ESMO 2016 Congress

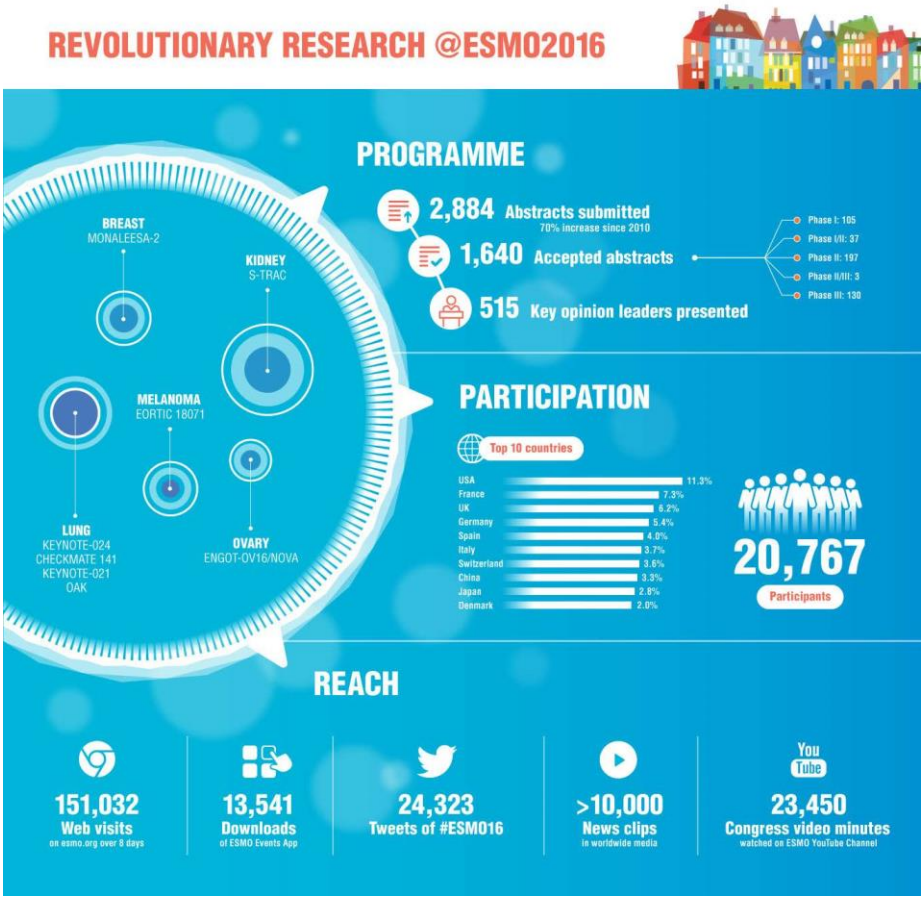
7-11 October, 2016

Copenhagen, Denmark

Table of Contents

Summary

The European Society for Medical Oncology (ESMO) 2016 Congress, held October 7 to 11 in Copenhagen, Denmark, was a record-breaker on all levels. It was resounding success and in a dedicated infographic you can find the congress programme statistics. A primary emphasis in the scientific programme was placed on two areas: precision medicine and immunology and immunotherapy across multiple tumour types and how these advances change the treatment landscape in oncology. This report is an overview of key scientific presentations made during the Congress by leading international investigators. It attempts to represent the diversity and depth of the ESMO 2016 scientific programme, as well as advances in oncology.



ESMO 2016 record breaking Congress

GASTROINTESTINAL TUMOURS - Non-colorectal

Olaparib in combination with paclitaxel did not improve survival over sole paclitaxel in patients with advanced gastric cancer that progressed on first-line therapy

Lead author Yung-Jue Bang, Department of Internal Medicine, Seoul National University Hospital (SNUH)-Yongon Campus, Seoul, Republic of Korea presented results of the phase III GOLD trial of olaparib added to paclitaxel in adult patients with advanced gastric cancer and at least one lesion that was detectable by imaging. The study included 525 patients from China, Japan, South Korea, and Taiwan with gastric and gastrooesophageal junction tumours who progressed following frontline therapy. Patients were randomised to olaparib at 100 mg tablet twice daily in combination with weekly paclitaxel at 80 mg/m^2 for a 28-day cycle or to receive the same dose of paclitaxel plus placebo. Tumour samples from resected tissue or a biopsy were tested for ATM expression, with 18% of the participants testing negative. The primary endpoint of the study was overall survival (OS) with secondary endpoints of progression-free survival (PFS), safety, and response.

Across the overall population, median OS was 8.8 versus 6.9 months, with and without olaparib, respectively (hazard ratio [HR] 0.79; 97.5% confidence interval [CI] 0.63, 1.0; p = .0262), which did not meet the primary endpoint. PFS was 3.7 months with olaparib/paclitaxel versus 3.2 months with paclitaxel alone (HR 0.84; 97.5% CI 0.67, 1.04; one-sided p = 0.157), The adjusted objective response rates were similar in each arm, odds ratio 1.69 (p = 0.0548). The trend towards OS benefit was independent of ATM status, the subgroup of patients that were ATM-positive demonstrated similar results to the overall population.

