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DEAR READER,

The 2019 annual meeting of the American Society of Clinical Oncology (ASCO) again proved to be the most important oncological meeting in the world. The theme of ASCO 2019 was “caring for every patient, learning from every patient” and the meeting featured a robust program designed to teach, engage, and bring the oncology fields together. In total, more than 32,000 oncology professionals from around the world attended the ASCO Annual Meeting in Chicago this year.

We are very proud to assemble a select group of Belgian key opinions leaders who were each willing to summarise the congress highlights in a specific cancer subtype. In this special issue of the Belgian Journal of Medical Oncology (BJMO) you will find an overview of the most important studies presented at the meeting in the field of melanoma, genitourinary cancer, breast cancer, head and neck cancer, respiratory oncology, digestive oncology, and in the field of gynaecological cancer. As such, this special issue of the BJMO offers you a thorough record of this year’s congress highlights. For an even more complete overview of the studies and research presented at ASCO 2019 we happily refer to the congress website: <https://meetings.asco.org/am/abstracts>

We would again like to extend our sincere gratitude to the authors who contributed to this issue of the BJMO and we wish you a very pleasant read.

Kind regards,
The publisher

Highlights in melanoma

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ASCO 2019 featured the presentation of several interesting studies in patients with metastatic melanoma. In addition to this, new data in the (neo)-adjuvant setting were presented.

HIGHLIGHTS IN METASTATIC MELANOMA

A Phase III international trial of adjuvant whole brain radiotherapy (WBRT) or observation following local treatment of 1-3 melanoma brain metastases was presented.¹

As known, patients with stage IV melanoma are at high risk of developing brain metastasis. The risk can go up to 25% within the first year and up to 40% within the first 2 years of disease progression. While surgery and stereotactic radiosurgery (SRS) are highly effective for individuals with a single, or only a few metastases, these patients are at a high risk of developing subsequent new brain metastases. The effect of WBRT vs. observation was therefore investigated following local treatment with SRS in patients with 1 to 3 melanoma brain metastases. The primary endpoint was distant intracranial failure within 12 months of randomization. Between 2009 and 2017, 207 eligible, consenting patients from 31 sites across Australia, the United Kingdom and Norway were randomized to receive WBRT (30 Gy in 10 fractions; N= 100) or observation (N= 107) after local treatment. Overall, 61% of patients had a single brain metastasis (mean size, 2 cm) and 67% had extracranial disease. Any form of systemic therapy was permitted during the trial. The median follow-up of the study was 48 months and the treatment completion rate for WBRT was 97%. At 12 months, 50.5% of patients in the observation group (54 of 107 patients) and 42% of patients randomized to radiotherapy (42 of 100 patients) suffered distant intracranial failure (hazard ratio [HR], 1.28; 95% confidence interval [CI], 0.89–1.84; p= 0.16). No differences were observed between the groups in terms of local failure (p= 0.100). Regarding overall survival (OS), 54% of patients in the observation group compared with 58.4% of those in the radiotherapy group were alive at 12 months (log-rank

p= 0.89). Patients who received WBRT experienced higher grade 1/2 fatigue (68.2% vs. 28.1), nausea (33% vs. 15.7%), alopecia (62.4% vs. 4.4%), and dermatitis (11.8% vs. 0%; all p<0.001) than patients in the observation group. In conclusion, WBRT should no longer be offered to patients with melanoma brain metastases.

At ASCO 2019, data were presented on the efficacy and safety of the combination of nivolumab plus ipilimumab in patients with symptomatic melanoma brain metastases.² In this trial, melanoma patients whose disease had spread to the brain were treated with dual PD-1 (nivolumab) and CTLA-4 (ipilimumab) checkpoint immunotherapy, followed by PD-1 immunotherapy alone. Of patients whose metastatic lesions were not active, 54% responded and 63% remained progression-free at the six-month landmark. More than half of all patients are still alive after a median follow-up of almost 21 months. Of the patients whose metastatic tumors were symptomatic, only 22% responded, although half of them saw their tumors completely disappear. Sixty-six percent of the patients in this group survived at least six months, and half the patients survived at least 8.7 months.

ASCO 2019 also featured the presentation of 5-year follow-up data in patients diagnosed with BRAF-V600-mutant metastatic melanomas after a first-line treatment with dabrafenib plus trametinib.³ These data were the result of a pooled analysis of patients treated with dabrafenib plus trametinib in the phase 3 COMBI-d (vs. dabrafenib + placebo, N= 211) and COMBI-v (vs. vemurafenib, N= 352) trials. The trials enrolled patients with previously untreated BRAF V600E/K-mutant unresectable or metastatic melanoma. Patients received dabrafenib 150 mg twice daily plus trametinib 2 mg once daily vs. either dabrafenib + placebo (COMBI-d) or vemurafenib

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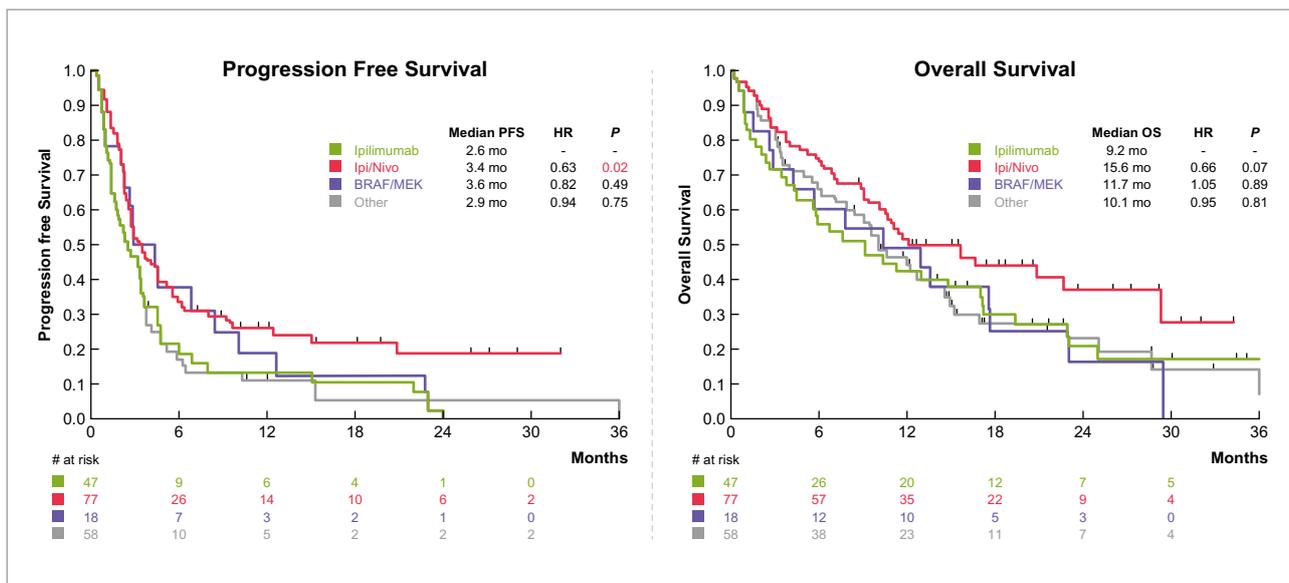


FIGURE 1. Progression Free Survival and Overall Survival with different treatment options after anti-PD-1 failure.²

(COMBI-v). This analysis represented the largest data set and longest follow-up in previously untreated patients with *BRAF* V600-mutant unresectable or metastatic melanoma treated with *BRAF* and *MEK* inhibitors. Five years out, one-third of patients remained alive following treatment with the dual targeted therapy, and 1 in 5 (19%) remained alive without progression. Patients who achieved a complete response (CR) had the best odds of attaining long-term benefit. Lower baseline tumor burden and less-aggressive tumor biology were associated with prolonged progression-free survival (PFS) and overall survival (OS).

In addition to this, updated results on safety and efficacy from parts 1 and 2 of the COMBI-i study were presented.⁴ Encouraging results were obtained with a first-line “triplet therapy” consisting of the PD-1 inhibitor spartalizumab (an anti-PD-1 monoclonal antibody), dabrafenib and trametinib in patients with advanced *BRAF* V600-mutant melanoma. Of the 36 patients enrolled in the study, 36% had stage IV M1c with elevated levels of lactate dehydrogenase (LDH), and 19% had stage IV M1c with normal LDH levels. “Triplet therapy” resulted in overall response rate (ORR) of 78% by investigator assessment and a CR in 42% (at a median follow-up of 19.9 months). The median duration of response (DoR) was 20.7 months with a 12-month DoR rate of 80.3%. In 10 of the 15 patients with a CR the response was ongoing at the time of the analysis (66.7%). The 12-month PFS rate was 66.7% and the median OS was not yet reached (8 [22%] patients had died, of which 7 had an elevated LDH level at baseline). All patients experienced at least 1 adverse event (AE) of any grade, and serious AEs occurred in 64% of the patients. Pyrexia was the most common AE, occur-

ring in 32 (89%) patients. There were no treatment-related deaths. In all patients, adverse events led to dose adjustments or interruptions. Adverse events led to discontinuation of any study drug in 17 (47%) patients and discontinuation of all 3 study drugs occurred in 6 (17%) patients. Correlative data from the biomarker cohort were presented in a separate poster. All patients had a consistent increase in T-cell inflamed gene expression signature levels from baseline to biopsy at 2 to 3 weeks. At data cut-off, 5 of 22 patients with DNA- and RNA-sequencing data available had a PFS event. Those with a PFS event prior to 12 months had relatively cold tumors at baseline, characterized by low tumor mutational burden values, low T-cell inflamed gene expression signature levels, or high levels of immunosuppressive tumor microenvironment signatures compared with the patients without a PFS event. The global placebo-controlled, randomized part 3 of COMBI-i is currently ongoing.

According to results of exploratory retrospective analyses of patients with advanced melanoma enrolled in clinical studies with immune checkpoint inhibitors, low or undetectable baseline serum levels of the acute phase reactant, C-reactive protein (CRP), and a marker of chronic inflammation that enhances liver production of CRP, interleukin-6 (IL-6), were associated with improved clinical outcomes.⁵ The researchers offered a possible rationale for these findings based on investigations of human T cells and dendritic cells from patients with melanoma. Results from this analysis showed a dose-dependent suppression of T-cell and dendritic cell function, decreased generation of antigen-specific T-cells, and inhibition of calcium flux in T-cells (a very early event in T-cell signaling and activation) when CRP levels were higher than 10 µg/

Systemic therapy; responses to first-line and subsequent therapy in evaluable patients (N=92 of 109)

Timing of initial recurrence	Systemic treatment	Best response				ORR
		N	CR/PR	SD	PD	
ON adj-PD1	Ipilimumab +/- anti-PD1	33	8	5	20	24%
	BRAF/MEKi	23	18	5	0	78%
	Anti-PD1 + novel agent	9	1	1	7	11%
	Anti-PD1	6	0	1	5	0%
OFF adj-PD1	Ipilimumab +/- anti-PD1	5	2	0	3	40%
	BRAF/MEKi	10	9	0	1	90%
	Anti-PD1 + novel agent	1	0	0	1	0%
	Anti-PD1	5	2	1	2	40%

FIGURE 2. A multicenter analysis of melanoma recurrence following adjuvant anti-PD1 therapy.⁷

mL. Therefore, serum IL-6 and CRP can be used as prognostic factors for checkpoint inhibition.

Treatment patterns and outcome of systemic therapy for patients after anti-PD-1 failure were analyzed by the German ADOReg melanoma registry.⁶ Patients fulfilling several inclusion criteria were consecutively included until a number of 200 cases was reached. Treatment patterns of patients after anti-PD-1 (and BRAF-/MEK-inhibitors in BRAF V600mutant melanoma patients) failure differed remarkably. Although lower than reported in treatment naive patients, the combination of ipilimumab and nivolumab appeared more favorable as compared to all other regimens, except for BRAF-/MEK inhibitor re-challenge which produced similar remission rates (Figure 1). Chemotherapies, including dacarbazine, are still being used in clinical practice but these data indicate that this therapeutic approach is associated with a poor outcome.

Investigators from the Melanoma Institute Australia looked at stage 3-4 melanoma patients from 16 different institutions who, after their tumors were surgically removed, were treated with PD-1 immunotherapy (nivolumab) to prevent recurrence.⁷ More than 800 patients were included in this analysis of whom 83% did not experience a disease recurrence. Among those who did have a recurrence under treatment, a change in treatment was recommended. Among those who experienced recurrence after their treatment ended, some of them responded after re-treatment with PD-1 immunotherapy alone or in combination with CTLA-4 immunotherapy as well as further treatment with targeted therapy against BRAF/MEK (Figure 2).

HIGHLIGHTS OF (NEO-)ADJUVANT THERAPY FOR MELANOMA

In another study conducted by the Melanoma Institute Australia and University of Sydney, investigators looked at six trials in which patients with stage 3 melanoma were treated prior to surgery with either PD-1 immunotherapy (nivolumab) or targeted therapy against BRAF/MEK.⁸ Of the 184 patients analyzed, 41% had a pathological CR (pCR), meaning that less than 10% of their tumors remained viable prior to surgery. Overall, 65% remained relapse-free for at least two years, including 83% of those who were treated with immunotherapy. Remarkably, of the patients who had a pCR to immunotherapy, none had a recurrence to date.

Investigators at 9 sites in 9 countries enrolled 150 patients (intention-to-treat population) with high-risk resectable stage IIIB-IVM1a melanoma to study Talimogene laherparepvec (T-VEC) as a neo-adjuvant treatment of loco-regionally advanced melanoma.⁹ The patients were randomized to immediate surgery or intralesional T-VEC, followed by surgery at week 13. The efficacy analysis included 57 patients who received at least one dose of T-VEC and next had surgery, and 69 patients who had immediate surgery. The safety cohort included 73 patients who received at least one dose of T-VEC, and 69 patients who had immediate surgery. There were no substantial differences in baseline characteristics of both treatment groups. The primary endpoint was relapse-free survival (RFS). In the efficacy analysis, 13 of 57 patients in the T-VEC arm had a pCR. By ITT analysis, the pCR rate was 17.1% (13 of 76) in the T-VEC arm. More patients in the T-VEC arm had R0 resection status (56.1% vs. 40.6%; p=

0.082). Rates of R1 resection were 42.1% and 55.1%, and R2 resection rates were 1.8% and 4.3% in the T-VEC and surgery-alone arms, respectively. At 1 year, 33.5% of patients who received preoperative T-VEC plus surgery remained recurrence free, as compared with 21.9% of patients who had surgery only (HR: 0.73; 80%CI: 0.56-0.93; $p=0.048$). By ITT analysis, neoadjuvant T-VEC reduced the 1-year recurrence hazard by 27% (80%CI: 0.56-0.93). The median RFS was not reached in any of the treatment groups. Before the start of follow-up, RFS events had occurred in 56.6% of patients in the T-VEC arm (no surgery in 23.7% and lack of R0 resection in 32.3%) and in 60.8% of patients who underwent immediate surgery (5.4%, 55.4%, respectively). After a median follow-up of 20.4 months, the median OS had yet to be reached in either treatment group. More patients randomized to T-VEC were alive at 1 year (95.9% vs. 85.8%; HR: 0.47; 80%CI: 0.27-0.82; $p=0.076$), but this difference did not reach statistical significance. Treatment-emergent adverse events in the T-VEC arm were consistent with previously reported data. The most commonly observed treatment-emergent adverse events were flu-like symptoms.

The United States Intergroup E1609 conducted a phase III randomized study of adjuvant ipilimumab versus high-dose interferon- α 2b for resected high-risk melanoma.¹⁰ In this trial, more than 1,000 patients with a surgically removed high-risk, stage 3-4 melanoma were subsequently treated with CTLA-4 checkpoint immunotherapy (ipilimumab, at one of two dose levels) or interferon- α 2b. Compared to the interferon treatment, the lower dose of CTLA-4 immunotherapy was associated with a 22% reduction in the risk of death and a 15% reduction in the risk of recurrence. As such, this regimen performs slightly better than the higher dose of ipilimumab while resulting in less toxicity and allowing more patients to complete their treatment regimen. However, adjuvant therapy with anti-PD-1 antibody therapy (either nivolumab or pembrolizumab) or the combination of dabrafenib plus trametinib in BRAF V600-mutant melanoma patients have replaced both ipilimumab and interferon- α 2b as standard of care adjuvant therapy in patients with lymph node melanoma metastases.

The EORTC 18071 study randomized 951 patients with high-risk, stage III, completely resected melanoma to receive ipilimumab ($N=475$) or placebo ($N=476$).¹¹ In the initial induction phase of the trial, ipilimumab was administered at 10 mg/kg every 3 weeks for 4 cycles. In a subsequent maintenance phase, ipilimumab was administered at 10 mg/kg every 12 weeks for a maximum of 3 years. Adjuvant ipilimumab resulted in a 25% reduction in the risk of recurrence or death compared with placebo for patients with surgically resected high-risk, stage III melanoma. In this updated analy-

sis, which was conducted after 6.9 years of median follow-up, the estimated 7-year RFS rate was 39.2% (95%CI: 34.5%-43.9%) for ipilimumab compared to 30.9% (95%CI: 26.7%-35.2%) for placebo (HR: 0.75; 95%CI: 0.63-0.88; $p<0.001$). At the 6.9-year analysis, 60.0% (95%CI: 55.0%-64.7%) of patients remained alive in the ipilimumab arm compared with 51.3% (95%CI: 46.5%-55.9%) in the placebo group (HR: 0.73; 95%CI: 0.60-0.89; $p=0.002$). In 2015, the FDA (but not EMA) approved ipilimumab as an adjuvant therapy for patients with stage III melanoma with pathologic involvement of regional lymph nodes >1 mm who have undergone complete resection including total lymphadenectomy. Since this approval, the PD-1 inhibitor nivolumab was shown to be superior to adjuvant ipilimumab, leading to an FDA and EMA approval for the PD-1 inhibitor in 2017 and 2018 respectively. Overall, 81% of patients in the ipilimumab arm who experienced a recurrence went on to receive a second-line treatment, as compared with 87.3% in the placebo group. The most common subsequent treatments in the ipilimumab and placebo arms, respectively, were surgery (39.6% vs. 36.2%), chemotherapy (31.1% vs. 32.5%), a BRAF inhibitor (25.6% vs. 27.6%), or radiotherapy (15.4% vs. 19.2%). The trial was conducted before the widespread use of immunotherapy. As such, just 12% of patients received a subsequent PD-1 or PD-L1 inhibitor. The median OS following first recurrence event was 1.8 months in the ipilimumab arm as compared to 1.9 months with placebo (HR: 0.90; 95%CI: 0.74-1.10). The phase III CheckMate-915 trial is comparing nivolumab plus ipilimumab with nivolumab alone after complete resection of stage III or IV melanoma. The study enrolled 1,943 patients, with primary results anticipated in November 2020 (NCT03068455).

Several studies suggested that patients with an immune-related adverse event (irAE) during immunotherapy have better outcomes than those without. It remains uncertain whether these observations can be explained by guarantee-time bias or the role of irAE as an indicator of drug activity. The association between irAEs and RFS in patients was investigated in the double-blind EORTC 1325/KEYNOTE-054 trial.¹² The incidence of irAE in this trial that compared pembrolizumab to placebo in high-risk stage III melanoma was 37.3% in the pembrolizumab arm ($N=509$) and 9.0% in the placebo arm ($N=502$) (similar in males and females in both arms). The occurrence of an irAE was significantly associated with a longer RFS in the pembrolizumab arm (HR: 0.61, 95%CI: 0.39-0.95, $p=0.03$). This was true for both males and females. However, in the placebo arm, no association between irAE incidence and RFS was observed (HR: 1.39, 95%CI: 0.83-2.32, $p=0.21$). In a small single center phase II trial, investigators from the Brussels University Hospital (Brussels, Belgium) reported

that adjuvant low-dose regimens of nivolumab with or without low-dose ipilimumab have an acceptable safety profile in patients with resected melanoma macrometastases.¹³ The irAE rate and severity was comparable to standard regimens, while also the survival rates resembled those of standard regimens. These regimens could therefore be economically advantageous alternatives for patients without access to standard regimens.

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Updated results of the phase III COLUMBUS trial further solidify BRAF/MEK combinations as standard of care for BRAF-mutated advanced melanoma

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Based on improved OS and manageable tolerability relative to BRAF inhibitor monotherapy, the combined use of a BRAF and a MEK inhibitor has become standard of care for patient with BRAF^{V600}-mutant locally advanced or metastatic melanoma.¹⁻³ However, the currently approved combinations are also associated with a unique toxicity profile that may impact the ability to deliver optimal therapy. In fact, dabrafenib-trametinib is particularly associated with pyrexia while the vemurafenib-cobimetinib combination was found to be associated with photosensitivity.²⁻⁴ Encorafenib is a highly selective ATP-competitive BRAF inhibitor that was developed with an aim to improve the efficacy and tolerability over other approved BRAF inhibitors.⁹ In preclinical studies encorafenib demonstrated an increased potency against BRAF^{V600} mutations with an extended duration of target inhibition and a shorter serum half-life which might result in delayed resistance development and improved tolerability.⁵ Binimetinib on the other hand is a potent, selective allosteric, ATP-uncompetitive MEK1/2 inhibitor. This agent also has a shorter half-life than other MEK1/2 inhibitors, which in turn might facilitate a faster resolution of toxicity upon dose interruption.⁶

The phase III COLUMBUS study compared a combination of encorafenib (450 mg once daily) with binimetinib (45 mg twice daily) (COMBO450) with either encorafenib (300 mg once daily, ENCO300) or vemurafenib monotherapy (960 mg

twice daily, VEM) in patients with BRAF^{V600}-mutant melanoma.⁷ In previous reports of this study the COMBO450 combination was shown to be associated with a doubling in both the median PFS (14.9 vs. 7.3 months) and median OS (33.6 vs. 16.9 months) compared to VEM monotherapy.⁷ During ASCO 2019, results of COLUMBUS with an additional 12 months of follow-up were presented.⁸

STUDY DESIGN AND PATIENT DISPOSITION

COLUMBUS was a two-part, multicenter, randomized, open-label, phase III study including patients from 162 hospitals in 28 countries. Enrolment occurred between December 2013, and November 2015. In Part 1 of COLUMBUS, 577 patients with advanced/metastatic BRAF^{V600}-mutant melanoma who were previously untreated or who progressed after first-line immunotherapy were randomized (1:1:1) to COMBO450 (N= 192), VEM (N= 191) or ENCO300 (N= 194). The median age of patients in the study was 56 years, and approximately 70% had an ECOG performance status of 0. In about a quarter of patients, the lactate dehydrogenase (LDH) level was higher than the upper limit of normal (ULN). More than 80% of patients in the study were staged IVM1b or 1c at study entry and 45% had 3 or more involved organs. Overall, tumor and patient characteristics were similar across the three treatment groups. At the time of the analysis, 81%, 89%

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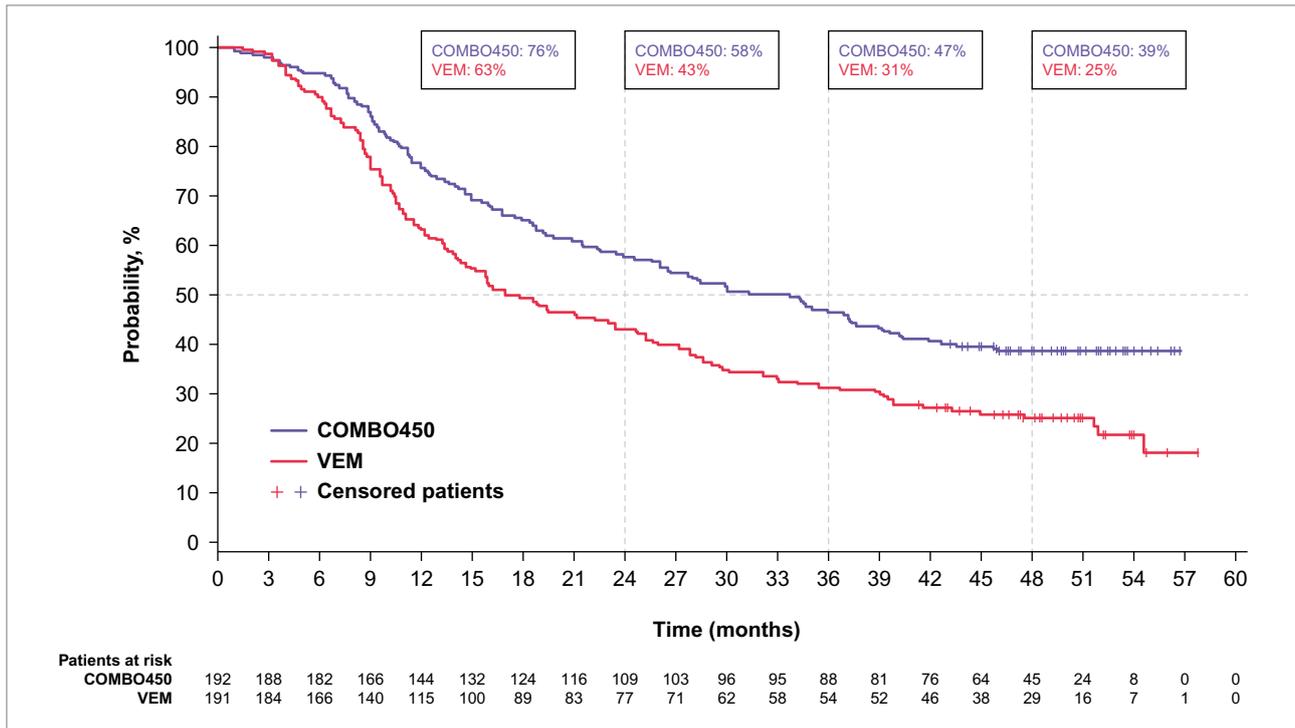


FIGURE 1. Overall survival and landmark analysis of COMBO450 vs. VEM in the phase III COLUMBUS trial.^{7,8}

and 93% had discontinued therapy in the COMBO450, ENCO300 and VEM arm, respectively. Discontinuations due to adverse events occurred in 10% of patients in the COMBO450 group, in 12% of ENCO300 treated patients and in 14% of patients receiving VEM.

