ESMO 2018 Congress

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PEER-REVIEWED CONFERENCE REPORT

Improved PFS in Breast Cancer

SOLOR-1 and PALOMA-3 studies show positive results with alpelisib and palbociclib in *PIK3CA*-mutant, HR+, HER2-negative advanced breast cancer.

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Radiotherapy Improves Outcome in Prostate Cancer

STAMPEDE trial demonstrates that radiotherapy to the primary tumour improves overall survival in prostate cancer patients with a low metastatic burden.

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Advancement in Ovarian Cancer

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Editor Dr Stefan Rauh, Centre Hospitalier Emile Mayrisch, Luxembourg

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Letter from the Editor

Dr Stefan Rauh

Dear Reader,

I am delighted to introduce this year's Medicom Conference Report of the ESMO Congress, which took place from 19-23 October in Munich.

A total of 28,000 attendees from 138 countries is again a record, which is becoming a yearly tradition by now. ESMO members have more than doubled in the last years and have reached over 20,000 by the end of this year's congress.

With 75% of its programme being scientific (rather than educational), it comes as no surprise that the conference was again loaded with important study results; some of which truly practice changing. In consequence, 13 abstracts have been simultaneously published in the highest-ranking medical journals.

In this report, you will find hallmark studies involving PIC3K inhibitors, the entry of immunotherapy in triple negative, metastatic breast cancer as well as advanced head and neck cancer, new potential standards in renal cell cancer, and first-line ovarian cancer (also underlying the importance of identifying subpopulations benefitting from targeting therapy) as well as data consolidating the roles of new combined androgen deprivation therapy and the role of irradiating the primary tumour in advanced prostate cancer.

Enjoy reading our peer-reviewed report on the ESMO 2018 Congress!

Yours sincerely,

Stefan Rauh

Biography

Dr Stefan Rauh is currently working as haemato-oncologist in the oncology department of Centre Hospitalier Emile Mayrisch, Esch, Luxembourg. He is mainly involved in clinical work but also in research and teaching activities and is interested in public policy and international cooperation projects in oncology. He is Chair of the ESMO Practicing Oncologist's Working Group since 2015, member of the ESMO Quality Task Force, extended member of the ESMO Public Policy Committee, Assistant Editor of ESMO Cancer Horizons, and has been an ESMO Executive Board member in 2015-2016. He is co-author of the 2017 ESMO European Cancer Patient Coalition (ECPC) Patient Survivorship Guide and an invited expert for the ECPC.

Conflict of Interest Statement:
Nothing to declare.

Lung Cancer

During the Opening Session of the ESMO 2018 Congress, ESMO honoured four distinguished oncology professionals with an annual award. A substantial part of their presentations was devoted to EGFR-targeting in non-small-cell lung cancer (NSCLC). In addition to these Award Lectures, many other oral and poster presentations focussed on the biology and treatment of lung cancer. For instance, the results of the randomised phase 2 EMERGING/CTONG-1103 study showed that neoadjuvant erlotinib vs gemcitabine plus cisplatin was associated with an improved objective response rate (ORR) and progression-free survival (PFS) in patients with stage 3A-N2, *EGFR*-mutant NSCLC. In addition, erlotinib had a favourable toxicity profile. Furthermore, preliminary data from the randomised phase 3 FLAURA study indicated that especially *MET* amplification and secondary *EGFR* mutations, but not the *EGFR-T790M* mutation, are candidate resistance mechanisms in patients with *EGFR*-mutated advanced NSCLC treated with osimertinib in the first line.

Award Lectures on EGFR-targeting

A landmark event in the history of lung cancer, was the award of the 1986 Nobel Prize in Physiology and Medicine to Stanley Cohen for the discovery and characterisation of epidermal growth factor (EGF) and its receptor. Based on this discovery, many scientists worked together to characterise the EGF/EGFR signalling pathway, and develop inhibitory drugs, such as monoclonal antibodies against the extracellular domain of EGFR and intracellularly-acting tyrosine kinase inhibitors (TKIs). Initially, patients were considered to gain benefit with a positive EGFR FISH test. However, in the whole patient population, early clinical results with drugs like gefitinib were disappointing despite the high prevalence of EGFR overexpression. Subsequent analyses indicated that only subsets of patients strongly benefit from EGFR-targeted therapies. The characterisation of *EGFR* mutations, such as EGFR exon 19 deletions and exon 21 point-mutations, revolutionised the whole field and changed the treatment of lung cancer [1,2]. The pivotal IPASS study demonstrated that treatment of *EGFR*-mutated NSCLC patients with EGFR TKIs is associated with improved outcome, as compared with chemotherapy [3]. Based on these results and other studies on EGFR-targeting drugs, NSCLC patients could be selected by *EGFR* mutation status, and their prognosis strongly improved. "Currently, many clinical studies intend to answer questions on the duration of treatment, the outcome of novel EGFR TKIs and combination treatments, and on the mechanisms of resistance, among others," said Prof. Tony Mok (Prince of Wales Hospital, Hong Kong, China).

"Over the past 15 years, tailor-made treatment by means of a stratification of NSCLC patients according to the presence of oncogenic driver mutations, such as those of *EGFR* and *ALK*, has become a reality.

Prof. Jean-Charles Soria (University of Paris Sud, France) informed the audience about a French nationwide, free of charge, molecular screening programme [4]. Thanks to this screening programme, French patients with oncogene-addicted tumours can now widely benefit from targeted therapies and next generation clinical trials. However, in order to convince political stakeholders to fund this kind of initiatives, scientific arguments should be translated into financial consequences. For example, results from the IPASS study demonstrated that treatment of *EGFR* wildtype NSCLC patients with EGFR inhibitors is of no clinical benefit [3]. Based on this information, it was made clear to the French Minister of Health that it is better to spend €1.7M on *EGFR* testing for lung cancer patients than to waste €69M on treating *EGFR* wildtype tumours with EGFR inhibitors.

"Soon after the successes of EGFR-targeted therapies in NSCLC, we learned that the benefit of these therapies did not last forever, and that resistance would ultimately emerge. The most common resistance mechanism appeared to be the *EGFR-T790M* mutation [5]. Subsequent preclinical and clinical studies led to the development of a number of novel EGFR inhibitors, of which osimertinib was shown to potently inhibit both the common *EGFR* mutations and the *T790M* resistance mutation, while largely sparing wildtype *EGFR* [6-8]. Based on these findings, and on the fact that osimertinib has a favourable toxicity profile and readily crosses the blood-brain barrier, the drug is now registered for the treatment of patients with *T790M*-positive NSCLC progressing on EGFR TKIs, and treatment-naïve NSCLC patients. Currently, one of the remaining questions is how to overcome resistance to first-line osimertinib," said Prof. Pasi Jänne (Dana Farber Cancer Institute, USA).

Neoadjuvant erlotinib improves response in *EGFR*-mutated, locally advanced NSCLC

The current treatment options for stage 3A-N2 NSCLC include chemoradiotherapy, surgery followed by adjuvant chemotherapy/immunotherapy, or neoadjuvant therapy followed by resection. However, the relative roles of the distinct treatment modalities are not clearly defined. In addition, although concurrent chemoradiotherapy remains a major treatment for stage 3A disease, its toxicity limits the field of indication.

Previously, the randomised phase 3 ADJUVANT/CTONG-1104 trial demonstrated that adjuvant gefitinib compared with chemotherapy was associated with less toxicity and a significantly prolonged disease-free survival in patients with *EGFR*-mutant, stage 2-3A (N1-N2) NSCLC [9]. Furthermore, clinical studies had shown that neoadjuvant therapy with EGFR-inhibitor erlotinib is safe and associated with considerable antitumour activity in patients with stage 3A-N2 NSCLC [10,11].

Now, the randomised, multicentre, phase 2 EMERGING/CTONG-1103 study evaluated the efficacy of erlotinib vs gemcitabine plus cisplatin as neoadjuvant treatment in patients with stage 3A-N2, *EGFR*-mutant NSCLC. Patients were randomised 1:1 to receive either erlotinib as 150 mg/day for 6 weeks, or gemcitabine as 1250 mg/m^2 on day 1 and day 8, plus cisplatin 75 mg/m^2 on day 1 of a 3-week schedule for 2 cycles. In the post-surgery phase, patients were treated with erlotinib for 1 year or until disease progression or unacceptable toxicity, or with gemcitabine plus cisplatin for another 2 cycles or until disease progression or unacceptable toxicity. The primary endpoint was ORR. Secondary endpoints were complete resection and lymph node downstage rates, complete response rate, PFS, and safety.

The efficacy analysis demonstrated that erlotinib was associated with a non-significantly improved ORR in the intention-to-treat population: 54% in the erlotinib arm (n=37) vs 34% in the chemotherapy arm (n=35; OR 2.26, 95% CI 0.87-5.84, P=0.092) [12]. Although no complete responses were observed in both arms, the major pathological response rate was 11% in the erlotinib arm and 0% in the chemotherapy arm. Furthermore, no significant differences were found in the overall rates of complete resection and lymph node downstage, or the type of resection. Median PFS in the intention-to-treat population was 21.5 months in the erlotinib arm and 11.9 months in the chemotherapy arm (HR 0.42, 95% CI 0.23-0.76, P=0.003). Subgroup analyses showed that the PFS benefit of erlotinib was particularly present in younger (<60 years) patients (P<0.001), females (P=0.001), patients with a multiple N2 pattern, and those whose tumour cells had a mutation in *EGFR* exon 19 (both P=0.006). However, the study was underpowered and the mentioned subgroup analyses had not been defined in the study protocol. Although there is a benefit for the erlotinib group, the response rate and major pathologic response is lower than expected.

Adverse events (AEs) of any grade associated with neoadjuvant therapy were observed in 76% of the patients treated with erlotinib and 88% of the patients treated with chemotherapy. The toxicity profiles of both treatments in the neoadjuvant phase were substantially distinct. The most common AEs of any grade in the erlotinib arm were rash (68% vs 29% in the chemotherapy arm), diarrhoea (24% vs 0%), and cough (16% vs 6%), while those in the chemotherapy arm were vomiting (44% vs 0% in the erlotinib arm), anorexia (41% vs 0%), neutropenia, and leukopenia (both 38% vs 0%). In the erlotinib arm, no AEs of grade 3 or 4 were observed. AEs of any grade associated with postoperative adjuvant treatment were more frequent in the erlotinib arm than in the chemotherapy arm: 70% vs 59%, respectively. In contrast, AEs of grade 3-4 were more common in the chemotherapy arm: 14% in the erlotinib arm and 29% in the chemotherapy arm.

"These results warrant further exploration of biomarkers-guided neoadjuvant treatment regimens in patients with stage 3A-N2 NSCLC," concluded presenting author Dr Wen-Zhao Zhong (Guangdong Lung Cancer Institute, China). According to discussant Prof. Suresh Ramalingam (Winship Cancer Institute of Emory University, USA), EMERGING/CTONG-1103 addressed an important and difficult to investigate topic in lung cancer, which, however, does need further evaluation before EGFR TKIs can take the main stage as neoadjuvant therapy in *EGFR*-mutant, locally advanced NSCLC.

MET amplification and secondary *EGFR* mutations are candidate acquired resistance mechanisms to osimertinib treatment

Osimertinib is a third generation TKI that inhibits EGFR TKI-sensitising mutations as well as the *EGFR-T790M* resistance mutation. The randomised phase 3 FLAURA study demonstrated previously that osimertinib is associated with increased efficacy in patients with previously untreated *EGFR*-mutated, advanced NSCLC, as compared with the standard EGFR TKI gefitinib and erlotinib [13].

Where the most frequently reported resistance mechanisms to second-line osimertinib are acquired *EGFR* mutations, and amplification of *MET* and *HER2*, the resistance mechanisms to first-line osimertinib are largely. To investigate these resistance mechanisms, plasma samples from patients who progressed or discontinued treatment in the FLAURA trial were analysed by next generation sequencing (NGS).

Paired NGS data were generated from 113 patients treated with osimertinib and 159 patients treated with a standard EGFR TKI. The plasma NGS analysis focussed on genomic alterations in circulating tumour DNA.

"*EGFR* mutations were detected in the baseline plasma samples of 91/113 (81%) patients treated with osimertinib, and 129/159 (81%) of the patients treated with a comparator EGFR TKI [14]. Furthermore, the most common candidate acquired resistance mechanisms following standard EGFR TKI treatment were the *EGFR-T790M* mutation (47%), *MET* amplification (4%), and *HER2* amplification (2%). Following first-line osimertinib, the most frequently observed aberrations were *MET* amplification (15%), secondary *EGFR* mutations, particularly C797X (7%), and *HER2* amplification (2%). Other aberrations included mutations in *PIK3CA* (7%), *BRAF*, and *KRAS* (both 3%). In this study arm no evidence was found for *EGFR-T790M*-mediated acquired resistance. We observed no suggestions of new mechanisms of resistance that lead to aggressive disease biology. Ongoing research, including the ELIOS trial, will address tissue analysis for mechanisms of resistance to first-line osimertinib," said presenting author Prof. Ramalingam.

