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INTELLIGENT INSIGHTS. SMART RESULTS

VIENNA 2012 ESMO congress

Vienna, Austria

28 September - 2 October, 2012

Non-Small Cell Lung Cancer (NSCLC)

Crizotinib - Standard of Care for Previously Treated Advanced ALK+ NSCLC

The results of a new Phase III, PROFILE 1007 trial showed that crizotinib is more effective treatment than...

Read more

Breast Cancer

Final Analysis of Phase III HERA Trial Confirmed 1 Year of Herceptin Treatment as SOC in Early-Stage HER2-Positive Breast Cancer

One year of adjuvant treatment with trastuzumab is as good...

Read more

Pancreatic Cancer

TH-302, in Combination with Gemcitabine, Shows Promise in Pancreatic Cancer

Combination therapy with the investigational hypoxia targeted drug, TH-302, and gemcitabine improved overall survival (OS) compared to gemcitabine alone in patients with...

Read more

Soft Tissue Sarcoma (STS)

Doxorubicin Remains the Gold Standard in the 1st Line Chemotherapy for Patients with Advanced or Metastatic STS

The EORTC 62012 trial attempted to find whether Ifosfamide...

Read more

Colorectal Cancer (CRC)

Treatment with Bevacizumab Beyond Progression in mCRC

The addition of bevacizumab to 5-FU-based chemotherapy has been a standard 1st line treatment option for patients with metastatic colorectal cancer (mCRC) for many years...

Read more

Hepatocellular Carcinoma (HCC)

Patients with Advanced HCC Show No Benefit from Adding Erlotinib to Sorafenib

Phase III SEARCH trial tested whether adjunct erlotinib, a direct and reversible EGFR tyrosine kinase inhibitor...

Read more

Ovarian Cancer

PM01183: A Promising New Drug for Ovarian Cancer

In platinum resistant/refractory ovarian cancer PM01183 (lurbinectedin) produced an overall response rate (ORR)...

Read more

Renal Cell Carcinoma (RCC)

COMPARZ Trial: Pazopanib and Sunitinib Similarly Effective in 1st Line Treatment of mRCC

Pazopanib has similar efficacy to sunitinib in controlling metastatic renal cell carcinoma, according to the results of the Phase III randomized, open-label...

Read more

Melanoma

Promising New Data from Trials Aimed to Delay Resistance to BRAF Inhibitors

Promising new data on drug combinations of BRAF and MEK inhibitors indicate delayed resistance to treatment with...

Read more

Gastrointestinal Stromal Tumor (GIST)

Phase III GRID Trial Update: Clinical Benefit with Regorafenib across Subgroups and Post-Progression in Patients with Advanced GIST

Regorafenib therapy significantly improved PFS in patients with...

Read more

The E-newsletter team: Dr. Loveleen Taneja, Dr. Shirish Kumar, Sarika Manchanda, Dr. Vinamrata Bhatia, Kimberly Scata, Monica Tuli.

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Non-Small Cell Lung Cancer (NSCLC)

Crizotinib - Standard of Care for Previously Treated Advanced ALK+ NSCLC

The results of a new Phase III, PROFILE 1007 trial showed that crizotinib is more effective treatment than standard chemotherapy for patients with advanced, ALK-positive NSCLC, who have been previously treated with 1st line platinum-based chemotherapy. The study results are reported at the ESMO 2012 Congress of the European Society for Medical Oncology in Vienna.

The current global randomized Phase III study compared the efficacy and safety of crizotinib with standard chemotherapy with pemetrexed or docetaxel, in 347 patients with ALK-positive, stage IIIB/IV NSCLC who had already been treated with chemotherapy. The study showed that crizotinib significantly prolonged the primary endpoint, median PFS and increased ORR compared to standard chemotherapy (Table 1).

Table 1:

	Crizotinib 250 mg PO BID (n=173)	Chemotherapy (pemetrexed [500 mg/m^2] or docetaxel [75 mg/m^2 IV q3w]) (n=174; 58% P, 42% D)
Median PFS	7.7 months	3.0 months (HR 0.49; 95% CI 0.37–0.64; P < 0.0001)
ORR	65%	20% (P < 0.0001)

The analysis of the OS rate with the two drugs is still immature, and there are not enough events to draw meaningful conclusions (with OS not yet adjusted for cross over to crizotinib arm), although interim analysis of OS (28% events) showed no statistically significant difference between Crizotinib and chemotherapy (preliminary median estimate 20.3 vs. 22.8 months; HR 1.02; P=0.5394).

The most common treatment-related adverse events with crizotinib reported were visual disturbance (59%), diarrhea (53%), nausea (52%), vomiting (44%), and elevated transaminases (36%). AEs with chemotherapy were nausea (35%), fatigue (29%), neutropenia (22%), decreased appetite (21%), and alopecia (20%). The incidence of grade 3-4 AEs was the same for both arms (31%). However, despite side effects, patients still reported improved quality of life on crizotinib compared with chemotherapy.

According to the lead study author, Dr Alice Shaw from Massachusetts General Hospital Cancer Center, Boston, USA, crizotinib is superior to standard single-agent chemotherapy in terms of response, PFS and quality of life in advanced ALK-positive NSCLC patients who have been previously treated with 1st line platinum-based chemotherapy.

Source: ESMO 2012 Congress, Abstract No: LBA1_PR

Phase III MISSION Trial of Sorafenib Monotherapy in Heavily Pre-treated Patients with NSCLC

Treatment with sorafenib as a 3rd or 4th line therapy does not result in improved OS among patients with relapsed/refractory NSCLC of predominantly non-squamous histology, according to results of Phase III MISSION trial. However, a post-hoc biomarker analysis of the trial data that was also presented at ESMO 2012 suggests that patients with EGFR-mutant tumors may benefit. Dr Luis Paz-Ares from Virgen del Rocio University Hospital in Seville, Spain, reported the findings of the Phase III MISSION trial, a randomized, double-blind, placebo-controlled study of monotherapy administration of sorafenib in 703 patients who were randomly assigned to either oral sorafenib 400 mg twice daily or placebo.

Median OS, the study's primary end-point, was similar in the two groups (248 vs. 253 days; P = 0.4687), although median PFS (84 vs. 43 days; HR 0.61; P<0.0001), TTP (89 vs. 43 days; HR 0.54; P<0.0001), ORR (4.9% vs. 0.9%; P<0.001) and DCR (47% vs. 25%; P<0.0001) significantly greater in the sorafenib group. However, serious adverse events were also higher (39% vs 32%) in the Sorafenib group. Post-hoc biomarker analysis of MISSION trial suggests that patients with EGFR mutant tumors may benefit from sorafenib.

Currently, there is no specific biomarker that can help select patients for treatment with sorafenib. Dr Tony Mok, a professor in the Department of Clinical Oncology at the Chinese University of Hong Kong, reported that data from an exploratory study which suggests that EGFR mutations may help to achieve this goal in patients with lung cancer. The analysis was conducted using tumor and/or plasma mutation data from 347 patients who took part in the MISSION trial. EGFR and KRAS mutations were detected in 89 (26%) and 68 (20%) patients, respectively, and were well balanced between treatment arms. Analysis of the interaction between EGFR mutation status and the effect of treatment on survival suggested that patients with EGFR mutations benefitted from

Back to top of NSCLC Section | Back to Top of Document

ESMO News
(Cont'd)

sorafenib, while those with wild-type EGFR did not. Median OS was two-fold longer in patients with EGFR mutations receiving sorafenib versus placebo (423 vs. 197 days, HR 0.48, P=0.002). No significant difference in OS between patients with wild type EGFR receiving sorafenib or placebo (253 vs. 256 days, HR 0.92, P=0.559) was seen. Researchers also observed an interaction between EGFR mutation status and the sorafenib effect on progression-free survival (P=0.015). However, KRAS mutation status was not predictive of sorafenib efficacy. Hence, sorafenib may be beneficial in EGFR mutant patients.