EFFICACY AND SAFETY UPDATE

Across arms, the median follow-up for OS was 48.8 months, with a median OS of 33.6 months for COMBO450, 23.5 months with ENCO300, and 16.9 months for VEM. Compared to VEM, COMBO450 decreased the risk of death by 39% (HR=[95%CI]: 0.61 [0.48–0.79]). In a landmark analysis, COMBO450 was shown to be associated with a higher OS rate at years 1 (76% vs. 63%), 2 (58% vs. 43%), 3 (47% vs. 31%) and 4 (39% vs. 25%) (Figure 1). The OS benefit of COMBO450 over VEM was seen irrespective of sex, age, the type of BRAF mutation, the ECOG performance status, the tumor stage, LDH level and the number of involved organs. Also with respect to PFS COMBO450 proved to be superior to ENCO300 and VEM with PFS medians of 14.9, 9.6 and 7.3 months, respectively. Compared to VEM, this translates into a statistically significant 49% reduction in the risk of disease progression or death with COMBO450. In the landmark analysis, the PFS rate was higher with COMBO450 than with VEM at years 1 (56% vs. 32%), 2 (37% vs. 20%), 3 (29% vs. 14%) and 4 (25% vs. 12%). A confirmed overall response (ORR) by blinded independent central review

was observed in 64% of patients for COMBO450 (13% complete response [CR]), 52% for ENCO300 (7% CR), and 41% for VEM (8%CR). Finally, the responses on COMBO450 also proved to be most durable, with a median duration of response by central review of 18.6 months in COMBO450 patients as compared to 15.5 and 12.3 months for ENCO300 and VEM, respectively.

The median exposure to study treatment was 51 weeks for COMBO450, which is substantially longer than the 31 and 26 weeks with ENCO300 and VEM, respectively. Nevertheless, the rate of grade 3/4 adverse events was comparable in the three arms (68%, 68%, 66% with COMBO450, ENCO300, and VEM). Importantly, the incidence of adverse events (all grades) associated with BRAF/MEK inhibitors did not increase substantially with the 12-months of additional follow up. Overall, the safety results were consistent with the known tolerability profile of COMBO450 without any new safety concerns in this update. The most frequent adverse events seen with COMBO450 were nausea (44%), diarrhea (39%), vomiting (32%), fatigue (30%) and arthralgia (29%). Pyrexia was seen in 20% of patients on COMBO450, reaching grade 3/4 in severity in 4% of patients. Photosensitivity was rare and was only seen in 4% of patients treated with the combination.

CONCLUSIONS

Updated results of the phase III COLUMBUS trial confirm

that a combination of the BRAF inhibitor encorafenib and the MEK inhibitor binimetinib (COMBO450) is associated with a significantly longer PFS and OS than BRAF inhibition with VEM alone in patients with BRAF^{V600}-mutant locally advanced unresectable or metastatic melanoma. The median OS and PFS among patients treated with COMBO450 was twice as long as what was seen with VEM. Landmark analyses show improved OS and PFS rates for COMBO450 vs. VEM at year 1, 2, 3 and 4. As such, these results for COMBO450 represent new benchmarks for the treatment of BRAF^{V600}-mutated melanoma and further solidify the role of combined BRAF/MEK inhibition as standard of care in this setting.

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Highlights in genitourinary cancers

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From June 1st till June 5th, Chicago was host for the 55th annual ASCO meeting. This report will highlight the most important studies concerning genitourinary cancers presented during the meeting.

PROSTATE CANCER (PC)

Several new treatment modalities for PC were presented on ASCO. An overview is given in *Table 1*.

The phase III trial GETUG-AFU 16 explored the addition of androgen deprivation therapy (ADT) to salvage radiotherapy (RT) after biochemical recurrence following prostatectomy. As RT + ADT resulted in an increased metastatic-free survival (MFS) after 9 years of follow up, standard addition of ADT to salvage RT could postpone aggressive treatment without increased toxicity or decline in quality-of-life (QoL).¹

The phase III study ENZAMET determined the possible addition of docetaxel or abiraterone acetate to testosterone suppression in metastatic hormone-sensitive prostate cancer (mHSPC) patients to improve overall survival (OS). Interim survival data demonstrate a significantly improved OS by adding enzalutamide to SOC for mHSPC.² Also the phase III trial TITAN assessed the addition of the androgen receptor (AR) inhibitor apalutamide to ADT in mHSPC. A clear improvement in progression-free survival (PFS) and OS were observed, with manageable toxicity profile and no changes in QoL.³ Both the ENZAMET and TITAN study indicate a clear shift of AR inhibitors for treatment of hormone-sensitive PC. Numerous trials assessed new treatment options for non-metastatic and metastatic castrate-resistant prostate cancer (nmCRPC and mCRPC). The phase III trial ARAMIS evaluated the use of the AR antagonist darolutamide in the nmCRPC setting. Darolutamide clearly prolongs MFS, is well tolerated, maintains QoL, and delays worsening of pain and disease-related symptoms compared to placebo.⁴

The phase II TAXOMET study reported no clinically meaningful addition of metformin to docetaxel for treatment of mCRPC patients. Data from the STAMPEDE trial (SOC + metformin) is expected.

The Alliance A031021 phase III trial compared the combination of enzalutamide + abiraterone acetate versus enzalutamide only. The combination showed no benefit in OS with more treatment-related AEs. The combination of enzalutamide + abiraterone acetate is therefore not recommended.⁶ The phase Ib/II trial KEYNOTE-365 explored the possibility of administering pembrolizumab + enzalutamide in patients who progressed on abiraterone acetate within six months. Promising results were observed (doubling of objective response rate [ORR] compared to pembrolizumab in monotherapy) indicating the possible role of immune checkpoint inhibition (ICI) in the mCRPC setting. The phase III trial KEYNOTE-641 is currently ongoing.⁷

The phase II TOPARP-B trial assessed the use of the poly(ADP-ribose) polymerase inhibitor olaparib in mCRPC patients with DNA damage repair alterations. The trial demonstrated antitumor activity, especially in patients with *BRCA1/2* loss, *PALB-2* mutations and *ATM* mutations.⁸

Additionally, another phase II trial evaluated cabazitaxel versus enzalutamide or abiraterone acetate in poor prognosis mCRPC patients. It was found that cabazitaxel gives high clinical benefit for poor risk mCRPC patients, although no gain in OS was observed. ctDNA fraction, AR amplification and *TP53* mutations proved to have prognostic value although larger study groups are needed to confirm this

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TABLE 1. New treatment modalities for prostate cancer.

Trial	GETUG-AFU16	ENZAMET	TITAN	ARAMIS	TAXOMET	A031021	KEYNOTE-365	TOPARP-B	NCT02254785
Reference	1	2	3	4	5	6	7	8	9
Phase	III	III	III	III	II	III	Ib/II	II	II
Type of patients	BCR after RP	mHSPC	mHSPC	nmCRPC (PSADT ≤ 10 mo)	mCRPC	mCRPC	mCRPC (post AA)	mCRPC with DNA damage repair alterations (≥ 1 prior taxane)	Poor prognosis mCRPC
Number of patients	743	1125	1052	1509	99	1311	69	98	95
Randomisation	1:1	1:1	1:1	2:1	1:1	1:1	-	1:1	1:1
Therapy	RT + ADT vs. RT	TS + Enza vs. TS + non-steroidal ADT	ADT + Apa vs. ADT + Pbo	ADT + darolutamide vs. ADT + Pbo	DOCE + metformin vs. Doce + Pbo	Enza + AA vs. Enza	Pembro + Enza	Olaparib 400 mg BID vs. olaparib 300 mg BID	Caba vs. Enza / AA
mFU	112 mo	34.0 mo	22.6 mo	40.4 vs. 18.4 mo	41.1 mo	-	9.0 mo	17.6 mo	-
mMFS	NR vs. NR HR = 0.73 (0.54 – 0.98)	-	-	HR = 0.41 (0.34 – 0.50)	-	-	-	-	-
mPFS	NR vs. 108 mo HR = 0.54 (0.43 – 0.68)	NR vs. 27 mo HR = 0.40 (0.33 – 0.49)	NR vs. 22.1 mo HR = 0.48 (0.39 – 0.60)	-	7.4 vs. 5.6 mo	52.2 vs. 20.7 mo HR = 0.85 (0.74 – 0.97)	6 mo	5.4 vs. 5.4 mo	HR = 0.94 (0.57 – 1.56) 2L: 3.7 vs. 2.9 mo HR = 0.92 (0.46 – 1.86)
mOS	NR vs. NR HR = 0.93 (0.63 – 1.39)	NR vs. NR HR = 0.67 (0.52 – 0.86)	NR vs. NR HR = 0.67 (0.51 – 0.89)	NR vs. NR HR = 0.71 (0.50 – 0.99)	24.6 vs. 19.7 mo	34.2 vs. 32.5 mo HR = 0.90 (0.78 – 1.05)	NR	-	37.0 vs. 15.5 mo HR = 0.77 (0.41 – 1.44)
Clinical benefit rate	-	-	-	-	-	-	-	-	1L: 88 vs. 70 % 2L: 63 vs. 74 %
PSA decline > 50%	-	-	-	-	66 vs. 63 %	80 vs. 82 %	26 %	37 vs. 30 %	1L: 61 vs. 62 % 2L: 41 vs. 48 %
ORR	-	-	-	-	28 vs. 28 %	-	20 %	24 vs. 16 %	1L: 23 vs. 17 % 2L: 20 vs. 0 %
Grade 3/4 AEs	No increase in toxicity	-	42 vs. 41 %	-	-	69 vs. 56 %	41 %	-	1L: 48 vs. 6 %

AA, abiraterone acetate; ADT, androgen deprivation therapy; AE, adverse event; Apa, apalutamide; BCR, biochemical recurrence; Caba, cabazitaxel; Enza, enzalutamide; HR, hazard ratio; mFU, median follow up; mHSPC, metastatic hormone-sensitive prostate cancer; mMFS, median metastatic-free survival; mo, months; NR, not reached; mOS, median overall survival; mPFS, median progression-free survival; (n)mCRPC, (non-)metastatic castrate-resistant prostate cancer; ORR, objective response rate; Pbo, placebo; Pembro, pembrolizumab; PSADT, PSA doubling time; RP, radical prostatectomy; RT, radiotherapy; TS, testosterone suppression.

finding.⁹

Finally, the phase III trial CABADOC determined the patient preference between cabazitaxel and docetaxel for first-line chemotherapy in mCRPC. Although cabazitaxel and docetaxel have similar efficacy when used as first-line treatment option, more patients prefer cabazitaxel. Preferable choice was mostly influenced by fatigue, patient-defined QoL, hair loss, and pain.¹⁰

RENAL CELL CARCINOMA (RCC)

It remains a constant point of discussion when to start systemic therapy in metastatic RCC (mRCC) patients, especially in patients with low tumor burden or slow growing disease. The Canadian Kidney Cancer information system identified 1711 patients who immediately started systemic therapy (N=848); started systemic therapy ≥ 6 months after diagnosis of mRCC (N=370) or never received systemic therapy (N=493). Five year-OS was significantly lower for patients who immediately started systemic therapy (32.1 versus 70.2%). After adjusting for IMDC risk criteria and age, both OS (HR 0.46, 0.38-0.56) and time to treatment failure (HR 0.79, 0.69-0.92) were greater for delayed versus immediate systemic treatment. These data suggest that a subset of patients may be safely observed without immediate initiation of systemic therapy, which could be explained by the fewer metastatic sites and increased performance of metastasectomies in this patient group. Prospective validation in the contemporary immunotherapy era is required.¹¹

Next, several treatment modalities for mRCC were presented at ASCO. An overview is given in *Table 2*.

The phase III trial E2810 evaluated the effect of pazopanib on MFS in mRCC treatment-naïve patients with no evidence of disease following metastasectomy. The primary end point was not reached and adjuvant pazopanib in this patient cohort is thus not recommended.¹²

The phase III CARMENA trial previously indicated that cytoreductive nephrectomy (CN) is not advised in mRCC. Updated results strengthen this statement. However, it was shown that patients with only 1 IMDC risk criteria could still benefit from CN.¹³

A phase II trial by Gao *et al.* evaluated the benefit of concomitant CN or metastasectomy in mRCC patients receiving first-line ICI. The authors suggest that ICI plus concomitant CN or metastasectomy is safe and shows promising clinical utility. Furthermore, response to therapy and survival outcome might be correlated to several biomarkers, such as CD8 tumor infiltrating lymphocytes and tumor IFN.¹⁴

The phase II CheckMate 920 study determined the clinical efficacy of ICI in patients with brain metastases. The current results show encouraging efficacy results with safety profile

comparable to previous reported studies.¹⁵

Finally, several subanalyses of large phase III studies were presented in which the effect of ICI on sarcomatoid mRCC and IMDC intermediate and poor risk mRCC were assessed. IMmotion 151, CheckMate 214 and KEYNOTE-426 all showed high benefit from ICI for patients with sarcomatoid features and intermediate and poor risk patients.¹⁶⁻¹⁸

The fact that sarcomatoid mRCC respond well to ICI can be partly explained by the retrospective analysis done by Bakouny *et al.* After performing next-generation sequencing on sarcomatoid and rhabdoid mRCC tumors, analysis showed that genomic alterations in *BAP1* were significantly more frequent in sarcomatoid and rhabdoid mRCC (25 vs. 4.3%) while other genomic alterations and tumor mutational burden were similar. This could account for the fact that sarcomatoid and rhabdoid mRCC tumors have better outcomes on ICIs compared to non-ICI-based therapies.¹⁹

In addition, patient reported outcomes from the IMmotion 150 suggested that atezolizumab, alone or with bevacizumab, maintained daily function with minimal symptom interference versus sunitinib.²⁰

UROTHELIAL CARCINOMA (UC)

Numerous novel therapies for treatment of (metastatic) urothelial carcinoma (mUC) were presented at ASCO. An overview is given in *Table 3*.

First, the most ideal adjuvant therapy following cystectomy in patients with locally advanced disease was determined. Comparison between adjuvant RT or chemotherapy proved comparable MFS, although local control is improved in the RT arm. Based on this study, this treatment option could be offered for patients unfit or unwilling to receive chemotherapy.²¹

The CALGB 90601 phase III study assessed the added value of bevacizumab to chemotherapy in treatment-naïve mUC. No OS benefit was shown. A small gain in PFS was observed, although not clinically significant. Bevacizumab has therefore no place in first-line therapy.²²

The HCRN GU14-180 phase II trial explored the role of maintenance ICI in patients who are stable after first-line chemotherapy. Maintenance ICI proved effective and prolonged PFS. Further validation is even though still required to verify if maintenance ICI “deepens” responses achieved with first-line chemotherapy.²³

Response to ICI may be dampened by *FGFR3* mutations. The phase Ib/II FIERCE-22 trial therefore explored the efficacy of the combination of the *FGFR3* inhibitor vofatamab and ICI. The combination seems well tolerated and prolongs PFS, especially in patients with wild type *FGFR3*. Further investigation is ongoing.²⁴

TABLE 2. New treatment modalities for metastatic renal cell carcinoma.

Trial	E2810	CARMENA	NCT02210117	CheckMate 920	IMmotion 151	CheckMate 214	KEYNOTE-426
Reference	12	13	14	15	16	17	18
Phase	III	III	II	II	III	III	III
Type of patients	Treatment-naïve (no evidence of disease following metastasectomy)	Treatment-naïve	Treatment-naïve	Treatment-naïve (asymptomatic brain metastases)	Treatment-naïve (sarcomatoid)	Treatment-naïve (sarcomatoid and IMDC intermediate / poor risk)	Treatment-naïve (sarcomatoid / IMDC intermediate / poor risk)
Number of patients	129	450	105	28	142/863	112/1096	IMDC: 592/861 sarcomatoid: 105/861
Randomisation	1:1	1:1	2:3:2	-	1:1	1:1	1:1
Therapy	Pazo vs. pbo	Sun + CN vs. sun	Nivo ± surgery vs. nivo + bev ± surgery	Nivo + ipi	Atezo + bev vs. sun	Nivo + ipi vs. sun	Pembro + axi vs. sun
mFU	30 mo	61.5 mo	24.6 mo	6.5 mo	-	30 mo	-
mMFS	17.3 vs. 14.2 mo HR = 0.85 (0.55 – 1.31)	-	-	-	-	-	-
mPFS	-	-	+ surgery: 17.3 vs. 7.6 vs. 8.9 mo - surgery: 14.5 vs. 7.6 vs. 7.5 mo	9.0 mo	8.3 vs. 5.3 mo HR = 0.52 (0.34 – 0.79)	8.4 vs. 4.9 mo HR = 0.61 (0.38 – 0.97)	IMDC: 12.6 vs. 8.2 mo HR = 0.67 (0.53 – 0.85) sarcomatoid: NR vs. 8.4 mo HR = 0.54 (0.29 – 1.00)
mOS	NR vs. NR HR = 2.65 (1.02 – 6.9)	15.6 vs. 19.8 mo HR = 0.93 (0.76 – 1.15)	All: NR vs. NR vs. NR	NR	NR vs. 15.0 mo HR = 0.56 (0.32 – 0.96)	31.2 vs. 13.6 mo HR = 0.55 (0.33 – 0.90)	IMDC: NR vs. NR HR = 0.52 (0.37 – 0.74) sarcomatoid: NR vs. NR HR = 0.58 (0.21 – 1.59)
ORR	-	-	+ surgery: 86 vs. 89 vs. 69 % - surgery: 55 vs. 44 vs. 43 %	28.6 %	49 vs. 14 %	56.7 vs. 19.2 %	IMDC: 55.8 vs. 29.5 % sarcomatoid: 58.8 vs. 31.5 %
Grade 3/4 AEs	-	-	All: 38 vs. 42 vs. 47 %	21 %	40 vs. 49 %	46 vs. 40 %	-

Atezo, atezolizumab; axi, axitinib; bev, bevacizumab; HR, hazard ratio; IMDC, International Metastatic RCC Database Consortium; ipi, ipilimumab; mFU, median follow up; mMFS, median metastatic-free survival; mo, months; mOS, median overall survival; mPFS, median progression-free survival; nivo, nivolumab; NR, not reached; ORR, objective response rate; pazo, pazopanib; pbo, placebo; pembro, pembrolizumab; sun, sunitinib.

TABLE 3. New treatment modalities for advanced urothelial carcinoma.

Trial	NCT01734798	CALGB 90601	HCRN GU14-182	FIERCE-22	NCT03333616	NCT03507166	EV-201
Reference	21	22	23	24	25	26	27
Phase	III	III	II	II/II	II	II	II
Type of patients	Chemo-naïve, local disease after cystectomy	Treatment-naïve (> 12 mo since adjuvant chemotherapy)	First line chemo-pre-treated patients with stable disease	≥ 1 prior chemotherapy or < 12 mo since adjuvant chemotherapy	Variant histologies, treatment-naïve or pretreated (no ICI)	HER2+, pretreated (≥ 1 prior systemic therapy)	Pretreated (prior platinum chemotherapy and ICI)
Number of patients	123	506	107	7/28	19	43	128
Randomisation	2:1	1:1	1:1	-	-	-	-
Therapy	RT vs. adjuvant chemotherapy	Chemotherapy + bev vs. chemotherapy + pbo	Pembro vs. pbo	Vofatamab + pembro	Nivo + ipi	RC48-ADC	Enfortumab vedotin
mFU	-	46.2 mo	14.7 mo	-	3.6 mo	-	4.6 mo
mMFS	HR = 0.65 (0.35 – 1.19)	-	-	-	-	-	-
mPFS	-	7.7 vs. 6.6 mo HR = 0.79 (0.66 – 0.95)	5.4 vs. 3.2 mo HR = 0.64 (0.41 – 0.98)	NR	3.8 mo	6.9 mo	5.8 mo
mOS	HR = 0.94 (0.52 – 1.69)	14.5 vs. 14.3 mo HR = 0.87 (0.72 – 1.06)	-	-	NR	NR	11.7 mo
ORR	-	40.4 vs. 33.0 %	22 vs. 12 %	36 %	37 %	51.2 %	44 %
Grade 3/4 AEs	8 vs. 2 % (late GI toxicity)	83.5 vs. 80.7 %	53 vs. 35 %	-	16 %	-	-

Bev, bevacizumab; HR, hazard ratio; ICI, immune checkpoint inhibition; ipi, ipilimumab; mFU, median follow up; mMFS, median metastatic-free survival; mo, months; mOS, median overall survival; mPFS, median progression-free survival; nivo, nivolumab; NR, not reached; ORR, objective response rate; pbo, placebo; pembro, pembrolizumab; RT, radiotherapy.