"The study by Ramalingam et al. provides substantial insight into mechanisms of osimertinib resistance and contributes to the existing datasets. Key caveats include the analysis of only plasma, because of which histological transformation might be missed, and amplification and fusion events are likely missed. However, overall, the data appear consistent with extant reports. Furthermore, multiple strategies are already in play to attempt to delay, prevent, or treat acquired resistance," said invited discussant Dr Charles Rudin (Memorial Sloan-Kettering Cancer Center, USA).

Another noteworthy study in lung cancer, was a phase 2 study evaluating the outcome of MET inhibitor tepotinib in combination with gefitinib (n=31) vs chemotherapy (n=24) in *MET*-positive, *EGFR*-mutant, *T790M*-negative, advanced NSCLC patients, resistant to prior treatment with an EGFR TKI. The results demonstrated that the targeted combination therapy, as compared with chemotherapy, was associated with significantly improved PFS in patients whose tumours harbour a *MET* amplification (HR 0.17, 90% CI 0.05-0.57) [15]. In addition, tepotinib plus gefitinib was associated with a higher ORR (45% vs 33% following chemotherapy), and generally well tolerated.

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Breast Cancer

The treatment of early and advanced breast cancer received substantial attention. The phase 3 SOLAR-1 study demonstrated that, in patients whose tumour harbours a mutated PI3-kinase, the PI3-kinase inhibitor alpelisib plus fulvestrant improves progression-free survival (PFS) and objective response rate (ORR), as compared with placebo plus fulvestrant. The randomised phase 3 Impassion130 study showed that the addition of atezolizumab to nab-paclitaxel improved PFS in patients with advanced triple-negative breast cancer, especially in patients with PD-L1-positive tumours. Moreover, the first interim overall survival (OS) analysis showed that the addition of atezolizumab was associated with an encouraging and clinically meaningful improvement.

The phase 3 PALOMA-3 study showed that in hormone receptor-positive, HER2-negative advanced breast cancer patients fulvestrant plus palbociclib vs placebo was not only associated with improved PFS, but also with OS in patients who responded to prior endocrine therapy. In addition, encouraging findings were reported on the treatment of triple-negative breast cancer. A presentation on the phase 3 HOBOE-2 study showed that in premenopausal patients with hormone receptor-positive (HR+) early breast cancer, triptorelin plus zoledronic acid and letrozole is associated with a significantly improved disease-free survival (DFS), as compared with triptorelin plus tamoxifen. Two studies reported on positive findings in HR+, HER2-negative advanced breast cancer.

Alpelisib plus fulvestrant improves progression-free survival in *PIK3CA*-mutant, HR+, HER2-negative breast cancer progressing on endocrine therapy

The standard of care in treatment-naïve patients with HR+, HER2-negative advanced breast cancer is endocrine therapy with or without an inhibitor of the cyclin-dependent kinases 4 and 6. However, half of the patients had progressed or died 25 months after the start of treatment [2].

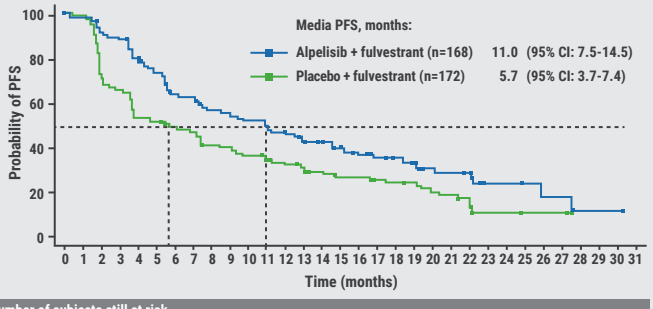
Alpelisib is a specific inhibitor of the α-isoform of PI3-kinase, encoded by the *PIK3CA* gene. In preclinical research, alpelisib displayed antitumour activity in cancer cells harbouring *PIK3CA* alterations [3]. Furthermore, in a phase 1b study, treatment of HR+ advanced breast cancer with alpelisib plus fulvestrant was associated with a median PFS of 9.1 months in patients whose tumour had a *PIK3CA* alteration, and of 4.7 months in patients with wildtype *PIK3CA* [4].

The randomised phase 3 SOLAR-1 study evaluated the outcome of fulvestrant plus either alpelisib or placebo in men or postmenopausal women with HR+, HER2-negative advanced breast cancer with or without mutations in *PIK3CA*. The primary endpoint of the study was locally-assessed PFS in the *PIK3CA*-mutant cohort. Secondary endpoints included PFS in the *PIK3CA* wildtype cohort, the ORR, and safety.

In patients with *PIK3CA*-mutant tumours, the locally-assessed median PFS was 11.0 months in the alpelisib arm (n=169) and 5.7 months in the placebo arm (n=172; HR 0.65, 95% CI 0.50-0.85, P=0.00065; Figure 1) [5]. Herewith, the primary endpoint crossed the prespecified boundary of significance. A similar benefit of alpelisib was observed when analysing centrally assessed PFS (HR 0.48). Furthermore, treatment benefit was consistent across patient subgroups, but not in the *PIK3CA* wildtype cohort. ORR was 27% in the alpelisib arm and 13% in the placebo arm (P=0.0006).

"The safety profile of alpelisib plus fulvestrant was as expected, and the majority of AEs were of grade 1 or 2. These results indicate that alpelisib plus fulvestrant potentially is a new treatment option for patients with *PIK3CA*-mutant, HR+, HER2-negative advanced breast cancer who have progressed on prior endocrine therapy," said presenting author Prof. Fabrice André (Institute Gustave Roussy, France).

Figure 1 Locally-assessed PFS in previously treated patients with *PIK3CA*-mutant, HR+, HER2-negative advanced breast cancer following treatment with fulvestrant plus either alpelisib or placebo [5]



Number of subjects still at risk																												
Alpelisib + Fulv	169	158	145	141	123	113	97	95	85	82	75	71	62	54	50	43	39	32	30	27	17	16	14	5	5	4	3	3	1	1	1	0
Placebo + Fulv	172	167	120	111	89	88	80	77	67	66	58	54	48	41	37	29	29	21	20	19	14	13	9	3	3	2	2	2	0	0	0	0

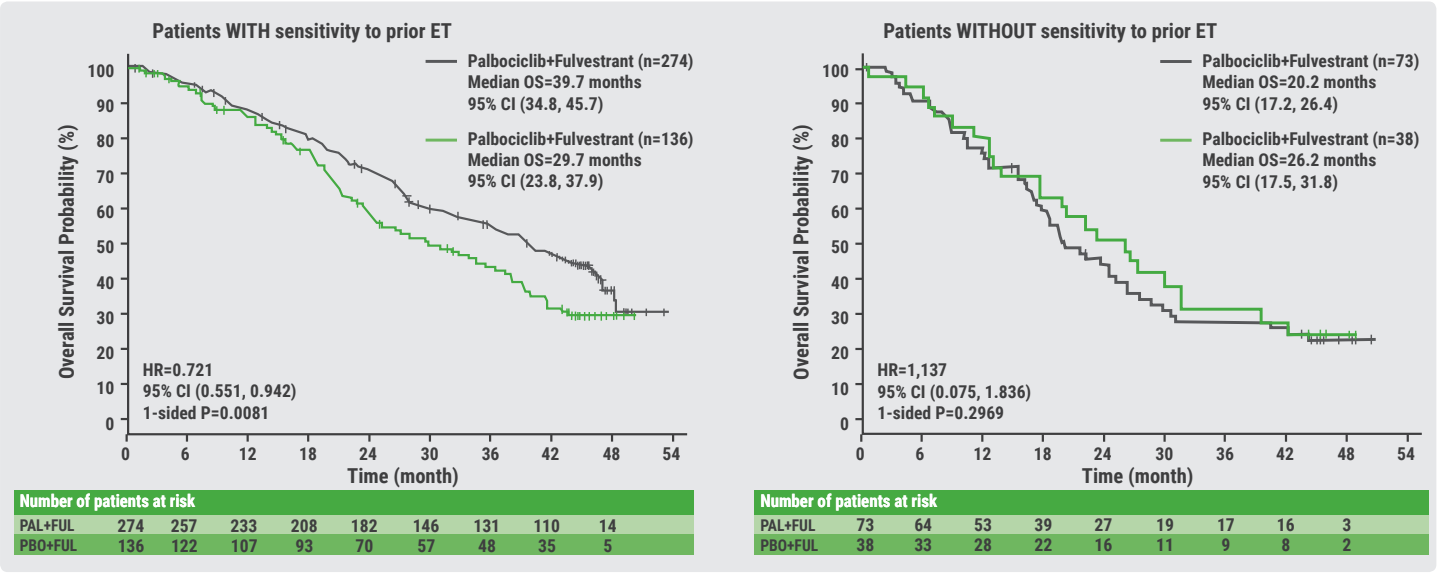
Data cut-off: Jun 12, 2018	Alpelisib + fulvestrant (n=169)	Placebo+ fulvestrant (n=172)
Number of PFS events, n(%)	103 (60.9)	129 (75.0)
Progression	99 (58.6)	120(69.8)
Death	4 (2.4)	9 (5.2)
Censored	66 (39.1)	43 (25.0)
Median PFS (95% CI)	11.0 (7.5-14.5)	5.7 (3.7-7.4)
HR (95% CI)	0.65 (0.50-0.85)	
P-value	0.00065	

Palbociclib plus fulvestrant improves overall survival in endocrine therapy-sensitive, HR+, HER2-negative breast cancer

Preclinical research indicated that breast cancer cells, especially those expressing the oestrogen receptor, are frequently sensitive for inhibition of the cyclin-dependent kinases (CDK) 4 and 6 [6]. The randomised phase 3 PALOMA-3 study compared the outcome of CDK4/6 inhibitor palbociclib plus fulvestrant vs placebo plus fulvestrant in patients with HR+, HER2- advanced breast cancer who had progressed on prior endocrine therapy. A previously published analysis of the study demonstrated that the addition of palbociclib to fulvestrant was associated with a significantly improved PFS [7,8]. Prof. Massimo Cristofanilli (Robert H. Lurie Comprehensive Cancer Center, USA) presented the final results on PFS and the first mature results on OS.

The results show that in the ITT population, the median PFS was 11.2 months in the palbociclib arm (n=347) and 4.6 months in the placebo arm (n=174; HR 0.497, 95% CI 0.40-0.62, 1-sided P<0.001)[9,10]. "In this population, the median OS was 34.9 months in the palbociclib arm and 28.0 months in the placebo arm (stratified HR 0.81, 95% CI 0.64-1.03, 1-sided P=0.043, an absolute improvement in median OS of 6.9 months (even though the CI crosses 1). Subgroup analysis showed a consistent magnitude of effect across most subgroups, with the exception of patients without sensitivity to previous endocrine therapy and premenopausal or perimenopausal women. Furthermore, the addition of palbociclib to fulvestrant was associated with a 10-month improvement in OS in patients with sensitivity to prior endocrine therapy (HR 0.72, 95% CI 0.55-0.94, 1-sided P=0.008; Figure 2). In contrast, palbociclib did not improve OS in patients without sensitivity to prior endocrine therapy," said Prof. Cristofanilli. Treatment with palbociclib did not interfere with the type or efficacy of standard treatment following progression.

Figure 2 OS in HR+HER2-negative advanced breast cancer treated with fulvestrant plus either palbociclib or placebo, per sensitivity to prior endocrine therapy [9]



ET, endocrine therapy; FUL, fulvestrant; PAL, palbociclib; PBO, placebo.

Atezolizumab improves progression-free survival in triple-negative breast cancer

Patients with locally advanced or metastatic triple-negative breast cancer (mTNBC) face poor outcomes in comparison to patients with other types of breast cancer. In the first line, patients with mTNBC are typically treated with chemotherapy consisting of a taxane or anthracycline. As yet, targeted therapies have not improved OS in mTNBC patients, although immune checkpoint blockade holds promise. For instance, the results of a phase 1 study showed PD-L1-inhibitor atezolizumab to be active in mTNBC, especially in patients whose tumours contained at least 1% PD-L1-positive immune cells [11].

The randomised phase 3 Impassion130 study evaluated the efficacy and safety of nab-paclitaxel plus either atezolizumab or placebo in patients with newly diagnosed mTNBC. The co-primary endpoints were PFS and OS in the ITT population and PD-L1-positive populations. Key secondary endpoints were ORR, duration of response, and safety.

The primary PFS analysis of the ITT population demonstrated a median PFS of 7.2 months in the atezolizumab arm (n=451) and 5.5 months in the placebo arm (n=451; stratified HR 0.80, 95% CI 0.69-0.92, P=0.0025) [12]. This difference was even larger among patients with PD-L1-positive tumours (≥1% PD-L1-positive immune cells): 7.5 months in the atezolizumab arm and 5.0 months in the placebo arm (stratified HR 0.62, 95% CI 0.49-0.78, P<0.001). A subgroup analysis showed that the PFS benefit of atezolizumab in the ITT population was consistent across most subgroups investigated, especially the group of patients ≥65 years (HR 0.69), 0-3 metastases (HR 0.76), no lung metastases (HR 0.74), and no prior (neo)adjuvant chemotherapy (HR 0.72).

