2013 European Cancer Congress

27 September-1 October 2013

Amsterdam, The Netherlands

Summary

The 17th ECCO - 38th ESMO - 32nd ESTRO European Cancer Congress (ECC), held from 27 September to 1 October in Amsterdam, was jointly organised by the European Cancer Organisation, the European Society for Medical Oncology and the European Society for Radiotherapy and Oncology. The ECC is the premier cancer congress in Europe, representing an international scientific collaboration that is truly without boundaries with attendees, presenters and delegates coming from 125 countries.

The Congress comprised the united efforts of all partner organisations to continue advancing multidisciplinarity as the way forward to best improve the prevention, diagnosis, treatment and care of cancer patients by encouraging participants to leverage knowledge, promote education and build awareness about patient-centred oncology.

Introduction

The Congress7 was attended by 18, 482 participants, a 16% increase over the record-breaking attendance at the Stockholm 2011 conference. Overall there were 15,504 delegates, 1621 exhibitors, 735 invited speakers, 349 media representatives and 273 VIPs and guests. The multidisciplinary setting of ECC 2013 featured a strong balance of representation from all cancer fields with participants including surgeons, researchers, radiation oncologists, pharmacists, nurses, clinical trial coordinators and general practitioners; however, representation by the medical oncology field was the strongest with 28.7% of attendees being medical oncologists.

With the Congress theme of “Reinforcing Multidisciplinarity,” ECC 2013 featured 3,176 scientific abstracts, 121 late-breaking abstracts and hundreds of lectures and special programmes that reflected the role the ECC plays as the largest European platform for presenting the latest, ground-breaking data and practice-changing scientific presentations. The comprehensive Scientific Programme was formulated by leading experts that ensured widespread multidisciplinary and multi-professional appeal by offering wide-ranging scientific tracks. Many educational programmes were scheduled that maintained the position of the European Cancer Congress as the largest CME ACOE accredited event in Europe. The Scientific programme offered new research and up to date educational symposia and teaching lectures but retained traditions like the Oxford style debates.

The Congress organisers included the President of ECCO, Cornelius van de Velde, who was the Congress Chair and ESMO President Martine Piccart. The Co-scientific Chairs were Cora Sternberg and John Yarnold and Marcel Verheij served as the National Organising Committee Chair.

Following is a brief summary in different tumour tracks of some of the diverse scientific results presented during the European Cancer Conference 2013.

Tracks

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Basic science

The landscape of tumour suppressors across human cancers

Breast cancer

EORTC 22922/10925, AMAROS, LEA, European pooled analysis of CTCs, TH3RESA studies

Cancer in adolescents and young adults

ARCAD, Adjuvant RT in young patients with luminal A tumours, AYA communication box

Cancer Prevention

VICTOR, Women's Health Initiative, NLST studies

Carcinoma of unknown primary

CUP molecular profiling

Drug development

DLT-TARGETT study

Gastrointestinal Malignancies

PETACC-6, PROCTOR/SCRIPT, FIRE-3, CAPRI GOIM, ALLIANCE studies

Genitourinary Malignancies

JASINT1, NCI/CTEP 7435, GOLD, CTCs analysis from MAINSAIL RAPTOR studies

Gynaecologic cancers

TRINOVA-1, ICON6, AURELIA, ICON7, oliparib in platinum sensitive recurrent serous ovarian BRCA mutated cancers, GOG 240 studies

Head and neck cancer

DAHANCA-9 study

Lung cancer

Phase I with MPDL3280A, MARQUEE, TAILOR, STOP studies

Melanoma

Pooled overall survival data from ipilimumab studies

Neuroendocrine cancers

CLARINET study

Thyroid cancer

DECISION, vemurafenib in RAI refractory, progressive papillary, BRAF V600E mutated cancers

Sarcoma

GEIS study of trabectedin and doxorubicin, PICASSO3 study in soft tissue sarcomas

Supportive care

POWER1, POWER2 studies

Basic science

The landscape of tumour suppressors across human cancers detects potential cancer drivers

Homozygous deletions often affect tumour suppression but their detection has been hindered by the cellular heterogeneity of most tumours and the relatively rare occurrence of homozygous deletion events. Novel bioinformatics techniques allowed Van Loo et al. to perform a systematic screen of homozygous deletions in over 10,000 human cancers, with the aim of identifying the 'landscape of tumour suppressors across human cancers. Their ambitious project seeks to identify known and novel tumour suppressors and to detect the homozygous deletions that occur either within tumour suppressor genes or over fragile sites (regions of increased genomic instability). They constructed a statistical model that separated fragile sites from regions showing signatures of positive selection for homozygous deletions that were likely to contain tumour suppressors and subsequently identified candidates from the patterns of homozygous deletions, the patterns of mutations in the College of Somatic Mutations in Cancer (COSMIC) Cell Lines Project and the literature.

A pilot series of 2218 primary tumours across 12 human cancers identified 96 genomic regions that were recurrently targeted by homozygous deletions; of these, 12 established tumour suppressors were confirmed and 24 candidate tumour suppressors were detected. In lung cancer, homozygous deletions targeting CPEB3, which encodes a sequence-specific RNA-binding protein that represses EGFR transcription, was most frequently detected. These findings suggest that lung cancer results not only from amplification of EGFR, but possibly also by using homozygous deletion of CPEB3 as an alternative mechanism for EGFR overexpression.

In other cancer types, homozygous deletions affecting the caspase family genes CASP3 and CASP9 or closely surrounding regions were found. CASP8 is a known tumour suppressor in breast cancer that mediates apoptosis following cleavage by either CASP8 and/or CASP9. Complete inactivation of either of these caspase family members may prevent apoptosis.

From the literature, the investigators were able to identify several other genes with recurrent homozygous deletions as tumour suppressors: FAT1, BIRC2/BIRC3, MGMT and USP44. Evidence of sequences suggesting possible tumour suppressive activity was found in KAT6B, BAZ1A, USP34, LINC00662 and KIAA1551 genes; several of these figure in either DNA repair or apoptosis, processes likely to include tumour suppressors. Van Loo P, et al., Abstract number 11. No conflict of interest reported.

Practice point and future research opportunities

This study identified tumour suppressors through the presence of recurrent homozygous deletions and provides evidence that mutations in these genes may act as drivers of human cancer.

Breast cancer

Higher survival rates at 10 years in patients with high-risk early breast cancer following irradiation of internal mammary-medial supraclavicular lymph nodes

Radiation therapy delivered to the internal mammary and medial supraclavicular lymph nodes in patients with early breast cancer improved overall survival and loco-regional control without increasing side effects. Results from a study that garnered 'Best Abstract' accolades presented by Philip Poortmans showing increased survival was achieved by women with high-risk early breast cancer (stage I-III) who were treated with irradiation of the internal mammary-medial supraclavicular (IM-MS) lymph nodes compared to those who received radiation therapy to the breast/thoracic wall alone. This phase III (EORTC 22922-10925) trial enrolled women from 46 institutions in 13 countries between 1996 and 2004 who were randomised to receive either radiation therapy of the IM-MS nodes (50 Gy in 25 fractions) or no radiation therapy of the IM-MS nodes.

The study included 4,004 women with high-risk early breast cancer; all had axillary lymph node involvement and/or a medially located primary tumour. The mean patient age was 54 years and 59.0% of women were postmenopausal; 55.6% had involved axillary lymph nodes and 33.8%, 52.0% and 14.2% had stage I, II and III disease, respectively. All of the women underwent mastectomy and the majority (76.1%) of patients were treated with breast-conserving therapy. Irradiation of the breast/thoracic wall was delivered to 73.2% of patients across both study arms. Axillary radiation therapy was given to 6.8% patients in the no IM-MS radiation group and to 7.8% patients of the IM-MS radiation group. Nearly all patients who were lymph node-positive (99.0%) and 66.3% of lymph node-negative patients in this study received adjuvant systemic treatment.

After median follow-up of 10.9 years, 382 patients in the IM-MS group had died compared with 429 in the non IM-MS group. Regional lymph-node recurrence rates were 4.2% and 2.7% for the IM-MS radiation therapy and no IM-MS radiation-therapy groups, respectively. Local recurrence rates in these cohorts were 5.3% and 5.6%; rates of distant metastases were 19.6% and 15.9% and rates of second breast cancers were 5.2% and 4.8%, respectively. Outcome was improved in patients receiving radiation therapy to the IM-MS; overall survival (OS) increased from 80.7% to 82.3% in the radiation group (hazard ratio [HR] 0.87 and was independent of the number of lymph nodes involved. Prespecified secondary endpoints of disease-free survival increased from 69.1% in the cohort not receiving nodal radiation to 72.1% in the IM-MS node cohort (HR 0.89; $p = 0.044$). Metastasis-free survival also favoured radiation therapy to the IM-MS nodes and increased to 78.0% in this cohort from 75.0% in the no irradiation to nodes group (HR 0.86; $p = 0.02$).

No increases in lethal toxicities and no serious complications related to the treatment were reported. Based on these results the authors recommended that radiation treatment of the IM-MS lymph nodes become standard clinical practice for patients with early breast cancer. They plan an average follow-up of 20 years of these patients with the next analysis at to be performed at 15 years. Poortmans P, et al., Abstract number 2. No conflict of interest reported.

Practice point and future research opportunities

The results of this study will help to fine tune individualised treatments for breast cancer patients to determine the delicate balance between under-treatment, possibly resulting in an increased risk of disease recurrence, and over-treatment accompanied by unnecessary toxicity. Radiotherapy as an adjunct to surgery was demonstrated to yield important improvements in loco-regional control and survival without increasing short and long-term toxicities and represents a valuable step towards this goal.

Direct comparison of morbidity following axillary lymph node dissection versus axillary radiotherapy favours radiotherapy and discourages use of combining both treatments

Although phase III trial findings showed similar low rates of axillary recurrence at five years, plus similar overall survival and rates of disease recurrence following treatment of women with early breast cancer and a positive sentinel node by axillary radiotherapy (ART) and/or axillary lymph node dissection (ALND), patients receiving ALND were at higher risk of developing shoulder mobility complications and lymphoedema.

Results from a morbidity analysis of data from the large international, prospective, multicentre AMAROS (After Mapping of the Axilla: Radiotherapy or Surgery?) trial were presented by Milla Donker. AMOROS compared ALND to ART that included the medial part of the supraclavicular fossa as breast cancer therapies. This analysis was done on data from 1400 of the 4806 breast cancer patients enrolled between 2001 and 2010 who also had a positive sentinel node (SN). The analysis was per treatment received and included the short term incidence of surgical complications and the presence of paraesthesia of the arm. Lymphoedema, as reported by the investigator, and shoulder mobility, defined by range of motion comparison of the ipsilateral side to the contralateral side, were analysed after one and five years follow-up. Factors that could be predictive for morbidity were evaluated by multivariate analysis.

In the ALND-group, surgical complications were observed in 23% of patients compared to just 9% in the ART-group ($p < 0.001$). The incidence of paraesthesia of the arm was similar in both groups at 10% and 9% in the ALND- and ART-groups, respectively. At a follow-up done one year after treatment, lymphoedema was recorded for 15% of ART patients, 25% ALND and 59% of patients who received both ALND/ART (both ALND and ALND/ART versus ART $p < 0.001$). At five years post treatment, these rates were 10%, 21% and 58%, with ART, ALND and ALND/ART, respectively (both $p < 0.001$ versus ART). Reduced shoulder mobility, especially during the first year, was seen in both ART and ALND groups.

By multivariate analysis, pre-menopausal status, body mass index > 25, treatment on the dominant side, and the type of axillary treatment associated with lymphoedema (odds ratio [OR] 2.2) of ALND versus ART. The risk of lymphoedema was highest for patients receiving both ALND/ART versus ART (OR 7.6). Predictors for impaired shoulder function were type of axillary treatment, supraclavicular radiation therapy (in the absence of ART) and level of ALND; patients receiving ALND level I plus II showed a better shoulder function compared to ART after one year. Donker M, et al., Abstract number 30. No conflict of interest reported.

Practice point and future research opportunities

Axillary radiotherapy is preferred over axillary lymph node dissection in breast cancer patients with a positive sentinel node; ART therapy results in fewer post-operative complications and the development of lymphedema than ALND and the risk for lymphedema rose substantially with combined ALND and ART treatment. Patient-related factors contributed to a higher risk of lymphedema, but not to reduced shoulder mobility which was influenced by the type and extent of the axillary treatment, particularly ALND. Combined axillary surgery and radiation increases morbidity and should be avoided whenever possible.

LEA study fails to demonstrate superiority with bevacizumab added to endocrine therapy as first-line treatment for advanced breast cancer

No significant increase in either progression-free survival (PFS) or overall survival (OS) was demonstrated by adding bevacizumab to first-line endocrine therapy with letrozole or fulvestrant in postmenopausal women with advanced HER2-negative, hormone receptor (HR)-positive breast cancer; however, overall response rates were almost doubled. Sibylle Loibl and colleagues conducted LEA, a multicentre, randomised, open-label, phase III trial of letrozole/fulvestrant plus bevacizumab compared to endocrine therapy alone as first-line therapy. Postmenopausal women with advanced HER2-negative, HR-positive breast cancer were randomised in a 1:1 ratio following stratification by prior adjuvant therapy with an aromatase inhibitor, the number of involved sites, whether measureable lesions were present and country, either Spain or Germany. Baseline characteristics were well balanced. Visceral metastasis was present in 48% of patients and 19.5% of patients had received prior aromatase inhibitor therapy; 30% had received prior chemotherapy in Germany and 52% in Spain ($p = 0.001$). In both countries combined, 184 patients received endocrine therapy with either letrozole or fulvestrant, 180 and 190 were given endocrine therapy plus bevacizumab.

The trial's primary endpoint was not met: PFS was 14.4 months for sole endocrine therapy compared to 17.7 months for endocrine therapy with bevacizumab (hazard ratio [HR] 0.855, $p = 2.02$. Interestingly, PFS was significantly improved in Germany with added bevacizumab (HR 0.549; $p = 0.0012$; interaction test $p = 0.733$). No difference in PFS was detected in other predefined subgroups. Secondary objectives were OS, overall response rate (ORR), response duration (RD), time to treatment failure (TTF), clinical benefit rate (CBR), and safety (previously reported). The median OS was 52.1 months with added bevacizumab compared to 51.8 months with endocrine therapy alone (HR 1.133; $p = 0.549$). The addition of bevacizumab yielded a significantly higher ORR of 32% over 17% with endocrine therapy ($p < 0.001$) and an improved CBR of 78% compared to 66%, respectively ($p = 0.012$); however, the median response duration was not significantly extended in the bevacizumab combination arm at 47.9 months compared to 30.7 months in the endocrine therapy arm ($p = 0.011$) and TTF was nearly the same at 14.0 and 13.8 months with bevacizumab and endocrine therapy, respectively ($p = 0.471$).

Adding bevacizumab significantly increased the incidence of lymphocytopaenia, thrombocytopaenia and leucopaenia, but grade 3 to 4 haematological toxicities did not differ between the two groups. Among non-haematological toxicities, hypertension, proteinuria and

elevated liver enzymes were reported more often in the bevacizumab arm. Loibl S et al., Abstract number 1851. No conflict of interest reported.

Practice point and future research opportunities

Down-regulating VEGF activity has been suggested to overcome resistance and improve efficacy to hormonal therapy. The current study did not confirm phase II trials showing bevacizumab combined with endocrine therapy to be active and safe. The overall risk-benefit analysis is unfavourable in light of the higher toxicity seen with bevacizumab plus endocrine therapy. A final conclusion about the strategy of using bevacizumab plus endocrine therapy awaits the results from ongoing trials conducted by the Cancer and Leukaemia Group B.

Increased statistical power obtained from analysis of pooled data supports circulating tumour cells as a prognostic marker in metastatic breast cancer: Findings from the European Pooled Analysis of CTC group1

The prognostic utility of circulating tumour cells (CTCs) counts in patients with metastatic breast cancer assayed before or during therapy have been a topic of active research, with most of the assessments done in small to medium-sized studies that had limited statistical power. **François-Clément Bidard** headed a team that aimed to increase the statistical power of this investigation by pooling data from European studies that evaluated the prognostic value of CTCs. Other markers that may be elevated in certain cancers, Carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15–3) levels were also analysed across different metastatic breast cancer (MBC) subtypes and the diverse therapies administered. They compiled data from studies done between 2003 and 2011 in European laboratories using CellSearch®. Employing likelihood ratio tests in Cox regression models stratified by study they assessed the independent prognostic value of CTC-positive, a CTC concentration of five or more CTCs per 7.5mL blood, CEA-positive and CA15–3-positive (normalised values) when added to a clinicopathological model for progression-free survival (PFS) and overall survival (OS). Landmark analyses were used to assess the prognostic effect of early changes in CTC.

Data from 1944 patients with MBC from 20 studies (some unpublished) from 17 centres in 7 European countries were evaluated that disclosed 1507 PFS events and 929 deaths. It was found that the baseline CTC count significantly associated with the following patient characteristics: performance status ($p < 0.0001$), the presence of synchronous metastasis ($p < 0.01$, the tumour subtype ($p < 0.0001$) and the presence of liver & bone metastases ($p < 0.0001$). An association was also seen between CTCs and CEA and CA15–3 levels ($p < 0.0001$). The clinicopathological model for OS included each patient's performance status, MBC subtypes, number of previous lines of treatment, age, the length of metastasis-free interval, the presence of liver and brain metastases, and treatment modality and was significantly associated with all of these parameters ($p < 0.01$ for all). The baseline CTC-positive level was a significant independent predictor of OS in 1444 patients (hazard ration [HR] 2.7; log rank $p < 0.0001$) in multivariate analysis. CEA showed a small added effect when entered into the baseline CTC-positive clinicopathological model for OS in 747 patients (HR 1.3; log rank $p = 0.024$). However, a significant increase in prognostic information was seen

when early changes in CTC-positive status during weeks three to five were added for OS to the clinicopathological model plus baseline CTC-positive in 569 patients (HR 1.8; log rank p < 0.001). Bidard C, et al., Abstract number 1854. No external funding was reported for this study. Authors reported corporate-sponsorship and participation in the advisory board of Veridex.

