

47th ASCO Annual Meeting

3-7 June, 2011

Chicago, USA

INTRODUCTION

The theme of the 2011 ASCO Annual Meeting: "Patients. Pathways. Progress" reflected compassion for patients and the focus on pathways representing the bench-to-bedside transition of research that has led to progress in oncology.

As a leading player in the field of oncology, ESMO had a strong presence at the 47th ASCO Annual Meeting with a dedicated booth to serve members and promote membership benefits. A major attraction at the ESMO booth was the demo of the unique ESMO educational and scientific web portal OncologyPRO which will be launched in July 2011. Equipped with an exclusive content offering, OncologyPRO promises to be a major membership benefit, responding to the needs of oncologists with access to a world literature service of over 100 journals; databases on clinical trials, biomarkers, and emerging drugs and biologics; targetsapes; oncology monographs; scientific meeting reports; slide resources; E-learning and E-books; clinical practice guidelines; abstracts, posters and webcasts; professional networking opportunities; patient information summaries; and Thomson Reuters world-renowned news and video services.



ESMO also celebrated the recognition of medical oncology as an independent medical specialty in Europe this year, after working towards this goal since its founding in 1975. The ESMO/ASCO Global Curriculum for Training in Medical Oncology supported that recognition and was considered by the European Commission when determining the length of training required for medical oncologists across the continent. Copies of the second edition of the curriculum were distributed in Chicago from the ESMO Booth and the ASCO International Desk. Meeting attendees were encouraged to promote adoption of the curriculum recommendations in the training system in their countries.

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

A special ASCO-ESMO Joint Session addressed the growing burden of cancer in low- and middle-income countries (LMICs). ESMO joined forces with ASCO to address the urgent needs associated with the rising cancer epidemic in these countries, where more than one-third of cancer-related deaths are preventable. In the developing world, African countries will be the hardest hit and the least able to cope because most Africans reside in rural areas with no, or very little, access to cancer screening, early diagnosis, treatment, or palliative care. The entire panel of speakers noted that the international community must take action together, combining their skills and resources to educate

and speak out on behalf of cancer patients in countries with limited resources.

Dr Peter Boyle of the International Prevention Research Institute, France, provided global cancer facts and illustrations, predicting that by 2030 there will be 26.4 million new cancer cases, 17.1 million cancer deaths, and 80 million people living with cancer. Dr Boyle indicated several obstacles in low-income countries, including a lack of trained staff, affordable cancer treatment, radiotherapy facilities, and even the most basic palliative care.

Logistical constraints and lack of trained cytopathologists, make PAP smear tests unfeasible. As a consequence, 90% of all deaths from cervical cancer occur in low and middle income countries.. Fortunately there are alternative screening tests that trained health-care workers can use, such as visualization and inspection with acetic acid, and human papilloma virus (HPV) (Fig. 1) DNA-detection methodology, developed specifically for low-resource countries. In addition, a simple inexpensive treatment with cryotherapy could result in better cure rates. Dr Jan M Agosti of the Bill & Melinda Gates Foundation discussed access to HPV vaccines. The importance of cervical cancer prevention through vaccination against HPV strains 16 and 18 was specifically highlighted because these two strains comprise 70% of all the strains associated with cervical cancer in developing countries. The cost-effectiveness of vaccination is related to vaccine cost as well as program costs to reach adolescents. The Global Alliance for Vaccination and Immunization Alliance is a partnership between several entities hoping to grant access in 2011 to HPV vaccines at tiered prices to eligible countries among the 73 lowest income countries.