"Furthermore, the interim OS analysis in the ITT population showed that the median OS was 21.3 months in the atezolizumab arm and 17.6 months in the placebo arm (stratified HR 0.84, 95% CI 0.69-1.02, P=0.084, which did not cross the significance boundary). As with PFS, the difference in median OS was larger in the PD-L1-positive population: 25.0 months following treatment with atezolizumab plus nab-paclitaxel, and 15.5 months following placebo plus nab-paclitaxel (stratified HR 0.62, 95% CI 0.45-0.86, significance not formally tested)," said presenting author Prof. Peter Schmid (Barts Cancer Institute, United Kingdom).

The toxicity profiles of both study arms were generally similar. Treatment-related AEs of any grade were observed in 96% of patients in the atezolizumab arm vs 94% in the placebo arm. In the atezolizumab arm, the most common AEs of any attribution and any grade were alopecia (56% vs 58% in the placebo arm), fatigue (47% vs 45%), and nausea (46% vs 38%).Treatment-related AEs of grade 3-4 occurred in 40% of patients in the atezolizumab arm vs 30% in the placebo arm. For treatment-related serious AEs, these percentages were 12% vs 7%, respectively. Any grade AEs leading to atezolizumab or placebo discontinuation, or dose reduction or interruption occurred in 6% and 31% of the patients in the atezolizumab arm, and 1% and 24% in the placebo arm, respectively.

Other noteworthy findings in breast cancer

The ShortHER study failed to show the non-inferiority of a shorter trastuzumab administration. However, a 9-week administration decreases the risk of severe cardiac toxicity and could be an option for patients with cardiac events during treatment and for those with a low risk of relapse [13], for patients with small tumours with low or intermediate risk. In the same treatment setting, the phase 3, non-inferiority PERSEPHONE study was performed. After a median follow-up of 4.9 years, the rates of DFS were 89.8% and 89.4% for 12 and 6 months of trastuzumab, respectively. The absolute difference of 0.4% was within the predefined confidence intervals for non-inferiority (P=0.01) [14]. Furthermore, a phase 3 trial demonstrated that exemestane in combination with chidamide (n=244), a subtype-selective histone deacetylase inhibitor, was associated with significantly improved investigator assessed PFS in the ITT population of HR+, HER2-negative advanced breast cancer patients progressing on endocrine therapy, as compared with exemestane plus placebo (n=121; HR 0.76, 95% CI 0.58-0.98, P=0.034) [15].Adjuvant triptorelin plus zoledronic acid associated with superior disease-free survival in early breast cancer

The efficacy of aromatase inhibitors, such as letrozole, and bisphosphonate zoledronic acid as adjuvant therapy for premenopausal, endocrine-responsive breast cancer patients is debated. Currently, the randomised, three-armed, phase 3 HOBOE-2 study evaluates the outcome of adjuvant gonadotrophin-releasing hormone agonist triptorelin plus either tamoxifen (T arm), letrozole (L arm), or zoledronic acid plus letrozole (ZL arm) in premenopausal patients with HR+ early breast cancer for 5 years. The primary endpoint of the study was DFS, including locoregional or distant recurrence, second breast or non-breast invasive cancer, and death without cancer as event. The analysis was based on intention-to-treat (ITT).

"Between March 2004 and August 2015, HOBOE-2 enrolled a total of 1,065 patients in 16 centres in Italy [1]. The 5-year DFS was 85% in the T arm and 93% in both the L and ZL arms. DFS in the ZL arm, but not the L arm, was significantly improved as compared with the T arm (HR 0.52, 95% CI 0.34-0.80, P=0.003; L arm vs T arm: HR 0.72, 95% CI 0.48-1.07, P=0.06). DFS in the ZL and L arms were not significantly different (HR 0.70, 95% CI 0.44-1.12, P=0.22).

Not previously defined subgroup analyses showed that treatment with ZL was more effective than T in all subgroups, with the exception of HER2-positive patients (interaction P=0.002)," said presenting author Dr Francesco Perrone (Istituto Nazionale Tumori, Italy).

Twenty-six (7%) patients with T, 26 (7%) with L, and 59 (17%) with ZL stopped the assigned treatment prematurely due to toxicity or refusal. Grade 3-4 adverse events (AEs) were reported in 4%, 7%, and 9% of patients in the T, L, and ZL arm, respectively.

"An important contribution of this trial will be its inclusion in the 2018 update of the bisphosphonates meta-analysis," said discussant Hervé Bonnefoi (University of Bordeaux, France).

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Gastrointestinal Cancer

Several late-breaking abstracts were presented on the positive outcome of treatment with immune checkpoint inhibitors in gastrointestinal cancer. For instance, the first results of the phase 2 NICHE study demonstrated that neoadjuvant immunotherapy with ipilimumab plus nivolumab followed by surgery was associated with major pathological responses in patients with DNA mismatch repair deficient early-stage colon cancer. In contrast, patients without this deficiency did not show any response. Additional data suggested that this difference in response seems to correlate with several immunological features. Furthermore, results from the phase 2 CheckMate 142 study showed that first-line treatment with nivolumab plus low-dose ipilimumab in patients with DNA mismatch repair deficient metastatic colorectal cancer is well tolerated and associated with a robust and durable clinical benefit.

Neoadjuvant immunotherapy associated with major pathological responses in DNA mismatch repair deficient colon cancer

Immune checkpoint blockade with PD-1 inhibitors with or without ipilimumab is associated with objective response rates (ORR) of up to 55% in previously treated patients with DNA mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) [1-3]. In contrast, patients with proficient MMR (pMMR) colorectal cancer are resistant to immune checkpoint inhibition. Furthermore, neoadjuvant immune checkpoint blockade has shown promising response rates in melanoma and lung cancer [4-5].

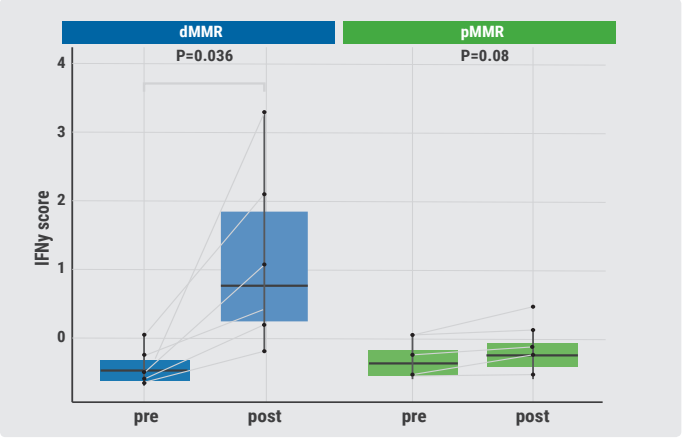
The exploratory, single-centre, phase 2 NICHE study determined the efficacy and safety of short-term neoadjuvant immunotherapy with ipilimumab (1 mg/kg on day 1) plus nivolumab (3 mg/kg on day 1 and 15) in patients with early stage, MMR deficient or proficient colon cancer. MMR status was defined by protein staining for MLH1, PMS2, MSH2, and MSH6. Safety was the primary study endpoint. Secondary endpoints were relapse-free survival and the association between response and tumour mutational burden, *IFNγ* gene signatures, T-cell infiltration, and T-cell receptor clonality.

"The first results of the NICHE study demonstrated that neoadjuvant treatment with dual immune checkpoint blockade was safe and feasible [6]. All patients received the planned doses of nivolumab and ipilimumab, and their tumours were radically resected. Treatment-related adverse events (AEs) of grade 1-2 and 3 were observed in 71% and 36% of the total population (n=15), respectively. Grade 4 treatment-related AEs were not observed," said Dr Myriam Chalabi (Netherlands Cancer Institute, the Netherlands) during the proffered paper session 'Immunotherapy of Cancer'.

The efficacy analysis demonstrated that 6 weeks after treatment, all 7 patients with dMMR colon cancer had a major pathological response: 2 patients had 2% residual vital tumour cells, 1 patient 1%, and 4 patients 0%. In contrast, in patients with pMMR tumours (n=8) no major pathological response were observed and hardly any tumour regression was seen.

Analysis of the tumour microenvironment showed that neoadjuvant immunotherapy followed by surgery was associated with a significant increase in the number of tumour-infiltrating CD3+ T-cells in dMMR tumours (P=0.031), but not pMMR tumours (P=0.461). Dr Chalabi: "Although pre-treatment dMMR tumours had a significantly higher number of tumour-infiltrating CD8+ T-cells compared with pMMR tumours (P=0.027), both types of colon cancer showed a significant increase in tumour-infiltrating CD8+ T-cells post-treatment. Furthermore, no significant differences were found in the T-cell receptor clonality of pre- and post-treatment dMMR and pMMR tumours, neither in their pre-treatment immune gene signature nor in their IFNγ score. However, post-treatment, the IFNγ score of dMMR tumours, but not pMMR tumours, was significantly increased as compared with the pre-treatment IFNγ score (Figure 3). We believe that these results warrant independent validation of neoadjuvant immunotherapy in dMMR tumours in larger trials."

Figure 3 IFNγ score increases significantly in dMMR, but not pMMR, early-stage CRC patients treated with neo-adjuvant immunotherapy and surgery [6]



"The results of the NICHE study demonstrated that neoadjuvant treatment with nivolumab plus ipilimumab is associated with a very good safety profile which may be due to the short duration of treatment. In addition, the results regarding the clinical and immunological response in dMMR tumours are impressive and certainly warrant further investigation in a pivotal study. Moreover, I anticipate that these results will lead to new approaches in understanding the biology of dMMR colon cancer," said discussant Prof. George Coukos (Ludwig Centre for Cancer Research, Switzerland).

Dual immunotherapy associated with robust and durable responses in patients with newly diagnosed DNA mismatch repair deficient metastatic colorectal cancer

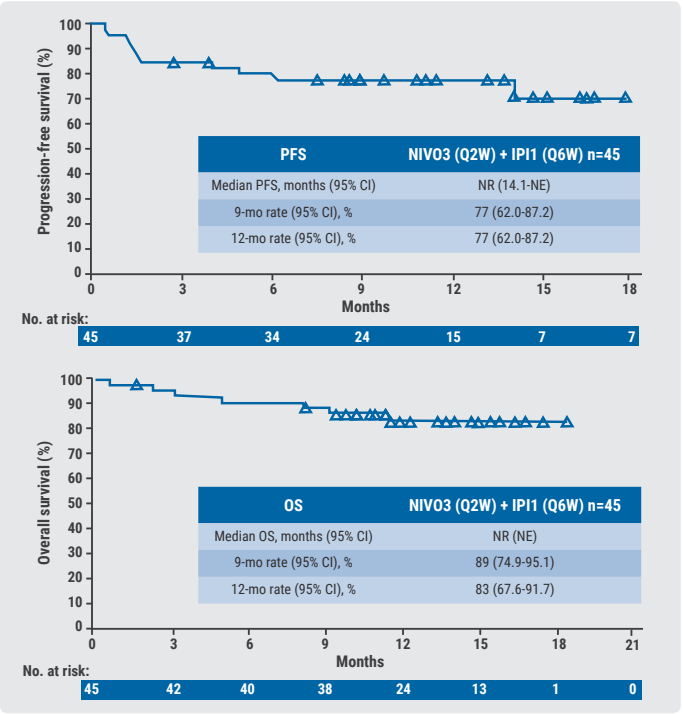
Despite advances in the treatment of mCRC, first-line chemotherapy-based regimens are generally associated with poor outcomes in patients with dMMR mCRC [7]. Inhibitors of immune checkpoint receptors, such as nivolumab, pembrolizumab, and ipilimumab, have recently shown promising response rates in previously treated patients with dMMR mCRC [1-3]. Moreover, since nivolumab and ipilimumab promote antitumour immune response by complementary mechanisms, their combined use might further improve the outcome in dMMR mCRC patients.

The multi-cohort, non-randomised, phase 2 CheckMate 142 study determined the efficacy and safety of nivolumab with or without low-dose ipilimumab in newly diagnosed or previously treated patients with dMMR mCRC. The primary endpoint was the investigator-assessed ORR. Additional key endpoints included ORR per blinded independent central review, disease control rate (DCR), progression-free and overall survival (PFS and OS), and safety. The current analysis evaluated the outcome of first-line treatment with nivolumab (3 mg/kg once every 2 weeks) plus ipilimumab (1 mg/kg once every 6 weeks).

Following a median follow-up of 14 months, treatment was associated with an ORR and DCR of 60% and 84%, respectively [8]. A complete response was observed in 3 patients (7%). The responses were durable: 74% of the responding patients had a response of at least 6 months, and the median duration of response was not reached. Median PFS and OS were not reached (Figure 4). PFS and OS at 1 year were 77% and 83%, respectively.

"Treatment-related AEs of any grade and grade 3-4 were observed in 78% and 16%, respectively. The most common treatment-related AEs of any grade were pruritus (24%), hypothyroidism (18%), and asthenia (16%). Three patients experienced treatment-related AEs of any grade that led to treatment discontinuation. Taken together, nivolumab plus low-dose ipilimumab may represent a new treatment option for patients with dMMR mCRC, which warrants evaluation in a phase 3 randomised controlled trial," said presenting author Prof. Heinz-Josef Lenz (USC Norris Comprehensive Cancer Center, USA).