KEY MESSAGES FOR CLINICAL PRACTICE

- 1. A clear shift is seen towards modern AR inhibitors for treatment of hormone-sensitive PC.**
- 2. Combinations of docetaxel plus metformin or enzalutamide plus abiraterone are not advised for treatment of mCRPC.**
- 3. Pembrolizumab plus enzalutamide show promising results in mCRPC (although phase III data are awaited).**
- 4. Genetic profiling will play a role in determining the most optimal treatment option for mCRPC.**
- 5. Active surveillance remains a valid option for mRCC, especially in patients with low tumor burden.**
- 6. Cytoreductive nephrectomy is only recommended in patients with low risk (IMDC 1) and might be plausible in patients receiving first-line ICI.**
- 7. ICI proves effective for mRCC patients diagnosed with asymptomatic brain metastases.**
- 8. Sarcomatoid mRCC patients respond well to ICI, probably due to the genomic alterations (especially *BAP1* mutations) that are associated with this histologic feature.**
- 9. Adjuvant RT for locally advanced mUC is a possible option for patients unfit or unwilling to receive chemotherapy.**
- 10. Bevacizumab is not to be given in addition to first-line chemotherapy in mUC.**
- 11. Maintenance ICI might “deepen” the responses achieved with first-line chemotherapy in mUC – results of first line combination trials are awaited.**
- 12. Combination of ICI and FGFR3 inhibitors might increase the ORR in mUC due to the inhibition of the dampening effect created by *FGFR3* mutations.**
- 13. mUC of variant histologies can respond to ICI and show a desirable safety profile.**
- 14. Novel treatment options are coming which show efficacy in mUC patients who progressed on first-line chemotherapy and second-line ICI (enfortumab vedotin and FGFR inhibition are the most important approaches in this setting).**

Patients with mUC of variant histologies have poor outcomes. A phase II trial was conducted to assess the use of ICI in this patient group. ICI showed clear efficacy with desirable safety profile. Further exploration of ICI in this patient population is therefore warranted.²⁵

Despite the use of ICI in mUC, the question remains which treatment to choose after progression on ICI. Two phase II trials were reported exploring this statement. RC48-ADC, an anti-HER2 antibody-drug conjugate, proved clinically meaningful in HER2+ patients pretreated with ICI (and chemotherapy).²⁶ Next, enfortumab vedotin, an antibody-drug conjugate targeting Nectin-4, proved effective for patients who progressed after chemotherapy and ICI.²⁷

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Clinically meaningful survival benefit with atezolizumab + nab-paclitaxel in previously untreated patients with PD-L1+ metastatic triple negative breast cancer

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Patients with metastatic triple-negative breast cancer (mTNBC) face a poor prognosis with a median overall survival (OS) of approximately 18 months if they are treated with the current standard of care chemotherapy.¹⁻³ Following the compelling successes with immune checkpoint inhibition in other solid tumors, IMpassion130 was the first phase III study to demonstrate a clinical benefit of cancer immunotherapy in PD-L1 positive mTNBC patients.⁴ In this study, the combination of the PD-L1 inhibitor atezolizumab with nab-paclitaxel was found to be associated with a significant 38% reduction in the risk of death compared to placebo plus nab-paclitaxel in mTNBC patient with PD-L1 expressing tumors (HR[95%CI]: 0.62[0.45-0.86]).⁴ ASCO 2019 featured the presentation of the second interim analysis of this trial after 59% of deaths occurred in the intent-to-treat population (vs. 43% in the first interim analysis).⁵

STUDY DESIGN AND PREVIOUS RESULTS

In IMpassion 130, 902 patients with metastatic or inoperable, locally advanced TNBC who were not previously treated for advanced TNBC were randomly assigned (1:1) to a treatment with atezolizumab (840mg IV q2w) plus nab-paclitaxel (100mg/m² IV on days 1, 8 and 15 of 28 day cycles) or placebo plus nab-paclitaxel. Patients were treated until disease progression or intolerable toxicity. The two primary endpoints of the trial were progression-free survival (PFS)(in the intention-to-treat population and in the sub-

group of patients with PD-L1 positivity on tumor-infiltrating immune cells) and OS (tested in the intention-to-treat population; if the finding was significant, then it would be tested in the PD-L1-positive subgroup).^{4,5} In both treatment arms, 41% of patients proved to be positive for PD-L1 ($\geq 1\%$ PD-L1 expression on tumor-infiltrating immune cells, using Ventana SP142).

In the primary analysis for PFS, the atezolizumab nab-paclitaxel combination was found to be associated with a significant improvement in the PFS compared to placebo plus nab-paclitaxel with a median PFS of 7.2 and 5.5 months, respectively (HR[95%CI]: 0.80[0.69-0.92]; $p=0.002$). This PFS benefit was entirely driven by a benefit in patients with PD-L1 positive tumors. In the PD-L1 positive subgroup, the HR for PFS was 0.62 (95%CI: 0.49-0.78; $p<0.001$) with a median PFS of 7.5 months for the immunotherapy containing treatment regimen and 5.0 months in the control arm.⁴

The median follow-up for this 1st interim analysis was 12.9 months, while this was 18 months for the presented second interim analysis. At that time, 9% of atezolizumab + nab-paclitaxel treated patients were still on treatment as compared to 3% in the placebo + nab-paclitaxel arm. In both arms, 30% of patients were alive and in follow-up. Fifty seven percent of patients in the experimental arm had died at the time of the second analysis as compared to 62% in the control arm.⁵

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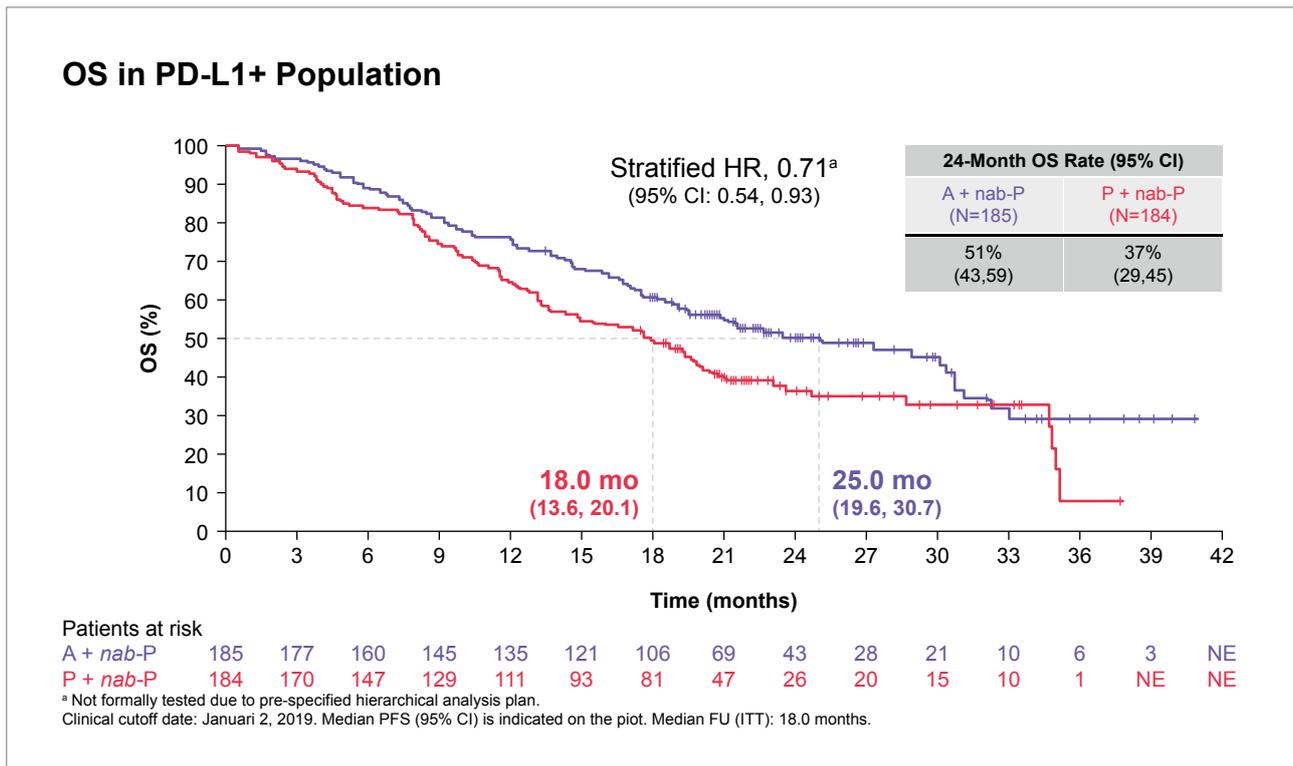


FIGURE 1. OS in the subgroup of patients with PD-L1 positive tumor infiltrating immune cells in the phase III Impassion 130 trial.⁵

SECOND INTERIM ANALYSIS CONFIRMS CLINICAL OS BENEFIT IN PD-L1 POSITIVE PATIENTS

The median OS reported in the entire intent-to-treat population was reported at 21 months for atezolizumab plus nab-paclitaxel and 18.7 months in the control, corresponding to a 14% reduction in the risk of death. This difference did however not reach statistical significance with the upper boundary of the 95% confidence interval being 1.01 (HR[95%CI]: 0.86[0.72-1.01]). At 24 months, 42% of atezolizumab treated patients was still alive as compared to 39% in the control arm. In contrast, the OS benefit seen with atezolizumab plus nab-paclitaxel over placebo plus nab-paclitaxel did reach statistical significance in the subgroup of PD-L1 positive patients. In this subgroup, the atezolizumab combination was associated with a median OS of 25 months as compared to 18 months with placebo plus nab-paclitaxel (HR[95%CI]: 0.71[0.54-0.93]). Atezolizumab plus nab-paclitaxel sets a new benchmark as the first therapy to cross the 2-year landmark OS benefit in first-line PD-L1-positive mTNBC. At 24 months, this corresponds to an OS rate of 51% and 37%, respectively. It is however important to stress that this OS benefit in PD-L1 positive patients was not formally tested given the hierarchical analysis plan discussed above.⁵ A comparison of the OS in PD-L1 positive and negative patients does show a remarkable difference. As indicated

before, the median OS was 7 months longer with atezolizumab plus nab-paclitaxel in PD-L1 positive patients, while in PD-L1 negative patients the median OS was almost identical with atezolizumab or placebo plus nab-paclitaxel (19.7 vs. 19.6 months; HR[95%CI]: 0.97[0.78-1.20]).⁵

NO NEW SAFETY SIGNALS WITH EXPANDED FOLLOW-UP

With this longer follow-up, no new safety signals were seen, and the safety profile remained consistent with what was previously reported, without any cumulative toxicities or late-onset safety signals. Overall, the immune-mediated adverse events were manageable and the time to the onset of these events was consistent with what was reported in atezolizumab monotherapy studies. The incidence of grade 3/4 adverse events was 49% in the atezolizumab arm as compared to 43% with placebo plus nab-paclitaxel. Adverse events leading to treatment discontinuation of any agent occurred in 16% of patients who received atezolizumab plus nab-paclitaxel and in 8% of the placebo plus nab-paclitaxel treated patients. Any grade immune-mediated adverse events were reported in 58% of patients on atezolizumab plus nab-paclitaxel and in 42% of patients in the control arm (grade 3/4 in 8% and 4%, respectively). The most frequent clinically relevant immune mediated adverse events in the trial were rash (34% vs. 26%), hypothyroidism

(18% vs. 5%), hyperthyroidism (5% vs. 1%), pneumonitis (4% vs. 0%) and colitis (2% vs. 2%).⁶

CONCLUSION

IMpassion130 is the first and only phase III study to show a clinically meaningful benefit of first-line immunotherapy in patients with mTNBC. The PD-L1 status on tumor infiltrating immune cells was found to be predictable of the clinical benefit of atezolizumab plus nab-paclitaxel. Although the investigators were not able to formally test the OS in the subgroup of PD-L1 positive patients (due to the hierarchical statistical plan), they did show a clinically meaningful OS improvement from 18 months with placebo plus nab-paclitaxel to 25 months with atezolizumab plus nab-pa-

clitaxel. The combination with nab-paclitaxel was well tolerated, without cumulative toxicity and no late-onset safety signals. These data establish atezolizumab plus nab-paclitaxel as the new standard of care for PD-L1-positive mTNBC patients, which also led to the CHMP positive opinion on June 27th 2019.

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Highlights in breast cancer

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At ASCO 2019, many presentations featured recent progress in the breast cancer field. A lot of attention went to biomarkers but also the treatment of triple negative breast cancer, luminal disease, HER2 positive disease as well as agnostic breast cancers subtypes were discussed.

BREAKING NEWS

ASCO 2019 will be remembered for the presentation of the Overall Survival (OS) results of MONALEESA 7, the randomized phase III trial which compared, in 672 pre/perimenopausal women with advanced hormone receptor positive/HER2 negative breast cancer (BC), goserelin with either a non-steroidal aromatase inhibitor or tamoxifen in addition to a placebo or the same endocrine therapy plus the CDK 4-6 inhibitor ribociclib.¹

The trial which reported earlier improved progression-free-survival (PFS) with the addition of ribociclib, now demonstrates, at a median follow up of 35 months, a significantly longer OS (HR 0.71; 95%CI: 0.54-0.95; p = 0.00973) (Figure 1). Of note, 60 percent of this patient population (median age 44) was endocrine-naïve and only 18% got treated with a CDK4-6 inhibitor at progression in the control arm. Also noteworthy is the fact that progression-free-survival on subsequent therapy tended to be better in the ribociclib arm (with similar distributions of post progression chemotherapy administration), providing reassurance that stopping CDK 4-6 inhibitors does not “fuel” metastatic progression.

MONALEESA 7 establishes the new standard of care for pre/perimenopausal women presenting with advanced luminal disease or pretreated for this condition with no more than one chemotherapy regimen.

BIOMARKERS

Three presentations are improving our knowledge of the genomic and immune landscape of metastatic disease:

Mutational signatures differ between metastatic foci and the primary tumor with an enrichment of signature 13 (which is APOBEC related) in a study of 209 metastatic biopsies from luminal BC and 62 matched primaries.²

Results of the Foundation Medicine NGS panel on 3871 metastatic biopsies (50% HER2+, 35% luminal and 15% TNBC) were examined for potential immunotherapy predictive biomarkers. The most important biomarkers were: tumor mutational burden (TMB) ≥ 10 mutations/Megabase (8-12%), TMB ≥ 20 mut/Mb (2-3%), PDL1 amplifications (1-3%) and a high MSI (0.1-0.4%).³

The genomic landscape of 212 *de novo* stage IV BC was compared to that of 714 recurrent cancers. Very few differences were noted in HER2+ disease while for TNBC, *de novo* cancers showed more MYB amplifications. In luminal BC, less p53 mutations, less aberrations in DNA repair genes and more alterations in epigenetic modeling genes characterized a *de novo* disease. In general, a number of genomic aberrations could be associated with a poorer OS of *de novo* MBC: p53 mutations, amplifications in RAD21, myc, myb, PTK2 and EGFR or deletions in CDKN2A/2B and MAP2K4.⁴

A range of biomarkers aimed at improving *treatment tailoring in early BC*:

In luminal BC, a secondary analysis of TailorX introduces the ONCOTYPE Recurrence Score integrated with Clinical Risk (as defined in Mindact) as an important way to refine the decision for more aggressive adjuvant therapy than tamoxifen in young women aged ≤ 50 years. Indeed, this integrated risk shows in some categories less distant metastases with the ad-

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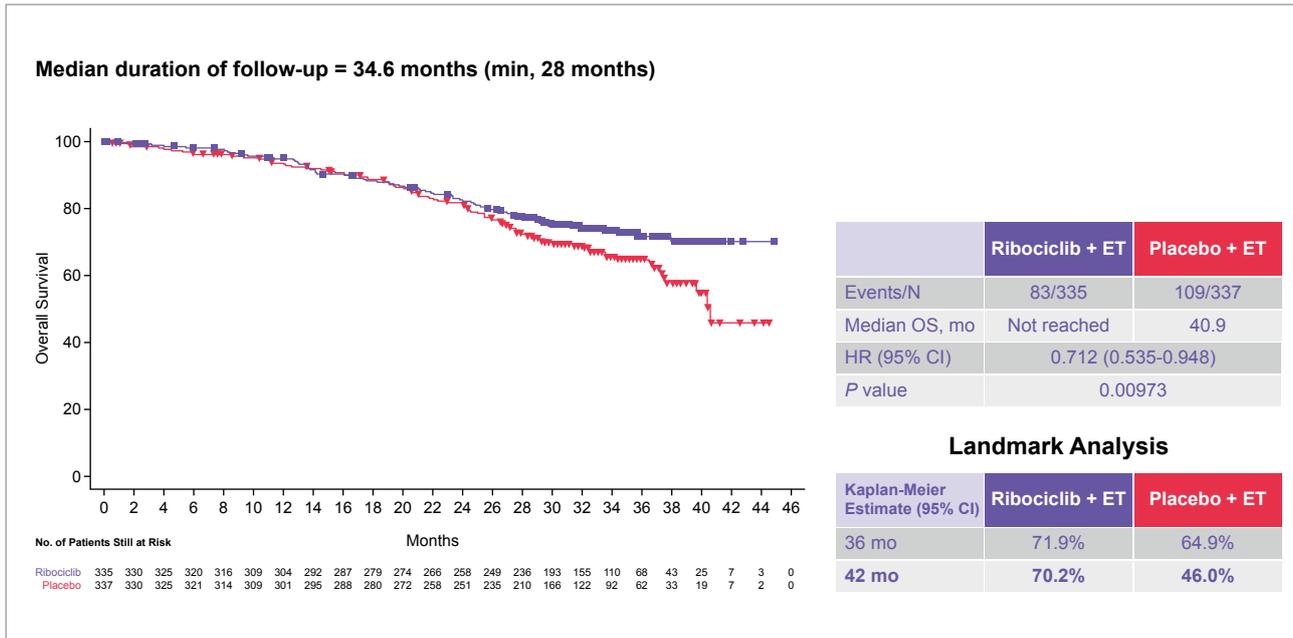
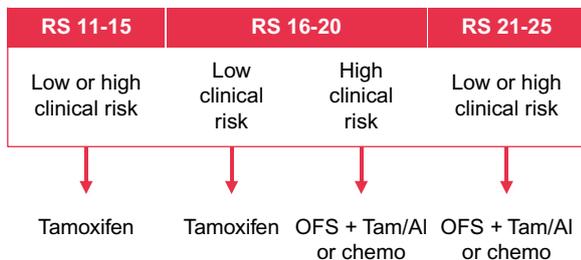


FIGURE 1. The MONALEESA-7 trial reports a substantial improvement in Overall Survival.¹

dition of chemotherapy to tamoxifen (which can be interpreted as an indirect ovarian function suppression effect since it is restricted to non-menopausal women between 40 and 50 years).⁵ The new treatment recommendation for these younger premenopausal women is depicted below.



The CTS-5 clinical score, developed by the Royal Marsden hospital and based on patient age as well as tumor grade/size and nodal status, has now been validated in disease-free non trial patients at 5 years; it identifies 41% of pre- or postmenopausal women with a low risk (4.9%) of distant relapses between year 5 and year 10 (who might be spared extended adjuvant endocrine therapy).⁶

Also of interest, as far as deciding to prolong or not adjuvant tamoxifen, is the BC index, an 11 gene signature able to identify a patient subgroup (among 583 node positive patients from the ATTOM trial) with a 10% absolute decrease in recurrence risk when receiving longer tamoxifen treatment.⁷ In triple negative BC, the search for biomarkers that are helpful for treatment tailoring has been less successful.

In the TBCRC030 neoadjuvant trial, comparing neoadjuvant cisplatin with neoadjuvant paclitaxel in 140 women, the Homologous Recombination Deficiency Score, (by the Myriad test) did not predict for residual cancer burden 0-1 at surgery.⁸

The BRIGHTNESS neoadjuvant trial (N=634) showed superior pCR with the addition of carboplatin to the anthracycline/taxane backbone, but could not show further gain with the addition of Veliparib. RNA sequencing was successful in 482 patient tumors and suggested a link between “immune” signatures and carboplatin benefit (High CD8 signature) or lack of benefit (High Macrophage M2 signature).⁹

In the GEPARNUOVO neoadjuvant trial, which failed to demonstrate a superior pCR for the addition of Durvalumab to standard neoadjuvant chemotherapy (N=171), continuous tumor mutational burden was linked to the probability of a pCR but not to Durvalumab benefit.¹⁰

In HER2 positive BC only tumor heterogeneity in HER2 expression, as assessed by 2 distinct core biopsies in the primary tumor (e.g. HER2 negativity in one area/HER2 positive by FISH in at least 5% but in < 50% of cells in another area), might be a clinically useful biomarker but needs further validation.

Indeed, this biomarker, found in 10% of HER2 positive tumors, mostly ER positive, was associated with NO pCR in a prospective trial of neoadjuvant T-DM1 plus pertuzumab (N=157).¹¹

Other biomarkers (BM), although interesting, are unlikely to be of help to the clinician.

A comprehensive BM study with a nested case control de-

sign (based on three controls for each distant relapse) suggests that the benefit of dual HER2 blockade in APHINITY is seen mostly in tumors with very high TILs (>75th percentile) and/or high degrees of HER2 amplification (HER2 copy number ≥ 6).¹²

In the NSABP-B41 neoadjuvant trial, higher pCR's on the trastuzumab arms were correlated with higher HER2/PDL1 expression and lower ESRI (Nanostring BC 360 panel performed in 194 biopsies/529 patients). No biomarker predicted the benefit from the addition of lapatinib to trastuzumab.¹³ In *advanced disease*, attempts were made at identifying biomarkers linked to the benefit of everolimus or CDK4-6 inhibitors added to endocrine therapy for luminal BC. The most robust BM presented was *p4EBP1*, originally found to be linked to the everolimus benefit in the TAMRAD study. P4EBP1 was now validated in the prospective single arm SAFIRTOR trial (N=108) in which its expression on fresh metastatic biopsies could be linked to an improved PFS (9.3 months vs. 5.8 months).¹⁴

Two translational research efforts based on archival tissue samples (MONALEESA7) or plasma samples (PALOMA3) led to putative BM of benefit from the addition of ribociclib (high cyclin D1), high IGFR1, high HER3, low cyclin E and low Myc with the Nanostring gene panel in MONALEESA7) or putative BM of decreased benefit from Palbociclib (cyclin E or F6FR gain, p53 mutations, high ctDNA fraction in PALOMA3).¹⁵⁻¹⁶

Finally, the MSKCC group found Rb1 loss or FAT1 loss to predict for early progression on a CDK4-6 inhibitor, while emergence of Rb1 or PTEN loss were found at late progression.¹⁷

TREATMENT OF TRIPLE NEGATIVE BREAST CANCER (TNBC)

In the *neoadjuvant setting*, a small randomized phase II trial found identical pCR rates ($\approx 53\%$) in an anthracycline-free arm [carboplatin (AUC6) + docetaxel 75 mg/m² x6] compared to the sequential administration of carboplatin (AUC6) x4 + paclitaxel 80 mg/m² x12 followed by 4 cycles of AC.¹⁸ *Trials for advanced TNBC* all focused on immune checkpoint-based therapy. The mature analysis of OS in IMPASSION130 (first line nabpaclitaxel with or without atezolizumab) still does not show a significant overall improvement [HR 0.86 (0.72-1.02)] while a 7 months improvement (from 18 to 25 months) is seen in the PDL1 positive subset [no p value ascribed because of the planned hierarchical testing]¹⁹

An attempt to improve upon nabpaclitaxel plus atezolizumab by antagonizing the MAPK pathway, particularly for PDL1 negative disease, was not convincing: the Triplet combination, e.g.; nabpaclitaxel (or paclitaxel) plus atezolizumab plus cobimetinib (a potent MEK 1/2 inhibitor) led to an objective

RR of 33-44% in PDL1 positive patients versus 11-27% in PDL1 negative patients at the cost of severe diarrhea and rash in 45% of patients.²⁰

Capecitabine appears as an interesting partner when combined to pembrolizumab (RR 43%) in a population including early relapses after adjuvant therapy. Although not randomized, paclitaxel plus pembrolizumab appeared somewhat less effective (RR 25%).²¹

Although not restricted to TNBC, the GEPAROLA trial enrolled 102 patients with a high Homologous Recombination Deficiency Score in a randomized phase II trial of Olaparib (100mg x2/day) plus paclitaxel (80mg/m² weekly x12) or carboplatin AUC2 weekly x12 plus paclitaxel.²²

The trial missed its primary endpoint, namely the demonstration of a 70% pCR in the PARP inhibitor arm. Instead, pCR rates were very similar (55% and 48%) but there were more serious adverse events in the carboplatin arm.

