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INTRODUCTION

The theme of the 2012 ASCO Annual Meeting "Collaborating to Conquer Cancer" reflects a need for collaborative efforts through a multidisciplinary approach to effective prevention, diagnosis, treatment and follow-up of cancer.

As a leading player in the field of oncology, ESMO had a strong presence at the 48th ASCO Annual Meeting with a dedicated booth to serve members and promote membership benefits. The booth concept brought its visitors closer to the unique ESMO educational and scientific web portal OncologyPRO, and provided information about forthcoming events organized by ESMO.

ESMO's role as a global partner of regional oncology societies worldwide was strengthened through fruitful leadership meetings with international societies. Exchanging the latest developments across continents and unifying the oncology community are essential to identify global strategies for the advancement of research and to reduce inequalities in cancer care.

A special ESMO-ASCO Joint Session this year is foreseen during the ESMO 2012 Congress in Vienna, Austria (28 September-2 October). It will feature issues on genomics in breast cancer.

Coverage of all scientific and clinical novelties and updates presented during the 2012 ASCO Annual Meeting is beyond the scope of this report. It instead focuses on selected presentations of the most significant new findings with potential to change current clinical practice and presentations that provided new evidence or research directions in ongoing controversies.

BREAST CANCER

Primary results from EMILIA, a phase III study of trastuzumab emtansine (T-DM1) in HER2-positive, previously treated, locally advanced or metastatic breast cancer

The highly anticipated results of the EMILIA phase III trial of trastuzumab emtansine (T-DM1) compared with capecitabine plus lapatinib, were presented by Dr Kimberly Blackwell of Duke Cancer Institute, during the Plenary Session (abstract LBA1).

T-DM1 is a three-part immunoconjugate consisting of trastuzumab and the potent maytansine derivative, DM1. This new compound incorporates the antitumor activity of trastuzumab with its ability to deliver a microtubule disrupting cytotoxic agent specifically to antigen-expressing tumor cells.

Patients previously treated with a taxane and trastuzumab who had progressive disease during treatment for metastases or had recurrent disease within 6 months of adjuvant therapy were eligible for the study. Although 991 patients were enrolled, 978 were finally treated in the study. Dose reduction was necessary for only 16.3% of patients in the T-DM1 arm; however, the capecitabine dose and the lapatinib dose had to be reduced for 53.4% and 27.3% of patients, respectively.

The objective response rate was significantly higher in the T-DM1 group, 43.6% compared with 30.8% in the capecitabine/lapatinib group (p=0.0002). Median progression-free survival was 9.6 months in the T-DM1 arm compared with 6.4 months in the capecitabine/lapatinib arm (p<0.0001). Median time to symptom progression was 7.1 months in the T-DM1 group and 4.6 months in the capecitabine/lapatinib group (p=0.0121).

Subgroup analyses performed according to baseline characteristics indicated that T-DM1 was better for all groups except for patients 65 years. Overall survival was improved for patients receiving T-DM1, but median overall survival has not been reached for these patients and the efficacy boundary has not been crossed. T-DM1 was much safer than capecitabine/lapatinib. The incidence of grade 3 or higher severe adverse events was lower in the T-DM1 group (40.8%) than in the capecitabine/lapatinib group (57.0%), as was the incidence of adverse events resulting in treatment discontinuation (5.9% vs. 10.7%, respectively). Cardiac toxicity was not increased in the T-DM1 group. There was one death due to toxicity in the T-DM1 group and five in the capecitabine/lapatinib group.

Practice point and future research opportunities

The EMILIA study provides convincing evidence that an immunoconjugate-targeting HER2 has potent antitumor activity. T-DM1 demonstrated greater efficacy and safety than capecitabine/lapatinib and could offer an important therapeutic option for the treatment of HER2-positive advanced breast cancer.

CNS MALIGNANCIES

Long-term follow-up of EORTC randomized phase III study on adjuvant PCV chemotherapy in anaplastic oligodendroglial tumors

A long-term follow-up of the European Organisation for Research and Treatment of Cancer (EORTC) 26951 study reported during the Plenary Session showed that patients with anaplastic oligodendroglioma who received chemotherapy with procarbazine, CCNU (lomustine), and vincristine (PCV) immediately following radiation therapy were 44% more likely to live longer if their tumors showed a co-deletion of the 1p and 19q arms of the respective chromosomes compared with patients receiving radiotherapy alone following disease progression (abstract 2).

Dr Martin van den Bent of Erasmus University Medical Center and Daniel den Hoed Cancer Center, Netherlands presented the study results that identified a subgroup of patients who benefit from adjuvant chemotherapy following radiotherapy. These data, with a median follow-up of 140 months, are in contrast to those initially reported in 2006 (with a median of 60 months follow-up), when survival benefits for patients were similar whether PCV was administered immediately following radiotherapy or at the time of recurrence.

Of the 368 patients initially enrolled in the study, 183 patients received radiotherapy and 185 received adjuvant PCV chemotherapy immediately following radiotherapy. At the time of this analysis, 281 patients had died. Although median progression-free survival and overall survival were significantly longer for patients receiving radiotherapy and adjuvant PCV (p=0.003 and p=0.018, respectively), of note were the clinical benefits reported for patients with anaplastic oligodendroglioma with the 1p/19q co-deletion. In this prospectively defined patient population, progression-free survival was 50 months if patients received radiotherapy alone and 157 months if they received PCV following radiotherapy (p=0.002). In addition, median survival was 9 years for patients receiving radiotherapy alone and was not yet reached after 12 years for patients receiving PCV immediately following radiotherapy (p=0.059). These data are impressive given that there was at least 70% of cross-over from patients in the radiotherapy arm of the study.

A similar Radiation Therapy and Oncology Group study (RTOG 9402), led by Dr Gregory Cairncross of the University of Calgary, Canada, and reported during the Central Nervous System Tumors Oral Abstract Session, shows the same benefit of early PCV chemotherapy as opposed to initial radiotherapy alone (abstract 2008b).

Practice point and future research opportunities

Taken together, these studies are practice changing and define the new standard of care for 1p/19q-codeleted anaplastic oligodendroglioma. EORTC 26951 and RTOG 9402 showed remarkable similarities in data in patients with 1p/19q-codeleted tumors. The upfront combination of radiotherapy and PCV demonstrated improved survival in patients with 1p/19q codeletion. In both studies patients were recruited over a long time period and they establish a predictive molecular marker that informs treatment decisions. The long-term follow-up provided very different conclusions from initial observations. When these studies were undertaken, the molecular marker that predicted treatment benefit had not yet been discovered, opening a door for prospective testing.

CANCER PREVENTION / EPIDEMIOLOGY

Results of a phase III prevention study of low-dose tamoxifen in hormone replacement therapy users: The HOT trial

Primary prevention trials have shown that tamoxifen lowers ER1 breast cancer incidence, but adverse events are a barrier to its broad use. The Italian Tamoxifen Prevention Trial showed a positive risk/benefit ratio in the subgroup of hormone replacement therapy (HRT) users in the tamoxifen arm, with fewer breast cancers and no cardiovascular disease excess. In a dose-ranging study, tamoxifen 5 mg/day showed a favorable biomarker modulation in hormone replacement therapy users. A group of Italian researchers, led by Dr Bernardo Bonanni of the European Institute of Oncology in Milan, conducted a multicenter, phase III, breast cancer prevention trial in current or de novo hormone replacement therapy users, randomized to either tamoxifen 5 mg/day or placebo for 5 years, with 5 years follow-up (abstract 1500).

Due to the Women's Health Initiative HRT trial results, recruitment in this study was lower than anticipated, with a total of 1884 women being randomized (946 in the placebo and 938 in the tamoxifen arm, respectively), 79% being >50 years of age at study entry, 66% with normal weight, 21% with history of prior hysterectomy, 80% were already on HRT at baseline, 53% were on transdermal route and 28% had 5 years-Gail risk >1.5%. At 7.7 years of mean follow-up, 43 breast cancers were diagnosed, 24 on placebo and 19 on tamoxifen. The efficacy of tamoxifen was greater in luminal-A type. Cardiovascular disease events were rare (including 1 deep venous thrombosis on tamoxifen), with no statistical difference between arms. A hazard ratio of 4.74 was observed for benign endometrial polyps, but no increase of uterine cancers. Menopausal symptoms were more frequent on tamoxifen, whereas headache was less frequent on tamoxifen.

Practice point and future research opportunities

The combination of low-dose tamoxifen and hormone replacement therapy is safe and provides a promising way to retain the benefits while reducing the risks of either agent. While the insufficient power of this study prevents firmer conclusions, it supports further studies of low-dose tamoxifen in the prevention setting.

DEVELOPMENTAL THERAPEUTICS

PD-1/PD-L1 pathway as a target for cancer immunotherapy

Dr Suzanne Louise Topalian of Johns Hopkins University Sidney Kimmel Comprehensive Cancer

Center in Baltimore presented results from a phase I study of the new agent BMS-936558 (abstract CRA2509). Once activated, immune T cells begin to express programmed death-1 (PD-1). By expressing the ligand PD-L1, tumor cells can co-opt this system and send a signal that can deactivate the T-cells, thereby protecting themselves from attack. BMS-936558 is a fully human monoclonal antibody that blocks PD-1.

In this dose-escalation study, 296 patients received BMS- 936558 intravenously. every second week at doses ranging from 0.1 to 10.0 mg/kg. From patients included in the study, 104 had melanoma, 122 non-small cell lung cancer (NSCLC), 34 renal cell carcinoma (RCC), 19 colorectal cancer (CRC), and 17 castration-resistant prostate cancer (CRPC); all with progressive disease after at least one standard therapy. The median duration of therapy was 15 weeks, with a maximum of 120 weeks.

The maximum tolerated dose was not reached over the course of the study; grade 3-4 adverse events occurred in 14% of patients, and the most common adverse events of any grade were fatigue, rash, and diarrhea. Of the 296 patients, fifteen (5%) discontinued treatment due to adverse events. Notably, nine patients had pneumonitis, and three of these patients (1% of the total cohort) died. The lower grade pneumonitis can be treated by stopping the drug or with steroids.

