European Society for Medical Oncology Copenhagen update: potential practice- changing findings

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The European Society for Medical Oncology (ESMO) held its annual conference in Copenhagen, Denmark, 7–11 October 2016, with over 20,000 participants and more than 1600 presented studies. This report covers some of the potential practice-changing studies that were presented during the conference.

First-line ribociclib plus letrozole impresses in human epidermal receptor 2-negative advanced breast cancer

An interim analysis of the Mammary ONcology Assessment of LEE011's Efficacy and Safety-2 (MONALEESA2) phase III study was presented by Professor Gabriel Hortobagyi (University of Texas MD Anderson Cancer Center, Houston, TX, USA). In this double-blind, randomized controlled trial (RCT) 668 treatment-naïve postmenopausal women with hormone receptor-positive (HR+), human epidermal receptor 2 (HER2)-negative advanced breast cancer (BC) received either ribociclib (a selective cyclin-dependent kinase 4/6 inhibitor, 600 mg/day, 3 weeks on/1 week off) plus letrozole (2.5 mg/day continuous), or letrozole plus placebo [Hortobagyi *et al.* 2016].

The results showed a 44% improvement in progression-free survival (PFS) (primary endpoint) among ribociclib patients compared with placebo recipients (hazard ratio [HR] 0.556; $p = 0.00000329$). The median PFS was 14.7 months in the placebo arm but had not been reached at cut-off for ribociclib. There was a significantly higher objective response rate (ORR) to combination therapy compared with letrozole alone (53% *versus* 37%; $p = 0.00028$), and an improved clinical benefit rate (80% *versus* 72%; $p = 0.02$) among patients with measurable disease at baseline.

Common grade 3/4 adverse events were higher in the ribociclib arm *versus* the placebo arm (e.g. neutropenia, leukopenia, elevated alanine aminotransferase and aspartate aminotransferase); however, serious adverse events occurred in less than 5% of patients in both arms.

These results show that ribociclib plus letrozole is superior to letrozole treatment alone in treating patients with HR+, HER2-negative advanced BC. It is still unknown if this impressive improvement in PFS will translate into significant gains in overall survival (OS), but even with the current data the addition of ribociclib to letrozole could set a new standard of care in HER-2 negative, HR+ BC.

Fulvestrant improves progression-free survival in advanced breast cancer

Results of the Fulvestrant and Anastrozole Compared in hormonal therapy Naïve advanced breast cancer (FALCON) phase III, RCT study were presented by Dr Matthew Ellis (Baylor College of Medicine, Houston, TX, USA). A total of 462 women with inoperable locally advanced or metastatic estrogen receptor-positive (ER+), HER-negative BC (no prior hormone therapy) were randomized to receive fulvestrant, a selective ER degrader (500 mg intramuscular, days 0, 14 and 28, then every 28 days) or anastrozole (1 mg daily). Patients were also allowed one line of chemotherapy [Ellis *et al.* 2016].

The results showed a 21% improvement in PFS (primary endpoint) with fulvestrant compared with anastrozole after a median follow up of 25 months (HR = 0.797; $p = 0.0486$; median PFS, 16.6 months *versus* 13.8 months, respectively), and a subgroup analysis showed further PFS benefit where disease had not spread to the liver or

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lungs at baseline (22.3 months *versus* 13.8 months). Common adverse events for fulvestrant and anastrozole groups were arthralgia (16.7% *versus* 10.3%) and hot flushes (11.4% *versus* 10.3%) with similar impact on quality of life in both groups.

Dr Ellis commented that fulvestrant could be a new standard of care compared with anastrozole, especially among patients with nonvisceral disease and in elderly patients, because of its good tolerability.

Niraparib improves progression-free survival in patients with platinum-sensitive recurrent ovarian cancer regardless of BRCA status

Dr Mansoor Raza Mirza (Copenhagen University Hospital, Denmark) presented results of the ENGOT-OV16/NOVA trial, the first RCT of maintenance therapy with a poly ADP ribose polymerase inhibitor following platinum chemotherapy in patients with platinum-sensitive recurrent ovarian cancer [Mirza *et al.* 2016].

