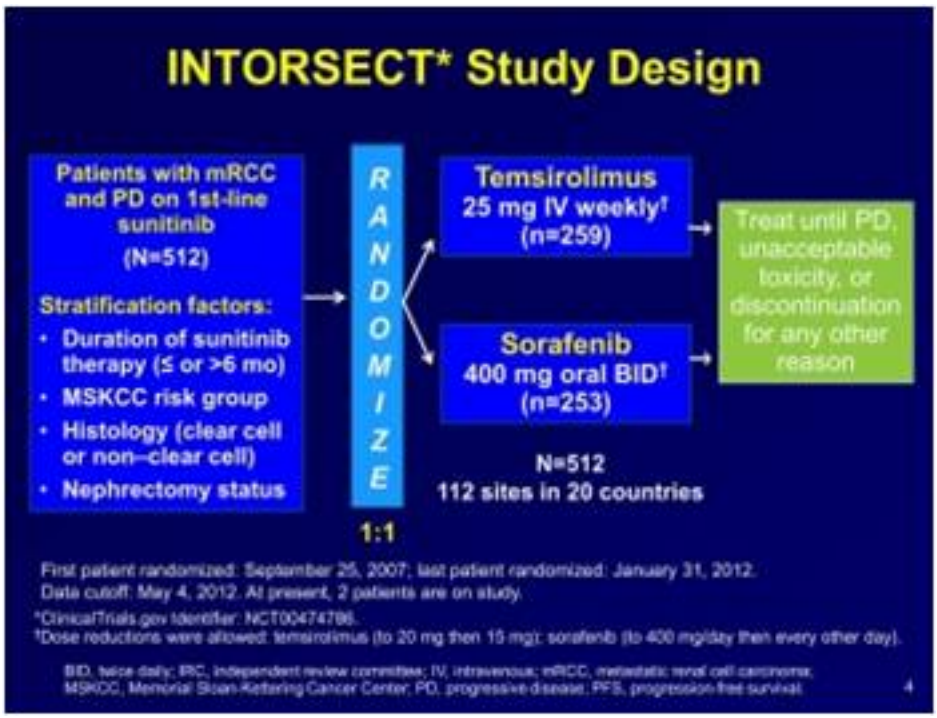

Figure 6. Design of the INTORSECT study

INTORACT: Temsirolimus and bevacizumab no improvement over interferon and bevacizumab in metastatic renal cell carcinoma

Patients with metastatic renal cell carcinoma did not show improved progression-free survival with first-line treatment with bevacizumab/temsirolimus in a global phase IIIb randomized, open-label, multicenter trial. The INTORACT trial stratified patients by MSKCC prognostic risk and nephrectomy status and randomized them (1:1) to receive either temsirolimus at 25 mg intravenously weekly or interferon at 9 MU subcutaneously 3 times weekly plus bevacizumab at 10 mg/kg IV every 2 weeks. Dose reductions were allowed for temsirolimus and interferon , but not for bevacizumab. Over a 2.5 year period, 792 patients were enrolled from 131 sites in 29 countries and randomized; 400 received bevacizumab/temsirolimus and 391 received bevacizumab/interferon . Baseline demographics were balanced between trial arms and the mean age was 58 years, with 70% of patients being male, 83%

white and 12% Asian. At the data cut-off of April 19, 2012, 489 patients had independently assessed progression-free survival (PFS) events and 409 had died. Median PFS with bevacizumab/temsirolimus was 9.1 months compared to 9.3 months with bevacizumab/interferon , p = 0.759. Median overall survival in the bevacizumab/temsirolimus group was 28.5 months and 25.5 months with bevacizumab/interferon , p = 0.638. Safety data were consistent with the known profiles of all agents. The frequency of pneumonitis was lower than expected at 1% in the bevacizumab/temsirolimus arm but grade 3 mucosal inflammation, stomatitis, hypophosphatemia, hyperglycemia, and hypercholesterolemia were more common, p < 0.001. Grade 3 neutropenia was more common with bevacizumab/interferon , p < 0.001. Rini, *et al.* Abstract LBA21_PR

Practice point and future research opportunities

Bevacizumab/temsirolimus treatment was not superior to bevacizumab/interferon as first-line therapy for patients with clear cell metastatic renal cell carcinoma who achieved nearly identical overall and progression-free survival with both treatments. Different adverse events occurred with each combination that could possibly alter the choice of treatment for patients with co-morbidities.

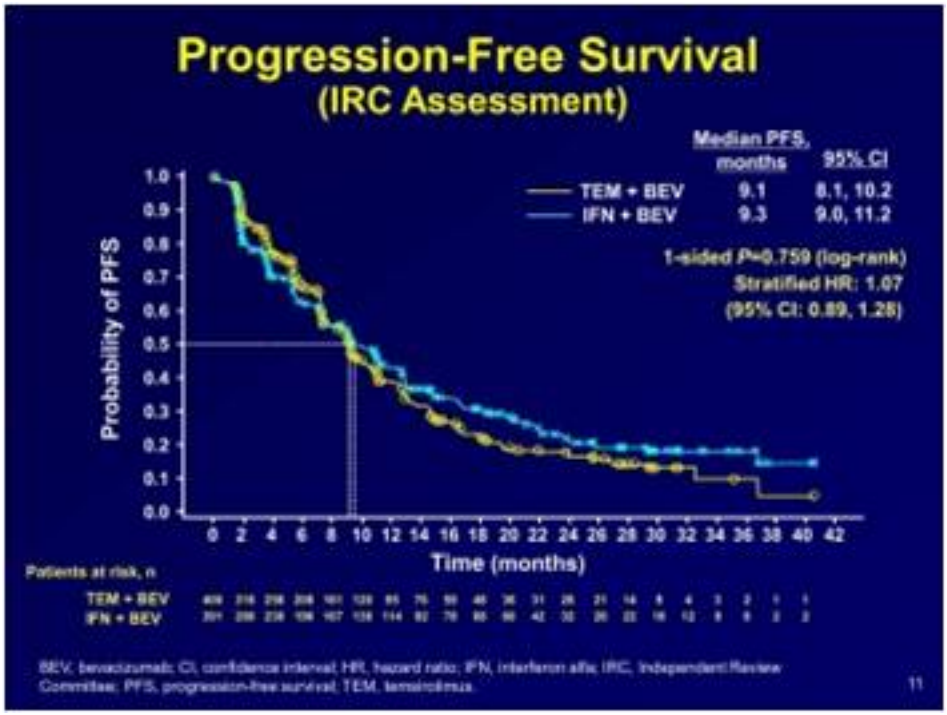

Figure 7. Progression-free survival in the INTORACT study according to independent committee review

Bevacizumab augments everolimus in patients with metastatic renal cell carcinoma

Based on prior results showing clinical benefit with the combination of interferon and bevacizumab in

patients with metastatic renal cell carcinoma (mRCC), a research team led by Ravaud investigated whether the addition of everolimus, an mTOR inhibitor, to bevacizumab could also improve progression-free survival (PFS) in these patients. They conducted the open-label, phase II RECORD-2 trial to compare both combinations as first-line treatment of patients with mRCC. The trial randomized therapy-naive patients with clear cell mRCC and prior nephrectomy to receive bevacizumab plus either everolimus or interferon. Patient characteristics were well balanced regarding age, gender and MSKCC risk in the 182 patients in the everolimus /bevacizumab arm and the 183 patients comprising the interferon/bevacizumab arm; 43% and 46% of patients had involvement in more than two organs, respectively. The median treatment duration was 8.5 months for everolimus/bevacizumab and 8.3 months with interferon/bevacizumab. No significant difference in PFS was seen between the two treatments. Median PFS per central review based on an estimate of the chance of a subsequent phase III trial success (50% threshold for phase II success) was 9.3 months with everolimus/bevacizumab and 10.0 months with interferon/bevacizumab (HR= 0.91, p = 0.485); the probability of subsequent phase III success was 5.1%. Results of central and local PFS analysis were consistent. The objective response rate was 27% with everolimus/bevacizumab and 28% with interferon/bevacizumab. Median overall survival (OS) was not reached in the everolimus/bevacizumab arm and was 25.9 months in the interferon/bevacizumab arm. Discontinuation due to adverse events occurred in 23 and 26% of patients in the two arms, respectively. Adverse events in the everolimus/bevacizumab arm of stomatitis proteinuria, diarrhea, hypertension, and epistaxis were reported by 63%, 49%, 39%, 38% and 35% of patients, respectively. Adverse events in the interferon/bevacizumab arm of decreased appetite, fatigue, proteinuria, and pyrexia occurred in 45%, 41% 37% and 45% of patients, respectively. Final OS analysis will be done after two-year follow-up. Ravaud *et al.* Abstract 783O

Practice point and future research opportunities

The RECORD-2 trial demonstrated similar progression-free survival and safety profiles with either everolimus plus bevacizumab or interferon plus bevacizumab combination treatment of patients with metastatic renal cell carcinoma.

BLADDER CANCER

Gemcitabine/platinum +/- trastuzumab in patients with HER2 over-expressed advanced/metastatic urothelial carcinoma

HER2 over-expression is seen in about 10% of metastatic urothelial carcinoma leading investigators to evaluate whether the addition of trastuzumab, which targets HER2 and blocks cell proliferation, to standard gemcitabine plus cis- or carboplatin chemotherapy would increase survival in these patients. HER2 over-expression was determined in 61 patients with advanced/metastatic urothelial carcinoma

based upon immunohistochemistry (IHC) score of 3+ (59 patients) or 2+ (2 patients) with positive FISH. Thirty-two (52%) chemotherapy naive patients with HER2 were randomized to arm A of standard treatment every 3 weeks for 6 cycles and 29 (48%) patients to arm B of standard therapy plus trastuzumab at 8 mg/kg charging dose then 6 mg/kg every cycle until progression. The median age was 64 years; 59 (98%) patients had undergone local surgery, 13 (22%) patients had received radiotherapy and 18 (30%) had received neoadjuvant chemotherapy. Fifty (82%) patients had baseline ECOG performance status (PS) of 0 and the remaining 11 (18%) patients had PS 1-2. The primary disease site was the bladder in 54 (89%) patients and locally advanced disease was seen in 11 (18%) patients, metastatic disease in 50 (82%) and visceral metastasis was seen in 34 (57%) patients. A median number of 6 cycles was administered (range 3-9). The overall response rate was 66% and 53% in arms A and B, respectively. Median progression-free survival (PFS) was similar in the two arms; PFS in arm A was 10.2 months and 9.3 months in arm B ($p = 0.7$). Median overall survival (OS) showed a trend in favor of arm B; OS was 15.7 in arm A and 16.8 months in arm B of chemotherapy plus trastuzumab. The longest OS of 28 months was observed in the gemcitabine/cisplatin/trastuzumab subgroup; however dyspnea was also more frequent in this arm. Grade 3/4 toxicities including neutropenia (72%, febrile 3%), thrombocytopenia (43%) and anemia (38%) were comparable between both arms. No toxic deaths occurred. Oudard *et al.* Abstract 786O

Practice point and future research opportunities

Since HER2 over-expression is rare in patients with advanced/metastatic urothelial cancer, lack of power prevented a conclusion regarding progression-free survival. However, the researchers hypothesized that overall survival results, especially in the gemcitabine/cisplatin/trastuzumab subgroup suggests that HER2 provides a target for trastuzumab that could work synergistically with cisplatin-based chemotherapy to increase clinical benefit.

TESTICULAR CANCER

Gemcitabine, oxaliplatin, and paclitaxel in the management of poor risk and refractory germ cell carcinoma

Results from a phase II study that tested whether the combination of gemcitabine, oxaliplatin, and paclitaxel (GOT) administered every two weeks would halt the progression of germ cell carcinoma (GCT) were reported by Dorff. The trial enrolled 30 men with refractory GCT who progressed following standard, salvage and stem cell treatments but excluded patients with growing teratoma syndrome. No prophylactic G-CSF was administered since the regimen intended to maximize oxaliplatin density. Patients had an absolute neutrophil count (ANC) 1000, or 700 with monocytosis, and platelets >75,000 to receive additional treatments and those demonstrating marker normalization received 3 further cycles. Primary sites of the carcinomas were the testis in 27 and mediastinal in 2

patients. Twenty patients had received prior surgery, 13 had resection of metastases and most patients had received two prior lines of chemotherapy. After treatment, 5 patients were eligible for resection. At one year, 7 (24%) patients were alive and showed no evidence of disease. Markers were normalized in 29% of patients. At a median follow-up of 28 months the median overall survival was 16.7 months, median progression-free survival was 10.8 months; the probability of achieving 2 year overall survival was 0.42 Serious adverse events were experienced by most patients: Grade 2/3 gastrointestinal toxicity was reported by 12 patients, 17 patients had grade 3/4 neutropenia, 7 experienced febrile neutropenia and neuropathy grades 1/2, and 3 were reported in 19 and 3 patients, respectively. One patient experienced grade 1 neuropathy and one patient died of pneumonia. Dorff *et al.* Abstract 79O

Practice point and future research opportunities

Gemcitabine, oxaliplatin, and paclitaxel shows a promise as a salvage treatment for patients with refractory germ cell carcinoma who achieved longer overall and progression-free survival than that demonstrated in a similar series of gemcitabine/oxaliplatin with and without paclitaxel.