Among patients who received at least two cycles of the study drug, complete or partial response was observed in patients with melanoma, NSCLC, and RCC. Of the 94 evaluable melanoma patients, 28% had an objective response; in 33 RCC patients, 27% had a response; and in 76 NSCLC patients, 18% showed some response. The response in NSCLC was most surprising, as this malignancy has proven refractory to immune-based therapies in the past.

The responses appeared to be durable. Among 31 patients with an objective response who had been followed for at least one year, 20 had a response lasting at least one year. Six melanoma patients, five NSCLC patients, and nine RCC patients had stable disease lasting at least 24 weeks.

The investigators performed immunohistochemistry on pre-treatment tumor biopsies in 42 patients to test PD-1 ligand's (PD-L1) efficacy as a biomarker for response. Nine out of the 25 of those patients with PD-L1-positive tumors achieved an objective response (36%), while none of the 17 with PD-L1-negative tumors showed any response (p=0.006).

Practice point and future research opportunities

Blocking the programmed death-1 receptor on activated T cells yielded objective responses in some patients with advanced NSCLC, melanoma, and RCC, suggesting that recent successes with immunotherapy are continuing. This early success with BMS-936558 will lead to controlled clinical

registration trials of the agent soon, specifically in patients with NSCLC, melanoma, and RCC. The use of PD-L1 as a biomarker will be explored further.

A first-in-human phase I study of LY2228820 dimesylate (an oral p38 MAPK inhibitor) in patients with advanced cancer

p38 MAPK regulates production of cytokines by the tumor microenvironment and its activation enables cancer cells to survive in the presence of oncogenic stress, radiation, chemotherapy, and targeted therapies. LY2228820 is a selective small-molecule inhibitor of p38 MAPK and preclinical studies demonstrate antitumor activity as a single agent and in combination with standard agents. A group of researchers led by Matthew Goetz of the Mayo Clinic, performed a phase I study to determine the maximum tolerated dose and dose-limiting toxicity of LY2228820 and to characterize its pharmacokinetics and pharmacodynamics (abstract 3001).

The researchers enrolled 54 patients who received either capsules at 8 dose levels or tablets at 5 dose levels. LY2228820 inhibited p38 MAPK induced phosphorylation of MAPKAP-K2 in peripheral blood with dose-dependent maximum inhibition from 10 to 70% across the dose range 10-200 mg.

The most common drug-related adverse events included fatigue, nausea, rash, constipation, vomiting, and pruritus. One patient (200mg) had dose-limiting toxicity of erythema multiforme (grade 3) and 2 patients (560mg) had dose-limiting toxicity of ataxia (grade 3) and dizziness (grade 2), respectively. Although the maximum tolerated dose was 420 mg, the frequency of grade 1/2 adverse events (mainly rash, dizziness, and tremor) and observation of clinical activity at lower dose levels led to a recommended dose of 300 mg. Early clinical activity has been observed in ovarian, breast, and renal cancers.

Practice point and future research opportunities

LY2228820 demonstrates acceptable pharmacokinetics, safety, and early clinical activity as a single agent in advanced cancer. A phase II study for patients with ovarian cancer is planned.

GASTROINTESTINAL (COLORECTAL) CANCER

Phase III CORRECT trial of regorafenib in metastatic colorectal cancer

Regorafenib is an oral multi-kinase inhibitor. The CORRECT trial evaluated regorafenib in patients with metastatic colorectal cancer (mCRC) who had progressed after all approved standard therapies (abstract 3502). Enrollment criteria included documented mCRC and progression during or 3 months after last standard therapy. Patients were randomized 2:1 to receive best supportive care plus either regorafenib or placebo. The primary endpoint was overall survival. Secondary endpoints included progression-free survival, overall response rate, disease control rate, safety and quality of life.

A total of 760 patients were randomized, and the overall survival endpoint was met at a preplanned interim analysis. The results were presented by Dr Eric Van Cutsem of the Digestive Oncology Unit, University Hospital Gasthuisberg, Leuven, Belgium. Both, overall- and progression-free survival were significantly improved in regorafenib arm compared to placebo: median overall survival was 6.4 vs. 5.0 months, and median progression-free survival was 1.9 vs. 1.7 months. Comparable overall- and progression-free survival benefits were observed in exploratory subgroup analyses by region, age, time from diagnosis to randomization, prior lines of treatment, and KRAS status. The most common grade 3+ adverse events related to regorafenib were hand-foot skin reaction, fatigue, hypertension, diarrhea and rash/desquamation.

Practice point and future research opportunities

Regorafenib demonstrated statistically significant improvement in overall- and progression-free survival over placebo, as well as comparable efficacy benefits across patient subgroups analyzed.

No clinical benefit seen from adding perifosine to capecitabine in patients with refractory metastatic colorectal cancer

Adding perifosine, an oral alkylphospholipid inhibitor, to oral capecitabine did not significantly change overall- or progression-free survival compared with capecitabine alone, according to data from the X-PECT study (abstract LBA3501). X-PECT is a phase III study that randomly assigned 468 patients with refractory colorectal cancer to receive perifosine/capecitabine (234 patients) or capecitabine (234 patients). In order to participate, patients were required to have colorectal cancer refractory to treatment with 5-fluorouracil (5-FU), oxaliplatin, irinotecan, bevacizumab, and therapies that targeted wild-type *KRAS*. The primary endpoint of the study was overall survival.

The median overall survival was 6.4 months and 6.9 months in two groups. The difference in overall survival was also not significant when analyzed based on *KRAS* status. The difference in progression-free survival was not significantly different for patients in two arms of the study (10.9 weeks for combination therapy with perifosine and 11.4 weeks for capecitabine only). However, in a subset of patients with wild-type *KRAS* who discontinued oxaliplatin because of toxicity, combination therapy with perifosine was shown to significantly increase progression-free survival (18.1 weeks vs. 6.6 weeks; p=0.003).

The X-PECT study was undertaken based on very promising data observed in a small, phase II randomized study that included 38 patients. Overall survival was 17.7 months for patients receiving perifosine/capecitabine and 7.6 months for patients receiving capecitabine alone (p=0.0052). However, in that study, patients received perifosine combination as second- or third-line therapy and may not have been refractory to oxaliplatin or 5-FU. In contrast, patients enrolled in the X-PECT study had received a median between 4 and 5 prior therapies and were required to be refractory to all currently available treatments. The phase II study was originally designed to test perifosine in seven tumor groups. When responses were seen in patients with refractory colorectal cancer, accrual of additional patients in the colorectal arm of the study was undertaken and the other arms of the study were closed.

Practice point and future research opportunities

This phase III study did not reach the primary endpoint despite earlier very promising data from a phase II study with perifosine. New directions for the treatment of patients with refractory colorectal cancer are needed. The clinical development of perifosine, which targets the AKT pathway, was undertaken based on the biology of colorectal cancer. Approximately 40% of patients with colorectal cancer show a deregulation of the PI3K/AKT/mTOR pathway. The study researchers hope that an analysis of biomarkers may provide guidance on whether perifosine provides clinical benefits in a subset of patients. For the biomarker substudy, tumor biopsies before and after treatment are available from a subgroup of patients.

Bevacizumab continued beyond first progression beneficial in patients with metastatic colorectal cancer previously treated with bevacizumab and chemotherapy

Bevacizumab administered in combination with fluoropyrimidine-based chemotherapy is the standard first-line treatment for metastatic colorectal cancer and second-line treatment in bevacizumab-naive patients. Preclinical observational studies have shown a rationale to continue bevacizumab from one treatment line to another treatment line.

In this international study, Dr Dirk Arnold, director of the Hubertus Wald Tumor Center, University Cancer Center and University Clinic Eppendorf, in Hamburg, Germany, and colleagues randomized 820 patients with unresectable, histologically confirmed metastatic colorectal cancer who had progressed within 3 months of discontinuation of first-line bevacizumab plus chemotherapy to either second-line fluoropyrimidine-based therapy plus bevacizumab or placebo (abstract CRA 3503).

The choice of oxaliplatin- or irinotecan-based chemotherapy as second-line therapy depended on the regimen used in the first-line setting. The primary end point was overall survival; secondary end points included progression-free survival, response rate, and safety.

According to the study researchers the trial clearly met its end point of overall survival, with a statistically significant improvement in overall survival. Median survival was longer with chemotherapy plus bevacizumab than with chemotherapy alone (11.2 vs. 9.8 months). Median progression-free survival was also improved in this setting (5.7 vs. 4.1 months, $p<0.0001$). The response rate was 5.4% with chemotherapy plus bevacizumab and 3.9% with chemotherapy alone.

Treatment was well tolerated in both study groups, and adverse events associated with bevacizumab were comparable with those observed in previous studies. Bevacizumab-related adverse events were no worse when the agent was continued after progression.

Many oncologists are already extending bevacizumab beyond first progression, and results from this study are the proof of concept in the clinical setting. The study results also raise the question of the financial impact of therapy continuation. Although it was well designed and demonstrates the benefit of bevacizumab continuation, the study doesn't address the magnitude of that benefit.

Practice point and future research opportunities

This is a first randomized study to prospectively investigate the impact of bevacizumab continuation beyond first progression. The results clearly provide a new second-line treatment option for patients who have already been treated with a combination bevacizumab regimen. Furthermore, these findings might serve as a potential new model for treatment approaches across multiple lines in metastatic colorectal cancer and across other tumor types, which is being investigated. Additional analysis of this study, including biomarker evaluation, is ongoing.