Source: ESMO 2012 Congress, Abstract No: LBA33_PR, ESMO 2012 Congress, Abstract No: LBA9_PR

FORTIS-M Trial with Talactoferrin-alfa Did Not Meet its Primary Endpoint of Improving OS in Advanced NSCLC

Talactoferrin alfa (TLF), an oral Dendritic Cell Mediated Immunotherapy (DCMI) plus best supportive care did not extend OS or PFS vs. placebo plus best supportive care in patients with advanced NSCLC, according to findings presented by Ramalingam SS, *et al.*

FORTIS-M trial Phase III study of TLF versus placebo for advanced NSCLC following ≥2 prior systemic therapy regimens enrolled a total of 742 patients (TLF = 497, placebo =245). The median OS for TLF was 7.49 months versus 7.66 months for placebo (HR 1.04, P = 0.6602); and the respective values for PFS were 1.68 and 1.64 months (HR 0.99, P = 0.8829). The DCR was 37.6% for TLF and 38.4% for placebo (P = 0.8336). 36.4% of patients had Grade 3-4 AEs in the TLF arm, 35.5% in the placebo arm. The nature and incidence of adverse events in the talactoferrin arm were similar to that of placebo and consistent with previous clinical trials. However, FORTIS-C trial of Talactoferrin alfa in combination with carboplatin-paclitaxel as first line management of NSCLC patients is ongoing. The co-primary endpoints for the FORTIS-C trial are PFS (required for accelerated approval) and overall survival (for full approval).

Source: ESMO 2012 Congress, Abstract No: LBA34; Agennix

Novel Agents Show Efficacy in with ALK-positive Patients and in EGFR Mutated NSCLC

Four new therapeutic agents, AUY922, AP26113, LDK378 and CH5424802, show considerable clinical benefit with acceptable toxicity in NSCLC patient populations. The results of studies evaluating these 4 new agents were presented during the proffered papers session of the Developmental therapeutics program track.

AUY922, a HSP90 inhibitor, was tested in a Phase II trial in patients with ALK-rearranged (ALK+) or EGFR-mutated advanced NSCLC patients who had progressed following at least one line of chemotherapy. 121 patients received AUY92270 mg/m^2 once-weekly. Partial response was seen in 29% ALK+ patients and 20% EGFR-mutated patients. No partial response was seen in 28 patients with KRAS-mutation, 33 EGFR/KRAS/ALK wild-type and 3 mutation undetermined patients. Median PFS rates at 18 weeks were 42% in ALK+ and 34% in EGFR-mutated patients. Median PFS rate at 18 weeks was greatest in EGFR-mutated patients who had progressed after EGFR tyrosine kinase inhibitor therapy compared to tyrosine kinase inhibitor-naive patients; 45% versus 21%, respectively. The most frequent adverse events were grades 1-2, and including eye disorders, diarrhea and nausea, which were reported in 77%, 74% and 46% of patients, respectively. Higher grade adverse events occurred in <10% of patients. The results were presented by Dr E. Felip on behalf of international study team.

Source: ESMO 2012 Congress, Abstract No: 438O

Dr S. Gettinger and colleagues reported results from a first-in-human Phase I/II dose-finding study of AP26113, as a novel, synthetic, orally-active tyrosine kinase inhibitor (TKI) that potently inhibits mutant activated forms of anaplastic lymphoma kinase (ALK+) and epidermal growth factor receptor (EGFRm) and which is also active against other tyrosine kinase inhibitor resistant forms, including L1196M (ALK) and T790M (EGFR), but does not affect wild type EGFR. AP26113 was administered daily to 15 patients with advanced malignancies including 11 patients with NSCLC. All patients were heavily pretreated; 4 ALK+ NSCLC patients had failed prior crizotinib and 4 EGFR-mutant patients had failed prior EGFR targeted therapy. All 4 ALK+ patients achieved partial responses, one patient at 60 mg and the remaining 3 at the 90 mg dose. The trial was discontinued by 8 patients due to disease progression, and by one patient discontinued due to investigator discretion; however, no treatment related serious events were observed. A Phase II expansion is planned to test AP26113 in four cohorts; two groups of patients with ALK+ NSCLC who are naive or resistant to prior ALK-targeted therapy; patients with EGFR-mutant NSCLC resistant to EGFR-targeted therapy and a fourth group of patients with other cancers with abnormalities in ALK or other AP26113 targets.

Source: ESMO 2012 Congress, Abstract No: 439O

Dr A. Shaw and colleagues reported results of a Phase I study in which 51% of patients showed a response to LDK378, a small molecule ALK inhibitor that had shown activity in ALK+ NSCLC xenografts. The trial

Back to top of NSCLC Section | Back to Top of Document

ESMO News
(Cont'd)

enrolled patients with ALK+ advanced solid tumors; 50 patients with primary NSCLC, 4 with primary breast cancer and two patients with other ALK+ cancers. Of the 50 lung cancer patients, 37 had been were refractory to prior crizotinib. All patients received LDK378 at doses of 50 to 750 mg/day. Response was seen in 42 of 47 patients with ALK+ NSCLC (FISH positive in ≥15%) evaluable for response (per investigator). A stronger response was seen in patients with NSCLC who had progressed following crizotinib and were treated at ≥400 mg/day with LDK378, where 21 of 23 (81%) patients responded. Dose limiting toxicities of diarrhea, vomiting, nausea, dehydration, and ALT elevation were recorded in 2 of the 14 patients who received LDK378 at 400 mg/day, 2 of 9 patients at 600 mg/day, and in 1 of the 9 patients dosed at 750 mg/day.

Source: ESMO 2012 Congress, Abstract No: 440O

Dr M. Nishio and colleagues reported interim safety and efficacy results from the Phase II portion of a Phase I/II trial of CH5424802, an oral ALK inhibitor, in patients with ALK+ NSCLC. 34 patients with ALK-positive NSCLC, measurable disease, and no prior ALK inhibitor therapy were enrolled and treated with CH5424802 at 300 mg BID until progressive disease or intolerable toxicity. Patients had received up to four prior chemotherapies and among the first 15 patients receiving CH5424802, one patient achieved complete response and 10 patients showed partial responses, with a response rate of 73.3%. Most treatment-related adverse events were grade 1, with two cases of grade 3 neutropenia reported; no dose reductions were made.

Source: ESMO 2012 Congress, Abstract No: 441O

Breast Cancer

Final Analysis of Phase III HERA Trial Confirmed 1 Year of Herceptin Treatment as SOC in Early-Stage HER2-Positive Breast Cancer

One year of adjuvant treatment with trastuzumab is as good as two years of treatment for women with HER2-positive early breast cancer who have already received initial treatment with surgery, chemotherapy and radiotherapy as needed, HERA (HERceptin Adjuvant) study researchers have found. The updated results of the study were reported at the ESMO 2012 Congress. The HERA trial, run by the Breast International Group (BIG) since 2001, is an international, multi-center, Phase III randomized study involving 5102 women with early HER2-positive breast cancer. Subjects were randomly assigned to trastuzumab therapy every 3 weeks for 1 year, 2 years or observation after finishing primary therapy with surgery, chemotherapy and radiotherapy as indicated.