There were 553 patients in the trial, which consisted of a cohort of 203 patients with the germline BRCA mutation and a cohort of 350 without the mutation. Within each cohort, patients were assigned 2:1 to receive niraparib 300 mg or placebo once daily. Median PFS (primary endpoint) with niraparib compared with placebo was assessed in prospectively defined populations as follows: 21.0 months *versus* 5.5 months in the germline BRCA mutation group (HR = 0.27; $p < 0.0001$); 9.3 months *versus* 3.9 months in the nongermline BRCA mutation group (HR = 0.45; $p < 0.0001$); 12.9 months *versus* 3.8 months in a subgroup of the nonmutation cohort who had homologous recombination DNA repair deficiencies (HR = 0.38; $p < 0.0001$). Secondary endpoints also showed statistically significant improvement. Patient-reported outcomes were similar in niraparib and placebo groups. The most common ($\geq 10\%$) grade 3/4 adverse events following niraparib treatment were thrombocytopenia (28%), anaemia (25%) and neutropenia (11%). There were no deaths during study treatment.

In summary, niraparib significantly improved PFS compared with placebo in both cohorts, as well as in all subgroups. These results show that if approved, niraparib could have the potential to

change the way that patients with recurrent ovarian cancer who respond to platinum regardless of BRCA status are treated.

High response rate with dabrafenib in paediatric brain cancer

Dr Mark Kieran (Pediatric Medical Neuro-Oncology, Dana-Farber Boston Children's Cancer and Blood Disorders Center Cancer and Blood Disorders Center, Boston, MA, USA) presented results of a phase I and phase II trial of dabrafenib [Kieran *et al.* 2016]. This drug is a potent and selective inhibitor of BRAF V600-mutant, a mutation that is seen in up to 10% of paediatric low-grade gliomas (LGG).

The studies included 32 patients, aged 2–17 years, with BRAF V600-mutant relapsed or refractory LGG, 15 in the phase I trial and 17 in the phase II trial. The phase I trial found no dose-limiting toxicities and determined the recommended dose for the phase II trial as 4.5 mg/kg/day in patients aged 12 years or older, and 5.25 mg/kg/day in patients under 12 years old, divided into two equal doses per day.

The phase II trial investigated the ability of dabrafenib to halt or reduce tumour growth, and any toxicity. A total of 24 patients from both studies received the recommended dose.

The ORR was 72%, that is 23 of 32 patients responded to the drug. A complete response was seen in 2 patients and a partial response (tumour shrunk by more than half) in 11 patients, with 8 of this group still on dabrafenib (median duration of response of 11 months). Minor side effects such as transient fever, upset stomach, fatigue and skin rash were similar to those seen in adults. There were no reports of cutaneous squamous cell carcinoma.

This high response rate with monotherapy is very encouraging and could set the scene for future combination trials, for example, with an MEK inhibitor, in paediatric LGG.

Nivolumab maintains quality of life and reduces symptoms in platinum-refractory relapsed squamous cell carcinoma of the head and neck

Patient-reported outcomes from the CheckMate 141 trial were presented by Professor Kevin

Harrington (Institute of Cancer Research and Royal Marsden NHS Foundation Trust, London, UK) [Harrington *et al.* 2016]. This trial consisted of 361 patients with platinum-refractory relapsed squamous cell carcinoma of the head and neck cancer who received nivolumab (3 mg/kg bodyweight) or standard-of-care chemotherapy (methotrexate, docetaxel or cetuximab). Median OS of 7.5 months with nivolumab *versus* 5.1 months standard therapy has already been reported for this study [Ferris *et al.* 2016]. Maintaining quality of life is a key consideration during the treatment course of this disease.

The patient-reported outcomes included functional capacity and symptoms using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), EORTC Head and Neck Cancer module (QLQ-H&N35) and the EuroQol five dimensions' questionnaire. The questionnaires were completed by 129 patients at baseline and at 9 weeks and 15 weeks during treatment. Functional and symptom burden was maintained/improved at both time points compared with baseline in patients who received nivolumab; however, scores worsened with time among patients who received standard-of-care chemotherapy.

Thus, in addition to its superior OS over standard-of-care treatment in head and neck cancer, nivolumab also appears to have benefits in terms of improving quality of life and symptoms.