GASTROINTESTINAL (NONCOLORECTAL) CANCER

Tivantinib holds promise in patients with unresectable cMET-expressing hepatocellular carcinoma who failed one systemic therapy

Tivantinib is a selective, oral inhibitor of c-Met, the tyrosine kinase receptor for hepatocyte growth factor involved in tumor cell migration, invasion, proliferation and angiogenesis. Tivantinib has shown previously promising results in hepatocellular carcinoma (HCC) in phase 1 studies as monotherapy and in combination with sorafenib. In a randomized, placebo-controlled phase II trial, conducted in 107 patients with unresectable HCC (abstract 4006), tivantinib demonstrated striking efficacy as a single agent. The benefits were specifically observed in the subgroup of patients with tumors showing high MET expression. The results were presented by Dr Lorenza Rimassa of the Department of Oncology, Humanitas Cancer Center, Rozzano, Italy.

These findings are the first randomized data in HCC showing an overall survival advantage with a MET inhibitor administered as a single agent and the first identification of a biologic subgroup of patients responding to a targeted therapy. Tivantinib is undergoing evaluation in several cancers. However, the findings in HCC are particularly provocative given the lack of second-line therapies after sorafenib for patients with advanced disease.

Tivantinib improved the time to progression (the primary study endpoint) by approximately 1 week compared with placebo in the overall population. Although significant, this modest improvement was much more striking when the analysis was restricted to patients harboring HCCs with high MET expression, a factor found to be associated with poor prognosis. Among these individuals, the median time to progression was extended from 6.1 weeks with placebo to 11.7 weeks with tivantinib ($p=0.03$). Moreover, this subgroup demonstrated a significant 3.4 month improvement in overall survival with tivantinib compared with placebo (7.2 months versus 3.8 months ($p=0.01$).

No improvements in time to progression or overall survival were observed with tivantinib in patients with tumors exhibiting low MET expression, nor was an overall survival benefit observed in the overall patient population.

The original tivantinib dose of 360 mg was reduced to 240 mg following an unexpectedly high incidence of drug-related neutropenia, which led to sepsis in 4 individuals. Grades 3 to 5 neutropenia dropped from 21% at the 360 mg dose to 6% at the 240 mg dose. Aside from neutropenia, the most common grade 3 to grade 5 drug-related adverse event was anemia (9% to 16%).

Practice point and future research opportunities

A phase III study of tivantinib in patients with high MET-expressing hepatocellular carcinoma is currently being planned to confirm these encouraging findings. Although it might be premature to plan

a large, randomized phase III trial on the findings of a very small subset analysis, the findings from this study are particularly provocative given the lack of second-line therapies after sorafenib in patients with advanced hepatocellular carcinoma.

A randomized, multicenter trial of epirubicin, oxaliplatin, and capecitabine plus panitumumab in advanced esophagogastric cancer

The REAL-3 study (abstract LBA4000) was presented by Dr Tom Waddell of the Royal Marsden Hospital NHS Foundation Trust, United Kingdom. The study enrolled 553 patients from the UK, all with untreated locally advanced or metastatic adenocarcinoma or undifferentiated carcinoma of the esophagus, gastroesophageal junction, and stomach. Patients were randomly assigned to epirubicin, oxaliplatin, and capecitabine (EOC) or modified EOC plus panitumumab. The chemotherapy dose modifications were established as a result of overlapping gastrointestinal toxicity, particularly diarrhea.

An independent data review revealed a significantly inferior overall survival outcome in the panitumumab-containing arm. At that point, the phase III trial was closed and all patients crossed over to the control arm. Data for patients still on treatment at that time were censored at the time of trial closure.

The updated analysis presented at 2012 ASCO Annual Meeting confirmed the shorter survival initially observed in the panitumumab-containing regimen, with a median overall survival of 8.8 months compared with 11.3 months for the standard EOC regimen. This outcome represents a 37% increase in the risk of death in the panitumumab-containing arm. There was also a trend toward shorter progression-free survival with panitumumab plus modified EOC compared with standard EOC, 6.0 vs. 7.4 months.

Dose intensity was reduced in the panitumumab-containing regimen, as evidenced by a lower median number of cycles (five vs. six) and lower capecitabine dose intensity, independent of protocol defined dose adjustments. The lower doses of oxaliplatin and capecitabine used in the modified EOC regimen may have contributed to the lower efficacy. This degree of chemotherapy dose reduction precluded the ability to completely evaluate the effect of panitumumab.

Regarding safety, there was no significant difference in the overall incidence of grade 3 or higher adverse events between arms. Compared with standard EOC, the panitumumab-containing regimen was associated with increased rates of grades 3 and 4 diarrhea, skin rash, and mucositis, and decreased rates of peripheral neuropathy and neutropenia. Overall, 77% of patients receiving panitumumab developed a grade 1 to grade 3 rash. The investigators reported a significant

association between the development of rash and survival among patients receiving panitumumab plus modified EOC; the median overall survival was 10.2 months in patients with rash and 4.3 months in those without rash ($p<0.001$).

Molecular biomarkers were explored in the first 200 patients. Factors associated with shorter survival in a multivariate analysis included KRAS mutations and PIK3CA mutation. However, both analyses involved small numbers of patients. This was an unselected patient population that was not enrolled based on epidermal growth factor receptor expression.

Practice point and future research opportunities

In the randomized, multicenter, phase II/III REAL-3 trial, the addition of panitumumab to a modified epirubicin, oxaliplatin, and capecitabine regimen did not improve outcomes in patients with previously untreated advanced esophagogastric cancer, and in fact was associated with significantly worse overall survival compared with the standard chemotherapy regimen. The researchers are currently trying to identify molecular or clinical characteristics that may predict better outcomes with a panitumumab-containing regimen. This translational work may offer further important insights into the targeting of this pathway.

GENITOURINARY CANCER

Tivozanib versus sorafenib as initial targeted therapy for patients with advanced renal cell carcinoma

Tivozanib, a potent, selective, long half-life tyrosine kinase inhibitor targeting all three VEGF receptors, showed activity and tolerability in a phase II trial in patients with clear cell advanced renal cell carcinoma (RCC). In a phase III, randomized, open label, multicenter study (abstract 4501), prior nephrectomy, patients with RECIST-defined measurable disease, and Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 were randomized 1:1 to tivozanib for 3 weeks followed by 1 week rest, or sorafenib daily continuously in a 4 week cycle.

All patients were treatment naive or received no more than 1 prior systemic therapy for metastatic disease. Patients who received prior VEGF- or mTOR-targeted therapy were excluded. The primary endpoint was progression-free survival per blinded, independent radiological review. In 500 patients,

researchers led by Dr Robert Motzer of the Memorial Sloan-Kettering Cancer Center, New York, planned to observe 310 events.

A total of 517 patients were randomized to tivozanib or sorafenib. Demographics were well balanced between the 2 groups, except ECOG 0 (tivozanib 45% vs. sorafenib 54%). Median progression-free survival was 11.9 months for tivozanib vs. 9.1 months for sorafenib. In the treatment-naive stratum (70% of patients enrolled in each arm), the median progression-free survival was 12.7 months for tivozanib vs. 9.1 months for sorafenib. In all patients, objective response rate for tivozanib was 33% vs. 23% for sorafenib. The most common adverse event for tivozanib was hypertension and for sorafenib hand-foot syndrome. Other important adverse events included diarrhea, fatigue, and neutropenia. Overall survival data are not mature yet.

Practice point and future research opportunities

Tivozanib demonstrated significant improvement in progression-free survival and objective response rate compared with sorafenib as initial targeted treatment for advanced renal cell carcinoma. The safety profile of tivozanib is favorable, and includes a low incidence of fatigue, diarrhea, myelosuppression, and hand-foot syndrome.

Continuous androgen-deprivation therapy remains standard of care in patients with metastatic prostate cancer

Dr Maha Hussain presented the results of Southwest Oncology Group (SWOG) 9346 (INT-1062), a collaboration among five cooperative groups from the United States, Canada, and Europe (in addition to SWOG, other groups were the Eastern Cooperative Oncology Group (ECOG), Cancer and Leukemia Group B (CALGB), the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG), and the European Organisation for Research and Treatment of Cancer (EORTC) (abstract 4). The trial accrued 3040 patients with newly diagnosed hormone-sensitive metastatic prostate cancer between 1995 and 2008. Those included had a prostate-specific antigen (PSA) level of 5 ng/mL or greater before initiation of androgen deprivation and a SWOG performance status of 0 to 2.

Patients were stratified by performance status, extent of disease, and prior hormone therapy. Eligible patients were treated with goserelin and bicalutamide for 7 months, and those who achieved a PSA of 4 ng/mL or less were randomly assigned to continuous androgen-deprivation (CAD) (765 patients) or intermittent androgen-deprivation (IAD) (770 patients).

In the IAD arm, therapy was reinitiated when PSA increased to 20 ng/mL or, for those who had a baseline value less than 20 ng/mL, when PSA returned to baseline. If the PSA after another 7-month

course met the normalization criteria, the patient started another observation period. If it was greater than 4 ng/mL at 6 or 7 months, the patient received CAD until progression. The trial was designed to assess whether overall survival with IAD was non-inferior to CAD.

The mean overall survival was 5.8 years for patients receiving CAD and 5.1 for patients receiving IAD, representing a 9% increase in relative risk of death for IAD. The non-inferiority criterion was not met. Therefore, IAD was not found to be non-inferior to CAD based on the prespecified definition of survival comparability. Dr Hussain and the abstract discussant referred to IAD as inferior to CAD in their presentations, and they were challenged on the use of this terminology during a later question-and-answer session.

In her presentation, Dr Hussain noted that when the trial was designed, it was assumed that the median survival in the control arm would be 3 years. With actual median survival of more than 5 years in the study, a hazard ratio of 1.2 translates into a larger difference in survival, which could be considered as inferior.

A previous study, NCIC PR7, showed that either CAD or IAD are appropriate standards of care in patients with non-metastatic prostate cancer. However, all previous trials have been underpowered to evaluate survival in metastatic prostate cancer.

Practice point and future research opportunities

In this international collaborative phase III clinical trial in patients with hormone-sensitive metastatic prostate cancer, intermittent androgen-deprivation therapy was not shown to be non-inferior to continuous androgen-deprivation therapy.