GYNECOLOGICAL CANCERS

AURELIA: Adjunct bevacizumab plus single agent paclitaxel, pegylated liposomal doxorubicin or topotecan improves response and progression-free survival in platinum-resistant recurrent ovarian cancer

The phase III, randomized AURELIA trial enrolled patients with ovarian cancer who had progressed within six months of the last four or more cycles of platinum-based therapy, but excluded patients with refractory ovarian cancer, a history of bowel obstruction or who had received two or more prior forms of anticancer treatment. Paclitaxel, pegylated liposomal doxorubicin (PLD), or topotecan was administered to each patient, based upon investigators' choice, prior to the patients being randomly assigned to receive the sole chosen chemotherapy or the agent plus bevacizumab until progression, unacceptable toxicity or withdrawal of consent. Of the 361 patients randomized, 115 received paclitaxel, 126 PLD and 120 patients were given topotecan. All six treatment arms were balanced regarding patient age, FIGO stage and platinum free interval. The hazard ratio (HR) for progression-free survival (PFS) by RECIST (primary endpoint) in the overall population in AURELIA was 0.4 ($p < 0.001$); results from the analysis of each treatment group were presented at ESMO 2012. Patients received a mean of 3 treatment cycles of sole PLD and topotecan, 4 cycles with sole paclitaxel and bevacizumab plus PLD and patients received 6 cycles of bevacizumab/paclitaxel or bevacizumab/topotecan. Median PFS in 55 patients receiving sole paclitaxel, 64 PLD patients and 63 patients receiving only topotecan was 3.9, 3.5 and 2.1 months, respectively. PFS was improved by

adjunct bevacizumab and increased to median 5.4 and 5.8 months in 62 patients in the bevacizumab/PLD and 57 patients receiving bevacizumab/topotecan. Median PFS was prolonged to 10.4 months in 60 patients treated with bevacizumab/paclitaxel over paclitaxel alone. The overall response rates by RECIST and/or CA-125 were 28.8% and 51.7% in the paclitaxel groups without and with bevacizumab, respectively. In the PLD cohort, the ORR was 18.3% in the PLD plus bevacizumab arm and 7.9% in the PLD alone arm, and in the topotecan cohort, the ORR was 22.8% in the bevacizumab arm and 3.3% in the topotecan alone arm. Hazard ratios for each cohort with bevacizumab plus chemotherapy compared to chemotherapy alone were 0.46, 0.57 and 0.32 for paclitaxel, PLD and topotecan, respectively. The incidence of grade 2 peripheral sensory neuropathy was 35% in the bevacizumab/paclitaxel cohort compared with 22% in patients receiving paclitaxel alone. The bevacizumab/PLD arm had an incidence of 27% grade 2 hand-foot syndrome compared with 14% in the PLD cohort. Grade 2 hypertension and proteinuria were seen in the paclitaxel and PLD plus bevacizumab cohorts but not in either of the topotecan cohorts. Grade 3 abdominal pain, vomiting and fatigue were more common with the sole agents than in any of those containing bevacizumab. Poveda, *et al.* Abstract LBA26

Practice point and future research opportunities

Bevacizumab plus chemotherapy should be considered the new standard of care for patients with platinum-resistant recurrent ovarian cancer; adding bevacizumab to chemotherapy with paclitaxel, pegylated liposomal doxorubicin or topotecan prolonged progression-free survival and the overall response rate in patients with across all cohorts over each chemotherapy regimen administered alone.

Subset results of a phase II randomized discontinuation trial of brivanib in advanced ovarian cancer

Brivanib is a novel oral selective dual inhibitor of FGF and VEGF that has shown preclinical activity against various tumor types. Previously reported data from this randomized discontinuation trial showed activity in patients with sarcoma and advanced solid tumors; data regarding the activity of brivanib in a subset of 126 patients with ovarian cancer are presented here. Patients with ovarian cancer who progressed following prior treatment were given open-label brivanib at 800 mg daily for a 12-wk lead-in period. They were then assessed by CT/MRI and patients showing complete (CR) or partial response (PR) continued on brivanib, with those experiencing progressive disease (PD) ending the study. Patients with stable disease (SD) were randomized to receive brivanib or placebo until PD or intolerance; patients receiving placebo with PD were allowed to crossover. Of the 126 participants, 63% had received more than three prior systemic regimens. The 111 (88%) patients who were FGF2 positive received brivanib. At week twelve, 12 patients, three who had received prior bevacizumab, achieved PR and SD was seen in 43 patients; the overall response rate (ORR) was

10% and disease control rate was 44%. After 12 weeks, 49 patients continued on study, 10 with PR remained on brivanib. Of 39 patients with stable disease, 19 were randomized to brivanib and 20 to placebo; two patients with PR were randomized in error. In this set of patients, median progression-free survival was 4 months with brivanib compared with 2 months for placebo, hazard ratio (HR) 0.54 ($p = 0.11$). In 36 FGF2+ patients the HR was 0.56 ($p = 0.14$). During this phase, three additional patients showed PR for a total of 15 PRs; ORR 12%. Patients who crossed over had a median subsequent progression-free survival of 1.5 months. The most frequent adverse events grade 3 were increased ALT (20%) and AST (14%), fatigue (12%), hyponatremia (9%), asthenia (7%), diarrhea (7%), hypertension (7%), abdominal pain (6%), and decreased appetite (6%). The trial was discontinued by 13% patients due to treatment-related adverse events. Kaye *et al.* Abstract 966O

Practice point and future research opportunities

Clinical activity of brivanib in patients with heavily pretreated ovarian cancer, including those with prior bevacizumab, was demonstrated by longer progression-free survival compared to placebo and by the overall response and disease control rates, warranting further study to confirm these results. Assessment of FGF2 as a predictive biomarker was prevented by the large number of FGF2+ patients on study. The results support further investigation of brivanib in ovarian cancer, potentially in patients with prior bevacizumab.

Updated overall survival from OCEANS: gemcitabine/carboplatin plus bevacizumab or placebo in platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer

The phase III, randomized controlled OCEANS trial showed significantly improved in patients with platinum-sensitive recurrent ovarian cancer ($p < 0.0001$). Overall response rate, duration of response, and independent review committee analyses all supported the clinical utility of adding bevacizumab to gemcitabine plus carboplatin. Overall survival (OS) data are now mature and results from the third interim analysis were presented at ESMO 2012. The OCEAN enrolled patients with ECOG performance status of 0 or 1, no prior bevacizumab or chemotherapy, who had a first recurrence of platinum-sensitive ovarian, primary peritoneal or fallopian tube cancer and measurable disease. Patients were randomized to arm A: gemcitabine/carboplatin/concurrent placebo or arm B: gemcitabine/carboplatin/concurrent bevacizumab followed by bevacizumab, until progressive disease (PD) or unacceptable toxicity. OCEAN met the primary endpoint of improving progression-free survival and response rate. At the data cutoff date, 286 events had occurred in 59% of patients and no difference in OS was seen between the arms. In a longer follow-up of a median 42 months, median OS was 33.7 months in arm A and 33.4 months in arm B. Long post progression survival was seen in both groups. Overall survival may have been confounded by cross over and by extensive therapy with bevacizumab given during the post progression period. Slightly fewer patients in arm B, 89% versus 86% of patients in arm A, received subsequent therapy. When given, subsequent

treatment included bevacizumab in 39% and 22% of patients in arms A and B, respectively. One patient per arm experienced grade 5 treatment-emergent adverse events and the number of deaths was balanced between arms, with the cause of death being primarily PD in both arms. Aghajanian et *al.* Abstract 967O

Practice point and future research opportunities

Overall survival was not enhanced by adding bevacizumab to gemcitabine/carboplatin but no detriment to overall survival was seen either, supporting the positive benefit: risk ratio of this regimen in significantly improving progression-free survival in patients with platinum-sensitive recurrent ovarian cancer. Overall survival could have been confounded by post progression bevacizumab treatment in the chemotherapy plus placebo arm.

Lurbinectedin shows activity in patients with platinum-resistant/refractory ovarian cancer

Preliminary results were reported from a randomized phase II trial of lurbinectedin (PM01183), a novel agent that binds the minor groove of DNA and is associated with inhibition of tumor growth resulting from reduced cell proliferation due to apoptosis of cells that undergo aberrations during mitosis. Lurbinectedin has shown activity in ovarian cancer cell lines, including several that display platinum-resistances, prompting investigators to test it in 22 patients with advanced platinum-resistant or refractory ovarian cancer. For inclusion in the exploratory part of the trial, patients must have had fewer than 3 prior chemotherapies, adequate major organ function and performance status between ECOG 0-2. One prior chemotherapy line had been received by 15 (68%) patients and 7 (32%) patients received 2 previous lines of chemotherapy for advanced disease. Six patients showed no response to the last platinum-containing chemotherapy (platinum resistant) and 16 were platinum-resistant, defined as having a platinum-free interval < 6 months. Patient age ranged from 35 to 77 years with a median of 59 years. Of the 22 patients evaluated for efficacy, 6 responded (two by Rustin and four by RECIST) for an overall response rate of 27% and one patient had a radiological complete response. Progression was seen in 6 (27%) patients at the first evaluation, yielding an overall disease control rate of 73%. Having demonstrated a minimum of two confirmed response rate, the trial was allowed to proceed to the second stage in April 2012 and enrolled 60 additional patients who were randomized to either lurbinectedin or comparator treatment with topotecan. This trial is ongoing; the preliminary toxicity profile showed myelosuppression, nausea/vomiting despite adequate prophylaxis, and fatigue to be the most common drug-related toxicity. Berton-Rigaud et *al.* Abstract 967O

Practice point and future research opportunities

Lurbinectedin showed promise for treating patients with platinum-resistant/refractory ovarian cancer

and is now being evaluated against comparator therapy with topotecan.

HEAD AND NECK CANCER

Panitumumab plus radiotherapy versus chemoradiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck

CONCERT-2 was a phase II, randomized estimation study with no formal hypothesis testing that demonstrated improved locoregional control rate with panitumumab compared to that of chemoradiotherapy in patients with unresected, locally advanced squamous cell carcinoma of the head and neck. Treatment-naive patients with stage III, IVA, or IVB disease of all sites, excluding the nasopharynx, were randomized 2:3 to open-label chemoradiotherapy with 2 cycles of cisplatin during accelerated fractionation radiotherapy or panitumumab given as 3 cycles plus radiotherapy. Key secondary endpoints were progression free survival (PFS), overall survival (OS), and safety. The 151 treated patients had a median age of 58 years, 64% had ECOG performance status 0 and 84% of patients were male; 90 patients received panitumumab plus radiotherapy and 61 chemoradiotherapy. The 2-year locoregional control rate was 51% and 40 versus 62%, respectively. Both PFS and OS favored chemoradiotherapy; PFS hazard ratio (HR) 1.73 ($p = 0.03$) and OS HR 1.59 ($p = 0.10$). Preplanned HPV subset analysis by p16 immunohistochemistry was done on available samples; of 99 patients with tumors evaluable for HPV, 24% were HPV positive. A difference was observed in PFS in 75 HPV- tumors (HR 2.04; $p = 0.04$), locoregional control rate and OS showed similar trends favoring chemoradiotherapy, but small sample size limited conclusions. Dose intensity was high for all components of therapy in both arms. Grade 3+ adverse events were similar between treatment arms with occurred in 85% of patients receiving panitumumab and 81% of chemoradiotherapy patients reporting adverse events; however, differences in grade 3+ toxicity between arms was seen, with 35% and 3% of panitumumab and chemoradiotherapy patients, respectively, reporting skin disorders. However, neutropenia and febrile neutropenia were seen more often with chemoradiotherapy. Giralt et *al.* Abstract 1016O

Practice point and future research opportunities

Both panitumumab and radiotherapy and chemoradiotherapy appeared well tolerated, but local regional control at 2 years, overall survival and progression-free survival all favored chemoradiotherapy over panitumumab plus radiotherapy.

GERCOR-IRC phase I/II study: Safety, and preliminary efficacy results of weekly everolimus, carboplatin and paclitaxel as an induction therapy for patients with unresectable locally advanced head and neck squamous cell carcinoma

Activated PI3K/mTOR survival pathway was seen in 57-81% of patients with head and neck squamous cell carcinoma (HNSCC) that could drive resistance to cytotoxics. Faivre *et al.* previously demonstrated synergistic cell-cycle dependent effects between rapamycin/everolimus plus either carboplatin or paclitaxel in HNSCC cells, leading to the design of this two-step phase I/II trial that administered nine consecutive weekly cycles of oral everolimus plus carboplatin and paclitaxel, followed by chemoradiotherapy in patients with untreated locally advanced HNSCC. A total of 27 patients with a median age of 58 years and ECOG performance status 0-2, stage IV HNSCC were enrolled in the phase I/II trial and 42 are planned for the phase II. Six of the 7 patients enrolled in the everolimus dose escalation phase I step were evaluable for safety; 3 received 30 mg and 3 patients received 50 mg per week. In this cohort, no dose-limiting toxicity during the first 4 weeks of treatment was reported. Transient asymptomatic grade 3 neutropenia and anemia occurred in 3 patients each, and thrombocytopenia was observed in one patient. The most frequently reported adverse events were mild to moderate asthenia, skin toxicity, and alopecia; based upon these safety results the recommended dose of everolimus was 50 mg/week for the phase II step. Of 13 patients treated in the phase I/II, 11 have demonstrated objective responses of 1 complete response, 10 partial responses and 2 patients showed stable disease. Interestingly, several major responses (ranging -60 to -80% by RECIST) were observed in large necrotic primary tumors and lymph nodes of more than 6 cm in diameter. A genetic analysis of tumors indicated that patients showing a response did not have KRAS, BRAF, PI3KCA, or EGFR mutations in their tumors. Faivre *et al.* Abstract 1017O

Practice point and future research opportunities

Everolimus added to carboplatin and paclitaxel was well tolerated, allowed repeated cycles and could be administered at 50 mg per week to patients with head and neck squamous cell carcinoma. Major clinical responses were observed, especially in patients with bulky, locally advanced and necrotic disease, warranting further evaluation of this combination treatment. The tumors of responding patients did not express KRAS, BRAF, PI3KCA, or EGFR mutations.