Figure 4 PFS (top) and OS in newly diagnosed patients with dMMR mCRC treated with nivolumab plus low-dose ipilimumab [8]



IPI1, ipilimumab at 1 mg/kg once every 6 weeks; NE, not estimable; NIVO3, nivolumab at 3 mg/kg once every 2 weeks); NR, not reached.

"The results of this new first-line schedule for nivolumab plus ipilimumab are impressive, with an ORR of 60%, and promising PFS and OS. The exposure to nivolumab and ipilimumab was substantial, with a median treatment duration of 1 year. Furthermore, the toxicity profile of this adapted combination treatment is not very different from that of nivolumab monotherapy, suggesting that the new treatment schedule improved the tolerability of this combination treatment [1]. However, we should also bear in mind that treatment was possibly associated with one death due to toxicity, and some cases of long-lasting skin and endocrine AEs. In addition, the results were derived from a small number of patients participating in a non-randomised trial after a relatively short follow-up of 14 months. For an optimal interpretation of the results, we will have to await results with a longer follow-up, and for those of the KEYNOTE-177 study investigating the outcome of pembrolizumab in dMMR mCRC," concluded discussant Prof. Julien Taieb (Paris Descartes University, France).

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Genitourinary Cancer

Immunotherapy with immune checkpoint inhibitors has shown to be efficacious and safe in a growing number of cancers, including renal cell carcinoma. Several presentations demonstrated improved outcomes with immunotherapy in this type of cancer. For instance, the results of the randomised, phase 3 JAVELIN Renal 101 study show that first-line treatment of advanced renal cell carcinoma (mRRC) with avelumab plus axitinib is associated with improved progression-free survival (PFS) and objective response rates (ORR), as compared with standard treatment with sunitinib. In addition, exploratory analyses of the phase 3 IMmotion151 trial demonstrated that angiogenesis and T-effector gene signatures predict PFS in metastatic renal cell carcinoma patients treated with atezolizumab plus bevacizumab. Other studies showed encouraging results in the treatment of prostate cancer. For example, the randomised STAMPEDE trial demonstrated that radiotherapy to the primary tumour was well tolerated, and significantly improved overall survival in prostate cancer patients with a low, but not a high, metastatic burden. Furthermore, a retrospective analysis of STAMPEDE demonstrated that the addition of abiraterone and prednisone/prednisolone to androgen-deprivation therapy is beneficial in both high-risk and low-risk patients with hormone-naïve, metastatic prostate cancer, with respect to overall survival (OS) and a number of key secondary endpoints.

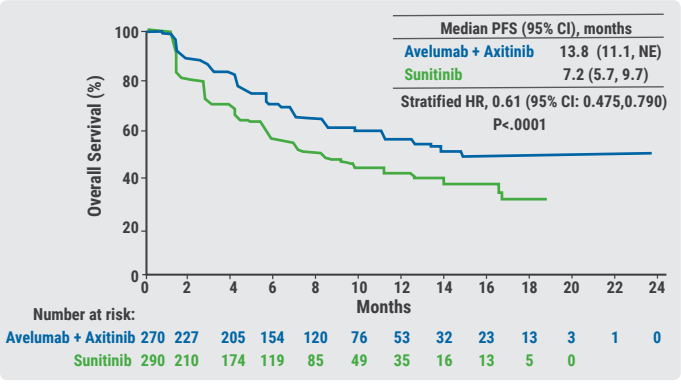
Avelumab and axitinib improve progression free-survival in treatment-naïve advanced renal-cell carcinoma

The PD-L1 inhibitor avelumab is approved for the treatment of metastatic Merkel cell carcinoma and, in North-America, advanced urothelial carcinoma progressing on platinum-based therapy. In the first and second line, avelumab monotherapy is associated with durable responses, promising survival outcomes, and an acceptable safety profile in patients with mRCC [1]. In preclinical models, simultaneous inhibition of the PD-1/PD-L1 and VEGF/VEGFR axes has been shown to induce synergistic antitumour activity [2]. Recently, the phase 1b JAVELIN Renal 100 study showed a manageable toxicity profile and ORR of 58% following first-line treatment with avelumab plus VEGFR TKI axitinib in patients with mRCC [3].

The current randomised phase 3 JAVELIN Renal 101 study compared the efficacy and safety of avelumab plus axitinib vs sunitinib as first-line treatment in mRCC. Patients were randomised 1:1 to receive avelumab at a dose of 10 mg/kg once every 2 weeks, plus 5 mg axitinib twice a day (6-week cycle), or 50 mg sunitinib once a day (4 weeks on, 2 weeks off). The co-primary endpoints were PFS per independent review committee (IRC) and OS, both in patients with PD-L1-positive (≥1% positive tumour-infiltrating immune cells) tumours. Key secondary endpoints included PFS per IRC and OS in the total population.

"With a median follow-up of 9.9 months in the combination arm and 8.4 months in the sunitinib arm, median PFS per IRC in the PD-L1-positive population was significantly improved by avelumab plus axitinib (n=270), as compared with sunitinib (n=290): 13.8 months vs 7.2 months (HR 0.61, 95% CI 0.48-0.79, P<0.0001; Figure 5) [4]. This PFS benefit was also observed in the total population, median PFS per IRC was 13.8 months in the combination arm (n=442) and 8.4 months in the sunitinib arm (n=444; HR 0.69, 95% CI 0.56-0.84, P=0.0001). A subgroup analysis demonstrated that the combination treatment improved IRC-assessed PFS in all subgroups investigated, including those based on IMDC or MSKCC risk criteria. In addition, the combination therapy also improved PFS per investigator assessment in both the PD-L1-positive and total population. In the PD-L1-positive population, ORR per IRC was 55% vs 26% in the combination and sunitinib arm, respectively. This was 51% vs 26% in the total population. In patients with PD-L1-positive tumours treated with avelumab plus axitinib, the median time to response was 1.6 months, and 73% of the patients had an ongoing response at the time of data cut-off. The OS data was still immature," said Prof. Robert Motzer (Memorial Sloan-Kettering Cancer Center, USA).

Figure 5 PFS per IRC in mRCC patients with PD-L1-positive tumours treated with avelumab plus axitinib, or sunitinib



Treatment-related adverse events (AEs) of any grade were observed in 95% of the patients in the combination arm and 96% in the sunitinib arm. The most frequently observed treatment-related AEs of any grade in the combination arm were diarrhoea (54% vs 45% in the sunitinib arm), hypertension (48% vs 32%), and fatigue (36% in both arms). Grade 3-4 treatment-related AEs occurred in 55% of the patients in both arms. Furthermore, immune-related AEs of all grades or grade 3-4 were observed in 38% and 9% of the patients treated with avelumab plus axitinib, respectively. Treatment-related AEs leading to discontinuation of all study drugs or death were observed in 4% and 1% of the patients in the combination arm, respectively, and 8% and <1% , in the sunitinib arm. According to Prof. Motzer, these results support the addition of avelumab to a TKI as a new first-line standard of care for patients with mRCC.

"Currently, sequential treatment with single agents is the standard of care in mRCC. It is unknown if and to which extend combination therapies can improve the treatment of mRCC. Now, the JAVELIN Renal 101 study demonstrated that combination treatment with avelumab plus axitinib compared with sunitinib doubles the ORR; an impressive result. Furthermore, the finding that the PD-L1-positive and total population behave similarly in terms of treatment efficacy, suggests that PD-L1-expression is not an optimal biomarker for patient selection in this setting. The similar PFS benefit among IMDC or MSKCC risk groups suggests that selection based on risk criteria does not apply to this combination treatment either. Another strength of this combination treatment is its tolerability, with a toxicity profile that is similar to sunitinib monotherapy. The question remains if this combination treatment is better than sequencing and other combination therapies, such as pembrolizumab plus axitinib. To answer this question, we have to await results on OS and/ or health-related quality of life," said discussant Prof. Viktor Grünwald (West-German Cancer Center, Germany).

Angiogenic and T-effector gene signatures predict progression-free survival in treatment-naïve advanced renal-cell cancer

The rationale to combine atezolizumab with bevacizumab is that these inhibitors exploit synergistic mechanisms for their antitumour activity. While PD-L1 inhibitor atezolizumab promotes T-cell mediated cell killing, the VEGF inhibitor bevacizumab normalises the tumour vasculature and decreases the activity of immunosuppressive cells. Previously, the phase 2 IMmotion150 study showed that treatment with atezolizumab plus bevacizumab, but not atezolizumab alone, significantly improved PFS in patients with newly diagnosed, PD-L1 positive (≥1% on tumour-infiltrating immune cells) metastatic renal-cell carcinoma (mRCC), as compared with sunitinib [5].

Furthermore, an exploratory biomarker analysis of the same study indicated that tumour mutation and neoantigen burden were not associated with PFS, whereas angiogenesis, effector T-cell response, and myeloid inflammatory gene expression signatures were strongly associated with PFS. Particularly, a T-effector-high, angiogenesis-low profile was associated with improved PFS. These results suggested that molecular profiles may predict the outcome of atezolizumab plus bevacizumab in treatment-naïve patients with PD-L1-positive mRCC. Dr Brian Rini (Cleveland Clinic Taussig Cancer Institute, USA) presented results of the successive IMmotion151 study. This randomised phase 3 study determined the efficacy and safety of atezolizumab plus bevacizumab vs sunitinib in treatment-naïve patients with PD-L1 positive and PD-L1 negative advanced RCC. The co-primary endpoints were investigator-assessed PFS in PD-L1 positive tumours, and OS in the intention-to-treat population.

Table 1 IMmotion15 Study design [6]

Progression-free survival (PFS) as determined by an IRC according to RECIST v1.1 in ITT Population		
Description	PFS was defined as time from randomisation to PD, as determined by an IRC per RECIST v1.1, or death from any cause, whichever occurred first. PD: >/=20% relative increase in the SoD of TLs, taking as reference the smallest SoD on study, including baseline, and an absolute increase of >/=5 mm; >/=1 new lesion(s); and/or unequivocal progression of non-TLs. Participants without PFS event were censored at the last tumour assessment date. Participants with no post-baseline tumour assessment were censored at the randomisation date + 1 day. Median PFS was estimated by Kaplan-Meier method and 95% CI was assessed using the method of Brookmeyer and Crowley.	
Time Frame	Baseline until documented PD or death, whichever occurred first (until data cut-off date 29 September 2017, up to approximately 24 months).	
Analysis was performed on the ITT population		
Arm / Group	**Sunitinib**	**Atezolizumab + Bevacizumab**
Description	Participants received sunitinib at a dose of 50 mg administered orally via capsules once daily on Days 1 to 28 of each 42-day cycle until loss of clinical benefit in the opinion of the investigator, unacceptable toxicity or symptomatic deterioration attributed to PD as determined by the investigator, withdrawal of consent, or death.	Participants received atezolizumab at a dose of 1200 mg and bevacizumab at a dose of 15 mg/kg administered via IV infusions on Day 1 and Day 22 of each 42-day cycle until loss of clinical benefit in the opinion of the investigator, unacceptable toxicity or symptomatic deterioration attributed to PD as determined by the investigator, withdrawal of consent, or death.
Patients analysed	461	454
Unit of measure: months	8.3 (7.0 to 9.7)	9.6 (8.3 to 11.5)

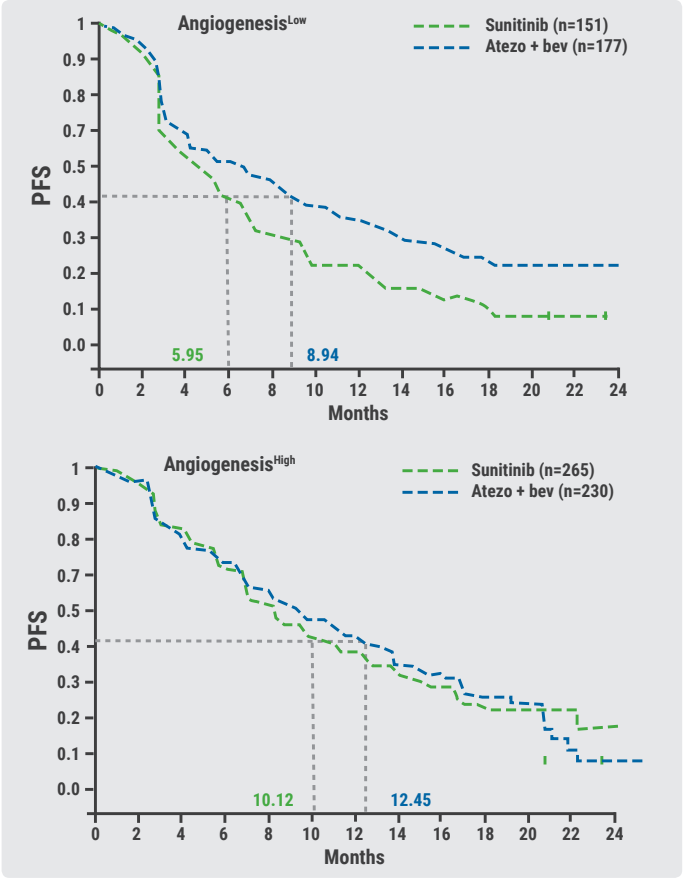
Exploratory endpoints included validation of gene signatures from IMmotion150 and their association with PFS, as well as biomarker characterisation in MSKCC risk subgroups and sarcomatoid tumours. The study enrolled 915 patients.