Interim analysis of a randomized, phase III study of abiraterone acetate in chemotherapy-naive patients with metastatic castration-resistant prostate cancer

Dr Charles Ryan of the Helen Diller Family Comprehensive Cancer Center at the University of California, San Francisco, presented results of the second planned interim analysis of the randomized, multicenter COUAA- 302 study (a bstract LBA4518). With 43% of total events reported, the independent data monitoring committee concluded that the co-primary endpoints of overall survival and radiographic progression-free survival and secondary endpoints all favored the abiraterone acetate arm and unanimously recommended unblinding the study and crossing patients over from placebo to abiraterone acetate treatment.

Abiraterone acetate plus prednisone previously demonstrated a benefit in overall survival over a prednisone control in patients with previous chemotherapy exposure, and these study results were

used to support the regulatory approval of the drug.

The natural history of progressive metastatic castration-resistant prostate cancer can be prolonged, and can appear over a period of years. Therefore, several hallmarks of disease progression (time to opiate use as a surrogate for cancer-related pain, time to initiation of chemotherapy, time to Eastern Cooperative Oncology Group performance status deterioration, time to PSA progression) were used as secondary endpoints, to provide a comprehensive assessment of the magnitude of the clinical benefit conferred by abiraterone acetate. Therapy with abiraterone acetate delayed, to a clinically significant degree, the onset of these meaningful events.

The co-primary endpoint included progressive disease as determined by bone scan with blinded review by a central radiologist, progressive disease as determined by soft tissue lesions seen on computed tomography or magnetic resonance imaging, or death from any cause. Despite longer treatment with abiraterone acetate than in the prior study in patients with previous chemotherapy, no new safety signals were seen in the trial.

Practice point and future research opportunities

In patients with asymptomatic or mildly symptomatic chemotherapy-naive metastatic castration-resistant prostate cancer, abiraterone acetate plus prednisone produced a statistically significant benefit in radiographic progression-free survival over placebo plus prednisone, according to a planned interim analysis of this phase III study. Abiraterone acetate plus prednisone delayed disease progression, increased survival, and extended time with minimal or no symptoms. It is the first study to show activity of abiraterone acetate in chemotherapy-naive patients, and the study data should be considered as providing a new standard approach in this highly prevalent patient population faced with unmet medical needs.

Primary, secondary, and quality-of-life endpoint results from the phase III study of MDV3100 (enzalutamide)

Dr Johann de Bono of the Institute of Cancer Research and the Royal Marsden NHS Foundation Trust, United Kingdom, presented results of a phase III AFFIRM trial, a randomized study that included 1199 men with castration-resistant prostate cancer (CRPC) (abstract 4519)**.** Overall survival rates were about 5 months longer among treated patients, with a 37% reduction in risk of death ($p<0.0001$).

The primary endpoint data on overall survival were first reported at the 2012 ASCO Genitourinary

Cancers Symposium in February. During the ASCO Annual Meting, Dr de Bono reported new data on the trial's secondary endpoints: the response indicators, which include prostate specific antigen (PSA) response, soft tissue objective response, and Functional Assessment of Cancer Therapy-Prostate (FACT-P) quality of life; and the progression indicators, which include time to PSA progression, radiographic progression-free survival, and time to first skeletal-related event. On all of these measures, enzalutamide was superior to placebo.

This international trial randomly assigned 800 patients in the enzalutamide arm and 399 patients in the placebo arm. Glucocorticoids were not required but were allowed. Median age was 69 in both groups, and the groups were well matched according Eastern Cooperative Oncology Group (ECOG) performance status, bone disease, pain, and soft tissue disease. About 50% of enzalutamide-treated patients had received three or more prior lines of hormonal therapy, compared to 53.1% of placebo-treated patients; the median number of prior docetaxel cycles and the number of prior chemotherapy regimens were similar between the two groups.

The planned interim analysis was conducted after 520 deaths. At that time, the Independent Data Monitoring Committee concluded that there was a statistically and clinically meaningful overall survival benefit with enzalutamide and determined that the AFFIRM study should be halted and unblinded, with eligible patients in the placebo arm offered enzalutamide therapy.

AFFIRM demonstrated a very high PSA response rate with enzalutamide, with 54% having a fall in PSA >50%. Quality-of-life responses as measured by FACT-P were significantly higher with enzalutamide on all measures ($p<0.0001$).

Enzalutamide was generally well tolerated with little difference in toxicity with placebo. There was, however, a higher and non-significant risk of fatigue and a small risk of seizures with the study drug.

Practice point and future research opportunities

The once-daily androgen receptor signaling inhibitor enzalutamide, or MDV3100, was well tolerated and significantly prolonged overall survival, slowed disease progression, and improved quality of life in the phase III AFFIRM trial, a randomized study in men with post-docetaxel castration-resistant prostate cancer. Most patients had a benefit within the first 3 to 6 months of treatment, but there were some patients with long-term responses to the agent.

GYNECOLOGIC CANCER

Randomized phase III study of erlotinib versus observation in ovarian cancer patients with no evidence of disease progression after first-line platinum-based chemotherapy

Dr Ignace Vergote of the University Hospital Leuven, Belgium, presented results of a phase III, multicenter study on behalf of the European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group (EORTC-GCG). The epidermal growth factor receptor (EGFR) is overexpressed in 55% to 98% of advanced epithelial ovarian cancer. This trial was designed to test the efficacy of erlotinib, an EGFR tyrosine kinase inhibitor, as a maintenance treatment following platinum-based chemotherapy (abstract LBA5000).

Eight hundred and thirty-five patients from 125 institutions in 10 countries participated in the study. All patients first received six to nine cycles of platinum-based chemotherapy three times weekly, and showed no signs of disease progression. They were then randomly assigned into two arms: one group received 150 mg of maintenance erlotinib daily for 2 years, the other group was observed. As a secondary analysis, immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) analyses were conducted in 330 patients to determine the predictive value of IHC and FISH for *EGFR* and *EGFR* mutations. The primary endpoint was progression-free survival, with secondary endpoints of overall survival, quality of life, and complications.

After 24 months of accrual, there were not enough events (632) to reach the study's endpoint. Patient accrual was stopped in November 2011 when 625 events were recorded. In a median follow-up of 51 months, progression-free survival was 12.7 months for patients treated with erlotinib and 12.4 for observed patients. Overall survival for the two groups was 51 months for patients treated with erlotinib and 59 months for observed patients (p=0.603).

Subsequent analyses of the data looked at the relationship between *EGFR* mutation status and progression-free survival. Among patients treated with erlotinib, 318 showed *EGFR*, *KRAS*, *NRAS*, *BRAF*, or *PI3KCA* mutations. Investigators found no significant relationship between progression-free survival and the development of rash during erlotinib treatment, and no differences based on International Federation of Gynecology and Obstetrics stage, age, or response at the end of first-line chemotherapy.

During the abstract discussion, Dr Michael Seiden of Fox Chase Cancer Center said that serous ovarian cancer is a genetically and molecularly complicated disease that poses significant research challenges. The genomic data for high-grade serous cancer strongly suggests that there are not large groups of genomically homogenous patients. Without predictive biomarkers or large groups of molecular homogenous patients, the currently used strategy of phase I through to phase III trials will not be successful in identifying new drugs for this disease.

Practice point and future research opportunities

The use of maintenance erlotinib after first-line platinum-based treatment did not improve survival in women with ovarian cancer. There was also no subgroup identified that might benefit from erlotinib maintenance therapy after first-line chemotherapy for ovarian cancer.

AURELIA, the randomized phase III trial of bevacizumab with standard chemotherapy in platinum-resistant ovarian cancer

Speaking on behalf of the AURELIA investigators (European ovarian cancer research groups), Dr Eric Pujade-Lauraine presented results from the first phase III trial combining bevacizumab with current standard of care - chemotherapy in the treatment of platinum-resistant recurrent ovarian cancer (LBA5002).

Patients eligible for the trial had ovarian cancer that progressed within 6 months of completing at least 4 cycles of platinum-based therapy and had no history of bowel complications. Chemotherapy was selected by the investigator based on each patient's prior drug exposure, and options included pegylated liposomal doxorubicin, topotecan, or weekly paclitaxel.

Patients were randomly assigned to receive chemotherapy alone or in combination with bevacizumab until progression or unacceptable toxicity (182 vs. 179). Those in the control arm could cross over to bevacizumab at disease progression. Median follow-up was 13.9 months for patients receiving standard chemotherapy and 13 months for the bevacizumab group. Both treatment groups had similar baseline characteristics.

Median progression-free survival was 3.4 months for those receiving standard chemotherapy alone and 6.7 months for those receiving bevacizumab ($p<0.001$). Subgroup analysis indicated that the addition of bevacizumab to standard chemotherapy improved progression-free survival regardless of age, relapse-free interval, extent of disease, presence of ascites or type of chemotherapy administered.

The 12.6% response rate in the standard chemotherapy group was about what was expected in this patient population, whereas the response rate in the bevacizumab group was significantly improved, whether evaluated by RECIST criteria or by CA-125 levels.

The safety profile of bevacizumab was consistent with previous clinical experience. Hypertension and proteinuria (grade 2 or worse) were more frequent in the bevacizumab group, 27% compared with 8% in the control group, and 12% compared with 1%, respectively; fatigue, abdominal pain, vomiting, and dyspnea occurred less frequently in the group treated with bevacizumab. Overall, seven women receiving bevacizumab experienced gastrointestinal perforation, and six had fistulas or abscesses.

The incidence of peripheral sensory neuropathy and of hand-foot syndrome (grade 3 or worse) was higher in the bevacizumab-treated patients. In the cohort receiving pegylated liposomal doxorubicin, the time-course for the cumulative incidence of hand-foot syndrome was similar in the two study groups. Likewise, in the cohort receiving paclitaxel, the time-course for the cumulative incidence of neuropathy was similar.