The unadjusted hazard ratio for a woman experiencing disease relapse in the 2-year treatment arm vs. the 1-year arm was 0.99 (95% CI 0.85-1.14; P = 0.8588), Prof. Richard Gelber of Harvard Medical School and Dana-Farber Cancer Institute, Boston, MA, USA, reported. The overall survival rate in the two arms was comparable [HR=1.05 (95% CI 0.86-1.28; P = 0.6333)]. The researchers found that the durable benefit in DFS and OS of 1-year trastuzumab compared to no trastuzumab that had been reported previously remained stable at 8 years of median follow-up. The study results confirmed the benefit of 1 year of adjuvant trastuzumab with no added advantage of a prolonged therapy.

Source: ESMO 2012 Congress, Abstract No: LBA6; Roche

PHARE Trial Results Comparing 6 to 12 Months of Adjuvant Trastuzumab in Early Breast Cancer support 1 year treatment

An academic randomized, non-inferiority, Phase III PHARE (Protocol for Herceptin as Adjuvant therapy with Reduced Exposure) trial was conducted by the French National Cancer Institute (INCa) comparing a shorter trastuzumab exposure of 6 months versus the standard 12 months treatment. The reduced treatment exposure with trastuzumab was attempted due to concerns over cardiotoxicity, which has resulted in a debate on the optimal treatment duration with trastuzumab. The results are presented at Presidential Symposium of the ESMO 2012 Congress.

The study recruited 3,382 patients. The primary objective of the study was to compare 6 months vs. 12 months of adjuvant trastuzumab therapy in terms of DFS according to a non-inferiority schema. The trial results were inconclusive for this non-inferiority hypothesis, according to Prof. Xavier Pivot, of the Université de Franche Comté, France. However, there was a trend in favor of 12 months treatment for the overall population and an analysis subgroups would be presented later in December. The median follow-up in the trial was 42.5 months and at the time of the analysis 395 DFS events were reported. According to the design of this trial, which allowed for a non-inferiority hazard ratio margin of 1.15, the 6-month trastuzumab arm was not demonstrated to be significantly inferior to 12-month trastuzumab, since the confidence interval contains the 1.15 non inferiority margin (HR=1.28 (95% CI: 1.04 – 1.56, P = 0.29). However, despite the inconclusive result in terms of non-inferiority, the HR of 1.28 suggests a trend favoring 12 months therapy.

Source: ESMO 2012 Congress, Abstract No: LBA5_PR

Back to top of NSCLC Section | Back to Breast Cancer Section | Back to Top of Document

ESMO News
(Cont'd)

T-DM1 Significantly Extended Survival in HER2-positive Locally Advanced or Metastatic Breast Cancer

Phase III EMILIA study showed that people with previously treated HER2-positive metastatic breast cancer (mBC) survived significantly longer (overall survival, a co-primary endpoint) when treated with trastuzumab emtansine (T-DM1) compared to those who received the combination of lapatinib and Xeloda (capecitabine). The study results are reported at the ESMO 2012 Congress of the European Society for Medical Oncology.

The study enrolled 991 patients. Median durations of follow-up were 12.9 with T-DM1. PFS was significantly improved with T-DM1 compared to lapatinib and Xeloda (9.6 months vs. 6.4 months, P<0.0001. The risk of death was reduced by 32% for people who received T-DM1 compared to those who received lapatinib plus Xeloda (HR=0.68; P=0.0006). People in the study Patients treated with T-DM1 survived a median of 5.8 months longer than those who received lapatinib and Xeloda (median OS: 30.9 months vs. 25.1 months). No new safety signals were observed and adverse events (AEs) were consistent with those seen in previous studies, with fewer people who received T-DM1 experiencing Grade 3 or higher (severe) (AEs) than those who received lapatinib plus Xeloda (40.8% vs. 57.0%). Findings establish T-DM1 as a potential new therapy for HER2+ MBC pts patients previously treated with trastuzumab and a taxane.

Source:ESMO 2012 Congress, Abstract No:LBA12; Roche

Combination of Panvac with Docetaxel in mBC Might Provide a Clinical Benefit Compared to Docetaxel Alone

A previous Phase I/II trial of PANVAC, a poxviral based cancer vaccine, suggested clinical efficacy in some patients with breast and ovarian cancer and evidence of immunologic activity. Preclinical data showed that docetaxel can modify tumor phenotype, making tumor cells more amenable to T-cell mediated killing. The goal of this trial was to determine if docetaxel and PANVAC could synergize and improve clinical outcomes compared with docetaxel alone.

An open-label randomized Phase II multi-center trial, designed to enroll 48 patients with metastatic breast cancer to receive docetaxel in combination with PANVAC (A) or alone (B). 1° endpoint was PFS. 2° endpoints included overall survival and immunologic correlative studies. Enrollment of 48 patients completed in February 2012 (A, n = 25; B, n = 23). Five patients remained on treatment (2 on A, 3 on B). Analysis through August 2, 2012 (median follow-up of 5.1 months for patients on study), indicated PFS of 6.6 vs. 3.8 months in A vs. B (p = 0.12, HR = 0.67) Toxicity was similar in both arms. Immune analysis and correlation to patient clinical outcomes is ongoing. This randomized study suggested the combination of PANVAC with docetaxel in metastatic breast cancer might provide a clinical benefit compared to docetaxel alone.

Source: ESMO 2012 Congress, Abstract No: LBA14

Circulating Tumor DNA, a More Sensitive Biomarker than CTCs for the Monitoring of mBC

Circulating tumor DNA is a more sensitive biomarker than CTCs for the monitoring of metastatic breast cancer (mBC) that often provides the earliest measure of treatment response according to the results of a study presented by a team of researchers from Cambridge/UK led by S-J. Dawson. They performed the first direct comparison of CTCs and circulating tumor DNA in relation to medical imaging, to compare the performance of these biomarkers for the non-invasive monitoring of mBC.

Concurrent CTC and circulating tumor DNA data was available from 16 women across 58 samples. Elevated CTCs (≥5 cells / 7.5ml blood) and ctDNA were identified in 11 (69%) and 15 (94%) cases respectively. Circulating tumor DNA levels were a median of 234-fold higher than CTC numbers and showed greater sensitivity for monitoring tumor dynamics. In several cases, rising circulating tumor DNA was identified months before progressive disease was detected by CTCs or imaging. Changes in circulating tumor DNA levels were also observed in a subset of women with no measurable disease using the other modalities. Multiple somatic mutations and structural variants were measured in parallel in circulating tumor DNA, demonstrating the utility of this methodology to follow clonal evolution during treatment.

The study concluded that circulating tumor DNA is a more sensitive biomarker than CTCs for the monitoring of MBC and often provides the earliest measure of treatment response. Investigators suggested that circulating tumor DNA has the potential to be used as a 'liquid biopsy' to directly monitor responses to targeted therapies and detect the emergence of resistant mutations.