TREATMENT FOR LUMINAL DISEASE

In the *adjuvant setting*, an Italian trial compared longer (5 years) versus shorter (2-3 years) therapy with aromatase inhibitor following 2-3 years of tamoxifen. The study enrolled 2056 women and showed, at a median follow up of 10 years, a modestly superior DFS for the longer therapy duration (DFS HR 0.81; p= 0.05).²³

In the US national database, an analysis of OS was performed in the subset of 25,000 fit elderly women diagnosed with small T1N0 tumors and treated with either radiotherapy or endocrine therapy. The former treatment was found to produce similar (if not better) outcomes.²⁴

In the *metastatic setting*, CDK4-6 inhibitors received the greatest attention, followed by attempts at improving the activity of endocrine therapy or chemotherapy.

A randomized Korean trial enrolled 184 premenopausal women, half of whom were previously untreated for their advanced disease, and compared the combination of a GNRH agonist plus exemestane plus palbociclib to capecitabine (1250 mg 2x/day). The PFS HR of 0.65 (0.43-0.99) was in favor of the endocrine treatment arm with a 6-month prolongation of median PFS (20 months instead of 14 months). Quality of life data will be presented at a later timepoint.²⁵ Bardia *et al.* studied patients progressing on a CDK4-6 inhibitor and tested the triplet combination of ribociclib plus exemestane plus everolimus. Although the toxicity was deemed to be manageable, it is difficult to judge if the anti-tumor activity seen (median PFS of 5.7 months, 6-month clinical benefit rate of 41%) is superior to the one of exemestane plus everolimus.²⁶

Abemaciclib on the other hand failed to show the "target" intracranial response rate in 58 patients with brain metastases

KEY MESSAGES FOR CLINICAL PRACTICE

- 1. Even a treatment-naïve tumor needs to be “hit” by the stronger therapy: in other words, there should no longer be an hesitation to introduce a CDK4-6 inhibitor in the first line advanced disease setting of luminal BC. While the OS advantage, so far, has been reported only in a trial for “premenopausal” women they were all “transformed” into postmenopausal women: therefore, it is likely that an OS advantage also exists for CDK4-6 inhibitors in the latter population.**
- 2. The use of oncotype-DX in women ≤ 50 years now requires the combined use of the clinical risk in order to refine adjuvant treatment selection.**

(41% of whom had not been treated with radiotherapy before). The observed response rate was only 6%. The UK randomized placebo controlled phase II trial FAKTION enrolled 140 postmenopausal women progressing on an aromatase inhibitor (but not pretreated with CDK4-6 inhibitors) and found a superior PFS (HR 0.58, 0.4-0.58) for the addition of capivasertib (an AKT1 inhibitor) to fulvestrant (with a median PFS of 10.3 months vs. 4.8 months). This improvement was obtained at the cost of increased grade 3 diarrhea and rash (14% vs. 3% and 20% vs. 0%). Unfortunately, there was no enhanced benefit seen in the case of piK3CA mutations or PTEN loss.²⁷

The Dana Farber team could not show any PFS or OS improvement with the addition of pembrolizumab to eribulin in a randomized phase II trial (N=88) (cross-over allowed), in which 2 toxic deaths occurred in the pembrolizumab arm.²⁸

TREATMENT FOR PATIENTS WITH HER2 POSITIVE DISEASE

In early disease, 3 presentations focused on T-DM1.

The neoadjuvant KRISTINE trial, which previously showed an inferior pCR rate for T-DM1 plus pertuzumab (for 6 cycles) compared to docetaxel/carboplatin plus trastuzumab/pertuzumab (for 6 cycles), now reports on event-free-survival (EFS) and invasive disease-free-survival (iDFS). EFS favored the docetaxel-carboplatin arm (HR 2.61 (1.36-4.48)) while no difference emerged in iDFS (HR 1.11 (0.52-2.4)). This is explained by a 6.7% local progression before surgery in the T-DM1 arm, which is not accounted for in iDFS (for which the clock starts after surgery). It should be noted, however, that the protocol allowed for postsurgical chemotherapy in the T-DM1 arm (in case of no pCR) and that chemotherapy was indeed given to 25% of these patients.²⁹

The Swedish PREDIX HER2 randomized trial found identical pCR rates (44-46%) following T-DM1 for 6 cycles or docetaxel/trastuzumab/pertuzumab for 6 cycles. Of note, all patients received anthracycline-based therapy after surgery.

Quality of life was better in the T-DM1 arm. Interestingly an early FDG-PET scan (at 5 weeks) predicted for pCR status (no pCR in 81% of women in whom the SUV max decreased by less than 45%).³⁰

T-DM1 in the post neoadjuvant setting for patients not reaching a pCR has been shown to markedly improve 3-year iDFS (by 11%) in comparison to the continuation of trastuzumab in the famous KATHERINE trial.

While the antibody-drug conjugate led to more adverse events and treatment discontinuations, patient reported outcomes, collected in 1252 of 1486 patients, indicate a better quality of life for T-DM1.³¹

In advanced disease, the CLEOPATRA trial now reports overall survival at 8 years follow up, with 37% of patients alive in the dual HER2 blockade arm (docetaxel plus trastuzumab plus pertuzumab) versus 23% in the single HER2 blockade arm.³² At ASCO 2019, two randomized phase III trials conducted beyond first line were presented:

In SOPHIA (N=536) the novel Fc engineered anti HER2 monoclonal antibody Margetuximab combined with chemotherapy was modestly superior to trastuzumab with chemotherapy : PFS HR 0.76 (0.59-0.98) [median PFS 5.8 months vs. 4.9 months]. This benefit was confined to the “low affinity” genotypes comprising an “F” allele.³³

In NALA (N=621) Neratinib plus capecitabine improved PFS in comparison with lapatinib plus capecitabine [PFS HR 0.76 (0.63-0.93)] at the cost of more grade 3 diarrhea but no worse quality of life.³⁴

STUDIES AGNOSTIC OF BC SUBTYPE

The CANTO study, conducted in France, reported outcomes collected at 2 years from diagnosis in 4262 BC survivors. Results showed frequent persistent symptoms, post-menopausal women were more severely impacted by endocrine therapy and premenopausal women were more affected by chemotherapy.³⁵

The *NSABP-B39 trial*, which failed to demonstrate “equivalence” between partial breast irradiation (PBI) and whole breast cancer irradiation [HR 1.22 (0.94-1.58)] also collected patient reported outcomes up to 36 months after therapy in 975 women stratified by the prior administration of chemotherapy (yes or no). In the no chemotherapy group, PBI was associated with less fatigue and less pain but cosmetic results were slightly worse at 3 years.³⁶

Finally, the “Women Health Initiative Low Dietary Fat” (N ≈ 49,000 post-menopausal healthy women with a fat intake ≥ 32% of total energy randomized to “follow up” or dietary intervention), which had reported 3374 breast cancers over 20 years and less non BC deaths, now reports less deaths from BC in the intervention group.³⁷

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Ribociclib plus endocrine therapy prolongs the survival of premenopausal women with advanced breast cancer

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It is well established that younger women with breast cancer tend to have a worse prognosis and a more aggressive cancer type than older patients. However, despite this high medical need premenopausal women are often underrepresented in clinical trials. In recent years, CDK4/6 inhibitors have dramatically changed the treatment landscape of women with advanced hormone receptor positive (HR+) advanced breast cancer, both in the first line setting and in patients with progressive disease. The MONALEESA-7 trial was the first trial to exclusively focus on the potential of a CDK4/6 inhibitor (ribociclib) in premenopausal women with advanced breast cancer for which they did not yet receive endocrine therapy (ET). In previous reports of this trial it was already shown that the addition of ribociclib to ET resulted in a significant improvement in the progression-free survival (PFS) for these women (median PFS: 23.8 vs. 13.0 months; HR[95%-CI]: 0.55[0.44-0.69]; $p < 0.0001$).¹ New data of this study, reported in a late breaking abstract at ASCO 2019, now also indicate a substantial overall survival (OS) improvement for women who receive the ribociclib-ET combination instead of ET + placebo.²

STUDY DESIGN AND PATIENT DISPOSITION

In MONALEESA-7, 672 pre- or perimenopausal women with HR+/HER2- advanced breast cancer who did not receive prior ET and not more than one line of prior chemotherapy for their advanced breast cancer were randomly assigned (1:1) to a treatment with ribociclib (600 mg/day in a 3 weeks on/1 week off schedule) + ET (goserelin plus either tamoxifen or

a non-steroidal aromatase inhibitor [NSAI]), or placebo plus ET. The primary endpoint of the trial was PFS, with OS as a key secondary study objective. In addition to this, the trial also looked into the health-related quality of life (HRQoL), the objective response rate (ORR), the time to deterioration of the ECOG performance status (PS) and the safety of the experimental regimen. A hierarchical testing strategy was applied in the study stipulating that the OS could only be evaluated if a significant improvement in PFS was observed. As indicated earlier, the latter was the case with a statistically significant hazard ratio for PFS of 0.55, allowing a statistical analysis of the OS.

The median age of patients in the study was 44 years and about 60% was white. Three quarters of patients had an ECOG PS of 0 at study entry and approximately 40% received prior ET in the (neo)adjuvant setting. Overall 14% of the study participants received prior chemotherapy in the context of their advanced disease. At the time of the OS analysis (median follow-up 34.6 months), the treatment was ongoing in 35% of patients randomized to ribociclib + ET and in 17% of the placebo + ET patients. In the vast majority of patients, disease progression was the reason to discontinue the therapy (52% with ribociclib + ET and 68% with placebo + ET).

SIGNIFICANT OS IMPROVEMENT FROM ADDING RIBOCICLIB TO ET

In the entire study population, the combination of ribociclib + ET was associated with a statistically significant 29% reduction in the risk of death compared to placebo + ET (median

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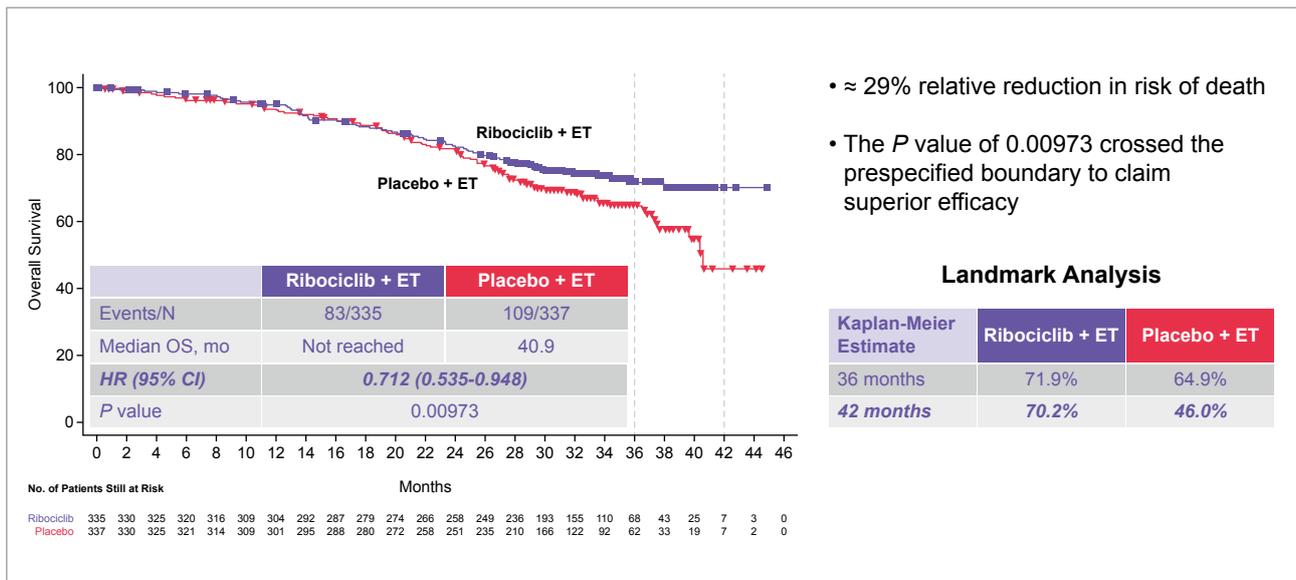


FIGURE 1. Overall survival in the phase III MONALEESA-7 trial.²

not reached vs. 40.9 months; HR[95%CI]: 0.712[0.535-0.948]; $p=0.00973$). In a landmark analysis for OS, this corresponded to a 42-months OS rate of 70.2% with ribociclib + ET as compared to only 46% with placebo + ET. Specifically, looking at the subgroup of patients who received a NSAI as endocrine therapy, the benefit of adding ribociclib was even more pronounced with a HR for OS of 0.699 (95%CI: 0.501-0.976). In this subgroup of patients, the OS estimates at 42 months were 69.7% and 43.0% with ribociclib and placebo + ET, respectively. Also in all the other investigated subgroups the ribociclib + ET combination proved to be associated with a better OS compared to placebo + ET, irrespective of age, race, the prior use of chemotherapy in the advanced setting, the use of (neo)adjuvant ET, the presence of liver, lung, or bone involvement and the number of metastatic sites.

Approximately 70% of patients who discontinued the study drug received some form of subsequent therapy. In the vast majority of patients this consisted of chemotherapy, hormone therapy or a combination of both. Interestingly, 10% of patients in the ribociclib arm and 19% of patients enrolled in the placebo arm received a CDK4/6 inhibitor as a subsequent therapy, which may have diluted the OS effect.

Another clinically relevant study endpoint in patients with premenopausal advanced breast cancer consists of the time to the first subsequent line of chemotherapy (i.e. the longer you can spare patients from receiving chemotherapy, the better). Also with respect to this study objective ribociclib + ET outperformed placebo + ET. While the median for this endpoint was not reached for the CDK4/6 arm this was reported at 36.9 months for placebo + ET. This corresponds to statistically significant 40% risk reduction (HR[95%CI]:

0.596[0.459-0.774]). At 42 months, 65.8% of patients in the ribociclib + ET were still free of chemotherapy, while this was only the case for 49% of patients in the placebo + ET arm. Finally, ribociclib + ET was also associated with a significantly longer time from randomization to progression on the next line of therapy (PFS2) (median not reached vs. 32.3 months; HR[95%CI]: 0.692[0.548-0.875]).

With respect to safety it is important to underline that the treatment duration was approximately 2 years in the ribociclib arm as compared to 1 year in the placebo arm. After the additional 15 months of follow up in this analysis, the safety profile remained consistent with previous reports. Grade 3/4 adverse events of special interest in the ribociclib and placebo arm were neutropenia (63.5% vs. 4.5%), hepatobiliary toxicity (11% vs. 6.8%) and a prolonged QT interval (1.8% vs. 1.2%).

CONCLUSIONS

MONALEESA-7 is the only study to date to exclusively evaluate a CDK4/6 inhibitor in premenopausal women. In addition to the previously reported PFS benefit seen with the ribociclib-ET combination, this updated analysis also demonstrates a significant improvement in OS for women treated with the CDK4/6 inhibitor combination. Moreover, the benefit of ribociclib was shown to extend beyond the initial treatment, reflected by a significant delay in the time to first chemotherapy and in the PFS2.

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Highlights in squamous cell carcinoma of the head and neck

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ASCO 2019 hosted several important presentations on Squamous Cell Carcinoma of the Head and Neck (HNSCC). Data on early stage and locally advanced HNSCC as well as recurrent/metastatic HNSCC were discussed.

EARLY STAGE AND LOCALLY ADVANCED HNSCC

Radiation therapy (RT) has historically been the standard treatment for oropharyngeal squamous cell carcinoma (OPSCC), but transoral robotic surgery (TORS) has surpassed radiotherapy in the United States as the most common approach. Thus far, no randomized trials had previously compared these treatments. In the ORATOR phase II trial, 68 patients with T1-T2 N0-2 (≤ 4 cm) OPSCC amenable to TORS were randomly assigned to either radiotherapy (RT) (with chemotherapy if N1-N2) or TORS \pm adjuvant (chemo) radiation based on pathology.¹ The primary endpoint was a definitive comparison of swallowing quality of life (QoL) at 1-year using the MD Anderson Dysphagia Inventory (MDADI), powered to detect a 10-point improvement (a clinically-meaningful change [CMC]) in the TORS arm. MDADI scores at 1-year were statistically superior in the RT arm (mean \pm SD: 86.9 ± 11.4 vs. 80.1 ± 13.0 in the TORS arm; $p = 0.042$), but not meeting the definition of a CMC. For the other QoL metrics, outcomes were similar at 1-year. Feeding tube rates at 1-year were 3% ($N = 1$) vs. 0% respectively. Rates of treatment-related grade ≥ 2 adverse events (AEs) were similar (91% vs. 100%, $p = 0.24$), with more neutropenia, constipation and tinnitus in the RT arm and more trismus in the TORS arm (all $p < 0.05$). There was one TORS bleeding-related death. After a median follow-up of 27 months, overall survival (OS) and progression-free survival (PFS) were similar.

Hasegawa conducted a study to evaluate the non-inferiority of survival, the superiority of postoperative disability, and the complication of the neck in neck dissections based on sentinel lymph node navigation in early oral cancer patients, compared with standard selective neck dissections (NDs).² Eligible were previously untreated patients with squamous cell carcinoma of the oral cavity, either cT1 with clinical invasion depth > 4 mm or cT2, cN0M0 (UICC 7th edition). Patients ($N = 271$) were randomly assigned (1:1) to receive either sentinel lymph node biopsy (SNB) or ND. The primary endpoint was 3-year OS with a non-inferiority margin of 12%. Sentinel nodes were detected using radioisotope method and examined with multi-slice frozen section analysis intraoperatively and hematoxylin eosin (HE) and cytokeratin stain for a final postoperative diagnosis. Patients with positive SNs had ND in a one-stage or back up procedure. Pathological positive nodal status was 34% in the SNB group and 26% in the ND group (Chi-Square $p = 0.10$). 3-year OS in the SNB group was 89% (95%CI: 82-93%), which was non-inferior to that in the ND group (86%; 95%CI: 79-91%). Three-year relapse-free survival (RFS) was 80% (95%CI: 72-86%) in the SNB group and 81% (95%CI: 73-87%) in the ND group. Five-arm abduction test in the SNB group was significantly less impacted one and three months after surgery. The Arbeitsgemeinschaft medikamentöse Tumorthérapie (AGMT) randomly assigned 100 patients with locally advanced (LA) or unresectable stage III or IV HNSCC to stan-

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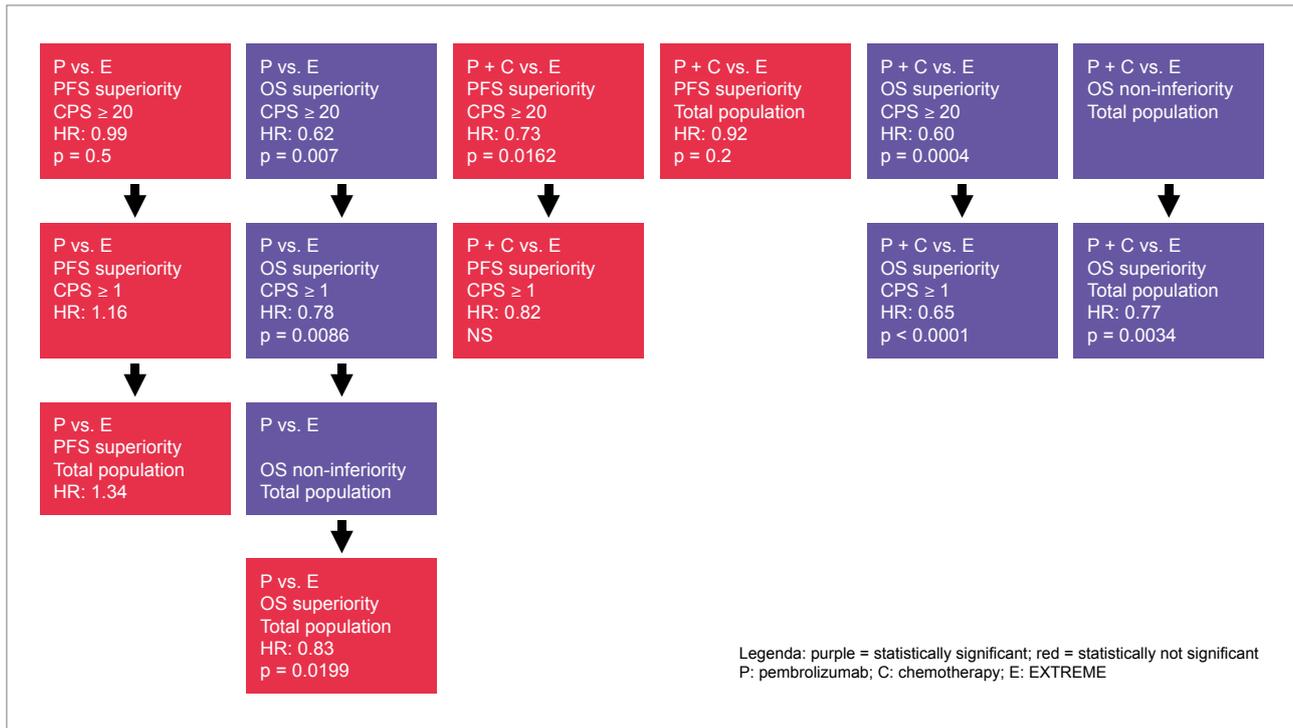


FIGURE 1. Statistical considerations and main efficacy results from the phase III Keynote-048 trial.

dard TPF (arm A) or TPC (arm B), in which 5-fluorouracil was replaced by cetuximab, both followed by radiotherapy plus cetuximab.³ The overall response rate (ORR) 3 months after radiotherapy plus cetuximab (primary endpoint) was 86.4% with TPC and 77.4 % with TPF. Overall survival and PFS were similar in both arms. TPF was associated with more hematologic toxicities whereas local toxicities were more common with TPC.