In abstract discussion, Dr Michael Seiden of Fox Chase Cancer Center posited that because the preponderance of ovarian cancers are serous carcinomas that have lost multiple suppressors, contain numerous somatic mutations, and have considerable genomic instability, there are not large groups of similar patients suitable for phase III trials, nor is there any compelling evidence for predictive biomarkers that would identify patients likely to benefit. In addition he offered the radical considerations of stopping all phase III trials, at least with molecularly targeted agents, deep sequencing the DNA, and instituting the requirement of submitting genomics data for each patient eligible for clinical trials.

Practice point and future research opportunities

This study is the first randomized phase III trial to demonstrate benefit with biologic therapy and benefit with combination therapy, rather than monotherapy, in patients with platinum-resistant ovarian cancer.

A phase II, open-label, multicenter study of ramucirumab monotherapy in the treatment of persistent or recurrent epithelial ovarian, Fallopian tube, or primary peritoneal carcinoma

VEGF receptor-mediated-signaling contributes to ovarian cancer pathogenesis. Elevated VEGF expression and serum levels are associated with poor clinical outcomes. The researchers led by Dr Richard Penson of the Massachusetts General Hospital, Boston, USA investigated ramucirumab, a fully human VEGFR-2 antagonist antibody, in patients with persistent or recurrent epithelial ovarian, Fallopian tube, or primary peritoneal carcinoma (abstract 5012).

Adult women with epithelial ovarian, Fallopian tube, or primary peritoneal carcinoma who had

completed one platinum-based chemotherapeutic regimen and had a platinum-free interval of 12 months, progression on, or persistent disease after platinum-based therapy were eligible. Any number of prior chemotherapy regimens was allowed; ECOG performance status 0 and 1, and adequate organ function were required. Primary endpoints were progression-free survival at 6 months and confirmed objective response rate by RECIST 1.0 criteria.

Investigators treated 60 patients, median age was 62 years (range 27-80). Median number of prior regimens was 3 (range 1- 14). A total of 51 patients (85%) received 2 prior regimens; 25 patients (42%) received 3 prior regimens, 45 patients (75%) were platinum resistant or refractory, and 65% (39 patients) had serous tumors. Progression-free survival at 6 months was 34.2%. Best overall response was determined as partial in 3 patients, stable disease in 34 patients, and progression of disease in 20 patients; 3 patients were not evaluable. Median duration of partial response was 5.6 months; median progression-free survival 3.5 months, and median overall survival was 11.1 months. No unexpected toxicities were observed. Grade 3 adverse events were observed in >5% of patients: headache (10%) and fatigue (8%). Grade 4 adverse events were observed in >5% of patients; 5 deaths occurred on ramucirumab or within 30 days of discontinuation; 4 due to disease progression, and 1 due to intestinal perforation. One grade 4 bowel perforation and one grade 4 colo-vaginal fistula were noted. All 3 cases of perforation/fistula occurred in the setting of progressive, large-volume disease.

Practice point and future research opportunities

Ramucirumab was reasonably tolerated and demonstrated single-agent activity in persistent or recurrent ovarian carcinoma, with approximately one-third of patients' progression free at 6 months. Correlative biomarker studies are ongoing to identify patients most likely to benefit.

HEAD AND NECK CANCER

An international, double-blind, randomized, placebo-controlled phase III trial of cabozantinib in medullary thyroid carcinoma patients

Medullary thyroid carcinoma arises from parafollicular cells of the thyroid gland. It accounts for 5-8% of thyroid cancers and represents a cancer type with unmet medical needs. A group of researchers led by Dr Patrick Schoffski of the Department of General Medical Oncology, University Hospitals Leuven, Belgium, conducted a phase III study of cabozantinib, an oral inhibitor of MET, VEGFR2, and

RET vs. placebo in patients with progressive, unresectable, locally advanced or metastatic medullary thyroid carcinoma (abstract 5508).

Eligible patients were required to have documented RECIST progression within 14 months of screening. The primary efficacy measure was progression-free survival as assessed by an independent review facility using RECIST criteria. Secondary efficacy measures included objective response rate and overall survival. Tumor assessments occurred every 12 weeks, and crossover between treatment arms was not allowed.

A total of 330 patients (median age 55 years; 67% male; 96% with measureable disease; RET mutation status: positive in 48%, negative in 12%, and unknown in 39%; prior TKI exposure in 21% patients) were randomized 2:1 in the study. Statistically significant prolongation in progression-free survival of 7.2 months was observed; median for cabozantinib was 11.2 months vs. 4.0 months for placebo. Progression-free survival results favored the cabozantinib group across subset analyses including RET status and prior TKI use. Objective response rate was 28% for cabozantinib vs. 0% for placebo. An interim analysis of overall survival (44% of the 217 required events) did not show a difference between cabozantinib and placebo. The most frequent grade 3 adverse events (cabozantinib vs. placebo) were diarrhea (15.9% vs. 1.8%), palmar-plantar erythrodysesthesia (12.6% vs. 0%), fatigue (9.3% vs. 2.8%), hypocalcemia (9.3% vs. 0%), and hypertension (7.9% vs. 0%).

Practice point and future research opportunities

This phase III study met its primary objective of demonstrating substantial progression-free survival prolongation with cabozantinib vs. placebo in a patient population with medullary thyroid carcinoma and documented progressive disease in need of therapeutic intervention.

HEMATOLOGIC MALIGNANCIES

Bendamustine plus rituximab more effective and better tolerated than standard R-CHOP in patients with indolent and mantle cell lymphoma

Dr Mathias Rummel of the University Clinic in Giessen, Germany, presented the updated results of the StiL NHL1, multicenter phase III trial, conducted in patients with indolent and mantle cell lymphomas and treated with first-line bendamustine plus rituximab or with standard cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (R-CHOP) regimen (abstract

3). Bendamustine was originally developed about 50 years ago in former East Germany, but it only became available in the United States in 2008 and the European Union in 2010. Some oncologists currently use bendamustine-rituximab regimen, but R-CHOP is the established regimen of choice in the United States and much of Europe.

The investigators recruited patients with previously untreated, CD20-positive, indolent non-Hodgkin or mantle cell lymphomas. Their initial intent was to demonstrate that bendamustine-rituximab was non-inferior to R-CHOP for progression-free survival at 3 years and also less toxic. After following 514 evaluable patients for a median of 45 months, median progression-free survival was 69.5 months in the bendamustine-rituximab group compared with 31.2 months in the R-CHOP group ($p=0.0000148$). Bendamustine-rituximab was not only superior in the overall patient population, but was also more effective than R-CHOP in exploratory analyses in the subgroups with follicular lymphoma, mantle cell lymphoma, and Waldenström macroglobulinemia. The investigators did not find a significant improvement with bendamustine-rituximab in marginal zone lymphoma.

No difference in overall survival between the two groups has emerged thus far. Dr Rummel commented that this is not surprising given the protracted nature of indolent lymphomas and potential confounding caused by use of a variety of salvage therapies among the patients with progressive disease.

Complementing its efficacy profile, bendamustine-rituximab also showed a more favorable tolerability profile compared with R-CHOP. Severe neutropenia was markedly decreased with bendamustine-rituximab (29% vs. 69% with RCHOP), although the authors pointed out a higher incidence of severe lymphocytopenia with bendamustine-rituximab versus R-CHOP (74% vs. 43%). The bendamustine-rituximab group also showed a higher incidence of all-grade skin reactions compared with R-CHOP (40% vs. 15%; $p=0.0003$); however, the bendamustine regimen resulted in a significantly lower incidence of paresthesias ($p<0.0001$), stomatitis ($p<0.0001$), and infections ($p=0.0025$). With bendamustine-rituximab not a single patient has had alopecia. There has been no increase in secondary malignancies with bendamustine-rituximab observed, based on data from nearly 4 years follow-up.

Practice point and future research opportunities

Long-term results of the German StiL NHL1 trial conducted in patients with indolent and mantle cell lymphomas show that the first-line treatment with bendamustine plus rituximab more than doubled progression-free survival compared with standard R-CHOP. Bendamustine plus rituximab also produced less toxicity. Bendamustine-rituximab could be established as a front-line regimen for patients with indolent B-cell and nontransplant-eligible mantle cell lymphoma.

Rapid and durable complete response in patients with newly diagnosed multiple myeloma treated with carfilzomib, lenalidomide, and dexamethasone

The researchers led by Dr Andrzej Jakubowiak of the University of Chicago Medical Center found that combining carfilzomib, a next generation proteasome inhibitor, with two standard drugs, lenalidomide and low-dose dexamethasone, compared favorably to other frontline regimens (abstract 8011).

The research team enrolled 53 patients with newly diagnosed myeloma in the trial at four centers. Patients, aged 35 to 81, all had newly diagnosed multiple myeloma. Every patient received all three drugs and the carfilzomib dose levels were increased twice for new patients as the study progressed. Most patients responded rapidly to the combination and continued to improve.

The longer patients stayed on the therapy, the better their response. After at least eight 4-week cycles of treatment, 61% of the 36 patients who remained on the therapy had a stringent complete response, defined as no detectable tumor cells or myeloma protein in the blood or bone marrow; 78% had at least a near complete response. More than 90% of patients had no progression of their disease at two years.

The study researchers have observed excellent efficacy, the best reported to date, and very good tolerability, including limited peripheral neuropathy that has been problematic with other drug combinations.

Practice point and future research opportunities

A three-drug treatment, with a next generation proteasome inhibitor, provided rapid, deep and potentially durable responses in patients with newly diagnosed myeloma. Rapid and durable response rates were higher than those achieved by the best established regimens. Newly diagnosed patients with myeloma are most sensitive to treatment. A rapid and sustained response to the initial phase of treatment, as in the case of this study, can typically project longer remission, and, possibly, longer overall survival.