Source: ESMO 2012 Congress, Abstract No: 171O

Back to top of Breast Cancer Section | Back to Top of Document

ESMO News
(Cont'd)

Pancreatic Cancer

TH-302, in Combination with Gemcitabine, Shows Promise in Pancreatic Cancer

Combination therapy with the investigational hypoxia targeted drug, TH-302, and gemcitabine improved overall survival (OS) compared to gemcitabine alone in patients with advanced pancreatic cancer. Results from an open label, Phase IIb study were presented by Dr Mitesh Borad from the Mayo Clinic, Scottsdale, Arizona, USA.

TH-302 is a hypoxia targeted prodrug with a hypoxia-triggered 2-nitroimidazole component designed to release the DNA alkylator, bromo-isophosphoramide mustard (Br-IPM), when reduced in severe hypoxia, thereby selectively targeting hypoxic tumor cells. In this Phase IIb study, 214 previously untreated patients with locally advanced, unresectable or metastatic pancreatic cancer were randomized 1:1:1 to receive either TH-302 240 mg/m^2 plus gemcitabine (n=71), TH-302 340 mg/m^2 plus gemcitabine (n=74) or gemcitabine alone (n=69). The study results showed that the addition of TH-302 improved the mPFS which was the primary endpoint of study. Although the combination appeared to improve median OS compared with gemcitabine alone, the difference was not significant (Table 2).

Table 2:

	TH-302 340 mg/m^2 plus gemcitabine	TH-302 240 mg/m^2 plus gemcitabine	Gemcitabine
mPFS	6.0 months (P=0.008)	5.5 months (P=0.031)	3.6 months
mOS	9.5 months	9 months	7 months
RECIST best response	27%	17%	12%
CA19-9 decrease	70%	50%	52%

Poorer prognostic factors (older age, poorer performance status, reduced albumin) were associated with larger treatment effect. Skin and mucosal toxicity and myelosuppression were the most common TH-302-related adverse effects. With TH-302 340 mg/m^2, rash and stomatitis occurred in 47% and 42% of patients, respectively, although this was rarely severe. But the amount of hematological toxicity reported with TH-302 340 mg/m^2 was much higher than that reported with gemcitabine alone with 63% thrombocytopenia (vs. 11%) and 60% neutropenia (vs. 31%). Dr Borad also added that the dose of 340 mg is identified as the way forward for future trials, and that a Phase III trial is to be initiated.

Source: ESMO 2012 Congress, Abstract No: 666O

Soft Tissue Sarcoma (STS)

Doxorubicin Remains the Gold Standard in the 1st Line Chemotherapy for Patients with Advanced or Metastatic STS

The EORTC 62012 trial attempted to find whether Ifosfamide had been previously tested at too low dose when used with doxorubicin by evaluating, or whether a higher dose of ifosfamide plus doxorubicin could improve response rate and PFS in patients with locally advanced or metastatic soft tissue sarcoma (STS). The findings were presented by Dr Winette van der Graaf at the Presidential symposium.

The study enrolled 455 patients aged 60 years and less who were randomized to doxorubicin (n=228) or ifosfamide/doxorubicin (n=227). With median follow-up of 56 months, OS at 1 year was slightly greater with ifosfamide/doxorubicin at 60% vs. 51% with doxorubicin alone, but the difference was not statistically significant (HR 0.82). No difference was seen in the 2-year OS rate which was 31% for ifosfamide/doxorubicin vs. 28% for doxorubicin. Median PFS was significantly increased at 7.4 months for ifosfamide/doxorubicin vs. 4.6 months for doxorubicin (HR 0.72).

Febrile neutropenia was more common with ifosfamide/doxorubicin (45.9% vs 13.6%) as was anaemia (35.3% vs 4.6%). Response rates favored the combination treatment; complete response were seen in 4 versus 1 patients, partial response in 56 (24.7%) versus 30 (13.2%) and stable disease was achieved by 114 (50.2%) ifosfamide/doxorubicin patients versus 105 (46.1%) doxorubicin patients, respectively. The study concluded that the lack of a significant improvement in OS does not support the routine use of combination of ifosfamide/doxorubicin for STS in the palliative setting. The higher response rate suggests that ifosfamide/doxorubicin might be justified in selected patients age <60 if tumor shrinkage is critical, but it is significantly more toxic. The findings also confirmed that doxorubicin remains the gold standard for comparative studies of 1st line chemotherapy in metastatic STS.

Source: ESMO 2012 Congress, Abstract No: LBA7

Back to Top of Pancreatic Cancer Section | Back to Top of STS Section | Back to Top of Document

ESMO News
(Cont'd)

Colorectal Cancer (CRC)

Treatment with Bevacizumab Beyond Progression in mCRC

The addition of bevacizumab to 5-FU-based chemotherapy has been a standard 1st line treatment option for patients with metastatic colorectal cancer (mCRC) for many years; but the use of bevacizumab beyond progression is an area of ongoing debate. Dr Gianluca Masi from the University Hospital of Pisa, Italy, presented data from a randomized Phase III trial, conducted by the Gruppo Oncologico Nord Ovest (GONO), which evaluated the continuation of bevacizumab beyond progression in patients with mCRC who had received bevacizumab as part of their 1st line therapy. In this trial, 184 patients who had progressed following 1st line chemotherapy (FOLFOX, FOLFIRI or FOLFOXIRI) + bevacizumab were randomized to receive 2nd line treatment with chemotherapy alone (either FOLFOX or mFOLFIRI) or in combination with bevacizumab 5 mg/kg every 2 weeks.

Despite accrual to this trial being stopped early, results showed that the addition of BEV was associated with a significant PFS benefit compared with chemotherapy alone (median PFS: 6.77 months vs. 4.97 months; P=0.0062), and that this benefit was maintained across various patient subgroups. The safety profile of bevacizumab + chemotherapy was consistent with previously reported data. This study demonstrated an increased PFS by continuing bevacizumab in 2nd line. However, OS data was still immature, with only 46 and 52 events observed in the bevacizumab + chemotherapy and chemotherapy alone arms, respectively.

Source: ESMO 2012 Congress, Abstract No: LBA17

Maintenance Treatment with MGN1703 After Standard 1st Line Treatment Prolongs PFS in Patients with mCRC

MGN1703 is a synthetic DNA-based immuno-modulator acting as an agonist of TLR-9 that showed preclinical activity in mCRC. The results of a Phase II/III study on maintenance therapy with MGN1703 following successful standard 1st line treatment in patients with metastatic colorectal cancer (mCRC) was reported by Dr Dirk Arnold.

The IMPACT study evaluated the clinical efficacy, immunogenicity and safety of MGN1703 compared to placebo in patients with mCRC who achieved complete response (CR), partial response (PR) or stable disease (SD) following 4.5 to 6 months of 1st line standard therapy with FOLFOX/XELOX or FOLFIRI, both with and without bevacizumab (investigator´s choice). Randomization following enrollment was halted after interim analysis of unblinded data demonstrated a strong therapeutic effect with MGN1703; the hazard ratio (HR) was 0.53; P = 0.062 in 55 patients comprising the intent to treat population. In the per-protocol population, which excluded screening failures and contained 50 patients the HR was 0.43; P = 0.015, again favoring MGN1703. PFS in the pre-defined target population of 46 patients (2 out of 3 factors: CEA <30 x ULN, GGT <2 x ULN, AP <2 x ULN) was 5.8 months with MGN1703 compared to 2.7 months with placebo, HR 0.39; P = 0.013. Following 3 months of treatment, PFS rates were 43% with MGN1703 and 8% with placebo (P < 0.001); after 6 months rates were 34% compared to 8% (P = 0.011) and at 9 months PFS rates were 22% compared to 0% (P = 0.010) for MGN1703 and placebo, respectively.