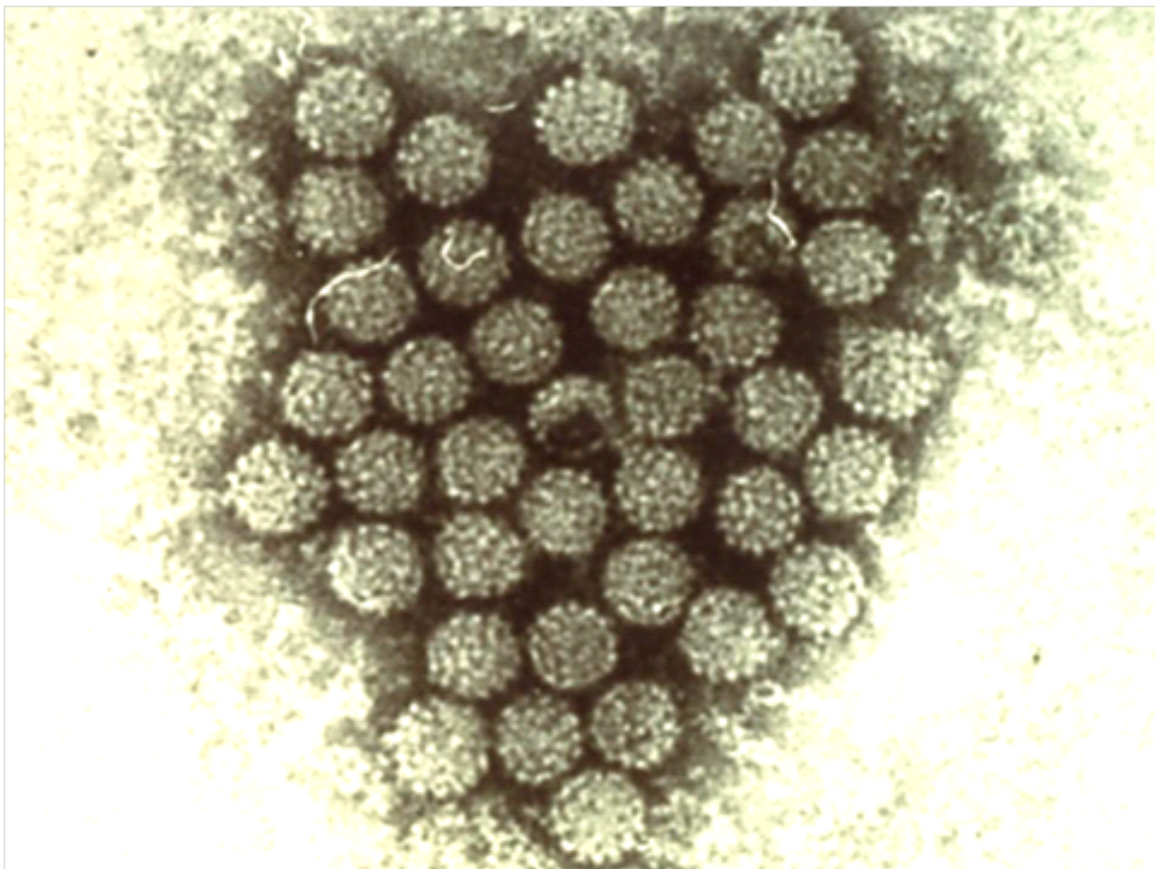


Fig. 1 Human papilloma virus (Courtesy of Prof. Harald zur Hausen, Laureate of the Nobel Prize in Physiology or Medicine "for his discovery of human papilloma viruses causing cervical cancer")

Dr Henry Lik-Yuen Chan of the Chinese University of Hong Kong provided insights into the prevention and control of hepatocellular carcinoma (HCC) in low- and middle-income countries. Dr Chan stressed that preventing infection of hepatitis B in Asia-Pacific countries was essential for preventing HCC. Since HCC can manifest approximately 40 to 50 years from the time of infection, the introduction of vaccination to new-born infants should decrease the incidence of HCC by 2040. Another important factor in reducing HCC onset is treating patients with hepatitis B effectively with immunotherapy and antiviral agents. According to Dr Chan, eradication of hepatitis C with pegylated interferon and ribavirin in Japan can be linked to a decrease in the incidence of HCC. In conclusion, he highlighted the challenges of HCC screening, which are associated with late diagnosis and elevated costs.

Prof. David Kerr, ESMO President, and Dr. George Sledge, ASCO President, co-chaired the session and urged the global oncology community to reaffirm its commitment to tackle cancer and to stand side-by-side in supporting the UICC World Cancer Declaration and the historical United Nations Summit on Non-Communicable Diseases taking place on 19-20 September 2011 in New York. A concise and action-oriented UN Summit Outcomes Statement, holding governments accountable for achieving global strategies, could turn the tide of cancer and provide the much-needed resources for chronic diseases that together account for 60% (35 million) of deaths worldwide. With 80% of these deaths occurring in LMICs, NCDs represent a major cause of poverty and a development issue that urgently needs our united support.

Coverage of all scientific and clinical novelties and updates presented during the 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.

THREE YEARS OF ADJUVANT IMATINIB MAY REPLACE THE STANDARD 12-MONTH TREATMENT IN HIGH-RISK PATIENTS WITH GIST

Results of the final analysis of the SSGXVIII/AIO study were presented by Dr Heikki Joensuu of the Helsinki University Central Hospital, Finland. In this open-label, multicenter, randomized phase III study, 400 patients with KIT-positive gastrointestinal stromal tumors (GIST) received imatinib at a daily dose of 400 mg for 12 months (200 patients) or 36 months (200 patients) following surgery. Recurrence-free survival was the primary endpoint of the study.

Although patients with operable, metastatic GIST were initially enrolled in the study, the protocol was later amended to exclude patients with advanced disease based on an observation in a different study, which showed that patients with advanced GIST experienced disease recurrence following cessation of active treatment.

After 54 months of follow-up, data in the intention-to-treat population indicated that patients who received imatinib for 36 months were 54% less likely to experience recurrence ($p < 0.0001$) compared with patients who received imatinib for 12 months.

Sub-group analyses indicated that a recurrence-free survival advantage was seen in patients on extended therapy regardless of age, sex, tumor site, tumor size, or tumor rupture. In addition, for patients receiving extended treatment with imatinib for 36 months there was a 55% reduction in mortality ($p = 0.019$). Ninety-two percent of those who received imatinib for 36 months were alive at 5 year follow-up, compared with 81.7% of those who received the drug for 12 months.

The study discussant, Dr Charles D Blanke of the University of British Columbia and the British Columbia Cancer Agency discussed these data, and concluded that three-year therapy with imatinib is a new standard in adjuvant treatment. Data from this study along with data from other trials might suggest that even longer treatment would be better. In this regard, PERSIST5 is a phase II study that will provide guidance for continuous treatment with imatinib for 5 years.

Dr Blanke's discussion addressed the question of which patients may derive the greatest clinical benefit from extended treatment with imatinib. Dr Joensuu reported that patients included in the study were at high risk for relapse, based on a 2002 classification scheme. Dr Blanke suggested that based on current definitions, the risk of recurrence for patients in this study was probably between 34% and 100%. Within different risk categories, higher- and lower-risk patients obtained the same benefits of longer-term therapy.

In this study, 36% of patients in the 3-year arm discontinued therapy early. Although 7% discontinued therapy due to disease recurrence, most discontinuations were associated with adverse events, or other reasons. Dr Blanke remarked that, in the light of high discontinuation rate, it is quite remarkable that the study still provided improved clinical outcomes for high-risk patients with GIST.

Practice point and future research opportunities

Extended treatment with imatinib for 3 years after surgery improves recurrence-free survival and overall survival in high-risk patients with GIST comparing to standard 12-month therapy with adjuvant imatinib. The rationale for changing the current practice is that the overall survival advantage demonstrated in this study cannot be obtained by treatment introduced later in the advanced disease

stage. This raises another question: whether patients would be compliant with extended therapy in the postoperative setting. In this study, 36% of patients in the 3-year arm discontinued therapy early and most discontinuations were associated with adverse events, or other reasons. In the long-term treatment setting, any low-grade adverse events may not be tolerable in the absence of visible disease.