HEMATOLOGICAL MALIGNANCIES

Brentuximab vedotin followed by CHOP benefits newly diagnosed patients with systemic anaplastic large cell lymphoma

Brentuximab vedotin is an anti-CD30 antibody that is conjugated by a protease-cleavable linker to a microtubule-disrupting agent, monomethyl auristatin, which has shown an objective response rate of 86% in patients with relapsed/refractory systemic anaplastic large cell lymphoma (sALCL). To evaluate the benefit in patients with newly diagnosed sALCL, Fanale *et al.* conducted a phase I, open-label, multicenter study of brentuximab vedotin administered to 13 newly diagnosed patients

with CD30-positive mature T- and NK-cell lymphomas either sequentially or in combination with chemotherapy. The results were reported at ESMO 2012 from arm I of the study, which tested sequential treatment of sALCL patients with brentuximab vedotin (1.8 mg/kg) for three cycles, followed by 2 to 6 cycles of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) chemotherapy. All 13 patents in Arm 1 had sALCL with the majority being ALK- and 3 were ALK+. All 13 patients achieved remission after two cycles of brentuximab vedotin. After receiving the entire sequence, 10 of 12 patients remained in remission, with 7 achieving complete remission (CR), 3 showing partial remission (PR) and two patients developing progressive disease during CHOP. Patients who achieved CR or PR following CHOP were eligible to receive up to 16 additional cycles of brentuximab vedotin; 3 patients have completed 16 cycles of therapy and all remain in CR. The most common adverse events (all grades) occurring in six or more patients were nausea, peripheral sensory neuropathy, and vomiting. Grade 3/4 adverse events seen in one or more patients included anemia, fatigue, and peripheral sensory neuropathy; all have improved or resolved. Thus far, no patient has had a grade 5 adverse event or discontinued the trial. A phase III randomized study is being planned to confirm these promising results. Fanale et *al.* Abstract 1063O

Practice point and future research opportunities

Approximately 85% of newly diagnosed patients with sALCL maintained remission after sequential treatment with brentuximab vedotin followed by CHOP. Brentuximab vedotin was well tolerated, both in the initial therapy and when given to maintain remission.

Impact of the number of prior treatment lines and pre-treatment with bortezomib or lenalidomide on efficacy of bortezomib / bendamustine / dexamethasone in patients with relapsed/refractory multiple myeloma

According to Ludwig *et al.* a combination of bortezomib / bendamustine / dexamethasone in patients with relapsed/refractory multiple myeloma yields 'remarkable' response rates and progression-free survival (PFS), but is negatively impacted by pretreatment with lenalidomide alone or with bortezomib. However, pretreatment with only bortezomib slightly increased the response. This study enrolled 71 patients with ISS stage I/II/III recorded in 22, 29, and 20 patients, respectively and ECOG performance status of 0/1/2 recorded for 37, 31, and 3 patients, respectively. Evaluation of response was done for 65 patients with a median follow up of 7.1 months. The overall response rate (ORR) following combination treatment was 58.5% with complete response (CR) achieved by 11 (16.9%) patients, partial response (PR) seen in 17 (26.2%) patients, very good partial response (VGPR) in 10 (15.4%), minimal response (MR) in 11 (16.9%), and stable disease (SD) reported for 16 (24.6%) patients. Median time to response was 77 days. Progression-free survival was 12.2 months with combination therapy and in 43 (76%) patients having exposure to bortezomib, but decreased to 5.9 and 6.0 months in 60 % and 44% of patients previously treated with sole lenalidomide or bortezomib

plus lenalidomide, respectively. Up to two pretreatments had a favorable effect on response then showed a deleterious effect with 3 or more; PFS increased to 13.0 months in 27 (61%) patients who received 1-2 previous lines of any treatment but decreased to 7.8 months in the 43 (54%) patients who had 3 to 4 previous lines of treatment. A significant, independent association between combined lenalidomide and bortezomib pre-treatment and ORR was shown by multivariate analysis ($p < 0.02$) and by multivariate analysis ($p < 0.02$). Median overall survival has not been reached. Less that 5% of patients experienced grade 4 anemia, leucopenia and thrombocytopenia and the incidence of grade 3-4 infections and gastrointestinal toxicities was low. At baseline, 18% of patients had grades1-2 peripheral neuropathy, which remained constant for most of these patients, with just three patients developing grade 3 and 1 progressing to grade 4 peripheral neuropathy. Ludwig *et al.* Abstract 1064O

Practice point and future research opportunities

Treatment of patients with relapsed/refractory multiple myeloma using a bortezomib/bendamustine/dexamethazone combination was highly effective, demonstrated by strong response rates and progression-free survival in all patients receiving this combination and also in those receiving prior bortezomib. However, in patients pretreated with lenalidomide or lenalidomide plus bortezomib or for those with more than two prior treatments, a sharp decline in progression-free survival was seen by this combination.

MELANOMA AND OTHER SKIN TUMORS

MELANOMA

BRIM7: Vemurafenib plus GDC-0973 in patients with unresectable or metastatic BRAFV600 mutated melanoma

In an ongoing trial of vemurafenib plus GDC-0973, preliminary results showed the combination could be delivered safely at the dose of either agent administered alone and was well tolerated by patients with unresectable or metastatic melanoma. The dose-escalation/expansion phase IB trial was based upon information from preclinical models that showed inhibition of both BRAF and MEK could delay the development of resistance compared to BRAF inhibitor monotherapy; vemurafenib has efficacy toward a specific mutated oncogenic BRAF-signalling mediator and GDC-0973 is an MEK inhibitor. The BRIM7 trial enrolled patients with BRAF V600-mutated unresectable or metastatic melanoma, who had ECOG performance status 0-1 and were either naive to vemurafenib or had disease progression on vemurafenib. Patients received vemurafenib 720 mg or 960 mg bid continuously and GDC-0973 was administered at doses of 60 mg, 80 mg or 100 mg qd in cycles of 14 days on and 14 days off, 21 days on and 7 days off or continuously. The study aimed to determine the maximum

tolerated dose (MTD), dose-limiting toxicity (DLT), safety and pharmacokinetics. As of 6 July, 2012, 70 patients had been treated; all patients had BRAF V600-mutated unresectable or metastatic melanoma and were either naive to vemurafenib or experienced disease progression while on vemurafenib (54.3%). The majority (74.3%) had stage IV M1c melanoma upon enrolment. The median number of cycles given was 3. Preliminary efficacy data was available for vemurafenib-naive patients that showed tumor reduction in all eight patients. One grade 3 dose limiting toxicity (QT prolongation) related to vemurafenib that led to trial discontinuation occurred in the vemurafenib 960 mg plus GDC-0973 60 mg dose cohort (n=6). The most commonly reported adverse events by all patients were diarrhea (51.4%), rash (52.9%), nausea (28.6%), fatigue/asthenia (30.0%), liver function abnormality (20.0%) and photosensitivity/sunburn (31.4%). Most frequent treatment-related grade 3 adverse events were diarrhea, rash, increased creatine phosphokinase and liver function abnormality which was seen in 6.8%, 6.8%, 6.8% and 4.5% of patients, respectively. Just one patient developed cutaneous squamous cell carcinoma. Dose interruptions were required for vemurafenib by 23.4% of patients, GDC-0973 by 21.4% of patients and both drugs for 8.6% of patients. Expansion was planned for two dose levels of vemurafenib at 720 mg and 960 mg bid plus GDC-0973 at 60 mg qd 21days on and 7 days off. A phase III trial of the combination at the single-agent MTDs of vemurafenib at 960 mg bid and GDC-0973 at 60 mg is underway. Gonzalez, *et al.* Abstract LBA28_PR

Practice point and future research opportunities

GDC-0973 in combination with vemurafenib showed promising preliminary results for tumor reduction in patients with BRAFV600-mutated unresectable or metastatic melanoma. The combination was delivered safely at the dose levels of either agents given alone and was tolerated by patients and the adverse events were manageable. A phase III trial of the combination of BRAF and MEK inhibitors is underway.

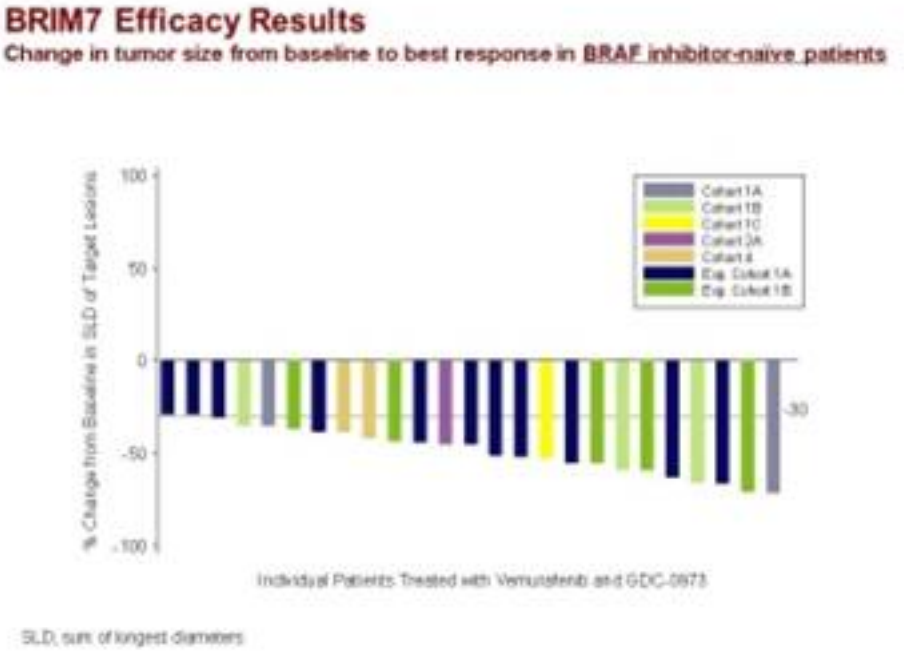

Figure 8. BRIM7 efficacy results - Change in tumor size from baseline to best response in BRAF inhibitor-naive patients

Dabrafenib plus trametinib significantly improves patient outcome over dabrafenib alone in patients with BRAF V600 mutation-positive metastatic melanoma

Patients with BRAF V600 mutation-positive metastatic melanoma had significantly improved progression-free survival (PFS) when trametinib was added to dabrafenib, according to results from a phase II, three-armed, randomized trial. This trial was done based on results from BRAF V600-mutated cancer cell lines and xenograft models that showed enhanced activity with dabrafenib plus trametinib compared with either drug alone and preclinical human data that showed the combination delayed resistance and prevented BRAFi-induced proliferative skin lesions. Patients with BRAFV600E/K mutation-positive metastatic melanoma who were naive to BRAF inhibition and MEK inhibition treatment and 18 years or older, with ECOG performance status <2 and RECIST measurable disease were randomized to receive dabrafenib at 150 mg bid or dabrafenib at 150 mg bid plus either trametinib at 1 mg qd or at 2 mg qd. Crossover from dabrafenib to the higher dose combination was allowed after progression. Primary endpoints were progression free survival (PFS), response rate (RR) and duration of response (DoR); secondary endpoints included overall survival (OS) and safety. Baseline characteristics were balanced across the 162 patients in all three arms. Results follow for dabrafenib plus trametinib at 2 mg QD compared to sole dabrafenib: Investigator assessed median PFS for combination was 9.4 months compared to 5.8 months for dabrafenib (HR 0.39; $p < 0.0001$). Confirmed RR was 76% for combination and 54% for dabrafenib ($p = 0.03$). Median DoR was 10.5 months with combination compared to 5.6 months for dabrafenib. The 12-

months OS rate was 79% for combination and 70% for dabrafenib, despite crossover of 43 (80%) patients to combination therapy; median OS has not been reached. Adverse events of pyrexia and chills were reported by 71% and 58% of patients receiving combination treatment compared to 26% and 17% of patients in the dabrafenib arm, respectively. Dose reductions and interruptions, respectively, were made in 35% and 42% of patients in the combination arm compared to 4% and 6% in the dabrafenib arm. With dabrafenib/trametinib the most common grade 3+ adverse events were neutropenia and hyponatremia, which were seen in 11% and 7% of patients, respectively. Incidence of hyperproliferative skin lesions was much lower with combination compared to dabrafenib; cutaneous squamous cell carcinoma was 7% versus 19%, skin papilloma 4% versus 15% and hyperkeratosis was 9% versus 30%, respectively. The results have been simultaneously published in the *New England Journal of Medicine* (*NEJM*). Long *et al.* Abstract LBA27_PR

Practice point and future research opportunities

Dabrafenib/trametinib treatment of patients with BRAFV600 mutation-positive metastatic melanoma provided statistically significant and clinically meaningful improvement in patient outcome compared to sole dabrafenib. Progression-free and overall survival, response and duration of response rates all favored the combination arm, which also had a lower incidence of hyperproliferative skin lesions. Phase III studies are underway. New drug applications have been submitted to the US Food and Drug Administration and the European Medicines Agency for both trametinib and dabrafenib monotherapy for the treatment of *BRAF* -positive metastatic melanoma.