The treatment was well tolerated with low toxicity. A confirmatory clinical study in patients with mCRC is currently planned.

Source: ESMO 2012 Congress, Abstract No: 518O

No Benefit of Adding Cetuximab to FOLFOX4 in Patients with Resected Stage III Colon Cancer

Final results of the PETACC8 Intergroup Phase III trial showed that adding cetuximab to FOLFOX4 did not improve DFS or OS in patients with resected stage III colon cancer whose tumors express KRAS-wild type (-wt) and KRAS/BRAF-wt, but a certain benefit was observed in several subgroups of patients.

Patients with colon cancer were randomized between 28 to 56 days following resection to receive either 12 biweekly cycles of FOLFOX4 alone (arm A) or together with weekly cetuximab (arm B) at 250 mg/m^2 following the initial dose of 400 mg/m^2. The primary endpoint was disease free survival (DFS). The trial enrolled 2,559 patients. From those patients 1,602 were with KRAS-wt tumors; arm A had 811 patients and 791 patients were randomly assigned to arm B. Analysis done at a median follow-up of approximately 40 months showed no difference between arms for either disease-free survival (DFS) (P = 0.66) or OS (P = 0.55) in KRAS-wt patients. Also, no differences were observed in 984 KRAS/BRAF-wt patients in DFS (P = 0.91) or OS (P = 0.92). Conversely, a trend towards a better outcome was seen in patients with poor prognosis tumors (i.e. those with high grade tumors, or perforation/obstruction) and was significant in patients with pT4N2 at diagnosis (n=146, P=0.01).

Back to Top of CRC Section | Back to Top of Document

ESMO News
(Cont'd)

In another analysis of PETACC8 Intergroup Phase III trial after the median follow-up of approximately 3.3 years, no difference was seen between the arms for DFS (P=0.6562) or OS (P=0.5583) in KRAS wt patients (n=1602) or for DFS (P=0.9117) or OS (P=0.9236) in KRAS/BRAF wt patients (n=984). Worse DFS was seen with cetuximab in patients aged >70 years (n=149, P=0.051), in females (n=666; P=0.031) and patients with right-sided colon cancer (n=570; P=0.043).

Dr Taieb concluded that the addition of cetuximab to FOLFOX4 offered no DFS or OS benefits patients with resected, stage III, KRAS wt or KRAS and BRAF wt colon cancer. He also explained that cetuximab may have a different form of activity in micrometastatic disease compared with that observed in stage IV disease as a possible explanation for why cetuximab did not provide any additional benefit in this setting.

Source: ESMO 2012 Congress, Abstract No: LBA4, 520O

Phase III CORRECT Trial Reveals the Robustness of the OS Benefit of Regorafenib Treatment in Patients with Previously Treated mCRC

The OS analysis from CORRECT trial demonstrated the robustness and consistency of the OS benefit of regorafenib, an oral multikinase inhibitor, over placebo in patients with previously treated mCRC. The CORRECT trial was conducted to evaluate the oral multikinase inhibitor regorafenib (REG) in patients with mCRC whose disease had progressed after all approved standard therapies. This trial met its primary endpoint at a pre-planned interim analysis. The updated OS data was reported at ESMO 2012 Congress. Patients were randomized 2:1 to receive best supportive care plus either REG (160 mg OD PO) or placebo (PL) on a 3 weeks on/1 week off schedule. The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), overall response rate, and disease control rate. Safety and quality of life were also evaluated.

The study enrolled 760 patients who were randomized (REG: 505; PL: 255). Analysis showed that the hazard ratio (HR, REG/PL) for OS was 0.79 (1-sided P = 0.0038). Median OS was 6.4 months in the REG arm vs. 5.0 months in the PL arm. OS rate at 6 and 12 months was 52.2% and 24.1% in the REG arm vs. 43.1% and 17% in the PL arm, respectively. These data served as an update to previously reported OS data from the earlier interim analysis based on 432 (74%) events, which showed a HR for OS of 0.77 (95% CI, 0.64-0.94, 1-sided P = 0.0052). Patients in the REG arm received an average of 78.9% of the planned dose, and patients in PL arm 90.2% of the planned dose. The mean treatment duration was 12.1 ± 9.7 wks (REG) and 7.8 ± 5.2 wks (PL), respectively. Updated OS analysis confirmed the robustness and consistency of the OS benefit of REG treatment over PL in patients with previously treated mCRC.

Source: ESMO 2012 Congress, Abstract No: LBA18

Hepatocellular Carcinoma (HCC)

Patients with Advanced HCC Show No Benefit from Adding Erlotinib to Sorafenib

Phase III SEARCH trial tested whether adjunct erlotinib, a direct and reversible EGFR tyrosine kinase inhibitor, could have synergistic or additive antitumor effects when used with sorafenib in patients with advanced hepatocellular carcinoma (HCC). However, the study results revealed that the approach did not improve OS or TTP.

This Phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib enrolled 720 patients with advanced HCC aged 18 or more years, ECOG performance status (PS) 0–1 and Child-Pugh class A. The patients were randomized 1:1 to receive either continuous treatment with oral sorafenib 400 mg BID plus erlotinib 150 mg daily or sorafenib 400 mg BID plus placebo 150 mg daily and monitored every 6 weeks by CT scans. The primary endpoint of the study, defined as 33% of increase in the OS, was not met in this study.

The study showed that median OS in the 362 patients receiving the sorafenib + erlotinib was 9.5 months compared with 8.5 months in the sorafenib + placebo arm. TTP also did not vary significantly between treatment arms and was 3.2 compared with 4.0 months, with sorafinib + erlotinib and sorafenib + placebo, respectively. The rates of treatment-emergent and drug-related adverse events were similar between arms; and treatment-emergent and drug-related serious adverse events were also similar (58.0% vs. 54.6% and 21.0% vs. 22.8% in the sorafenib + erlotinib and sorafenib + placebo arms, respectively). The results reported by Dr. Andrew Zhu and colleagues during Presidential Symposium of the ESMO 2012 Congress, indicate that erlotinib added to sorafenib do not improve OS or TTP over sorafenib alone in patients with advanced HCC.

Source: ESMO 2012 Congress Abstract No: LBA2

Back to Top of CRC Section | Back to Top of HCC Section | Back to Top of Document

ESMO News
(Cont'd)

Ovarian Cancer

PM01183: A Promising New Drug for Ovarian Cancer

In platinum resistant/refractory ovarian cancer PM01183 (lurbinectedin) produced an overall response rate (ORR) of 27%, reported the results of a Phase II trial.

PM01183 is a new synthetic entity belonging to the tetrahydroisoquinoline family, which binds to the DNA minor groove inducing DNA breaks and transcription blockage. Dr Dominique Berton-Rigaud from the Center René Gauducheau, Nantes, France, presented the first stage of a randomized Phase II trial for PM01183. For the first stage, the trial enrolled 22 patients with platinum-resistant or refractory ovarian cancer, who had received no more than 2 prior chemotherapy lines for metastatic disease.