VEMURAFENIB IMPROVED OUTCOMES IN BRAF-MUTATED MELANOMA

Dr Paul B Chapman of the Memorial Sloan-Kettering Cancer Center presented a planned interim analysis of the phase III BRAF Inhibitor in Melanoma (BRIM3) trial. The treatment with vemurafenib was associated with a 63% decrease in the risk of death ($p < 0.0001$) and a 74% decrease in the risk of tumor progression ($p < 0.0001$) in patients with the BRAFV600E mutation, which is present in 40% to 60% of melanomas.

A benefit of vemurafenib was seen in all subgroups in the trial, including patients with metastatic disease (stage M1c) and high levels of lactate dehydrogenase, conditions that are usually associated with poor prognosis. Vemurafenib had a manageable safety profile and there were few drug-related discontinuations from the trial.

Patients with previously untreated, unresectable stage IIIC or IV melanoma who tested positive for the BRAFV600E mutation were randomly assigned to 60 mg of twice-daily oral vemurafenib or to standard chemotherapy with dacarbazine for 3 weeks. Of the patients screened, 47% were mutation positive.

Dr Chapman explained that, during the trial enrollment period in 2010, emerging data from a phase II study made it clear that the phase III trial design, as originally conceived, had underestimated the treatment effect of vemurafenib.

A revised statistical plan was established in October 2010 before any data in the trial were analyzed. When the study's independent Data and Safety Monitoring Board (DSMB) reviewed the data in January 2011, it determined that there was compelling evidence of vemurafenib's treatment benefit over dacarbazine.

The DSMB recommended that patients in the chemotherapy arm should be allowed to cross over to treatment with vemurafenib and this change was quickly implemented.

The revised statistical plan included two primary endpoints: overall survival, with a lower number of required events than originally planned (196, reduced from 468), and progression-free survival. The revised plan called for one interim analysis at 50% of the number of deaths needed for final analysis,

and the presented data are from this analysis.

Of the 675 patients enrolled at 104 centers worldwide, 337 received vemurafenib and 338 received dacarbazine. At the planned interim analysis, the hazard ratio for overall survival was 0.37 ($p < 0.0001$) and the hazard ratio for progression-free survival was 0.26 ($p < 0.0001$), both in favor of vemurafenib (Fig. 2).

Estimated 6-month survival was 84% for vemurafenib and 64% for dacarbazine. In the 65% of patients who were evaluable, the overall response rate was 48.4% for vemurafenib and 5.5% for dacarbazine.

The most frequent adverse events in patients receiving vemurafenib included arthralgia, rash, and diarrhea. Cutaneous squamous cell carcinomas and other cutaneous tumors, which are associated with vemurafenib and other drugs in its class, were seen in the patients receiving the drug and all of them were excised by dermatologists. None of the lesions were associated with metastases.

During a discussion of the study, Dr Kim Margolin of the University of Washington and the Fred Hutchinson Cancer Research Center said that the study was based on a molecular biology analysis and rational drug development, and showed a strong survival benefit of vemurafenib over dacarbazine in patients with melanoma whose tumor had the BRAFV600E mutation.

The drug is already being made available through an expanded access program to patients with qualifying BRAF mutations, and it is anticipated that it may be approved by the USA Food and Drug Administration later this year.

According to Dr Margolin, the drug's rapid relief for symptomatic patients is spectacular and something that melanoma specialists were not able to offer previously. She noted that the median progression-free duration in the study was 7 months, and that the nature of relapse from this form of targeted therapy is still being investigated.

Practice point and future research opportunities

In patients with previously untreated melanoma with a mutation in the BRAF gene, vemurafenib is associated with improvements in overall survival and progression-free survival when compared with dacarbazine. A benefit of vemurafenib was seen in all subgroups in the trial, including patients with metastatic disease (stage M1c) and high levels of lactate dehydrogenase, conditions that are usually associated with poor prognosis. Vemurafenib is a promising new therapy for patients with metastatic BRAFV600E-mutated melanoma and a foundation upon which to build combination therapies in the future.

induction therapy went on to receive ipilimumab or placebo every 12 weeks as maintenance therapy.

Exposure to study therapy differed markedly between the two arms. Whereas 66% of patients assigned to placebo/dacarbazine received the first four doses of induction therapy, only 37.2% of patients assigned to ipilimumab/dacarbazine did so. Small proportions of patients in each arm received maintenance therapy (17.4% in the ipilimumab/dacarbazine arm and 21.1% in the placebo/dacarbazine arm), thus precluding the ability to draw conclusions regarding the effect of such treatment.

Despite the difference in exposure to induction therapy, ipilimumab/dacarbazine significantly prolonged overall survival - the primary study endpoint - by 2.1 months compared with dacarbazine alone (11.2 vs. 9.1 months, $p < 0.0009$; Fig. 3).

Other key endpoints mirrored this benefit: ipilimumab/dacarbazine prolonged progression-free survival compared with placebo/dacarbazine (2.8 vs. 2.6 months, respectively; $p < 0.006$), and responses appeared to be much more durable for ipilimumab/dacarbazine compared with those for placebo/dacarbazine (median of 19.3 vs. 8.1 months). No appreciable differences in the disease control rate (33.2% vs. 30.2%) and the best overall response rate (15.2% vs. 10.3%) were observed between the two respective arms.

The combination of ipilimumab and dacarbazine resulted in a higher incidence of grade 3/4 adverse events compared with the control arm (56.3% vs. 27.5%). Ipilimumab-associated adverse events were consistent with previous studies and predominantly affected the liver, endocrine system, gastrointestinal tract, and skin.