Selumetinib does not improve survival in KRAS-mutant nonsmall cell lung cancer

Results from the SELECT-1 trial were presented by Dr Pasi Jänne (Dana-Farber Cancer Institute, Boston, MA, USA). This phase III, double-blind, RCT consisted of 510 patients with *KRAS*-mutant nonsmall cell lung cancer (NSCLC) who were randomized to receive selumetinib (75 mg twice daily orally), a mitogen-activated protein kinase (MEK) 1/2 inhibitor, plus docetaxel (75 mg/m² intravenously on day 1 of every 21-day cycle), or docetaxel plus placebo [Jänne *et al.* 2016].

At data cut-off, there was no significant difference in the median PFS (primary objective) between selumetinib and placebo groups (3.9 months *versus* 2.8 months, HR = 0.93; *p* = 0.44). Also, there was no significant difference in the secondary

objectives of OS and ORR. Serious adverse events and adverse events leading to hospitalization occurred more frequently in the selumetinib group of patients.

Thus, there appears to be no clinical benefit to add selumetinib to docetaxel in patients with advanced *KRAS*-mutant lung cancer. These results mirror similar negative data with MEK inhibitors in other cancers with (K)RAS mutation. It is conceivable that MEK inhibitors need to be combined with other biologics to inhibit redundant pathways and activate feedback loops to exert an antitumour effect in RAS-mutated cancers.

Neoadjuvant nivolumab is safe and feasible in early nonsmall cell lung cancer

Dr Patrick Forde (Johns Hopkins, Baltimore, MA, USA) reported initial results of the first study of neoadjuvant programmed cell death protein 1 (PD-1) inhibition in early-stage NSCLC [Forde *et al.* 2016].

Treatment-naïve patients with resectable stage I–IIIA NSCLC had a tumour biopsy then received nivolumab 3 mg/kg at 4 weeks and 2 weeks prior to surgical resection. (Standard adjuvant chemotherapy was given upon investigator discretion postoperatively.) The results of the first 16 patients were presented at the conference.

There was pathological evidence of tumour regression in 12 of 15 resected patients (80%), and 6 (40%) had major pathologic responses (< 10% residual viable tumour). The researchers concluded that nivolumab is safe and feasible to administer as neoadjuvant therapy to patients with early stage NSCLC prior to resection of the tumour. The study is now being expanded to look at the effect of pre-operative third dosing with nivolumab, and at a nivolumab plus ipilimumab combination.

Selective use of first-line nivolumab indicated from the CheckMate 026 trial results

The CheckMate 026 trial is an open-label, randomized phase III study of the efficacy of nivolumab (3 mg/kg intravenously every 2 weeks) compared with platinum-based doublet chemotherapy in patients with advanced NSCLC and programmed death-ligand 1 (PD-L1)-positive tumours (i.e.

1% or more tumour cells, no epidermal growth factor receptor [EGFR] mutation or anaplastic lymphoma kinase [ALK] translocation) [Socinski *et al.* 2016].

A total of 541 treatment-naïve patients were randomized 1:1 to nivolumab or chemotherapy. (Patients on chemotherapy who progressed were allowed to cross over to nivolumab.) Nivolumab did not improve PFS (primary outcome): 423 patients with 5% or greater PD-L1 expression had a PFS of 4.2 months *versus* 5.9 months with chemotherapy (HR = 1.15; $p = 0.25$). OS was 14.4 months and 13.2 months for nivolumab and chemotherapy groups, respectively (no significance). Serious treatment-related adverse events were 71% and 18% with nivolumab, and 92% and 51% with chemotherapy, respectively.

Thus, nivolumab did not show superior PFS compared with chemotherapy in this group of patients. Key researcher of the study Dr Mark Socinski (Florida Hospital Cancer Institute, Orlando, FL, USA) said that greater patient selection may be needed for first-line nivolumab to improve PFS in advanced NSCLC. He added that combination immunotherapies (e.g. with ipilimumab as in the CheckMate 227 trial) may improve first-line results.

First-line pembrolizumab effective in patients with advanced nonsmall cell lung cancer and high programmed death-ligand 1 expression...