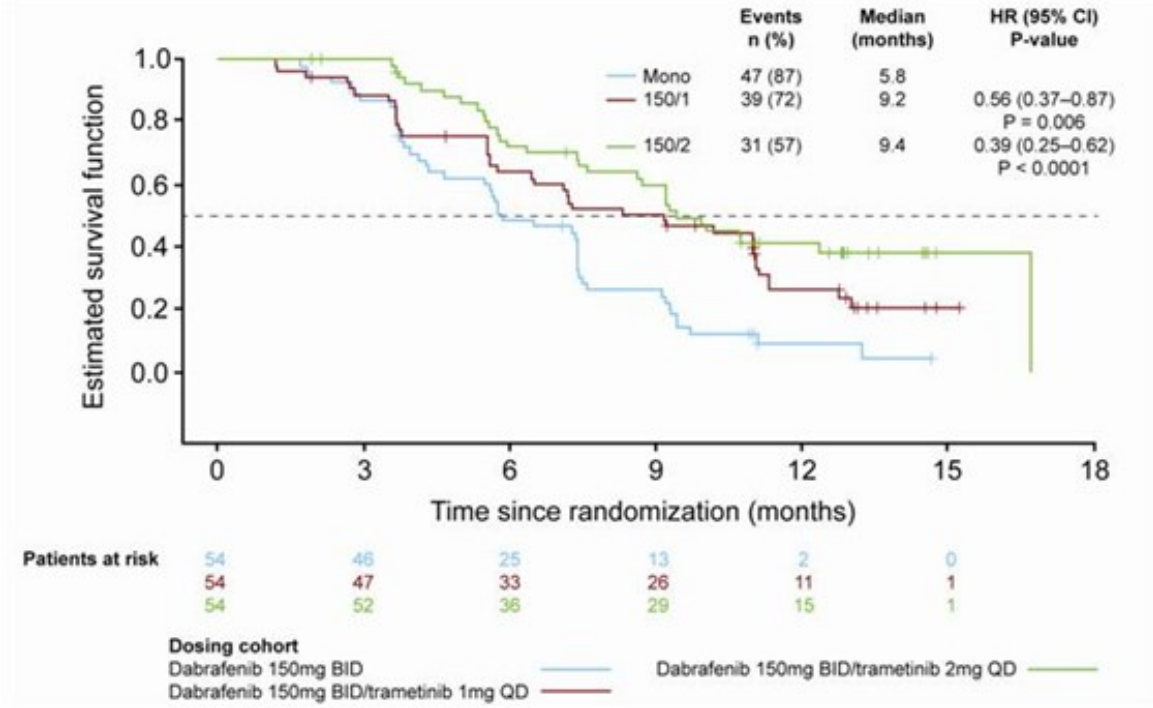

Figure 9. Estimated survival time since randomization

Ramucirumab +/- dacarbazine in patients with metastatic melanoma

Phase II trial results showed that ramucirumab, which inhibits angiogenesis by blocking VEGF receptor-2 (VEGFR-2) ligand binding and signaling, has clinical activity in patients with metastatic melanoma. The trial enrolled 106 patients with stage IV cutaneous melanoma who were randomized to receive sole ramucirumab (arm A) or ramucirumab plus dacarbazine (arm B). All patients were ECOG performance status 0-1 and had adequate liver and kidney function; other patient characteristics were well balanced between the two arms. Although the patients in arm A showed longer median progression-free survival (PFS) and more partial response, overall survival (OS) and stable disease rates were higher in patients receiving the combination treatment (arm B). Progression-free survival was 2.6 months in 52 patients in arm A compared with 1.7 months seen in the 50 patients in arm B. Progression-free survival rates at 6 and 12 months were 31% and 24% in arm A and 18% and 16% in arm B, respectively. Partial responses (PR) were reported for 9 (17%) patients in arm A and for 2 (14%) in arm B. Nineteen (37%) patients on arm A had stable disease compared with 21(42%) patients on arm B. Median OS was 8.7 months on arm A and 11 months on arm B. Elevated LDH was reported in a similar number of patients in both arms but 23% of arm A patients were stage M1c compared with 36% of arm B patients. Non-hematologic adverse events considered at least possibly related to ramucirumab included fatigue, hypertension, infusion-related reactions, proteinuria and headache that occurred at similar levels in both arms that was investigator-determined to be acceptable. Hematologic adverse events included neutropenia (33%; 19% grade 3), thrombocytopenia (39%; 15% grade 3), anemia (14%; 4% grade 3) on arm A whereas no neutropenia was seen in arm B, and the incidence of thrombocytopenia and anemia was lower (6%; 0 grade 3) and (2%; 0 grade 3), respectively, on Arm B. Carvajal *et al.* Abstract 1115PD

Practice point and future research opportunities

Ramucirumab shows clinical activity in patients with metastatic melanoma. Although the study was not powered for definitive comparison between treatment arms, patients who received only ramucirumab achieved longer progression-free survival, but enhanced overall survival was noticed in patients treated with ramucirumab plus dacarbazine; this group also showed fewer serious adverse events.

BASAL CELL CARCINOMA

Vismodegib shows impressive efficacy and consistent safety following two years of treatment in patients with advanced basal cell carcinoma

Results from the ERIVANCE trial presented by Dirix at ECCO/ESMO2011 demonstrated that

vismodegib, an inhibitor of the Hedgehog signaling pathway, had efficacy in patients with basal cell carcinoma (BCC). At this congress Sekulic presented new, updated investigator-assessed efficacy and safety results from an additional 12 month follow-up of this multicenter, two-cohort trial. Patients with histologically confirmed locally advanced BCC or metastatic BCC who had no viable treatment options were given 150 mg oral vismodegib daily. At a median follow-up of 22.3 months patients in both groups showed remarkable survival rates; patients with metastatic BCC had one- and two-year survival rates of 78% and 60%, respectively, while 93.1% of patients with locally advanced BCC survived for one year and 85% were still alive at two years. Overall response rates at one and two years were 45.5% and 48.5% in 33 patients with metastatic BCC and 60.3% at both timepoints in 63 patients with locally advanced BCC. Median progression-free survival (PFS) was 9.2 months at one year and 9.3 months at the two year data cut-off in patients with metastatic BCC, whereas PFS of 11.2 and 12.9 months was achieved by patients with locally advanced BCC at one and two years, respectively. Overall survival data are not yet mature. The most frequently reported adverse events were muscle spasms, alopecia, dysgeusia, weight decrease, fatigue, nausea, and two of 6 nonmenopausal female patients had amenorrhea. Serious adverse events were reported in 25% and 32% of patients at years one and two. Sekulic et *al.* Abstract 1112PD

Practice point and future research opportunities

The significant clinical benefit of vismodegib in patients with metastatic or locally advanced basal cell carcinoma was confirmed by data from an additional 12 month follow-up. Vismodegib may be considered as an effective treatment option for these patients.

NEUROENDOCRINE TUMORS

Efficacy of everolimus by baseline marker level: prognostic and predictive effect analyses from RADIANT-3

Everolimus was shown to significantly prolong progression-free survival (PFS) in patients with advanced pancreatic neuroendocrine tumors (pNET) in the RADIANT-3 trial. Using data from patients participating in this phase III study, Yao evaluated whether soluble VEGF pathway biomarkers could be predictive of everolimus activity; since everolimus, as an inhibitor of the mammalian target of rapamycin (mTOR) could have an effect on levels of downstream molecules. Plasma levels at baseline of VEGF-A, PlGF, sVEGFR1, and sVEGFR2 had been determined by ELISA and a Cox proportional hazards model was used to evaluate their predictive ability. Progression-free survival (PFS) was significantly improved to a similar extent in patients receiving everolimus compared with patients who received placebo, regardless of baseline levels of markers ($p < 0.001$), suggesting that none of these markers are associated with the efficacy of everolimus in patients with pNET. However,

significantly longer PFS was seen with everolimus in patients with lower levels of VEGF-A (8.3 versus 5.5 months), PlGF (8.0 versus 4.2 months), and sVEGFR1 (8.3 versus 5.5 months). These results suggest that these three markers are prognostic in pNET. Multivariate analysis demonstrated that sVEGFR1 and PlGF were significant prognostic markers for angiogenisis HR 1.54, and 1.35; $p < 0.001$ and $p = 0.046$, respectively in pNET. Yao *et al.* Abstract 1154O

Practice point and future research opportunities

This biomarkers exploratory analysis demonstrated consistent everolimus efficacy in all patients with advanced pNET irrespective of their baseline VEGF levels. However, baseline levels of PlGF and sVEGFR1 are potential prognostic factors for pNET.

Pazopanib benefits patients with progressive metastatic NET who received or were naive to prior targeted therapies

Efficacy and safety results from a phase II trial of pazopanib were presented on behalf of the Spanish Task Force for neuroendocrine tumors (NETs) which also sought to determine an association between efficacy and potential biomarkers. Pazopanib is a tyrosine kinase inhibitor of the VEGFR, PDGFR and KIT. The trial enrolled patients with pancreatic or extra-pancreatic progressive metastatic NETs who were treatment naive or who had received previous antiangiogenic or mTOR inhibitor treatment. Pazopanib at 800 mg was administered daily until disease progression or unacceptable toxicity occurred. The trial met the primary endpoint of clinical benefit rate (CBR) at 6 months defined as complete response (CR) plus partial response (PR) plus stable disease (SD) by RECIST v1.0. Of the 41 patients evaluable for response at 6 months, PR was achieved by 3 (7.36%) patients, SD was reported for 33 (78.4%) patients and disease progression occurred in 6 (14.3%) patients, yielding a CBR of 85.4%. Global median progression-free survival (PFS) was 48.3 weeks, range: 13.9 to 82.7 weeks. Clinical benefit rate and median PFS were 100% and 25.7 weeks in 9 patients who received no prior targeted therapy, 88.9% and 48.3 weeks in 9 patients receiving previous mTOR inhibitors, 83.3% and 50.3 weeks in 16 patients receiving previous antiangiogenics and 71.4% and 20.6 weeks in 7 patients treated with both targeted therapies previously. The sum of the longest diameter of target lesions decreased by more than 10% in 32.5 % of patients' (37.5% without previous biological treatment, 22.2% with previous mTOR inhibitor, 31.3% with prior multitargeted inhibitor, and 42.9% with a history of both treatments ($p = 0.506$). Translational studies on angiogenesis and immunohistochemistry biomarkers and CTCs are ongoing. The most frequently occurring toxicities of any grade were asthenia, experienced by 75%, diarrhea seen in 63% and nausea, reported by 42% of patients. Grande *et al.* Abstract 1157O

Practice point and future research opportunities

Pazopanib has promising activity for treatment of patients with advanced NET regardless of previous treatment with other targeted therapies; however reduced response is seen in patients who received two prior targeted therapies. This trial suggests treatment sequencing with novel targeted agents may play a beneficial role in the treatment of NETs.

Updated overall survival analysis of sunitinib in patients with advanced, unresectable pancreatic neuroendocrine tumor

Updated overall survival data were presented from a phase III trial wherein sunitinib was shown to improve progression-free survival (PFS) and overall survival (OS) compared with placebo in patients with pancreatic NET (Raymond et al, NEJM 2011). Upon the trial's end or disease progression, 69% of the patients randomized to placebo crossed over to sunitinib, potentially confounding OS analysis. The data presented at ESMO 2012 showed OS of 33.0 versus 26.7 months in the sunitinib and placebo arms, respectively, hazard ratio (HR) 0.71, p = 0.115. Subsequently the data were adjusted for the effect of crossover using four different methods: 1) censoring of placebo-arm data at crossover, 2) Cox model analysis with treatment as a time-dependent covariate, 3) rank-preserving structural failure time (RPSFT) analysis (which models the absence of crossover while respecting the randomization), and 4) RPSFT analysis adjusted for time of crossover. Data were analyzed from a total of 171 patients; 86 were randomized to sunitinib and 85 to placebo. Subsequent to disease progression or trial end, 56 of the 85 (70%) patients in the placebo arm crossed over and were treated with sunitinib. At two years post trial end, median follow-up of 34.1 months, there were 87 deaths (51%), including 40 patients treated with sunitinib and 47 patients who received placebo. There was a non significant trend towards increased OS with sunitinib compared with placebo. By the methods 1 to 4 used to adjust for crossover, HR of mortality was 0.428 (p = 0.004), HR 0.492 (p = 0.010), HR 0.431 (p = 0.115) and HR 0.568 (p = 0.115), respectively. The updated survival analysis continued to show an improvement in OS of 6.3 months with sunitinib. Faivre *et al.* Abstract 1155O

Practice point and future research opportunities

Sunitinib continues to show clinical benefit for patients with pNETS, who achieved prolonged progression-free survival compared with placebo. Updated overall survival data continues to favor sunitinib, although this result was not statistically significant for reasons that may include treatment crossover and limited statistical power.