The most notable differences in grade 3/4 adverse events between the ipilimumab/dacarbazine and placebo/dacarbazine arms involved alanine aminotransferase increases (21.9% vs. 0.8%), aspartate aminotransferase increases (18.2% vs. 1.2%), and diarrhea (4.0% vs. 0%). No cases of gastrointestinal perforation or hypophysitis were observed in association with ipilimumab.

According to Dr Kim Margolin of the University of Washington and the Fred Hutchinson Cancer Research Center who discussed results from this study, it would not be advisable to include dacarbazine in the standard clinical use of ipilimumab because of the increased hepatotoxicity of such a combination, and the strong sense that there was no therapeutic advantage from adding the cytotoxic agent. It is further needed to determine whether specific patient subsets have a better response to ipilimumab. It was notable that a difference in the progression-free survival, although statistically significant, is not clinically meaningful. However, responses appeared to be much more durable for ipilimumab/dacarbazine compared with those for placebo/dacarbazine. Dr Wolchok noted that further development of ipilimumab is ongoing in both metastatic disease and the adjuvant setting,

both alone and in combination with alternative agents.

Practice point and future research opportunities

Results of this phase III trial confirm the overall survival benefit conferred by ipilimumab in frontline treatment of metastatic melanoma in combination with dacarbazine. These findings may soon change the treatment landscape for metastatic melanoma by establishing ipilimumab-based therapy as a first-line regimen of choice over dacarbazine, which is currently considered as the standard of care. It is further needed to determine whether specific patient subsets have a better response to ipilimumab.

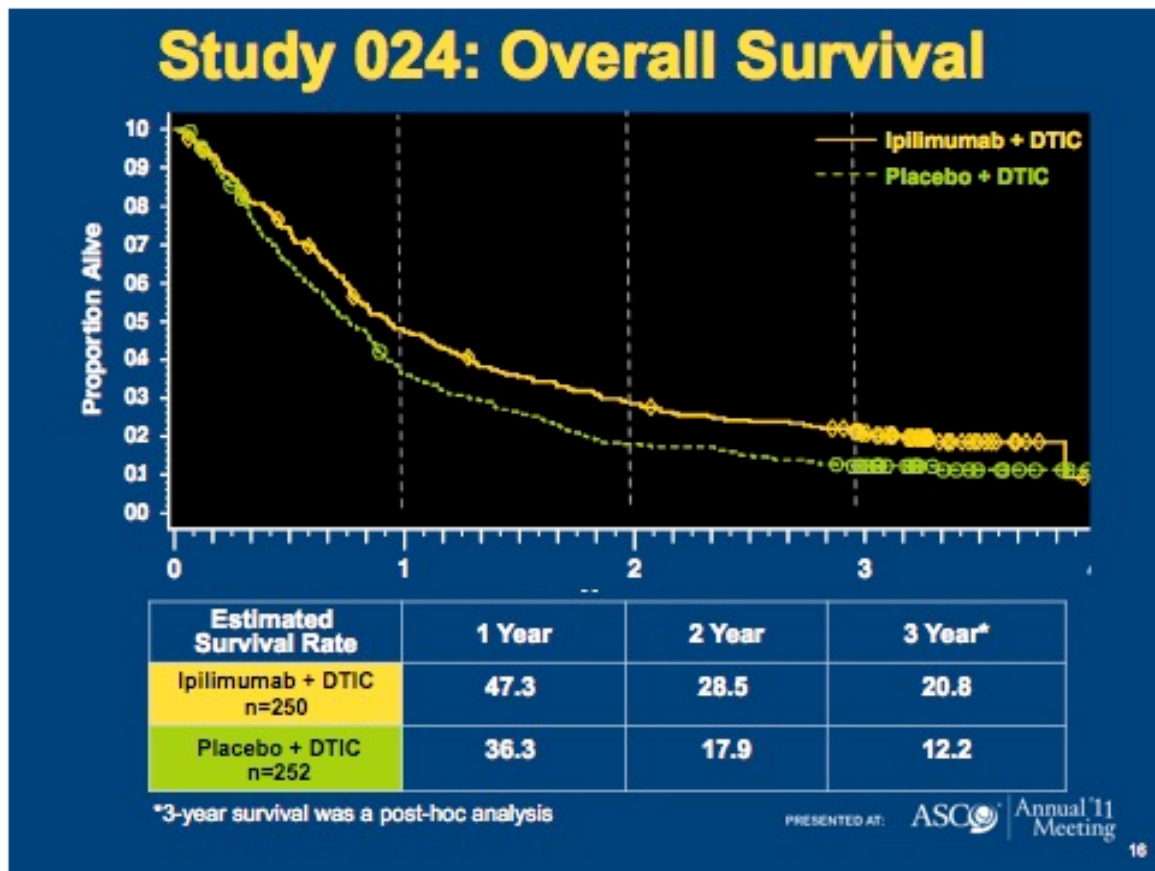


Fig. 3 Kaplan- Meier curves of overall survival show advantage of ipilimumab-dacarbazine combination (Courtesy of Dr Jedd D Wolchok)

CABOZANTINIB SHOWS ACTIVITY IN PATIENTS WITH CASTRATION-RESISTANT PROSTATE CANCER

Cabozantinib (XL184) is a tyrosine kinase inhibitor (TKI) with multiple activities. It blocks MET and vascular endothelial growth factor receptor (VEGFR). MET is implicated in tumor invasion and metastases, and the synergistic effects of MET and VEGFR promote tumor angiogenesis.