The efficacy analysis demonstrated that the combination treatment significantly improved the investigator-assessed PFS, as compared with sunitinib [6]. In the PD-L1-positive population, median PFS was 11.2 months in the combination arm (n=178) and 7.7 months in the sunitinib arm (n=184; HR 0.74, 95% CI 0.57-0.96, P=0.02). Median PFS was 11.2 months vs 8.4 months in the intention-to-treat population (n=915; HR 0.83, 95% CI 0.70-0.97, P=0.025).

Efficacy analyses in biomarker-evaluable patients showed that the combination vs sunitinib treatment was associated with a significantly improved PFS in patients with angiogenesis-low (HR 0.68, 95% CI 0.52-0.88), but not angiogenesis-high tumour profiles (HR 0.95, 95% CI 0.76-1.19; Figure 6). Similar findings were observed in patients whose tumours had a T-effector-high gene profile (HR 0.76 95% CI and P-value?), as opposed to those with a T-effector-low profile (HR 0.91, 95% CI and P-value). Among patients treated with sunitinib, but not those treated with atezolizumab plus bevacizumab, an angiogenesis-high tumour profile was associated with an improved PFS, as compared with those with angiogenesis-low profile (HR 0.59). Furthermore, subgroup analysis showed that the PFS benefit of the combination treatment was only present in patients with sarcomatoid tumours. PFS in MSKCC risk groups was comparable. However, angiogenesis gene expression was significantly higher in favourable MSKCC risk groups. In addition, angiogenesis gene expression was significantly lower and PD-L1 expression higher in sarcomatoid tumours. Of note, different molecular profiles were evident in risk groups.

Favourable risk patients showed more frequently an angiogenesis-high signature than intermediate/poor risk (74% vs 26%) whereas intermediate/poor risk patients more frequently had a T-effector-high signature and PD-L1+ than favourable risk (64% vs 36%). Patients with sarcomatoid RCCs showed more frequently an angiogenesis-high signature and T-effector-high/PD-L1+ profiles.

Figure 6 Treatment with atezolizumab plus bevacizumab vs sunitinib improves PFS in treatment-naïve mRCC patients with an angiogenesis-low, but not angiogenesis-high profile [6]

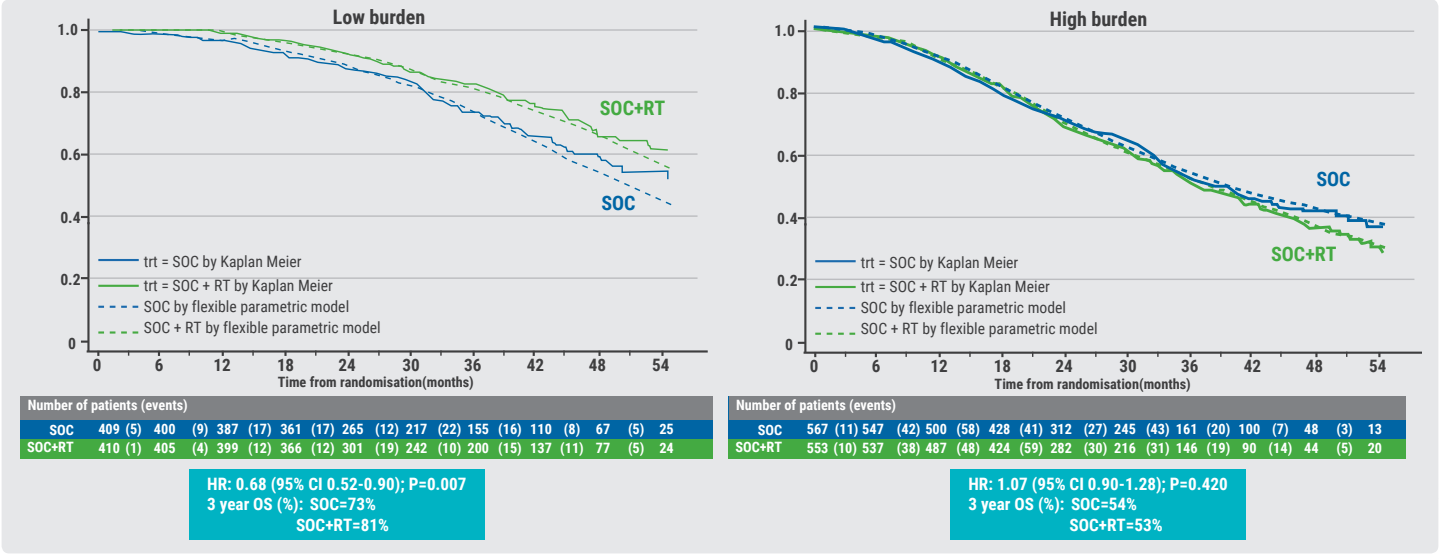


Radiotherapy improves overall survival in prostate cancer with low metastatic burden

Patients with metastatic prostate cancer might benefit from radiotherapy to the primary tumour, in addition to systemic therapy. Therefore, as part of the multi-arm, multi-stage, randomised STAMPEDE trial, the addition of radiotherapy to systemic treatment with androgen-deprivation therapy (ADT) with or without docetaxel was investigated in men with newly diagnosed metastatic prostate cancer. Radiotherapy was either provided following a 'daily' (55 Gy in 20 fractions over 4 weeks) or 'weekly' schedule (36 Gy in 6 weekly fractions), nominated before randomisation. OS was the primary endpoint of the study. Secondary endpoints included failure-free survival (FFS), symptomatic local events (SLE), and toxicity.

"The efficacy analysis demonstrated that in the total population the two treatment arms did not show a significant difference in OS at 3 years: 65% in the radiotherapy arm (n=1,032) and 62% in the control arm (n=1,029; HR 0.92, 95% CI 0.80-1.06, P=0.266) [7,8]. However, in patients with a low metastatic burden, according to the CHAARTED volume classification, the 3-year OS was 81% in the radiotherapy arm (n=410) and 73% in the control arm (n=409); a significant difference (HR 0.68, 95% CI 0.52-0.90, P=0.007; Figure 7) [9]. In contrast, no significant difference was observed between the two treatments in patients with a high metastatic burden (HR 1.07, 95% CI 0.90-1.28, P=0.420). Furthermore, no evidence was found that the OS effect size differs by radiotherapy schedule," said presenting author Dr Chris Parker (The Royal Marsden NHS Foundation Trust, United Kingdom).

Figure 7 OS in metastatic prostate cancer patients with a low and high metastatic burden treated with standard of care androgen-deprivation therapy with or without radiotherapy [7]



RT, radiotherapy; SOC, standard of care.

FFS in the total population at 3 years was 32% in the radiotherapy arm and 23% in the control arm (HR 0.76, 95% CI 0.68-0.84, P<0.0001). In patients with a high metastatic burden, FFS was similar in the two treatment arms but differed significantly in patients with a low metastatic burden. In the latter patients, 3-year FFS was 50% in the radiotherapy arm and 33% in the control arm (HR 0.59, 95% CI 0.49-0.72, P<0.0001). Time from randomisation to life-prolonging treatment was not significantly different in the two treatment arms. Neither were the time from randomisation to first SLE, nor the time from randomisation to first grade 3-5 toxicity. Furthermore, the addition of radiotherapy to the standard of care was well tolerated.

Dr Parker concluded that "Even though the benefit of radiotherapy was found in a subgroup analysis, we believe that it is a robust finding, among others because the results meet all 10 criteria of the subgroup credibility checklist published by Sun et al. [10]. In addition, the results are consistent with the recently published results of the smaller, but similar, HORRAD study [11]. "This is a practice-changing phase 3 study within the STAMPEDE series. Based on its findings, guideline committees should review ADT plus radiotherapy as a possible new standard of care," said discussant Prof. Robert Bristow (University of Manchester, United Kingdom).

Abiraterone is beneficial for both low-risk and high-risk patients with hormone-naïve metastatic prostate cancer

Two randomised, controlled trials compared the outcome of abiraterone plus prednisone vs prednisolone in hormone-naïve metastatic prostate cancer: LATITUDE and STAMPEDE. "LATITUDE recruited 1,199 patients with de *novo* high-risk metastatic prostate cancer, and showed that, after a median follow-up of 30 months, ADT plus abiraterone plus prednisone was associated with a significantly improved OS, as compared with ADT plus placebo (HR 0.62, 95% CI 0.51-0.76) [12]. The STAMPEDE trial compared the outcome of ADT plus abiraterone plus prednisolone vs ADT alone in 1,917 patients with either metastatic or non-metastatic prostate cancer. The results of the metastatic cohort (n=1,002) demonstrated that abiraterone was associated with a similar OS benefit (HR 0.61, 95% CI 0.49-0.75) as found in the LATITUDE trial, after a follow-up of 40 months [13]. The HR in the non-metastatic cohort was slightly higher (0.75) and had a wide 95% CI (0.48-1.18), possibly suggesting that the trial was immature and the event rate fairly low. Based on these findings, it can be concluded that the beneficial effect of abiraterone plus prednisone/prednisolone is similar in metastatic and non-metastatic disease," said presenting author Dr Alex Hoyle (The Christie NHS Foundation Trust, United Kingdom). Dr Hoyle: "The EAU and NCCN suggested that treatment with abiraterone should be considered for all men with hormone-naïve, metastatic prostate cancer, but in 2018 the FDA and EMA licenced the drug for high-risk disease only. Therefore, the position of patients with low-risk disease became uncertain."

The multi-arm, multi-stage phase 2/3 STAMPEDE trial determined the outcome of new, ADT-based treatment approaches in patients with hormone-naïve, advanced prostate cancer. The current retrospective analysis compared the outcome of ADT plus prednisolone plus abiraterone

vs ADT alone in both high-risk and low-risk patients with hormone-naïve, metastatic prostate cancer. Risk was defined by the criteria of the LATITUDE study (primary stratification: any 2 or more of: 3 or more bone lesions , visceral lesions, gleason 8 or higher), which were based on both radiological and pathological factors, and the disease volume-based criteria of the CHAARTED trial (exploratory stratification: 4 or more bone lesion or one /more outside the vertebral column /spine or visceral metastasis).

Characterisation of the whole cohort (n=901) indicated that, according to the LATITUDE risk criteria, 47.5% of the patients was defined as low-risk, and 52.5% as high-risk [14]. According to the CHAARTED criteria, this distribution was 44.6% and 55.4%, respectively. After a median follow-up of 42 months, treatment with ADT plus abiraterone plus prednisolone vs ADT only was associated with a significantly improved OS, FFS, skeletal related events rate, PFS, and prostate cancer-specific death in patients with both a LATITUDE-defined high-risk and low-risk (Figure 8). For instance, the HR for OS was 0.66 (95% CI 0.44-0.98, P=0.041) in low-risk patients and 0.54 (95% CI 0.41-0.70, P<0.001) in high-risk patients. Similar results were found when subgroups were based on the CHAARTED risk criteria. Furthermore, the interaction between high-risk and low-risk patients defined by either the LATITUDE or CHAARTED criteria was insignificant for all endpoints. "Taken together, these results suggest that ADT plus abiraterone and prednisolone should be considered as a treatment option for all patients with hormone-naïve, metastatic prostate cancer, irrespective of risk and/or volume classification," concluded Dr Hoyle.

"The analysis by Hoyle et al. resulted in very important information for many men with hormone-naïve, metastatic prostate cancer," said discussant Prof. Karim Fizazi (Institute Gustave Roussy, France). Limitations of the analysis were that it was unplanned and underpowered. Furthermore, central imaging reading was performed by one person only. Furthermore, it is unknown how the patients were treated beyond progression. As yet, the standard of care for fit patients with de *novo*, high-risk disease is ADT plus either abiraterone or docetaxel. For patients with de *novo*, low-risk disease, the standard treatment is debated, with ADT alone or ADT plus docetaxel as possible options. Based on the current data, ADT plus abiraterone probably becomes the new standard of care for low-risk patients. The introduction of generic abiraterone will likely promote its reimbursement. The remaining question is if the combination of ADT, abiraterone and docetaxel further improves the outcome in patients with de *novo*, metastatic prostate cancer. The randomised phase 3 PEACE-1 trial anticipates to answer this question in the near future.