Results showed that 6 patients responded to PM01183 (2 according to Rustin criteria and 4 according to RECIST), giving an ORR of 27% (95%CI: 11%–50%) including one radiological complete response. The first evaluation showed that only six patients (27%) had progressed. Drug-related toxicity was tolerable, with the most common adverse events being anemia (90%), neutropenia (grade 1: 16%, grade 2: 19%, grade 3: 18%, and grade 4: 18%) and fatigue (55%). PM01183 was tolerable and demonstrated a very promising activity in platinum-resistant/refractory ovarian cancer patients. The second stage started in April 2012 and the trial has enrolled 60 additional patients who will be randomized to PM01183 or topotecan, in order to confirm the initial results.

Source: ESMO 2012 Congress, Abstract No: 968O

OCEANS Phase III Trial: Updated OS Analysis

In OCEANS trial, bevacizumab in combination with gemcitabine and carboplatin (GC) resulted in a statistically significant and clinically meaningful improvement in PFS in patients with platinum-sensitive (Plat-S) recurrent epithelial ovarian cancer (median PFS, 12.4 vs. 8.4 months; P < .0001). Updated interim OS data was presented at ESMO 2012 Congress.

Patients were randomized 1:1 to arm A: GC + concurrent placebo, followed by placebo until disease progression or unacceptable toxicity; or arm B: GC + concurrent bevacizumab followed by bevacizumab until disease progression or unacceptable toxicity. As of data cut-off date, 286 events (59% of patients) had occurred. No difference in OS between the arms, with an HR of 0.960 (95% CI, 0.760–1.214; log-rank P = 0.736) was observed. With a median follow-up of 42 months, median OS was 33.7 months in the GC + PL arm and 33.4 months in the GC + bevacizumab arm. No difference was seen in the number of grade 5 treatment-emergent adverse events between arms (1 in each), the number of deaths was balanced between arms, and the cause of death in the majority of cases was progressive disease in both arms. Investigators concluded that these data provide assurance that there is no detriment to OS with the addition of bevacizumab in this setting, and supports the positive benefit: risk ratio of the GC + bevacizumab regimen in significantly improving PFS in patients with platinum-sensitive recurrent epithelial ovarian cancer.

Source: ESMO 2012 Congress, Abstract No: 967O

Analysis by Chemotherapy Cohort in the GCIG AURELIA Phase III Trial in Platinum Resistant Recurrent OC

In platinum-resistant ovarian cancer, the improvement in PFS and ORR gained by adding bevacizumab to single-agent chemotherapy was observed across all chemotherapy cohorts. Exploratory analysis findings from AURELIA, Phase III study were presented at ESMO 2012 Congress. AURELIA is the first trial to compare bevacizumab + chemotherapy vs. chemotherapy in platinum (PT)-resistant recurrent ovarian cancer (OC).

Eligible patients had OC that had progressed <6 months after at least 4 cycles of PT-based therapy. Investigators chose single-agent chemotherapy (paclitaxel, pegylated liposomal doxorubicin or topotecan) for each patient before randomization to chemotherapy either alone or with bevacizumab until progression, unacceptable toxicity or withdrawal of consent. Between Oct 2009 and Apr 2011, 361 patients were randomized.

Table 3:

	Paclitaxel (N=115)		PLD (pegylated liposomal doxorubicin) (N=126)		Topotecan (N=120)	
	CT (N=55)	BEV + CT (N=60)	CT (N=64)	BEV + CT (N=62)	CT (N=63)	BEV + CT (N=57)
Median PFS (months)	3.9	10.4	3.5	5.4	2.1	5.8
HR (95% CI)	0.46 (0.30–0.71)		0.57 (0.39–0.83)		0.32 (0.21–0.49)	
ORR, %	28.8	51.7	7.9	18.3	3.3	22.8
Difference (95% CI)	22.9 (3.9–41.8)		10.4 (–2.4 to 23.2)		19.5 (6.7–32.3)	

Bevacizumab + chemotherapy was associated with a higher incidence of grade 2 peripheral sensory neuropathy in the paclitaxel cohort (35% vs 22% with chemotherapy), grade 2 hand-foot syndrome in the pegylated liposomal doxorubicin cohort (27%

Back to Top of Ovarian Cancer Section | Back to Top of Document

ESMO News
(Cont'd)

vs 14%) and grade 2 hypertension and proteinuria in the paclitaxel and pegylated liposomal doxorubicin but not the topotecan cohort. Grade 3 abdominal pain, vomiting and fatigue were more common with chemotherapy than bevacizumab + chemotherapy in all cohorts. The study concluded that in PT-resistant OC, the improvement in PFS and ORR gained by adding bevacizumab to single-agent chemotherapy was observed across all chemotherapy cohorts. However, increased chemotherapy exposure associated with prolonged PFS accounts for some increase in cumulative chemotherapy toxicity.

Source: ESMO 2012 Congress, Abstract No: 967O

Renal Cell Carcinoma (RCC)

COMPARZ Trial: Pazopanib and Sunitinib Similarly Effective in 1st Line Treatment of mRCC

Pazopanib has similar efficacy to sunitinib in controlling metastatic renal cell carcinoma, according to the results of the Phase III randomized, open-label COMPARZ trial. Dr Robert Motzer from Memorial Sloan Kettering Cancer Center, New York, US and colleagues set out to compare the efficacy, safety, and quality of life for pazopanib and sunitinib in a global, 1100-patient Phase III trial. The primary endpoint was to establish non-inferiority of progression-free survival, and safety and quality of life were evaluated as secondary endpoints, as well. The trial showed that pazopanib had similar efficacy (i.e. non-inferiority) compared to sunitinib in 1st line treatment of mRCC. For both drugs, the median PFS by the treating physician's assessment was slightly more than 10 months. Both drugs resulted in side effects, but fatigue and skin sores, occurred with less frequency for pazopanib than with sunitinib. The study concluded that pazopanib has similar efficacy to sunitinib with a differentiated safety and QoL profile.

Source: ESMO 2012 Congress, Abstract No: LBA8_PR

INTORSECT Trial: Temsirolimus Does Not Demonstrate Superiority in Survival over Sorafenib in 2nd Line Treatment in mRCC

The results of a Phase III trial INTORSECT comparing two commonly used drugs in the 2nd line treatment of metastatic renal cell carcinoma (mRCC) suggest that temsirolimus does not improve survival over sorafenib in the 2nd line setting. This is the first head-to-head Phase III trial comparing sorafenib, a VEGF inhibitor to temsirolimus, a mTOR inhibitor in renal cell carcinoma.

The INTORSECT trial included 511 RCC patients, whose disease progressed after 1st line sunitinib therapy and who had an ECOG performance status of 0 or 1. Median PFS with temsirolimus was 4.28 months compared to 3.91 months with sorafenib (HR = 0.87). Median OS for the temsirolimus group was 12.27 months compared to 16.64 months for those who received sorafenib (HR= 1.31). The most common adverse events (all grade, all cause) with temsirolimus were rash, fatigue, diarrhea, anemia, and hyperglycemia; with sorafenib, they were diarrhea, rash, hand-foot syndrome, and decreased appetite. Based on these results, the researchers found that temsirolimus did not show superiority to sorafenib in the primary end point of PFS or in the secondary end point of OS.