Dr Maha Hussain of the University of Michigan Comprehensive Cancer Center presented the interim data from the phase II randomized discontinuation study in patients with metastatic castration-resistant prostate cancer (mCRPC). After a 12-week lead-in period when all patients were treated with 100 mg of once-daily oral cabozantinib, the further treatment protocol was based on the week-12 tumor staging.

Patients with partial or complete response continued on open-label cabozantinib. Patients with stable disease were randomly assigned in a blinded manner to receive cabozantinib, or placebo. Patients with progressive disease discontinued cabozantinib. Although the study enrolled patients with multiple solid tumors, data were provided only for the cohort of patients with mCRPC.

After 171 patients were enrolled in the study, randomization was suspended after 122 patients receiving cabozantinib showed clinical benefits. Of the 171 patients with mCRPC, lymph node, visceral, and bone metastases were seen in 87%, 37%, and 87% of patients, respectively. At baseline, 54% of patients had bone pain and 42% of patients were using narcotics for pain relief. Forty-three percent of patients had previously been treated with docetaxel.

At 12 weeks, disease-control rate, defined as partial response, or stable disease, was seen in 68% of patients. For the 31 patients randomly assigned to either the placebo group (17 patients) or the cabozantinib group (14 patients), median progression-free survival was significantly longer for patients on cabozantinib (21 weeks vs. 6 weeks for placebo; $p = 0.0007$).

Patients receiving cabozantinib were 87% less likely to experience tumor progression ($p = 0.0007$).

The most dramatic observations of cabozantinib were its effects on soft-tissue lesions and bone metastases. Seventy-four percent of patients showed evidence of measurable regression of soft-tissue lesions. Of 108 patients with evaluable bone scans, 21 patients (19%) showed complete resolution and 61 patients (56%) showed partial resolution of bone metastases. Only three patients (3%) showed progression of bone metastases.

Improvement in pain from baseline was seen in 56 patients (67%), and 31 patients (56%) decreased or discontinued narcotics for pain. Resolution of bone lesions was associated with corresponding decreases in levels of alkaline phosphatase and type I collagen C-telopeptides, which define osteoblast and osteoclast activities.

Because docetaxel is the principal chemotherapy recommended for patients with mCRPC, progression-free survival was determined for the subsets of patients based on docetaxel pretreatment. Ninety docetaxel-naive patients and 64 patients previously treated with docetaxel

experienced progression-free survival of 29 weeks and 24 weeks, respectively.

Adverse events were moderate and manageable in most patients receiving cabozantinib and were similar to those seen in patients receiving TKIs. Grade 3 fatigue, palmar-plantar erythrodysesthesia syndrome, and hypertension were seen in 16%, 6%, and 6% of patients, respectively.

Practice point and future research opportunities

Based on interim data from a phase II study, cabozantinib shows unprecedented changes in bone scan and dramatic effects on bone pain in a cohort of patients with metastatic castration-resistant prostate cancer. It reduces measurable soft-tissue lesions; shows complete or partial resolution, or stabilization of bone metastases; decreases bone pain, and reduces narcotic use. Future research on this drug will show whether these endpoints can be translated to prolonged survival.

ADJUVANT XELOX SHOWS PROMISE IN GASTRIC CANCER

Dr Yung-Jue Bang of the Seoul National University College of Medicine presented the findings of the randomized, open-label phase III CLASSIC study, conducted at multiple centers in South Korea, China, and Taiwan. Eligible patients had stage II, IIIA, or IIIB disease and were either chemotherapy or radiotherapy naive. Within 6 weeks of D2 gastrectomy 1,035 patients were randomly assigned to receive eight cycles of capecitabine plus oxaliplatin (XELOX) or undergo observation. The primary intent was to compare disease-free survival between the two arms at 3 years.

Based on a pre-planned interim analysis conducted in March 2011, the Independent Data Monitoring Committee recommended that the results should be fully evaluated and reported given the highly significant and clinically meaningful patient outcomes observed with XELOX. Dr Bang reported that the primary endpoint was met at the interim analysis, as 3-year disease-free survival was 74% in the XELOX arm compared with 60% in the observation arm, reflecting a 44% reduction in the risk for disease progression ($p < 0.0001$). Moreover, the significant disease-free survival benefit conferred by XELOX was observed for all disease stages.

Although longer follow up is needed to discern the possible effect of adjuvant XELOX on overall survival, a preliminary analysis conducted at a median follow up of 34.4 months showed a trend toward superiority with XELOX ($p = 0.0775$).

The safety of adjuvant XELOX in gastric cancer was consistent with the known safety profile of this regimen, with no new or unexpected findings. A total of 54% of patients assigned to chemotherapy experienced grade 3/4 adverse events, compared with 6% of patients assigned to observation. The most common grade 3/4 adverse events observed in association with XELOX included neutropenia

(22%), thrombocytopenia (8%), nausea (8%), and vomiting (7%).

A study discussant, Dr Florian Lordick of the Technische Universitaet Muenchen, Germany said that the benefits of adjuvant XELOX identified in Asian patients with gastric cancer may not be transferrable to the Western world. Furthermore, compelling results for adjuvant chemotherapy following radical D2 resection, which is the standard of care in Asia, were seen in this study but for centers that perform subradical resection, the addition of chemoradiation makes sense.

Practice point and future research opportunities

No universally accepted adjuvant regimen for gastric cancer currently exists despite the critical need for such therapy based on high recurrence rates following surgical resection. Capecitabine plus oxaliplatin (XELOX) may soon fill this role, at least in Asia, based on the positive findings of the phase III CLASSIC trial. This study represents one of the largest trials ever performed in the curative setting in gastric cancer and identified a substantial improvement in disease-free survival with adjuvant XELOX compared with observation alone following D2 resection. Longer follow up is needed to discern the possible effect of adjuvant XELOX on overall survival. Benefits of adjuvant XELOX identified in Asian patients with gastric cancer may not be transferrable to the Western population based on differences in patient age, tumor location, and resection aggressiveness.