Adverse events (AEs) with the combination were similar to those seen with single-agent paclitaxel.

Grade ≥3 AEs occurred in 78% of patients treated with olaparib plus paclitaxel compared with 62% of those receiving paclitaxel alone. Serious AEs were higher in the paclitaxel/placebo arm compared with olaparib (35% versus 25%). The most common AE that led to a dose modification was neutropenia (54.1% with olaparib versus 37.1% with placebo). AEs leading to discontinuation occurred in 16% of combination and 10% of paclitaxel patients. D081BC00004; NCT01924533. Bang *et al.* Abstract LBA25

Practice point and future research opportunities

In the phase III Gold study, the combination of olaparib and paclitaxel failed to improve OS compared with paclitaxel and placebo for patients with advanced gastric cancer.

Olaparib is a selective inhibitor of PARP-1 and PARP-2 that is currently approved in the United States as a treatment for women with BRCA-mutant advanced ovarian cancer following three or more prior lines of chemotherapy. Additionally, the agent has received a breakthrough therapy

designation as a potential treatment for men with BRCA1/2 or ATM-mutated metastatic castration-resistant prostate cancers. Outside of gastric cancer, a number of phase III studies continue to assess olaparib for patients with cancer across a variety of indications, including breast, pancreatic, and prostate cancer. A study is exploring the agent as an adjuvant treatment for patients with BRCA-mutant, HER2-negative breast cancer (NCT02032823), and another is assessing frontline olaparib for patients with germline BRCA-mutant pancreatic cancer (NCT02184195). Phase III studies are also assessing the combination of olaparib with the angiogenesis inhibitor cediranib (NCT02502266, NCT02446600).

Irinotecan added to S-1 significantly improves PFS over S-1 alone in patients with advanced esophageal squamous cell carcinoma that failed platinum- or taxane-based chemotherapy

Juan Huang, of the Medical Oncology Department, Cancer Institute and Hospital, Chinese Academy of Medical Sciences, in Beijing, China, and colleagues conducted a phase III trial in patients with advanced oesophageal squamous cell carcinoma that was refractory to platinum-based or taxane-based first-line chemotherapy. The patients were randomised to irinotecan at 160 mg/m^2 intravenously on day 1 every 2 weeks plus S-1 at an initial oral dose of 40 to 60 mg twice a day on days 1-10 every 2 weeks or to S-1 at an initial oral dose of 40 to 60 mg twice a day on days 1-14 every 3 weeks. The patient baseline characteristics were similar between the 53 patients receiving irinotecan/S-1 and the 49 patients receiving S-1 only; approximately 85% were aged 65 or younger, 90% were male, and 90.6 versus 81.6% of patients in the irinotecan/S-1 arm versus S-1 arm had 0 to 2 metastatic sites. The primary end point was progression-free survival (PFS), and secondary end points included response rate, disease control rate (DCR) and overall survival (OS).

At an interim analysis, superior efficacy with the combination treatment over S-1 alone was observed; significantly improved median PFS of 3.9 months with irinotecan and S-1 versus 1.8 months with S1 only (p = 0. 0019) was demonstrated. The response rate was doubled at 28.3% with irinotecan and S-1 compared to 12.2% in the S1 arm (p = 0.045). Median OS was numerically longer with irinotecan and S-1 at 7.0 months compared to 6.3 months with S-1 (p = 0.2622). The most frequently reported adverse events in the irinotecan and S-1 arm were nausea, vomiting, and neutropenia. NCT02319187. Huang *et al.* Abstract LBA27

Practice point and future research opportunities

No standard second-line treatment has been determined for patients with advanced oesophageal squamous cell carcinoma following failure of prior platinum- or taxane-based chemotherapy. These phase III trial results indicate that PFS is improved with the addition of irinotecan to S-1 therapy over sole S-1 in this setting.

Regorafenib represents a potential second-line treatment option for patients with HCC that progress on sorafenib

Jordi Bruix, Liver Unit Hospital Clinic, University of Barcelona in Barcelona, Spain presented results from the phase III RESOURCE trial of regorafenib in patients with hepatocellular carcinoma (HCC) who progress on sorafenib. The investigators enrolled 573 patients from centres in 21 countries who were stratified by Asia versus non-Asia, the presence/absence of microvascular invasion or extrahepatic disease, ECOG performance status of 0 versus 1, and α-fetoprotein less than 400 ng/mL versus 400 ng/mL or greater. All patients had Barcelona Clinic Liver Cancer (BCLC) stage B or C designated HCC plus documented radiologic progression after a minimum of 20 days of sorafenib at 400 mg or more per day. Baseline characteristics were balanced between the regorafenib and placebo arms. The patients' median age was 63 years, 88% were male, and 87% of patients had BCLC stage C disease. The patients were randomised 2:1 to oral regorafenib at 160 mg or placebo once daily for 1 to 3 weeks of a 4-week cycle. The median treatment duration was 3.6 (range: 0.03 to 29) months for regorafenib versus 1.9 (range: 0.2 to 27) months for placebo.