Pembrolizumab (a PD-1 antibody) has been studied as first-line therapy in a phase III trial of treatment-naïve patients with advanced NSCLC in the KEYNOTE-024 trial. Professor Martin Reck (Lung Clinic, Grosshansdorf, Germany) and colleagues compared the efficacy of pembrolizumab to standard of care with platinum-based chemotherapy in 305 patients with high PD-L1 expression (typical of 27–30% of those with advanced NSCLC) [Reck *et al.* 2016]. (Patients with EGFR-activating mutations and ALK translocations were excluded.)

Patients were randomized 1:1 to pembrolizumab (200 mg every 3 weeks) or chemotherapy: 44% of patients in the latter group progressed and were allowed to cross over to pembrolizumab treatment.

The results showed that pembrolizumab significantly improved PFS (primary endpoint)

compared with chemotherapy (10.3 months *versus* 6.0 months, HR 0.50; $p < 0.001$). OS (secondary endpoint) was significantly prolonged by pembrolizumab, when assessed at 6 months, with 80% alive compared with 72% on chemotherapy (HR = 0.60; $p = 0.005$). There was a longer duration of response, and lower incidences of all and serious (3/4) adverse events.

The significantly improved PFS and OS with pembrolizumab in patients with advanced NSCLC and high PD-L1 expression plus the better tolerability compared with chemotherapy augur well for its first-line use in this group of patients. The different results compared with nivolumab in the CheckMate 026 trial are conceivably due to a difference in patient selection, in particular, the cut-off for PD-L1 positivity, which allowed patients to enter the trial.

... and significantly improves outcomes in advanced nonsmall cell lung cancer when added to chemotherapy

Cohort G results of the multicentre, open-label, phase I/II KEYNOTE-021 trial were presented by Dr Corey Langer (Abramson Cancer Center at the University of Pennsylvania, PA, USA). The researchers sought to establish the efficacy and safety of adding the checkpoint inhibitor, pembrolizumab, to carboplatin plus pemetrexed as a first-line therapy for advanced nonsquamous NSCLC [Langer *et al.* 2016].

A total of 123 patients (Eastern Cooperative Oncology Group performance status 0–1, no EGFR mutation or ALK translocation) were randomized to receive four cycles of carboplatin and pemetrexed (500 mg/m² every 3 weeks) with or without 24 months treatment with pembrolizumab (200 mg every 3 weeks).

A significantly greater ORR (primary endpoint) was found in the group of patients who received pembrolizumab (55% *versus* 29% for chemotherapy alone; $p = 0.0016$) after a median follow up of 10.6 months. This early assessment also showed an improved PFS with pembrolizumab (median 13.0 months *versus* 8.9 months for chemotherapy alone) and similar OS between the groups. A higher incidence of grade 3 or above adverse events was seen in the pembrolizumab group (39% *versus* 26%) but discontinuation rates were similar. With regard to common treatment-related

adverse events, fatigue and nausea were more common in patients receiving pembrolizumab, and anaemia was more common in those receiving chemotherapy alone.

These initial positive results need to be confirmed in other phase III studies, but the results to date show that adding pembrolizumab to chemotherapy in the first-line treatment of advanced NSCLC is an effective and manageable option.

Second-line atezolizumab improves overall survival compared with docetaxel in nonsmall cell lung cancer

Dr Fabrice Barlesi (Aix-Marseille University, and Assistance Publique Hôpitaux de Marseille, France) presented a primary analysis of the phase III OAK study of atezolizumab, a PD-L1 inhibitor, in previously treated patients with NSCLC [Barlezi *et al.* 2016]. A total of 1225 patients with previously treated NSCLC enrolled in the study and were stratified according to PD-L1 status, number of prior chemotherapy regimens and histology, then randomized 1:1 to receive atezolizumab (1200 mg intravenously every 3 weeks) or docetaxel (75 mg/m² every 3 weeks).