Source: ESMO 2012 Congress, Abstract No: LBA22_PR

INTORACT Trial: Bevacizumab Plus Temsirolimus Offers No Advantage Over Bevacizumab Plus Interferon

A Phase III trial has failed to confirm early clinical results with the combination of bevacizumab and temsirolimus over bevacizumab and interferon as 1st line therapy for clear cell mRCC, investigators from the INTORACT trial reported.

The INTORACT trial, a global Phase IIIb, randomized, open-label, multi-center study, compared temsirolimus plus bevacizumab with interferon plus bevacizumab as 1st treatment in 791 patients with predominantly clear cell mRCC. At the data cut off for final analysis, 489 patients had independently assessed PFS events. Median PFS with the temsirolimus combination was 9.1 months, compared to 9.3 months in the interferon group (P = 0.759). Median OS was 25.8 months in the temsirolimus group and 25.5 months for the interferon group (P = 0.638). Grade ≥3 mucosal inflammation, stomatitis, hypophosphatemia, hyperglycemia, and hypercholesterolemia were more common with temsirolimus plus bevacizumab (P < 0.001); grade ≥3 neutropenia was more common with interferon plus bevacizumab (P < 0.001). This study failed to find an advantage to the combination of bevacizumab and temsirolimus over bevacizumab and interferon in 1st line treatment of clear cell mRCC.

Source: ESMO 2012 Congress, Abstract No: LBA21_PR

Phase III AXIS Trial: Axitinib Resulted in Prolonged PFS and Similar OS Compared with Sorafenib for 2nd Line mRCC

In the Phase III AXIS trial, axitinib prolonged PFS compared with sorafenib as 2nd line therapy for

ESMO News
(Cont'd)

metastatic renal cell carcinoma (mRCC). At ESMO 2012 Congress, mature overall survival (OS) data was presented from the same trial.

The study enrolled 723 patients with clear cell mRCC, progressive disease after 1 systemic therapy, who were randomized 1:1 to axitinib 5 mg twice daily (BID) or sorafenib 400 mg BID. OS was analyzed as a secondary endpoint based on 425 events and compared using a 1-sided log-rank test stratified by ECOG PS and prior therapy. Pre-treatment prognostic factors were studied by multivariate analyzes. Patients were grouped by diastolic blood pressure (dBP) on therapy (≥1 dBP measurement ≥90 vs dBP <90 mmHg) and OS was evaluated. Median OS (mOS) was 20.1 months in the axitinib arm and 19.2 months in the sorafenib arm; HR 0.969; P = 0.3744. In prior therapy subsets, mOS with axitinib vs. sorafenib was: prior cytokine, 29.4 vs. 27.8 months (HR 0.813); prior sunitinib, 15.2 vs. 16.5 months (HR 0.997); prior bevacizumab plus interferon-α, 14.7 vs. 19.8 months (HR 1.825); and prior temsirolimus, 14.0 vs. 8.5 months (HR 0.45). Prognostic factors for longer OS with 2nd -line therapy (P < 0.01) included type of prior therapy, ECOG PS = 0, no bone metastases, elevated haemoglobin, and low corrected calcium. In a 12-week landmark analysis, mOS was significantly longer in the dBP ≥90 mmHg group (axitinib arm: 20.7 vs. 12.9 months, HR 0.725, P = 0.014; sorafenib arm: 20.9 vs. 14.8 months, HR 0.657, P = 0.002). The study results demonstrated that axitinib resulted in prolonged PFS and similar OS compared with sorafenib for 2nd line mRCC. OS results and prognostic factors might be used in clinical trial design for novel agents in 2nd line therapy.

Source: ESMO 2012 Congress, Abstract No: 793PD

Melanoma

Promising New Data from Trials Aimed to Delay Resistance to BRAF Inhibitors

Promising new data on drug combinations of BRAF and MEK inhibitors indicate delayed resistance to treatment with BRAF inhibitors alone in metastatic melanoma. The Phase I and II trials focus on combination therapy to slow the development of resistance to drugs that inhibit BRAF, a gene that is mutated in about half of melanomas. The results are presented at the ESMO 2012 Congress.

Phase II of the BRAF Inhibitor, Dabrafenib Alone vs. Combination with MEK1/2 Inhibitor Trametinib

Dr Georgina Long from Westmead Hospital and the Melanoma Institute Australia and colleagues reported that combining the new drugs dabrafenib and trametinib provided a clinically meaningful improvement in PFS, response rate and duration of response in 162 patients with melanoma that had BRAF V600 mutations.

Patients enrolled in the study received either dabrafenib 150 mg twice daily; twice-daily dabrafenib plus once-daily 1 mg trametinib; or twice daily dabrafenib plus once-daily 2 mg trametinib. The combination prolonged PFS over single-drug therapy from 5.8 months to 9.4 months, which represents a 60% improvement. Among patients who received both drugs at the higher dose, 41% had not progressed 12 months after treatment began, compared to 9% in the monotherapy arm of the study. Dose reductions and interruptions, were made at 35% and 42% of patients in the combination arm compared to 4% and 6% in the dabrafenib arm. With dabrafenib + trametinib the most common grade 3+ adverse events were neutropenia and hyponatremia, which were seen in 11% and 7% of patients, respectively. Incidence of hyperproliferative skin lesions was much lower with combination compared to dabrafenib; cutaneous squamous cell carcinoma was 7% versus 19%, skin papilloma 4% versus 15% and hyperkeratosis was 9% versus 30%, respectively. The study concluded that dabrafenib plus trametinib provided a statistically significant and clinically meaningful improvement in PFS, RR and DoR compared to dabrafenib monotherapy in patients with BRAF V600 mutation-positive metastatic melanoma.

Source: ESMO 2012 Congress, Abstract No: LBA27_PR

Phase IB Study of Vemurafenib in Combination With the MEK Inhibitor, GDC-0973

A Phase I, BRIM7 study showed that the combination of the MEK inhibitor GDC-0973 and vemurafenib can be delivered safely, Dr Rene Gonzalez of the University of Colorado Cancer Center, Denver, and colleagues reported.

The study was not designed to evaluate efficacy. While early data in a small number of patients did show tumor reduction, it would be premature to comment on efficacy based on these preliminary results and further research is warranted, according to Dr Gonzalez. The most commonly reported adverse events by all patients regardless of attribution were diarrhea (54.5%), rash (50.0%), nausea (38.6%), fatigue/asthenia (34.1%), liver function abnormality (25.0%) and photosensitivity/sunburn (25.0%). Most frequent treatment-related grade ≥3 adverse events were diarrhea, rash, increased creatine phosphokinase and liver function abnormality which

Back to Top of RCC Section | Back to Top of Melanoma Section | Back to Top of Document

ESMO News
(Cont'd)

was seen in 6.8%, 6.8%, 6.8% and 4.5% of patients, respectively. Only one patient developed cutaneous squamous cell carcinoma. GDC-0973 in combination with vem was tolerable and AEs were manageable. The study concluded that the combination could be delivered safely at the respective single-agent MTDs of vemurafenib (960 mg BID) and GDC-0973 (60 mg 21/7). Plans are underway for Phase III testing of vemurafenib + GDC-0973.

Source: ESMO 2012 Congress, Abstract No: LBA28_PR

Gastrointestinal Stromal Tumor (GIST)

Phase III GRID Trial Update: Clinical Benefit with Regorafenib across Subgroups and Post-Progression in Patients with Advanced GIST

Regorafenib therapy significantly improved PFS in patients with gastro-intestinal stromal tumor (GIST) after failure of both imatinib and sunitinib. Results of subgroup and post-progression analyzes from Phase III GRID trial was presented at ESMO 2012 Congress.