Regorafenib improved overall survival (OS), the trial's primary endpoint, by nearly 3 months over placebo; median OS was 10.6 months versus 7.8 months, respectively. Regorafenib patients had a 38% reduction in the risk of death and a 54% reduction in the risk of progression compared to placebo. Patients receiving regorafenib also demonstrated significantly prolonged median PFS of 3.1 compared to 1.5 months in patients receiving placebo, hazard ratio [HR] 0.46 (p <0 .001). Similarly, median time to progression (TTP) was 3.2 versus 1.5 months with regorafenib versus placebo, respectively, HR 0.44 (p <0 .001). A higher disease control rate of 65.2% was observed with regorafenib compared to 36.1% with placebo (p < 0 .001), and 10.6% of patients receiving regorafenib showed either complete or partial response versus 4.1% of placebo patients (p = 0.01).

Treatment emergent adverse events (TEAEs) grades 3/4 occurred in 58% versus 29% and drug related TEAEs leading to treatment interruption occurred in 42% versus 8% of patients in the regorafenib and placebo arms, respectively. The most commonly reported grade adverse events ≥3 were hypertension (15.2% versus 4.7%), hand–foot skin reactions (12.8% versus 0.5%), fatigue (9.1% versus 4.7%), and diarrhoea (3.2% versus 0.0%) in the respective arms.

Quality of life data that was collected using the EQ-50 index, EQ-50 VAS, Fact-G, FACT-Hep total, and Trial Outcome scales demonstrated significant differences between patients receiving regorafenib and placebo only on the last 2 scales; the difference between the groups was -8.85 on the FACT-Hep total, and -4.05 on the Trial Outcome Index (both p < 0.001). NCT01774344. Brix *et al.* Abstract LBA28

Practice point and future research opportunities

No second-line systemic treatment options have been approved to date for hepatocellular

carcinoma. Regorafenib, an oral multikinase inhibitor, treatment resulted in a higher response rate and disease control rate that was twice that of placebo in patients with late stage hepatocellular carcinoma who progressed during sorafenib treatment. Results from this phase III trial also showed that regorafenib significantly improved overall survival in these patients. Regorafenib may have the potential to become the standard of care as second-line treatment in patients with previously treated hepatocellular carcinoma that are unsuited to loco-regional therapy and have progressed on sorafenib because regorafenib significantly improved overall survival over placebo.

Arguments against regorafenib as second-line treatment in this setting state that no clinically meaningful differences in patient-reported quality of life outcomes were observed on most scales between patients treated with regorafenib and placebo, and there was a high rate of regorafenib treatment interruption due to adverse events, suggesting that regorafenib was not well-tolerated. However, nearly 50% of patients with hepatocellular carcinoma in this study received the full dose of regorafenib.

Centralisation of surgery is the key to lowing the risk of post-operative mortality in oesophago-gastric cancer patients

Caroline Gronnier, Department of Digestive and Oncological Surgery, Lille University Hospital in Lille, France and colleagues conducted a systematic review of all 11,196 consecutive patients undergoing oesophago-gastric cancer surgery in France between 2010 and 2012 to determine whether centre volume impacted postoperative mortality (POM). The investigators compared the 30- and 90-day POM according to the centre volume in patients attending the centre. Each centre was categorised by low or less than 20 cases per year, intermediate with 20 to 39, or high with 40 to 59, and very high, which was defined a 60 or more cases per year. Centres were also evaluated following stratification of patients by Charleson scores of 0, 1-2, ≥3. The patients were sub-grouped into the oesophageal cancer group with 3286 patients and 7910 patients comprised the gastric cancer subgroup for comparisons of 30-day and 90-day POM per centre.

The majority, 64.2% of patients overall, were treated in low-volume centres. However, a reduction in the relative risk of nearly 70% in both 30- and 90-day POM was observed in very-high versus low volume centres, that remained constant regardless of the patient's Charleson score or tumour location. An inverse relationship between decreasing POM rates was observed as the volume of the centre increased; a significant linear decrease in 30- and 90-day POM was observed with increased centre volume. The rates for 30-day POM were 5.7%, 4.3%, 3.3%, and 1.7%, whereas the rates for 90-day POM were 10.2%, 7.9%, 6.7%, and 3.6% in low-, intermediate-, high- and very high-volume centres, respectively ($p < 0.001$). The comparison of low- and very high-volume centres by Charleson score showed 30-day POM rates were 4.0% versus 1.1% for the patients with a Charleson score of 0 ($P=0.001$), 7.5% versus 3.4% for Charleson scores 1-2 ($p < 0.001$), and 14.7% versus 3.7% for Charleson scores ≥3 ($p = 0.003$). Assessment of the oesophageal and gastric cancer subgroups demonstrated a similar linear decrease. Gronnier *et al.* Abstract 609O

Practice point and future research opportunities

Recent reports have demonstrated that centralisation of cancer services improves the outcome and quality of care for patient, and centralisation has been particularly recommended for less common cancers. This large analysis of a French database demonstrated that the risk of 30- and 90-day post-operative mortality was significantly reduced as the case-volume of the centre increased, with the risk substantially lower in very high volume centres, indicating that oesophago-gastric cancer surgery should be centralised to reduce the risk of post-operative mortality. The patients fared better in high volume centres irrespective of the patient's Charleson score or the location of the tumour.