In the preliminary analysis of data from the first 850 patients, atezolizumab produced a significant improvement in OS compared with docetaxel (HR 0.73; $p = 0.0003$), regardless of PD-L1 expression levels and even in patients with no PD-L1 expression. Stratification of patients according to level of PD-L1 expression showed that OS was 59% greater among patients in the highest tertile of PD-L1 expression who were treated with atezolizumab, compared with the same group treated with docetaxel ($p < 0.0001$). There was however still a significant 25% improvement in OS with atezolizumab compared with docetaxel in patients with no PD-L1 expression. Patients with squamous and nonsquamous histology showed similar OS improvement.

This result confirmed the OS benefits that were found in the POPLAR and CheckMate trials. Thus, atezolizumab seems to be a feasible second-line therapy for patients with NSCLC regardless of the PD-L1 status of the tumour. The results of this study led to US Food and Drug Administration approval of atezolizumab in second-line NSCLC.

Ceritinib lines up as second-line therapy for anaplastic lymphoma kinase-rearranged nonsmall cell lung cancer

Professor Giorgio Scagliotti (University of Turin, Italy) presented results of the confirmatory phase III ASCEND-5 study, which investigated the effect of ceritinib *versus* chemotherapy in patients, previously treated with chemotherapy plus crizotinib, with advanced ALK-rearranged NSCLC [Scagliotti *et al.* 2016]. A total of 231 patients received crizotinib, and were randomized 1:1 to receive therapy with ceritinib or chemotherapy (pemetrexed or docetaxel). (Patients on chemotherapy were allowed to cross over to ceritinib if disease progression occurred.)

The median PFS (primary endpoint) was significantly improved with ceritinib chemotherapy (5.4 months *versus* 1.6 months for chemotherapy, HR = 0.49; $p < 0.001$). Ceritinib also increased ORR compared with chemotherapy (39.1% *versus* 6.9%), but there was no comparative improvement in OS with ceritinib possibly due to the 75 chemotherapy patients who crossed over to ceritinib during the trial.

Frequent grade 3/4 adverse events with ceritinib included nausea (7.8%), vomiting (7.8%) and diarrhoea (4.3%), while chemotherapy produced neutropaenia (15.5%), fatigue (4.4%) and nausea (1.8%). Patient-reported outcomes, including lung cancer-specific symptoms and overall health status, were significantly improved with ceritinib compared with placebo ($p < 0.05$).

Ceritinib produced longer PFS than chemotherapy in patients with NSCLC with the ALK rearrangement who had already received crizotinib. This study supports the use of ceritinib after crizotinib fails in this group of patients.

Nintedanib improves progression-free survival but not overall survival in the LUME-colon 1 trial in metastatic colorectal cancer

Professor Eric Van Cutsem (University Hospitals Leuven, Belgium) and colleagues have conducted the LUME-colon 1 trial, a global, randomized phase III study of nintedanib (a multiple tyrosine kinase inhibitor with anti-angiogenic activity) in patients with metastatic colorectal cancer (mCRC) where standard therapies had failed [Van Cutsem *et al.* 2016].

The study comprised 768 patients refractory to treatments such as oxaliplatin, irinotecan, fluoropyrimidines, anti-vascular endothelial growth factor and anti-EGFR in RAS wild type, who were randomized 1:1 to nintedanib (200 mg twice daily) or placebo. All patients received best supportive care.

The median PFS was 1.5 months *versus* 1.4 months for nintedanib and placebo groups, respectively (HR = 0.58; $p < 0.0001$), but there was no significant OS difference between the groups (co-primary endpoints). Nintedanib produced better disease control than placebo (26% *versus* 11%; $p < 0.0001$).

Serious adverse events were encountered by 39% and 35% of nintedanib and placebo group patients, respectively, and treatment discontinuation occurred in 14% and 11% of patients in each respective group.

While nintedanib increased PFS and was well tolerated, the OS result is disappointing. Further subgroup analysis may reveal some answers.

Dabrafenib/trametinib/panitumumab combined in BRAF V600E-mutated metastatic colorectal cancer

BRAF V600E-mutated (BRAFFmmCRC) occurs in 5–10% of patients with mCRC and is hard to treat. BRAF and MEK inhibitors show minimal activity, although a rationale for combination therapy has been trialled and presented by Dr Ryan Corcoran (Massachusetts General Hospital, Boston, MA, USA) [Corcoran *et al.* 2016].