PIK3CA is the most frequently mutated gene in HPV-associated OPSCC, with a prevalence of 20-30%. PIK3CA mutation was associated with worse disease-free survival (DFS) in a prospective cohort of 78 newly diagnosed HPV-associated OPSCC patients treated with definitive chemoradiation.⁴

RECURRENT/METASTATIC HNSCC

Rischin *et al.* presented the protocol-specified final analysis of KEYNOTE-048.⁵ KEYNOTE-048 is a phase III study of pembrolizumab or pembrolizumab plus chemotherapy vs. chemotherapy as first-line treatment for recurrent/metastatic (R/M) HNSCC. Patients (N = 882) were randomized to pembrolizumab 200 mg every 3 weeks (Q3W) for up to 24 months (N = 301), pembrolizumab 200 mg Q3W for up to 24 months plus 6 cycles of cisplatin 100 mg/m² or carboplatin at an area under the curve (AUC) of 5 mg/mL*min followed by 5-FU 1000 mg/m²/day for 5 days Q3W (N = 281), or weekly cetuximab plus 6 cycles cisplatin 100 mg/m² or carboplatin at an AUC of 5 mg/mL*min followed by 5-FU

1000 mg/m²/day for 5 days Q3W (EXTREME) (N = 300). The trial had a complex statistical design with multiple primary endpoints: OS and PFS in the combined positive score (CPS) (number of PD-L1 positive cells [tumor cells, lymphocytes, macrophages] divided by total number of tumor cells x 100 > 20, CPS ≥ 1, and total populations). The statistical considerations are summarized in Figure 1. The hypotheses in the top row were tested first and in parallel. The remaining hypotheses were tested only when the hypothesis immediately above was positive. Overall survival (OS) superiority was tested sequentially for pembrolizumab plus chemotherapy vs. EXTREME in the CPS ≥ 20 population, then the CPS ≥ 1 population, and for pembrolizumab vs. EXTREME in the total population (superiority thresholds: one-sided p = 0.0023, 0.0026, and 0.0059, respectively). Efficacy results are summarized in figure 1 and table 1. Pembrolizumab plus chemotherapy significantly improved OS vs. EXTREME in the CPS ≥ 20, CPS ≥ 1, and total population, with comparable safety. Unfortunately, data on the CPS < 1 and CPS ≥ 1 < 20 populations (14.6 % of patients) are not presented separately. The hazard ratio for OS increases with decreasing CPS (Figure 2 and Table 1). Pembrolizumab had superior OS in the CPS ≥ 20 and ≥ 1 populations, and non-inferior OS in the total population, with a favourable safety profile. The risk of progressive disease is higher with pembrolizumab vs. EXTREME in all subgroups. In none of the subgroups did pembrolizumab or pembrolizumab plus chemotherapy show a benefit in PFS.

TABLE 1. Overview of efficacy results in the Keynote-048 trial.⁵

		P vs. EXTREME		P + C vs. EXTREME	
CPS ≥20	N (%)	133 (44.2%)	122 (40.2%)	126 (44.8%)	110 (39.6%)
OS	Median (mos)	14.9	10.7	14.7	11
	HR(95%CI), p-value	0.62 (0.45-0.83), 0.00007		0.6 (0.45-0.82), 0.0004	
	24-month rate	38.3%	22.1%	35.4%	8.0%
PFS	Median (mos)	3.4	5.0	5.8	5.2
	HR(95%CI), p-value	0.99 (0.75-1.29), 0.5		0.73 (0.55-0.97), 0.0162	
ORR		23.3%	36.1%	42.9%	38.2%
	CR	7.5%	3.3%	9.5%	3.6%
	PD	31.6%	10.7%	15.1%	8.2%
CPS ≥1	N (%)	257 (85.5%)	255 (85.0%)	242 (86.1%)	235 (84.5%)
OS	Median (mos)	12.3	10.3	13.6	10.4
	HR(95%CI), p-value	0.78 (0.64-0.96), 0.0086		0.65 (0.53-0.80), < 0.0001	
	24-month rate	30.2%	18.6%	25.6%	6.5%
PFS	Median (mos)	3.4	5.0	5.0	5.0
	HR(95%CI), p-value	0.99 (0.75-1.29), 0.5		0.82 (0.67-1.00)	
ORR		19.1%	34.9%	36.4%	35.7%
	CR	5.4%	2.7%	6.6%	3.0%
	PD	38.9%	13.3%	17.4%	12.3%
CPS ≥1<20	N (%)	124 (41.2%)	133 (44.3%)	116 (41.3%)	125 (45.0%)
ORR		14.5%	33.8%	29.3%	15.5%
	CR	3.2%	2.3%		
	PD	46.8%	15.8%		
CPS <1	N (%)	44 (14.6%)	45 (15.0%)	39 (13.9%)	43 (15.5%)
ORR		4.5%	15.0%		
	CR	0.0%	2.2%		
	PD	50.0%	6.7%		
Total population	N (%)	301	300	281	278
OS	Median (mos)	11.5	10.7	13.0	10.7
	HR(95%CI), p-value	0.83 (0.70-0.99), 0.0199		0.72 (0.60-0.87), 0.0034	
	24-month rate	27.0%	18.8%	29.4%	18.8%
PFS	Median (mos)	2.3	5.2	4.9	5.1
	HR(95%CI), p-value	1.34 (1.13-1.59)		0.92 (0.77-1.10), 0.2	
ORR		16.9%	36.0%	35.6%	36.3%
	CR	4.7%	2.7%	6.0%	2.9%
	PD	40.5%	12.3%	17.1%	12.2%

P: pembrolizumab; C: chemotherapy; OS: overall survival; PFS: progression-free survival, ORR: overall response rate; CR: complete response; PD: progressive disease; HR: hazard ratio; N: number of patients; CI: confidence interval.

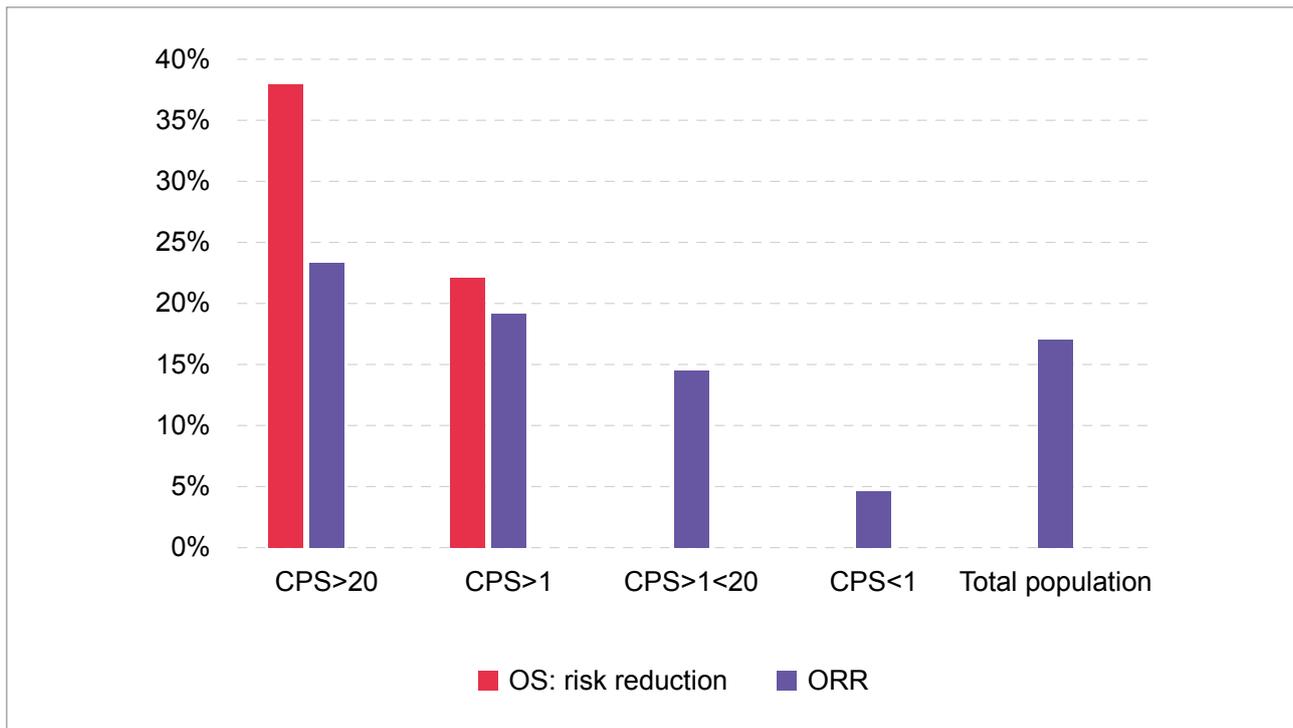


FIGURE 2. OS and ORR by CPS in Keynote-048.⁵

Alfieri *et al.* retrospectively analysed all advanced HNSCC patients treated with immune checkpoint inhibitors (ICI) between October 2014 and December 2018 at the Istituto Nazionale di Tumori in Milan.⁶ Three scans, performed before ICI, at baseline and at first evaluation during ICI, were assessed according to RECIST 1.1. Tumor Growth Kinetics (TGK). Pre- (TGKpre) and post-baseline (TGKpost) were measured as previously reported by Saâda-Bouزيد E. *et al.*⁷ Hyperprogression (HPD) was defined as progression at first radiological evaluation with a TGKpost/TGKpre ≥ 2 . Ninety patients were eligible. Hyperprogression was observed in 7.9% of patients. HPD patients were significantly younger and had a significantly higher median neutrophil-lymphocyte ratio (NLR). Hyperprogression was associated with a significantly worse PFS and correlated with a non-significant trend in lower OS.

Economopoulou *et al.* compared TGK prior and TGK upon immunotherapy in 62 patients with R/M HNSCC treated with PD-1/PD-L1 inhibitors and observed hyperprogression in 25.8% of patients.⁸

GORTEC enrolled 539 R/M HNSCC patients in the phase III TPEx trial. The combination of docetaxel and cisplatin, both at 75 mg/m² every 3 weeks for up to 4 cycles, and cetuximab, with mandatory G-CSF support, followed by maintenance cetuximab 500 mg/m² every 2 weeks (arm B), was compared to the EXTREME regimen for up to 6 cycles, fol-

lowed by weekly cetuximab maintenance at a dose of 250 mg/m² (arm A).⁹ The trial had a power of 88% to detect a HR of 0.72 for OS (median OS increase from 10.1 months to 14.0 months). Overall survival was not significantly different between arms (HR=0.87; 95%CI: 0.71-1.0; p=0.15). Median OS was 13.4 and 14.5 months in arm A and B, respectively. Toxicity was lower in arm B: 34% of the patients had grade ≥ 4 adverse events during chemotherapy in arm B vs. 50% in arm A (p<0.001). The trial suggests that the TPEx regimen might be a new treatment option in first line HNSCC. However, non-inferiority of TPEx vs. EXTREME was not been formally demonstrated as the study was not powered nor designed to demonstrate non-inferiority.

ASCO 2019 meeting also featured several presentations on second line therapy.

EAGLE is a phase III study evaluating efficacy of the anti-PD-L1 monoclonal antibody durvalumab either as monotherapy or in association with the anti-CTLA-4 monoclonal antibody tremelimumab vs. standard of care (SOC) in R/M HNSCC patients who progressed following platinum-based therapy.¹⁰ Two hundred and forty patients were randomized 1:1:1 to durvalumab 10 mg/kg every 2 weeks, durvalumab 10 mg/kg every 4 weeks plus tremelimumab 1 mg/kg every 4 weeks for four doses followed by durvalumab 10 mg/kg every 2 weeks, or SOC (cetuximab, taxane, methotrexate, or fluoropyrimidine-based regimen). The primary endpoint

was OS of durvalumab or durvalumab plus tremelimumab vs. SOC. The study failed to meet its primary endpoint. The risk of death was not statistically different for durvalumab compared with SOC (HR 0.88; 95%CI: 0.72–1.08; $p = 0.20$) or durvalumab plus tremelimumab vs. SOC (HR 1.04; 95%CI: 0.85–1.26; $p = 0.76$).

Other immunotherapy options, such as SD-101, were discussed as well. SD-101 is a synthetic CpG-ODN agonist of TLR9, which stimulates dendritic cells to release IFN- α and mature into antigen presenting cells, activating T cell anti-tumor responses. In an ongoing phase Ib/II trial, Cohen *et al.* treated 28 anti-PD-1/PD-L1 naïve R/M HNSCC patients with pembrolizumab 200 mg Q3W and 2 mg SD-101 intratumorally in 1 - 4 lesions (weekly x 4 doses then Q3W x 7 doses). The combination was well tolerated and showed promising early response data.¹¹

Sacco *et al.* reported an interim futility analysis of cohort 1 of an ongoing phase II trial, combining pembrolizumab 200 mg Q3W and weekly cetuximab in platinum refractory or ineligible patients.¹² The protocol specifications for trial continuation were met with an ORR of 42.8% and a disease control rate of 71.4 %.

In LUX-Head & Neck 1, second-line afatinib significantly improved PFS vs. methotrexate in patients with R/M HNSCC. In LUX-Head & Neck 3 Guo *et al.* randomly assigned 340 Asian patients progressing on or after platinum therapy to receive afatinib 40 mg/day or methotrexate 40 mg/m²/week.¹³ Afatinib significantly improved PFS by independent review (primary endpoint) with a HR of 0.63 (95 %CI: 0.48- 0.82; $p = 0.0005$). Median PFS was 2.9 and 2.6 months, respectively. There was no difference in OS. The overall response rate was 28% with afatinib and 13% with methotrexate.

In a double-blind randomized phase II trial, 125 patients with platinum-resistant, cetuximab-naïve, HPV-unrelated HNSCC were treated with cetuximab plus either palbociclib (arm A) or placebo (arm B).¹⁴ The trial had an 80% power to detect a HR of 0.6 (corresponding to a median OS of 10 months in arm A and 6 months in arm B). The primary endpoint was not met. Median OS was 9.7 (7.3–13.9) months in arm A and 7.8 (6.7–10.6) months in arm B (HR=0.82; 95% CI: 0.54–1.25, $p = 0.18$). Median PFS was 3.9 months in arm A and 4.6 months in arm B (HR = 1.00; 95%CI: 0.7-1.5, $p = 0.5$). Hematologic AEs were more common in arm A.

When looking at salivary gland tumors, ado-trastuzumab emtansine is highly efficacious in patients with HER2 amplified salivary gland cancers as identified by next generation sequencing (NGS). Li *et al.* observed an objective response in 9 out of 10 patients including 5 complete responses after prior trastuzumab, pertuzumab, and anti-androgen therapy.¹⁵ After a median follow up period of 12 months (range 4-20

months), median duration of response (DOR) (range 2-19+) and median PFS (95%CI: 4–22+ months) were not reached. Tchekmedyian *et al.* treated 32 R/M adenoid cystic carcinoma patients with nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks. The trial did not meet its primary endpoint (ORR > 20 %).¹⁶

THYROID CANCER

ASCO 2019 also featured an interesting presentation on thyroid cancer. Anlotinib (AL3818) is a novel multi-target tyrosine kinase inhibitor (TKI), inhibiting tumor angiogenesis and proliferative signalling. Li *et al.* conducted a multicentre, randomized, double-blind, placebo-controlled phase IIB trial enrolling 91 locally advanced or metastatic medullary thyroid carcinoma (A/M MTC) in Chinese patients (ALTER01031).¹⁷ Median PFS (primary endpoint) was 20.7 months (95%CI: 14.0-34.6) in the anlotinib arm vs. 11.1 (95% CI: 5.8-14.3) months in the placebo arm (HR 0.53, $p = 0.0289$). The ORR was 48.4% and 3.45%, respectively ($p < 0.0001$). Anlotinib is the third TKI demonstrating an improved PFS vs. placebo in A/M MTC. In the EXAM trial, median PFS was 11.2 months with cabozantinib versus 4.0 months for placebo (hazard ratio 0.28; 95%CI: 0.19 to 0.40; $p < 0.001$). In the ZETA trial, a significant prolongation was observed for patients receiving vandetanib (HR 0.46; 95%CI: 0.31-0.69; $p < 0.001$). The ZETA and EXAM trial enrolled 331 and 330 patients respectively, as compared to 91 patients in ALTER01031. As for now, it is still unclear whether anlotinib will become available outside China. Cabozantinib is approved by the European Medicines Agency for this indication but not reimbursed by the National Institute for Health and Disabilities Insurance (NIHDI). Vandetanib is reimbursed by the NIHDI.

The combination of durvalumab, tremelimumab and stereotactic body radiotherapy is inactive in metastatic anaplastic thyroid cancer.

NASOPHARYNGEAL CANCER

With respect to nasopharyngeal cancer, the results of two randomized phase III trials conducted in China support the use of induction chemotherapy in patients with LA nasopharyngeal carcinoma (NPC). Ma *et al.* randomly assigned 1:1 480 patients with previously untreated, non-metastatic stage III-IVB (except T3-4N0M0, AJCC 7th) NPC to receive 3 cycles of gemcitabine 1 g/m² on days 1 and 8 and cisplatin 80 mg/m² on day 1 Q3W followed by concurrent intensity modulated RT plus cisplatin 100 mg/m² Q3W for 3 cycles (CCRT) or CCRT alone.¹⁸ The primary endpoint was failure-free survival (FFS). After a median follow-up of 39 months, 3-year FFS was 85.8% in the induction chemotherapy plus CCRT group and 77.2% in the

CCRT alone group (intention-to-treat population HR 0.53, 95%CI: 0.34–0.81; $p = 0.003$).

Chen *et al.* randomly assigned 476 patients with stage III-IVB (except T3N0-1) NPC to receive CCRT (cisplatin 80 mg/m² Q3W) either alone or preceded by two 3-weekly cycles of cisplatin 80 mg/m² on day 1 followed by 5-FU 800 mg/m²/day on day 1-5.¹⁹ After a median follow-up of 82.6 months, the 5-year DFS rate was 73.4% (95%CI: 67.7-79.1) in the group who received induction chemotherapy and 63.1% (95%CI: 56.8-69.4) in the CCRT alone group ($p = 0.005$). Induction chemotherapy was also associated with a significantly higher 5-year distant metastasis-free (DMFS) rate (82.8% [95%CI: 77.9-87.7] vs. 73.1% [95%CI: 67.2-79.0; $p = 0.013$] and 5-year OS (80.8% vs. 76.8%; $p = 0.045$).

Apatinib is a selective inhibitor of the vascular endothelial growth factor receptor-2. Jiang *et al.* treated 33 patients with NPC carcinoma who failed first-line chemotherapy with apatinib 500 mg/day and observed an ORR of 33.6%.²⁰ At a median follow-up time of 14 months, median PFS was 5.0 months (95%CI: 2.3-7.7) and median OS had not been reached. The 1-year OS rate was 83.1%.

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KEYNOTE-048 supports pembrolizumab alone or in combination with chemotherapy as standard first-line therapies for recurrent/metastatic head and neck cancer

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The current standard treatment for patients with recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) consists of platinum-based chemotherapy (5-fluorouracil (5-FU) with cisplatin or carboplatin) plus the EGFR inhibitor cetuximab, also known as the EXTREME regimen. Around 35% of patients respond to this treatment, which leads to a median survival of just over ten months. Immune checkpoint inhibition is already being used in the second-line treatment of R/M HNSCC patients where it was shown to prolong the survival in comparison to chemotherapy.^{1,2} The phase III KEYNOTE-048 study examined whether the anti-PD-1 monoclonal antibody pembrolizumab could also prolong the survival compared to standard treatment in the first-line setting.^{3,4}

STUDY DESIGN AND PREVIOUS RESULTS

KEYNOTE-048 enrolled patients with head and neck cancer who had not received prior chemotherapy or targeted therapy for recurrent or metastatic disease. Patients were randomly allocated in a 1:1:1 ratio to standard treatment with EXTREME (cetuximab 250 mg/m² q1w + carboplatin AUC 5 or cisplatin 100 mg/m² + 5-FU 1000 mg/m²/d for 4 days for 6 cycles, followed by cetuximab 250 mg/m² q1w maintenance), pembrolizumab alone (200 mg q3w for up to 35 cycles); or a novel combination of pembrolizumab and platinum-based chemotherapy (pembrolizumab 200 mg + carboplatin AUC 5 or cisplatin 100 mg/m² + 5-FU 1000 mg/m²/d for 4 days for a total of 6 cycles, followed by pembrolizumab monotherapy 200mg q3w for up to 35 cycles in total).

At the 2018 annual meeting of the European Society for

Medical Oncology (ESMO), results of the protocol-specified second-interim analysis of this trial demonstrated that pembrolizumab resulted in a significantly better OS compared to EXTREME in the subgroup of patients with a PD-L1 combined positivity score (CPS) of ≥ 20 and in patients with a CPS of ≥ 1 . In addition, the safety profile of pembrolizumab was superior to that of EXTREME. The comparison of pembrolizumab + chemotherapy with EXTREME demonstrated a significant OS benefit in the total study population (irrespective of PD-L1 CPS) with a comparable safety profile.³ During ASCO 2019, the final results of the trial were presented.

FINAL KEYNOTE-048 RESULTS

The first comparison in the trial zoomed in on the 281 patients who received the novel combination of pembrolizumab and platinum-based chemotherapy vs. 278 patients who received EXTREME. An update of the OS in the overall population confirmed the previously described OS benefit of the pembrolizumab combination. The median OS was 13.0 months with pembrolizumab + chemotherapy as compared to 10.7 months with EXTREME resulting in an updated HR of 0.72 (95%CI: 0.60-0.87). At 36 months, this translates into a survival rate of 22.6% with pembrolizumab + chemotherapy compared to only 10% with EXTREME.

This OS benefit was even more pronounced when looking at patients with a PD-L1 CPS of ≥ 20 (median OS: 14.7 vs. 11.0 months; HR[95%CI]: 0.60[0.45-0.82]; $p < 0.0004$). In this subgroup of patients, 33.2% of patients was still alive at 36 months when they received pembrolizumab + chemotherapy as compared to 8% with EXTREME. Also the progres-

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TABLE 1. Final OS data of the phase III Keynote-048 study.⁴

Population	HR (95%CI)	24-months OS	36-months OS
Pembrolizumab monotherapy vs. EXTREME			
PD-L1 CPS ≥ 20	0.58 (0.44-0.78)	35.3% vs. 19.1%	29.3% vs. 9.2%
PD-L1 CPS ≥ 1	0.74 (0.61-0.90)	28.9% vs. 17.4%	22.1% vs. 8.0%
Total	0.83 (0.70-0.99); p= 0.0199	29.0% vs. 18.8%	19.7% vs. 10.0%
Pembrolizumab + chemotherapy vs. EXTREME			
PD-L1 CPS ≥ 20	0.60 (0.45-0.82), p= 0.0004	35.4% vs. 19.4%	33.2% vs. 8.0%
PD-L1 CPS ≥ 1	0.65 (0.53-0.80), p< 0.0001	30.8% vs. 16.8%	25.6% vs. 6.5%
Total	0.72 (0.60-0.87)	29.4% vs. 18.8%	22.6% vs. 10.0%

sion-free survival (PFS) proved to be significantly better with pembrolizumab + chemotherapy vs. EXTREME in these CPS ≥ 20 patients (median PFS: 5.8 vs. 5.2 months; HR[95%CI]: 0.73[0.55-0.97]; p= 0.0162). At two years, this translated into an absolute benefit in PFS rate of 11.4% (14.7% vs. 3.3%). In patients with a CPS ≥ 1 , the median PFS was identical with both treatments (5.0 months), but the two-year PFS rate was substantially better for pembrolizumab + chemotherapy than with EXTREME (11.1 vs. 4.0%; HR[95%CI]: 0.82[0.67-1.00]). Finally, the responses seen with the pembrolizumab-combination were also more durable than what was seen with EXTREME, both in CPS ≥ 20 (median duration of response [DoR]: 7.1 vs. 4.2 months) and CPS ≥ 1 patients (DoR: 6.7 vs. 4.3 months).⁴

The final analysis of the pembrolizumab vs. EXTREME comparison revealed that pembrolizumab was non-inferior to EXTREME in terms of OS (median OS: 11.5 vs. 10.0 months; HR[95%CI]: 0.83[0.70-0.99]; p= 0.0199; not superior given the superiority threshold of p= 0.0059). At three years, almost twice as much patients in the pembrolizumab arm were alive than in the EXTREME arm (19.7% vs. 10.0%). With respect to PFS, there seemed to be a detrimental effect of using pembrolizumab vs. EXTREME with a median PFS of 2.3 and 5.2 months, respectively (HR[95%CI]: 1.34[1.13-1.59]). This was mainly the result of a difference in early progression in favour of EXTREME. However, at about 10 months the PFS curves cross and at 24 months, the PFS rate of 9.5% with pembrolizumab is higher than the 6.1% seen with EXTREME. The objective response rate with pembrolizumab (16.9%) was lower than what was seen with EXTREME (36%), but the responses obtained with the immune checkpoint inhibitor were found to be much more durable than the responses to EXTREME with a median DoR of 22.6 and 4.5 months, respectively.