Practice point and future research opportunities

Findings from an analysis performed on a large database of pooled circulating tumour cell studies yielded previously unreached statistical power that provides level of evidence 1 supporting the independent prognostic value of CTCs before and during treatment and also of early changes in CTC levels during the first weeks of treatment in patients with metastatic breast cancer.

T-DM1 improves progression-free survival over treatment of physician's choice in pretreated HER2-positive metastatic breast cancer; primary results from TH3RESA study

A trastuzumab emtansine combination (T-DM1) demonstrated improved efficacy and safety over treatment by the physician's choice in previously treated women with human epidermal growth factor receptor 2 (HER2)-positive advanced breast cancer. T-DM1 is a conjugate of the **cytotoxic** agent emtansine and the **monoclonal antibody trastuzumab**, which targets the **HER2/neu** receptor, thus achieving specific killing of HER positive tumour cells.

Findings from an interim analysis of data from the TH3RESA Study (NCT01419197) were presented by Hans Wildiers. TH3RESA was an open-label, phase III study that randomised (2:1) 602 women to either T-DM1 or the treatment of physician's choice (TPC). Most (75%) patients had visceral disease; all patients had unresectable tumours or tumour recurrences or metastases after a median of four prior treatments, including trastuzumab and lapatinib. TPC comprised HER2-directed regimens in 83.2% of patients and single-agent chemotherapy in 16.8% of patients.

Among patients with measurable disease, the response rate for TPC was 8.6% compared to 31.3% for T-DM1 (p < 0.0001). A significant difference in median progression-free survival (PFS) favouring T-DM1 was demonstrated, from 3.3 months with TPC to 6.2 months with T-DM1 (stratified hazard ratio [HR] 0.528; p < 0.0001). A first interim overall survival (OS) analysis revealed a similar pattern that was not statistically significant favouring T-DM1 of 14.9 months for TPC compared to not reached for T-DM1. Following disease progression, 44 patients crossed over from the TPC arm to the T-DM1 arm.

Grade 3 or higher adverse events were reported more commonly in the TPC group (43.5% versus 32.3%) specifically for diarrhoea (4.3% versus 0.7%), neutropenia (15.8% versus 2.5%) and febrile neutropenia (3.8% versus 0.2%). Grade 3 or higher thrombocytopaenia was more common with T-DM1 (1.6% versus 4.7%).The rates for trial discontinuation due to adverse events were 10.9% in the TPC group and 6.7% in the T-DM1 group. Dose reductions were required for twice as many patients in the TPC group (19.6% versus 9.4%). The overall rates for study discontinuation were 36.9% for TPC and 21.0% for T-DM1; trial discontinuation due to death occurred in 22.1% of TPC patients and 15.1% of patients receiving T-DM1.

The TH3RESA study is ongoing and will continue either until the final overall survival analysis takes place or the survival benefit for treatment with T-DM1 reaches statistical significance at an interim analysis. T-DM1 is also being tested in the MARIANNE trial, where it is administered alone or combined with pertuzumab to patients with previously untreated HER2 positive metastatic breast cancer. Wildiers H, et al., Abstract number 15. No conflict of interest reported.

Practice point and future research opportunities

Despite the availability of improved treatments, nearly all patients with HER2 positive metastatic breast cancer develop progressive disease; currently there is no clear standard of care for patients who progress after two or more treatments. T-DM1 extends progression-free survival and may offer promising treatment for this cohort.

Cancer in adolescents and young adults

Younger age at diagnosis of metastatic colorectal cancer associates with poorer outcome: ARCAD clinical trials programme analysis.

New data from an analysis using the large ARCAD database identifies patients with metastatic colorectal cancer (mCRC) under the age of 40 years as a high-risk population for treatment failure and poorer overall survival (OS) and progression-free survival (PFS). The median age at diagnosis of colorectal cancer is 69 years, making it a disease that mostly affects the older population; just 4.6% of the total incidence of CRC represents patients younger than 50 years of age. However, CRC incidence in younger people is on the rise despite a trend towards decreased overall incidence in the western population, largely due to screening; overall incidence rates of CRC per 100,000 young adults (ages 20-49 years) increased 1.5% per year in men and 1.6% per year in women from 1992 to 2005. Furthermore, younger patients present more commonly with advanced stage III or IV disease. Importantly, hereditary factors account for just 5 to 7% of young-onset CRC cases, making screening the only way to detect CRC in young adults but screening is currently only recommended for persons aged 50 and older.

Christopher Lieu and colleagues conducted this study which aimed to assess whether age may be prognostic for OS and PFS in patients with mCRC. Previous investigations have made direct comparisons between patients who were categorised into groups of less than 40 years versus aged 40 and more years, thus giving broad pooled risk. This analysis used the French ARCAD Foundation (Aide et Recherché en Cancerologie Digestive) CRC database with data from 20,326 patients who participated in 23 frontline phase III clinical trials, including trials with biologic agents. The endpoints of these trials were OS and PFS and primary covariates included age, sex, and performance status (PS). Cox proportional hazards models stratified by treatment arm within a study were used to model primary age effects, as well as interactions with and/or adjustments for sex and PS. Patients without events by one year were right-censored. Non-linearity of age on the log relative hazard of PFS and OS was modelled using restricted cubic splines to determine whether risk changes as a function of age.

The OS and PFS results were available for 19,900 patients; of these, 695 (3%) patients were younger than 40 years. Age was found to be significantly prognostic for both OS ($p < 0.0001$) and PFS ($p < 0.0001$) with U-shaped risk for each endpoint, indicating that the highest risk of poorer OS and PFS was evident in the youngest and oldest patients, while 57- to 61-year olds demonstrated the lowest risk of OS and PFS, respectively. Patients with CRC in the youngest cohort had a 30% increased risk of death and 28% increased risk of progression or death during the follow-up period. Patients with CRC in the oldest cohort experienced a 72% increased risk of death and 19% increased risk of progression or death in the follow-up period. Sex was statistically but not clinically significant as an adjustment variable in these models. The authors found that, although the assessment of PS may be subject to bias, poor PS significantly associated with decreased survival in younger but not older patients (interaction $p = 0.0001$). Lieu C, et al., Abstract number 2158. No conflict of interest was reported.

Practice point and future research opportunities

This study confirms that colorectal cancer patients younger than 40 have a worse prognosis, an important finding since incidence is rising in this age group. These results were obtained using the ARCAD database, one of the largest in gastrointestinal oncology, and are intriguing since they indicate that younger people diagnosed with colorectal cancer have poorer survival than older patients in spite of being in better overall condition and having less co-morbidity. An evaluation of the prognostic significance of age warrants further analysis aimed at identifying any biological characteristics or markers that make the cancer disease of young people more aggressive and less responsive to drugs.

Premenopausal high-risk breast cancer patients with luminal A tumours benefit from postmastectomy radiation therapy

Findings from a data analysis of two small independent randomised trials suggesting that adjuvant radiotherapy should not be omitted in young patients with high-risk luminal A tumours were presented by Tinne Laurberg. Luminal A tumours are a double edged sword: While they are associated with a good prognosis they also carry a substantial risk for late loco-regional relapses. Laurberg and colleagues conducted an analysis of data representing 20 years of follow-up from two independent, similarly designed randomised trials to determine whether intrinsic subtypes identified by PAM50 classification could be predictive of long term loco-regional relapse after adjuvant radiation therapy was administered to premenopausal women following mastectomy. The analysis was done only on data where accompanying biological samples were available from participants in either of the postmastectomy randomised adjuvant radiation trials conducted by the British Columbia Cancer Agency [Ragaz et al. NEJM 1997; 337(14):956-62] and the Danish Breast Cancer Cooperative Group (DBCG 82b) [Overgaard et al. NEJM 1997; 337:949-955]. Gene expression profiles using the Nanostring Counter® were done on 128 formalin fixed paraffin embedded tissues that were available from the British Columbia (BC) trial and the Human Genome Survey Microarray version 2.0 (Applied Biosystem) for the 87 fresh frozen samples from the Danish Breast Cancer Cooperative Group (DBCCG). Each tumour was classified into Luminal A (LumA), Luminal B (LumB), Her2-enriched (Her2-E), Basal-like breast cancer (BLBC) and Normal-like subtypes according to the PAM50 assay. The differences per subtype in local-regional relapse free survival (LRFS) and overall survival (OS) were determined by Kaplan-Meier analysis and the log-rank test.

All patients had node positive breast cancer. Following mastectomy patients in both trials received adjuvant cyclophosphamide, methotrexate, fluorouracil (CMF) chemotherapy and were randomised to receive either radiation therapy (RT) that entailed irradiation of the chest wall and regional lymph nodes or no RT. The BC trial had a second randomisation; patients with oestrogen receptor positive tumour were randomised to receive oophorectomy and data from 42 of these patients were included in this correlative study. At 20 years after treatment, premenopausal women with luminal A tumours showed significantly decreased local disease recurrence with the addition of radiation to chemotherapy following surgery. The LRFS rate evaluated according to subtypes showed that women with LumA tumours who received postmastectomy radiotherapy had a

significantly better LRFS; 94% of 41 women with LumA tumours participating in the BC study who received adjuvant radiotherapy had no local recurrence compared to 66% of women who received chemotherapy only (p = 0.05). Similar results were seen in the 20 women with LumA tumours in the DBCG trial where 92% of women in the radiotherapy group had no local recurrence compared to just 25% of women who received only chemotherapy (p = 0.01).

No statistically significant differences were observed for LRFS regarding LumB and Her2-E subtypes in either trial. However, 92% of women with BLBC subtype receiving radiotherapy compared to 23% in the chemotherapy only group achieved LRFS in the BC trial (p = 0.004); the rates for LRFS for BLBC were similar between treatment groups in the DBCG trial.

No differences in OS between the tumour subgroups were found in either trial. However, findings from the DBCG trial showed OS was increased at a 10 year follow-up in the entire population with radiotherapy plus chemotherapy over chemotherapy alone; 54% of adjuvant radiotherapy patients versus 45% of patients receiving chemotherapy alone were alive at 10 years (p < 0.001). Laurberg T, et al., Abstract number 1850. No conflict of interest reported.

Practice point and future research opportunities

The results suggest that PAM50 Luminal A classification identifies patients with slow growing tumours who may obtain the benefit from regional radiotherapy following mastectomy and carries the clinical implication that radiation should not be omitted in young premenopausal patients with high-risk tumours. While this is a very interesting study using modern gene expression techniques to evaluate 20 year follow-up data from two large, prospectively randomised phase III trials, there are pitfalls which need to be addressed. The main criticism remains that women only received cyclophosphamide/methotrexate/fluorouracil-5FU chemotherapy which is no longer the standard for node-positive breast cancer. Additionally, only a small number of women had available tumour material for PAM50 assessment, meaning the number of events on which the results are based within the subgroups becomes really small. This is an interesting study to build upon to identify young women who may benefit from postmastectomy radiotherapy. Although actual recommendations support postmastectomy radiotherapy in very young women with additional risk factors, their risk profile is probably different and they might benefit from additional therapy even if they have a Luminal A tumour, which warrants further investigation.

Tool improves communication between adolescents and young adults with cancer and their care giving team: The AYA box

Ann Decoene spoke about the growing recognition that adolescents and young adults (AYAs) diagnosed with cancer perceive their disease differently than children or adults and, in turn, their disease is looked at differently by their family and caregivers. Reasoning that overall improved care for these patients would result from better understanding of how the AYAs experience their cancer and treatment and by conveying this understanding to the parents, the AYA Box, a patient centred tool, was developed. A qualitative study was performed that used patient interviews to determine how AYAs view their diagnosis, hospitalisation, treatment and survivorship to develop the AYA

box, which can be used by patients, parents and by the multidisciplinary team to provide optimal care.

In all, 24 semi-structured interviews were held with AYAs who were aged between 15 and 25 years and with 21 care giving parents, 19 mothers and 2 fathers. Sampling was based on situational diversity, such as gender, age, social context, education and time since diagnosis. The interviews were transcribed and coded. Data collection and analyses took place by a cyclic process and data were processed by constant comparison, a quantitative technique whereby the narrative content of interviews is evaluated for key patterns, which, once identified, are categorised, and coded in order to uncover themes. This process allows the categories and the meaning of the categories to emerge from the data.

The investigators found that AYAs perceive their cancer as something temporarily affecting their lives and their interests and coping strategies are more focused on preserving their emerging identities and protecting their normal lives during treatment and throughout their lives. Further findings suggested that AYAs prefer care to be tailored to their needs, which resulted in the AYA box development, which is a tool to identify these needs and to communicate them to parents and caregivers The box belongs only to the AYA and contains a booklet with personal stories of the experiences of other AYAs, postcards and a unique AYA tag. The box also contains stickers that may be used to mention feelings or concerns, cards with information or instructions, a brief symptom scale and aids in communication with their relatives and professional caregivers. These stickers and other aids can be used by the entire multidisciplinary team to broach more difficult or emotional topics and facilitate communication. Decoene A, et al., Abstract number 1712. No conflict of interest was reported.

Practice point and future research opportunities

This study revealed that cancer seems to have a different meaning for adolescents and young adults than for their care giving parents who face various fears and insecurities. Building on patient and parent interviews, the investigators identified needs specific to adolescents and young adults and their parents and caretakers. They developed the AYA box, which may be used as a tool to convey these needs and to improve communication about emotions and treatment concerns between adolescents and young adults with cancer and the entire team of caregivers.

Cancer Prevention

PIK3CA mutation in tumours may be predictive for benefit from aspirin therapy but not rofecoxib in patients with colorectal cancer

Reports that aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) protect against colorectal cancer (CRC) and are associated with reduced disease recurrence and improved outcome following primary treatment have been counter balanced by a growing appreciation of NSAID-related toxicities that has limited their use. Benefit from aspirin following diagnosis of CRC has been recently suggested to be limited to patients with PIK3CA-mutant cancers, leading Church et al. to evaluate whether the presence of PIK3CA mutation could be predictive of benefit from both COX-2 inhibition and aspirin. They performed a molecular analysis on tumours from 896 patients participating in VICTOR, a large randomised trial that compared rofecoxib, a NSAID COX2 inhibitor, to placebo following primary CRC resection. The endpoints were relapse-free survival (RFS) and overall survival (OS) with rofecoxib therapy compared to placebo and the use of low-dose aspirin compared to non-use according to the PIK3CA mutation status of the tumour.

By multivariate analysis, rofecoxib treatment did not show greater benefit compared to placebo in patients whose tumour had PIK3CA mutation (adjusted hazard ratio [HR] 1.2; $p = 0.66$; $p^{\text{INTERACTION}} = 0.47$), compared with PIK3CA wild-type cancers (HR 0.87; $p = 0.34$). However, an association was seen between a reduced rate of CRC recurrence and regular aspirin use after CRC diagnosis in patients with PIK3CA-mutant tumours (HR 0.11; $p = 0.027$; $p^{\text{INTERACTION}} = 0.024$). This benefit was not observed in patients with tumours without PIK3CA mutation (HR 0.92; $p = 0.71$). Church D, et al., Abstract number 2161. The VICTOR trial was supported by Merck.

Practice point and future research opportunities

These results suggest the presence of PIK3CA mutation in colorectal cancer tumours may have a role as a predictor of response to aspirin therapy. Tumour PIK3CA mutation does not predict benefit from rofecoxib treatment, which showed no benefit over placebo. Findings from this study showed a reduced rate of CRC recurrence with adjuvant aspirin in PIK3CA-mutant CRC and support further investigation.

Results from large clinical trial support continuous combined oestrogen plus progestin to reduce risk of endometrial cancer in postmenopausal women

Continued treatment with oestrogen added to progestin is protective against the development of endometrial cancer in postmenopausal women, according to Rowan Chlebowski who presented findings from an extended follow-up of the Women's Health Initiative (WHI; NCT000000611) randomised, placebo-controlled trial. The WHI enrolled 16,608 postmenopausal women aged 50 to 79 years who had intact uteri between 1993 and 1998 at forty clinical centres in the United States to test the benefit of trial of hormone therapy in this cohort. The women had normal endometrial histology, confirmed by endometrial biopsy upon study entry. Following randomisation, 8506 women received a once-daily tablet of 0.625 mg conjugated equine oestrogen plus 2.5 mg medroxyprogesterone acetate and 8102 received a matching placebo.

The intent-to-treat analysis done after a median of 13.2 years of combined intervention and follow-up showed there were 35% fewer endometrial cancers among women given combined oestrogen and progestin compared with placebo (hazard ratio [HR] 0.65; p = 0.007); 66 women treated with hormone therapy compared to 95 given placebo had developed endometrial cancer. While fewer endometrial cancers occurred during intervention, 25 with hormone therapy versus 30 with placebo (HR 0.77), a greater difference emerged during follow-up with 41 endometrial cancers occurring with hormone therapy compared to 65 with placebo (HR 0.59, p = 0.008). The yearly incidence rates were 0.06% in the intervention arm and 0.10% in the placebo arm (HR 0.65; p = 0.007). Of the endometrial cancers that did occur, there were fewer poorly differentiated or anaplastic tumours (HR 0.51) and fewer cases of regional or distant disease (HR 0.43) in the hormone therapy group than placebo group.

Subgroup analyses found a similar effect of the oestrogen plus progestin influence on endometrial cancer risk, even when body mass index (BMI) was taken into account. BMI is a known risk factor for endometrial cancer, with risk increasing with increasing body weight. There was a statistically non-significant reduction in deaths from endometrial cancer in the oestrogen plus progestin group of 5 compared to 11 deaths with placebo (HR 0.42). Chlebowski R, et al., Abstract number 13. The study was supported from the USA National Institutes of Health.