LUNG CANCER

Pivotal phase III results of afatinib as first-line treatment in patients with advanced adenocarcinoma of the lung harboring EGFR-activating mutations

Afatinib is a selective, orally bioavailable, irreversible ErbB family blocker of EGFR (ErbB1), HER2

(ErbB2), and ErbB4. LUX-Lung 3, a phase III global study investigated the efficacy and safety of afatinib in comparison to pemetrexed/cisplatin (LBA7500). Primary endpoint was progression-free survival by central independent review.

Following central testing for EGFR mutations by companion diagnostic kit, 345 patients with stage IIIB/IV non-small cell lung cancer (NSCLC), performance status 0-1, chemo-naive, were randomized 2:1 to daily afatinib or intravenous standard chemotherapy regimen, pemetrexed/cisplatin. Baseline characteristics were balanced in both arms regarding median age, sex, ethnicity, smoking status, and presence of mutations.

Treatment with afatinib led to a significantly prolonged progression-free survival (median 11.1 vs. 6.9 months, p=0.0004). In 308 patients with common mutations (Del19/L858R), median progression-free survival was 13.6 vs. 6.9 months, p<0.0001. Objective response rate was significantly higher with afatinib (56% vs. 23%, p<0.0001). Significant delay in time to deterioration of cancer-related symptoms, such as cough and dyspnea, was seen with afatinib vs. pemetrexed/cisplatin.

Most common drug-related adverse events were diarrhea (95%), rash (62%) and paronychia (57%) with afatinib, and nausea (66%), decreased appetite (53%) and vomiting (42%) with pemetrexed/cisplatin. Drug-related adverse events led to discontinuation in 8% (afatinib, 1% due to diarrhea) and 12% of patients in the pemetrexed/cisplatin arm.

Practice point and future research opportunities

LUX-Lung 3 is the largest prospective trial in EGFR mutation positive lung cancer and the first study using pemetrexed/cisplatin as a comparator. Treatment with afatinib significantly prolonged progression-free survival compared to pemetrexed/cisplatin, with significant improvements in secondary endpoints. Adverse events with afatinib were manageable, with a low discontinuation rate. With 4.2 months improvement in progression-free survival in the overall study population and 6.7 months in patients with common mutations, afatinib may represent a clinically relevant first-line treatment option.

TAILOR: A phase III trial comparing erlotinib with docetaxel in the second-line treatment of NSCLC patients with wild-type EGFR

While the benefit of EGFR tyrosine kinase inhibitors in the treatment of patients with non-small cell lung cancer (NSCLC) harboring EGFR mutations has been widely established, their value in treating patients with wild-type (wt) EGFR is still debated. To assess the role of erlotinib in these patients, a group of Italian researchers led by Dr Marina Garassino of the Fatebenefratelli e Oftalmico hospital in

Milan, Italy performed an independent multicenter phase III trial (Tarceva Italian Lung Optimization Trial - TAILOR), comparing erlotinib to docetaxel in second line treatment (LBA 7501). Overall- and progression-free survival were the principal and secondary endpoints, respectively.

EGFR and KRAS mutational status were assessed by direct sequencing in all eligible patients; only patients with wt EGFR NSCLC (exons 19 and 21) at progression, and previously treated with a first line platinum-based regimen, were randomized to receive either erlotinib or docetaxel until disease progression or unacceptable toxicity.

On the planned analysis date, 221 patients had been randomized and 218 were evaluable (110 with docetaxel, 108 with erlotinib; three major violations were excluded). At a median follow-up of 20 months, 199 relapses and 157 deaths were recorded. The Kaplan-Meier progression-free survival curves showed a highly significant increase favoring docetaxel (p=0.016) over erlotinib regimen. The hazard ratio translated into an estimated absolute difference in 6-months progression-free survival of 12% (16% vs. 28%). Data concerning toxicity were consistent with the literature.

Practice point and future research opportunities

In terms of progression-free survival, these results indicate a clear superiority of docetaxel over erlotinib as second line treatment for patients without EGFR mutations in exons 19 or 21. Analysis of overall survival will be conducted as far as the planned number of 199 deaths is reached.

A randomized phase III trial of single-agent pemetrexed versus carboplatin-pemetrexed in patients with advanced NSCLC and performance status 2

No standard of care exists for patients with advanced non-small cell lung cancer (NSCLC) and performance status (PS) 2; clinical practice ranges from supportive care to combination chemotherapy. In a Brazilian multicenter phase III randomized trial, presented by Dr Rogerio Lilenbaum of the Cleveland Clinic Florida, USA, patients with advanced NSCLC, and any histology at first, amended to non-squamous only, PS 2, no prior chemotherapy, and adequate organ function, were randomized to pemetrexed alone or carboplatin-pemetrexed. Stratification factors included stage (IIIB vs. IV), age, and weight loss. The primary endpoint was overall survival and the study was powered to demonstrate an improvement in median survival from 2.9 to 4.3 months based on a prior CALGB trial (abstract 7506).

A total of 217 patients were enrolled from 8 centers in Brazil and 1 in the USA. Twelve patients were ineligible and excluded. The two arms were balanced for patient characteristics. The response rates were 10% and 24% (pemetrexed vs. carboplatin-pemetrexed). In the intent to treat (ITT) population,

the median progression-free survival was 3.0 vs. 5.9 months in favor of the combination regimen and median overall survival was 5.6 vs. 9.1 months, again in favor of the combination therapy. One-year survival rates were 22% and 39%, respectively. Similar results were seen when squamous patients were excluded from the analysis. Grade ¾ anemia (5.5% and 12%) and neutropenia (2.8% and 5.6%) were more frequent in combination arm. There were 4

treatment-related deaths in the carboplatin-pemetrexed arm. Second-line therapy was administered in 30% of patients in each arm.

Practice point and future research opportunities

Combination chemotherapy with carboplatin-pemetrexed significantly improves survival, with acceptable safety, in eligible patients with advanced NSCLC and performance status 2.

Clinical activity of crizotinib in advanced NSCLC harboring ROS1 gene rearrangement

In cell lines, ROS1 rearrangements lead to expression of oncogenic ROS1 fusion kinases and sensitivity to ROS kinase inhibition. A group of researchers led by Dr Alice Tsang Shaw of the Massachusetts General Hospital Cancer Center, Boston, USA, examined the efficacy and safety of crizotinib, a small molecule tyrosine kinase inhibitor of MET, ALK and ROS, in patients with advanced, ROS1-rearranged non-small cell lung cancer (NSCLC) (abstract 7508).

ROS1 rearrangement was determined by using a break-apart FISH assay, and patients were recruited into an expansion cohort of a phase 1 study of crizotinib. The objective response rate was determined based on RECIST 1.0 criteria. The disease control rate (stable disease, partial response, complete response) was evaluated at 8 weeks.

Thirteen patients within the ROS expansion cohort received crizotinib and all were evaluable for response. The median age was 47 years (range 31-72), and all but one of the patients were never-smokers. All patients had adenocarcinoma histology. Twelve out of 13 patients were tested for ALK rearrangement and all were negative. The median number of prior treatments was 1 (range 0-3). At the time of publication of the abstract the objective response rate was 54% (7/13), with 6 partial responses and 1 complete response, with 6 responses achieved by the first restaging scan at 7-8 weeks. There was 1 additional unconfirmed partial response at the time of data cut-off. The disease-control rate at 8 weeks was 85% (11/13). Median duration of treatment was 20 weeks (range 4+-59+). All responses are ongoing, and 12 patients continue on study. One patient had disease progression at first restaging and was discontinued from the study. The pharmacokinetics and safety profile of crizotinib in this group of patients were similar to that observed in patients with ALK-positive NSCLC.

Practice point and future research opportunities

Chromosomal rearrangements of the ROS1 receptor tyrosine kinase gene define a new molecular subset of NSCLC. Crizotinib demonstrates marked antitumor activity in patients with advanced NSCLC harboring ROS1 rearrangements. Like ALK, ROS defines a distinct subpopulation of NSCLC patients for whom crizotinib therapy may be highly effective. This study represents the first clinical validation of ROS as a therapeutic target in cancer.

Investigational ALK inhibitor highly active in crizotinib-refractory ALK-positive NSCLC

A new compound that targets anaplastic lymphoma kinase-positive (ALK+) non-small cell lung cancer (NSCLC) is well-tolerated by patients and is already showing early signs of activity, including patients who no longer respond to crizotinib. The results of this dose-escalation phase I study (abstract 3007) were presented by Dr Ranee Mehra of the Fox Chase Cancer Center, USA.

The compound LDK378 targets ALK, a key cancer gene in a subset of lung cancer, lymphoma and the childhood cancer neuroblastoma, and which may be associated with other cancers, including breast and colorectal cancer. The study's authors looked at patients with ALK+ lung cancer, as well as other ALK+ solid tumors.

Early data from this phase I study show that the majority of patients treated with active doses of LDK378 responded, including those who had progressed after treatment with crizotinib. In the meantime investigators around the world are continuing to enroll patients in the trial. The next phase of the study will test the maximum tolerated dose of LDK378 in all patients enrolled.

Practice point and future research opportunities

Early data from this phase I study show that the majority of patients treated with active doses of LDK378 responded, including those who had progressed after treatment with crizotinib. The results are encouraging in patients who have tumors with alterations involving ALK, even if they have relapsed from previous treatments. The results are certainly encouraging, and merit additional research into whether LDK378 is effective in different types of cancers with alterations involving ALK.

MELANOMA

Dabrafenib extends progression-free survival in metastatic melanoma and has high clinical activity in patients with brain metastases

Updated results from the phase III BREAK-3 trial were presented on behalf of the trial group by Dr Axel Hauschild of the University Hospital, Schleswig-Holstein, Germany (abstract LBA8500). At the same session, Dr John Kirkwood of the University of Pittsburgh Cancer Institute, reported the final data from BREAK-MB, a phase II trial in patients with brain metastases (abstract 8501). Both studies included patients with confirmed *BRAFV600E* mutations.