The researchers allocated 134 patients with BRAFFmmCRC to groups to receive dabrafenib (BRAF inhibitor) plus panitumumab (anti-EGFR inhibitor; DP, $n = 20$), trametinib (MEK inhibitor) plus panitumumab (TP, $n = 31$), or dabrafenib plus trametinib plus panitumumab (DTP, $n = 83$). Clinical responses and evidence of downstream target inhibition were monitored. Results can be summarized as follows: (a) complete response/partial response, stable disease rates: DP = 10%, 80%; TP = 0%, 53%; DTP = 18%, 67%, respectively; (b) PFS: DP = 3.4 months, TP = 2.8 months; median PFS for DTP was not reached; (c) protein kinase RNA-activated endoplasmic reticulum kinase reduction (biopsy before and during treatment): DP = 23%, TP = 50%, DTP = 54%; (d) DTP: > 70% reduction in BRAF V600E-mutant fraction (MF) in 12 of 14

subjects by week 4 (assessed by serial circulating tumour DNA (ctDNA) analysis), with a partial response in 6 of 12 subjects by week 6; (e) there was evidence of a BRAF V600E MF increase and RAS mutations upon progression in some patients; (f) DTP: adverse events were manageable, commonly they were diarrhoea, fatigue, nausea, rash.

Thus, DTP therapy had good activity, with evidence of downstream target inhibition, in this group of BRAFFmmCRC patients, and was manageable. Dr Corcoran stated that ctDNA analysis may be useful in monitoring disease response and progression.

Adjuvant ipilimumab in high-risk stage III melanoma: overall survival results

The adjuvant ipilimumab was shown to improve recurrence-free survival (RFS) in the EORTC 18071 phase III trial [Eggermont *et al.* 2015]. Professor Alexander Eggermont (Institut Gustave Roussy, Villejuif, France) presented OS results at ESMO [Eggermont *et al.* 2016].

The trial consisted of 851 patients with high-risk stage III melanoma who were randomized 1:1 to receive ipilimumab (10 mg/kg) or placebo every 3 weeks for four doses followed by 3-monthly administration for up to 3 years (completion/disease recurrence/unacceptable toxicity).

Now at 5.3 years median follow-up time, a 28% risk reduction of death has been revealed, that is a significant improvement in OS (HR = 0.72; $p = 0.001$). The RFS was maintained (HR = 0.76; $p = 0.001$) as was distant metastases-free survival (HR = 0.76; $p = 0.002$). There have been no additional toxicities or deaths since the initial report at 2.3 years. Grade 3/4 adverse events included gastrointestinal (16%), hepatic (11%) and endocrine (8%) events.

Professor Eggermont concluded that the OS result combined with the good risk–benefit ratio suggests that adjuvant ipilimumab is a realistic treatment option for stage III melanoma.

Signs that first-line cabozantinib improves progression-free survival in metastatic renal cell carcinoma

Dr Toni Choueiri (Dana-Farber Cancer Institute, Boston, MN, USA) presented results of the

CABOzantinib *versus* SUNitinib (CABOSUN) study, a phase II RCT of 157 treatment-naïve patients with clear-cell metastatic renal cell carcinoma (RCC) (intermediate or poor risk categorized) who received either cabozantinib (60 mg once daily) or sunitinib (50 mg once daily, 4 weeks on/2 weeks off) [Choueiri *et al.* 2016]. (Cabozantinib and sunitinib both target vascular EGFRs but cabozantinib also inhibits MET and AXL, both of which may be upregulated during sunitinib therapy.)

A significant increase in median PFS was observed with cabozantinib (8.2 months) *versus* sunitinib (5.6 months), that is a 31% reduction in the rate of progression or death (adjusted HR = 0.69; $p = 0.012$). The ORR was also significantly higher in the cabozantinib group (46% *versus* 18% for sunitinib).

A similar rate of all-causality grade 3 or higher adverse events was observed between the groups (70.5% and 72.2% for cabozantinib and sunitinib, respectively), and included diarrhoea, fatigue, hypertension, palmar-plantar erythrodysesthesia and haematological events. Toxicity resulted in treatment stoppage for 16 patients in each group.