A LONGER FOLLOW-UP IS NEEDED TO DETERMINE BENEFITS OF ADJUVANT OXALIPLATIN IN LOCALLY ADVANCED RECTAL CANCER

Dr Claus Rödel of the University of Frankfurt, Germany presented the first results of the German Rectal Cancer Study Group CAO/ARO/AIO-04 trial. The objective of the study was to determine if oxaliplatin added to adjuvant 5-fluorouracil (5-FU) based chemotherapy would increase 3-year disease-free survival by 7% in patients with locally advanced rectal cancer - an approach that has shown benefits in colon cancer.

The study enrolled 1,265 patients to receive preoperative chemoradiation (CRT), surgery, and adjuvant chemotherapy with 5-FU (624 patients; control) or preoperative CRT with 5-FU and oxaliplatin, surgery, and adjuvant chemotherapy with a modified FOLFOX6 regimen (613 patients).

In this study, 50 mg/m² of oxaliplatin was given on days 1, 8, 22, and 29 preoperatively together with radiation therapy (RT). The cumulative dose of oxaliplatin during preoperative treatment was lower than in similar trials (STAR-01, ACCORD 12/0405), which showed high toxicity and impaired compliance when oxaliplatin was included with preoperative CRT. In addition, there was a 1-week break in the third week of RT. This regimen was established by phase I/II testing prior to embarking

on a large phase III trial and was associated with lower toxicity. The regimen was completed as scheduled by the vast majority of patients.

A quality assurance program was included to determine the quality of total mesorectal excision which was high; complete resection was reported in 92% of patients in the control arm and 90% of patients in the oxaliplatin arm. A median of 15 and 14 lymph nodes were examined following preoperative CRT and surgery in patients in the control and oxaliplatin arms of the study, respectively. These data were indicative of good-quality pathology and surgery. Although not a predefined endpoint, pathologic complete response (pCR) was significantly higher in patients receiving oxaliplatin (16.5% vs. 12.8% for the 5-FU-only arm; $p = 0.045$).

The toxicity during preoperative CRT was similar across both arms of the study; compliance with preoperative treatment was high. Ninety-five percent and 94% of patients in the control and oxaliplatin arms, respectively, received the full dose of RT; 80% and 85% of patients in the control and oxaliplatin arms, respectively, received the full dose of preoperative chemotherapy.

Besides the European PETACC 6 trial, which is still accruing patients, this is the only phase III trial worldwide that has included oxaliplatin preoperatively and postoperatively for treating locally advanced rectal cancer.

In his discussion, Dr Robert Glynne-Jones of the Mount Vernon Centre for Cancer Treatment, UK said that the quality control was excellent for surgery and pathology and that the study sets the benchmark for future rectal cancer studies.

Practice point and future research opportunities

The addition of oxaliplatin to 5-FU before and after surgery for the treatment of locally advanced rectal cancer can be done with high compliance. A long-term follow-up is necessary to determine if the inclusion of oxaliplatin into combined modality treatment for rectal cancer translates to a significantly higher 3-year disease-free survival rate.

BEVACIZUMAB PROLONGS PROGRESSION-FREE SURVIVAL FOR WOMEN WITH PLATINUM-SENSITIVE RECURRENT OVARIAN CANCER

Dr. Carol Aghajanian of the Memorial Sloan-Kettering Cancer Center presented data from the OCEANS ovarian cancer study comparing efficacy and safety of chemotherapy and antiangiogenic therapy in platinum-sensitive recurrent ovarian cancer.

In this phase III, double-blind study of treatment for first relapse, six cycles of standard carboplatin

and gemcitabine were administered, with responders receiving up to 10 cycles. Bevacizumab or placebo was given every 3 weeks during chemotherapy and continued until disease progression or unacceptable toxicity. Women with primary peritoneal or Fallopian tube cancers were also eligible. Stratification variables were platinum-free interval (6 to 12 months vs. more than 12) and cytoreductive surgery for recurrent disease (yes vs. no).

Two hundred forty-two women were allocated to each arm of the study; median follow-up was 24 months. Patient characteristics were well-matched in the two treatment groups with regard to age (median age 60), race (91% white), performance status (75%, PS = 0), histologic subtype (80% serous), cytoreductive surgery (11%), and platinum-free interval more than 12 months (60%).

The median number of chemotherapy cycles was six for each group, and a median of 11 cycles of bevacizumab or placebo was given. At least one-third of the patients received more than six cycles of carboplatin and gemcitabine, although slightly more of the placebo-treated group continued chemotherapy beyond six cycles.

Progression-free survival was significantly longer for women given bevacizumab (12.4 months compared with 8.4 months in the placebo-treated group ($p < 0.0001$)). These results were corroborated by the analyses of an independent review committee. Analyses according to platinum-free interval, cytoreductive surgery, age, and baseline performance status indicate a consistent benefit in all subgroups.

Objective response rate increased by 21.1% ($p < 0.0001$), from 57.4% in the placebo group to 78.5% in the bevacizumab treated group; duration of response increased from a median of 7.4 months to 10.4 months, respectively ($p < 0.0001$). Overall survival data are still premature, with median survival of 29.9 months in the placebo group and 35.5 months in the treatment group.

Sixty-five percent of the patients in the placebo group were withdrawn from the protocol due to disease progression compared with only 41% of the treatment group, but 23% of the discontinuations in the bevacizumab group were due to adverse events, compared with only 5% in the placebo group. Much of this increase was due to grade 3 or worse hypertension and proteinuria associated with bevacizumab therapy; the safety profile of bevacizumab was consistent with other trials.