The BREAK-MB phase II protocol for stage IV BRAF-positive melanoma enrolled patients with one or more intracranial metastases who had no prior brain therapy (Cohort A) or patients with disease progression following prior brain therapy (Cohort B). Overall, 325 patients were screened and 172 patients were enrolled. Demographics and clinical characteristics were similar for the two cohorts: 70% male, 54% with elevated lactate dehydrogenase levels (LDH) levels, and 46% with two to four target brain metastases. Thirty-eight percent had received prior chemotherapy and 30% had received prior immunotherapy.

An unprecedented overall intracranial disease control rate was seen in 81% in Cohort A and 89% in Cohort B for patients with *V600E* mutations, with a median duration of intracranial response of 20.1 weeks and 28.1 weeks, respectively. Both cohorts had an overall survival rate over 30%. Results were positive for overall intracranial response, overall response, and median progression-free survival.

A subset of 33 patients with *BRAFV600K* mutations had more limited responses to dabrafenib, with an overall response rate of 7% in Cohort A and 22% in Cohort B. However, the intracranial disease control rate was 33% for Cohort A and 50% for Cohort B; the overall disease control rate was 33% and 50%, respectively.

Serious adverse events occurred in 30% of the patients in both cohorts, 17% were related to study treatments. Only 2% of patients discontinued treatment due to toxicity and no deaths were attributable to dabrafenib therapy.

In BREAK-3, patients with previously untreated, unresectable stage III or IV disease were stratified by stage after random allocation at a ratio of 3:1 to oral dabrafenib or intravenous dacarbazine. Patients in the dacarbazine arm were allowed to cross over once progression was confirmed by independent review. The primary endpoint was investigator-assessed progression-free survival.

The trial enrolled 250 patients, 187 were allocated to the dabrafenib arm and 63 were given dacarbazine. Demographic and clinical characteristics were well-balanced between the two treatment groups. Approximately 60% of the patients were men, 65.6% had stage IV (M1c) disease, and 34.4% had elevated LDH levels.

Median investigator-assessed progression-free survival was 5.1 months for patients taking dabrafenib and 2.7 months for those receiving dacarbazine ($p<0.0001$). Results from independent review were similar (6.7 months and 2.9 months, respectively). The progression-free survival curves were similar whether the data were censored for crossover patients or not.

Subgroup analysis demonstrated dabrafenib to be superior regardless of performance status, LDH levels, age, gender, or disease stage. The confirmed overall response rate was 53% for patients taking dabrafenib and 19% for patients receiving dacarbazine. The most common adverse events for patients taking dabrafenib were skin-related (hyperkeratosis - 51%, palmarplantar hyperkeratosis - 21%, and squamous cell carcinoma/keratoacanthoma - 7%), headache (17%), arthralgia (16%), and pyrexia (15%). Photosensitivity was seen in 3% of patients taking dabrafenib and 5% of patients receiving dacarbazine.

Few serious adverse events were reported, mainly squamous cell carcinomas (5%), pyrexia (4%), and new primary melanomas (2%). Both dabrafenib and dacarbazine were well-tolerated, with only 3% of patients discontinued due to adverse events in each group.

Practice point and future research opportunities

Utilization of dabrafenib, the selective BRAF kinase inhibitor, is safe, with unprecedented responses and overall survival, supporting its use as first-line therapy. This shifts the current paradigm of treatment for brain metastases to systemic therapy in patients with melanoma. Based on the data from BREAK-MB, there is no reason to exclude patients with melanoma brain metastases from studies of dabrafenib; however, the study design did not address the use of stereotactic radiosurgery. The positive results from BREAK-3 have opened the pathway to combination trials with dabrafenib for stage IV melanoma, as well as adjuvant trials. BREAK-3 establishes dabrafenib as the second *BRAF* inhibitor with proven efficacy.

Updated overall survival results for BRIM-3, a phase III randomized, open-label, multicenter trial comparing vemurafenib with dacarbazine in previously untreated patients with BRAFV600E-mutated melanoma

Dr Paul Chapman of the Memorial Sloan-Kettering Cancer Center, New York, USA reported the results of an updated overall survival analysis with approximately 10 months median follow-up of the BRIM-3, a phase III randomized, open-label, multicenter trial comparing BRAF inhibitor vemurafenib with dacarbazine (abstract 8002).

A total of 675 patients with previously untreated, unresectable stage IIIC or IV melanoma, tested

positive for BRAFV600E mutation, were randomized (1:1) to vemurafenib or dacarbazine. Co-primary endpoints were overall survival and progression-free survival. Overall survival data for dacarbazine patients who crossed over to vemurafenib were censored at the time of crossover.

Median lengths of follow-up on vemurafenib and dacarbazine were 10.5 months (range 0.4 -18.1) and 8.4 months (range 0.1-18.3), respectively. There were 334 deaths. Median overall survival rates with vemurafenib and dacarbazine were 13.2 months and 9.6 months, respectively. Twelve-month overall survival rates were 55% for vemurafenib and 43% for dacarbazine. Hazard ratio for death was 0.62 in favor of vemurafenib. Eighty-one dacarbazine patients crossed over to vemurafenib; 44 (13%) patients treated by vemurafenib and 65 (19%) by dacarbazine received ipilimumab after progression.

Practice point and future research opportunities

With longer follow-up, vemurafenib treatment continues to be associated with improved overall survival in the BRIM-3 study.

Analysis of molecular mechanisms of response and resistance to vemurafenib in BRAFV600E melanoma

Vemurafenib induces frequent clinical responses and improved survival in patients with BRAF-mutated metastatic melanoma. Multiple mechanisms of escape from vemurafenib have been proposed. A group of researchers led by Dr Jeffrey Sosman of the Vanderbilt-Ingram Cancer Center, Nashville, USA performed a centralized analysis of pretreatment, cycle 1, day 15, and progression tumor samples collected during the phase II BRIM-2 trial (abstract 8503).

Of 132 patients enrolled, archival tumor samples were analyzed by immunohistochemistry for signaling molecules in the MAPK, PI3K/AKT, and cell cycle pathways. Genetic analyses of signaling genes and direct DNA sequencing were performed.

High levels of ERK phosphorylation were seen at baseline indicating constitutive MAPK signaling due to the BRAF mutation. In 19 out of 22 paired samples, pERK levels were reduced following vemurafenib. Mean absolute pERK reduction in patients with clinical response according RECIST criteria to vemurafenib was significantly greater than in non-responders. Baseline cytoplasmic PTEN H-score was higher in responders vs. non-responders. At progression, upregulation of pERK was frequently, but not uniformly found vs. day 15 tumors. At progression, increases in Cyclin D1 and Ki67 were seen, without obvious changes in PTEN or pAKT. NRAS mutations occurred in 3 out of 13 samples taken at progression; 2 had paired baseline samples without NRAS mutations. Only 1 out of 82 patients had a concomitant NRAS and BRAF mutation at baseline, and did not respond to

vemurafenib. MAP2K1 (MEK1) codon 124 mutations occurred in 7 out of 92 baseline and 1 out of 20 samples at progression. Two patients with baseline MEK1 mutations had partial responses.

Practice point and future research opportunities

MAPK signaling was effectively inhibited by vemurafenib early in the treatment, and in the subset of patients with matched tumor samples the degree of pathway inhibition correlated with clinical response. MAPK signaling is upregulated in many lesions at progression. NRAS mutations appear to be a mechanism of acquired resistance in a few tumors, while the role of MEK1 mutations in resistance is less clear.

Updated safety and efficacy results from a phase I/II study of dabrafenib combined with the oral MEK 1/2 inhibitor trametinib in patients with BRAFi-naive metastatic melanoma

In preclinical models, the BRAFi/MEKi combination has demonstrated enhanced activity against BRAF-mutant cancer cells compared with either drug alone, delayed emergence of BRAFi resistance, and prevented BRAFi-related proliferative skin lesions. A 3-part study investigating the dabrafenib/trametinib combination was conducted in patients with V600 BRAF mutant solid tumors. Interim data from the study were previously reported, and updated safety and efficacy data were presented by Dr Jeffrey Weber of the Comprehensive Melanoma Research Center, Lee Moffitt Cancer Center, Tampa, USA (abstract 8510).

In Part 2, 125 patients with V600 BRAF mutant solid tumors were enrolled, including 77 melanoma patients with no prior BRAFi, and measurable disease according to RECIST 1.1 criteria. Patients were treated on 4 escalating dose levels of dabrafenib/trametinib. Among 77 melanoma patients, median age was 52 years, 61% male, 57% ECOG performance status 0, 91% V600E, 65% M1c stage, 26% prior brain metastases, and 52% LDH at upper normal limit. Confirmed objective response rate was 56%. Median progression-free survival in months for each dose level, respectively, was: 8.7, 8.3, 5.5; and not mature. Overall progression-free survival was 7.4 months. Among the 125 patients, there were 2 grade 5 adverse events, pneumonia and hyponatraemia. The most common grade 3/4 adverse vents were pyrexia (5%), fatigue (5%) and dehydration (5%). Skin toxicity grade 2 occurred in 17 (14%) patients. Cutaneous squamous cell carcinoma occurred in 3 (2%) patients and actinic keratoses in 2 (2%).

Practice point and future research opportunities

The combination of dabrafenib/trametinib has an acceptable safety profile, with a lower incidence of MEKi-related rash and BRAFi-induced hyperproliferative skin lesions compared with the single

agents. The clinical activity of dabrafenib/trametinib observed in patients with V600 BRAF mutant metastatic melanoma is encouraging and will be investigated further in a phase III trial.

