European Society for Medical Oncology (ESMO) 2012

Highlights from ESMO 2012, September 29th - October 2nd 2012, Vienna, Austria

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From September 29th till October 2nd, Vienna formed the spectacular background for the annual meeting of the European Society for Medical Oncology (ESMO). It was the third time that Vienna played host to the ESMO Congress, with previous congresses taking place in 1996 and 2004. However, this years' edition proved to be the biggest and best congress yet with an astonishing 16,394 delegates from all over the world. Given the vast amount of data presented at ESMO 2012, this report does not aim to summarise the entire meeting, but will focus on ten important take-home messages from the meeting, presented during one of the presidential or proffered paper sessions. All abstracts presented during ESMO 2012 can be consulted at http://abstracts.webges.com/esmo2012/myitinerary.
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1. Optimal treatment duration defined for trastuzumab

One year of adjuvant trastuzumab should remain the standard of care for HER2-positive early breast cancer patients. This was the conclusion for both the HERA trial and the PHARE study, presented during the presidential symposium at ESMO 2012. The HERA trial is an international, multi-centre, phase III randomised study involving 5,102 women with early HER2-positive breast cancer. After finishing primary therapy with surgery, chemotherapy and radiotherapy as indicated, they were randomly assigned to trastuzumab therapy every three weeks for one year, two years or observation. As of April 12th 2012, the unadjusted hazard ratio for a woman experiencing disease relapse in the two-year treatment arm versus the one-year arm was 0.99 (95%CI 0.85-1.14; p=0.8588). Also the overall survival (OS) rate in the two arms was comparable (HR[95%CI]: 1.05[0.86-1.28]; p=0.6333).[1] Furthermore, researchers found that the durable benefit in disease-free survival (DFS) and OS of one-year trastuzumab compared to no trastuzumab that had been reported previously remained stable at eight years of median follow-up.[1]

In the PHARE trial, 3,384 patients with HER2-positive early breast cancer who had received at least four cycles of (neo)-adjuvant chemotherapy and who were receiving adjuvant trastuzumab for a maximum of six months were randomised to either complete twelve months of trastuzumab, or to stop trastuzumab at six months. Since the confidence interval contained the 1.15 non inferiority margin, the 6-month trastuzumab arm was not demonstrated to be significantly inferior to 12-month trastuzumab, (HR[95%CI]: 1.28[1.04-1.56], p=0.29).[2] However despite the inconclusive result in terms of non-inferiority, the HR of 1.28 suggests a trend favouring 12 months, according to the study researchers interpretation.

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2. Crizotinib is superior to single-agent chemotherapy for ALK-positive advanced NSCLC

New phase III data show that crizotinib is more effective treatment than standard chemotherapy for patients with advanced, ALK-positive non-small cell lung cancer (NSCLC), who were previously treated with first-line, platinum-based chemotherapy. The phase III study at hand 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 prolonged progression-free survival (PFS) to a median of 7.7 months compared to 3.0 months among those patients who received the chemotherapy (HR[955CI]: 0.49[0.37-0.64]; p<0.0001) (*Figure 1*).[3] The overall response rate (ORR) was also significantly higher in patients treated with crizotinib (65% versus 20%; p<0.0001). So far, the analysis of the OS rate with the two drugs is still immature. Moreover, given the high amount of crossover from patients in the chemotherapy arm to crizotinib, the determination of OS benefit will be very challenging. Both treatment groups had the same incidence of grade 3/4 treatment-related adverse events (31%). Six percent of crizotinib patients compared to 10% of pemetrexed/docetaxel patients discontinued the trial due to treatment-related adverse events.

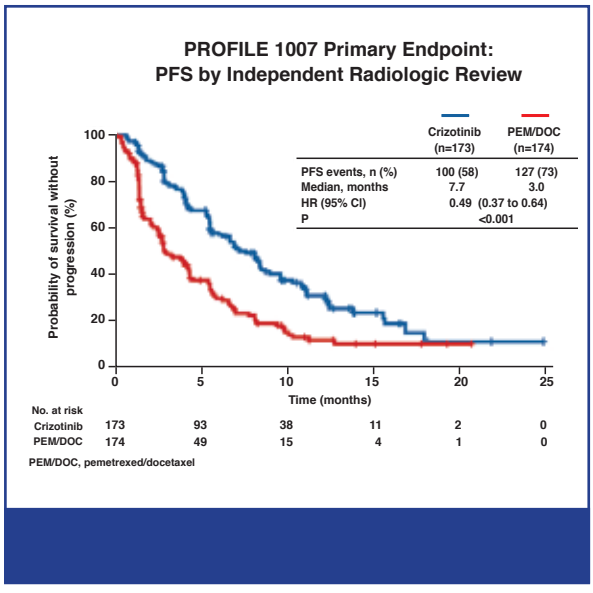

Figure 1. PFS in the PROFILE 1007 study, comparing crizotinib to single-agent chemotherapy in ALK positive advanced NSCLC.