Next generation sequencing of oesophagogastric adenocarcinomas identifies molecular signatures that correspond to response following HER2 inhibition, first-line 5FU/platinum and PD1/CTLA4 blockade

Yelena Y. Janjigian, of the Memorial Sloan-Kettering Cancer Center, in New York, USA reported that her team was able to identify several potential therapeutic targets that were specific to oesophagogastric (EG) subtypes of adenocarcinoma by next generation sequencing (NGS). The putative targets included receptor tyrosine kinase (RTK) alterations in tumours with chromosomal instability, in tumours driven by the Epstein-Barr Virus (EBV), and tumours with microsatellite instability (MSI). DNA from patients with stage IV EG adenocarcinoma was evaluated using the NGS MSK-IMPACT assay, which is capable of detecting somatic mutations, deletions and amplifications and determined the association of these results with clinical outcomes.

The investigators analysed 429 tumours from 319 patients with stage IV EG adenocarcinoma; of these, 33% were from the oesophagus, 52% were of gastric origin, and 15% were located at the gastro-oesophageal junction (GEJ). Of the 80 HER2-positive tumours, as determined by immunohistochemistry and FISH, 71 were obtained prior to treatment with trastuzumab and 38 were taken afterwards; there were also 28 paired pre/post samples.

An evaluation of the paired samples showed a post-therapeutic loss of HER2 amplification in 16% of cases, the gain of new MET amplification in 7%, new amplification of EGFR in 4%, and new amplification of IGF1R in 4% of cases. Investigation of the paired samples also showed new mutations post-treatment in 14% of ERBB4 case, 11% of KRAS, 7% of PIK3CA, and 7% of cases showed newly mutated mTOR.

Analysis of the post-treatment tumours revealed co-occurring EGFR/HER2 amplification in 4 of 20 patients receiving afatinib, which corresponded to 3 of these patients achieving partial response (PR). In 20 (6%) of patients with deleterious somatic (n=15) or germline (n=5) BRCA1/2 mutations, 4 of 5 patients with BRCA1/2 germline showed loss of the wild-type allele and exhibited dramatic tumour regression following 5FU/platinum treatment; of these, 2 patients achieved complete response (CR) with a time to progression ranging from 15 to 22 months, and demonstrated overall survival (OS) of 18 to 35 months. The one patient with germline BRCA1

but without loss of heterozygosity experienced rapid disease progression and OS of just 9 months. One patient with an inactivating somatic BRCA1 mutation (germline wild-type) and LOH achieved CR after receiving 5FU/platinum that is ongoing at 28 months. MSI tumours were reported in 12 (4%) of patients; 3 of these patients were treated with an anti-PD1 agent, which resulted in one patient achieving a CR that was durable at 14 months, and one patient each demonstrated PR and stable disease after 3 months of therapy. One patient with a microsatellite stable EBV-positive tumour that was treated with PD1/CTLA4 blockade achieved a CR that is ongoing at 17 months. Patients acquiring trastuzumab resistance demonstrated loss of ERBB2 amplification and secondary alterations in the RTK/RAS/PI3K pathway. NCT01775072. Janjigian *et al.* Abstract 612O

Practice point and future research opportunities

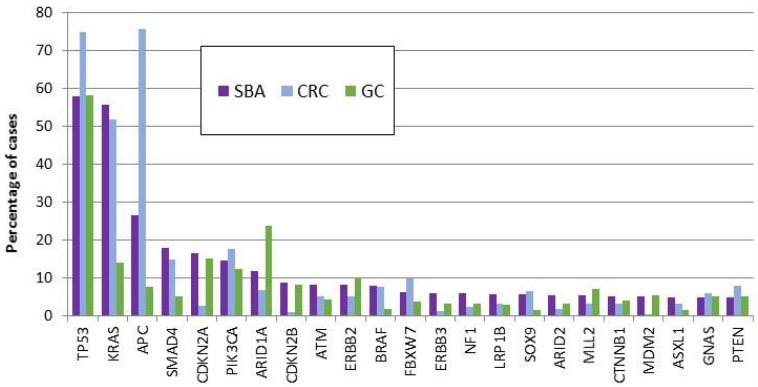
The study supports testing of patients with oesophagogastric cancer for germline and somatic BRCA1 and BRCA2 by next generation sequencing which may identify patients most likely to respond to platinum-based chemotherapy. Promising activity was observed with immunotherapy in patients having microsatellite instability and EBV+ tumours.