Practice point and future research opportunities

The latest findings from the Women's Health Initiative confirm the combination of oestrogen plus progestin protects against endometrial cancer; a reduction in endometrial cancers was seen in postmenopausal women treated with hormone therapy even in a high risk group with a greater overall body mass index. Despite this effect on endometrial cancer, there remains an overall balance of risk and benefit of oestrogen plus progestin.

Analysis of screening programmes using computed tomography of high risk populations favours yearly screening to decrease lung cancer mortality

Harry de Koning presented data from an in-depth analysis that identified a small number of efficient annual lung cancer screening programmes that comprised the results of the National Lung Screening Trial (NLST) policy. The NLST showed that lung cancer-specific mortality in a high risk population of volunteers aged 55 to 74 could be reduced by three annual computed tomography (CT) screens. However, this trial did not address other issues, including whether there may be long-term harm from repeated screening, the effect of additional rounds of screening or whether other types of screening programmes could be as or more effective. The authors evaluated five models that estimated harms and benefits in 100,000 USA individuals born in 1950 and followed from the ages of 45 to 90; the models used programmes that varied the criteria for age, pack-years of smoking, years since quitting and screening intervals. In all, 576 scenarios were evaluated the authors reported on the 26 programmes they considered to be efficient and in accord with NLST-scenario.

Annual screening for lung cancer had the greatest impact on mortality rates, with lung cancer mortality decreased by 5 to 6% by screening every three years, 7 to 10% with biennial screening

and by 11 to 21% when screening was done every year. It was determined in the age group from 55 to 80, that yearly screening of ever-smokers with at least 30 pack-years and ex-smokers with less than 15 years since quitting would lead to 19.3% of the cohort (per 100,000) being screened at least once. This would result in 287,000 CT screens and 1,971 screen-detected cases. This would mean detection of 50% of cases at an early stage of I/II leading to a 14% reduction in lung cancer; 520 deaths from lung cancer would be averted and 5,500 life-years gained. It was estimated that 550 screens are needed to avoid one death from lung cancer. These benefits were contrasted by disadvantages: 330,000 CT exams generally yield 66,000 false-positive test results, an estimated 4% over diagnosis rate or 190 lung cancers. More importantly, this many screens could cause as many as 24 deaths due to radiation exposure. de Koning H, et al., Abstract number 14. No conflict of interest reported.

Practice point and future research opportunities

Annual lung cancer screening programmes of individuals between the ages of 55 and 80 with at least 30 pack-years of smoking improved detection and reduced lung cancer deaths. There is limited over-diagnosis in this cohort. Extending screening eligibility to individual having fewer pack-years could yield additional benefits but may increase the risk from radiation exposure.

Carcinoma of unknown primary

Molecular profiling of patients with cancers of unknown primary site yields paradigm shift in treatment approach

An estimated 3% of all cancers are cancers of unknown primary (CUP), which are associated with a poorer prognosis. The quest to identify the primary origin in CUP has been led by testing for biomarker expression indicative of a potential site of origin in order to tailor the therapy based on the presumption of the primary tumour type. However, this approach is often limited by providing just the statistical odds of one site being correct over another and, for the most part, does not provide information on actionable biomarkers. Pathway analysis and identification of the oncogenic drivers of these pathways can provide information on druggable targets, even for CUP, and may open the door to new treatment options for these patients. Recent identification of actionable molecules occurring in common oncogenic pathways has provided druggable targets that are independent of the primary cancer site and may avail CUP patients to new treatment options.

Zoran Gatalica presented late breaking findings from a study that aimed to shift the treatment focus from detecting the origin of CUP to identifying the relevant pathways and targetable molecules within them. The team analysed data from a large scale profiling of 1350 patients with CUP from a referral laboratory at Caris Life Sciences, Phoenix, USA to obtain information on biomarkers associated with the potential for drug response. Biomarker expression was determined using mutational analyses, including next generation sequencing, Sanger pyrosequencing, quantitative polymerase chain reaction (qPCR) and restriction fragment length polymorphism (RFLP), in-situ hybridisation by fluorescent and chromogenic methods, immunohistochemistry, reverse transcriptase (RT)-qPCR and fragment analysis.

Actionable biomarkers were identified in 77% of cases and included targetable protein overexpression, such as steroid receptors and MET, protein loss as seen with PTEN loss of expression, activating mutations that included EGFR, BRAF, PIK3CA and gene copy number variations, such as HER2, TOP2A and MET gene amplification. The analysis also identified disease-defining gene mutations, such as somatic GNA11 mutation, that resulted in reclassification of the disease from metastatic melanoma of unknown primary to primary leptomeningeal melanocytoma. Gatalica cited the example of a recently published case study where an treatment with an EGFR inhibitor (gefitinib) was used successfully in a patient with CUP based on the detection of an activating mutation (L858R) that resulted in a remarkable and durable response (JCO 2013;31:e237). Gatalica Z, et al., Abstract number 39. The authors are employed by Caris Life Sciences and own stock options. The study was funded by Caris Life Sciences.

Practice point and future research opportunities

Pathway analysis can be used to identify druggable targets even in patients with cancer of unknown primary origin thus expanding treatment options not traditionally considered for this patient cohort. Pathway analysis has also allowed the re-classification of disease that result in successful treatment indicated by a durable response.

Drug development

Determining dose limiting toxicities and the re-assessing the recommended dose for non-cytotoxic agents

Jean-Charles Soria reported on an European Organisation for Research and Treatment of Cancer (EORTC)-led initiative, DLT-TARGETT, a study being conducted in collaboration with academia and the pharmaceutical industry that collected data from phase I trials evaluating non-cytotoxic agents (NCAs) as monotherapy. All toxicity that was at least possibly drug-related that occurred during treatment cycles one through six was recorded. The driving force behind this study was to evaluate whether the traditional classification for dose-limiting toxicity (DLT), developed for standard chemotherapeutical agents, is really applicable to measuring toxicity from chronic use of NCAs and, if not, to formulate more relevant criteria for these agents. DLT classification is currently based upon grade 3-4 toxicity data from treatment cycle one only; however, at least one recent report (Postel-Vinay et al, JCO 2011) has raised the issue that toxicities from non-cytotoxic agents may occur at later treatment stages and/or be of a lower grade.

Data from 27 centrally reviewed phase I trials that evaluated NCAs as monotherapy between May 1999 and Sept 2011 comprise the study; dossiers on 1126 evaluable patients participating in these trials were compiled that included possible drug-related toxicities occurring during treatment cycles one through six, the type of toxicity, grade according to CTCAE v3.0, the duration of the episode and the patients' relative dose-intensity (RDI). It was determined that NCAs had been administered orally in 13 treatments, intravenously in 14 treatments (7 multiple- and 7 single-dosing) or subcutaneously in 1 therapy. The type of NCA delivered was 18 small molecule agents, 3 antibodies, and 2 antisense oligodeoxynucleotides. Determination of a maximal tolerated dose (MTD) was possible in 18 trials wherein 92 (8.2%) patients experienced DLTs; however, 12.2% of patients received a RDI below 75% during cycle one and between 13.5 to 15.1% received <75% of the planned RDI at cycles beyond cycle one.

In all, 2534 toxicities were recorded during the first cycle delivered; of these 1558 were grade 1; other toxicities included 714 grade 2 and 262 of grades 3-5. A total of 120 DLTs was seen. Toxicities were also recorded in subsequent cycles; a total of 884, 592 and 292 patients experienced toxicity of any grade during cycles one, two and three, respectively. The majority (2306) of toxicities of any grade were reported after cycle one and included, 1492 grade 1 toxicities, 608 grade 2, 206 grades 3 to 5 and12 DLTs. Grade 2 toxicities were first reported during cycle one for 32.1% of patients and 14.7% of patients presented grade 3-5 toxicities during this cycle. However, the first grade 2 and grade 3-5 toxicities occurred after cycle one in 25.4% and 13.9% of patients, respectively. In patients experiencing grade 3-5 toxicities, 56.8% presented their first episode by the end of cycle one and 89.0% of patients presented by the end of cycle three.

The most commonly reported toxicity throughout trial was fatigue. The database is undergoing further expansion towards the aim of establishing a new classification for DLT and dose

recommendations for future trials. Soria JC, et al., Abstract number 8. The study was sponsored by the EORTC.

Practice point and future research opportunities

Dose expansion in phase I studies should be used to fine-tune the dose-finding process per the following recommendations: Assessment of dose limiting toxicity, especially for non-cytotoxic agents, needs to take into account lower grade toxicities that may lead to a significant decrease in relative dose intensity. The recommended dose for future studies should be based also upon toxicities observed in cycles following cycle one to maintain a dose greater than > 75% relative dose intensity.

Gastrointestinal Malignancies

Similar benefit but increased toxicity following preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine plus oxaliplatin compared to the same regimen with capecitabine alone in locally advanced rectal cancer: PETACC-6 trial

Findings of the PETACC-6 phase III trial presented by Hans-Joachim Schmoll indicated that there was no significant benefit from adding oxaliplatin to preoperative oral fluoropyrimidine-based chemoradiation (CRT) followed by postoperative adjuvant fluoropyrimidine-based chemotherapy in patients with locally-advanced rectal cancer within 12 cm from the anal verge. PETACC-6 enrolled patients between November, 2008 and September, 2011 that were considered resectable at the time of entry or expected to become resectable; all 1094 enrolled patients were stage T3/4 and/or node-positive but with no evidence of metastatic disease. Patients were randomised to receive either 5 weeks of preoperative CRT (45 Gy in 25 fractions with an optional boost to a total dose of 50.4 Gy) with capecitabine, followed by six cycles of adjuvant chemotherapy with capecitabine(arm 1, n=547) or to the same regimen plus oxaliplatin prior to surgery and post-surgery every three weeks (arm 2, n=547). Primary endpoints included disease-free survival (DFS), pathological staging and sphincter preservation following preoperative, as well as, pathological down-staging (pT0–2N0) rate, complete remission (pT0N0) rate and tumour regression grade according to Dworak (assessment was based on specimen review and scoring by the local pathologist). Non-resected patients were recorded as failures in the intent-to-treat analysis.

A minimum of 45 Gy of preoperative RT was delivered to 98% and 92% of patients in arms 1 and 2 respectively. More than 90% of arm 1 patients received more than 90% of the full dose of concurrent chemotherapy, as did 63% of patients in the arm 2 oxaliplatin cohort. The R0 resection rate was 92.0% in arm 1 and 86.3% in arm 2. The ypT0N0 rate was nearly the same in both arms with 11.3% of arm 1 and 13.3% of arm 2 patients achieving complete remission (p = 0.31). The pathological down-staging rate was 43.5% in arm 1 compared to 41.5% in arm 2. In arm 2, the tumour regression was minimal in 19%, moderate in 36.2%, good in 19.4% and total in 12.4% of the patients in cohort 1 and was minimal in 13.7%, moderate in 35.5%, good in 20.5% and total in 13.5% of cohort 2 patients. Sphincter perseveration was achieved in 70% compared to 65% of patients in arms 1 and 2, respectively (p = 0.09). Schmoll HJ, et al., Abstract number 2155. Conflict of interest: Advisory board: H.J. Schmoll, R. Hofheinz, T. Price have a consultant or advisory role for Roche to disclose. H.J. Schmoll has a consultant or advisory role for Sanofi and Bayer to disclose. Corporate-sponsored research: H.J. Schmoll, E. Van Cutsem, K. Haustermans, R. Hofheinz have research funding from Roche to disclose. H.J. Schmoll has research funding from Merck to disclose. E. Van Cutsem has research funding from Sanofi to disclose.

Practice point and future research opportunities

Adding oxaliplatin to preoperative fluoropyrimidine-based chemo-radiotherapy did not provide a significant improvement in tumour down staging or anal sphincter preservation in patients with locally advanced rectal cancer; these results may be affected by the high degree of treatment non-compliance in the oxaliplatin arm.

Adjuvant chemotherapy after preoperative radiotherapy or chemoradiation followed by TME-surgery has no clear advantage for rectal cancer patients: The PROCTOR/SCRIPT study

Controversy shrouds the role of adjuvant chemotherapy after preoperative radiotherapy or chemoradiation followed by total mesorectal excision (TME) surgery; findings from an analysis of pooled data from the PROCTOR and SCRIPT studies done by the Dutch Colorectal Cancer Group showed no clear benefit from adding chemotherapy to the current treatment for rectal cancer patients. According to Anne Breugom, results from a recently reported Cochrane review demonstrated a significant reduction (17%) in the risk of death and a 25% reduction in disease recurrence in patients undergoing postoperative chemotherapy, as compared to the observation arm but many of the trials that comprised this review did not evaluate current treatment strategies. She reported findings from an analysis of PROCTOR/SCRIPT data, which merited a 'Best Abstract' credit that evaluated whether adding postoperative chemotherapy could improve overall survival and the risk of disease recurrence. PROCTOR/SCRIPT was a multicentre trial that enrolled 470 patients with stage II or III rectal adenocarcinoma; PROCTOR randomised 177 patients to observation or to postoperative chemotherapy with 5-FU]/leucovorin with or without preoperative radiotherapy followed by TME and SCRIPT randomly assigned 292 patients to observation or to postoperative chemotherapy with capecitabine after preoperative radiotherapy or chemoradiation followed by TME. In all, 238 patients received adjunct chemotherapy and 232 underwent observation only. Approximately three-quarters of the patients had stage III disease and nearly all had R0 resections. More than 82% had received neoadjuvant radiotherapy and approximately 13% received chemoradiation. Chemotherapy was completed by 75% of patients in this group.

Findings from a median follow-up of four years showed no significant difference in overall survival between treatment arms (hazard ratio [HR] 0.878, p = 0.527). The 5- and 10-year overall survival rates, respectively, were 74.4% and 65.1 with chemotherapy and 75.9% and 55.8% with observation. At 10 years post treatment, fewer than 15 patients were at risk in either group. Similar trends were seen for disease-free survival rates at 3 and 5 years, which were 67.4% and 62.0%, respectively, for chemotherapy and 66.1% and 58.4% for observation (HR 0.835; p = 0.247). The data suggested there may be possible benefit in tumours 10 cm and larger from chemotherapy (HR = 0.552; p = 0.028). The study was limited by being underpowered due to poor accrual. The authors have started a meta-analysis of pooled data from the 470 PROCTOR/SCRIPT patients plus 113 patients from the CHRONICLE trial of postoperative adjuvant capecitabine/oxaliplatin, and 634 patients from an Italian study evaluating postoperative adjuvant 5-FU/leucovorin. Breugom A, et al., Abstract number 1. No conflict of interest was reported.

Practice point and future research opportunities

PROCTOR/SCRIPT findings do not alter current practice and reinforce the existing guidelines. The role of adjuvant chemotherapy after preoperative radiotherapy or chemoradiation followed by total mesorectal excision surgery is still being evaluated but currently there is no indication to administer adjuvant chemotherapy as a standard treatment.

Analysis of phase III FIRE-3 trial data shows most patients with wild-type RAS metastatic colorectal cancer benefit from first-line FOLFIRI plus cetuximab treatment whereas FOLFIRI/bevacizumab treatment favoured patients with RAS mutations

Previously reported results that first line treatment with FOLFIRI plus the anti-epidermal growth factor receptor (EGFR) agent cetuximab improves overall response rate and overall survival in most patients with KRAS wild-type (exon 2) metastatic colorectal cancer (mCRC). A preplanned analysis by mutational status done on data from the FIRE-3 trial also showed benefit to patients with wild-type KRAS exon 3/4 and wild-type NRAS exon 2/3/4. The study expanded genetic evaluations to establish predictive factors for resistance to more rare NRAS gene mutations and to BRAF also found that a subgroup of patients with mutated RAS did not show similar benefit from FOLFIRI/cetuximab but did achieve improved progression-free survival following treatment with FOLFIRI plus the anti-vascular endothelial growth factor (VEGF) agent bevacizumab. The FIRE-3 phase III trial (AIO KRK-0306; NCT00433927) was a head to head comparison of FOLFIRI plus either cetuximab or bevacizumab as first-line treatment in patients with metastatic colorectal cancer (mCRC); KRAS wild-type tumours were confirmed in 592 patients who were then randomised 1:1 to receive first-line FOLFIRI every two weeks plus either cetuximab (arm A) or bevacizumab (arm B).

Results of a preplanned analysis were presented by Volker Heinemann that evaluated the effect of KRAS mutations in exon 3 (codon 59/61), exon 4 (codon 117/146)), NRAS exon 2 (codons 12/13), exon 3 (codons 59/61) exon 4 (codons 117/146)) and BRAF (V600E) on the overall response rate (ORR), progression-free survival (PFS) and overall survival (OS) on treatment arms of the FIRE-3 trial. Mutational analyses were done by pyrosequencing in 592 patients who were wild type for KRAS exon 2. A total of 444 (75%) patients had available tumour tissue; of these, sequencing of all RAS mutations was possible in 396 patients.

Results from the overall study population favoured arm A with cetuximab patients showing median OS nearly four months longer than in the bevacizumab arm; median OS was 28.7 months with FOLFIRI/cetuximab versus 25.0 months with FOLFIRI/bevacizumab (log rank p = 0.017). Although median PFS was similar in both study arms at 10.0 months in arm A versus 10.3 months in arm B (p = 0.547), benefit was also demonstrated with FOLFIRI plus cetuximab in the overall intent to treat population of 592 patients with KRAS wild type disease with respect to the ORR, which was 62.0% and 58.0% in arms A and B, respectively (p = 0.183). Moreover, 301 patients within the wild-type RAS subgroup (wild-type KRAS exon 2/3/4 and NRAS exon 2/3/4) showed improved ORR of 76.0% with FOLFIRI/cetuximab over patients who received FOLFIRI/bevacizumab (ORR = 65.2%; Fischer's one-sided p = 0.026, Fischer's two-sided p = 0.044). The ORR in 40 patients with mutated BRAF (KRAS exon 2 wild-type and BRAF V600E mutant) was 63.2% in arm A versus 42.9% in arm B (p = 0.167).