LUNG CANCER

NON-SMALL CELL LUNG CANCER

Crizotinib superior to pemetrexed or docetaxel chemotherapy in patients with advanced ALK-positive non-small cell lung cancer

Results were reported from a randomized phase III PROFILE 1007 study that compared the efficacy and safety of crizotinib to standard chemotherapy with pemetrexed or docetaxel as second-line therapy for patients with advanced FISH-determined ALK positive non-small cell lung cancer (NSCLC). Over a two year period the study enrolled 347 patients with stage IIIB/IV ALK+ NSCLC who had previously received one prior platinum-based regimen; 173 patients were randomized to crizotinib and 174 to either pemetrexed (58%) or docetaxel (42%). Patients who progressed on pemetrexed or docetaxel were offered crizotinib. The trial's primary endpoint was progression-free survival (PFS) per independent radiologic review; with secondary endpoints of objective response rate (ORR), overall survival (OS), safety, and patient-reported outcomes. The study met the primary endpoint by showing crizotinib superiority over pemetrexed or docetaxel with a median PFS 7.7 months compared 3.0 months, ($p < 0.0001$). Crizotinib treated patients also had a significantly higher ORR of 65.3% compared with 19.5%; $p < 0.0001$. Interim analysis of OS done at 28% events showed no statistically significant difference between crizotinib and pemetrexed or docetaxel; preliminary median estimate 20.3 months compared with 22.8 months, respectively; however, no adjustment for the 111 (63%) patients who crossed over to crizotinib was made. Comparison of crizotinib to either sole agent showed PFS was 7.7 months with crizotinib versus 4.2 months with pemetrexed HR 0.59, $p = 0.0004$ and 2.6 months with docetaxel HR 0.30, $p < 0.0001$. Duration of treatment was longer for crizotinib where a median of 11 cycles compared to 4 with pemetrexed or docetaxel were started by patients. More patients receiving crizotinib over chemotherapy reported improvement in symptoms from baseline of cough, dyspnea, fatigue, alopecia, insomnia and pain, $p < 0.0001$ and improved global quality of life also favoured crizotinib $p < 0.0001$. The most common treatment-related adverse events with crizotinib were vision disorder, which was reported by 60% of patients; 60% of patients reported diarrhea, 55% had nausea, 47% vomiting and 36% of patients reported elevated transaminases. Adverse events including nausea, constipation, fatigue, constipation, and rash were reported by 37%, 23% 33% 21% and 17% of patients receiving pemetrexed or docetaxel. All treatment groups had a similar incidence of grade 3/4 treatment related adverse events. A total of 25 deaths occurred in the crizotinib arm and 7 in the chemotherapy arm; 8% and 2% of deaths, in the respective arms was due to disease progression. Two and 1% of death were considered treatment-relation in the crizotinib and chemotherapy arms, respectively. The trial was discontinued for 17% of crizotinib patients compared to 13% of chemotherapy patients. Six percent of crizotinib patients compared to 10% of pemetrexed/docetaxel patients discontinued the trial due to treatment related adverse events. Shaw, *et al.* Abstract LBA1_PR

Practice point and future research opportunities

Crizotinib may be considered the standard of care for second-line treatment of patients with

previously treated advanced ALK positive NSCLC. Results from this study showed significantly improved progression-free survival, response rate and quality of life with crizotinib over pemetrexed or docetaxel. Lack of a difference in overall survival rates was most likely due to the immaturity of data at the interim analysis and to the large number of patients who crossed over to crizotinib.

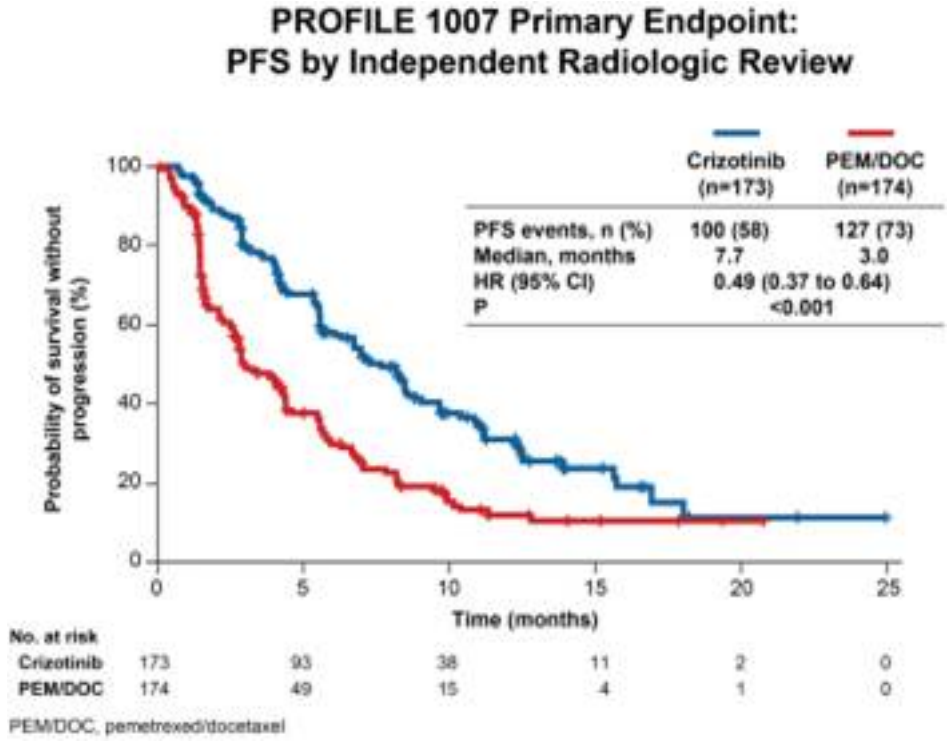

Figure 10. Progression-free survival by independent radiologic review in the PROFILE 1007 study

MISSION trial of sorafenib monotherapy in heavily pretreated patients with non-small cell lung cancer

Previously reported results from a randomized phase II trial (ECOG 2501) demonstrated activity of sorafenib monotherapy in patients with advanced non-small cell lung cancer (NSCLC) who had failed 2 to 3 prior chemotherapies, leading to the phase III MISSION study. MISSION evaluated whether overall survival (OS) in patients with advanced relapsed/refractory NSCLC of predominantly non-squamous histology could be improved by 3rd- or 4th-line sorafenib plus best supportive care (BSC) relative to placebo plus BSC. A total of 703 patients were randomized; 350 to sorafenib and 353 to placebo. Baseline demographics and prior treatments were generally well balanced, excepting differences in female gender (47% vs. 41%) and never smokers (46% vs. 38%) that favored the sorafenib arm. Fewer patients, 44% in the sorafenib arm compared to 56% of placebo patients, had received post-progression therapy. Sorafenib did not significantly affect OS, which was similar between arms. However, median progression-free survival (PFS), time to progression (TTP) overall response rate (ORR) and disease control rate (DCR) all significantly favored the sorafenib arm: PFS

was 84 compared to 43 days, $p < 0.0001$ with sorafenib and placebo, respectively. TTP was 89 compared to 43 days, $p < 0.0001$; the ORR was 4.9% compared with 0.9%, $p < 0.001$; and DCR was 47% compared to 25%, $p < 0.0001$ in patients receiving sorafenib and placebo, respectively. Patients in the sorafenib arm had longer median treatment duration of 12.0 versus 6.3 weeks. When sorafenib benefit was analyzed by EGFR mutation status, 44 EGFR-mut patients had PFS of 83 versus 42 days with placebo HR 0.27, $p < 0.001$. Patients with EGFR-wt (n=122) showed similar PFS of 82 versus 46 days in 136 placebo treated patients HR 0.62, $p < 0.001$. More sorafenib patients required dose reductions, 35% compared to 6%, and dose interruptions, 52% compared to 19% of placebo patients. Adverse events were high in both groups: 99% and 91% of patients in the sorafenib and placebo groups reported adverse events. Serious adverse events occurred in 39% of sorafenib and 32% of placebo treated patients. Paz-Ares *et al*. Abstract LBA 33

Practice point and future research opportunities

Although the primary endpoint of improved overall survival was unmet by the phase III MISSION trial of sorafenib as 3rd- or 4th-line treatment in patients with advanced non-small cell lung cancer, progression-free survival was nearly doubled and time to progression was twice that seen with placebo and best supportive care. Overall response and disease control rates were significantly improved with sorafenib, warranting further consideration of sorafenib as monotherapy in previously treated patients with NSCLC of predominantly non-squamous histology.

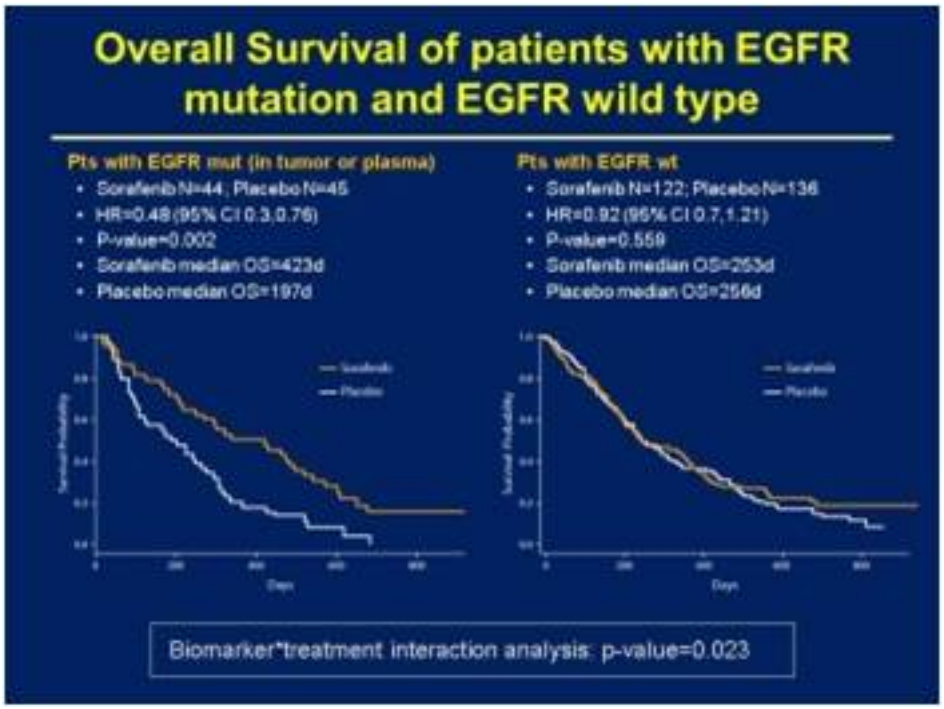

Figure 11. Overall survival of patients with EGFR mutation and EGFR wild type

Biomarker subanalysis of the phase III MISSION trial: Tumor expression of EGFR mutation but not KRAS status predicts 3rd/4th line sorafenib response in NSCLC

Mok *et al.* used data from the 703 participants in the global, randomized, placebo-controlled, phase III MISSION trial to evaluate the association between known biomarkers, tumor EGFR and KRAS mutations, and outcome following 3rd/4th line sorafenib in patients with advanced relapsed/refractory non-small cell lung cancer (NSCLC) of predominantly non-squamous histology. EGFR and KRAS mutations were analyzed using archival tumor samples and circulating tumor DNA that was isolated from the plasma of 347 (49%) patients included in the in MISSION study. EGFR and KRAS mutations were detected in 89 (26%) and 68 (20%) patients, respectively, and at similar frequency in both arms. Analysis of the interaction between EGFR mutation status and the effect of sorafenib on overall survival (OS) suggested that patients with wild-type EGFR (wt-EGFR) did not benefit from sorafenib and those with EGFR mutations (mEGFR) did, $p = 0.023$; patients with mEGFR receiving sorafenib had OS that was twice as long as patients without mutations. Median OS was also two-fold longer in mEGFR patients receiving sorafenib versus placebo; OS was 423 days in mEGFR patients compared with 197 days in patients with wt-EGFR, $p = 0.002$. No significant difference was seen in OS between patients with wt-EGFR, whether they received sorafenib or placebo, OS was 253 and 256 days, respectively. EGFR mutation also associated with the effect of sorafenib on progression-free survival (PFS) $p = 0.015$. Sorafenib treated patients with mEGFR had better median PFS of 82 compared to 42 days with placebo, $p < 0.001$and longer median PFS of 82 days compared to 46 days with placebo in patients with wt-EGFR, $p < 0.001$. KRAS mutation status was not predictive of sorafenib efficacy. Mok, *et al.* Abstract LBA9_PR

Practice point and future research opportunities

A small sample size prevents to conclude that EGFR mutation is predictive for sorafenib response; but patients with NSCLC whose tumors express EGFR mutations were more likely to have a survival benefit from receiving 3rd/4th line sorafenib in this study than patients whose tumors express wild type EGFR. However caution is advised when interpreting these results due to the small, non-representative nature of the genetic biomarker subpopulation analyzed in this trial. Further prospective investigation may be warranted.