Comprehensive genomic profiling identifies potentially actionable mutations in small bowel adenocarcinoma

Results from the largest and most comprehensive genomic characterisation of 3 large series of small bowel adenocarcinoma (SBA) revealed different mutational frequencies in SBA, colorectal carcinoma (CRC), and gastric carcinoma (GC) that were potentially druggable, according to Alexa Schrock, Clinical Development, Foundation Medicine in Cambridge, USA. Dr. Schrock and colleagues used hybrid-capture based comprehensive genomic profiling (CGP) to prospectively analyse clinical samples from 358 patients with SBA, 6,353 patients with CRC, and 889 patients with GC. Complete molecular profiles were prepared and compared with available clinical features. The majority (52-55%) of patients in the 3 series were male; SBA patients tended to be marginally older than the patients with the other two cancer types with a median age of 60 years.

The alterations identified included APC alterations, which occurred at a frequency of 76% in CRC and 27% in SBA ($p < 0.001$). BRAF alterations were found in 8% each of CRC and SBC samples. BRAF V600E mutations occurred less commonly in SBA, and represented just 10% of BRAF-mutated samples in this series. ERBB2 and EGFR amplifications were detected more often in GC, but ERBB2 (7%) and EGFR (1.4%) point mutations were most common in SBA compared to the other tumour types tested.

High microsatellite instability (MSI-H) more frequently occurred in SBA (6.9% of cases) than in CRC (3.9%), or GC (4%). Targetable alterations including EGFR and ERBB2 alterations, BRAF mutations, PI3K pathway and MEK1 mutations, and RTK fusions were detected in all three series, according to Dr. Schrock, who noted that one SBA patient whose tumour harboured a GOPC-ROS1 fusion had demonstrated a clinical response to the ALK/ROS1 inhibitor crizotinib.



Gene	P-Value		
	SBA vs CRC	SBA vs GC	CRC vs GC
TP53	<0.0001	0.9784	<0.0001
KRAS	0.1678	<0.0001	<0.0001
APC	<0.0001	<0.0001	<0.0001
SMAD4	0.1587	<0.0001	<0.0001
CDKN2A	<0.0001	0.6281	<0.0001
PIK3CA	0.1379	0.3823	0.0001
ARID1A	0.0004	<0.0001	<0.0001
CDKN2B	<0.0001	0.7599	<0.0001
ATM	0.0137	0.0080	0.3357
ERBB2	0.0099	0.4351	<0.0001
BRAF	0.8167	<0.0001	<0.0001
FBXW7	0.0320	0.0821	<0.0001
ERBB3	<0.0001	0.0226	0.0002
NF1	<0.0001	0.0302	0.1241
LRP1B	0.0103	0.0288	0.8614

Frequency of genomic alterations in SBA, CRC and GC.
Graph includes genes altered in > 5% of SBA cases in this series. Corresponding P values comparing frequency of alteration a gene across tumor types. Cases for which the difference was statistically significant (P <0.05) are highlighted in green.

Frequency of genomic alterations in small bowel adenocarcinoma, colorectal carcinoma, and gastric carcinoma.

© Alexa Schrock.

Overall, the molecular profile of SBA was distinct from either CRC or GC, and the genomic alterations identified in unspecified SBA were similar to those identified in duodenal adenocarcinoma. The authors also noted that the higher incidence of microsatellite instability identified in SBA suggests that a subset of patients with SBA may benefit from treatment with anti-PD-1/PD-L1 therapies. Schrock *et al.* Abstract 613O

Practice point and future research opportunities

Small bowel adenocarcinomas are cancers that occur rarely and have a lower incidence than other intestinal derived cancers. Since diagnosis is often made at a later stage, patients often have poorer overall survival than patients with colorectal or gastric cancer. This study offers the first large scale genomic comparison of the 3 cancer types, as well as a comparison of unspecified small bowel adenocarcinomas with tumours of the duodenum. It illustrates that using comprehensive genomic profiling over the course of clinical care can identify targetable genomic alterations across diverse intestinal tumour types and allows patients to be matched with

appropriate targeted therapies.

Nivolumab demonstrates efficacy in patients with advanced HCC

Ignacio Melero, Laboratory of Immunology, Universidad de Navarra, Pamplona, Spain, presented interim data on behalf of colleagues from the phaseI/II CheckMate-040 study of nivolumab in patients with histologically confirmed advanced hepatocellular carcinoma (aHCC). CheckMate-040 comprises 2 cohorts: 48 patients had completed the dose escalation portion of the trial and had previously failed, refused, or who were intolerant to sorafenib and were subcategorised into uninfected, infected with the hepatitis B virus (HBV), or infected with hepatitis C (HCV), patients in this cohort received nivolumab at 0.1 to 10 mg/kg for up to 2 years and had Child-Pugh scores ≤7; the expansion cohort comprised 214 patients subcategorised as uninfected and sorafenib naive/intolerant, uninfected patients progressing on sorafenib, HBV-infected, and HCV-infected patients, in this cohort, Child-Pugh scores were ≤6 and patients were treated with nivolumab at 3 mg/kg across all subgroups. The primary endpoints were safety in the escalation cohort, overall response rate (ORR) by RECIST 1.1 in the expansion cohort, and other endpoints included overall survival (OS), duration of response (DOR), and assessment of PD-L1 expression status. At baseline, 85% of escalation versus 75% of expansion patients had a Child Pugh score 5, extrahepatic lesions were present in 77% versus 75%, and 77% versus 68% had received sorafenib in the escalation versus expansion arms, respectively.