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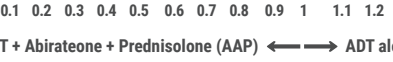
Figure 8 Outcome of ADT plus abiraterone plus prednisolone vs ADT alone in LATITUDE-defined risk groups of patients with hormone-naïve, metastatic prostate cancer [14]

		ADT alone	AAP	Adjusted HR (95% CI)		P-value	Interaction by metastic volume P-value
		No. of events/No. of patients					
Overall survival	All patients	195/452	135/449		0.609 (0.488-0.789)	<0.001	
	Low risk	59/220	41/208		0.657 (0.438-0.983)	0.041	0.385
	High risk	136/232	94/241		0.536 (0.411-0.699)	< 0.001	
Failure free survival	All patients	354/452	191/449		0.316 (0.264-0.378)	<0.001	
	Low risk	152/220	56/208		0.238 (0.174-0.325)	<0.001	0.294
	High risk	202/232	135/241		0.313 (0.250-0.392)	<0.001	
Skeletal related survival	All patients	164/452	93/449		0.467 (0.362-0.602)	<0.001	
	Low risk	49/220	17/208		0.311 (0.179-0.543)	<0.001	0.207
	High risk	115/232	76/241		0.477 (0.356-0.639)	<0.001	
Progression free survival	All patients	267/452	158/449		0.446 (0.366-0.544)	<0.001	
	Low risk	101/220	41/20		0.334 (0.232-0.482)	<0.001	0.159
	High risk	166/232	117/241		0.463 (0.364-0.588)	<0.001	
Prostate cancer specific death	All patients	172/452	114/449		0.587 (0.462-0.746)	<0.001	
	Low risk	49/220	27/208		0.511 (0.312-0.836)	0.008	0.728
	High risk	123/232	87/241		0.570 (0.432-0.754)	<0.001	



Gynaecologic Cancer

Several results were presented that could potentially be practice-changing. For instance, the results of the randomised phase 3 SOLO1 study convincingly demonstrated that olaparib maintenance was associated with improved progression-free survival (PFS) in patients with newly diagnosed, *BRCA*1/2-mutated, advanced ovarian cancer. In addition, olaparib significantly improved the time to second progression or death, suggesting that olaparib did not diminish patients' ability to benefit from subsequent therapy. Furthermore, the results of the randomised phase 3 AGO-OVAR 2.21/ENGOT ov-18 study demonstrated that carboplatin plus pegylated liposomal doxorubicin and bevacizumab was associated with significantly improved PFS in patients with recurrent ovarian cancer, as compared with carboplatin plus gemcitabine and bevacizumab. This PFS benefit was also observed in patients previously treated with antiangiogenic agents

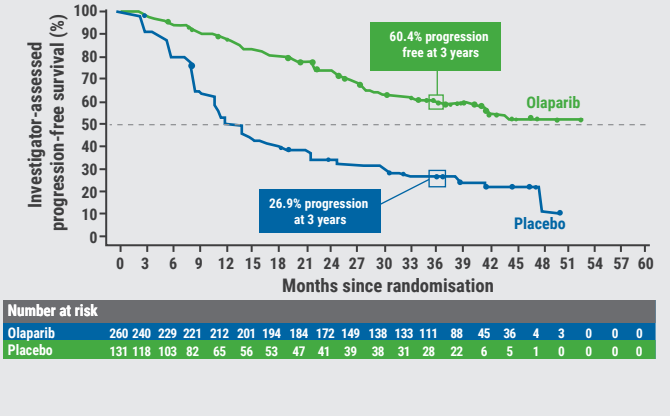
Improved progression-free survival following olaparib maintenance therapy in newly diagnosed, *BRCA*-mutant, advanced ovarian cancer

Cytoreductive surgery and platinum-based chemotherapy is a standard treatment in treatment-naïve patients with advanced ovarian cancer, but most patients relapse within 3 years. In many countries, the PARP inhibitor olaparib is an approved maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer, regardless of the presence of *BRCA*1/2 mutations (*BRCA*m). In addition, in the USA, olaparib is registered as monotherapy in patients with advanced ovarian cancer and a germline *BRCA*m who have received at least 3 lines of chemotherapy.

Dr Kathleen Moore (Stephenson Oklahoma Cancer Center, USA) presented results of the randomised phase 3 study SOLO1, which evaluated maintenance treatment with olaparib vs placebo in newly diagnosed patients with *BRCA*m advanced ovarian cancer, and a complete or partial response after surgery and platinum-based chemotherapy (without bevacizumab) (not all patients received same cycles of chemo). Study treatment was stopped after 2 years in patients without evidence of disease, or continued until disease progression in the remaining patients. The primary endpoint was investigator-assessed PFS. Secondary endpoints included PFS per blinded independent central review, time to second progression or death (PFS2), overall survival (OS), health-related quality of life (HRQoL), and safety.

With a minimum follow-up of 3 years, olaparib was shown to significantly improve the investigator-assessed PFS [1,2]. Median PFS was not reached in the olaparib arm and 13.8 months in the placebo arm (HR 0.30, 95% CI 0.23-0.41, P<0.0001). PFS at 3 years was 60.4% following maintenance treatment with olaparib, and 26.9% after placebo (Figure 9). Similar results were reported regarding PFS per blinded independent central review: the median PFS was not reached in the olaparib arm and 14.1 months in the placebo arm (HR 0.28, 95% CI 0.20-0.39, P<0.0001). Subgroup analysis showed that the PFS benefit of olaparib was evident in all subgroups investigated, but especially those with a partial response following chemotherapy (HR 0.19) or a *BRCA*2 mutation (HR 0.20). Moreover, both patients with stage 3 and 4 disease responded well to the treatment (HR 0.32 and 0.49, respectively). Furthermore, olaparib also significantly improved PFS2 (HR 0.50), median time to first subsequent therapy or death (HR 0.30), and median time to second subsequent therapy or death (HR 0.45). The HRQoL was not different in the two treatment arms, and the OS data were still immature.

Figure 9 Olaparib maintenance treatment vs placebo significantly improves investigator-assessed PFS in patients with newly diagnosed, *BRCA*m, advanced ovarian cancer [1]



Treatment-related adverse events (AEs) of all grades were observed in 99% of the patients treated with olaparib, and 92% of those receiving placebo. Grade ≥3 treatment-emergent AEs were found in 39% of the patients in the olaparib arm and 19% of the patients in the placebo arm. In the olaparib arm, the most common treatment-emergent AEs of grade ≥3 were anaemia (22% vs 1.5% in the placebo arm), neutropenia (9% vs 5%), and fatigue/asthenia (4% vs 2%). AEs leading to dose reduction or discontinuation were observed in 29% and 12% of patients in the olaparib arm, respectively, vs 3% and 2% of the patients in the placebo arm, respectively. Finally, 3 cases of AML/MDS occurred 1.7–5.7 months after stopping olaparib vs none following placebo. New primary malignancies were detected in 5 patients treated with olaparib, and 3 patients who had received placebo.

Discussant Prof. Jonathan Ledermann (UCL Cancer Institute, United Kingdom) cocnluded that "SOLO1 is a well-conducted landmark study with an established drug in patients with a *BRCA* mutation. Treatment was associated with a significant improvement in PFS, with robust data at 3 years. These results provide a sound basis for the establishment of olaparib as maintenance therapy in patients with newly diagnosed, *BRCA*m, advanced ovarian cancer. At the same time, these results confirm the need for swift *BRCA* testing as diagnosis, especially when considering first-line treatment with bevacizumabb.

CD-BEV associated with improved progression-free survival in recurrent ovarian cancer

Carboplatin plus gemcitabine and bevacizumab (CG-BEV), and carboplatin plus pegylated liposomal doxorubicin (CD) are standard regimens in the treatment of patients with recurrent ovarian cancer eligible for platinum-based retreatment. The aim of the phase 3 AGO-OVAR 2.21/ ENGOT ov-18 study was to evaluate whether CD is superior to CG when given in combination with BEV. Patients were randomised 1:1 to receive either CD-BEV or standard CG-BEV. The primary endpoint was investigator-assessed PFS. Secondary endpoints included biological PFS (PFSBIO) by serum cancer antigen 125, safety, and QoL.

Analysis of the primary endpoint demonstrated that CD-BEV significantly improved investigator-assessed PFS, as compared with CG-BEV [3]. Median PFS was 13.3 months in the CD-BEV arm (n=345) and 11.7 months in the CG-BEV arm (n=337; HR 0.81, 95% CI 0.68-0.96, P=0.013). Similar results were found for PFSBIO: median PFSBIO was 11.5 months in the CD-BEV arm and 10.0 months in the CG-BEV arm (HR 0.76, 95% CI 0.64-0.90, P=0.001). The PFS benefit of CD-BEV was observed in several patient subgroups, such as the group of patients with a platinum-free interval of more than 12 months (HR 0.81, P<0,05) or those previously treated with antiangiogenic agents (HR 0.73, P<0,05). OS analysis, for which the study was not powered, showed that the median OS was 33.5 months in the CD-BEV arm and 28.2 months in the CG-BEV arm (HR 0.83, 95% CI 0.68-1.02, P=0.079).

AEs of any grade were observed in virtually all patients, and grade 3-5 AEs in 75% of the pateints in the CD-BEV arm and 81% of those in the CG-BEV arm. AEs of special interest included grade ≥3 neutropenia, occurring in 12% of patients treated with CD-BEV vs 22% in the CG-BEV arm, and grade ≥3 hypertension, which was observed in 28% vs 21% of the patients, respectively. Furthermore, there were some minor differences in global QoL (EORTC QLQ-C30) score, favouring CD-BEV, although this was not statistically significant over time. "Taken together, these results suggest that CD-BEV is a new treatment option for patients with recurrent ovarian cancer suitable for platinum-based retreatment," concluded presenting author Dr Jacobus Pfisterer (Gynaecologic Oncology Center, Germany).

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Melanoma

Treatment approaches in advanced melanoma increasingly concentrate on combination therapies. For instance, the updated results of the randomised phase 3 CheckMate 067 study at a 4-year follow-up confirm the previously observed overall survival (OS) benefit of nivolumab with or without ipilimumab, compared with ipilimumab alone, in patients with newly diagnosed advanced melanoma. Grade 3-4 treatment-related adverse events (AEs) occurred in more than twice as many patients in the combination arm, as in the nivolumab and ipilimumab monotherapy arms. Furthermore, longer-term follow-up of the randomised phase 3 COMBI-AD trial confirmed previous results showing that adjuvant dabrafenib plus trametinib vs placebo improved relapse-free survival (RFS) in patients with resected, stage 3, *BRAF*-mutant melanoma, regardless of tumour mutational burden. In addition, the KEYNOTE-022 study showed that first-line pembrolizumab combined with dabrafenib and trametinib was associated with a promising efficacy and manageable toxicity in patients with *BRAF*-mutant, advanced melanoma. However, the difference in progression-free survival (PFS) following dabrafenib plus trametinib and either pembrolizumab or placebo did not reach statistical significance in this relatively small phase 2 study.

Durable and sustained clinical benefit of first-line nivolumab with or without ipilimumab in advanced melanoma

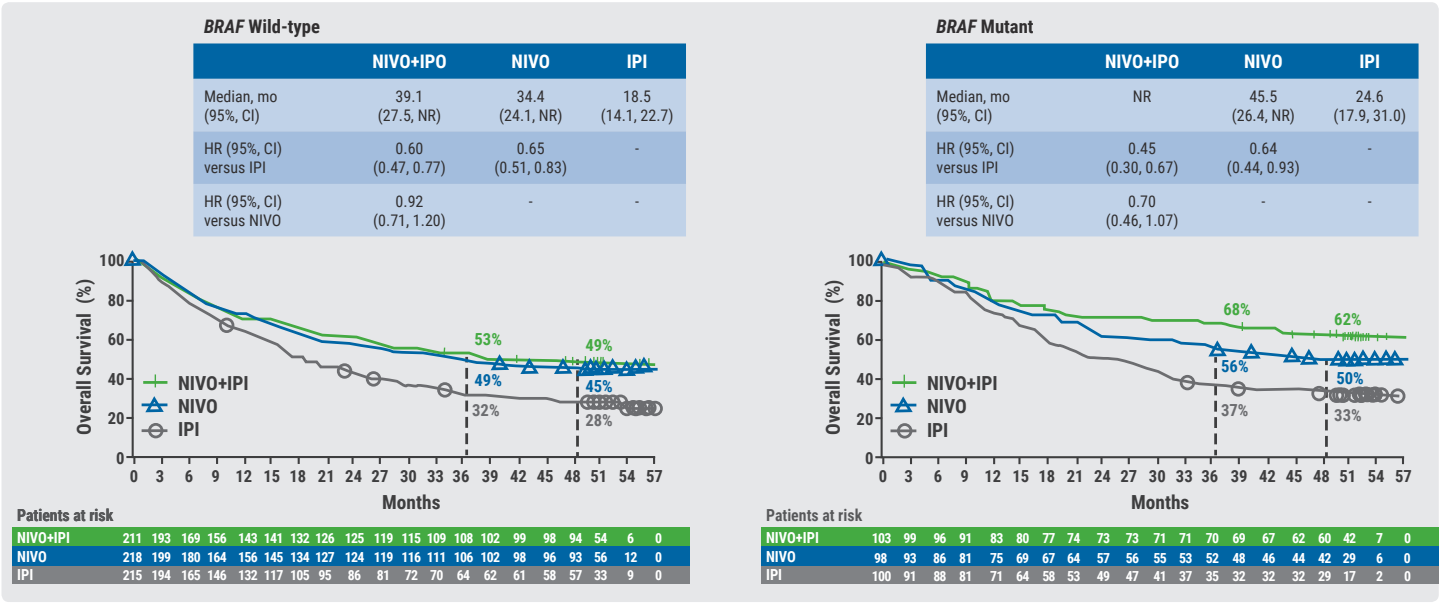
Previously, the randomised, three-armed, phase 3 CheckMate 067 study showed that nivolumab with or without ipilimumab significantly improved overall survival (OS) in patients with newly diagnosed advanced melanoma, as compared with ipilimumab alone [1]. The 3-year survival rate was 58% in the combination arm, 52% for nivolumab alone, and 34% for ipilimumab alone. Moreover, combination immunotherapy was associated with a longer time to subsequent therapy, and an increased proportion of patients free of subsequent therapy at 3 years. However, the improved efficacy was accompanied by increased toxicity. For instance, grade 3-4 treatment-related AEs were observed in 59% of the patients in the combination arm, in 21% of those in the nivolumab arm, and in 28% of the patients in the ipilimumab arm.