Updated results in the subgroup of patients with a CPS ≥ 20 and ≥ 1 confirmed the results reported at ESMO 2018. In the CPS ≥ 20 subgroup, pembrolizumab was associated with a significant 42% reduction in the risk of death compared to EXTREME (median OS: 14.8 vs. 10.7 months; HR[95%CI]: 0.58[0.44-0.78]), translating into a 3-year OS rate of 29.3% for pembrolizumab and 9.2% for EXTREME. In CPS ≥ 1 patients the HR for OS was slightly less pronounced (median OS: 12.3 vs. 10.3 months; HR[95%CI]: 0.70[0.61-0.90]), but at three years this still corresponded to an absolute benefit of OS rate of 14.1% (22.1% vs. 8.0%).⁴

A complete overview of the final OS results of KEYNOTE-048 is depicted in *Table 1*.⁴

CONCLUSIONS

Overall, KEYNOTE-048 showed that compared with EXTREME, pembrolizumab + chemotherapy is associated with a superior OS in patients with a PD-L1 CPS ≥ 20 , a CPS ≥ 1 and in the total population with a comparable safety profile. In addition, pembrolizumab-treated patients had a superior OS compared to EXTREME if they had a CPS ≥ 20 or ≥ 1 , with a non-inferior OS in the total population. Moreover, the safety profile of pembrolizumab was more favourable than that of EXTREME. These results support pembrolizumab and pembrolizumab + platinum + 5-FU as new first-line standards of care for patients with R/M HNSCC.⁴

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Highlights in respiratory oncology

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In this article, the ten key messages with respect to thoracic oncology presented at ASCO 2019, are summarized.

EARLY STAGE NSCLC: ADJUVANT CHEMOTHERAPY

Current ESMO guidelines recommend adjuvant chemotherapy with a two-drug combination with cisplatin in resected stage II and IIIA NSCLC. The cisplatin-pemetrexed (cis-pem) regimen – superior in stage IV non-squamous NSCLC – until now had only been studied in the adjuvant phase II randomized TREAT trial where it was better tolerated and achieved better dose delivery.¹

In a phase III randomized controlled trial (RCT) cisplatin-pemetrexed versus cisplatin-vinorelbine is compared in resected stage II-IIIa non-squamous NSCLC (JIPANG study, UMIN000006737).² With 784 patients in the efficacy analysis and a median follow-up of 45 months, median relapse-free survival was similar: 38.9 months for cis-pem and 37.3 months for cis-vino (hazard ratio (HR) 0.98, $p=0.948$) (Figure 1). Overall survival (OS) rates at 3 years were comparable: 83.5% vs. 87.2%. Cis-pem was better tolerated (e.g. grade 3-4 febrile neutropenia 0.3% vs. 11.6%, $p<0.001$), and more patients could complete treatment with cis-pem (87.9% vs. 72.7%, $p<0.001$). This trial thus confirms the TREAT findings and adds phase III data, showing that the efficacy of cis-pem is similar to cis-vino. Therefore, cis-pem can also be considered as a possible regimen for non-squamous tumors. Neoadjuvant immunotherapy (IO) in upfront resectable stage I-IIIa NSCLC recently gained a lot of attention based on a feasibility trial in which all resectable patients could proceed to surgery, with a major pathological response (MPR) in 45% of the resection specimens.³ Updates were presented on other trials with neoadjuvant IO. Of caution, in the atezolizumab

trial (LCMC3), 11 out of 101 patients (11%) did not make it to surgery (all stage III), and MPR was seen in 15 out of 90 (17%) resected patients.⁴ In the trial with nivolumab ± ipilimumab (NEOSTAR), 7 out of 44 patients (16%) did not go to surgical resection, and MPR was seen in 24% of the ITT population.⁵

LOCALLY ADVANCED NSCLC: ROLE OF IO

Current ESMO guidelines recommend concurrent chemo-radiotherapy (cCRT) for fit patients with unresectable stage III NSCLC. Not yet added to these guidelines is the substantial benefit in OS when one year of consolidation IO with durvalumab is added in patients without progression after cCRT (PACIFIC trial). In this setting with curative intent, long-term OS benefits are crucial.

Gray *et al.* reported on mature 3-year OS data in the PACIFIC trial.⁶ After a median duration of follow-up of 33.3 months, updated OS curves remain clearly separated: HR 0.69 (95%CI: 0.55-0.86), with 3-year OS rates 57% vs. 43.5%. This long-term clinical benefit with durvalumab following cCRT reinforces the PACIFIC regimen as the standard of care in this population. Ongoing studies are investigating an earlier start of IO during the cCRT phase in unresectable stage III NSCLC. Feasibility of this approach is being revealed, however with a higher incidence of grade ≥ 2 pneumonitis than in PACIFIC.^{7,8}

In resectable stage IIIa (N2 or T4N0), Provencio *et al.* presented the final data of patients who underwent surgical resection in the Spanish phase II NADIM study with neoadjuvant chemo + IO (carboplatin-paclitaxel and nivolumab) 3 cycles, with nivolumab post-surgery for up to one year.⁹ 41 of the

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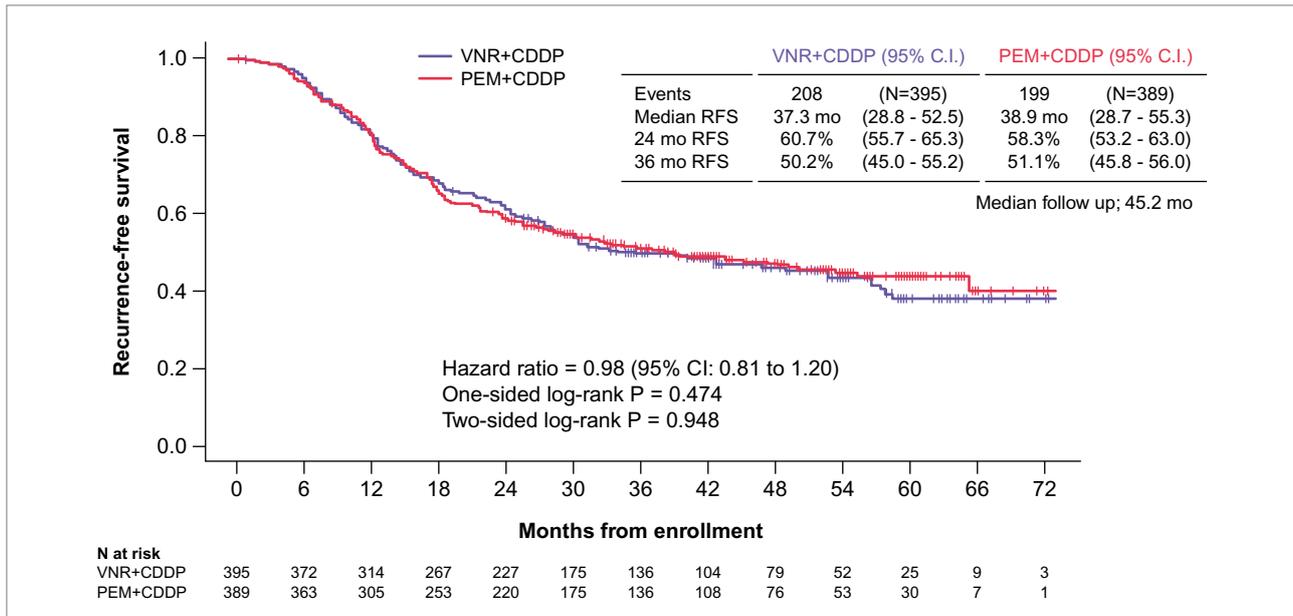


FIGURE 1. Similar RFS with cisplatin-pemetrexed and cisplatin-vinorelbine in resected stage II-IIIa non-squamous NSCLC.²

46 included patients had R0 resection. 34 out of 41 (83%) patients achieved MPR and 58% of the patients had a complete pathologic response. These major and complete pathologic response rates are unprecedented and promising for long-term outcomes. The results also indicate that neoadjuvant chemo + IO is probably a better research strategy than neoadjuvant IO alone, certainly in patients with node positive disease.

ADVANCED NSCLC: EGFR-TKI – ANTI-ANGIOGENIC DRUG COMBINATION FOR EGFR-MUTATED DISEASE

The focus of upcoming treatment strategies for EGFR-mutated advanced NSCLC is on delaying and overcoming resistance to EGFR TKIs. A synergistic role for dual EGFR and tumor angiogenesis blockade has been suggested for a longer time. The recently published interim analysis of the Japanese phase III NEJ026 trial showed a significant improvement in progression-free survival (PFS) with the upfront combination of the first generation EGFR TKI erlotinib and the VEGF-A blocking monoclonal antibody bevacizumab (16.9 months vs. 13.3 months, HR=0.60).¹⁰ Toxicity was substantial in the experimental arm, leading to discontinuation of bevacizumab in 30% of cases. Improvement in OS still has to be confirmed.

A study presented a double-blinded placebo-controlled phase III trial (RELAY, N=449) that evaluated the superiority of “1L erlotinib + ramucirumab vs. 1L erlotinib + placebo” in a mainly Asian population (77%).¹¹ Patients with central nervous system (CNS) involvement were excluded.

The addition of ramucirumab, a monoclonal antibody blocking VEGFR2, significantly prolonged investigator-assessed PFS: 19.4 months vs. 12.4 months (HR 0.59, p<0.0001). This was not driven by a difference in objective response rate (ORR), but by a significantly longer duration of response. As expected, the improved outcome was at the cost of increased toxicity: grade ≥3 AEs in 72% vs. 53%, leading to a discontinuation rate of 33% for ramucirumab. OS data are not yet mature. Incidence of the T790M resistance mutation was similar in both treatment arms (42% vs. 47%), as was the frequency of patients that received second-line osimertinib (28% vs. 30%).

Although the improvement in PFS with the upfront combination of erlotinib and ramucirumab is clinically relevant, erlotinib can no longer be regarded as an appropriate comparator in first-line setting given the FLAURA data.¹² Indeed, the FLAURA trial established the 3rd generation EGFR TKI osimertinib as the current standard of care upfront treatment. Superiority of osimertinib is not only based on the significantly longer PFS compared with 1st generation TKIs (18.9 months vs. 10.2 months, HR=0.46) - an improvement that is actually in the same range as that observed with erlotinib and ramucirumab - but also on the very favorable toxicity profile, good CNS activity and better quality of life (QoL). OS data for upfront osimertinib are now eagerly awaited. Meanwhile, a study reported a phase II trial (N=49) on the safety and efficacy of combining osimertinib and bevacizumab in first-line.¹³ PFS at one year (primary endpoint) was 76%. All patients with measurable CNS disease had a partial response (5/5). Treatment was largely well tolerat-

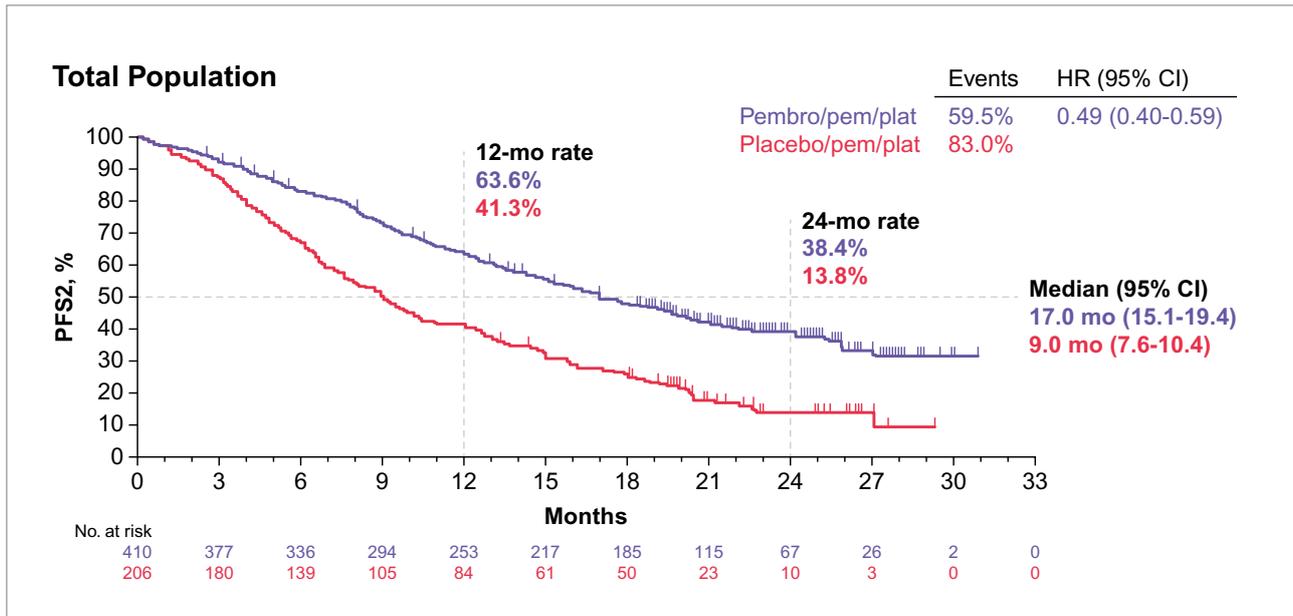


FIGURE 2. Significantly longer PFS on subsequent therapy for patients treated with pembrolizumab-chemotherapy vs. chemotherapy alone in the phase III Keynote-189 trial.²⁹

ed, with toxicity as expected. In total, 18% of patients had to discontinue bevacizumab and 24% needed a dose reduction of osimertinib. A randomized study of osimertinib compared to osimertinib and bevacizumab as initial treatment is planned.

ADVANCED NSCLC: EGFR TKI – CHEMOTHERAPY COMBINATION FOR EGFR-MUTATED DISEASE

All previously published phase III RCTs comparing a 1st/2nd generation EGFR-TKI to chemotherapy could not demonstrate an OS benefit for the TKI, which was attributed to crossover in subsequent treatment line. At ASCO 2018, two phase III trials (NEJ009 and ARCHER1050) demonstrated an OS benefit of the experimental regimen over the 1st generation TKI gefitinib. In particular, the NEJ009 trial showed a clear OS benefit with the upfront combination of gefitinib and chemotherapy vs. gefitinib followed by chemotherapy at progression (52.2 months vs. 38.3 months). An early effect of chemotherapy on ‘TKI tolerant’ cells was hypothesized to drive the OS benefit.

Noronha *et al.* reported on a phase III trial that randomly assigned 350 untreated EGFR-mutant advanced NSCLC patients (including 21% of PS2 patients) to “1L gefitinib in combination with carboplatin-pemetrexed vs. gefitinib alone”.¹⁴ Patients with stable brain metastasis were allowed in the study (17% vs. 19%) and the majority of them received prior whole brain RT (13% vs. 18%). ORRs and depth of response were increased in the combination arm, leading to

a significantly longer investigator-assessed median PFS (16 months vs. 8 months, HR 0.51, $p < 0.0001$). OS was improved (median NR vs. 17 months, HR 0.45, $p < 0.0001$) was confirmed, hereby corroborating the findings of NEJ009. Of note in the current trial is that few patients received second-line therapy: only 24% received platinum-doublet chemotherapy in the gefitinib arm. Eleven % vs. fifteen % of the patients received osimertinib. As expected, toxicity was significantly increased with the combination (grade ≥ 3 AEs in 51% vs. 25%). As mentioned above, osimertinib is now considered as the standard of care first-line treatment in EGFR-mutated advanced NSCLC based on the best mix of PFS improvement, mild toxicity profile, CNS control, QoL and practicality. However, chemotherapy still plays a role in the treatment of EGFR-mutated patients. Currently, platinum-doublet chemotherapy is the standard second-line treatment after osimertinib resistance. Neal *et al.* reported retrospectively on the addition of chemotherapy to osimertinib (used in $\geq 2L$) at osimertinib resistance.¹⁵ The combination appeared tolerable, with need of treatment discontinuation in only 8 % of the patients. Prospective data of this approach are needed to confirm safety and efficacy in front-line setting.

At ESMO 2018 (Ramalingam *et al.*), resistance mechanisms to upfront osimertinib identified in ctDNA of FLAURA patients were presented, including both on-target (e.g. EGFR C797S) and off-target genetic events (e.g. MET amplification).¹⁶ These data are now stimulating the development of more targeted strategies to overcome acquired osimertinib resistance. During ASCO 2019, Oxnard *et al.* introduced the upcom-

ing phase II trial evaluating the combination of osimertinib and savolitinib (MET inhibitor) in *MET*-amplified patients, a combination that resulted in a partial response (PR) of 25% in the prior phase Ib TATTON trial.¹⁷ Very early data (phase I) on two monoclonal antibodies after progression on osimertinib were also presented: a first one revealed a PR of 28% with an EGFR- and cMET-bispecific antibody (JNJ-372)¹⁸, while the second one revealed a PR of 31% with a HER3 antibody drug conjugate (U3-1402).¹⁹ More data on targeted strategies to overcome osimertinib resistance are expected in the near future.

ADVANCED NSCLC: ACTIVITY AND RESISTANCE TO MET TKIS

MET exon 14 (*METex14*) skipping mutations are present in 3-4% of cases with stage IV non-squamous NSCLC and are mutually exclusive with other established driver mutations. Although controversial for quite some time, they by now have been established as primary oncogenes that can effectively be targeted in advanced NSCLC. At the 2018 ESMO meeting, data of the GEOMETRY mono-1 trial showed high response rates to capmatinib, an oral highly selective MET inhibitor.²⁰ Wolf *et al.* now presented results on duration of response (DoR) and PFS, as well as updated results for ORRs of GEOMETRY mono-1 in previously treated (cohort 4, N=69) and untreated (cohort 5b, N=28) patients.²¹ Although immature at the time of data analysis, data on DoR and PFS by an independent review committee (IRC) are promising. In cohort 4, ORR, median DoR, and median PFS were 40.6%, 9.7 months, and 5.4 months respectively. For cohort 5b, this was 67.9%, 11.1 months and 9.7 months.

ORR in both cohorts were confirmed. In the subgroup of patients with brain metastasis at inclusion (N=13), intracranial responses were confirmed by IRC in 54%. The safety profile remained favorable. These data establish capmatinib as a promising treatment option for patients with *MET* exon 14-mutated stage IV NSCLC, for which it was granted Breakthrough Therapy Designation by the FDA.

Paik *et al.* presented an update on the phase II study of tepotinib, another highly selective MET inhibitor (VISION trial).²² In this study, *METex14* skipping mutations could have been identified in a liquid (DNA-based assay) or a tissue biopsy (RNA-based assay). Overall ORR by IRC was 50% in patients with the driver mutation detected in a liquid biopsy (with highest ORRs in first-line setting), and 45.1% in those selected based on a tissue biopsy. Median PFS by IRC was 9.5 months and 10.8 months in the liquid and tissue biopsy group, respectively. No data on intracranial responses were provided. Grade 3 treatment-related adverse events occurred in 19.5% of cases.

The consistently higher ORRs to MET-directed therapy in the first-line setting support the routine testing of *MET* exon 14 skipping mutations at diagnosis. Testing is preferably performed as part of a broader DNA sequencing panel. However, as exemplified by ²², RNA-based approaches are now being assessed to more comprehensively capture *MET* exon 14 skipping events, given the various genomic locations of exon 14 skipping alterations.

Guo *et al.* presented an early report on resistance mechanisms to MET TKIs in *METex14*-mutated disease, mainly (91%) with crizotinib, a non-specific MET inhibitor with ORR of 32%.²³ Primary resistance appeared to correlate with *MET* protein expression: ORR 0% in the absence of *MET* expression vs. 54% with *MET* expression in the tumor. Acquired resistance was analyzed by use of 14 paired pre- and post-treatment biopsies and revealed on-target or off-target resistance mechanisms in 50% of cases. Data on resistance mechanisms to the newer more specific MET TKIs are needed to further guide MET-directed therapy.

ADVANCED NSCLC: KNOWN TARGETS, NEW DRUGS

EGFR exon 20 insertions are present in about 6% of EGFR-mutated advanced NSCLC patients, however, currently approved EGFR TKIs are largely ineffective in these patients. Janne *et al.* presented an update on a phase I/II trial exploring the safety and efficacy of the selective TAK-788 in 28 pretreated patients.²⁴ Overall ORR was 43% and was higher in patients without brain metastasis at baseline: 56% vs. 25%. Median PFS was 7.3 months, and longer in patients with no CNS involvement at baseline (8.1 months vs. 3.7 months). Grade 3 or higher treatment-related AEs occurred in 40% of cases, mainly diarrhea.

In RET fusions, few responses to multikinase inhibitors have been observed. At ASCO 2018, phase I data on the selective RET inhibitor LOXO-292 showed an ORR of 77%.²⁵ This year, Gainor *et al.* discussed a phase II trial with the selective RET inhibitor BLU-667 (ARROW trial).²⁶ Overall ORR was 58%: 71% in treatment-naïve patients and 60% in patients previously treated with platinum-based chemotherapy. Responses were seen regardless of the presence of CNS metastases. The drug was well tolerated with mainly low-grade treatment-related AEs. The FDA granted Breakthrough Therapy Designation to BLUE-667 for RET-driven NSCLC with progression after platinum-based chemotherapy.

KRAS G12C mutations are prevalent in advanced NSCLC, however, not yet effectively targeted by a drug. These mutations are present in 13% of cases and are selectively and irreversibly inhibited by AMG510. Fakih *et al.* reported on the phase I first-in-human study with AMG 510.²⁷ Responses

were promising in 5 out of 10 NSCLC patients that were previously treated with standard therapy. The drug was generally well tolerated with no serious drug-related AEs. The phase II part of the study will soon start enrollment.

For the ROS1 fusions, crizotinib is currently approved for ROS1-mutated NSCLC, with an ORR of 72% and median PFS of 19.3 months. Repotrectinib is developed specifically to overcome the most common resistance mutation G2032R. Cho *et al.* reported preliminary results of the TRIDENT-1 trial with repotrectinib.²⁸ Confirmed ORR was 82% in treatment-naïve patients and 55% in pretreated patients (ORR influenced by the dose). Activity against G2032R was confirmed with an ORR of 40%. Promising CNS activity was present in 100% of untreated patients and 75% of pretreated patients. Overall, the drug was well tolerated. Outcome data, as well as the recommended phase II dose, are awaited.