In his discussion of the study, Dr Anil K Sood of the University of Texas MD Anderson Cancer Center suggested that further elucidation of the timing and dosing of bevacizumab should be pursued in light of its great cost and reports that inhibition of angiogenesis in animal models reduces primary tumor growth, but accelerates invasion and metastasis - unintended consequences that might be linked to the failure of bevacizumab to extend overall survival in most clinical trials.

Practice point and future research opportunities

Inhibiting angiogenesis demonstrates a statistically significant and clinically relevant benefit when bevacizumab is added to carboplatin and gemcitabine but before this regimen could be considered as a new option for treatment of recurrent, platinum-sensitive ovarian cancer, further elucidation of the timing and dosing of bevacizumab is needed.

OLAPARIB SHOWS PROMISE AS MAINTENANCE THERAPY IN RELAPSED SEROUS OVARIAN CANCER

Dr. Jonathan Ledermann of the University College London, UK presented findings of the randomized, double-blind, placebo controlled study with 265 ovarian cancer patients enrolled from 82 sites in 16 countries. Eligible patients had received at least two previous platinum-based chemotherapy regimens.

After ensuring that the partial or complete response achieved during the last platinum containing regimen was sustained, patients were randomly assigned to receive 400 mg of oral olaparib twice daily or placebo until evidence of disease progression.

Olaparib improved progression-free survival - the primary study endpoint - by 3.6 months following the completion of chemotherapy as compared with placebo, translating to a 65% reduced risk of progression.

Importantly, in a pre-planned subgroup analysis, the progression-free survival benefit associated with olaparib was not restricted to patients who were BRCA-mutation positive - a status thought to enhance responsiveness to PARP inhibition. In fact, all subgroups, including those broken out by BRCA-mutation status, age, race or Jewish ethnicity, prior response to the last platinum regimen, and time to disease progression on the penultimate platinum regimen, showed a substantial progression-free survival benefit in favor of olaparib.

The time to progression according to either CA-125 concentration or RECIST criteria was also significantly longer with olaparib compared with placebo (median: 8.3 vs. 3.7 months; $p < 0.00001$). Overall survival data are not yet mature, as only 19 deaths were observed at the time of analysis (nine deaths in the olaparib group; 10 deaths in the placebo group).

Olaparib was generally well tolerated, with a safety profile consistent with that seen in previous studies. The most common adverse events associated with olaparib compared with placebo included nausea (68% vs. 35%), fatigue (49% vs. 37%), and vomiting (31% vs. 14%); the majority of these events were mild or moderate in severity. The most common grade 3/4 events were fatigue (7%) and

anemia (5%). Very few patients discontinued olaparib because of adverse events (three patients; 2%).

According to Dr Stanley B Kaye of the Royal Marsden Hospital, UK who discussed the study results, single-agent olaparib demonstrated a significant clinical activity in both BRCA-mutated and sporadic ovarian cancer, with a favorable toxicity profile.

Practice point and future research opportunities

Evidence supporting the benefit of olaparib in advanced ovarian cancer continues to grow. The current study is the first to demonstrate a substantial clinical benefit following maintenance therapy with olaparib. In this phase II study olaparib (orally active PARP inhibitor) markedly prolonged progression-free survival when used as maintenance therapy in patients with high-grade relapsed serous ovarian cancer who had responded to previous treatment with platinum-based chemotherapy. Currently, standard practice is to observe such patients after chemotherapy until further disease progression and there is a great need to find treatments that might delay the reappearance of disease.

JAK INHIBITOR RUXOLITINIB DEMONSTRATES SIGNIFICANT CLINICAL BENEFIT IN MYELOFIBROSIS

Myelofibrosis is characterized by dysregulation of JAK-STAT signaling, making this pathway an attractive therapeutic target. The JAK 1/2 inhibitor ruxolitinib (INC424) had previously demonstrated activity in a phase I/II trial, leading to the design of two phase III Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment (COMFORT) trials.

In the COMFORT-I study, presented by Dr Srdan Verstovsek of the University of Texas MD Anderson Cancer Center, ruxolitinib was compared with placebo. The trial enrolled 309 patients with intermediate-2 or high-risk primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF), who were randomly assigned to twice-daily oral ruxolitinib (155 patients) or to placebo (154 patients). Ruxolitinib was dosed at 15 mg or 20 mg, depending on the baseline platelet count. Patients in the placebo arm could cross over to the ruxolitinib arm upon disease progression, and nearly a quarter of patients did cross over (11% prior to week 24 and 13% after week 24).

After a median follow-up of 32 weeks, a significantly higher proportion of patients on the ruxolitinib arm attained the primary endpoint of at least a 35% reduction in spleen volume after 24 weeks of therapy (41.9% vs. 0.7% with placebo; $p < 0.0001$). Ruxolitinib was also more effective than placebo

regarding the proportion of patients with at least a 50% improvement in symptom burden (45.9% vs. 5.3%; $p < 0.0001$). Symptoms that improved with ruxolitinib included abdominal discomfort, pain under the left ribs, early satiety, night sweats, itching, bone or muscle pain, and inactivity. For each parameter, comparisons between ruxolitinib and placebo were highly significant ($p < 0.01$). Ruxolitinib was generally well tolerated. The two grade 3/4 adverse events observed more frequently with ruxolitinib compared with placebo were thrombocytopenia (12.9% vs. 1.3%) and anemia (45.2% vs. 19.2%); both were manageable with dose adjustments. Only one patient on each arm discontinued treatment because of toxicity.

The COMFORT-II trial, presented by Dr Alessandro Maria Vannucchi of the University of Florence, Italy compared ruxolitinib with the best-available therapy. This open-label trial enrolled 219 patients with intermediate-2 or high risk PMF, PPV-MF, or PET-MF who were randomly assigned to oral twice-daily ruxolitinib administered at 15 or 20 mg (146 patients) or to best-available therapy (73 patients). Patients received the assigned treatment for 48 weeks, although 25% of patients in the control arm crossed over to ruxolitinib due to disease progression.