EURTAC: Concomitant actionable mutations are markers for overall survival in patients with EGFR-mutant non-small cell lung cancer

Rosell reported on the association between progression-free survival (PFS) and EGFR T790 and TP53 mutations, the EML4-ALK translocation and BIM mRNA expression in tumor samples taken prior to treatment with erlotinib from 95 patients with non-small cell lung cancer (NSCLC) participating in the EURTAC trial. EURTAC showed improved PFS with first-line erlotinib over chemotherapy in

European patients with EGFR-mutation-positive NSCLC ($p < 0.0001$) but no significant difference was seen in overall survival (OS) (22.9 vs. 20.8 months). Analysis showed concomitant T790M in 37.89%, TP53 in 24.21% and EML4-ALK in 15.8% of patients. BIM expression was low to intermediate in 55.8% and high in 31.6% of patients. Cross-over at the time of progression to EGFR tyrosine kinase-inhibitors had occurred in 86.7% of the 45 patients receiving chemotherapy. Following treatment with erlotinib these patients showed overall response rates (ORR) that associated with BIM expression; ORR were 87.5% in patients with high BIM expression and 34.6% in patients with low/intermediate BIM, whereas, ORR in the chemotherapy group were 11.1% and 14.2% with high and low/intermediate expression, respectively ($p = 0.0002$). Patients without T790M mutations who received erlotinib had an ORR of 100% with high BIM expression compared and 35.2% for patients with low/intermediate BIM levels ($p = 0.01$). By multivariate analysis, longer PFS associated only with erlotinib ($p < 0.0001$) and high BIM expression ($p = 0.03$). Overall survival in patients with T790M mutations was 40.1 months in patients who also had high BIM levels and 15.4 months in patients with low/intermediate BIM levels ($p = 0.04$); only high BIM expression emerged as a marker of longer OS ($p = 0.02$) of all the markers evaluated. Rosell*, et al.* Abstract LBA 31

Practice point and future research opportunities

High BIM expression was associated with longer overall survival and improved progression-free survival, overall survival was associated with T790M mutations plus high BIM levels following erlotinib treatment in patients with non-small cell lung cancer. T790M mutations and BIM levels may serve as markers for selecting patients who will respond well to first-line erlotinib. A clinical trial of treatment based on the presence of the EGFR T790M mutation and BIM expression levels is currently underway.

FORTIS-M: Oral talactoferrin with best supportive care shows no benefit in patients with advanced non-small cell lung cancer

Talactoferrin is an oral dendritic dell mediated immunotherapy that showed promising results for treatment of non-small cell lung cancer (NSCLC) in two randomized phase II trials, leading members of the Fortis-M study group to conduct a randomized, double-blind, placebo-controlled phase III study of talactoferrin versus placebo for advanced NSCLC. The study enrolled patients with measureable NSCLC, aged 18 or more years, who had failed two or more systemic regimens, including one platinum-based regimen, had ECOG performance status 0 to 2, and life expectancy of more than 12 weeks. Patients were randomly assigned 2:1 to receive 1.5 grams of talactoferrin or placebo bid, plus best supportive care for a maximum of five 14-week cycles. Overall survival (OS) was the primary endpoint with secondary endpoints of 6-month and 1-year survival rates, progression-free survival (PFS), objective response rate (ORR), and objective disease control rate (DCR). A total of 742 patients were enrolled between November 2008 and March 2011 at 163 centers worldwide and

randomized, 496 patients to receive talactoferrin and 245 to receive placebo. Ninety percent of patients in each group had stage IV disease; patients in the talactoferrin arm had a median age of 62 years and 56.5% of patients had received three or more prior therapies, whereas in the placebo group the median age was 63 years and 58.4% of patients had received three or more prior regimens. The median OS for talactoferrin was 7.49 months versus 7.66 months for placebo ($p = 0.6602$). Median PFS was 1.68 and 1.64 months, for talactoferrin and placebo, respectively. The DCR was also similar between the arms at 37.6% for talactoferrin and 38.4% with placebo. Adverse events were reported by 87.3% and 86% of talactoferrin and placebo patients, respectively, and grade 3-4 adverse events were reported for 36.4% of talactoferrin patients and 35.5% of placebo patients; serious adverse events were seen in 43.7% and 41.7% of patients, respectively with 14.5% of talactoferrin patients compared to 15.7% of placebo patients discontinuing the trial due to adverse events. Ramalingam, *et al.* Abstract LBA 34

Practice point and future research opportunities

Nearly identical results were seen with talactoferrin and placebo plus best supportive care for safety and both overall and progression-free survival in patients with advanced NSCLC.

NVALT10: A randomized phase II study comparing erlotinib versus erlotinib alternating with chemotherapy in relapsed non-small cell lung cancer patients

Patients with relapsed non-small cell lung cancer (NSCLC) and non-squamous histology did not show improvement in progression-free survival but did achieve prolonged overall survival following combination treatment of erlotinib alternating with chemotherapy over erlotinib alone. The rationale for the phase II randomized NVALT10 study arose from the synergistic effect seen in preclinical models and early phase non-comparative studies with pharmacodynamic separation of chemotherapy and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), noting that concurrent administration of EGFR-TKIs and chemotherapy did not improve outcome. The randomized open label phase II NVALT10 study enrolled patients with advanced NSCLC who had progressed on or following first-line platinum containing chemotherapy. The trial randomized 231 patients to receive erlotinib monotherapy (arm A) or erlotinib plus four cycles of docetaxel for squamous or pemetrexed for non-squamous patients (arm B). Erlotinib was continued following completion of chemotherapy. The primary endpoint was progression-free survival (PFS) with secondary endpoints of toxicity and overall survival (OS) and the study included a preplanned subgroup analysis of patients with squamous and non-squamous histology. Arm A contained 115 patients, 42 squamous and 73 non-squamous and arm B had 116 patients, 35 squamous and 81 with non-squamous histology. The trial's primary endpoint was not met; the adjusted hazard ratio (HR) for PFS for all patients was 0.80; $p = 0.12$. The overall survival HR was 0.68; $p = 0.02$ and patients in arm B with non-squamous histology had improved overall survival of 8.7 month compared to 5.5 months in arm B patients with

squamous histology and 5.5 months in overall patients. Grade 3+ toxicity was reported for 19% of arm A patients and 55% of patients in arm B. Rash and febrile neutropenia were most frequently reported by 7% and 0% versus 15% and 6% of patients in arms A and B, respectively. Aerts, *et al.* Abstract LBA29

Practice point and future research opportunities

Progression-free and overall survival were not significantly different between patients receiving sole erlotinib or erlotinib alternating with chemotherapy. However, patients with relapsed non-squamous non-small cell lung cancer who received erlotinib alternating with pemetrexed showed significantly improved overall survival.

FASTACT-2: Biomarker analyses and overall survival from trial of intercalated erlotinib with first-line chemotherapy in advanced non-small cell lung cancer

FASTACT-2 is a randomized, placebo-controlled, phase III study of first-line intercalated erlotinib and chemotherapy in patients with advanced NSCLC, which met its primary endpoint of significantly prolonged progression-free survival (PFS) ($p < 0.0001$): PFS results were previously reported by Mok at ASCO 2012 with overall survival (OS) results and correlations of biomarkers with PFS being reported here at ESMO 2012. Patients with untreated stage IIIB/IV NSCLC and ECOG performance status 0/1 received up to 6 cycles of gemcitabine plus platinum; 226 patients received this combination plus intercalated erlotinib and 225 receive the combination treatment plus placebo. Patients received maintenance erlotinib or placebo until progression, unacceptable toxicity or death. Tests on tumor samples were conducted at a central laboratory and prioritized as follows: EGFR mutation; KRAS mutation (both by PCR-based test [COBAS]); ERCC1 expression by immunohistochemistry (IHC; median cut-off); EGFR gene copy number by fluorescence in-situ hybridization (FISH); and EGFR IHC. 73% of placebo patients received a second-line EGFR tyrosine kinase inhibitors. A trend towards prolonged overall survival of median 18.3 months with chemotherapy plus erlotinib compared to 14.9 with placebo was observed: hazard ratio (HR) 0.78, $p = 0.0686$. A total of 283/451 pts (62.7%) provided samples for biomarker analyses. Significant association with PFS was seen in 97 tumors with EGFR Mut+ ($p< 0.0001$), 202 KRAS wt ($p < 0.0001$), 34 EGFR FISH+ ($p = 0.0017$) and in 70 patients with ERCC1 IHC+ ($p = 0.0091$). Mok et *al.* Abstract 1226O

Practice point and future research opportunities

Patients in the EGFR mutation-positive subgroup had the strongest progression-free survival benefit from erlotinib added to first-line chemotherapy. ERCC1 positive status by immunohistochemistry was also associated with longer progression-free survival, even in patients with known EGFR wt status.

The significant associations with progression-free survival should identify patients who will most benefit from the addition of erlotinib to first-line chemotherapy.

Activity of afatinib/cetuximab in patients with EGFR mutant non-small cell lung cancer and acquired resistance to EGFR inhibitors

Acquired resistance to reversible epidermal growth factor receptor (EGFR)-specific tyrosine kinase inhibitors (TKIs) in EGFR mutant (-mut) non-small cell lung cancer (NSCLC) is associated with an exon 20 EGFR T790M mutation that occurs in approximately 50% of cases. Nearly complete tumor regression was reported following treatment of T790M transgenic murine models with the targeted combination of afatinib, a potent ErbB family blocker, plus cetuximab. Early clinical data from Janjigian suggested that afatinib/cetuximab at the recommended dose is tolerable and has activity (ASCO 2011). Safety and efficacy data from an expanded cohort of patients with NSCLC and acquired resistance were presented here. The cohort included 100 patients with EGFR-mut advanced NSCLC who progressed on erlotinib or gefitinib, who were transitioned within a minimum of three days to receive oral afatinib at 40 mg daily plus intravenous, bi-weekly cetuximab for a median duration of 4.1 months, range 1-14+ months. Tumors were biopsied after the development of acquired resistance before receiving study therapy. Progression-free survival (PFS) was determined by imaging at week 4, 8, 12 and every 8 weeks thereafter and was 4.7 months in the first 60 evaluable patients enrolled at least six months before data cut-off. The overall response rate (ORR) of 40% was similar in 90 patients available for efficacy; 38% of patients had T790M+ and 47% had T790M- tumors and showed a median duration of response of 7.7 months. EGFR del 19 and L858R mutation were present in 63% and 31% of patients, and EGFR T790M mutation was seen in 53% of patients. The rate of disease control was 94% and probability of PFS at 3, 6 and 9 months was 70, 42 and 18%, respectively. Adverse events included grade 1/2 rash in 65% of patients, grade 3 in 12%, grade 1/2 diarrhea in 63% and grade in 6% of patients. Janjigian *et al.* Abstract 1227O

Practice point and future research opportunities

Further studies are planned to confirm the encouraging clinical efficacy of combination afatinib/cetuximab treatment in patients with NSCLC and acquired resistance to erlotinib or gefitinib. Afatinib activity demonstrates the importance of ErbB signaling in many EGFR-mut NSCLC tumors and efforts to elucidate the underlying mechanisms are ongoing.

Dacomitinib in first-line treatment of EGFR-mutant or HER2-amplified or HER2-mutant lung cancers

Dacomitinib irreversibly inhibits EGFR, HER2 and HER4 in EGFR-mutant lung cancer models, including resistant forms, and has shown superior activity over reversible EGFR tyrosine kinase

inhibitors. Kris reported on an open-label phase II study that evaluated dacomitinib in patients with EGFR-mutant or HER2-amplified or mutant stage IIIB/IV non-small cell lung cancer (NSCLC). The study enrolled patients with adenocarcinoma, no prior systemic treatment who had smoked fewer than 10 pack years, none within 15 years of enrolment, or had known EGFR mutation (EGFR cohort). Also enrolled were patients with HER2 amplifications or mutations who were allowed any number of prior lines of therapy. Patients received dacomitinib orally once daily continuously at 45 mg, or 30 mg with the option to escalate to 45 mg and were evaluated every 28 days. Of the 46 patients enrolled and dosed in the EGFR cohort, 25 had EGFR mutation in exon 19 and 21 had mutations in exon 21. Patients with EGFR exon 19 or 21 mutations had a partial response rate (PR) of 74%; PR of 72% in patients with 19 and 76% in patients with exon 21. Preliminary progression-free survival (PFS) at four months was similar for exons 19 and 21; PFS rate was 96% and 74% at 12 months. The preliminary median PFS was 17 months; median duration of treatment was 14 months. To date, 17 patients have been dosed in the HER2 cohort, 3 with amplification. For 16 patients with response data, two patients with HER2 mutation achieved PR. Stable disease was seen in 5 patients. Common side effects included grade 3/4 acneiform dermatitis in 16.9% of patients and diarrhea in 13.5% of patients in the EGFR cohort only. Five patients overall discontinued treatment due to drug-related toxicity. Kris et *al.* Abstract 1228O

Practice point and future research opportunities

Partial response was achieved by 74% of patients with EGFR exon 19 or 21 mutant lung cancers and preliminary data also show activity of dacomitinib in targeting HER2 advanced NSCLCs following first-line dacomitinib, warranting further recruitment to this trial and research in the use of dacomitinib in these patient populations.