ADVANCED NSCLC: OUTCOME AFTER COMBINED CHEMO-IO IN FIRST-LINE

KEYNOTE-189 (platinum-pemetrexed plus pembrolizumab) has revolutionized the approach to stage IV non-squamous NSCLC. ASCO 2019 featured updated OS data and the first data on post-study therapy and PFS2 (progression after the Keynote-189 therapy and the next line of therapy).²⁹ With a median follow-up of 18.7 months, OS remained strongly in favor of the triplet: HR 0.56 (95CI: 0.45-0.70, $p < 0.00001$, median 22.0 vs. 10.7 months). Second-line therapy was received by 45% in the chemotherapy/pembrolizumab arm and 59% (54% IO) in the chemotherapy arm. Even with 54% crossover to 2L IO, PFS2 was longer for 1L chemotherapy/pembrolizumab: HR 0.49, 95%CI: 0.40-0.59, $p < 0.00001$; median 17.0 vs. 9.0 months) (Figure 2), and this in all PD-L1 cohorts.

ADVANCED NSCLC: RESPONSE PREDICTION WITH IO

While PD-L1 expression on tumor cells now is universally recognized as an enrichment biomarker of single agent anti-PD-(L)1 IO, further refinement of response prediction is a high need.

In a science symposium, Skoulidis reported on how next-generation sequencing (NGS) may help with the identification of genomic predictors of IO response.³⁰ It has already been reported that STK11/LKB1 gene alterations predict resistance to single agent IO. The new data now reported the findings for response to platinum-pemetrexed + pembrolizumab.

STK11/LKB1 genomic alterations were present in 102 out of 377 patients treated with platinum-pemetrexed + pembrolizumab, and were associated with significantly shorter PFS (median 4.8 vs. 7.2 months, $p = 0.0063$) and OS (medi-

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an 10.6 vs. 16.7 months, $p = 0.0083$). Importantly, this was not only prognostic, but predictive as well: in patients with STK11/LKB1-mutant NSCLC, addition of pembrolizumab to platinum-pemetrexed did not improve PFS or OS (median 4.8 vs. 4.3 months, $p = 0.75$, and median 10.6 vs. 10.3 months, $p = 0.79$, respectively). This information also reinforces the evidence that broad NGS profiling is to be preferred for molecular analysis of NSCLC, rather than single gene PCR tests.

ADVANCED NSCLC: IO IN PATIENTS WITH AUTOIMMUNE DISORDERS

Patients with active autoimmune disorders (AD), or even those with a history of AD, have in general been excluded from clinical trials with IO in lung cancer. Nevertheless, in clinical practice, they are estimated to represent about 13.5% of patients with lung cancer.³¹

Khozin *et al.* presented a retrospective real-world study of IO in NSCLC patients with AD. Among 2425 patients, AD was present in 22% (N=538).³² There was no association between AD status and outcomes: median OS in all patients was 12.4 months (95%CI: 11.3-13.5). Time-to-treatment-discontinuation (3.68 vs. 4.24 months, $p = 0.10$) and OS (11.5 vs. 12.8 months, $p = 0.20$) did not differ between the two cohorts. There was no overall increased incidence of AEs in the AD group, but sub-analysis in patients with active AD showed higher rates of select AEs including endocrine, GI and blood disorders.

SCLC: NEW AGENTS

Over the last decades, the only progress in systemic therapy for metastatic SCLC was the addition of atezolizumab to carboplatin-etoposide, resulting in a (modest) improvement in survival.³³

Paz-Ares *et al.* reported on the relapsed SCLC cohort of a multicenter phase II basket trial with lurbinectedin (N=105).³⁴ Lurbinectedin is a novel anti-cancer drug that inhibits activated transcription and induces DNA double-strand breaks, leading to apoptosis. Response rate was 35%: 21% in platinum-resistant relapse (<90 days), 47% in platinum-sensitive relapse (≥ 90 days). Median duration of response was 5.3 months: 4.7 months in resistant and 6.2 months in sensitive

patients. Median OS was 10.8 months: 5.1 months in resistant and 15.2 months in sensitive relapse. These data are comparable, or even slightly superior, to Topotecan, but with an improved tolerability profile (febrile neutropenia in 3.8%, treatment-related discontinuations in 3.8%). These promising data have been further explored in a phase III trial comparing doxorubicin + lurbinectedin vs. standard second line chemotherapy. Data are awaited.

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Updated results of the TAGS trial reinforce the clinical benefit and safety of TAS-102 in patients with advanced gastric cancer

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In the randomized, double-blind, placebo controlled, phase III TAGS (TAS-102 Gastric Study) study, the efficacy and safety of TAS-102 (trifluridine/tipiracil) was evaluated in 507 adult patients with previously treated metastatic gastric (mGC) or gastro-esophageal junction cancer (mGEJC). In this trial, patients with mGC/mGEJC who were previously treated with ≥ 2 prior chemotherapy regimens were randomized (2:1) to receive best supportive care in combination with TAS-102 (35 mg/m² BID on days 1–5 and 8–12 of each 28-day cycle) or placebo. As reported earlier, the study met its co-primary endpoints by demonstrating a statistically significant improvement in overall (OS) and progression-free survival (PFS) with TAS-102 compared to placebo. The median OS improved from 3.6 months with placebo to 5.7 months with TAS-102 (HR[95%CI]: 0.69[0.56-0.85]; $p=0.00058$).¹ During ASCO 2019, two subgroup analysis of this study were presented with a focus on elderly and GEJC patients, together with an analysis of the quality of life of patients in TAGS.²⁻⁴ In addition to this, a fourth abstract described the outcome of a safety analysis of patients receiving at least one dose of TAS-102 in the TAGS trial and in RECOURSE, a phase III trial that evaluated TAS-102 in patients with metastatic colorectal cancer (mCRC).⁵

TAS-102 IN MGC/MGEJC PATIENTS AGED 65 YEARS OR MORE

Of the 507 patients included in TAGS, 228 (45%) were aged ≥ 65 years (range 65 to 89). Overall, the patient and disease characteristics of these elderly patients were similar to the

overall population, except for a higher incidence of moderate renal impairment in the elderly subgroup (31% vs. 17%). For patients aged ≥ 65 years, baseline characteristics were generally well-balanced across the treatment groups, although more patients treated with TAS-102 had an ECOG performance status of 1 (69% vs. 59% with placebo).² The efficacy benefit of TAS-102 over placebo was similar in patients aged ≥ 65 years than the benefit seen in the overall patient population. The median OS with TAS-102 in this subgroup of patients was 6.2 months as compared to 5.4 months with placebo (HR[95%CI]: 0.73[0.52-1.02]). In addition, the risk of disease progression or death was reduced by 56% with TAS-102 compared to placebo (median PFS: 2.2 vs. 1.8 months; HR[95%CI]: 0.44[0.32-0.61]). The exposure to TAS-102 was similar between patients aged 65 or more and the overall population and also the overall safety profile was similar to what was described for the intent-to-treat population. No drug-related deaths were reported in these elderly patients. Although dose modifications were used more often in this subgroup, there was no increase in treatment discontinuations compared to the overall population.²

SUBGROUP ANALYSIS IN PATIENTS WITH MGEJC

In total, 145 of the 507 patients that were randomized in TAGS had GEJC as the sole primary disease site (TAS-102: 98 of 337; placebo: 47 of 170). Of these patients, 85% were male and 83% were white (overall population, 73% and 70%). Overall, the baseline patient and disease characteristics were

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well balanced across the two treatment groups, although there were fewer patients who underwent a prior gastrectomy (40% vs. 55%) and more patients who received at least 3 prior treatment regimens (74% vs. 66%) in the TAS-102 group compared to placebo. The TAS-102 treatment resulted in clinical benefit over placebo in the subgroup of GEJC patients with a HR for OS of 0.75 (95%CI: 0.50-1.11; median OS: 4.8 vs. 3.5 months) and of 0.60 for PFS (95%CI: 0.41-0.88; median PFS: 1.9 vs. 1.8 months). Interestingly, the ECOG performance status was also maintained longer in TAS-102 treated patients compared to placebo (median time to a deterioration of the ECOG performance status of 2 or more: 3.7 vs. 2.3 months; HR[95%CI]: 0.68[0.46-1.01]).³ The safety profile of TAS-102 in the subgroup of GEJC patients was similar to what was described in the primary analysis of the study, although the percentage of patients discontinuing therapy was lower in the GEJC subgroup than in the overall study population (9% vs. 13%).³

LOWER RATE OF QUALITY OF LIFE DETERIORATION WITH TAS-102

Especially in patients with a limited life expectancy it is important to balance any potential survival benefit of a given therapy against the treatment toxicity and potential effects on the health-related quality of life (HRQoL) of patients. In the TAGS trial, the HRQoL was evaluated using the EORTC QLQ-C30 and the gastric cancer-specific EORTC QLQ-STO22 questionnaires. Patients filled in these questionnaires at baseline, prior to treatment administration on day 1 of each cycle and during the 30-day safety follow-up. The HRQoL remained stable for most functional and symptom scales in both arms, suggesting that the HRQoL was largely maintained under TAS-102. Moreover, there seemed to be a trend towards a lower risk of HRQoL deterioration with TAS-102 compared to placebo across most of the scores. Not surprisingly, the investigators found a significant association between changes in the

HRQoL and the ECOG PS, with patients who maintained their HRQoL being more likely to have a maintenance of their ECOG PS.⁴

POOLED TAS-102 AND RECOURSE DATA INDICATE THAT TAS-102 IS WELL TOLERATED

A final TAS-102 related abstract consisted of a pooled safety analysis of mCRC or mGC/mGEJC cancer who received at least 1 dose of TAS-102 in either RECOURSE or TAGS.⁵ TAS-102 and placebo were given to 335 and 168 patients, respectively in the TAGS trial and to 533 and 265 patients in RECOURSE. In the pooled patient population across both studies, 66% of patients were male, 62% were white and 44% were 65 years or older. Three quarters of patients had received 3 or more systemic treatments. Grade 3-5 adverse events (AEs) were experienced by 80% and 69% of patients in TAGS and RECOURSE, respectively. The most common high-grade hematological AEs were neutropenia (34% and 35%) and anemia (19% and 17%). Other frequent AEs were mainly gastro-intestinal in nature (nausea, vomiting, diarrhea, etc. Grade 3-5 cardiac disorders were rare with TAS-102 at an incidence of 1% in TAGS and <1% in RECOURSE. In both studies, 1 treatment related death on TAS-102 was reported. With respect to AE management, dosing delays (57% and 52% in TAGS and RECOURSE, respectively) were used more frequently than dose reductions (11% and 14% in TAGS and RECOURSE, respectively). The rate of permanent treatment discontinuation due to AEs was low in both TAGS (13%) and RECOURSE (10%).⁵

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Highlights in digestive oncology

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At ASCO 2019, several clinical trials regarding upper and lower gastro-intestinal tumors were presented.

UPPER GASTRO-INTESTINAL TUMORS

After a press release in February 2019, claiming that the POLO pancreatic cancer study was positive, clinicians were eagerly waiting for the presentation of the full data at the plenary session of the ASCO 2019 conference. The randomized phase III POLO trial revealed that maintenance therapy with the poly ADP-ribose polymerase (PARP) inhibitor olaparib significantly delayed the progression of metastatic pancreatic cancer patients with germline BRCA gene mutations compared with placebo (progression-free survival (PFS) 7.4 versus 3.8 months respectively) (Figure 1).¹ It is even though important to keep in mind that only four to seven percent of metastatic pancreatic cancer patients harbor a germline BRCA1 and/or BRCA2 mutation. Moreover, in the POLO trial, olaparib or placebo were administered only in patients not progressing after a minimum of 16 weeks of platinum-based chemotherapy. After 2 years, 22% of patients receiving olaparib had no disease progression, versus 9.6% of patients treated with placebo. The overall survival data of the study are not mature yet. In view of the results of the POLO study, we would advise to discuss testing for cancer susceptibility (including BRCA) with individuals diagnosed with pancreatic cancer, even if family history does not suggest an inheritable cancer related syndrome.

Another important study is the phase III open label, randomized APACT trial evaluating the use of adjuvant nab-paclitaxel plus gemcitabine vs. gemcitabine for surgically resected pancreatic adenocarcinoma.² In contrast with the metastatic setting where the phase III MPACT trial demonstrated a longer overall survival (OS) with nab-paclitaxel plus gemcitabine

versus gemcitabine alone (median OS 8.7 vs. 6.6 months), in the adjuvant setting the primary endpoint of independently assessed disease free survival (DFS) was not met. However, the investigators stated that the median DFS with gemcitabine monotherapy was longer than historical data and that additional OS follow-up may better support nab-paclitaxel plus gemcitabine as an option in the adjuvant setting.

More and more treatment options are available for hepatocellular carcinoma (HCC) such as sorafenib and lenvatinib in first line and regorafenib, cabozantinib and ramucirumab in second-line. Small studies already showed promising results with checkpoint inhibitors in sorafenib pretreated advanced HCC patients and therefore the FDA already granted accelerated approval to nivolumab and pembrolizumab in this setting. At ASCO 2019, the results of the phase III KEYNOTE-240 study with pembrolizumab versus placebo in sorafenib progressing HCC patients were presented (Figure 2). Although pembrolizumab reduced the risk of death by 22% and improved PFS in patients with advanced HCC, significance was not reached per pre-specified statistical criteria.³ Subsequent anticancer therapy in the placebo arm likely impacted the OS results. Overall, these results are consistent with those of KEYNOTE-224, further supporting second line therapy with pembrolizumab in HCC patients. Better predictive biomarkers are even though still needed.

Results with pembrolizumab were also presented from the KEYNOTE-062 study in HER2-negative, PDL1 positive (CPS ≥ 1) metastatic gastric or gastroesophageal junction patients in a first-line setting.⁴ Patients were randomized between pembrolizumab monotherapy, pembrolizumab in

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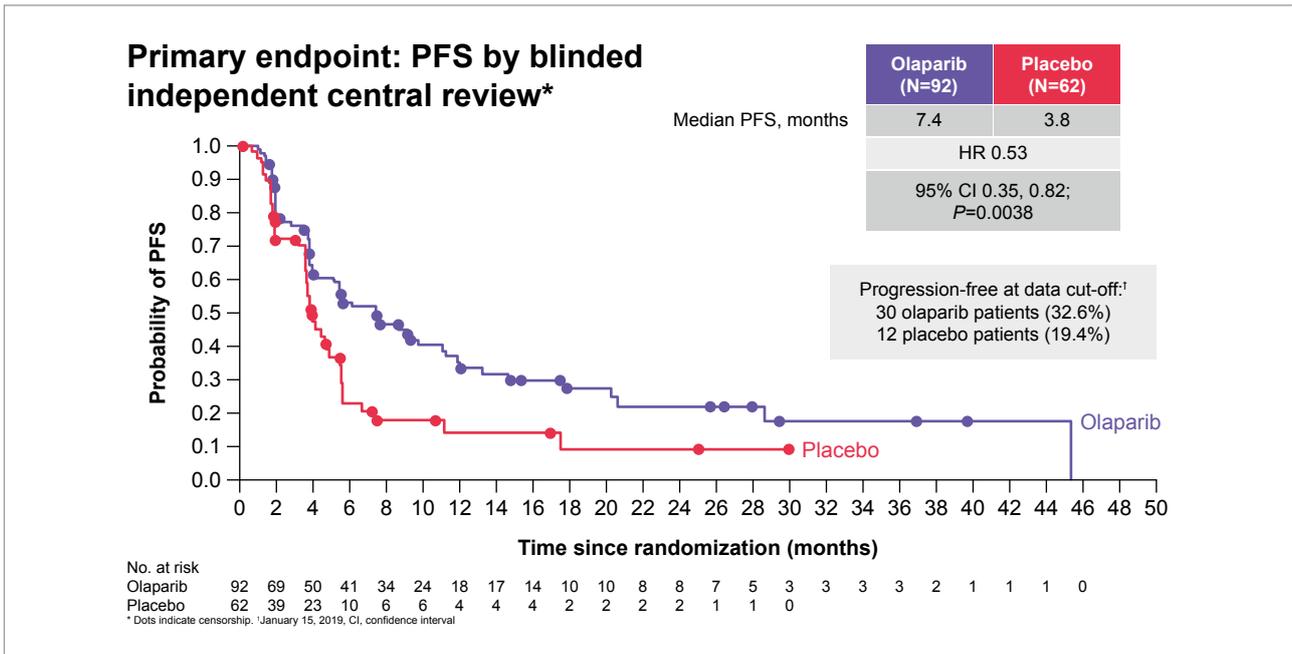


FIGURE 1. Progression free survival in metastatic pancreatic cancer patients with germline BRCA gene mutations.¹

combination with chemotherapy or placebo plus chemotherapy. Pembrolizumab was non-inferior to chemotherapy for overall survival in CPS \geq 1, with clinically meaningful improvement for overall survival in CPS \geq 10. The safety profile was more favorable for pembrolizumab vs. chemotherapy and the combination pembrolizumab and chemotherapy could not show superiority to chemotherapy.

LOWER GASTRO-INTESTINAL TUMORS

In the adjuvant setting of stage III colon cancer, practice changing results have already been presented and published of the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaborative studies, evaluating three versus six months of chemotherapy. Four out of six studies however also included patients with high risk stage

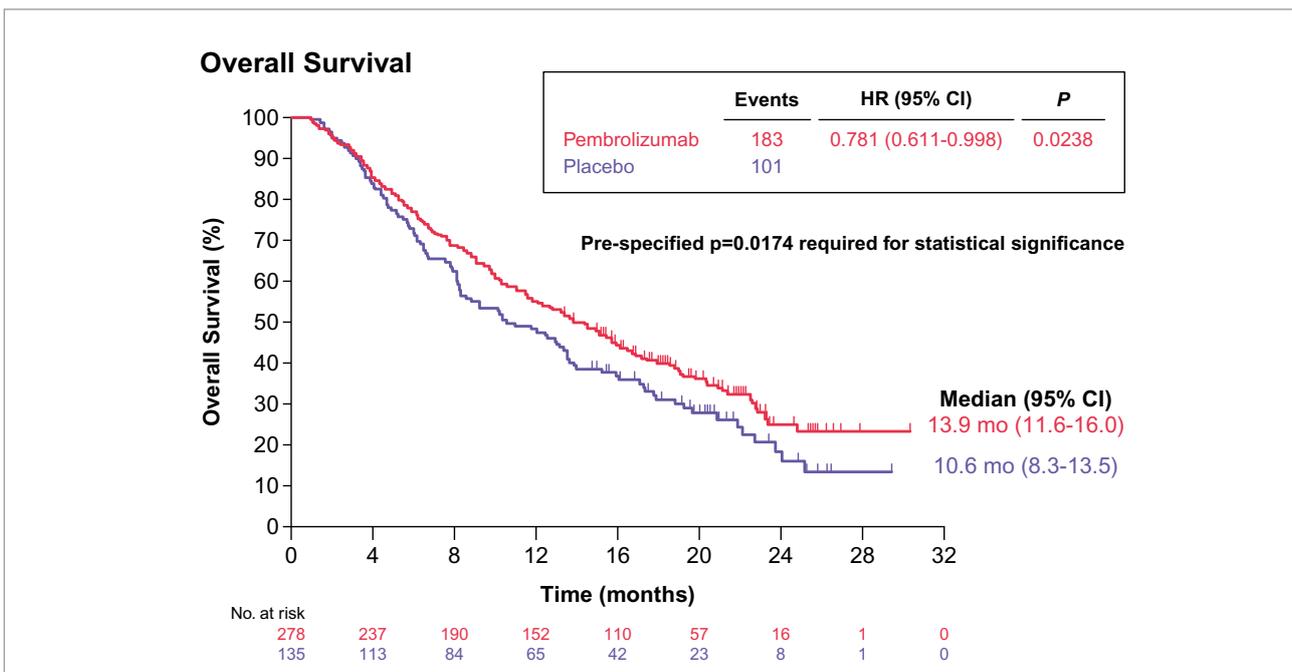


FIGURE 2. Overall survival in the phase III KEYNOTE-240 study with Pembrolizumab vs. placebo in Sorafenib progressing HCC patients.³

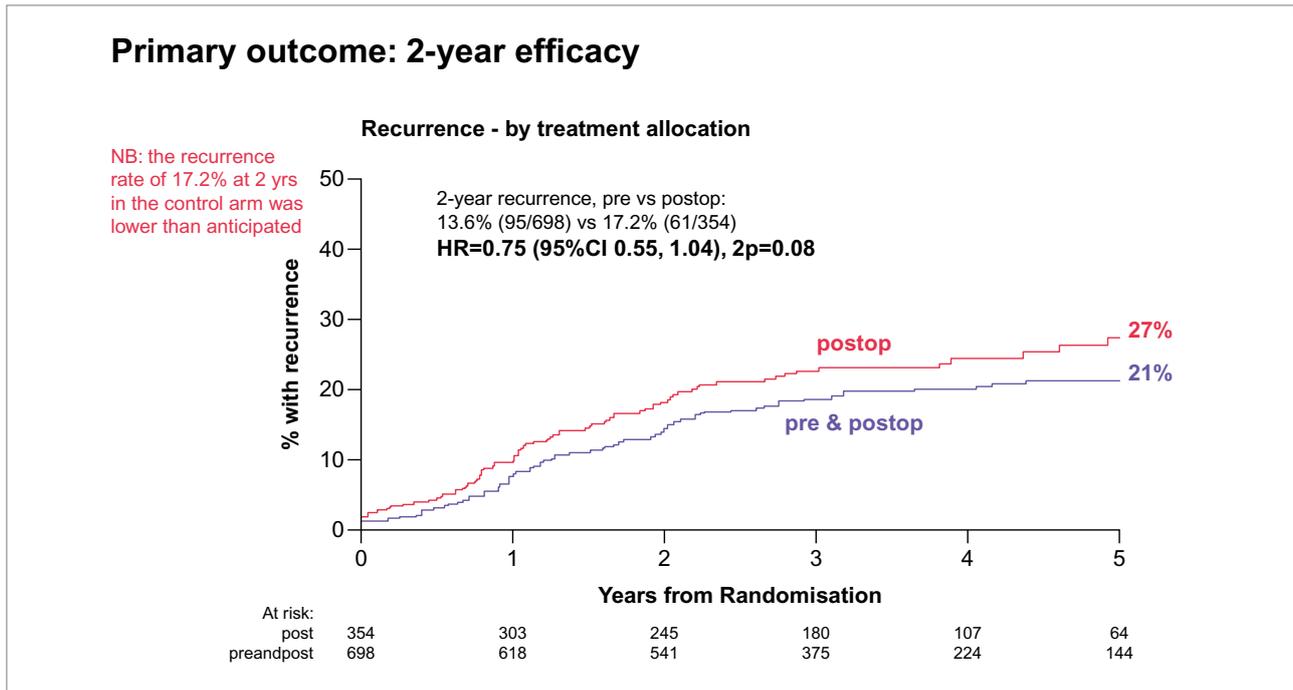


FIGURE 3. Improved two-year efficacy of neo-adjuvant chemotherapy in colon cancer.⁶

II disease of which the pooled results were now presented at ASCO 2019.⁵ In the overall population, non-inferiority for 3 months adjuvant treatment in patients with high-risk stage II colon cancer could not be shown. In line with the stage III population, the results suggest non-inferiority for 3 months CAPOX (vs. 6 months CAPOX), although this was not statistically significant. Data strongly suggest inferiority of 3 months FOLFOX therapy vs. 6 months FOLFOX. However, as 3 months treatment resulted in significantly less toxicity, we can therefore state that three months of CAPOX is certainly a valuable option in high risk stage II colon cancer.