The interim analysis revealed nivolumab was effective regardless of the underlying aetiology of HCC or the degree of PD-L1 expression. The ORR in the escalation and expansion cohorts were 15% and 15%, with 3 (6%) versus 2 (1%) patients in the respective cohorts achieving complete responses (CR), while 4 (8%) versus 33 (15%) had partial responses (PR). Stable disease was experienced by 24 (50%) versus 11 (52%) and disease progression occurred in 15 (31%) versus 63 (29%) of escalation and expansion patients, respectively. The median DoR was months 17 months, the median OS was14.3 months, and the OS rate was 59.1% at 12 months in the escalation cohort. Median DoR, OS and the OS rate at 12 months were not reached in the expansion cohort. Response across all subcategories was similar to the response observed in the overall cohort, regardless of infection or prior sorafenib.

Treatment with nivolumab was generally safe and well-tolerated; 65% of expansion patients experienced any drug-related adverse events (AEs), including 18% with grade 3/4 events. The most commonly reported treatment-emergent AEs grade 3/4 were ALT, AST, and amylase elevations, which occurred in 3%, 4%. And 3% of expansion patients, respectively. Tolerability profiles in the escalation cohort were consistent with the expansion cohort and were previously reported. Melero *et al.* Abstract 615O

Practice point and future research opportunities

The RR with nivolumab in this study of patients with HCC compare favourably with the ORR of approximately 2% with sorafenib, the current first-line indication. An encouraging 12-month overall survival was also observed; both the objective response and OS rates for the escalation cohort compare favourably with historic best supportive care data. In addition, nivolumab

monotherapy had a manageable safety profile in patients with hepatocellular carcinoma, including those with HBV or HCV infection, and showed durable responses across all dose levels and aetiologic cohorts, and in patients with high PD-L1 expression, which has been associated with a poorer prognosis in hepatocellular carcinoma. Further evaluation of nivolumab is ongoing in this trial and warranted.

No statically significant added benefit with intraperitoneal paclitaxel plus S-1/paclitaxel over standard chemotherapy in patients with gastric cancer and peritoneal metastasis

Primary author Yoshiyuki Fujiwara, Department of Gastroenterological Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan presented findings from the phase III PHOENIX-GC trial of intraperitoneal paclitaxel plus S-1/paclitaxel compared with S-1/cisplatin in patients with gastric cancer patients and peritoneal metastasis. The trial enrolled 183 patients with pathologically confirmed gastric adenocarcinoma and peritoneal metastasis that had either received no chemotherapy or short-term chemotherapy lasting less than 2 months. Patients were randomised 2:1 to the IP arm where they received intraperitoneal paclitaxel at 20 mg/m^2 plus intravenous paclitaxel at 50 mg/m^2 on days 1 and 8 plus S-1 at 80 mg/m^2/day on days 1 to 14 every 3 weeks or to a SP arm of intravenous cisplatin at 60 mg/m^2 on day 8 plus S-1 80 mg/m^2/day on days 1 to 21 every 5 weeks. Randomisation was stratified by centre, prior chemotherapy, and the extent of peritoneal disease. The primary endpoint was overall survival (OS) and secondary endpoints included response rate and safety.

The efficacy analysis included 164 patients and showed well-balanced baseline characteristics in both arms, except for ascites; 38 (84%) patients with ascites beyond the pelvic cavity were randomised to the IP arm versus 7 (16%) to the SP arm.

Although a trend towards improved OS was seen in the IP arm, the primary analysis did not support statistical superiority of the IP over the SP regimen; the median OS for the IP and SP arms was 17.7 and 15.2 months, respectively (stratified log-rank test, p = 0.080; hazard ratio [HR] 0.72, 95% confidence interval [CI] 0.49, 1.04; p = 0.081). However, adjustment for the baseline ascites by sensitivity analysis using a stratified Cox regression model yielded HR 0.59 (95%CI 0.39, 0.87, p=0.0079) for the comparison of the two regimens. The response rates were 53% in the IP arm versus 60% in the SP arm (p = 1.0). Subgroup analysis revealed that female patients, patients with histologically undifferentiated tumours, and patients with ascites beyond the pelvic cavity had prolonged OS with IP regimen. The safety profile was similar in both arms and demonstrated that both regimens were tolerable. UMIN000005930. Fujiwara *et al.* Abstract 616PD

Practice point and future research opportunities

Efficacy with intraperitoneal paclitaxel has been reported in ovarian cancer due to the sustained high local concentrations provided. The authors showed prior promising results with intraperitoneal paclitaxel plus with S-1/paclitaxel in gastric cancer. This phase III study did not show statistically significant superior efficacy with intraperitoneal paclitaxel plus with S-1/paclitaxel compared to standard systemic chemotherapy in gastric cancer with peritoneal metastasis, although a sensitivity analysis, adjusting for an imbalance of patient's ascites in the treatment arms, suggested clinical efficacy of intraperitoneal paclitaxel plus with S-1/paclitaxel. Subgroup analysis suggested that female patients, those with undifferentiated tumours and patients with ascites beyond the peritoneal cavity may derive greater benefit from the intraperitoneal regimen.