SMALL-CELL LUNG CANCER

Belotecan/etoposide is similar to standard treatment in patients with small-cell lung cancer

Kim reported results from a multicenter, randomized, prospective comparative study to demonstrate the non-inferiority of first-line belotecan/cisplatin compared to standard etoposide/cisplatin treatment of patients with small-cell lung cancer (SCLC). Belotecan is a novel camptothecin derivative, which has anticancer effects by inhibiting topoisomerase I. The trial enrolled 129 patients and randomized 63 to belotecan/cisplatin and 66 to etoposide/cisplatin; of these, evaluation of response was possible for 60 and 61 patients in the two cohorts respectively. Patients in the belotecan group achieved 1 complete response, 32 partial responses (PR) and 7 stable disease (SD), compared to patients receiving etoposide who had 33 PR and 11 SD. The overall response rates (ORR) and disease control rates were similar in both cohorts: ORR with was 66.0%, compared with 54.1% ($p = 0.25$) and disease control rate was 80.0% versus 72.1%, ($p = 0.38$) in the belotecan/cisplatin and

etoposide/cisplatin arms, respectively. No significant difference was seen between overall survival (OS) and progression-free survival (PFS) between the two treatments: with belotecan/cisplatin and belotecan/cisplatin, the median OS was 483 compared to 340 days, respectively ($p = 0.21$) and PFS was 192 compared to 150 days, ($p = 0.08$), respectively. The frequency of grade 3 anemia ($p < 0.01$) and thrombocytopenia ($p = 0.02$) were significantly higher with belotecan/cisplatin than with etoposide/cisplatin but non-hematologic toxicities were not similar between the groups. Kim *et al.* Abstract 152PD

Practice point and future research opportunities

Based on results of this interim analysis, belotecan administered with cisplatin may be a future alternative to standard therapy of patients with extensive stage small-cell lung cancer as similar response rates, and non-hematological toxicities were seen with belotecan plus cisplatin and standard etoposide/cisplatin treatment.

ONCOLOGY AND PUBLIC HEALTH

Economic burden of malignant neoplasms in the European Union

Malignant neoplasms (cancer) are second main cause of mortality in the European Union (EU), after cardiovascular diseases and significantly impact family and friends who provide unpaid care and on society in general. Luengo-Fernandez reported on an assessment of the economic burden of cancer on the healthcare systems of the EU to formulate public health policies and prioritize the allocation of future funding for treatment and research. The cost arising from the four main cancers responsible for mortality (lung, colorectal, female breast, and prostate) was estimated for the year 2009 in the 27 countries that then comprised the EU. Using a "top down" approach that identified the resources associated with each category per year and respective unit costs and data from international and national sources, including the World Health Organization, literature searches, and EU-wide individual-patient household surveys, such as the Survey of Health, Ageing and Retirement in Europe. The economic cost of cancer included primary and hospital care plus estimated unpaid care costs by family and friends and lost earnings due to disease and premature mortality. The annual cost to the EU of cancer was estimated to be €124 billion each year , or €234 per EU citizen; healthcare accounted for 36% of the total, representing €84 per EU citizen, and over 58 million hospital bed days. Another 36% of the total cost was due to lost earnings due to premature mortality and lost earnings due to morbidity represented 8%. Unpaid care accounted for 20% of the total estimated cost. The economic burden of cancer varied considerable by country; the lowest per capita cost for cancer was in Lithuania (€32/year) and the highest was in Germany (€165/year). . The total cost paralleled the prevalence of disease, with lung, colorectal, female breast and prostate cancer

representing 16%, 21%, 10% and 5% of the economic burden, respectively. Luengo-Fernandez *et al.* Abstract 1415PD

Practice point and future research opportunities

The need for greater evidence based policymaking is highlighted by the huge yearly economic cost, approximately €124 billion in the EU, due to cancer.

Analysis of FDA Advisory Committee approval of cancer drugs

Chan *et al.* evaluated the number and characteristics of applications for cancer drug approval in the United States (US) over the last decade and established trends in the process. Over the decade beginning in 2001, 46 applications were reviewed by the Oncologic Drug Advisory committee; 34 (74%) applications sought approval of drugs for solid tumors and 12 (26%) applications targeted hematologic tumors. Eight (17%) drugs each were indicated for leukemia or lymphoma and 5 (11%) drugs each targeted breast or prostate cancer. The remaining 20 (44%) applications involved drugs that targeted other cancers. Supporting data for the applications were derived from 30 (65%) phase III and 16 (35%) phase II trials. A total of 31(67%) standard applications were filed and accelerated approval was sought in 15 (33%) applications. Nearly half, 22 (48%) applications for new drugs were not approved due to missing or inadequate data (65%), excessive toxicity (55%) and inappropriate study endpoints (45%). Further analysis showed data reporting used hazard ratios (HR) (median 0.67) in 19 applications and response rates (median 0.42%) were used in 18 applications. A significant increase from 0% to 50% and finally to 70% in the proportion of applications that used progression-free survival (as an endpoint was seen over the ten years ($p = 0.01$). Analysis of efficacy and toxicity using a predictive model showed that 89% of drugs with lower HR or higher response rate plus lower toxicity were approved compared to 46% of other drugs ($p = 0.025$). Upon grouping the applications into three time periods it became apparent that corresponding approval rates rose toward the end of the decade: there were 11 (55%) approvals during the four year period from 2001 to 2004, 12 (50%) from 2005 to 2008 and 23 (53%) applications were approved over the three years from 2009 to 2011. Chan *et al.* Abstract 1416PD

Practice point and future research opportunities

A significant rise occurred over the last decade in the use of progression-free survival as the primary endpoint in trials supporting applications for approval of new drugs in the US. Investigators noted that applications most likely to gain FDA approval showed a combination of low toxicity and either lower hazard ratios or higher response rates. Applications were rejected on the basis of missing or inadequate data, reports of excessive toxicity or inadequate study endpoints.

NICE guidelines influence uptake of breast cancer drugs in the UK

In the United Kingdom (UK), it is compulsory for the National Health Service (NHS) to fund drugs recommended according to National Institute of Health and Clinical Excellence (NICE) guidelines, but it remains unclear whether NICE guidance influences UK drug uptake as intended. To avoid the limitations of sales data-based analyses, a British team evaluated whether health technology appraisal (HTA) recommendations of new drugs are being implemented according to (NICE) guidelines, which are intended to standardize health care throughout the National Health System (NHS) and to introduce new, cost-effective medicines or changes in drug use. The investigators used IMS Health's Oncology AnalyzerTM as the primary data source instead of often used sales data, which may be limited by omitting the indication or line of therapy of the drug or the patient sub-group it targets. Alternatively, the Oncology AnalyzerTM contains detailed records for a representative sample of patients that permits analyses of the indication and treatment criteria specified in NICE HTAs. The HTAs for all breast cancer drugs appraised by NICE from January 2005 to December 2008 were analyzed. The proportion of the eligible patient sub-groups that received the recommended or non-recommended drugs during this period was determined. Additionally, changes in drug uptake in the target UK populations were assessed and compared to uptake in European countries with similar health care policies. Over the three year period, 8 drugs for treatment of breast cancer were appraised in 6 HTAs produced by NICE. Five of these 6 HTAs resulted in the recommended change in UK drug uptake, but the UK uptake of drugs recommended by NICE compared poorly to the uptake of the same drugs in France, Germany, Italy and Spain with the UK ranking lowest. Bertwistle *et al.* Abstract 1417PD

Practice point and future research opportunities

Although the changes in uptake of reference breast cancer drugs in the UK generally follow guidance provided by NICE HTAs, the UK lags behind levels attained in four European countries regarding uptake of the same drugs.

Providing care to patients with cancer negatively impacts caregivers

An ambitious attempt to quantify the burden imposed on caregivers of patients with cancer was made by Mori *et al*. using data from the 2010 EU National Health and Wellness Survey (NHWS), a self-administered online survey participated in by 57,805 adults in France, Germany, Italy, Spain, and the United Kingdom. "Caregivers", who reported providing care for a patient with cancer and "non-caregivers" who reported providing no care were evaluated in terms of health status, work impairment, diagnosed comorbidities and self-reported healthcare resource use. Predictions of health outcomes as a function of caregiving vs. non-caregiving, controlling for demographics, health risk behaviors, and Charlson Comorbidity Index were made by regression models. Significantly worse

health status was reported by 847 caregivers than by 52,127 non-caregivers regarding physical, mental and health utilities measurements of health (all $p < 0.001$). Higher levels of work absenteeism during the prior week were seen in the caregivers (8.39%) compared with non-caregivers (4.76%), overall work impairment was 26.43% in caregivers and 18.09% in non-caregivers and activity impairment was by 28.85% and 21.91% of caregivers and non-caregivers, respectively (all $p < 0.001$). During the prior six months, caregivers reported more mean healthcare provider visits (6.53 vs. 4.89, $p < 0.001$), emergency room visits (0.26 vs. 0.16, $p = 0.002$) and hospitalizations (0.19 vs. 0.10, $p = 0.003$) than non-caregivers. Caregivers were more likely than non-caregivers to be diagnosed with depression, anxiety, insomnia, migraine and gastrointestinal problems than non-caregivers, Odds Ratios 1.455, 1.972, 1.945, 1.697, and 644 (all $p < 0.001$). Mori *et al.* Abstract 1418PD

Practice point and future research opportunities

Cancer caregivers experience a significantly higher burden than non-caregivers, adding to the already high societal cost of cancer. Special attention to caregivers should be given based on their pivotal role in maintaining the health and well-being of patients with cancer, fulfilling a need not addressed by the healthcare system. Increased awareness is needed regarding caregivers of patients with cancer who fulfill needs and provide services not addressed by the healthcare system that negatively affects their physical, mental health and general activities, including their employment.

Under-reporting of alcohol use affects cancer risk assessment

A team of investigators from Oakland, USA evaluated whether underreporting of alcohol consumed could confound data and prevent establishing a link between light to moderate drinking and the risk for certain types of cancer. A relationship between heavy drinking and cancer has been established, but a clear threshold amount in light/moderate drinkers remains undefined. Out of 129,987 individuals enrolled from 1978 to 1985 and followed until 2008, a total of 15,080 of study participants developed cancer during this time. Cox proportional hazard models were controlled for by age, sex, ethnicity, smoking, education, and body mass index. The risk of any cancer and the risk of a composite of the five alcohol-related cancers (upper airway digestive, liver, breast, lung, colorectal) were studied in relation to alcohol use. The moderate drinking categories (<1 and 1-2 drinks per day) were further divided into groups of persons suspected of under-reporting ("suspect") and those not suspected ("not suspect"). To be placed in the "suspect" group individuals had to have either reported heavier intake at another time or had an alcohol-related diagnosis (out-patient, in-patient, or death) at any time. The relative risks (RR) among the alcohol categories for any cancer were: ex-drinkers 1.17 ($p < 0.001$), <1 drink per day 1.05 ($p = 0.04$), 1-2 drinks per day 1.09 ($p < 0.001$) and 3 drinks per day 1.16 ($p < 0.001$). Relationships of light-moderate drinking (<3 drinks per day) were similar in men, women, whites, blacks, Asians, never smokers, persons diagnosed within or after 10 years. For all persons reporting 1-2 drinks per day, the RR of cancer among "suspect" and "non-suspect" individuals was

1.14 (p = 0.004) and 1.00, respectively. For those reporting <1 drink per day the RR for "suspect" was 1.17 (p = 0.001); for "non-suspect" it was 1.00 For the alcohol-related composite among "suspect" persons reporting 1-2 drinks per day RR was 1.41 and for "not suspect" persons it was 1.06 (0.89-1.25), while at < 1 drink per day for "suspect" was the RR 1.39 (p < 0.00) and for "non-suspect" it was 1.03. Klatsky *et al.* Abstract 1421PD

Practice point and future research opportunities

Relative risk evaluations for developing cancer may be confounded by under-reporting in persons claiming light to moderate alcohol consumption where an increased risk is observed.