Patients with RAS wild-type mutational status demonstrated longer OS with FOLFIRI/cetuximab of 33.1 versus 25.9 months in the FOLFIRI/bevacizumab arm (p = 0.010). RAS wild-type patients who also had BRAF mutations showed OS of 12.9 versus 11.0 months (p = 0.448), respectively. The hazard ratio (HR) for adding cetuximab versus bevacizumab for OS in patients with wild type RAS

was 0.69 (p = 0.01). However, the comparator arm was favoured in 55 patients with mutated RAS (KRAS exon 2 wild-type and KRAS exon 3/4 or NRAS exon 2/3/4 mutant) who showed ORRs of 42.9% and 66.7% in the FOLFIRI plus cetuximab or bevacizumab arms, respectively (p = 0.066). Patients with mutated RAS achieved OS of 19.1 months with cetuximab and 20.6 months with bevacizumab (p = 0.622).

PFS results by mutational status showed patients with RAS wild-type and BRAF mutation obtained slightly more benefit from FOLFIRI/cetuximab treatment. RAS wild-type patients had PFS of 10.5 versus 10.4 months (p = 0.627) and PFS in patients with mutated BRAF was 6.3 and 5.7 months (p = 0.626), for cetuximab versus bevacizumab, respectively. The hazard ratio for PFS in wild-type RAS patients was 0.94 (p = 0.63). Patients with RAS mutations showed significantly improved PFS with bevacizumab: PFS was 6.1 months with cetuximab versus 12.2 months with bevacizumab (p = 0.006). Heinemann V, et al., Abstract number 17. The FIRE-3 trial was supported by Merck; no external funding was reported for this analysis. The authors stated the following conflicts of interest: Research sponsored by Merck and Roche; participation on the advisory board of Merck, Roche, BMS and travel support from Merck, Roche.

Practice point and future research opportunities

KRAS activating mutations in exon 2 had been shown previously to correlate with primary resistance to anti-EGFR therapy and other reports show that activating RAS mutations can predict poorer outcome from treatment with cetuximab and panitumumab in metastatic colorectal cancer patients. This head to head comparison of FOLFIRI plus either cetuximab or bevacizumab as first-line treatment in patients with mCRC provides the first phase III results according to the KRAS exon 2 status demonstrating the influence of KRAS exon 3, 4 and NRAS exon 2, 3, 4 mutations on the efficacy of these treatments. These findings may impact daily clinical decisions since subgroups of patients were identified that were most likely to benefit from different treatments and suggest that better identification of other RAS mutations can improve both the overall response rate and the overall survival in patients receiving cetuximab as compared to bevacizumab, and vice versa, highlighting the importance for detecting other RAS mutations to better select patients who may benefit from anti-EGFR therapies.

Interim analysis of molecular profiling in the CAPRI GOIM trial

Recent data suggested that cetuximab, an epidermal growth factor receptor (EGFR) inhibitor, may not be indicated for patients with tumours containing exon 3/4 KRAS and NRAS mutations because they may confer resistance to anti-EGFR therapies. Also, somatic mutations in BRAF, PIK3CA and PTEN genes could be prognostic and/or predictive in metastatic colorectal cancer (mCRC).

Fortunato Ciardello reported results from the CAPRI GOIM trial (Eudract 2009-014041-81), which enrolled 356 patients with mCRC whose tumours contained wild-type KRAS exon 2 (codon 12/13) that was detected by local laboratory assessment. All patients received first line cetuximab plus FOLFIRI treatment and were randomised 1:1 at progression to receive either FOLFOX (Arm A) or FOLFOX plus cetuximab (Arm B). The primary endpoints for both first and second line were progression-free survival (PFS). Next generation sequencing (NGS) using the Ion AmpliSeq™

technology was used to centrally assess tumour samples and 10 ng of genomic DNA were analysed for 500 hotspot mutations in 22 genes with Ion Ampliseq Colon and Lung cancer panel using Ion Reporter™ Software.

Data for the first line treatment was available for 340 evaluable patients; NGS was performed in 182 (53.5%) patients and found that 58 (31. 9%) of these 182 patients had no mutations in the 22 investigated genes. However, even though initial assays showed in patients to be wild-type KRAS for exon 2, mutations in this gene were identified in 29 (15.9%) samples. The most frequently detected mutation was TP53, which appeared in 39.6% of samples. Other frequently detected mutated genes were: KRAS exon 3 and 4 in 8.8% of samples, NRAS exon 2 and 3 in 7.1% of samples and PIK3CA was mutated at exon 9 in 7.7% and at exon 20 in 5.5% of samples. BRAF was found to be mutated in codon 600 for 5.5% of samples and in other codons in 2.7% of samples.

The results confirmed that cetuximab had greater activity in patients whose tumours expressed fewer mutated genes and who showed a stronger overall response. Clinical activity was correlated to the genetic subgroups and results were reported for the cohort of 182 patients having samples for NGS: Complete response (CR) was achieved by 12 (6.6%) patients overall, by 8 (6.4%) patients with KRAS/NRAS wild-type tumours and by 8 (7.7%) patients with KRAS/NRAS/BRAF/PIK3CA wild-type tumours. In these respective genetically defined cohorts, partial response (PR) was achieved by 92 (50.5), 69 (55.6) and 59 (54.7) patients. The overall response rate was 51% in patients, 62% in KRAS/NRAS wild-type patients and 64.4% in patients with tumours expressing KRAS/NRAS/BRAF/PIK3CA wild-type. Stable disease (SD) was reported in 62 (33.5%) patients overall, 35 (28.2%) patients with KRAS/NRAS wild-type and for 28 (26.9%) patients with multiple wild-type genes. Progressive disease by the respective subgroups was seen in 17 (9.3%), 12 (9.7%) and 9 (8.6%) patients, respectively.

The study's endpoint, median PFS was 9.9 months in the entire NGS group, compared to 11.1 and 11.3 in patients with wild-type KRAS/NRAS and in patients wild-type for KRAS/NRAS/BRAF/PIK3CA, respectively. As of 30 June 2013, 150 patients of all 340 enrolled patients have progressed and have been randomised within the ongoing second line part of the study, 74 to receive FOLFOX (Arm A) and 76 to receive FOLFOX plus Cetuximab (Arm B). Ciardiello F, et al., Abstract number 31. No conflicts of interest were reported

Practice point and future research opportunities

Results from this study demonstrate the feasibility of performing molecular classification of wild-tape KRAS exon 2 using the next generation sequencing. Furthermore, first-line treatment with cetuximab plus FOLFIRI showed greater benefit in patients with metastatic colorectal cancer who had tumours with wild-type KRAS, NRAS, BRAF and PI3K genes. The detection of codon 12/13 KRAS mutations in previously analysed tumours raises the possibility that false negative results in KRAS may occur in routine clinical practice.

KRAS mutations in codon 12 and 13 are prognostic for poorer disease-free survival in patients with BRAF-wild-type colon cancers: Results from phase III Alliance trial

Mutations in KRAS, most commonly in codons 12 and 13 are seen in approximately 40% of patients with colorectal cancer. Recent data suggest that mutations in codon 13 may not represent an aggressive phenotype and may not predict for resistance to anti-EGFR therapy, casting doubt on whether these mutations should be routinely assayed. Furthermore, previously reported data suggesting that specific mutations in KRAS may differentially impact prognosis of colorectal cancer patients are inconsistent, possibly due to patient populations with heterogeneous disease stages and the different therapies received. To resolve this controversy, Harry Yoon and colleagues examined the prognostic impact of specific KRAS mutations in colon cancer patients with only stage III disease who were given FOLFOX alone and/or combined with cetuximab as adjuvant therapy in a large phase III clinical trial (Alliance, NCCTG N0147). Their analysis was done on 2,165 colon adenocarcinomas that were found to carry wild-type BRAF tumours; KRAS mutations in codon 12 including G12A, G12R, G12D, G12C, G12S and G12V and one mutation in codon 13 (G13D) were examined using the DxS mutation test kit in a CLIA-certified laboratory. Specimens from both treatment arms were able to be pooled for this analysis due to the lack of an interaction between KRAS status and treatment ($p > 0.30$). The primary endpoint was disease-free survival (DFS) as described by hazard ratios (HR) obtained using Cox models. Univariate and multivariate analyses were adjusted by age, gender, race, tumour stage, the number of positive/examined nodes, grade, performance status, tumour site and treatment.

Patients with tumours expressing KRAS mutations in either codon 12 or 13 showed significantly shorter DFS compared to patients whose tumours contained wild-type copies of KRAS and BRAF; three year DFS rates were 68% in 528 patients with codon 12 mutation and 65% in 158 patients with codon 13 mutation compared to 77% in 1479 patients with wild-type KRAS status. Multivariate analysis showed that codon 12 mutations significantly associated with shorter DFS as compared to KRAS wild-type cancers (HR 1.44; $p = 0.0001$). The association between shorter DFS and codon 13 mutations was observed by multivariate analysis. Tumours bearing codon 12 and 13 mutations were each associated with a right-sided as opposed to left sided tumour site ($p < 0.001$). Yoon H, et al., Abstract number 2160. The ALLIANCE trial was funded by the National Cancer Institute, USA.

Practice point and future research opportunities

Phase III clinical trial results show that KRAS mutations in either codon 12 or 13 significantly associate with inferior disease-free survival following FOLFOX adjuvant therapy in patients with stage III BRAF wild-type colon cancer, highlighting the role KRAS codon 12 and 13 mutations play in disease progression. These findings stress the importance of accurate molecular characterisation of KRAS codon 12 and 13 mutations in patients with colon tumours.

Genitourinary Malignancies

Preliminary data show first-line vinflunine plus gemcitabine or carboplatin safely controls advanced urothelial carcinoma in patients who are unfit for cisplatin treatment

Although carboplatin and gemcitabine are often used either as a doublet or as single agents there is no standard treatment for patients with advanced or metastatic urothelial carcinoma who are not fit enough for cisplatin-based first-line chemotherapy. Vinflunine, a vinca alkaloid, has been approved in the post-platinum setting and demonstrated safety in patients with impaired renal function, leading Maria De Santis and colleagues to evaluate the benefit to risk ratio of two chemotherapy regimens containing vinflunine in patients with urothelial carcinoma in a randomised international phase II trial (JASINT1). The trial enrolled 68 patients with a creatinine clearance (CrCl) < 60mL/min but ≥30, with urothelial carcinoma, performance status (PS) 0/1 who had received no prior systemic chemotherapy, except neoadjuvant or adjuvant chemotherapy where relapse occurred six or more months after last dose. Patients with CrCl <4 0 or ≥ 40mL/min were randomised to arm A to receive vinflunine plus gemcitabine or to arm B with vinflunine plus carboplatin at AUC 4.5. The primary endpoint was the disease control (DC) rate, defined as complete response (CR) plus partial response (PR) plus stable disease (SD) by RECIST 1.1); other endpoints included safety, response rate, progression-free survival (PFS) and overall survival (OS).

Preliminary safety results from the first 43 patients enrolled from February 2011 to February 2012 were reported. The median follow-up was 7 months in 21 arm A and 22 arm B patients who had a median age of 70 years. ECOG PS was 0 in 46.5% and PS 1 in 53.5% of patients, with 53% and 47% of patients diagnosed with cancer of the bladder or upper tract primary sites, respectively. Just 14% had received prior chemotherapy and most of the patients had multiple co-morbidities, including 26% with cardiac issues. The mean baseline CrCl was 46.7mL/min and 19% of patients had CrCl less than 40. The median (range) number of cycles administered was 5 (1–12) and the median vinflunine relative dose-intensity was 98% in arm A and 93% in arm B.

More haematological grade 3/4 events occurred in arm B with 68% of patients reporting neutropenia in arm B compared to 43% of arm A patients and febrile neutropenia was recorded 9.1% and 0% of patients in arms B and A, respectively. Overall, the most frequently reported non-haematological grade 3/4 adverse events that were determined to be possibly treatment related were asthenia-fatigue, which was seen in 18.6% of patients, infection in 11.6%, and constipation which occurred in 7.0% of patients overall and without major difference between arms. A non-haematological drug-related event was the reason given for treatment discontinuation by 9.5% of arm A patients and 18% of patients in arm B. The ORR was nearly 50%: 20 of 41 patients showed a response that was confirmed in 16 patients and disease control was achieved in 17 arm A and 19 arm B patients. Data collection for the entire cohort is ongoing. De Santis M, et al., Abstract number 2703. Conflict of interest: Ownership: Pierre Fabre Médicament. Advisory board: M. De Santis. Corporate-sponsored research: Coordinator of trials involving vinflunine: M. De Santis, S. Culine. Other substantive relationships: Speaker: M. De Santis, S. Culine Employee of Pierre Fabre Research Institute: C. Lucas, N. Vaissière, J.P. Burillon.

Practice point and future research opportunities

Although preliminary, these data confirm that vinflunine plus either gemcitabine or carboplatin is feasible and safe when administered for five or more cycles. Disease control was equivalent between both regimens but haematological toxicity was higher with the vinflunine/carboplatin combination.

Eribulin activity in platinum-treated, tubulin naive patients with advanced urothelial cancer confirmed by phase II findings

Agents such as taxanes and vinca alkaloids that target tubulin in dividing cells have demonstrated activity in patients with locally advanced and metastatic urothelial cancer but novel agents are needed. Previous reports from the California Cancer Consortium demonstrated that eribulin, a microtubule modulator derived from the black Pacific sea sponge toxin had activity in urothelial cancer in the frontline setting (Quinn et al, ASCO A4359, 2010) leading the group to conduct a phase II study (NCI/CTEP 7435) of eribulin in patients who had received prior platinum-based therapy but were anti-tubulin naive. David Quinn reported that trial accrual has been completed and 46 patients with any histological type of urothelial cancer with a calculated creatinine clearance rate (CrCl) ≥ 20mL/m and prior platinum-based cytotoxic therapy for advanced disease were enrolled. All trial participants received intravenous eribulin. The primary endpoint was an overall response rate (ORR) of more than 20%; secondary endpoints included progression-free survival (PFS) and overall survival (OS).

Data analysis was not possible for 7 patients who had not been on study long enough. In 39 evaluable patients, the patient median age was 67 years (range: 25 to 86 years) and 87% were male. Karnofsky Performance Status (PS) of 90% or higher was reported in 64% of patients and PS was 80% or less in 33% of patients. Histology was transitional in 36 (92%) patients, unclassified in 2 (6%) patients and adenocarcinoma in 1 (2%) patient. Bajorin risk groups of 0, 1 and 2 were recorded for 33%, 62%, and 5% of patients, respectively. Following eribulin treatment, the ORR was 36% including one patient with complete response; 7 patients achieved partial response (PR) which was unconfirmed in 6 patients; therefore the confirmed RR was 21%. Twelve (31%) patients maintained stable disease for 12 or more weeks and progressive disease was the best response demonstrated by 11 (28%) patients. At median follow-up of 5.9 months (range 1.4 to 17.1months), median PFS was 4.1 months (range 2.6, to 6.4months), median OS was 9.6 months (range 5.3 months to not reached) and 16 patients had died. PFS associated with Bajorin risk group ($p = 0.005$ for trend).

Grade 3/4 neutropenia was seen in 24 (62%) patients, 3 (8%) experienced grade 3 febrile neutropenia and 14 (36%) patients showed grade 1/2 sensory neuropathy. Non-haematologic toxicities included hyperglycemia in 1 (3%) patient, grade 3 hyponatraemia occurred in 8 (21%) patients, grade 1 alopecia occurred in 16 (41%) patients and 2 (5%) patients reported grade 1/2 leg fatigue and aching. A parallel study evaluating eribulin in patients who received prior anti-tubulin drug treatment is ongoing. Quinn D, et al., Abstract number 2704. No external funding was reported.

Practice point and future research opportunities

Eribulin showed promising single agent activity in patients with advanced urothelial cancer who received prior platinum-based chemotherapy but no previous anti-tubulin treatment. Phase III evaluation of eribulin in these patients may be warranted to determine whether eribulin has the potential to improve outcomes in patients with advance urothelial cancer and to establish it as a treatment option.

Similar phase III results reported for dovitinib and sorafenib in patients with metastatic renal cell carcinoma who progressed on anti-VEGF and mTOR inhibitors

Although a head to head comparison of dovitinib with sorafenib in patients with metastatic renal cell carcinoma (mRCC) who had progressed following therapies targeting the VEGF and mTOR pathways did not demonstrate superiority of dovitinib, this large, phase III trial did establish a role for the use of tyrosine kinase inhibitors in this patient cohort. Dovitinib, a multi-targeted receptor tyrosine kinase inhibitor that offers broader inhibition of the FGFR by binding FGFRs 1, 2, and 3 and also targets the PDGFR, FLT3, cKIT plus VEGFR, showed similar activity to sorafenib. Dovitinib demonstrated a generally well tolerated safety profile and may offer an additional treatment alternative that addresses the unmet needs of patients with mRCC progressing on therapies that target the VEGFR and mTOR.

Late breaking results were presented by Robert Motzer from the GOLD trial (Global Oncologic Leanings for Dovitinib, NCT01223027), an open-label randomised multicentre phase III trial. GOLD enrolled 570 patients with clear cell mRCC who showed disease progression within six months of their last therapy and had received one prior treatment with an agent targeting the VEGF pathway plus one prior treatment with an mTOR inhibitor. Patients were allowed to have had prior cytokine and other anticancer therapies. The majority, 92% of patients, had received an anti–VEGF pathway agent followed by an mTOR inhibitor. Patients were stratified by region and by MSKCC risk group: 21% of patients showed favourable, 57% intermediate and 22% of patients showed poor risk. The patients were randomised 1:1 to receive either dovitinib (n= 284) or sorafenib (n=286) orally twice daily. Patient characteristics were well balanced between groups. The trial's primary endpoint was progression-free survival (PFS) by central review. Secondary endpoints included overall survival (OS), response rate and safety.