Molecular characteristics vary among patients with HCC according to age group

Celina Ang, Department of Haematology Oncology of the Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai in New York, USA and colleagues evaluated gene sequencing, amplification, and protein expression data from 421 hepatocellular carcinoma (HCC) specimens to determine whether molecular characteristics differ among patients with HCC according to age. They noted that in the Western hemisphere patients are usually diagnosed with HCC in the middle years and HCC is less frequently diagnosed in young adults or the elderly, whereas world-wide HCC diagnoses at the extremes of the age spectrum are associated with distinct geography and aetiologies. The investigators stratified patients with HCC into subgroups of young adult, aged 18-39 years, intermediate aged 40 to 74 years, and elderly, aged 75 years and more for comparison of molecular characteristics associated with HCC. Only pathogenic or presumed pathogenic (P/PP) mutations were analysed and the Chi-square test was used for statistical comparisons.

The data revealed 39 young adults, 336 intermediate aged, and 46 elderly patients were diagnosed with HCC. In the young adult subgroup, 54% of patients were female compared to 23% of intermediate aged ($p < 0.0001$), and 33% of elderly patients ($p = 0.0483$). Young adults had lower MRP1 expression of 60% versus 86% in intermediate ($p=0.04$), and 95% in elderly patients with HCC ($p = 0.02$). PDGFR and PD-L1 expression was not observed in this subgroup and PIK3CA, PTEN, and PTPN11 mutations were also not detected in young adults. One ATM mutation was detected in young adult patients but in no other age group. The overall frequency of P/PP mutations was 0.38 in young adults compared with 0.71% of intermediate aged ($p = 0.012$), and 0.93 in elderly patients ($p = 0.038$). MGMT was expressed in 71% of intermediate aged patients versus 49% in young adults ($p = 0.007$), and SPARC was expressed in 13% of elderly patients but not in young adults ($p = 0.005$). PDGFR and PD-L1 were expressed in 14% and 19% of intermediate aged versus 29% and 17%, respectively, of elderly patients. Of 47 genes analysed, TP53 was the most frequently altered in young adults at 19% of cases, while CTNNB1 was the most frequent in 30% of intermediate aged, and 33% of elderly patients compared with just 9.5% of young adults.

Among male patients, androgen receptor (AR) expression was much lower in young adults at 6% versus 35% in intermediate aged ($p = 0.02$), and 32% in elderly patients ($p = 0.05$), whilst among females, expression of the AR increased with age from 6%, to 7% and to 15% in young

adult, intermediate, and elderly patients, respectively ($p > 0.05$). PIK3CA, PTEN, and PTPN11 mutations were more prevalent in the elderly and occurred in 13.3%, 7.1% and 6.7%, of elderly patients, respectively, versus 1.4%, 0.7% and 0% of intermediate aged patients (all $p < 0.05$). ANG *et al.* Abstract 618PD

Practice point and future research opportunities

This study showed an association between female sex, decreased drug resistance protein, and AR expression with young adult patients diagnosed with HCC, indicating that these patients may be more sensitive to alkylating agents. The data also suggest that elderly patients with HCC may derive more benefit from PIK3CA/Akt/mTOR or MAPK pathway inhibitors. These findings warrant further investigation and may provide information that is useful to the network of cancer centres planning prospective studies; which may be improved by the incorporation of aetiological factors and molecular features.

The lymph node ratio is a prognostic factor in curative treatment of gallbladder cancer

Immediate radical re-resection (IRR) is often needed after simple cholecystectomy for incidental gallbladder carcinoma (IGBC) and the forthcoming S3- guidelines will extend the current recommendations for aggressive surgery in T2 and more advanced stages to patients with stage T1b, according to Thorsten O. Goetze, Institute of Clinical Cancer Research, Nordwest-Krankenhaus, Frankfurt Am Main, Germany. This change is based upon data from the German-Registry, the largest gallbladder cancer registry in Europe, which showed the indication for IRR depended more on the experience in liver surgery of the hospitals than on guideline compliance. This suggested to the authors that most of patients with IGBC could be staged incorrectly and do not receive sufficient therapy. The investigators used data from the German Registry for this analysis of 950 cases of IGBC.

From this analysis, it has emerged that an IRR was performed in 42 of 113 T1b cases which yielded a significant survival benefit for these T1b patients. A survival benefit was also seen for the 228 patients with stage T2 and 80 patients with stage T3 that were treated with IRR compared to the 461 patients with T2 and 215 patients with T3 tumours not receiving IRR. The investigators found that good results were obtained with the wedge resection technique in T1b and T2 patients but stage T3 disease showed better results with more radical techniques.