As there were no ground-braking results presented in the metastatic setting of colon cancer at this year's ASCO meeting, we would like to focus on a study in the neo-adjuvant setting of colon cancer, the FOxTROT study.⁶ This is an international randomized controlled trial in 1,052 patients evaluating neo-adjuvant chemotherapy (NAC) with FOLFOX/XELOX for 6 weeks followed by surgery and adjuvant 18 weeks the same regimen versus upfront surgery and postoperative 24 weeks of FOLFOX/XELOX. In conclusion, NAC was well tolerated and safe, with no increase in perioperative morbidity and a trend towards fewer serious postoperative complications. Evidence of histological regression was seen in 59% of patients after NAC, including some pCRs. This resulted in marked histological down staging and a 50% reduction of the rate of incomplete resections. Seymour *et al.* observed an improvement in two-year failure rate (HR=0.75),

but this fell short of statistical significance (p=0.08) (Figure 3). In conclusion, NAC for colon cancer improves surgical outcome but longer follow-up and further trials are required to confirm the long-term benefits, refine its use and optimize case selection.

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Highlights in gynaecological cancers

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The highlights in gynecologic cancers from ASCO 2019 include data on the outcome of chemotherapy or PARP inhibitors as monotherapy or combination therapy in (elderly) patients with ovarian cancer, as well as results of immune checkpoint blockade in patients with advanced or recurrent endometrial cancer with or without a mismatch repair deficiency. Novel findings in (early-stage) cervical cancer include the efficacy and safety of neoadjuvant chemotherapy followed by surgery vs. chemoradiation, and of minimally invasive hysterectomy compared to open radical hysterectomy.

OVARIAN CANCER

ADDITION OF BEVACIZUMAB TO NIRAPARIB IMPROVES PFS IN PATIENTS WITH RECURRENT OVARIAN CANCER

Although platinum-based chemotherapy with or without bevacizumab is a standard treatment for patients with platinum-sensitive, recurrent ovarian cancer (PSROC), it is also considerably toxic. Previously, maintenance therapy with PARP inhibitor niraparib vs. placebo was associated with improved progression-free survival (PFS) in patients with PSROC, and the phase I AVANOVA study demonstrated the safety and activity of niraparib plus bevacizumab in PSROC.^{1,2} Now, the randomized phase II ENGOT-OV24/NSGO-AVANOVA2 study evaluated the outcome of niraparib plus bevacizumab vs. niraparib alone in patients with PSROC, irrespective of the number of previous lines of therapy. Investigator-assessed PFS was the primary endpoint. The results demonstrate that the combined treatment (N=48) significantly improved PFS compared to niraparib alone (N=49): median PFS was 11.9 vs. 5.5 months, respectively (HR 0.35; 95% CI 0,21-0,57; $p < 0,0001$; *Figure 1*).³ The PFS-benefit of niraparib plus bevacizumab was evident in patients with a short (6-12 months; N=37; HR: 0.29) and long (>12 months; N=60; HR: 0.42) chemotherapy-free interval (CFI), in patients with (N=58; HR 0.38) or without

(N= 39; HR: 0.40) a homologous recombination deficiency, as well as in patients with a wild-type (N= 64; HR: 0.32) or mutant (N= 33; HR: 0.49) BRCA status. Objective response rate (ORR) was 60% in the combination arm and 27% in the niraparib only arm; and disease control rate was 79% vs. 53%, respectively.

No major differences in grade ≥ 3 adverse events (AEs) between the two arms were observed, apart from hypertension (grade ≥ 3 : 26.5% in the combination arm vs. 0% in the niraparib arm) and neutropenia (12.2% vs. 2.1%). The percentage of patients with dose reductions was 52% in the niraparib plus bevacizumab arm and 57% in the niraparib only arm and the percentage of patients with treatment discontinuations due to AEs was 13% vs. 10%, respectively. Furthermore, no significant differences were observed with respect to the patients' quality of life (QoL) determined by EORTC QLQ-C30.

Taken together, these results demonstrate that the combination therapy of niraparib plus bevacizumab as compared to niraparib monotherapy significantly improves PFS, regardless of CFI, HRD, or BRCA status. Furthermore, the combination treatment was well tolerated, and did not have a detrimental on the QoL. The phase III NSGO-AVATAR study will compare the niraparib plus bevacizumab vs. the standard of care in patients with PSROC.

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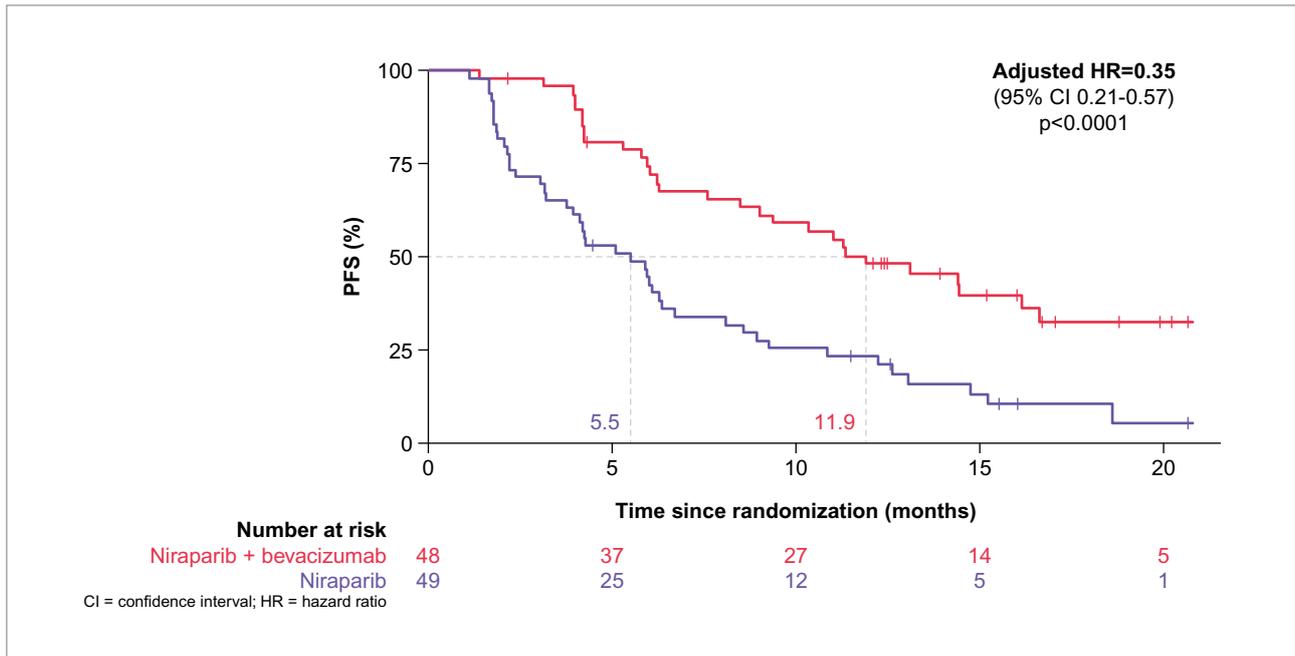


FIGURE 1. PFS in patients with PSROC treated with niraparib with or without bevacizumab.³

BENEFICIAL OUTCOME OF OLAPARIB FOR GERMLINE BRCA-MUTATED ADVANCED OVARIAN CANCER

PARP inhibitor olaparib is approved for the treatment of advanced ovarian cancer in patients with a germline BRCA mutation previously treated with chemotherapy. The confirmatory, phase III, open-label SOLO-3 trial determined the efficacy and safety of olaparib vs. physician’s choice of non-platinum chemotherapy in patients with a germline BRCA mutation and PSROC who had received at least two prior lines of platinum-based chemotherapy. Patients were randomized (2:1) between olaparib and non-platinum chemotherapy, consisting of pegylated liposomal doxorubicin, paclitaxel, gemcitabine and topotecan. The primary endpoint was ORR by blinded independent central review (BICR).

The results show that olaparib (N= 151) as compared to chemotherapy (N= 72) significantly improved ORR by BICR: 72% vs. 51% (OR[95%CI]: 2.53[1.40-4.58]; p= 0.002), including complete response (CR) rates of 9% and 3%, respectively.⁴ The ORR benefit was observed in patients with two prior lines of chemotherapy (OR: 3.44), as well as those treated with at least three lines of chemotherapy (OR: 2.21). In addition, both BICR and investigator-assessed PFS were significantly improved by olaparib vs. chemotherapy (PFS by BICR: HR[95%CI]: 0.62[0.43-0.91]; p= 0.013; PFS by investigator: HR[95%CI]: 0.49[0.35-0.70]; p< 0.001).

Grade ≥3 AEs were seen in 50% of the patients in the olaparib arm and 47% of those in the chemotherapy arm. Although olaparib was associated with a higher rate of serious AEs

(24% vs. 18% in the chemotherapy arm), the rates of dose reductions and treatment discontinuations due to AEs were lower in the olaparib arm than in the chemotherapy arm (reductions: 27% vs. 33%; discontinuations: 7% vs. 20%). No clinically or statistically significant difference in health-related QoL was observed between the two arms. Furthermore, olaparib was associated with four cases of myelodysplastic syndrome or acute myeloid leukemia, vs. three in the chemotherapy arm.⁴

FIRST-LINE CHEMOTHERAPY FOR VULNERABLE OLDER WOMEN WITH OVARIAN CANCER

Three weekly carboplatin-paclitaxel is a standard first-line treatment for women with advanced ovarian cancer. However, even though clinical evidence is largely lacking, older women are frequently treated with other regimens in daily practice. In vulnerable older (>70 years) patients with advanced ovarian cancer, the phase II EWOC-1 study compared the outcome of three frequently used chemotherapy regimens: the standard regimen of 3-weekly carboplatin-paclitaxel (arm A), 3-weekly carboplatin (arm B), and weekly carboplatin-paclitaxel (arm C). Vulnerability was determined by the GINECO Geriatric Vulnerability Score (GVS).⁵ Primary endpoint was the feasibility to complete all six cycles of chemotherapy.

The feasibility analysis demonstrated that chemotherapy was completed in 65%, 47.5% and 60% of patients in arms A-C, respectively.⁶ The occurrence of AEs varied significantly per

Toxicity	Arm A (3wCb-P)		Arm B (3wCb)		Arm C (wCb-P)	
Haematological toxicity (%)	Grade ≥ 3					
Anaemia	10		32.5		7.5	
Thrombocytopenia	5		15		0	
Neutropenia	12.5		20		32.5	
Febrile neutropenia	7.5 (1†)		0		0	
Non-haematological toxicity	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Nausea/vomiting	52.5	5	37.5	2.5	55	0
Constipation	45	0	32.5	0	45	0
Diarrhea	35	7.5	17.5	0	35	2.5
Neuropathy sensory	55	5	7.5	0	32.5	7.5
Total alopecia	32.5	0	2.5	0	15	0
Fatigue	70	10	72.5	7.5	85	10
Pain	42.5	5	47.5	2.5	50	5
General physical health deterioration	2.5	2.5 (1†)	10.0	0	2.5	2.5 (1†)

TABLE 1. AEs in vulnerable older women with advanced ovarian cancer treated with 3-weekly carboplatin-paclitaxel (arm A), 3-weekly carboplatin (arm B), and weekly carboplatin-paclitaxel (arm C).⁶

regimen (Table 1), and treatment was stopped due to toxicity in 20%, 15% and 22.5% of patients in arms A-C, respectively. In the three study arms, treatment was stopped because of lack of efficacy 7.5%, 30% and 5% of patients, respectively. Median PFS was 12.5 months, 4.8 months (HR 2.51; 95% CI 1.56-4.04; $p < 0.001$ vs. arm A) and 8.3 months (HR[95% CI]: 1.41[0.87-2.28]; $p = 0.162$ vs. arm A). Median OS was not reached, 7.4 months (HR[95% CI]: 2.79[1.57-4.96]; $p < 0.001$ vs. arm A) and 17.3 months (HR[95% CI]: 1.6[0.88-2.92]; $p = 0.123$ vs. arm A, non-significant). Carboplatin monotherapy was associated with the worst efficacy in the most vulnerable patients (GVS 4-5). These results indicate that even vulnerable, older patients with advanced ovarian cancer should be offered a carboplatin-paclitaxel regimen.

ENDOMETRIAL CANCER ENCOURAGING RESPONSES ON DURVALUMAB IN MISMATCH REPAIR DEFICIENT PATIENTS WITH ADVANCED OR RECURRENT ENDOMETRIAL CANCER

Almost one fifth of endometrial cancers is associated with mismatch repair deficiency (dMMR) due to acquired hypermethylation, or germline or somatic mutation of MMR-genes. Furthermore, up to 90% of endometrial cancers express PD-L1, and early-phase clinical studies have shown encouraging results with PD-1/PD-L1/2 pathway inhibitors.^{7,8} The non-comparative phase II PHAEDRA trial evaluated the outcome of PD-L1 inhibitor durvalumab in MMR proficient (pMMR; cohort 1; 1-3 prior lines of chemotherapy) and dMMR patients (cohort 2; 0-3 prior lines of chemotherapy) with advanced or recurrent endometrial cancer not eligible for cu-

rative surgery. Primary endpoint was the objective tumor response rate (OTRR) according to iRECIST.

The efficacy analysis demonstrated that the OTRR and disease control rate in pMMR patients (N=35) were 3% and 29%, respectively, while in dMMR patients (N=35) these rates were 43% and 66%, respectively.⁹ In the cohort of dMMR patients the CR rate was 14%, against 0% in the pMMR cohort. Among dMMR patients, OTRR was 52%, 31% and 0% in patients previously treated with 0 (N=21), 1 (N=13) or 2 (only 1 patient) lines of chemotherapy. In both cohorts combined the rate of a grade ≥ 3 AEs was 34%. Common immune-related AEs of all grades included hyperthyroidism (11%), hypothyroidism (10%), pneumonitis (3%) and hepatitis (1%). According to the authors, these results warrant further exploration of immune therapy in the setting of advanced endometrial cancer.

MISMATCH REPAIR DEFICIENCY AND RESPONSE TO AVELUMAB IN PATIENTS WITH ADVANCED OR RECURRENT ENDOMETRIAL CANCER

In a phase II trial quite similar to the PHAEDRA study, the efficacy and safety of PD-L1 inhibitor avelumab was evaluated in patients with advanced or recurrent endometrial cancer. Hereto, a cohort of pMMR patients was selected, as well as one with patients with either dMMR or a mutation in polymerase epsilon (mutPOLE). The co-primary endpoints were PFS of at least six months after initiating therapy (PFS6), and ORR by RECIST 1.1.

The efficacy analysis showed that PFS6 was 6% in the pMMR cohort (N= 16) and 40% in the dMMR/mutPOLE cohort (N=

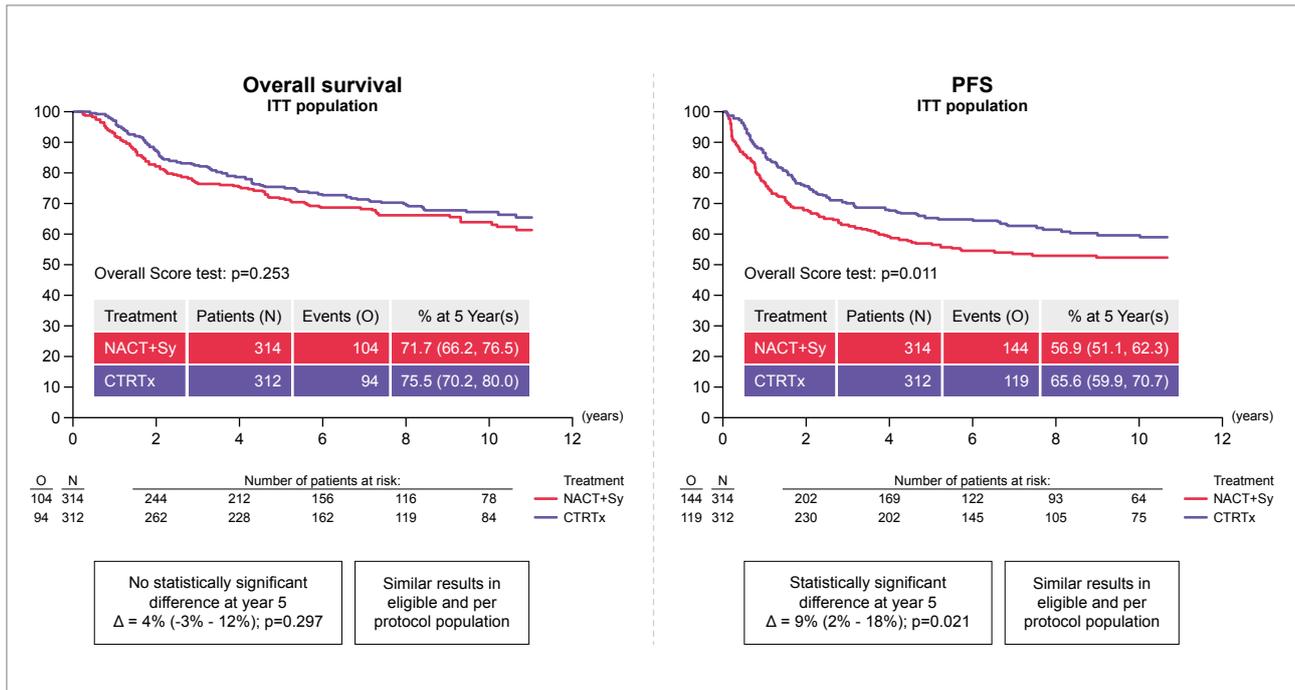


FIGURE 2. 5-year OS and PFS in patients with stage IB2-IIB cervical cancer treated with neoadjuvant chemotherapy followed by surgery, or chemoradiation.¹²

15).¹⁰ In these cohorts ORR was 6% and 26.7%, respectively. Responses in both cohorts occurred irrespective of PD-L1 expression, and in the dMMR/*mut*POLE cohort irrespective of germline or somatic aberrations. Furthermore, tumor mutational burden and the number of tumor-infiltrating lymphocytes did not predict response to avelumab in the dMMR/*mut*POLE cohort. After a median follow-up of 18.6 months, median PFS was 1.9 months in the pMMR cohort and 4.4 months in the dMMR/*mut*POLE cohort. Median OS was 6.6 months and not reached, respectively.

The most common treatment-related AEs of any grade in the two cohorts combined were fatigue (35.5%; 0% grade ≥3), nausea (16.1%; 0% grade ≥3), hypothyroidism (12.9%; 3.2% grade ≥3) and decreased neutrophil count (12.9%; 0% grade ≥3).

What was striking is that immunohistochemistry did not miss any case of dMMR determined by PCR or next generation sequencing (NGS; Oncopanel), but PCR missed one case of dMMR, as determined by IHC and NGS.

An exploratory analysis suggested that mutations in JAK1 and B2M may be involved in *de novo* resistance to avelumab in dMMR patients with advanced endometrial cancer.

Taken together, the results of this study, as well as those of the PHAEDRA study, demonstrate that the PD-L1 inhibitors avelumab and durvalumab, are active in dMMR advanced or recurrent endometrial cancer. Although monotherapy with PD-L1 inhibitors showed low activity in pMMR endo-

metrial cancer, combinations of checkpoint inhibitors with or without targeting agents could be more efficacious in this group: Recently, the interim results of the phase II KEYNOTE-146 trial in advanced endometrial cancer showed that treatment with pembrolizumab plus lenvatinib was associated with significant anti-tumor activity, including an ORR of 40%, and tolerable safety profile.¹¹ This combination therapy was therefore granted an FDA breakthrough designation, and is currently being evaluated in the randomized phase III KEYNOTE-775/ trial.

CERVICAL CANCER NO SURVIVAL DIFFERENCE BETWEEN NEOADJUVANT CHEMOTHERAPY FOLLOWED BY SURGERY VS. CHEMORADIATION FOR EARLY-STAGE CERVICAL CANCER

The value of neoadjuvant chemotherapy followed by surgery compared to chemoradiation for early-stage cervical cancer is unclear. Therefore, the randomized phase III EORTC GCG 55994 study determined the outcome of neoadjuvant cisplatin-based chemotherapy followed by radical hysterectomy vs. concomitant radiation (45-50 Gy plus external boost or brachytherapy) plus cisplatin in patients with FIGO stage IB2-IIB cervical cancer. The primary study endpoint was overall survival (OS) at 5 years. Secondary endpoints included PFS, safety and QoL.

The preliminary results at ASCO 2019, showed that of the

314 patients randomized to neoadjuvant chemotherapy and surgery, 217 patients (69%) completed protocol treatment. On the other hand, 230 of 312 patients (74%) randomized to chemoradiation completed treatment.¹²

Pathological evaluation demonstrated that of the 240 patients who underwent protocol surgery, 23% had a complete response (no microscopic residual disease), 15% an optimal response, and 52% a suboptimal response. AEs of grade 3-4 were observed in 41% of patients treated with neoadjuvant chemotherapy and surgery, and in 23% of patients treated with chemoradiation. The most common grade 3-4 AEs in the neoadjuvant chemotherapy and surgery arm were gastrointestinal AEs (11% vs. 7% in the chemoradiation arm), blood or bone marrow AEs (12% vs. 5%), and infection (8% vs. 3%). The long-term toxicity (Chassagne score grade 3-4) was higher in the chemoradiation arm: 21% vs. 15% in the neoadjuvant chemotherapy and surgery arm.

The efficacy analysis demonstrated that there was a significant difference in 5-year PFS: 56.9% vs. 65.6%, respectively ($p=0.021$; *Figure 2*). 5-year PFS was indifferent in the subgroup of patients who completed treatment. In the intention-to-treat population, there was no statistically significant difference in 5-year OS between the two arms: 71.7% in the neoadjuvant chemotherapy and surgery arm vs. 75.5% in the chemoradiation arm ($p=0.297$; *Figure 2*). A difference in OS was again not observed among patients who completed treatment. Subgroup analysis suggested that chemoradiation was associated with an OS-benefit in older patients (>50 years), those with a low body mass index (<25), and possibly patients with stage IIB disease.

MINIMALLY INVASIVE HYSTERECTOMY COMPARED TO OPEN RADICAL HYSTERECTOMY ASSOCIATED WITH INCREASED RISK OF RECURRENCE IN EARLY-STAGE CERVICAL CANCER

Previous studies demonstrated that minimally invasive radical hysterectomy was associated with lower rates of disease-free survival and shorter OS as compared to open abdominal radical hysterectomy among women with early-stage cervical cancer.^{13,14} However, according to *dr. Shitanshu Uppal (University of Michigan, USA)* these studies did have several limitations, including the preference for laparoscopic surgery to robotic surgery, and the limited availability of detailed pathologic data. Now, a retrospective study evaluated the outcome of minimally invasive radical hysterectomy vs. open abdominal radical hysterectomy in a large cohort of patients with stage IA1/2 or IB1 cervical cancer in high volume centers.

The two groups were fairly well balanced, with the exception of some minor imbalances, including race ($p<0.001$), pre-

operative tumor size ($p=0.017$), and the percentage of unknown tumor grades ($p=0.008$).¹⁵ Patients were treated in eight high volume academic centers, and the majority of cases were treated with robotic surgery. The recurrence rate was 6.9% in the open hysterectomy group ($N=204$) vs. 9.3% in the minimally invasive group ($N=527$; $p=0.18$). Compared to open hysterectomy, minimally invasive hysterectomy was associated with shorter unadjusted recurrence-free survival (RFS; HR[95%CI]: 2.06[1.06-4]). Similar results were found when RFS was adjusted according to preoperative tumor size (HR 4.16 or final pathology tumor size (HR: 3.71). In conclusion, given the data that have repeatedly shown inferiority of minimally invasive hysterectomy over open surgery, the latter option should be preferred.

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