Although dovitinib demonstrated promising anti-tumour activity in heavily pre-treated RCC patients, the trial did not meet the primary endpoint; median PFS was 3.7 and 3.6 months in the dovitinib and sorafenib arms, respectively (hazard ration [HR] 0.86; p = 0.063). Median OS was also similar at 11.1 months with dovitinib and 11.0 months with sorafenib (HR 0.96; p = 0.357). Best overall response was the same with both agents; 4% of patients in each arm demonstrated partial response and stable disease was achieved by 52% of patients in each arm.

However, safety profiles differed between treatments. The adverse events (AEs) most commonly reported by patients receiving dovitinib were diarrhoea, nausea and vomiting; 68% versus 45% of patients reported diarrhoea, 53% versus 29% of patients had nausea and 44% versus 16% of patients reported vomiting, respectively, with dovitinib compared to sorafenib. AEs more

commonly reported in the sorafenib arm than in the dovitinib arm were palmarplantar erythrodysesthesia, hypertension and alopecia; 40% of sorafenib patients reported palmarplantar erythrodysesthesia compared to 11% of dovitinib patients, 28% versus 19% reported hypertension and 21% versus 1% of patients reported alopecia, respectively in the sorafenib and dovitinib arms. Motzer R, et al., Abstract number 34.

This study was sponsored by Novartis Oncology. The authors disclosed the following conflicts of interest: Novartis stock ownership by C. Cai, R. Motzer is on the advisory boards of Pfizer and AVEO Oncology, C. Szczylik is on the advisory boards of Astellas, Novartis, GlaxoSmithKline and Pfizer, C.N. Sternberg is on the advisory boards of Novartis, GlaxoSmithKline and Pfizer, N.J. Vogelzang is on the advisory boards of Celgene and Sanofi, C. Porta is on the advisory boards of Novartis, Bayer-Schering, Pfizer, Hoffman La Roche and GlaxoSmithKline, C. Kollmannsberger is on the advisory boards of Novartis, Pfizer and GlaxoSmithKline, G.A. Bjarnason is on the advisory board of Novartis, B. Melichar is on the advisory boards of Novartis, Roche, Astellas, Pfizer and GlaxoSmithKline, U. Di Giorgi is on the advisory boards of Novartis, Pfizer, GlaxoSmithKline and Bayer, B. Escudier is on the advisory boards of Novartis, Pfizer, Bayer, GlaxoSmithKline and Astellas. The following authors disclosed the following corporate-sponsored research: R. Motzer: Novartis, Pfizer, GlaxoSmithKline, AVEO Oncology; N.J. Vogelzang: Algeta, Arqule, Cougar Bio-Tech, Johnson&Johnson/Centocor, GlaxoSmithKline, Novartis, Pfizer, Takeda/Millennium, Tokai, Veridex, Wilex; C. Porta: Novartis, Bayer-Schering. Other substantive relationships were disclosed by R. Motzer from Novartis that include support for congress attendance to present research, by N.J. Vogelzang who reported employment at US Oncology and by G. Urbanowitz, C. Cai, and M. Shi who reported employment at Novartis.

Practice point and future research opportunities

GOLD is an important randomised phase III trial comparing two tyrosine kinase inhibitors in the third line setting in patients progressing after at least one prior VEGF targeted therapy and one prior mTOR inhibitor, a patient group in urgent need of novel treatment options. Dovitinib targets not only the VEGFR, PDGFR and cKIT but also the FGFR 1-3, which may play a role in the mechanisms of escape from VEGF-targeted therapies, was promising and reasonable to study in this patient population. Although this was a negative study that did not show an improvement in progression-free survival with dovitinib over sorafenib, important data were generated: Very few objective responses (4%) were seen, but disease stabilisation was achieved in about half of the patients. Demonstrating PFS of nearly 4 months and OS of 11 months in third line patients sets a benchmark that novel therapies for metastatic renal cell cancer will have to surpass. Results from this large phase III trial defined the activity and safety profiles of tyrosine kinase inhibitors in patients with metastatic renal cell cancer.

Benefit seen with first-line everolimus monotherapy in patients with papillary metastatic renal cell carcinoma: RAPTOR final analysis

Papillary carcinomas comprise 10% to 15% of renal cell cancers; when the disease is confined to one location surgical removal results have an excellent prognosis but, upon metastasis, limited treatment options currently exist. Everolimus inhibits the mammalian target of rapamycin (mTOR)

and is currently approved for patients who progress after treatment with sunitinib or sorafenib. RAPTOR (NCT00688753) was the first prospective phase II study to investigate everolimus as first-line treatment of patients with papillary metastatic renal cell cancer (mRCC).

According to findings presented by Bernard Escudier, everolimus showed clinical efficacy in these patients. RAPTOR was an open-label study wherein 92 treatment-naive adult patients with type I or type II papillary mRCC and an ECOG performance status of ≤1, were given everolimus until disease progression or unacceptable toxicity occurred. Data were analysed after 3.5 years of study and included three populations: All 92 enrolled patients comprised the safety cohort, 83 were included in the intention-to-treat (ITT) analysis and 63 patients who received ≥1 dose of everolimus and had no major protocol violations were included in the per-protocol (PP) analysis. Most (92%) patients were white and the majority (78%) were male with a mean age of 60 years (range 23 to 84 years). Papillary RCC was confirmed per local review in 99% of patients, of whom 77% were confirmed centrally. Per local review, 58% of patients had type II and 16% had type I (25% missing) and per central review 59% had type II and 33% had type I (9% missing).

The primary end point, the proportion of patients who remained progression-free at six months, was met. Furthermore, at least 50% of the patients were alive at nearly two years (20 months) after treatment. The six month progression-free survival (PFS) was 58.7% in the per-protocol analysis, and 34.9% by central review; median PFS was 7.8 months and 3.7 months, respectively. Results in the ITT population confirmed these results and demonstrated PFS of 7.6 months by local review and 3.7 months by central review. Median overall survival (OS) was 20.0 months (95% confidence interval [CI] 11.1, 28.0 months) in the PP population and 21.0 months (95%CI 15.4, 28.0) in the ITT population. Commonly reported adverse events (AEs) of grade ≥3 included asthenia, fatigue and anaemia which were reported by 10.9%, 5.4% and 5.4% of patients, respectively. In all, 27.2% of patients discontinued due to AEs. Escudier B, et al., Abstract Number 2706. This study was funded by Novartis pharmaceuticals. Conflict of interest: Advisory board: Astellas, Aveo, Aveo-Astellas, Bayer, Bayer-Schering, Boehringer-Ingelheim, GlaxoSmithKline, Jansen, Novartis, Pfizer, Roche, and Sanofi-Aventis. Corporate-sponsored research: Pfizer and GlaxoSmithKline. Other substantive relationships: One author is an employee of Novartis Pharma GmbH.

Practice point and future research opportunities

Papillary tumours are difficult to treat with no current standard of care. These tumours have been excluded from many of the targeted therapy trials; this study targets the mTOR pathway with everolimus in patients with advanced papillary renal cell cancer and the strong findings indicate that more than half of these cancer patients are getting some kind of benefit from everolimus treatment and support a phase III trial. The result differences between central and local reviews also highlight the need for expert pathology. These clinical findings are potentially practice changing and suggest everolimus may offer new treatment option to patients with papillary mRCC, following phase III trial confirmation.

Baseline levels of circulating tumour cells are indicators for overall survival in patients with metastatic castration-resistant prostate cancer: Analysis of MAINSAIL trial data

Circulating tumour cells (CTCs) have been proposed as a possible prognostic factor in patients with metastatic castration-resistant prostate cancer (mCRPC) and have been shown to associate with overall survival (OS) and response to therapy (DeBono. Clin Cancer Res. 2008; Vogelzang. J Clin Oncol 30:15s, 2012 (suppl: abstr e15089). Nicholas Vogelzang reported findings from an analysis of data from the phase III MAINSAIL trial that evaluated the relationship between CTC counts and overall survival following docetaxel/prednisone treatment both with and without adjunct lenalidomide in patients with mCRPC. MAINSAIL enrolled chemotherapy-naive patients with progressive mCRPC who were randomised to receive intravenous docetaxel and oral prednisone plus either lenalidomide (arm A, n= 105) or placebo (arm B, n=103). Lenalidomide failed to improve survival when added to docetaxel and prednisone in men with mCRPC in the phase III MAINSAIL trial. For this analysis, baseline CTC counts were analysed using Southwest Oncology Group (SWOG) prognostic groups; blood samples for CTC analysis were collected from 208 patients in the North American cohort. At baseline, 87 patients had CTC counts of less than five cells per 7.5 ml blood (n=49 in arm A and n=38 in arm B) and 121 patients had five or more cells per 7.5 ml blood (n=56 in arm A; and n=65 in arm B).

Results showed that 2-year overall survival (OS) was shorter in patients with higher baseline CTC levels of five or more cells in both arms A and B (arm A: hazard ratio [HR] 3.63; p = 0.0044 and arm B: HR 3.41; p = 0.0459). An early increase in CTC during cycles one to four associated with significantly shorter OS (HR 5.24; p = 0.0251). Evaluation of OS by SWOG prognostic subgroups showed that OS was not reached in patients in both arms with levels of 0 to 5 CTCs compared to 1.9 years and 1.1 years in patients with 6-53 CTCs and 54 or more CTCs, respectively. The OS of arm A results stratified by CTC counts reflected the negative findings of this trial with patients receiving adjunct lenalidomide showing poorer OS than patients receiving placebo. Arm A patients with 1-5, 6-53 and ≥ 54 CTCs showed overall survival of 1.5 years, 1.9 years and 0.8 years, respectively, whereas OS was not reached in arm B patients receiving placebo until CTC levels were greater than 54; in this subgroup, OS was 1.4 years. Significant differences in PSA or tumour response were not found in patients according to baseline CTC levels. CTC change between cycles zero to four associated with response to adjunct lenalidomide; patients with baseline CTC < 5 and ≥ 5 and no early increased counts showed a response of 61.5% and 75%, respectively, whereas 25% and 0% of patients who had an early increase in CTCs respectively responded to lenalidomide (p = 0.024). Vogelzang N, et al., Abstract number 23. MAINSAIL was sponsored by the California Cancer Consortium.

Practice point and future research opportunities

Overall, higher CTC counts at baseline associated with shorter overall survival, suggesting that elevated baseline CTC counts are a prognostic factor for overall survival. An early rise following treatment of CTC is predictive both for overall survival and poor response to lenalidomide and may be considered as a surrogate endpoint in future phase III trials.

Gynaecologic cancers

Adding trebananib to paclitaxel significantly increases progression-free survival in women with recurrent epithelial ovarian cancer: Results from TRINOVA-1 phase III trial

The first reported findings from the phase III TRINOVA-1 trial evaluating trebananib plus paclitaxel compared to placebo plus paclitaxel in women with recurrent epithelial ovarian cancer showed that the trial's primary endpoint had already been met; progression-free survival (PFS) was significantly improved with the trebananib combination and overall survival (OS) data, though not yet mature, demonstrated a promising trend towards improved OS at an interim analysis. Since epithelial ovarian cancer is often symptomless, many women have advanced disease upon diagnosis; 80% of these women will experience recurrence and eventually die from their disease.

Bradley Monk reported preliminary results from the TRINOVA-1 (NCT01204749) phase III randomised double-blind trial that compared paclitaxel plus trebananib to paclitaxel and placebo. Trebananib is an anti-angiogenesis peptibody that inhibits the binding of angiopoietin 1/2 to the Tie2 receptor, thus interfering with angiogenisis, which provides the additional blood supply that supports the tumour. The trial enrolled 919 women aged 18 years and older with measurable or evaluable recurrent epithelial ovarian cancer and adequate organ function; patients could have received one prior front-line platinum-based regimen and were allowed to receive two additional cytotoxic regimens but patients with a platinum-free interval (PFI) >12 months or who were platinum-refractory were excluded. Patients were stratified according to duration of PFI, measurable disease and region and then randomised to receive paclitaxel plus either placebo or trebananib. The primary endpoint was PFS and OS was a secondary endpoint.

Treatment arms were similar with regard to age, race, primary tumour site, performance status, tumour grade, and number of prior regimens. At the data cut-off date of March 2013, results showed a statistically significant difference in PFS, which was prolonged by 52% with trebananib; median PFS was 7.2 months in the trebananib arm versus 5.4 months in the control arm (hazard ratio [HR] 0.66; $p < 0.001$). A 34% reduction in the risk of disease progression or death was also seen. The response rate increased from 30% with placebo to 38% with trebananib. The OS data are expected to be mature in 2014; however at an interim analysis preplanned at 313 deaths, a trend towards improved OS of median 19.0 versus 17.3 months favouring trebananib over placebo was observed (HR 0.86; $p = 0.19$).

With trebananib the most frequently reported adverse events (AEs) were localised oedema, nausea and alopecia. The rate of trial discontinuation due to adverse events was 20% in the trebananib arm versus 7% in the control arm. While localised oedema was increased, the investigators noted that class-specific anti-VEGF associated AEs such a hypertension, proteinuria, wound-healing complications or arterial thrombotic events were not increased with trebananib. Monk B, et al., Abstract number 41. TRINOVA trial was sponsored by Amgen. The first author reported the following conflicts of interest in term of corporate-sponsored research: he has received money for research from Amgen, but this was not paid to him directly but to his institution.

Practice point and future research opportunities

The demonstration of prolonged progression-free survival taken together with an overall good safety profile suggests that trebananib may offer an alternative treatment option in the near future for women with recurrent epithelial ovarian cancer. Further study of trebananib is warranted and several trials of different trebananib formulations are underway.

Cediranib shows benefit in women with relapsed, platinum-sensitive ovarian cancer (ICON6)

The average reported time to disease progression with platinum based chemotherapy is 8 to 9 months, which was shown to be improved by adding cediranib to this regimen to an average of 12.6 months. Similarly, overall survival was prolonged from 17.6 with chemotherapy to 20.3 months with added cediranib, making it the first oral inhibitor of its kind to slow disease progression and, subsequently, improve overall survival in recurrent ovarian cancer. Cediranib is a tyrosine kinase inhibitor that blocks vascular endothelial growth factor (VEGF) receptors, thus inhibiting a signalling process involved in forming the blood vessels that support tumours.

Jonathan Ledermann presented results from ICON6, an international randomised three armed, double-blind, phase III trial of cediranib. ICON6 enrolled 456 patients from 63 centres who were then randomised 2:3:3 to one of three cohorts: platinum-based chemotherapy with placebo maintenance (reference), concurrent cediranib during chemotherapy followed by placebo for up to 18 months (concurrent), or cediranib followed by maintenance cediranib (concurrent/maintenance). Chemotherapy consisted of up to six cycles of platinum/paclitaxel, carboplatin/cisplatin, or platinum/gemcitabine. The primary endpoint was progression-free survival (PFS) in the reference arm as compared to both the concurrent and maintenance arms. Secondary endpoints were overall survival (OS), toxicity and quality of life. Survival time was estimated using restricted means estimates. Baseline characteristics were balanced between the three arms. The patients' median age was 62 years, and their ECOG performance status was 0/1. The interval from previous treatment was more than 12 months in 67% of patients.

Patient benefit was demonstrated in the cediranib concurrent/maintenance arm over the reference chemotherapy arm with time to progression, OS and PFS all being extended by several months; restricted means estimates showed an increased time to progression of 3.2 months over two years, from 9.4 with chemotherapy to 12.6 for the cediranib concurrent/maintenance arm. Similarly restricted means showed OS increased by 2.7 months from 17.6 in the reference arm to 20.3 in the cediranib concurrent/maintenance arm (hazard ratio [HR] 0.70; log-rank test $p = 0.0419$). Restricted means evaluation of PFS demonstrated a significant increase in PFS with cediranib of 2.0 months, from 9.4 for the reference to 11.4 months in the concurrent/maintenance arm (HR 0.68; $p = 0.0022$). More patients discontinued treatment in the cediranib arm. Significantly more adverse events occurred with cediranib given during chemotherapy, including hypertension ($p = 0.004$), diarrhoea ($p < 0.001$) and nausea ($p = 0.008$). Ledermann J, et al., Abstract number 10. ICON6 was sponsored by the British Medical Council. Astra-Zeneca provided the study drug.

Practice point and future research opportunities

Phase III trial results showed for the first time that the addition of cediranib to platinum-based chemotherapy increased progression-free survival by about three months in women with recurrent platinum-sensitive ovarian cancer. Additional benefit was obtained when cediranib was used as maintenance therapy, increasing both overall- and progression-free survival over chemotherapy alone.

Bevacizumab added to paclitaxel doubles progression-free survival in patients with platinum-resistant recurrent ovarian cancer: Final results from AURELIA study

Bevacizumab is the first single agent to show superiority over weekly paclitaxel, topotecan, or liposomal doxorubicin in patients with platinum-resistant ovarian cancer, according to results reported by Petronella Witteveen from AURELIA (NCT00976911), an open-label randomised phase III trial of chemotherapy with or without bevacizumab for platinum-resistant recurrent ovarian cancer. Platinum resistance was defined as progression within six months of the last platinum-containing therapy. In AURELIA, 361 patients were randomised to bevacizumab plus investigator's choice of chemotherapy or investigator's choice of chemotherapy alone until progression, unacceptable toxicity, or consent withdrawal occurred. Upon progression, cross-over was allowed from sole chemotherapy to the bevacizumab arm but bevacizumab was discontinued in the adjunct bevacizumab arm following progression. The two arms were well balanced for demographic and disease characteristics. Progression-free intervals of less than three months were reported for 25% of patients.