On the best-available therapy arm, 67% of patients received at least one medication, while the remaining 33% received no medication. The most commonly administered agent was hydroxyurea (47% of patients) and glucocorticoids (16% of patients).

The primary endpoint, the proportion of patients achieving at least a 35% reduction in spleen volume at week 48, was 28.5% for ruxolitinib and 0% for best available therapy ($p < 0.0001$). The median time to response was 12 weeks, although this also was the first point at which responses were assessed.

This highly significant improvement in spleen volume was accompanied by marked improvement in quality-of-life measures, which were observed beginning at week 8 and continuing through week 48. In contrast, patients receiving best available therapy experienced either no change or worsening of symptoms during the study.

As in COMFORT-I, ruxolitinib was associated with myelosuppression. Grade 3/4 thrombocytopenia was observed in 8% of patients receiving ruxolitinib and in 7% of patients receiving best available therapy; grade 3/4 anemia was reported in 42% and 31% of patients, respectively. Nearly two-thirds of patients had grade 1/2 anemia at baseline. Although a higher proportion of ruxolitinib-treated patients required red blood cell transfusions during the study (51% vs. 38% with best-available therapy), the mean volume transfused per month was similar between arms (0.86 and 0.91 units/month, respectively).

Neither study reported a significant survival benefit, although the follow-up period was too short to

evaluate effects on survival. Moreover, the investigators noted that crossovers from the placebo arm would complicate the analysis.

Ruxolitinib is now under review by the USA Food and Drug Administration. According to Dr Verstovsek, for the first time ever in hematologic malignancies, this agency is accepting symptom improvement as a secondary endpoint. In addition, he noted that shrinking the spleen without improvement in quality of life is of little value.

Practice point and future research opportunities

The JAK 1/2 inhibitor ruxolitinib is associated with significant and sustained clinical benefits in patients with myelofibrosis. In two phase III trials, ruxolitinib was significantly superior to the best available therapy with regard to spleen size reduction, symptom burden, and quality of life. The benefit of ruxolitinib was observed regardless of JAK mutational status. Neither study reported a significant survival benefit, although the follow-up period was too short to evaluate effects on survival. For the first time, there is a drug that meaningfully reduces spleen size and addresses the burden of disabling symptoms in this rare condition.

R-CHOP 14 NOT SUPERIOR TO STANDARD R-CHOP 21 IN NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMA

Dr David Cunningham of The Royal Marsden Hospital presented the results on behalf of the UK National Cancer Research Institute Lymphoma Clinical Study Group of a randomized phase III trial involving 1,080 patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma and treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP 14) administered every 14 days or by 21-day treatment.

Treatment-naive patients were randomly assigned in equal numbers (540 patients in each arm) to receive either eight cycles of RCHOP 21 or six cycles of R-CHOP 14 plus granulocyte colony-stimulating factor (GCSF) succeeded by two cycles of single-agent rituximab. The trial arms were balanced with respect to median age, B symptoms, bulky disease, disease stage, and International Prognostic Index (IPI). Fifty-two percent of patients were age 60 or older; none were younger than age 19.

The study was designed to demonstrate an 8% difference in 2-year overall survival, the primary endpoint, from 75% to 83% with 5% significance level and 90% power following 233 deaths. However, after a median follow-up of 37 months and 237 deaths, Kaplan- Meier curves did not reveal differences in overall survival and progression-free survival. The comparison of 88% overall

response rate among patients receiving R-CHOP 21 with a 90% overall response rate in the R-CHOP 14 arm was not significant.

Furthermore, patient status at 39 months as measured by death, survival without progression, survival with progression or relapse, deaths without documented progression, and progression or relapse followed by death was virtually identical for the two cohorts. No obvious subgroup appeared to derive a greater benefit from accelerated R-CHOP, including age older than 60, high IPI score, and two presumed predictors of prognosis in this disease: MIB1 status and the non-germinal center phenotype.

Although grade 3/4 non-hematologic toxicities were comparable in the two trial arms, neutropenia and febrile neutropenia were significantly more frequent in patients receiving the 21-day regimen ($p < 0.01$). This was probably a result of primary prophylaxis with G-CSF in patients receiving accelerated treatment. In contrast, thrombocytopenia was significantly more frequent ($p < 0.01$) in the R-CHOP 14 arm, probably as a consequence of greater therapeutic intensity. Toxicities, progressive disease, death, and patient choice contributed substantially to early termination of treatment in the accelerated arm (58 patients) and with standard treatment (107 patients).

The rationale for this trial was based on two established premises. First, it has been demonstrated that the addition of rituximab to six to eight cycles of CHOP improves overall survival in this disease setting by 10% to 16%. Second, six cycles of CHOP 14 has been shown to be superior to an equal number of cycles of CHOP 21 in patients older than age 60, improving 5-year overall survival by 13%. Dr Cunningham concluded, however, that there is no evidence that combining these two premises clinically supports a shift in standard practice to R-CHOP 14.

According to the study discussant, Dr Julie M Vose of the University of Nebraska Medical Center, R-CHOP 21 remains the standard treatment for patients older than age 60 and for younger patients with low IPI. For younger patients with high IPI, however, R-CHOP 21 followed by consolidation auto-transplantation of peripheral stem cells should be offered as a standard of care.

Practice point and future research opportunities

Data generated by this randomized phase III trial involving 1,080 patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma indicate that treatment with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP 14) administered every 14 days does not improve overall survival or progression-free survival compared with standard 21-day treatment (R-CHOP 21).

AFFILIATIONS AND DISCLOSURE

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

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