However, despite side-effects, patients still reported improved quality of life on crizotinib compared to chemotherapy.[3]

3. No evidence-supporting routine use of doxorubicin-ifosfamide for soft tissue sarcoma

The randomised, phase III EORTC62012 study was designed to evaluate single agent doxorubicin versus doxorubicin plus ifosfamide as first-line chemotherapy in patients with advanced or metastatic soft tissue sarcoma. This study was initiated to address concerns that previous studies comparing these agents in soft tissue sarcomas had used suboptimal doses of ifosfamide as non-randomised data had suggested that a higher dose of this drug could increase response rate and PFS.

In the trial at hand, 455 patients with locally advanced or metastatic, grade 2 or 3 soft tissue sarcoma, were randomised to receive either doxorubicin (75mg/m^2, bolus or 72h IC) alone or in combination with ifosfamide (10g/m^2 over four days with mesna and pegfilgrastim) as first-line treatment. After a median follow-up of 56 months, no significant difference in OS was seen between both treatment arms. Median OS was 14.3 months with doxorubicin/ifosfamide and 12.8 months with doxorubicin (HR[95%CI]: 0.83[0.67−1.03],; p=0.076). At one year, the OS rate was 60% with doxorubicin/ifosfamide and 51% with doxorubicin. Interestingly, doxorubicin/ifosfamide was associated with a longer PFS (7.4 versus 4.6 months; HR[95%CI]: 0.74[0.60−0.90]; p=0.003) and higher ORR (26.5% versus 13.6%) compared with doxorubicin alone. However, this advantage comes at the cost of increased toxicity.[4]

4. No gain from adding cetuximab to adjuvant FOLFOX4 in patients with resected stage III colon cancer

Final results of the PETACC8 trial showed that adding cetuximab to FOLFOX4 does not improve OS in patients with resected stage III colon cancer whose tumours express KRAS-wild type (-wt) and KRAS/BRAF-wt. However, certain benefit was observed in specific subgroups of patients.

In PETACC8, 2,559 patients with colon cancer were randomised to receive either 12 biweekly cycles

of FOLFOX4 alone (Arm A) or in combination with weekly cetuximab (250 mg/m^2 following the initial dose of 400 mg/m^2) (Arm B). From those patients 1,602 had KRAS-wt tumours (811 in Arm A and 791 in arm B). BRAF status was determined in 1,134 (71%) KRAS-wt patients. After a median follow-up of approximately 40 months no difference was observed between both arms for either DFS (HR:1.047; p=0.66) or OS (HR:1.09; p=0.55) in KRAS-wt patients. No differences were observed in 984 KRAS/BRAF-wt patients in DFS (HR:0.985; p=0.91) or OS (HR:0.98; p=0.92).[5]

Interestingly, poorer DFS outcomes were seen with cetuximab in patients older than 70 years (HR:1.97; p=0.051), in females (HR:1.45; p=0.03) and in patients with right-sided colon cancer (HR:1.40; p=0.04). A trend towards better outcome was seen in patients with poor prognosis, high grade, T4N2 tumours, perforation/obstruction or VELI+ tumours and was significant in 146 patients who were staged as pT4N2 at diagnosis (HR:0.55; p=0.01).[5]

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

The phase III SEARCH trial evaluated whether adjunct erlotinib, a direct and reversible EGFR tyrosine kinase inhibitor, could have synergistic or additive antitumour effects when used with sorafenib in patients with advanced hepatocellular carcinoma (HCC). However, according to a presentation of the SEACH data during the presidential symposium at ESMO 2012, this approach did not improve OS or time to progression (TTP).