Median follow-up was 27.4 months in both arms and showed that 264 patients had died, 72% of bevacizumab patients and 75% of chemotherapy patients. AURELIA met its primary endpoint of improved progression-free survival (PFS), showing that adding bevacizumab to chemotherapy significantly improved PFS over sole chemotherapy from median 3.4 to 6.7 months in patients with platinum-resistant ovarian cancer (hazard ratio [HR] 0.48; $p < 0.001$). Also, bevacizumab improved median overall survival (OS) from 13.3 months with chemotherapy alone to 16.6 months but this did not reach statistical significance. Response rate, a second primary endpoint, was improved to 30.9% with bevacizumab from 12.6% with chemotherapy ($p < 0.001$).

An exploratory subgroup analysis of OS by the mode of chemotherapy administered, showed that greatest gains were achieved when bevacizumab was added to weekly paclitaxel; median overall survival was 22.4 months for bevacizumab/paclitaxel compared to 13.2 months in controls, which was a 35% relative improvement favouring bevacizumab. However, OS was not improved by adding bevacizumab to liposomal doxorubicin where a median OS of 13.7 months with adjunct bevacizumab compared to 14.1 months with sole chemotherapy was observed. Similar results were seen for PFS in the topotecan-treated cohort where median PFS was 13.8 with adjunct bevacizumab and 13.3 months with sole chemotherapy. No new safety concerns were raised; grade 3 or higher toxicities seen in the bevacizumab arm were hypertension and proteinuria, which were seen in 7.8% and 2.2% of patients, respectively.

Study limitations included insufficient power to detect a statistically significant difference in OS by the preplanned non-randomised crossover to bevacizumab in the chemotherapy arm; 72 patients crossed over to bevacizumab and received a median of 4.5 cycles of therapy. Witteveen P, et al., Abstract Number 5. This study was sponsored by Roche.

Practice point and future research opportunities

Bevacizumab interferes with angiogenesis, a driver of advanced disease, but doesn't improve the cure rate, which raises the question of whether maintenance therapy with bevacizumab would improve survival. AURELIA doubled progression-free survival in group of patients with ovarian cancer where there is significant clinical need. AURELIA is a practice-changing study; bevacizumab with weekly paclitaxel should be considered the standard in platinum-resistant ovarian cancer.

Final overall survival results from the phase III ICON7 trail show clinical benefit with bevacizumab plus standard chemotherapy in newly diagnosed ovarian cancer

Impressive overall survival (OS) gains were demonstrated when bevacizumab was added to standard chemotherapy in the ICON7 trial in women with newly diagnosed ovarian cancer; the primary safety and efficacy analysis was previously reported (NEJM 2011;365:2484-96). Amit Oza reported results from a preplanned final analysis of OS from ICON7 data in a predefined subgroup of women with a poor prognosis who were at high risk of disease progression showing the time to progression was delayed by four to five months with bevacizumab.

The seven-year ICON7 study began in 2004 and enrolled 1,528 women with ovarian cancer with high-risk early (FIGO stage I-IIa) or more advanced (stage IIb-IV) epithelial ovarian, primary peritoneal or fallopian tube cancer at 263 worldwide centres. The patients were randomised 1:1 to receive either six cycles of carboplatin and paclitaxel or the same chemotherapy plus five or six cycles of concurrent bevacizumab followed by continued single-agent bevacizumab for 12 additional cycles or until progression. The median patient age was 57 years and the ECOG performance status PS was 0-1 in 47% of patients. High-risk early-stage disease was diagnosed in 9% of patients with 69% of patients displaying serous, 8% endometrioid and 8% of patients had clear cell histology. Baseline characteristics were well balanced between treatment arms.

A pre-specified poor prognosis group at high risk of progression contained 502 (33%) women; 290 patients had operated stage III and >1cm residuum, 182 operated stage IV, and 30 patients with non-operated (11 stage III and 19 stage IV). Using the Grambsch-Thernau test, comparison of hazard functions for control and research groups showed non-proportional hazards across all analyses; therefore, Restricted Mean Survival Time (RMST) was used as the primary estimate instead of the hazard ratio.

The final analysis performed at a follow-up of median 49 months, found that 714 women had died in the overall study group, 352 control and 362 in the bevacizumab arm. Bevacizumab added to carboplatin and paclitaxel did not improve survival by a clinically relevant amount in the overall randomised population: Median OS was 58 months with a RMST improvement of 0.9 months with bevacizumab from 44.6 to 45.5 months (log-rank p = 0.85, P-H test p = 0.02). However, in the pre-specified poor prognosis subgroup at a high risk for disease progression, a benefit of 4.8 months

in the RMST was observed with adjunct bevacizumab. In this cohort, 332 (64%) patients had died, 174 in the control arm and 158 in the bevacizumab arm. Patients in this group achieved an improvement of 4.8 months in RMST from 34.5 in the chemotherapy control arm to 39.3 months with bevacizumab (log-rank p = 0.03, P-H test p = 0.007). No new safety concerns were reported during the long-term follow up. Oza A, et al., Abstract number 6. ICON was funded and led by the Medical Research Council UK.

Practice point and future research opportunities

ICON7 is a practice changing trial. Findings from this large, randomised phase III trial of bevacizumab added to standard carboplatin and paclitaxel support the consideration of this regimen as a potential new standard of care for women with newly diagnosed ovarian cancer. Adjunct bevacizumab treatment demonstrated improved outcome and prolonged overall survival in patients with ovarian cancer who had a poorer prognosis and were at high risk of disease progression.

Women with platinum-sensitive recurrent serous ovarian cancer and BRCA mutation benefit from oliparib plus chemotherapy followed by oliparib maintenance monotherapy

Findings from an interim analysis according to BRCA mutation status of progression-free (PFS) and overall survival (OS) following treatment with carboplatin and paclitaxel plus oliparib, an oral PARP inhibitor, were presented by Amit Oza. It was previously demonstrated that adding oliparib to chemotherapy with carboplatin AUC4 plus paclitaxel, followed by oliparib as maintenance monotherapy significantly improved PFS compared to the chemotherapy regimen alone with no maintenance therapy in patients with platinum-sensitive recurrent serous ovarian cancer (Oza et al., ASCO 2012).

Germline BRCA mutation status was known for 35 of 162 patients who participated in the open-label, randomised phase II trial (NCT01081951 and tumour BRCA mutation status could be determined for 91 patients by retrospective testing of archival samples. The efficacy endpoints for the BRCA mutation analyses were PFS by central review by RECIST 1.1 and PFS2, defined as the time to start of second subsequent therapy after first progression, or death. The OS was a secondary endpoint.

Of 162 patients that were randomised, 81 received the oliparib/carboplatin/paclitaxel regimen; 66 patients in this arm also received oliparib maintenance therapy. Carboplatin/paclitaxel was given to 71 patients and 55 of these patients entered the maintenance phase but received no further therapy. BRCA mutation status was known for 107 patients; 41 (38%) patients had a BRCA mutation and 7 more had BRCA mutation of unknown significance. Treatment comparisons were made between two groups of patients: Patients with mutated BRCA compared with patients having no mutation plus patients having BRCA mutation of unknown significance.

Significantly longer PFS was seen in patients with BRCA mutation following treatment with oliparib/carboplatin/paclitaxel compared to carboplatin/paclitaxel (hazard ratio [HR] 0.21) and compared to patients with no BRCA mutation and BRCA mutation of unknown significance (HR 0.77; p = 0.0015). No statistically significant difference was seen between arms in the overall

population, regarding interim OS (38% maturity (HR 1.37; p = 0.2238). The authors noted that this analysis was potentially affected by an imbalance in early censoring of two patients in the oliparib/carboplatin/paclitaxel arm and 15 patients in the carboplatin/paclitaxel after 16 patients withdrew consent and one patient was lost to follow up.

The retrospective assessment of PFS2 showed an improvement in patients with BRCA mutation, but not in the overall population, favouring oliparib/carboplatin/paclitaxel over carboplatin/paclitaxel (HR=0.35; p = 0.0258). Due to insufficient events in patients with a BRCA mutation, OS analyses have yet to be performed according to BRCA mutation status. Olaparib maintenance therapy will be further evaluated in two phase III trials patients with ovarian cancer and BRCA mutation. Oza A, et al., Abstract number 3002. This study was sponsored by AstraZeneca. Conflict of interest: Ownership: E. Lowe & J. Read are employees of AstraZeneca and own AstraZeneca stock. Advisory board: C. Poole has been a remunerated consultant and advisory board member for AstraZeneca. Other substantive relationships: C. Poole has been CI and PI of other AstraZeneca-sponsored clinical trials.

Practice point and future research opportunities

Oliparib plus carboplatin and paclitaxel followed by maintenance oliparib monotherapy showed clinical benefit and improved progression-free survival in patients with platinum-sensitive recurrent serous ovarian cancer who harboured mutations in BRCA. PFS2 results also demonstrated benefit in patients with BRCA mutation from this regimen, suggesting that benefit is maintained beyond the first progression in this subgroup. No benefit from the oliparib/carboplatin/paclitaxel therapy over carboplatin/paclitaxel was demonstrated in an interim overall survival analysis using data from the overall patient population.

Improved pain scores on patient reported outcomes accompany improved overall survival when bevacizumab is added to standard chemotherapy for the treatment of advanced cervical cancer

Penson et al. reported late breaking findings from a Quality of Life (QoL) analysis of data from the randomised phase III Gynaecologic Oncology Group (GOG) 240 trial, a four-armed study that enrolled 452 women with recurrent or metastatic cervical cancer who were randomised to receive one of two chemotherapy regimens alone or with bevacizumab. The chemotherapy regimens were cisplatin or topotecan, both with paclitaxel. Each chemotherapy was given with or without bevacizumab over 21-day cycles until complete response, unacceptable toxicity, or disease progression occurred. The study concluded that bevacizumab given together with either of these chemotherapy backbones improved overall survival and response rates over chemotherapy alone in these patients and results were considered practice changing. This analysis evaluated the quality of life aspects of participants in the GOG240 trial; the primary and co-primary endpoints were measured using the Trial Outcome Index of the Functional Assessment of Cancer Therapy-Cervix (FACT-Cx TOI) and FACT/GOG-Neurotoxicity (Ntx) subscale. The secondary QoL endpoint was worst pain in 24 hours, as measured by the Brief Pain Inventory (BPI). Evaluations were done at treatment pre-cycle and at one, two, five, six and 9 months following the first cycle administered. Evaluations were made using a linear mixed model that adjusted for baseline score and age.

Baseline QoL assessments were completed by 96% of GOG240 participants and the final assessment at nine months was completed by 63% of patients. Completion rates did not differ statistically between treatment arms at any of the assessment points (p = 0.67). Quality of life evaluations favoured patients receiving chemotherapy plus bevacizumab over sole chemotherapy; fitted mixed model estimates (MEMD) indicated that patients receiving adjunct bevacizumab had an average of 1.2 points lower FACT-Cx TOI scores than those receiving only chemotherapy (p = 0.3). Patients receiving bevacizumab reported neurotoxicity symptoms less often; fitted MEMD model estimates again favoured bevacizumab/chemotherapy over chemotherapy (overall odds ratio ORR 0.58; p = 0.053). However, when reported, the severity of neurotoxic symptoms was similar between the treatment groups (p = 0.7). Also similar between groups by fitted MEMD model estimates were the amount of complaining of pain (odds ratio = 0.89; p = 0.7) and the severity of pain reports (p = 0.16). The authors explained that the trend to be less likely to report neurotoxic symptoms observed in patients receiving bevacizumab could be attributed to secondary gain from increased tumour shrinkage or be regarded as a consequence of the gate theory of pain. Penson R, et al., Abstract number 42. No conflict of interest reported.

Practice point and future research opportunities

Patient-reported outcomes comparing quality of life between patients receiving chemotherapy plus bevacizumab or chemotherapy alone indicated that the survival gains associated with bevacizumab do not come at the expense of quality of life; several parameters, including reported pain, actually showed better scores in patients receiving either bevacizumab combination over both sole chemotherapy regimens. Results from this quality of life study support the addition of bevacizumab to a chemotherapy backbone for the treatment of women with recurrent or metastatic cervical cancer.

Head and neck cancer

No benefit seen from adding zalutumumab to radiotherapy in patients with squamous cell carcinoma of the head and neck

Adding the epidermal growth factor receptor (EGFR) inhibitor zalutumumab to primary (chemo-) radiotherapy and nimorazole did not improve loco-regional control, disease-specific or overall survival over primary (chemo-)radiotherapy and nimorazole alone for the treatment of patients with head and neck squamous cell carcinoma (HNSCC). First results of the DAHANCA-9 randomised phase III trial (NCT00496652) were reported by Jesper Eriksen. The trial was conducted by the Danish Head and Neck Cancer Group (DAHANCA) to evaluate whether the addition of zalutumumab, a fully humanised IgG1 monoclonal antibody directed towards EGFR, to concurrent radiotherapy could improve outcome in patients with HNSCC.

DAHANCA-9 enrolled 619 patients with biopsy-verified HNSCC from November 2007 to June 2012. Patients were stratified by tumour-site, stage, p16 status and whether they were receiving concurrent cisplatin. The tumour site was the oral cavity in 4% of patients, oropharynx in 69%, hypopharynx in 12% and larynx in 14% of patients. Stage III-IV disease was confirmed in 554 (89%) patients and 75% of the oropharyngeal carcinomas were positive for p16. In all, 70% of patients were receiving concurrent cisplatin; patients with stage III-IV carcinomas received weekly cisplatin during radiotherapy. Patients were randomised to receive either sole radiotherapy (control arm, n=309) or radiotherapy plus zalutumumab (n=310). Patients in the zalutumumab arm received the first dose the week prior to beginning radiotherapy and continued to receive it weekly during irradiation. Patient and tumour characteristics were well balanced between arms. Both arms received the same radiotherapy: Primary accelerated radiotherapy predominantly 66-68Gy, 2Gy/fx, 6fx/wk and concomitant daily hypoxic radiosensitisation with nimorazole. Elective neck dissection was not performed.

The trial's primary endpoint was loco-regional control (LRC) and secondary endpoints included disease-specific survival (DSS) and overall survival (OS).

At time of final data collection for primary outcome measure (July 2013), the median observation time was 36 month (range 12 - 67 months). Results showed that 71 patients had died of HNNSC and 45 had died of other causes. Although 126 cases of LRC were verified, no difference was demonstrated between arms in the rate of LRC; the three-year LRC rate was 78% in the zalutumumab arm compared to 79% in the control arm, (hazard ratio [HR] 0.8; 95% confidence interval [CI] 0.6, 1.2). Similar results of comparable response between arms were seen for DSS (HR 1.0; 95% CI 0.7, 1.7) and OS (HR 0.9; 95% CI 0.6, 1.3). The effect of zalutumumab was neither influenced by p-16 positivity HR (1.0; 95% CI 0.6, 1.8) nor by p-16 negativity (HR 0.8; 95% CI 0.5, 1.4). Treatment was generally well tolerated. However, nearly all (94%) of patients in the zalutumumab arm reported a skin rash, with 29% of these patients experiencing a grade 3-4 rash; skin rash was the reason given for 13% of patients to stop zalutumumab treatment. These results represent the first report of data from this randomised phase III trial and additional analyses are

underway. Eriksen J, et al., Abstract number 12. This trial was sponsored by the Danish Head and Neck Cancer Group.

Practice point and future research opportunities

The DAHANCA-9 trial did not meet the primary endpoint of improving loco-regional control compared to primary curative radiotherapy and the addition of zalumumab did not increase overall or disease specific survival. It is unknown whether a molecularly defined subgroup of patients may benefit from zalumumab. So far, addition of zalutumumab to primary curative treatment for patients with HNNSCC is not indicated.

Lung cancer

A novel antibody shows impressive clinical benefit in patients with squamous and non-squamous NSCLC that parallels the degree of PD-L1 expression in tumours

A novel antibody, MPDL3280A, elicited response in 26% of patients with non-small cell lung cancer (NSCLC) who were current or former smokers and showed activity even in a small percentage (10%) of never-smokers. MPDL3280A targets programmed death ligand 1 (PD-L1); the expression of PD-L1 may inhibit the antitumour immune response by binding to PD-1 and B7.1, thus triggering PD-L1/PD-1 pathway activation. The antibody acts to restore immune surveillance and immune cell attack upon cancer cells.

According to Jean-Charles Soria, longer smoking history may associate with tumours that harbour more genetic mutations and the magnitude of response to the antibody blockade of this pathway could be expected to be stronger in patients with higher levels of PD-L1 expression. He presented efficacy data for 53 patients and safety data for 85 patients from an ongoing international phase I expansion study that continues to enrol patients with squamous or non-squamous metastatic NSCLC who have failed first-line chemotherapy. The patients received an intravenous infusion of MPDL3280A; among the responding patients, treatment duration ranged from 170 to 534 days. PD-L1 tumour expression was measured by immunohistochemistry (IHC) using a scoring system of 0 to 3 and the objective response rate (ORR) was assessed according to RECIST v1.1.

The response reflected the degree of PD-L1 expression by the tumour; the response rate was 83% in patients with IHC 3 and 46% in those with lower IHC scores of 2/3. The median average time to first response was 11.9 weeks. A response was demonstrated by 9 of 37 patients with squamous and non-squamous histologies, yielding an ORR of 24%. Progression-free survival (PFS) at 24 weeks was achieved by 46% of patients. The duration of response was 1 to 214+ days; at the time of analysis, all responses were ongoing or improving. Some patients showed delayed responses after apparent radiographic progression and were, therefore, not included in the ORR. Biomarker analysis of archival tumour samples again demonstrated that response associated with PD-L1 status: An ORR of 100% was seen in 4 of 4 patients with PD-L1-positive tumours and just 4 of 37 patients who were PD-L1 tumour status-negative responded (15% ORR). Baseline recording of smoking status showed 31 (84%) patients were either former or current smokers and 6 (16%) patients were never smokers; the response rates were 25% compared to 16%, respectively in former/current smokers and never smokers. Responding patients had a median pack year history of 15 pack years compared to 5 pack years for patients demonstrating a best overall response of progressive disease. Treatment with MPDL3280A was well tolerated, with no deaths due to grades 3 to 5 pneumonitis reported. The overall incidence of grade 3/4 adverse events was 34%; pericardial effusion occurred in 6% of patients, 4% of patients each experienced dehydration, dyspnoea and fatigue. No grades 3 to 5 diarrhoea was reported. This trial is ongoing and larger phase II/III trials of the drug have begun. Soria JC, et al., Abstract number 3408. This research on MPDL3280A was sponsored by Roche and Genentech. Jean-Charles Soria reported serving on the advisory boards of Roche and Genentech.