Patients were randomized (2:1) to receive best supportive care plus either regorafenib 160 mg or placebo. The primary endpoint was PFS. Upon progression in either arm, unblinding could occur. Patients on placebo were eligible for crossover to open-label regorafenib and progressive patients on regorafenib were allowed to continue regorafenib upon local physician's choice. GRID screened 234 patients and randomized 199 (Regorafenib: 133, Placebo: 66). The PFS primary endpoint (according to RECIST) was met both per central review (median PFS 4.8 months for regorafenib vs. 0.9 months for placebo), and by investigator assessment (median PFS 7.4 months for regorafenib vs. 1.7 months for placebo). Exploratory sensitivity analyzes demonstrated similar positive impact on PFS across pre-specified subgroups by number of prior systemic therapy, geographical region, age, baseline ECOG score, duration of prior treatment with imatinib, or KIT/PDGFRA mutation. Median OS has not been reached in either arm. Taking the double-blind and open label periods together, 188 patients received regorafenib. Post-progression PFS per investigator assessment was 5.0 months for patients in the placebo arm who crossed over to regorafenib (n = 56), and 4.5 months for patients in the regorafenib arm who continued to receive regorafenib after unblinding (n = 41). The study concluded that regorafenib induced significant PFS benefit in GIST patients following resistance to both imatinib and sunitinib across all pre-specified subgroups. Only 41 patients on regorafenib (out of 133) whose physicians decided to continue regorafenib after RECIST progression had an additional PFS benefit which was in the same range.

Source: ESMO 2012 Congress, Abstract No: 1478O

EXPAND Study Shows No Benefit from Adding Cetuximab to 1st Line Chemotherapy in Advanced Gastric Cancer

EXPAND is a large open-label, randomized, controlled, Phase III trial of cetuximab plus capecitabine and cisplatin in patients with advanced gastric cancer, who has a poor prognosis and no established standard treatment. The results from the study do not show a benefit from adding cetuximab. The study data was reported by Dr Florian Lordick at the ESMO 2012 Congress.

The current trial compared capecitabine and cisplatin with and without anti-EGFR agent cetuximab in patients with gastric and gastroesophageal junction cancer. The primary of the EXPAND study was PFS, assessed by an independent review committee. Between June 2008 and December 2010, 904 patients were enrolled and randomized; 455 patients received capecitabine and cisplatin plus cetuximab and 449 received only capecitabine and cisplatin. Patient outcome was similar between treatment groups and the primary and secondary endpoints were not met; PFS was 4.4 vs. 5.6 months and OS was 9.4 vs. 10.7 months with cetuximab combination and control treatment, respectively. ORR was 29% with cetuximab and 30% with control. Safety profiles were consistent with those known for each agent but more grades 3/4 and serious adverse events were reported in the cetuximab arm. In conclusion no general benefit was seen from adding cetuximab to 1st line capecitabine and cisplatin for treating patients with advanced gastric cancer and more studies are needed to find effective treatments for these patients.

Source: ESMO 2012 Congress, Abstract No: LBA3

Combining S-1 and Docetaxel Improves Survival in Advanced Gastric Cancer

An analysis of a Japanese Phase III, START trial showed that the combination of the oral fluoropyrimidine, S-1 with docetaxel is beneficial for metastatic gastric cancer patients. S-1 is used as a standard treatment for advanced and recurrent gastric cancer in East Asia.

START trial was performed in Japan and Korea to evaluate potential benefits of adding docetaxel to S-1 in patients with advanced gastric cancer. Results of

Back to Top of Melanoma Section | Back to Top of GIST Section | Back to Top of Document

ESMO News
(Cont'd)

this study were reported through planned analysis at ASCO GI Symposium 2011 (YH Kim, *et al*). However, an independent biostatistician pointed out that there was a large number of censored cases which led to insufficient number of events for proper analysis. According to the recommendations by the statistician, further follow up of survival status was performed to analyze the START trial properly.

Patients with unresectable or recurrent gastric cancer were randomly assigned to docetaxel plus S-1 (DS) or S-1 alone (S-1). The primary end point was OS and the secondary endpoints were including PFS and RR. Of the 639 patients enrolled, 635 were eligible for analysis. The median survival time was 12.48 months in the DS group and 10.78 months in the S-1 group (P=0.0319). PFS was 5.29 months in the DS group and 4.17 months in the S-1 group (P=0.001). RR was 38.8% (32.8-45.2) in the DS group and 26.8% (21.6-32.6) in the S-1 group (P=0.0048). As for adverse events, Neutropenia was more frequent in the DS group and one patient died by Grade 4 thrombocytopenia in the DS group. Adding docetaxel to S-1 significantly improved OS, PFS and RR, but resulted in some increasing proportion of haematological toxicities. The study concluded that docetaxel in combination with S-1 is a new treatment option for patients with untreated advanced gastric cancer.

Source: ESMO 2012 Congress, Abstract No: LBA19_PR

COG Study: Addressing the Need for 2nd/3rd Line Treatments in Esophageal Cancer

The first Phase III trial to address the need for 2nd/3rd line treatments in esophageal cancer showed that gefitinib improved important quality-of-life measures and extended PFS, as reported by researchers from Cancer Research UK.

The COG study included 450 patients who had already progressed after 1st line treatment with up to two chemotherapy regimens, and were administered either placebo or the EGFR-inhibitor gefitinib. Median PFS was 35 days for patients who received placebo, and 49 days for those administered gefitinib. Treatment with the drug also improved dysphagia and odynophagia, two important indicators of quality of life in this patient group. In addition to the quality-of-life improvements and modest improvements in PFS, some patients saw durable benefits from the treatment. A further study, TRANSCOG, is planned to analyze over 300 patients' biopsies in an effort to identify a molecularly defined subgroup where the benefit is enriched, said study author Prof. David Ferry from New Cross Hospital in Wolverhampton, UK.

Source: ESMO 2012 Congress, Abstract No: LBA20_PR

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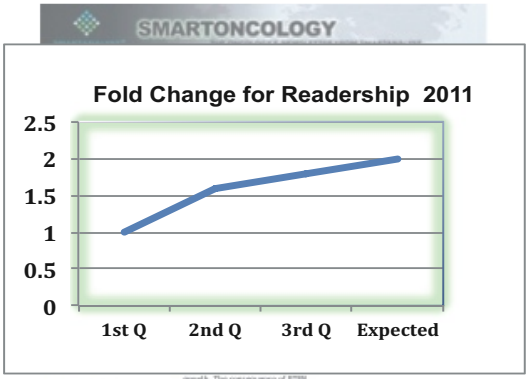

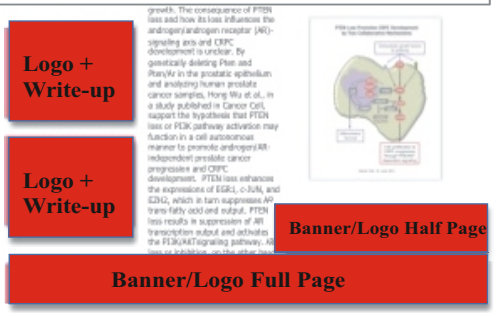

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Back to top of Newsletter Sponsorship Section | Back to Top of Document