In SEARCH, 720 patients with advanced HCC were randomised to receive either continuous treatment with oral sorafenib plus erlotinib or sorafenib plus placebo. The primary endpoint of the study, defined as 33% of increase in the OS, was not met in this study. Median OS in the 362 patients receiving the sorafenib/erlotinib was 9.5 months compared to 8.5 months in the sorafenib/placebo-treated patients. Furthermore, TTP also did not vary significantly between treatment arms and was 3.2 compared to 4.0 months, with sorafinib/erlotinib and sorafenib/palcebo respectively. The disease control rates of 43.92% and 52.51% favoured the sorafenib/placebo arm. Safety profiles were similar between the two treatment groups and consistent with those of each individual agent; however, the withdrawal rate was higher in the erlotinib/sorafenib arm, with fewer patients completing one or more cycles.[6]

As such, sorafenib remains the standard treatment for patients with advanced HCC.

6. Cetuximab in combination with capecitabine and cisplatin as first-line treatment in advanced gastric cancer

In the Phase 3 EXPAND trial, patients with advanced gastric cancer were randomised to receive 3-week cycles of capecitabine (1000mg/m^2 twice daily on days 1-15) and cisplatin (80mg/m^2 IV on day 1) plus weekly cetuximab (400 mg/m^2 loading dose on day 1 and 250 mg/m^2 thereafter) (N=455), or the capecitabine/cisplatin combination alone (N=449). Unfortunately, PFS, OS and best ORR were similar between both treatment arms *(Table 1)*. Furthermore, the addition of cetuximab was associated with more grade 3/4 adverse events, in particular skin rash (13% versus 0%), diarrhea (8% versus 4%), hand-foot syndrome (7% versus 2%), hypomagnesaemia (11% versus 1%) and hypokalaemia (13% versus 9%).[7]

As such, the addition of cetuximab showed no benefit compared to chemotherapy alone for the first-line treatment of advanced gastric cancer.

7. COMPARZ, INTORSECT & INTORACT: three phase III studies investigating treatments of renal cell carcinoma

During ESMO 2012, results of three eagerly awaited phase III trials in patients with advanced renal cell carcinoma (RCC) were presented.

In the COMPARZ study, pazopanib was shown to be as effective as sunitinib in the first-line treatment of metastatic RCC. A total of 1,110 patients with treatment-naive advanced RCC were randomised between pazopanib or sunitinib. The primary endpoint of PFS by independent review was shown to be comparable for both agents (8.4 versus 9.5 months; HR[95%CI]: 1.047[0.898-1.220]) *(Figure 2)*. Both drugs resulted in side-effects, but more troublesome adverse events such as fatigue and skin sores, occurred less frequently with pazopanib than with sunitinib. Moreover, the quality-of-life question-

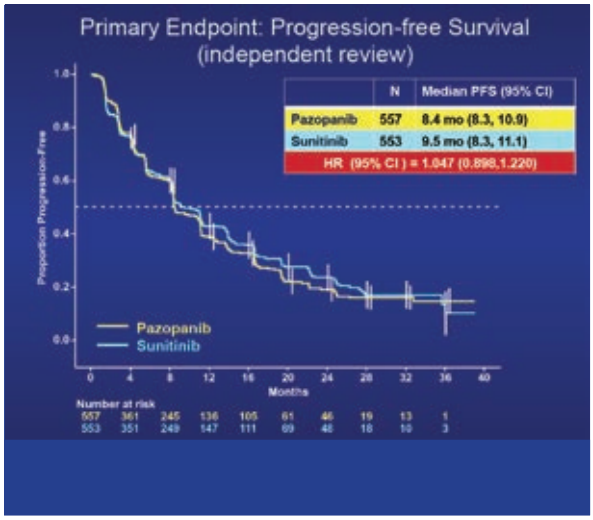

Figure 2. Progression-free survival by independent review in the COMPARZ study.

naires were in favour of pazopanib, suggesting improved tolerability for pazopanib over sunitinib.[8] Results of the phase III INTORSECT, a trial comparing two commonly used drugs in the second-line treatment of RCC suggest that temsirolimus does not improve survival over sorafenib in the second-line setting. This study included 511 RCC patients whose disease progressed after first-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. Median OS for the temsirolimus group was 12.27 months compared to 16.64 months for those who received sorafenib.[9] As such, this trial suggests that drugs inhibiting the VEGF pathway may be a better option than mTOR inhibitors for RCC patients progressing on sunitinib.