Practice point and future research opportunities

A new therapeutic approach was successful in patients with squamous or non-squamous NSCLC who showed a quick and durable response to MPDL3280A. This novel immunotherapy showed few serious adverse side-effects. Immunohistochemistry staining intensity of PD-L1 in tumours could identify patients most likely to respond to treatment with this antibody and also determined a potential association between smoking history and stronger response to treatment.

Biomarker-selected subgroup of patients with NSCLC shows benefit from combined inhibition of MET and EGFR with tivantinib and erlotinib

MARQUEE, a randomised, double-blind, placebo-controlled, phase III trial of the c-Met inhibitor, tivantinib (ARQ 197), plus erlotinib versus placebo plus erlotinib in previously treated patients with locally advanced or metastatic, non-squamous, non-small-cell lung cancer (NSCLC) did not meet its primary endpoint of prolonged overall survival; however better progression-free survival (PFS) and overall survival (OS) rates were demonstrated that bore out the promising results from a randomised phase II study showing that tivantinib plus erlotinib had clinical benefit over erlotinib and placebo in a subset of patients with non-squamous histology – a population enriched for MET overexpression.

MARQUEE enrolled 1048 patients with locally-advanced or metastatic non-squamous NSCLC who had previously received one or two lines of systemic therapy but no prior treatment with any EGFR inhibitor. Patient median age was 62 (range 24-89) years; 66% and 34% of patients, respectively, had received one or two prior therapies and the ECOG performance status was 0 in 32% or 1 in 68% of patients. EGFR mutations were confirmed in 10.4% of the patients and 27.1% of patients harboured KRAS mutations. These characteristics were well balanced between treatment arms. The patients were stratified by the number of prior therapies, sex, smoking history and by mutation status and then randomised 1:1; 526 patients received oral tivantinib at 360 mg twice daily plus erlotinib at 150 mg once daily and 522 patients received the same dose of erlotinib plus placebo until disease progression. Results from the pre-planned interim analysis did not show a significant patient benefit with adjunct tivantinib regarding the primary endpoint of OS, leading the independent data monitoring committee to recommend trial discontinuation in September, 2012 because the data had crossed the predefined futility boundary. At the data cut-off in December, 2012 the median OS was 8.5 months with the tivantinib/erlotinib combination compared to 7.8 months with placebo plus erlotinib (hazard ratio [HR] 0.98; $p = 0.81$). A trend toward clinical benefit with tivantinib/erlotinib was demonstrated in the PFS and overall response rate (ORR, complete response plus partial response) data; median PFS significantly favoured adjunct tivantinib and was 3.6 months with tivantinib/erlotinib compared to 1.9 months with placebo/erlotinib (HR 0.74; $p < 0.001$). The ORR was 10.3% for the tivantinib-containing regimen and 6.5% for the placebo-containing regimen ($p < 0.05$).

Clinical benefit was demonstrated in an analysis of a biomarker-selected population that had higher MET tumour expression; approximately 40% of trial participants had tumour samples that yielded valid measurement. Georgio Scagliotti presented efficacy data from these subsets according to the MET protein expression showing prolonged PFS and OS were achieved by patients treated with

combined treatment whose tumours showed at least 2+ positive MET immunostaining in more than 50% of their tumour cells. In this high-MET subgroup; median PFS was 3.6 months for 104 patients in the tivantinib/erlotinib arm compared to 1.9 months in the 107 patients receiving erlotinib/placebo (HR 0.72; p = 0.014). Also improved median OS of 9.3 months versus 3.6 months, respectively (HR 0.70; p = 0.03) was seen in the trivantinib/erlotinib compared to the placebo/erlotinib arms.

In the low-MET expression group, 107 were treated with trivantinib and 127 patients received placebo; median PFS was 3.7 months for the tivantinib arm versus 1.9 months for placebo but median OS showed no significant difference between the groups (8.5 months versus 7.7 months, p = 0.53). Combination treatment was well tolerated and toxicity of tivantinib and erlotinib was similar to that of placebo and erlotinib with the exception of a higher rate of grade 3 or 4 neutropenia (10% compared to 1%, respectively). Scagliotti G, et al., Abstract Number 3410. The MARQUEE trial was supported by ArQule Inc., Daiichi Sankyo and the Experimental Cancer Medicine Centre. No conflicts of interest for the analysis were reported.

Practice point and future research opportunities

MARQUEE trial data contributes to the consideration of blocking MET, a receptor for hepatocyte growth factor, as a promising therapeutic strategy in several malignancies, particularly lung and gastric cancers. The combination of tivantinib, a selective MET inhibitor, plus erlotinib, an EGFR inhibitor, showed only a trend towards improved PFS and response rate in the overall trial population but this regimen demonstrated improved PFS and OS in molecularly selected cohorts of patients with high and low MET tumour expression. Molecular assessments should be used to identify patients most likely to benefit from this therapy.

Second-line docetaxel chemotherapy superior to erlotinib in patients with NSCLC and wild-type EGFR regardless of KRAS mutation

Effective second-line therapies are increasingly important due to development of resistance or lack of response to initial anticancer treatments. KRAS mutations in the tumours of patients with non-small cell lung cancer (NSCLC) have been associated with poorer prognosis and response to anticancer treatment given in the first line. According to Marina Garassino this evidence is often conflicting and mostly is derived from retrospective series, leading to the design of TAILOR, a prospective study evaluating KRAS mutations as prognostic and predictive indicators of response to erlotinib or docetaxel as second-line treatment of patients with NSCLC. Findings were presented from a preplanned analysis of data from the TAILOR trial (NCT00637910) which strived to identify particular subgroups of patients who experienced a differential treatment effect from erlotinib or docetaxel. TAILOR enrolled patients with a diagnosis of metastatic NSCLC who had already received platinum-based chemotherapy. Patients' EGFR and KRAS mutational status had been centrally assessed by direct sequencing in two independent laboratories; only wild-type EGFR patients were randomly allocated to receive erlotinib or docetaxel until disease progression. A total of 220 patients (necessary to detect a 33% mortality reduction with a 2 sided α=0.05 at 80% power) were enrolled. The primary endpoint was overall survival (OS).

Results favoured docetaxel over erlotinib in patients with wild-type EGFR: Median OS with docetaxel versus erlotinib was 8.2 months compared to 5.4 months, respectively (adjusted hazard ratio [HR] 0.73; p = 0.05). Progression-free survival (PFS) significantly favoured docetaxel over erlotinib: Median PFS was 2.9 months compared to 2.4 months with docetaxel and erlotinib respectively (adjusted HR 0.71; p = 0.02).

Out of 220 patients, 51 were found to be mutated in KRAS; however, upon analysis, no interaction effect was found by KRAS status. The HR for OS was 0.81 in the subset of patients with mutated KRAS favouring chemotherapy as opposed to HR 0.79 in patients with wild-type KRAS (p Interaction = 0.82). PFS results were similar, the HR was 0.89 in patients with mutated and wild-type KRAS (HR 0.68; p Interaction = 0.33). No prognostic effect for KRAS was shown; HR for associations of mutated KRAS status and mortality in OS was 1.24 (p = 0.23) and the HR was 1.00 for the association between mutated KRAS status and PFS (p = 0.98). Garassino M, et al., Abstract number 32. TAILOR was sponsored by Agenzia Italiana del Farmaco.

Practice point and future research opportunities

Patients with NSCLC and wild type EGFR showed superior benefit from chemotherapy with docetaxel over erlotinib as second-line but KRAS had neither prognostic nor predictive value for benefit from either second-line treatment. TAILOR trial results do not support erlotinib as second-line therapy for patients with EGFR wild-type NSCLC.

A phase III study of belagenpumatucel-L therapeutic tumour cell vaccine did not meet the predefined end point in the entire of study population

Although overall survival (OS) results from the phase III STOP trial of second-line treatment with the therapeutic tumour cell vaccine belagenpumatucel-L did not meet the predefined end point in the entire population of patients with late stage non-small cell lung cancer (NSCLC), the FDA allowed further study of the vaccine based on data from a subgroups of patients that did benefit from treatment. Belagenpumatucel-L (Lucanix®) is comprised of four transforming growth factor (TGF)-ß2 antisense irradiated, allogeneic NSCLC cell lines genetically modified to stimulate the patient's immune system, particularly natural killer cells, to attack the tumour. The design of belagenpumatucel-L is based on reports that higher levels of TGF-β2 often associate with immunosuppression, which in turn inversely correlates with a poorer prognosis in NSCLC. Belagenpumatucel-L is immunostimulatory and the activity of the vaccine may be potentiated by suppression of TGF-β2 production by the tumour due to the antisense RNA expressed by the plasmid TGF-β2 transgene element of the vaccine. Previously reported results from a phase II clinical trial of belagenpumatucel-L showed a 15% partial response rate in patients with NSCLC. In addition, clinical responders showed increased production of immunostimulatory cytokines interferon gamma, IL-6 and IL-4 that was accompanied by an elevated antibody response to vaccine HLA antigens.

Giuseppe Giaccone presented new findings from the placebo-controlled, randomised, multinational phase III STOP trial that evaluated the utility of vaccination with belagenpumatucel-L in prolonging OS when given as maintenance therapy for patients with stages T3N2-IIIA, IIIB, and IV NSCLC who

did not progress after front-line chemotherapy. Of 532 patients enrolled in the STOP trial, 42 patients had stage IIIA and 490 patients had stage IIIB/IV disease. All patients were undergoing front-line therapy and were eligible for randomisation between 4 and 17.4 weeks from the end of this treatment. The patients were randomised 1:1 to receive either belagenpumatucel-L (n=270) by one monthly and two quarterly intradermal injections or placebo (n=262) until disease progression or study withdrawal. Patient median age was 61 years; 57% of patients had adenocarcinoma, 27% squamous and 6% of patients had large cell carcinoma. These characteristics were balanced between the two arms.

STOP did not meet its predefined primary end point in the entire patient population; median OS was 20.3 months with the vaccine compared to 17.8 months with placebo (hazard ratio [HR] 0.94; p = 0.594). However, prognostic factors for improved outcome were identified by predefined Cox regression. Significant, clinically meaningful greater OS with belagenpumatucel-L over placebo was shown when there was a shorter time interval between the end of frontline chemotherapy and vaccination (p = 0.002). The OS was improved by 7.3 months with belagenpumatucel-L in 305 stage IIIB/IV patients who were randomised within 12 weeks of chemotherapy completion; this cohort showed median OS of 20.7 months with belagenpumatucel-L compared to 13.4 months with placebo (hazard ratio HR 0.75; p = 0.083).

Other factors prognostic of better outcome were disease stage, whether prior radiation was received and histology. The patients with confirmed pretreatment radiation showed median OS of 29.8 months with the vaccine over placebo; median OS was 40.1 months with belagenpumatucel-L compared to 10.3 months with placebo (HR 0.45; p = 0.014). Analysis of overall survival by disease subtype showed that 99 patients with stage IIIB/IV non-adenocarcinoma who were randomised within 12 weeks of the completion of chemotherapy experienced median OS of 19.9 months with belagenpumatucel-L versus 12.3 months with placebo, a prolongation of 7.6 months (HR 0.55; p = 0.036). Belagenpumatucel-L was well tolerated, with just one serious adverse event, grade 2 allergic rash, reported. Giaccone G, et al., Abstract number 2. The study was sponsored by NovaRx Corporation.

Practice point and future research opportunities

Despite failing to demonstrate improved overall survival in the entire population of patients with NSCLC, analysis of STOP trial data identified specific subgroups of patients who achieved marked improvement in survival from treatment with belagenpumatucel-L. Continued development of this tumour vaccine in these subgroups was further supported by a strong safety profile.

Melanoma

Patients with advanced unresectable melanoma demonstrate survival up to ten years following ipilimumab therapy

An analysis of pooled overall survival (OS) data from twelve trials plus additional data from patients who receive ipilimumab outside of clinical trials as part of an expanded access programme showed ipilimumab treatment had a durable, long-term effect on survival in patients with advanced non-resectable melanoma, with some of these patients still alive nearly ten years following treatment. Ipilimumab, a monoclonal antibody, works by targeting the cytotoxic T-lymphocyte antigen (CTLA-4) which is blocked in melanoma and does not function to aid in the recognition and destruction of tumour cells; ipilimumab disrupts the inhibitory mechanism and restores CTLA-4 activity.

Results from the largest analysis of ipilimumab done so far were reported by Stephen Hodi; the analysis was done on pooled data from 1,861 patients who participated in 10 prospective studies that included two phase III and eight phase II trials plus two retrospective, observational studies. Further analysis was done on additional data from 2,985 patients who received ipilimumab outside of a clinical trial; this cohort was composed of patients who tended to have more advanced disease, an ECOG performance status of 2, brain metastases, and patients with non-cutaneous primaries. Most (965) clinical trial patients received the approved ipilimumab dose of 3 mg/kg and 706 patients received an investigational dose of 10 mg/kg. Ipilimumab was given every three weeks for four doses during an induction phase and most studies included either retreatment or maintenance therapy with ipilimumab for eligible patients.

Analysis of the data from the 1,861 clinical trial participants showed a median overall survival of 11.4 months (95% confidence interval [CI] 10.7, 12.1), with 254 (22%) patients still living three years after beginning ipilimumab. Ipilimumab showed greatest benefit in treatment naive patients who experienced median overall survival of 13.5 months compared to 10.7 months for previously treated patients. Three-year survival rates were 26% in 604 treatment naive and 20% in 1257 pre-treated patients. In these patients the OS seen with ipilimumab therapy seemed to plateau around three years and extended through year 10, with no deaths occurring past seven years post treatment. This survival plateau was observed regardless of the dose or previous treatment received by patients, or whether they continued to receive ipilimumab as maintenance therapy.

Median overall survival for the entire population of 4846 patients was not as long at 9.5 months (95% CI 9.0, 10.0) and the three-year overall survival rate was 22%. Again a plateau in the OS curve beginning around year three was observed for 21% of patients. The authors acknowledged that the study was limited by being a pooled analysis from phase II and phase III trial plus observational data and not from a single randomised, controlled study, but the results are consistent with findings from randomised clinical trials and confirm the durability of the response plateau in OS that now has been shown to extend to ten years. Hodi S, et al., Abstract number 24. No external funding for this analysis was received.

Practice point and future research opportunities

This is the largest overall survival analysis for ipilimumab done to date and clearly demonstrates that ipilimumab can lead to long-lasting tumour control in patients with advanced metastatic melanoma. The data show that three to ten years survival can be achieved in 17 to 25% of patients who have received only a few doses of ipilimumab, suggesting that patients can keep residual tumours under control for a long time after the immune system is properly 'reset' making the concept of 'clinical cures' a reality. These results set a benchmark for future melanoma therapies.

Neuroendocrine cancers

Phase III trial results favour lanreotide therapy in patients with gastroenteropancreatic neuroendocrine tumours: the CLARINET trial

Lanreotide, a somatostatin analogue, demonstrated an anti-proliferative response in patients with gastroenteropancreatic (GEP) neuro-endocrine tumours. Martyn Caplin presented the final analyses of data from a phase III trial that showed lanreotide treatment significantly prolonged progression-free survival (PFS) in patients with GEP neuroendocrine tumours (NETs) compared to treatment with placebo. CLARINET (LanreotideAntiproliferativeResponse in patients with GEP-NET) is the largest phase III, randomised, double-blind, placebo-controlled, multinational trial done to date evaluating the anti-proliferative effect of lanreotide in patients with GEP-NETs. Although somatostatin analogues are indicated for treating patients with GEP-NET, there were limited data on their antiproliferative activity; results from one prospective trial in patients with midgut tumours had shown that treatment limited liver tumour burden. CLARINET (NCT00353496; EudraCT 2005-004904-35) is the first trial to prospectively evaluate the antiproliferative effects of lanreotide Autogel (a lanreotide preparation preloaded in a syringe) in 240 patients with well or moderately differentiated non-functioning GEP-NETs, defined as having less than 10% of proliferation marker Ki67. All patients were 18 or more years, with no hormone-related symptoms, and had not received somatostatin analogues, interferon, chemoembolisation or chemotherapy with six months prior to study entry.

Patients were randomised to receive either 120 mg lanreotide Autogel (n=101) or placebo (n=103) every 4 weeks for 96 weeks or until progressive disease (PD) or death. The trial's primary endpoint was PFS by RECIST criteria. Secondary endpoints were the percentage of patients who died or showed PD and safety. Computed tomography (CT) scans taken at baseline and at restaging timepoints throughout the study were centrally assessed. At baseline 45% of patients had primary tumours in the pancreas, 36% in the midgut, 7% in the hindgut and 13% of patients had tumours in unknown locations. The majority (96%) of patients had stable disease (SD) and 81% were treatment-naive. Levels of Ki67 between 3% and 10% (WHO grade 2) were recorded in 22% of patients and 33% had a hepatic tumour load greater than 25%.