To date, less than 50% of T2–3 tumours in the registry have been re-resected. According to the authors, local resection was performed significantly more often in high-volume clinics. The lymph node ratio could be calculated in 212 patients, which emerged as a significant prognostic factor in gallbladder cancer. The investigators are planning a multimodal therapy trial that has the support of over 300 clinics to further improve the cure rate in T2-3 gallbladder cancer patients. Goetz *et al.* Abstract 619PD

Practice point and future research opportunities

This analysis provides data supporting radical surgery for patients with incidental gallbladder cancer up to stage T1b and that the wedge resection technique provides good results in stages T1b/T2 due to the lower invasiveness. Implementation of these recommendations should also be possible in low volume institutions having little experience in liver surgery. The study also describes the utility of the lymph node ratio as a prognostic factor in gallbladder cancer.

Comparative molecular analyses of pancreatic cancer in younger and older patients

Mohamed E. Salem, Division of Haematology and Oncology, Lombardi Cancer Centre, Georgetown University, Washington, DC, USA, remarked that less is known about the molecular tumour characteristics and outcome in younger patients with pancreatic cancer, leading Dr. Salem and colleagues to examine 2426 pancreatic tumours to evaluate the molecular profiles of these tumours and to determine the association to outcome in younger versus older patients. The investigators reviewed protein expression by immunohistochemistry, gene amplification and sequencing data of the tumours to correlate genetic alterations with outcome. The comparison between age groups was made by Chi-squared test and survival estimates were by Kaplan-Meier methodology.

This large analysis revealed the most frequently mutated genes in this cohort of pancreatic tumours: KRAS was altered in 85% of tumours, TP53 in 63%, SMAD4 in 13%, BRCA2 in 12%, ATM/APC/NTRK1 in 5% each, BRCA1 in 4%, and cMET/PIK3CA were each altered in 3% of cases overall. The molecular profile of 568 tumours from the subgroup of younger patients with median age of 50 (range: 21 to 55) years was then compared to the profiles of 1113 tumours from older patients with a median age of 71 (range: 65 to 90) years. Interestingly, comparison between the age groups yielded a different profile for each. The tumours from younger versus older patients showed a greater frequency of mutations in MLH1 at 4% versus 0.3% ($p = 0.003$), PTEN at 3% versus 0.5% ($p = 0.008$), CTNNB1 at 2.3% versus 0.5% ($p = 0.04$), and c-KIT at 2% versus 0.3% ($p = 0.02$), respectively. Two genes were altered in younger patients' tumours but not in older patients: EGFR at 2.2% ($p = 0.003$), and NTRK1 at 20% ($p = 0.002$); however, NTRK1 was assessed in only 10 younger and 45 older patients' samples. Younger patients had higher TOP2A expression of 59% versus 50% in older patients ($p = 0.02$).

Older patients showed significantly higher KRAS mutations of 80% versus 70% in younger patients ($p = 0.0003$), as well as higher rates of low RRM1 expression at 85% versus 79% ($p = 0.03$) and high PDGFR expression of 22% versus 7% ($p = 0.03$), respectively.

Similar mutation rates were seen in some specific genes when older versus younger patient samples were compared: BRCA1 was 5%, BRAF was1%, and PIK3CA was 3% in both subgroups. BRCA2 was altered in 14% versus 12%, GNAS at 2.4% versus 1.6%, NOTCH1 at 0.9% versus 1.6%, cMET at 2.8% versus 3.9%, and RET was altered in 0.4% versus 0.8% in the respective older versus younger patient subgroups. PD-L1 expression in tumour cells was

also similar in both age groups at 8% versus 7%, and on tumour-infiltrating lymphocytes at 41% versus 37% in older versus younger patients, respectively.

Outcomes were evaluable for 73 patients. Although no survival differences were observed between the age groups, lower expression of ERCC1, MGMT, PRM1, and TLE3 appeared to be associated with prolonged survival in older but not younger patients. The authors commented that larger studies are needed to confirm and define the significance of this finding. Salem *et al.* Abstract 620PD

Practice point and future research opportunities

This large analysis made a start in defining the genetic landscape of pancreatic cancer and determined that some genetic alterations harboured in pancreatic tumours of younger patients may differ from older patients, whereas the frequency of mutation for several genes was similar. A wider gene panel would aid in the discovery of targetable mutations.

RELATED INFORMATION

Click here to access the Congress abstracts.

Click here to access the meeting webcast page.

Save the date

ESMO 2017 Congress, Madrid, Spain, 8-12 September 2017.

Affiliations and Disclosure

Affiliation

Dr Svetlana Jezdic, ESMO Head Office.

Disclosure

No conflicts of interest to disclose.

Acknowledgment

ESMO would like to thank you Virginia Powers, PhD for editorial assistance in preparation of this report.

ESMO would like to thank you Drs Judith Balmaña, Mark Andrew Glaire, Pierre Laurent-Puig, Sara Pusceddu, Antoni Ribas, Phillipe Rochigneux, Alexa Schrock and Yibing Yan for giving their permission to publish the images from the studies presented during the ESMO 2016 Congress in the ESMO Scientific report.

© Copyright 2016 European Society for Medical Oncology. All rights reserved worldwide.