SARCOMA

EORTC 62012 trial: Single agent doxorubicin versus doxorubicin plus ifosfamide as first line chemotherapy for patients with advanced or metastatic soft tissue sarcoma

The EORTC 62012 trial attempted to resolve controversy regarding whether ifosfamide had been previously tested at too low dose when used with doxorubicin by evaluating whether a higher dose of ifosfamide plus doxorubicin could improve response rate and progression-free survival (PFS) in patients with locally advanced or metastatic, grade 2 or 3 soft tissue sarcoma (STS). The phase III randomized trial enrolled patients with STS aged 60 years and less who were randomized to doxorubicin at 75 mg/m2 or doxorubicin at the same dose plus ifosfamide given at 10 g/m2 over four days together with mesna and pegfilgrastim as first-line treatment. Randomization was stratified by performance status (0 or 1), patient age of less than 50 years or 50 years and older, the presence or absence of liver metastases and histological grade of 2 versus 3. Patients were treated every three weeks for a maximum of six cycles or until progression. A total of 455 patients from 38 centers were randomized; 228 received doxorubicin and 227 were given doxorubicin plus ifosfamide. At a median follow-up of 56 months, overall survival, the primary endpoint, at one year was slightly, but not significantly, improved with the combination; overall survival was 60% with ifosfamide/doxorubicin compared to 51% with sole doxorubicin, hazard ratio (HR) 0.82; p = 0.061. No difference between treatment arms was seen in the two years overall survival rates of 31% ifosfamide/doxorubicin compared with 28% doxorubicin. Median progression-free survival was significantly increased to 7.4 months in ifosfamide/doxorubicin patients compared to 4.6 months with doxorubicin, HR 0.72; p = 0.002. Response rates favored the combination; complete response were seen in 4 versus 1 patients, partial response in 56 (24.7%) versus 30 (13.2%) and stable disease was achieved by 114 (50.2%) ifosfamide/doxorubicin patients versus 105 (46.1%) doxorubicin patients, respectively. Combination therapy was associated with increased adverse events; 45.9% versus 13.6% and 35.3% versus 4.6% of ifosfamide/doxorubicin patients compared to doxorubicin patients, respectively, reported neutropenia and anemia. Judson, *et al.* Abstract LBA7

Practice point and future research opportunities

Doxorubicin remains the gold standard first line chemotherapy of patients with metastatic soft tissue sarcoma. Significantly improved overall survival was not demonstrated by combination therapy and routine use of ifosfamide/doxorubicin was not supported, although response rates suggest that ifosfamide/doxorubicin may be justified in selected patients younger than 60 years where tumor shrinkage is critical, bearing in mind the higher toxicity rate.

Clinical benefit across subgroups and after progression to second line regorafenib in patients with GIST

Subgroup and post-progression analyses of a phase III trial of the multikinase inhibitor regorafenib were presented by Casali. Previously published results (ASCO 2012) showed that patients with gastro-intestinal stromal tumors (GIST) who had failed both imatinib and sunitinib had significantly improved progression-free survival (PFS) with regorafenib. In the study, 199 patients were randomized (2:1) to receive best supportive care plus either 160 mg of regorafenib or placebo once daily for 3 weeks plus 1 week off. Unblinding and crossover were allowed at progression. The trial's primary endpoint of PFS (RECIST) was met by central review and by investigator assessment when regorafenib treated patients achieved PFS approximately 5 times longer than placebo patients. According to new data presented at ESMO, PFS was improved in a total of 188 patients who received regorafenib initially or upon crossover; post-progression PFS by investigator assessment was 5.0 months for 56 crossover patients and 4.5 mo for 41 patients in the regorafenib arm who continued to receive regorafenib after RECIST progression and unblinding. The improved PFS in these 41 patients suggested to the investigators that tumor progression may be slowed by continuous kinase inhibition after progression or, that RECIST criteria for progression applied by blind central review have clinical shortcomings. Improved PFS was demonstrated across all prespecified subgroups that included the number of prior systemic therapies, geographical region, age, baseline ECOG performance score, duration of prior treatment with imatinib, or the presence of KIT/PDGFRA mutation. Casali *et al.* Abstract 1478O

Practice point and future research opportunities

Patients receiving regorafenib following disease progression on imatinib and sunitinib achieved progression-free survival similar to placebo patients who crossed over to regorafenib, suggesting that additional patient benefit may be due to slower tumor growth with continued kinase inhibition.

Dovitinib benefits patients who failed tyrosine kinase inhibitors

Results from a phase II study showed dovitinib, an orally administered inhibitor of VEGFR and FGFRs that induces apoptosis, was effective in 30 patients with advanced gastrointestinal stromal tumors (GISTs) who had failed previous treatment with imatinib and sunitinib. All patients had metastatic disease: 22 in the peritoneum, 20 liver, 4 lung or 4 patients had metastases to the bone. In addition to not responding well to imatinib and sunitinib, 13 (43%) patients had also failed other agents including 8 who failed nilotinib, 2 regorafenib and 3 patients failed both nilotinib and regorafenib. All patients received dovitinib orally at 500 mg once daily for 5 consecutive days followed by a 2 day rest period. By RECIST criteria, there were no objective responses but 19 (63.3%) patients achieved stable disease, with only 5 (16.7%) patients experiencing progressive disease. Six (20.0%) patients were not evaluable. At four weeks post treatment with dovitinib 3 (10.0%) patients achieved a partial response, 15 (50.0%) had stable disease, 10 (33.3%) showed progressive disease and 2 (6.7%) patients were not evaluable by EORTC PET criteria. PET response at four weeks was predictive of progression-free survival (PFS) ($p = 0.003$). The median PFS and overall survival at a follow-up of 4.8 months were 3.6 months and 6.2 months, respectively. Grade 3 or 4 adverse events with dovitinib occurring in more than 5% of patients included asthenia (16.7%), leucopenia (6.7%), thrombocytopenia (6.7%), and hypertension (6.7%). No treatment-related deaths occurred and toxicities were manageable with dose modification. Kang *et al.* Abstract 1481PD

Practice point and future research opportunities

Dovitinib shows benefit in tyrosine kinase resistant patients with advanced and metastatic GIST and the response at 4 weeks by PET predicts progression-free survival.

First-line dasatinib shows promise for treating tyrosine kinase inhibitor-naive patients with gastrointestinal stromal tumors

Patients with gastrointestinal stromal tumor (GIST) demonstrate a strong response to first-line imatinib but often develop primary and secondary resistance, creating a need for new treatment options. Dasatinib is a second generation tyrosine kinase inhibitor (TKI) of BCR-ABL, Src-family kinases and several other oncogenic kinases including KIT that has shown activity against imatinib-resistant cell lines in vitro. Results from a two-stage phase II trial of dasatinib in patients with histologically proven, FDG-PET positive, TKI-naive GIST were reported. The trial was terminated due to slow accrual after 47 of planned 52 patients had been enrolled; of these, 43 patients were eligible, 24 male, 19 female with a median age of 61 years. Thirty patients had a performance status of 0 and thirteen had 1. Mutational data show 20 patients had a KIT exon, 11 with a KIT exon 9 mutation and 7 patients were wild-type. At a median follow-up of 12.4 months, 15 patients were still on treatment, which began as 70 mg dasatinib starting dose twice daily. Response evaluation was done by serial CT and FDG-PET using EORTC PET response criteria, with PET centrally reviewed. The primary endpoint, FDG-PET response rate, defined as complete response plus partial response(CR+PR) at 4

weeks, was 72%, with 14 CR, and 17 PR. Seven patients achieved stable disease, 3 had progressive disease and 2 were not evaluable. The response rate in 20 patients with a KIT exon 11 mutation was 80% compared with 57% in wild-type patients. Median progression-free survival was 11.1 months and median overall survival has not been reached. Six patients went off trial for elective surgery, which was allowed after 6 months of treatment. In all, 13 patients went off trial due to progression, 4 because of toxicity, 2 left for other reasons and three patients died. Grade 4 toxicity was seen in 4% of patients and grade 3 toxicity, consisting primarily of gastrointestinal or pulmonary events, was experienced by 38% of patients. Dose reduction/interruption was required in 28 patients. Montemurro *et al.* Abstract 1482PD

Practice point and future research opportunities

Dasatinib shows promising efficacy in TKI-naive patients with FDG-PET positive GIST, particularly those with KIT exon 11 mutations.

Selective internal radiation therapy effective for patients with GIST liver metastases who progressed with tyrosine kinase inhibitors

A team of investigators from Germany evaluated selective internal radiation therapy (SIRT), which delivers 90Y-loaded particles, as an alternative treatment for patients with gastrointestinal stromal tumors (GIST). SIRT was administered to patients with GIST who progressed on tyrosine kinase inhibitor (TKI) treatment; 5 patients had liver metastases only and 4 patients also had extrahepatic disease. One or both liver lobes were treated with SIRT and follow-up was done at three month intervals using dynamic MRI, contrast-enhanced-CT and 18F-FDG-PET-CT by modified RECIST criteria. TKI therapy was continued in all patients having targetable KIT mutations or progressive disease. A total of 14 liver lobes were treated in the 8 patients. At a medial follow-up of 16 months (range 4-52 months) complete remission was achieved by three patients, four patients had a partial remission and two patients had stable disease. The mean progression free interval for hepatic disease was 9.6 months. Radiation induced liver disease was not seen, but one male patient developed a stomach ulcer that did not respond to high dose antacid therapy. Hohenberger *et al.* Abstract 1484PD

Practice point and future research opportunities

SIRT can be used as a safe, effective treatment for liver metastases in patients with GIST who progress with tyrosine kinase inhibitor therapy.

SUPPORTIVE AND PALLIATIVE CARE

E-MOSAIC: Real-time electronic monitoring of patient-reported symptoms and syndromes

SAKK 95/06 is a multicenter phase III study testing the utility of real-time electronic monitoring using a computerized platform, E-MOSAIC, of patient-reported symptoms and syndromes (PRSS) in patients with incurable cancer. The effect of E-MOSAIC on global quality of life (G-QOL) and patient care was assessed in this prospective, cluster oncologist, randomized trial. The trial enrolled patients with defined PRSS who were beginning a new line of palliative chemotherapy and had completed a mobile computer-based (E-MOSAIC) assessment that included the Edmonton Symptom [SYM] Assessment Scale, 3 additional SYM, nutritional intake, body weight, Karnofsky Score and medications for main PRSS prior to six consecutive weekly visits. Eligible oncologists received a cumulative computer printout of their patients' assessments to determine the changes from baseline to week 6 in G-QOL, evaluated according to EORTC-QLQ-C30. A total of 264 patients were treated by 84 oncologists in 8 centers. Patients had various tumors, a median age of 66 years and were equally divided into the intervention arm or control arm (no intervention). Overall survival (OS) in the intervention arm was 6.3 months compared with 5.4 months in the control arm. A total of 102 patients, 55 and 47 in the intervention and control arms, respectively, had four of the 6 planned uninterrupted patient-oncologist sequences required for evaluation of the change in QoL; change in QoL from baseline comparison between the two arms was 6.8 ($p = 0.11$) favoring the intervention arm. In a sensitivity analysis with oncologists treating 2 patients in the 50 patient in the intervention and 39 patients in the control groups, the change in QoL was 9.0 ($p = 0.07$). The most influential factor was good-QOL at baseline ($p < 0.01$). An intention to treat analysis revealed improvement in symptom distress, with changes from baseline to the last study visit of -4.9 compared to 2.0 in the intervention and control arms, respectively ($p = 0.003$). Score changes from baseline in compassion, communication, treatment burden and coping were seen and all favored the interaction arm. More patients with high symptoms received oncologist management. Blum *et al.* Abstract 1423O

Practice point and future research opportunities

The MOSAIC intervention of real-time monitoring of patient-reported symptoms and syndromes that was delivered to the oncologist, significantly improved symptom distress and allowed for better symptom management, communication and quality of life, warranting further development and implementation.

Utility of fatigue and anemia scores for prognosis of overall survival

Gornadha *et al.* evaluated data from patients participating in the PROCHE program to determine whether the incidence of fatigue episodes and anemia could be expressed by scores and associated with overall survival (OS), which could be useful for treatment management. Episodes of fatigue experience by patients between each chemotherapy session were collected using a patient subjective

scale (PSS): 0=none, 1=mild, 2=moderate, 3=severe, 4=3+long-term condition). Hemoglobin (Hb) levels were also assessed at least once before each chemotherapy cycle, using the scale for Hb: 0>12, 1=12-10, 2=10-9, 3=9-8 and 4<8. Of 1279 patients entering the program, 662 patients underwent 4327 chemotherapy cycles and experienced at least 1 assessment of fatigue plus Hb. The 617 patients who were excluded due to no Hb results were similar to the included patients. Patient median age was 64.9 years; there were an equal number of males and females. Disease was localized in the lung in 23% of patients, breast in 21%, prostate in 13% and in the ovary in 10% of patients. At least 1 or 2 Hb results at each cycle were obtained for 229 and 433 patients, respectively. There were 5376 episodes of fatigue (PSS>0), with 694 patients having at least one episode. At least one anemia episode of scale 1, 2, 3 and 4 was experienced by 516, 232, 101 and 35 patients, respectively. Median linear fatigue scores were 1.08 and linear anemia scores were 0.78; non-linear scores were skewed and discarded. Overall survival was 24.8 months; anemia and fatigue scores associated with OS by ANOVA ($p < 0.0001$). Linear fatigue score was a good predictor of OS, HR 2.5 ($p < 0.0001$); 72 patients with a linear fatigue score > 2 showed increased risk of mortality of 4.65 compared to 247 patients with a score of less than one. Hemoglobin mean and linear anemia scores were good predictors for OS, HR 1.45 and HR 1.86, respectively. Gornadha *et al.* Abstract 1545O

Practice point and future research opportunities

Linear scores of anemia and fatigue based upon a scale of patients' subjective reports were easily calculated and significantly associated with overall survival. These scores could serve as efficient predictors of overall survival and also provide a helpful tool in the clinical management of fatigue and anemia.

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AFFILIATIONS AND DISCLOSURE

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