The CLARINET trial met both primary and secondary endpoints. At two years following initiation of treatment, median PFS was not reached with lanreotide compared to 18 months with placebo, hazard ratio (HR) 0.47($p = 0.0002$). Neither disease progression nor death occurred in 62% of lanreotide patients compared to 22% of placebo patients. Lanreotide showed favourable safety and tolerability that was consistent with its known safety profile. Treatment-related adverse events (AEs) occurred in 50% of patients receiving lanreotide and 28% of placebo patients, with diarrhoea being the most frequently reported AE in 26% versus 9% of patients receiving lanreotide and placebo, respectively. Serious AEs were reported in 3% patients receiving lanreotide and in 1% of placebo patients. Adverse events led to withdrawal from the study for a total of six patients, three from each treatment group. Caplin M, et al.,Abstract number 3. Funding for the CLARINET study was provided by Ipsen, Paris, France.

Practice point and future research opportunities

The anti-proliferative effect of somatostatin analogues was observed in the CLARINET study; this activity also appeared to apply to a wider group of NET patients. Lanreotide may provide an alternative treatment option for patients with wider spectrum of GEP NETs.

Thyroid cancer

Sorafenib in patients with radioactive iodine-refractory differentiated thyroid cancer

Marcia Brose recently reported that sorafenib treatment of patients with differentiated thyroid cancer (DTC) who were radioactive iodine (RAI)-refractory reduced the risk of progression or death by 42% compared to placebo. Several genetic abnormalities have been identified that play a role in the etiology of DTCs, leading the investigators to use data from DECISION trial to evaluate BRAF and RAS mutations as possible prognostic biomarkers and as predictors of sorafenib efficacy in RAI-refractory DTC patients. The randomised, phase III DECISION trial enrolled patients with locally advanced/metastatic RAI-refractory DTC who had progressed during the preceding 14 months who were then randomised 1:1 to receive sorafenib or placebo; placebo patients were allowed crossover to sorafenib upon progression. Archived tumour samples were analysed for 238 mutations in 19 common oncogenes (Sequenom OncoCarta 1.0).

Tumour mutation data was available from 256 (61.4%) patients, 126 sorafenib patients and 130 placebo patients. Demographics of the subgroup with mutational data were similar to the overall study population. BRAF and RAS mutations were detected in 30.1% and 19.5% of patients, respectively, and were balanced across treatment arms. Point mutations other than in BRAF and RAS were found in less than 5% of patients and nearly half (47.3%) of the patients had no detectable mutations. Poorer PFS outcomes were seen in placebo patients with mutant RAS tumours compared to patients with wild-type RAS (hazard ratio [HR] 1.78, $p = 0.03$), while mutated BRAF tumours associated with better PFS outcomes in patients receiving placebo compared to these patients who tumours expressed wild type BRAF (HR=0.53, $p = 0.01$). No significant difference in overall survival (OS) was observed with either mutation.

Improved PFS with sorafenib treatment was seen in 92 patients with wild type BRAF and 34 patients with mutated BRAF compared to 87 and 43 patients with wild-type and mutated BRAF in the placebo arm, respectively; wild-type BRAF: HR 0.54, $p < 0.001$; mutated BRAF: HR 0.47; $p = 0.02$ ($p^{interaction} = 0.68$). The prolonged PFS with sorafenib treatment was also independent of RAS mutation status; wild-type RAS was detected in 102 sorafenib patients and in 104 placebo treated patients, HR=0.60; $p = 0.004$; mutated RAS was detected in 24 and 26 patients, respectively, in the sorafenib and placebo arms, HR=0.45, $p = 0.037$ ($p^{interaction} = 0.39$). Patients receiving sorafenib whose tumours had mutated BRAF appeared to have a better OS compared to placebo despite a small number of events (HR 0.32; $p = 0.03$) and no difference in OS was seen regarding RAS mutation status. Brose M, et al., Abstract number 3155. Conflict of interest: Service on Advisory boards: Brose – Bayer HealthCare Pharmaceuticals, Onyx Pharmaceuticals. Sherman: AstraZeneca, Bayer, Eisai, Exelixis; Smit: Bayer HealthCare Pharmaceuticals; Schlumberger: Astra Zeneca, Bayer, Eisai, Exelixis, Genzyme. Corporate-sponsored research: Brose: Bayer HealthCare Pharmaceuticals; Sherman: Genzyme, Pfizer; Schlumberger: Genzyme. Other substantive relationships: Chung: employee of Bayer HealthCare Pharmaceuticals; Molnar: employee of Bayer HealthCare Pharmaceuticals; Jeffers: employee of Bayer HealthCare Pharmaceuticals; Pena: employee of Bayer HealthCare Pharmaceuticals.

Practice point and future research opportunities

Exploratory analyses from phase III trial data suggest that the presence of mutant RAS in tumours was a negative prognostic factor for progression-free survival in RAI-refractory differentiated thyroid cancer patients, whereas mutated BRAF was prognostic for better prognosis. Patients showed improved PFS with sorafenib over placebo that was independent of either BRAF or RAS mutation status.

Encouraging phase II study results from vemurafenib in patients with RAI refractory, progressive papillary thyroid cancer and mutated BRAFV600E tumours

Vemurafenib demonstrated anti-tumour activity in a subset of patients with metastatic or unresectable papillary thyroid cancer that had shown resistance to radioactive iodine therapy (RAI) and who also had BRAF V600E-mutated tumours. Vemurafenib was active in patients who were either tyrosine kinase inhibitor (TKI) treatment naive or had received prior TKI treatments; however, treatment naive patients showed greater benefit.

Findings were reported by Marcia Brose from an open-label, multi-centre phase II trial (NCT01286753, NO25530) of vemurafenib in patients with metastatic or unresectable papillary thyroid cancer that was positive for the BRAF V600 mutation and resistant to radioactive iodine. Vemurafenib is a kinase inhibitor that targets tumours with BRAF V600E mutation; activating BRAFV600E mutations have been reported in approximately 50% of patients with papillary thyroid cancer and are an established indicator of poorer prognosis. Vemurafenib is approved by the European Medicines Agency and USA Food and Drug Administration for the treatment of melanoma where BRAF V600E mutation has been identified and was the first drug approved for BRAF mutated cancer. Following the demonstration of response or stable disease in 3 patients with BRAF V600E-mutated papillary thyroid cancer in a phase I trial, this trial was designed to evaluate the possible benefit of vemurafenib in this patient population; the primary endpoint was the best overall response rate (BORR) as determined by RECIST criteria in the TKI naive arm. The secondary endpoints were BORR in the pre-treated arm, progression-free survival (PFS) and overall survival (OS) in both treatment arms.

The trial enrolled 51 patients at ten world-wide centres between June 2011 and January 2013. Patients had progressive papillary thyroid cancer that was refractory to RAI and had been confirmed positive for BRAF V600E mutation by cobas®4800 V600 mutation assay. Overall, patients had ECOG performance status 0 or 1 and slightly more than half (53%) were aged 65 years. Patients were assigned to either cohort 1 (n= 26) if they were TKI treatment naive or cohort 2 (n= 25) if they had been previously treated with TKIs. All patients had undergone prior surgery and RAI treatment. Three (12%) patients in the cohort 1 and 7 (28%) cohort 2 patients had previously received chemotherapy and 21 (84%) cohort 2 patients had received prior sorafenib. Both cohorts received vemurafenib and were assessed for tumour response after every eight weeks of treatment.

The primary endpoint analysis was preplanned for six months after enrolment of the last patient and demonstrated that cohort 1 patients had BORR of 35% compared to 26% in cohort 2 patients;

BORR were all partial response (PR). The clinical benefit rate (defined as complete response (CR) plus PR plus stable disease (SD) = 6 months) was 58% and 36%, in cohorts 1 and 2, respectively. Median PFS at the time of data cut-off was 15.6 months (95% confidence interval [CI] 11.2, NR) in cohort 1 and 6.8 months (95% CI 5.38, NR) in cohort 2.

Seven patients and 11 patients in cohorts 1 and 2, respectively, discontinued treatment due to progressive disease. The overall toxicity profile was consistent with that seen with vemurafenib treatment of melanoma patients with the exceptions of higher rates of weight loss, dysgeusia, anaemia, increased creatinine, and liver laboratory abnormalities in patients with papillary thyroid cancer. Common adverse events included rash, fatigue, weight loss, and increased bilirubin. Brose M, et al., Abstract number 28. The study was sponsored by Hoffmann-La Roche.

Practice point and future research opportunities

Vemurafenib may offer sorely needed treatment for both treatment-naive and TKI-pretreated patients with RAI refractory, progressive, BRAF V600E-mutated papillary thyroid cancer. Anti-tumour activity and prolonged progression-free survival were shown, especially in TKI treatment-naive patients, which warrant further evaluation.

Sarcoma

No benefit from adding trabectedin to doxorubicin over sole doxorubicin as first-line treatment of patients with advanced non-resectable or metastatic soft tissue sarcomas

For the past 25 years doxorubicin has remained the standard first-line systemic treatment for patients with metastatic soft-tissue sarcoma (STS) and trabectedin has been recently been approved as second line of therapy in STS, leading Javier Martin-Broto and colleagues from the Spanish Group for Sarcoma Research (GEIS) to investigate the activity of both agents combined. Synergistic activity between doxorubicin and trabectedin demonstrated in cell lines and an additive effect seen in murine models plus a favourable toxicity profile for the combination supported the trial rationale.

This randomised phase II trial compared the efficacy and toxicity of trabectedin plus doxorubicin versus sole doxorubicin as first-line treatment in 114 patients with non-resectable locally advanced or metastatic STS, who had adequate marrow, hepatic, cardiac and renal function and performance status of 0–2 (most patients with 0–1 after amendment). Patients positive for hepatitis B surface antigen and those whose disease had metastasised to the central nervous system were excluded. Patients were randomly assigned to receive trabectedin plus doxorubicin or doxorubicin. Oral dexamethasone was also given in trabectedin/doxorubicin arm. A maximum of six cycles were given in both arms. The trial's main endpoint was progression free survival (PFS) and an interim analysis was planned at approximately 62 progression events. Patient median age was 53 years (range 21 to 74 years). Locally advanced disease was reported for 33% and 22% of patients in the control and experimental arms, respectively; metastatic disease was reported in 67% and 78% of control and experiments patients.

Trabectedin added to doxorubicin was not superior over sole doxorubicin and no synergistic effect was demonstrated. Median of PFS was 5.8 months (range 3.6 to 8months) for sole doxorubicin compared to 5.7 months (range 2.9 to 8.5 months) with added trabectedin, hazard ratio [HR] 1.32; p = 0.18. The one-year OS rates were 53% and 54% in the control and experimental arms, respectively. The response rates per RECIST were calculated for 107 evaluable patients; 20% of patients in the control and 13% in the experimental arm showed a partial response. Similarly, stable disease was reported for 47% of control versus 54% of experimental patients and equal rates were seen for progressive disease of 33% in both arms (p = 0.63). Following this interim analysis the trial was halted for futility since the risk reduction demonstrated for PFS was less than 9.64% in the experimental arm. Four toxic deaths, two per arm, occurred mainly in patients with ECOG 2 status. Grade 3/4 adverse events were more often reported in the experimental; leucopaenia was reported by 23% versus 9% and febrile neutropenia was reported by 11% versus 8% of patients receiving trabectedin compared to sole doxorubicin, respectively and grade 3 nausea was reported only by 8% of patients in the experimental arm. The rate of grade 3 asthenia was 20% in the experimental arm versus 7% of control patients. Martin-Broto J, et al., Abstract number 3800. No conflict of interest was reported.

Practice point and future research opportunities

Despite promising phase I results regarding the combination treatment of soft tissue sarcoma with trabectedin plus doxorubicin, the results from this phase II trial do not support the addition of trabectedin to doxorubicin as first-line treatment for patients with soft tissue sarcoma.

Primary endpoint unmet in a phase III trial of first-line treatment with palifosfamide plus doxorubicin in patients with metastatic soft tissue sarcoma; PICASSO 3 trial

Although results from a phase II trial of palifosfamide, a bi-functional DNA alkylating agent with potential activity against multiple tumour types looked promising, disappointing findings were reported by Christopher Ryan for the phase III PICASSO 3 trial. The study was designed to evaluate the safety and efficacy of palifosfamide when added to doxorubicin as first-line treatment of patients with metastatic soft tissue sarcoma (mSTS) compared to doxorubicin and placebo. Progression-free survival (PFS) per RECIST v1.1 as assessed by independent, blinded radiographic review was the primary endpoint and secondary endpoints included overall survival (OS), response rate, quality of life, safety and tolerability. The trial was conducted at 113 clinical centres worldwide and enrolled patients with measurable mSTS, centrally confirmed by independent pathology review, who had not received previous chemotherapy for metastatic disease. PICASSO 3 stratified 447 enrolled patients by histological type and age and randomly assigned them 1:1 to receive doxorubicin plus either palifosfamide (n=226) or placebo (n=221) for up to 6 cycles. No crossover was allowed. Synovial disease was reported in 6% of patients, 34% had leiomyosarcoma and 60% of patients presented with other sarcomas. Twenty-six percent of patients were aged 65 years or older.

The study did not meet its primary endpoint of PFS, despite showing a statistically non-significant trend towards improved PFS of 3.1 weeks; median PFS was 5.98 months for palifosfamide/ doxorubicin compared with 5.23 months for placebo/doxorubicin (hazard ratio [HR] 0.87; p = 0.18). An interim analysis showed that median OS slightly favoured placebo and was 15.91 months for palifosfamide/doxorubicin compared to 16.89 months with placebo/ doxorubicin (HR 1.05; p = 0.74). Subgroup analyses of PFS and OS by stratum are ongoing.

Since palifosfamide is the active metabolite of ifosfamide and able to bypasses resistance pathways it should demonstrate activity without producing the toxic metabolites associated with prodrug activation; in fact, palifosfamide was well tolerated and showed a safety profile in combination with doxorubicin that was comparable with other palifosfamide clinical trials in soft tissue sarcoma. The adverse event (AE) profiles were similar in both treatment arms with an increase in the rate of febrile neutropenia of 17.8% observed for palifosfamide/ doxorubicin over 9.8% for placebo/doxorubicin. Other commonly reported AEs were nausea, constipation, fatigue, vomiting, diarrhoea, and anaemia. Grade ≥ 3 AEs were neutropenia, febrile neutropenia, nausea, anaemia, constipation and dehydration. Patient health-related quality of life was maintained with palifosfamide/doxorubicin, as demonstrated in patient reported questionnaires. Ryan C, et al., Abstract number 3802. PICASSO 3 was sponsored by ZIOPHARM Oncology.

Practice point and future research opportunities

Although PICASSO 3 did not meet its primary endpoint, patients with metastatic soft tissue sarcoma receiving first-line palifosfamide/doxorubicin showed a trend of 3.1 weeks improved median progression-free survival compared with placebo/doxorubicin. Palifosfamide/doxorubicin was well tolerated with a similar toxicity profile to placebo/doxorubicin in the PICASSO 3 study.

Supportive care

Results from two phase III randomised trials look promising for enobosarm in preventing and treating muscle wasting in patients with NSCLC

Cancer induced muscle wasting begins early in the course of non-small cell lung cancer (NSCLC). It is seen in more than 50% of patients at the time of diagnosis and increases to affect more than 80% of NSCLC patients before they die of their disease. Enobosarm is a first in class nonsteroidal oral selective androgen receptor modulator (SARM) that may modify the reduced anabolic and increased catabolic activities that fuel muscle wasting. Jeffrey Crawford reported results from the Prevention and treatment Of muscle Wasting in patients with cancER (POWER1 and POWER2) trials. Both POWER trials were phase III clinical trials enrolling patients diagnosed with stage III or IV NSCLC; POWER1 enrolled 321 patients to receive platinum plus a taxane and POWER2 enrolled 320 patients to receive platinum plus a non-taxane. Subjects in both trials were randomised to receive either oral enobosarm or placebo upon the initiation of first-line chemotherapy with either platinum/taxane or platinum/non-taxane. Patients were males and postmenopausal females aged 30 years or older. Baseline characteristics were mostly similar between the enobosarm and placebo groups; all subjects had an ECOG score of 1 or less, and a body mass index (BMI) of 32 or less.

An analysis planed for day 84 showed both trials met one of the co-primary endpoints of lean body mass but not physical function response assessed by stair climb power (SCP). In patients receiving platinum/taxane, 41.9% in the enobosarm arm compared to 30.4% in the placebo arm maintained or increased their lean body mass ($p = 0.036$). Patients receiving platinum/non-taxane showed slightly better results with 46.5% in the enobosarm arm versus 37.9% in the placebo arm maintaining or increasing their lean body mass ($p = 0.113$). Regarding physical function, SCP showed no significant difference between the enobosarm and control arms; the proportion of patients with improvement of over 10% was not significantly different between either group ($p = 0.315$ for platinum/taxane and $p = 0.285$ for platinum/non-taxane).

Further analyses done at day 147 using mixed-model repeated measures for slopes and means showed significant improvement in lean body mass with enobosarm versus control ($p < 0.0001$ and $p = 0.0036$ in the platinum/taxane versus platinum/non-taxane groups, respectively. Significantly improved SCP of 12.5% over baseline was seen at this time point favouring enobosarm over control in the platinum/taxane group only ($p = 0.0486$). In the pre-specified secondary continuous variable analyses, enobosarm had a significant effect on lean body mass at both time points in both trials (POWER1: $p = 0.0003$ and $p < 0.0001$ and POWER2: $p = 0.0227$ and $p = 0.0036$ at days 84 and 147, respectively). Safety profiles were similar between the enobosarm and control groups. Decreased appetite was experienced by 16.8% of patients in the platinum/taxane placebo group compared to just 6.9% of patients in the enobosarm group. Crawford J, et al., Abstract number 21. Trial funding from GTX, INC.

Practice point and future research opportunities

Enobosarm had an unambiguous effect on muscle that may translate into improvement in physical function and survival in NSCLC patients. Lean body mass responders showed a greater increase in SCP at the later time point. These benefits together with the good safety profile seen with the addition of enobosarm to chemotherapy suggest that enobosarm could be considered in patients with NSCLC. Further analyses of the effect of maintaining lean body mass on survival are underway.

Affiliation and disclosure

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