The current update of the CheckMate 067 study, presented by Prof. Stephen Hodi (Dana Farber Cancer Institute, USA), included an analysis of the objective response rate (ORR), OS, PFS, treatment-free interval, and of the proportion of patients who are treatment-free at 4 years. At a minimum follow-up of 4 years, ORR was 58% in the combination arm (n=314), 45% in the nivolumab arm (n=316), and 19% in the ipilimumab arm (n=315) [2,3]. The median duration of response was 50.1 months, not reached, and 14.4 months in the three treatment arms, respectively. The combination treatment, but also nivolumab monotherapy, significantly improved PFS and OS, as compared to ipilimumab alone. Median PFS was 11.5 months in the combination arm, 6.9 months in the nivolumab arm, and 2.9 months in the ipilimumab arm (combination vs ipilimumab: HR 0.42, 95% CI 0.35-0.51; nivolumab vs ipilimumab: HR 0.53, 95% CI 0.44-0.64). Median OS was not reached in the combination arm, 36.9 months in the nivolumab arm, and 19.9 months in the ipilimumab arm (combination vs ipilimumab: HR 0.54, 95% CI 0.44-0.67; nivolumab vs ipilimumab: HR 0.65, 95% CI 0.53-0.79). The OS benefit was observed across clinically relevant subgroups, including those based on *BRAF* mutation status (Figure 10), and appeared to be independent of PD-L1 tumour expression.

Median treatment-free interval at 4 years in patients who discontinued study therapy was 15.4 months in the combination arm, 1.7 months in the nivolumab arm, and 1.9 months in the ipilimumab arm. At the time of the 4-year follow-up, 71% of patients in the combination arm were treatment-free, as compared with 50% in the nivolumab arm, and 39% in the ipilimumab arm. In addition, the median time from randomisation to subsequent systemic therapy was not reached in the combination arm, 25.2 months in the nivolumab arm, and 8.1 months in the ipilimumab arm.

At 4 years of follow-up, no new safety signals were observed, and no additional deaths due to study drug toxicity were reported since the prior analysis. Treatment-related AEs of grade 3-4 occurred in 59% of the patients in the combination arm, 22% of those in the nivolumab arm, and 28% of the patients in the ipilimumab arm. Treatment-related deaths occurred in 0.6%, 0.3%, and 0.3% of the patients in those

Figure 10 OS in patients with newly diagnosed, BRAF wildtype or mutant, advanced melanoma treated with either nivolumab plus ipilimumab, nivolumab alone, or ipilimumab alone [2]



IPI, ipilimumab; NIVO, nivolumab; NIVO+IPI, nivolumab plus ipilimumab.

arms, respectively. Furthermore, patients who discontinued treatment with nivolumab plus ipilimumab during induction due to a treatment-related AE had similar 4-year PFS (35%) and OS (54%) compared with patients in the overall population (37% and 53%, respectively).

Discussant Prof. Reinhard Dummer (University Hospital Zurich, Switzerland) observed that "in recent years, the treatment of advanced melanoma has become increasingly complex, with multiple options in the treatment of both BRAF wildtype as well as BRAF mutant tumours. Emerging questions are 'which treatment is optimal for which patient?', 'what is the best timing and sequence?', and 'what are meaningful combination treatments?'. The answers to these questions should be guided by the benefit for our patients, in other words, by the ratio of efficacy vs toxicity. How does this add up for the combination treatment of nivolumab plus ipilimumab? With a decent follow-up time, the descriptive analysis suggested that on the one side, the combination therapy improves ORR, PFS, and OS, as compared to nivolumab alone. On the other side, it was also associated with an increase in transient, life-threatening, and non-resolving toxicity. Moreover, the study was not powered to compare the combination treatment with nivolumab alone. Therefore, I'm not yet convinced that the combination treatment is so much better than nivolumab monotherapy. However, the improved outcome of nivolumab monotherapy vs ipilimumab alone is impressive and encouraging."

Immune gene expression signatures hold prognostic value in stage 3, *BRAF*-mutant melanoma

Previously, results of the randomised phase 3 COMBI-AD trial demonstrated that adjuvant dabrafenib plus trametinib vs placebo improved the outcome in patients with resected, BRAF V600–mutant, stage 3 melanoma [4]. The combination treatment was shown to significantly improve RFS and was associated with a trend towards improved OS. The safety profile of dabrafenib plus trametinib was consistent with that observed in metastatic melanoma.

To better characterise the longer-term benefit with the adjuvant combination therapy, Prof. Georgina Long (Melanoma Institute Australia, Australia) and colleagues determined RFS with extended follow-up and performed cure-rate modelling and biomarker analyses. For the latter, mutational landscape and gene expression signatures were examined in baseline tissue samples by sequencing 570 genes, and gene expression profiling was examined using a customised NanoString panel for 800 genes.

With a median follow-up of 44 months, RFS was significantly improved by adjuvant dabrafenib plus trametinib, as compared with placebo (HR 0.49, 95% CI 0.40-0.59) [5, 6]. RFS at 3 years was 59% in the combination arm (n=438) and 40% in the placebo arm (n=432), at 4 years this was 54% vs 38%, respectively. The estimated cure rate was 54% in the combination arm and 37% in the placebo arm. Furthermore, analysis of biomarker data sets showed that immune gene expression signatures, the IFN-γ

gene signature in particular, were strongly prognostic for RFS (Figure 11). In contrast, genetic alterations in the MAPK pathway were not prognostic. Moreover, a high tumour mutational burden (TMB) added positive prognostic value to immune gene signatures in the placebo arm, while in the dabrafenib plus trametinib arm, the IFN-γ gene signature identified patients with longer RFS, independently of TMB status. An exploratory analysis suggested that low TMB or high TMB/high IFN-γ may be associated with greater RFS benefit than high TMB/low IFN-γ. Since no biomarker has been characterised in this setting, further investigation of the predictive value of immune gene signatures and TMB status is warranted.

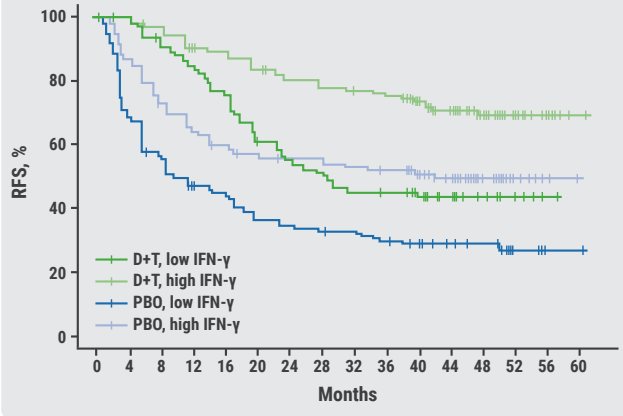
"The current results of the COMBI-AD trial confirm that adjuvant dabrafenib plus trametinib vs placebo is associated with a strong RFS benefit in patients with resected, *BRAF* V600–mutant, stage 3 melanoma," concluded discussant Prof. Caroline Robert (Institute Gustave Roussy, France). "In addition, according to the cure rate modelling performed by Long et al., the combination therapy is anticipated to result in a 17% higher cure rate in this population, which is a very promising result. Furthermore, Long et al. made a huge effort to translate preclinical findings to the clinic. For instance, they concluded that where mutations known to convey resistance did not impact the outcome, the immune signature was a strong prognostic factor in both treatment arms. Interestingly, it seems that the high TMB signature might not be that favourable in the combination arm, even in the presence of an IFN-γ signature. Possibly, the high TMB signature is more favourable in patients treated with immunotherapy than in those treated with targeted therapy, it might be better to analyse signatures in samples of primary tumours and metastases separately in future studies, even though both tumour types were balanced between the arms, as was the case in this study. Remaining questions are how the outcome of adjuvant dabrafenib plus trametinib will compare to that of adjuvant immunotherapy, and with neoadjuvant targeted and immunotherapy."

Combined immunotherapy and targeted therapy in previously untreated, *BRAF*-mutant, advanced melanoma

Since BRAF inhibitors have been shown to promote the expression of PD-1 and PD-L1 in patients with *BRAF*-mutant melanoma, it seems rational to combine BRAF inhibitors with immunotherapy in this setting [7]. Results of parts 1 and 2 of the phase 1/2, 5-part KEYNOTE-022 study indeed showed promising antitumour activity and acceptable tolerability of PD-1 inhibitor pembrolizumab in combination with BRAF inhibitor dabrafenib and MEK inhibitor trametinib in patients with unresectable or metastatic melanoma [8]. Treatment was associated with an ORR of 73%, and a median duration of response of 19.4 months. Treatments-related AEs of grade 3-4 occurred in 73% of the patients and led to discontinuation of treatment in 40% of the patients. Treatment-related deaths were not observed.

In part 3 of the KEYNOTE-022 study, patients with newly diagnosed, *BRAF*-mutant, advanced melanoma were randomised 1:1 to receive dabrafenib plus trametinib and either pembrolizumab or placebo. The primary endpoint was PFS. Secondary endpoints included ORR, OS, and duration of response. In general, both study arms (n=60 each) were well balanced.

Figure 11 Immune gene expression signatures predict RFS in *BRAF V600*–mutant, stage 3 melanoma patients treated with adjuvant dabrafenib plus trametinib or placebo [5]



No.at risk																
D+T, low IFN-γ	120	118	107	99	89	71	64	58	52	51	39	25	14	6	1	0
D+T, high IFN-γ	131	127	124	114	110	105	99	96	94	92	72	63	37	17	5	1
PBO, low IFN-γ	134	89	72	57	53	44	42	40	39	35	31	27	20	9	1	1
PBO, high IFN-γ	122	104	88	76	70	66	62	61	59	57	51	40	20	7	2	0

Placebo

Factor	HR	Lower	Upper	P value
(Baseline)[a]	(1)	-	-	-
IIIB	1.63	0.94	2.84	0.076
IIIC	1.89	1.07	3.36	
Ulceration	1.13	0.80	1.59	0.488
IFN-γ	0.76	0.67	0.86	<0.001

Dabrafenib + Trametinib

Factor	HR	Lower	Upper	P value
(Baseline)[a]	(1)	-	-	-
IIIB	131	0.67	2.55	0.045
IIIC	2.04	1.05	3.96	
Ulceration	0.99	0.64	1.53	0.952
IFN-γ	0.61	0.52	0.73	<0.001

Multivariate Cox analysis
aStage IIIA, no ulceration, IFN-γ = 0

D, dabrafenib; PBO, placebo; T, trametinib.

The efficacy analysis demonstrated that the addition of pembrolizumab to dabrafenib and trametinib improved PFS as compared with placebo; although the improvement did not reach statistical significance per study design [9]. Median PFS was 16.0 months in the pembrolizumab arm vs 10.3 months in the placebo arm (HR 0.66, 95% CI 0.40-1.07, P=0.043). Subsequently, a subgroup analysis suggested that the PFS benefit of pembrolizumab was larger in males than in females (HR 0.53 vs 1.22), and in patients with a performance status of 1 as opposed to 0 (HR 0.37 vs 0.79). Remarkably, ORR was higher in the placebo arm than in the pembrolizumab arm: 43% vs 38%, although this difference was not statistically significant. Furthermore, median duration of response was 18.7 months following treatment with pembrolizumab, and 12.5 months after placebo. Median OS was not reached in the placebo arm and 23.4 months in the placebo arm (HR 0.76, 0.41-1.39, descriptive P=0.185).

Treatment-related AEs of grade 3-4 occurred in 57% of patients in the pembrolizumab arm, and 27% of those in the placebo arm. The most common treatment-related AEs of grade 3-4 in the pembrolizumab arm were pyrexia (10% vs 3% in the placebo arm), increased aspartate aminotransferase levels (8% vs 5%), increased alanine aminotransferase levels (7% vs 5%), and pneumonitis (7% vs 2%). Treatment-related AEs led to discontinuation of at least 1 study drug in 40% of the patients treated with pembrolizumab and 20% of patients receiving placebo. In the pembrolizumab arm, 1 patient died due to a treatment-related AE vs none in the placebo arm.

"Early results of trials combining BRAF, MEK, and PD-1/PD-L1 inhibitors have shown promising results, including high response rates," said discussant Prof. Reinhard Dummer (University Hospital Zurich, Switzerland). "Now, the awaited results of the KEYNOTE-022 study show that combination treatment with dabrafenib, trametinib, and pembrolizumab does not significantly improve ORR as compared with dabrafenib, trametinib, and placebo. Furthermore, the results on PFS (HR 0.66) and OS (HR 0.76) were more encouraging and met the expectation with this triple combination therapy. However, the safety results were disappointing, demonstrating that pembrolizumab was associated with increased toxicity. Based on the results of this phase 1/2 study, with a relatively small patient population and short follow-up, it cannot be determined if the triple combination is better than dabrafenib plus trametinib, and the results of subsequent clinical trials should be awaited."