Table 1. Efficacy data from the phase III EXPAND study[7].

	Capecitabine/ cisplatin	Guidelines
Number of patients	455	449
PFS (months, 95%CI)	4.4 [4.2-5.5]	5.6 [5.1-5.7]
	HR[95%CI]: 1.091 [0.920-1.292]; p=0.3159	
OS (months, 95%CI)	9.4 [8.3-10.6]	10.7 [9.4-11.3]
	HR[95%CI]: 1.004 [0.866-1.165] p=0.9547	
Best ORR (CR+PR)	30%	29%

The INTORACT study is a global phase IIIb, randomised, open-label, multi-centre study, comparing temsirolimus plus bevacizumab to interferon plus bevacizumab as first-line treatment in 791 patients with predominantly clear cell metastatic RCC. The median PFS with the temsirolimus combination was 9.1 months, compared to 9.3 months in the interferon group. Median OS was 25.8 months in the temsirolimus group and 25.5 months for the interferon treated patients.[10] As such, this study failed to find an advantage to the combination of bevacizumab and temsirolimus over bevacizumab and interferon, and did therefore not confirm preliminary results of this combination.

8. First results of TURANDOT comparing two bevacizumab-containing regimens as first-line treatment for HER2-negative metastatic breast cancer

In TURANDOT, chemotherapy-naive, HER2-negative metastatic breast cancer patients were randomised to placebo or one of two bevacizumab-containing regimens: 10 mg/kg d1 bevacizumab plus 90 mg/m^2 d1 paclitaxel four times weekly or 15 mg/kg d1 bevacizumab plus 1000 mg/m^2 bid capecitabine three times per week until disease progression or unacceptable toxicity occurred. The primary endpoint of non-inferiority in OS was not met at the level of statistical significance. The pre-planned interim analysis done at a median of nineteen months post-treatment showed one year OS rates of 81% in patients treated with bevacizumab plus paclitaxel and 79% in patients receiving the bevacizumab/capecitabine combination.[11] Response rates were 44% and 27%, in the two arms respectively (p=0.0001). Median PFS in the bevacizumab/paclitaxel and bevacizumab/capecitabine arms was eleven months and 8.1 months respectively (p=0.0052). No new safety issues were raised; adverse events were consistent with the known safety profiles of all three drugs.[11]

9. Dual therapy shows potential in melanoma

In the presented phase II study, 162 melanoma patients with BRAF V600 mutations were randomised to receive either dabrafenib 150mg twice

daily; dabrafenib 150mg twice daily plus once-daily 1mg trametinib; or dabrafenib 150mg twice daily plus once-daily 2mg trametinib. Results show that the PFS was 9.4 months for patients receiving dabrafenib plus tramentinib 2mg versus 5.8 months for patients receiving dabrafenib alone (HR[95%CI]: 0.39[0.25-0.62]; p<0.0001). Furthermore, the confirmed response rate was 76% for patients receiving dabrafenib plus tramentinib 2mg versus 54% for dabrafenib monotherapy (p=0.026).[12] Pyrexia and chills were the most common adverse events, occurring in 71% and 58% of patients respectively receiving dual therapy. Interestingly, the combination also decreased the rate of the cutaneous toxicities compared to dabrafenib monotherapy, particularly the oncogenic cutaneous toxicity of squamous cell carcinoma.[12]

10. treatment with bevacizumab beyond progression: a new standard in metastatic colorectal cancer?

The randomised Phase 3 BEBYP trial evaluated the continuation of bevacizumab beyond progression in patients with mCRC who had received bevacizumab as part of their first-line therapy. In total 184 patients who progressed following first-line chemotherapy (FOLFOX, FOLFIRI or FOLFOXIRI) plus bevacizumab were randomised to receive second-line treatment with chemotherapy alone (either FOLFOX or mFOLFIRI) or in combination with bevacizumab 5mg/kg every two weeks.

Accrual to this trial was stopped early, based on results from the similarly designed TML trial, which demonstrated that bevacizumab continued with second-line chemotherapy was associated with a significant improvement in OS. Nevertheless, results of BEBYP showed that the addition of BEV was associated with a sign to chemotherapy alone (6.77 versus 4.97 months; HR[95%CI]: 0.65[0.48-0.89]; p=0.0062). The safety profile of bevacizumab + chemotherapy was consistent with previously reported data.[13]

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