Efficacy and safety of oral MEK162 in patients with locally advanced and unresectable or metastatic cutaneous melanoma harboring BRAFV600 or NRAS mutations

BRAF and NRAS mutations occur in 50-60% and 15-20% of cutaneous melanomas, respectively. MEK162, a selective inhibitor of the kinases MEK1 and MEK2, has shown pre-clinical activity in BRAF and NRAS mutant (mt) melanoma models. This open label, phase II study assessed the antitumor activity of MEK162 in patients with BRAFV600 and NRAS mt advanced cutaneous melanoma. MEK162 was administered until unacceptable toxicity, disease progression or investigator or patient refusal. Tumor response was assessed by computed tomography imaging every 8 weeks according RECIST 1.0 criteria, until disease progression. The results were presented by Dr Paolo Ascierto of the Unit of Medical Oncology and Innovative Therapy, Istituto Nazionale Tumori Fondazione Pascale, Napoli, Italy (abstract 8511).

The full analysis and safety populations comprised 66 patients: 42 BRAF mt and 24 NRA*S* mt. Median age was 58.0 years; 57.6% male; 72.7% WHO performance status 0. All NRAS patients and all but 2 BRAF (1 each stage IIIB and IIIC) patients had stage IV disease, and 87.5% of NRAS patients and 66.7% of BRAF patients had received prior therapy at study entry. Median time from first diagnosis to first dose of drug was 40.4 months. Median time on study was 10.4 and 8.5 weeks for the *BRAF* and NRAS arms. Among 29 BRAF mt and 13 NRAS mt patients evaluable for efficacy, 1 confirmed and 6 unconfirmed partial responses and 9 patients with stable disease were recorded in the BRAF arm, and 2 confirmed partial responses, 1 unconfirmed partial response and 4 patients with stable disease were recorded in the NRAS arm. Common treatment-related adverse events, all grades and all patients, were rash (40.9%), diarrhea (33.3%), acneiform dermatitis (27.3%), creatine phosphokinase elevation (25.8%), fatigue (18.2%) and peripheral edema (21.2%). Central serous retinopathy-like retinal events (grade 1/2 only) were reported in 8 (12.1%) patients (6 grade 1, 2 grade 2). All retinal events were reversible. Grade 3/4 adverse events in >1 patient were diarrhea (4.5%) and creatine kinase elevation (15.2%). Five patients discontinued treatment due to toxicity, and 34 patients are ongoing with more responses under current review.

Practice point and future research opportunities

MEK162 showed clinical activity and good tolerability in patients with BRAF and NRAS mt advanced melanoma. This is the first targeted therapy to show activity in patients with NRAS mt melanoma.

BRAF-wt mutation accounts for nearly 60% of melanoma molecular profiles, one-third of which

includes patients with NRAS-mutation melanoma. This is a large group with no driver mutation identified. These undefined driver mutations potentially can be targeted by the right drug or by immunotherapy. Efforts are underway to investigate approaches to NRAS-mutant melanoma, including identification of potential therapeutic targets downstream of NRAS, and understanding the role of MEK inhibitors alone or in combination with inhibitors of the PI3K/AKT and mTOR pathway, or with immunotherapy. The definition of other driver kinases within the BRAF-wt population can allow for the development of personalized treatment options for this patient population.

PATIENT AND SURVIVOR CARE

A phase III double blind trial of duloxetine to treat painful chemotherapy-induced peripheral neuropathy

CALGB 170601 is a randomized, placebo-controlled phase III trial to determine whether duloxetine reduces painful chemotherapy-induced peripheral neuropathy. The secondary study endpoint was treatment-related adverse events. The study used a double-blinded placebo-controlled crossover design with equally weighted randomization to one of two arms. Arm A participants received duloxetine followed by placebo. Arm B participants received placebo followed by duloxetine. The initial and crossover periods each consisted of six weeks of drug/placebo followed by one week of washout.

Randomization was stratified by neurotoxic agent and high risk for developing painful chemotherapy-induced peripheral neuropathy. Eligible patients were 18 years or older with an average chemotherapy-induced peripheral neuropathy pain score > 4/10 attributed to prior single agent taxane or platinum treatment. Participants took one capsule daily (30mg) for one week, and then two capsules (60mg) daily for four additional weeks. Participants completed the Brief Pain Inventory-Short Form (BPI-SF) at baseline and then weekly. The primary study endpoint was the change in BPI-SF scores within the initial treatment period. Analysis of covariance with an intent-to-treat approach was used to test the effect of treatment on change in pain score. The study results were presented by Ellen Lavoie Smith, PhD of the University of Michigan, Ann Arbor, USA (abstract CRA9013).

The target accrual goal of 231 patients was met, and 185 (80%) completed the initial treatment period. Oxaliplatin was the most commonly received neurotoxic agent (59%). Individuals receiving duloxetine over the initial treatment period had a larger average decrease in pain score than those receiving placebo (p=0.004). There was no difference in duloxetine efficacy based on the specific neurotoxic agent received. Severe, grade 3, non-hematologic toxicity was reported by 11%, and 41% reported moderate (grade 2) toxicities. The incidence of grade 2+ fatigue, the most commonly reported side effect, was significantly higher in the duloxetine arm as compared to placebo (p=0.029).

Practice point and future research opportunities

The problem of treatment-induced neuropathy is common with taxanes and platinum-based chemotherapy drugs and can be debilitating. Duloxetine is an efficacious and well-tolerated intervention for the treatment of painful chemotherapy-induced peripheral neuropathy. The next step for researchers will be to figure out predictors of response. Duloxetine is the first drug to show activity against chemotherapy-induced peripheral neuropathy in the context of clinical trial.

SARCOMA

Regorafenib improves progression-free survival and disease-control rate in patients with advanced GIST after failure to prior therapy with at least imatinib and sunitinib

Oral multikinase inhibitor regorafenib demonstrated substantial activity in a previous phase II trial in patients with gastrointestinal stromal tumor (GIST) after failure of both imatinib and sunitinib. The GRID phase III, randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of regorafenib in this population with unmet clinical need. The results were presented by Dr George Demetri of the Dana-Farber Cancer Institute, Boston, USA (abstract LBA10008).

Eligible patients had metastatic and/or unresectable GIST, objective failure to prior therapy with imatinib and sunitinib (progressive disease on, or intolerance to imatinib, and progressive disease on sunitinib), 1 measurable lesion, ECOG performance status 0 or 1. Patients were randomized 2:1 to receive best supportive care plus either regorafenib or placebo. The primary endpoint was progression-free survival measured according to modified RECIST 1.1 criteria by independent central review. Secondary endpoints included overall survival, disease-control rate (defined as rate of partial response plus stable disease lasting for 12 weeks), response rate and duration, safety and correlative genotype analyses. At time of progressive disease, patients were eligible for unblinding and crossover to open-label regorafenib.

In only 8 months, 234 patients were screened, and 199 were randomized (133 in regorafenib arm and 66 to placebo). Patients were stratified at randomization according to number of prior systemic therapies and geographical region. Baseline characteristics were balanced between the two arms.

The primary endpoint was met: median progression-free survival was 4.8 months for regorafenib vs. 0.9 months for placebo. Hazard ratio for progression-free survival was 0.27, $p<0.0001$. Progression-free survival rates at 3 and 6 months were 60% and 38% for regorafenib vs. 11% and 0% for placebo. Disease-control rate was 53% with regorafenib vs. 9% with placebo. The hazard ratio for overall survival was 0.77 with 85% patients in placebo arm having crossed over to regorafenib.

The most common treatment-emergent adverse events (> grade 3) in the regorafenib arm during double-blind study were hypertension (28%), hand-foot skin reaction (21%), and diarrhea (8%).

Practice point and future research opportunities

The randomized phase III, GRID trial demonstrated that regorafenib significantly improves progression-free survival and disease-control rate in patients with advanced GIST after failure of prior therapy with at least imatinib and sunitinib. Regorafenib was well tolerated, with adverse effects as expected for this class of agents and manageable with dose modifications. These improvements are clinically meaningful in the patient population with unmet clinical needs.

TUMOR BIOLOGY

Circulating DNA analysis and concordance with tumor section analysis in the detection of KRAS and BRAF point mutations from metastatic colorectal cancer

A group of researchers led by Dr Alain Thierry of the Sysdiag UMR3145-CNRS unit in Montpellier, France developed a specific method for circulating cell-free DNA (ctDNA) enabling detection of point mutations. CtDNA exists at high level in patients with different types of cancer, and presents great potential regarding, in particular, its low invasiveness, rapid data turnaround and cost effectiveness. The researchers described the first blinded prospective study on the comparison of KRAS and BRAF mutational status data obtained from the analysis of ctDNA and tumor section (abstract 10505).

The researchers used a refined Q-PCR-based method, specifically designed to analyze ctDNA. It allows not only the detection of point mutations, but also the determination of tumor-ctDNA concentration and fragmentation index simultaneously. Its sensitivity is 0.01% (mutant to wild type ratio) and is unprecedented among Q-PCR-based methods. The study was conducted from a multicenter cohort of 79 metastatic patients with colorectal cancer, who did not receive chemo- or radiotherapy within the month prior to blood sample collection.

Mutational status could not be determined in 9 samples with one of the two methods. CtDNA analysis showed 100% specificity and 87% sensitivity for KRAS detection (only three samples are misclassified) as compared to tumor section analysis with 23 out of 70 (33%) positive samples, the concordance value was 96%. For BRAF mutation, the method exhibited a specificity and a sensibility of 100% with 5 out of 70 (7%) positive samples (concordance of 100%). When combining KRAS and BRAF mutations, 100% specificity, 89% sensibility and 98% concordance were determined. The three discordant samples may be explained by the malignant genotype of primary tumor versus metastasis, or by the sensitivity of the detection method. The mutation load (median 12.4%) expressed as the

proportion of mutant allele in ctDNA was highly variable (0.037% to 69%) among mutated samples showing a very high inter-individual heterogeneity.

Practice point and future research opportunities

This blinded prospective multicenter study showed for the first time that tumor section analysis might be advantageously replaced by circulating DNA analysis, enlarging personalized medicine power for cancer patients.

AFFILIATIONS AND DISCLOSURE

Dr Svetlana Jezdic, Medical Oncologist, ESMO Head Office, Lugano, Switzerland.

The author has declared that she has no conflicts of interest to report.