The results suggest that first-line cabozantinib has the potential to produce significant PFS and ORR advantages over sunitinib in intermediate or poor-risk metastatic RCC patients. Dr Choueiri added that this advantage probably applies to 'good-risk' patients, but phase III studies are needed to clarify the role of cabozantinib in the first-line setting.

Assured efficacy of adjuvant sunitinib in kidney cancer?

The use of adjuvant sunitinib in 615 postnephrectomy patients at high risk of RCC recurrence has been studied in a phase III RCT [Ravaud *et al.* 2016]. Patients with locoregional RCC who were treatment naïve were included in the study and randomly received sunitinib (50 mg/day) or placebo, 4 weeks on/2 weeks off for 1 year. (One dose reduction to 37.5 mg/day was allowed.)

Sunitinib produced a significantly longer disease-free survival (DFS) (primary endpoint) than placebo (6.8 years *versus* 5.6 years, respectively, HR = 0.761; $p = 0.03$). Median OS (secondary endpoint) had not been reached at data cut-off. There were more adverse events ($\geq$ grade 3) with sunitinib than placebo (62.1% *versus* 21.1%, respectively), and no deaths due to treatment toxicity.

The combination of increased DFS and manageable tolerability shows that adjuvant sunitinib, as per the dosing and patients' characteristics of this trial, may be an option in RCC, although the results of the recent Adjuvant Sorafenib and Sunitinib for Unfavorable Renal Carcinoma (ASSURE) study showed no DFS or OS advantage for adjuvant treatment with sunitinib or sorafenib [Haas *et al.* 2016].

First-line pembrolizumab shows encouraging results in metastatic bladder cancer...

The open-label phase II KEYNOTE-052 study is looking at the efficacy and safety of pembrolizumab in first-line cisplatin-ineligible patients with metastatic or locally advanced urothelial cancer. A total of 374 patients were enrolled to receive pembrolizumab (200 mg every 3 weeks) for 24 months or until progression or toxicity leads to necessary cessation.

Dr Arjun Balar (NYU Langone Medical Center, New York, NY, USA) presented results for the first 100 patients [Balar *et al.* 2016]. The ORR (primary endpoint) was 24%. There were 30 patients who had a $\geq 10\%$ PD-L1 expression in tumour and immune cells, which was determined as the 'combined positive score' (CPS) high biomarker cut-point (secondary objective). In this subset of patients, the ORR reached 37%. Complete response rate was 6% and 13.3% of all and CPS-high patients, respectively. Median duration of response had not been reached and toxicity was manageable.

Thus, pembrolizumab showed substantial activity and was manageable in this group of patients

...and second-line nivolumab succeeds in the CheckMate 275 trial

Nivolumab has been studied in the large CheckMate 275 phase II trial of 270 patients with metastatic urothelial cancer who had progressed after first-line platinum-based chemotherapy [Galsky *et al.* 2016].

Patients received nivolumab (3 mg/kg intravenously every 2 weeks) until progression or toxicity leading to cessation. The ORR was 19.6% among the 265 evaluable patients, and was higher among

those with high PD-L1 expression. Median duration of response had not yet been reached (median follow up 7 months). Toxicity was manageable and quality of life was stable.

Professor Matthew Galsky (Mount Sinai School of Medicine, New York, NY, USA) said that the results of this study will support the registration of nivolumab in this group of patients, and it follows on from the earlier approval of atezolizumab in May 2016.

Conclusion

Targeted therapy continues to be studied across all cancers, in specific groups, at early and late stages, and with an increasing array of new and established agents. For example, adjuvant ipilimumab may now become a realistic treatment option for stage III melanoma, as may adjuvant sunitinib following nephrectomy in RCC. In NSCLC, pembrolizumab is set to change the future of first-line treatment, as will atezolizumab in the second-line setting, and ceritinib provides a further option in ALK-rearranged NSCLC. Studies using combination therapies (such as nivolumab and ipilimumab in the CheckMate 227 trial) are eagerly awaited. At the same time, we need to be observant about the need for biomarkers with targeted therapies, their risk–benefit ratios and their cost, which limits real-world accessibility.

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