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Head and Neck Cancer

Multiple studies on head and neck cancer were presented during oral and poster sessions. One of the key studies presented was the three-armed phase 3 KEYNOTE-048 study, which demonstrated that patients with newly diagnosed recurrent or metastatic head and neck cancer benefit from pembrolizumab with or without chemotherapy in terms of overall survival (OS) and duration of response (DoR) in patients whose tumours expressed PD-L1, as compared with standard treatment. In addition, pembrolizumab plus chemotherapy significantly improved OS in the total population. Furthermore, the randomised phase 3 De-ESCALaTE trial evaluated if cetuximab vs standard chemotherapy with cisplatin improved the outcome in patients with low-risk human papillomavirus-positive head and neck cancer treated with radiotherapy. In contrast to what was anticipated, cetuximab resulted in similar toxicity and quality of life, but significantly worsened OS and loco-regional and distant control.

First-line pembrolizumab with or without chemotherapy improves overall survival in recurrent or metastatic head and neck squamous cell carcinoma

PD-1 inhibitors pembrolizumab and nivolumab have been approved as second-line therapy in patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) following treatment with platinum-containing chemotherapy. Furthermore, by inducing rapid disease control, releasing tumour antigens, and overcoming immune exclusion, chemotherapy might enhance the efficacy of PD-1-targeted therapy.

The three-armed phase 3 KEYNOTE-048 study evaluated the outcome of first-line pembrolizumab (35 cycles; P arm) vs pembrolizumab plus chemotherapy (6 cycles) followed by pembrolizumab (29 cycles; P+C arm) vs standard treatment with cetuximab plus chemotherapy (6 cycles) followed by cetuximab (29 cycles; EXTREME or E arm) in R/M HNSCC patients who had previously undergone PD-L1 testing. Chemotherapy consisted of carboplatin or cisplatin, plus 5-FU. The co-primary endpoints were OS and progression-free survival (PFS) in the whole population or in patients whose tumours had a combined positive score (CPS; expression on tumour cells, lymphocytes, and macrophages) for PD-L1 of either ≥20 or ≥1. Secondary endpoints included ORR in those populations, and safety in the total population. DoR in all populations was a key exploratory endpoint.

With a median follow-up of at least 10.7 months, patients in the P arm with a CPS score of ≥1 had a significantly improved median OS as compared with patients with the same CPS score in the E arm: 14.9 months vs 10.7 months (HR 0.61, 95% CI 0.54-0.83, P=0.0007) [1]. In the CPS ≥20 and ≥1 populations, the median PFS in the P arm was not significantly different from the E arm. Among patients with CPS ≥20, ORR was 31% in the P arm and 44% in the E arm. Median DoR in this population was 21 months in the P arm and 4 months in the E arm. Furthermore, in patients with a CPS score of ≥1, ORR was 49% in the P arm and 89% in the E arm. Median DoR in this population was 21 months in the P arm and 5 months in the E arm.

Comparison of P+C with E in the total population showed that P+C also improved OS as compared with E. Median OS was 13.0 months in the P+C arm and 10.7 months in the E arm (HR 0.77, 95% CI 0.63-0.93, P=0.0034). PFS was not significantly different between these populations. Furthermore, ORR was 36% in both arms, and median DoR was 7 months in the P+C arm and 4 months in the E arm.

Grade 3-5 treatment-related adverse events (AEs) were observed in 17%, 71%, and 69% of the patients in the P, P+E, and E arm, respectively. AEs led to discontinuation of treatment in 5%, 23%, and 20% of cases in these arms, respectively. "These results demonstrate that, although pembrolizumab with or without chemotherapy is not associated with a benefit in PFS and ORR as compared with standard treatment, both treatments did improve OS and DoR," said Barbara Burtness (Yale School of Medicine, USA). "Moreover, pembrolizumab monotherapy has a more favourable safety profile than cetuximab plus chemotherapy, while the safety profile of pembrolizumab plus chemotherapy is comparable to cetuximab plus chemotherapy. This data support pembrolizumab with or without chemotherapy as new first-line standard of care for PD-L1-expressing R/M HNSCC

Taken together, according to discussant Jean-Pascal Machiels (UCL Brussels, Belgium), these results suggest that pembrolizumab monotherapy is the preferred treatment in patients with a CPS score of ≥20, and pembrolizumab plus chemotherapy for patients with CPS between 1 and 20. For R/M HNSCC patients whose tumours do not express PD-L1, cetuximab plus chemotherapy should remain the standard of care.

Cetuximab does not improve outcome in low-risk human papillomavirus-positive head and neck cancer

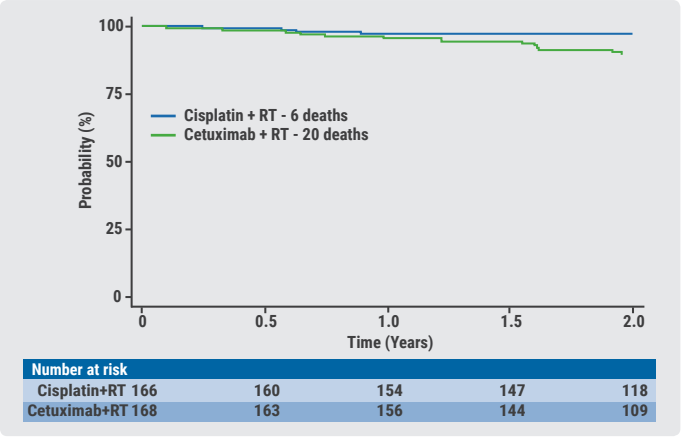
The incidence of human papillomavirus-positive oropharyngeal squamous cell carcinoma (HPV+ OPSCC) is increasing rapidly, especially in Western countries. HPV+ OPSCC is a distinct disease entity, characterised by a relatively younger age, a higher socioeconomic status, and an association with oral sex. Furthermore, HPV+ OPSCC has a much better prognosis than HPV-negative disease [2]. However, the current standard of care, cisplatin in combination with radiotherapy, is associated with severe acute and late toxicity. Hence, there has been wide consensus on the need of de-escalation, reducing toxicity while maintaining disease control. The replacement of cisplatin with EGFR inhibitor cetuximab could result in such de-escalation, since the addition of cetuximab to radiotherapy was previously shown to result in similar severe toxicity as radiotherapy alone in head and neck cancer, with the exception of skin rash and infusion reactions [3].

Prof. Hisham Mehanna (Institute of Cancer and Genomic Sciences, United Kingdom) presented results from the randomised phase 3 De-ESCALaTE trial, which evaluated the

outcome of cisplatin vs cetuximab in 334 patients with low-risk HPV+ OPSCC, receiving radical radiotherapy. Patients were randomised 1:1 to receive radiotherapy (70G in 35 fractions) plus either cisplatin (3 doses of 100 mg/m2) or cetuximab (400 mg/m2 loading dose followed by weekly 250 mg/m2). The primary endpoint was overall (i.e. acute plus late) severe toxicity. Secondary endpoints included acute and late severe toxicity, OS, and QoL.

The safety analysis demonstrated that both treatment arms had the same rate of severe and all-grade toxicity [4]. The overall all-grade toxicity rate (events per patient) was 29.15 in the cisplatin arm and 30.05 in the cetuximab arm (P=0.49). For severe toxicity, the number of events per patient was 4.81 vs 4.82 (P=0.98), respectively. With respect to QoL, no between arms difference was observed in global health status (EORTC QLQ-C30) or global score according to the MD Anderson Dysphagia Inventory. However, cetuximab was associated with significantly less severe AEs as compared with cisplatin. At the same time, cetuximab was associated with a significantly worse OS compared with cisplatin (Figure 12). At 2 years, OS was 97.5% in the cisplatin arm and 89.4% in the cetuximab arm (adjusted HR 5.94, 95% CI 1.98-17.79, P=0.001). Similar results were found in the TNM I/II very low-risk population and the TNM III population. Also, the overall recurrence rate was higher following treatment with cetuximab than with cisplatin (HR 3.39), as were the rates for locoregional recurrences and distant metastases.

Figure 12 Overall survival in low-risk HPV+ OPSCC patients treated with radiotherapy and either cisplatin or cetuximab [4]



"The survival differences reported are similar to the differences found in the NRG-RTOG 1016 study, as presented at ASTRO 2018 [5]. "Together, these findings indicate that changes in standard of care should only be made on the basis of high level, phase 3, comparative evidence, even if treatments are approved, and that cisplatin remains the standard of care in low-risk HPV+ OPSCC." These results will soon be published in The Lancet.

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Sarcoma

Multiple presentations focussed on merging each sarcoma subtype with the optimal treatment. An example is the presentation on the large sarcoma network and database NETSARC. An extensive analysis of over 35,000 patients with sarcoma, gastrointestinal stromal tumour, or tumour of intermediate malignancy revealed valuable information on tumour characteristics, predisposing conditions and clinical outcome.

Treatment in a NETSARC reference centre associated with improved outcome in sarcoma

NETSARC is a network of 26 sarcoma reference centres in France, established in 2010. The network is linked to the pathology network RREPS, and the bone tumour network RESOS, with which it will merge in 2019. The aim of NETSARC is to provide the nation with guidelines, to guide the best clinical practice and patient pathways, to advice in the measurement of patient outcomes, and to provide research in sarcoma. Currently, the NETSARC database contains data from over 50,000 patients diagnosed with sarcoma.

Initially, the population for the current analysis, presented by Prof. Jean-Yves Blay (Centre Léon Bérard, France), consisted of 47,023 patients diagnosed with sarcoma who presented at a NETSARC multidisciplinary tumour board. However, further characterisation of disease demonstrated that 21% of patients had a benign lesion, 4% a non-mesenchymal malignant tumour, and 3% received another diagnosis. This led to a population of 35,784 patients with sarcoma (75%), gastrointestinal stromal tumour (GIST; 18%), or tumour of intermediate malignancy (8%). The analysis regards a cohort

of the incident patient population (n=29,497) diagnosed since 1 January 2010, and a cohort of prevalent patients diagnosed at an earlier time point (n=6,287).

The male to female ratio in the total population of 35,784 patients was close to 1, the median age at first diagnosis was 60.8 years, and 5% of the patients was <18 years [1]. Most of the tumours originated from soft tissue (64%) and was "deep-seated" (profound, comment of the Editor) (65%). Among the more than 140 histological subtypes, the most common subtypes were leiomyosarcoma (12%), undifferentiated pleomorphic sarcoma (UPS; 11%), and GIST (7%). Furthermore, most tumours were of grade 3 (32%), the most common site of the primary tumour was the lower limb (26%), and 12% of patients had metastases at diagnosis. An analysis of predisposing conditions showed that most patients were lacking a clear predisposing condition (57%), 12% had a previous cancer, and 3% had previously been irradiated at the location of the subsequent tumour.

An evaluation of the quality of clinical resections within the incident population indicated that, following initial surgery, 53% of the tumours resected in an NETSARC centre (n=9,954) had a resection margin that was qualified as R0, as compared with 16% of the tumours resected outside NETSARC (n=19,543). Moreover, 6% of the patients operated on in a NETSARC centre underwent secondary surgery, vs 21% of those operated in another centre. Prof. Blay: "A univariate analysis of prognostic factors showed that, as expected, male gender, age, bone involvement, deep-seated (and high-grade tumours, retroperitoneal sarcoma, but also previous radiotherapy, and history of neurofibromatosis type 1 were associated with a worse outcome for local relapse-free survival, metastasis-free survival, and/or overall survival."

In contrast, surgery in a NETSARC centre was associated with a better outcome. According to Prof. Blay this offers an opportunity for survival improvement at a lower cost. To further improve the benefit of NETSARC, the substantial amount of missing information should be retrieved, and the distance between patients and reference centres should be decreased in the future.

An analysis of the outcome in patients with advanced disease (incident population; n=4,713) demonstrated that median overall survival in sarcoma patients is close to 24 months, and much better for GIST patients and patients with a tumour of intermediate malignancy (Figure 13). Interestingly, patients operated in a NETSARC reference centre had a significantly improved overall survival, as compared with those operated outside NETSARC. The latter result was confirmed in a multivariate analysis.

Invited discussant Dr Rick Haas (Netherlands Cancer Institute, the Netherlands) concluded that "the study by Blay et al. confirms previous findings, indicating that, in sarcoma, secondary pathology review by specialised multidisciplinary tumour boards is of great importance for a correct diagnosis [2]. Furthermore, the study demonstrates that, while two times more patients underwent surgery outside NETSARC, the percentage of R0 resections was three times less in this population, and the percentage of reoperations a factor two larger, as compared with those treated in a NETSARC centre. The study indicates that the impact of NETSARC on outcome is significant and might lead to lower costs.

References

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Figure 13 Relation between OS and disease type (left), and operation in a NETSARC centre (right) in patients with advanced disease in the incident population