Highlights in breast cancer

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During ESMO 2018 an entire presidential session was dedicated to breast cancer. In addition to exciting immuno-oncology data in the treatment of triple negative breast cancer (TNBC), this session featured the presentation of the overall survival (OS) data of the phase III PALOMA-3 trial, evaluating the alpha-specific PI3K-inhibitor alpelisib in *PI3KCA*-mutant advanced breast cancer, and results of a clinical trial demonstrating improved outcomes when adding a histone deacetylase (HDAC) inhibitor to exemestane in hormone-receptor positive advanced breast cancer. In early breast cancer it was further demonstrated that non-compliance with adjuvant endocrine treatment is an under-appreciated and under-reported problem. In addition, the HOBOE-2 adds to the evidence that adjuvant bisphosphonates also improve the disease-free survival (DFS) in premenopausal luminal breast cancer patients who have received ovarian function suppression combined with an aromatase inhibitor. Finally, a subgroup analysis of the ShortHER trial suggests that for low- and intermediate risk cancer HER2-positive early breast cancer, 9 weeks of trastuzumab might be non-inferior to the standard 1-year treatment duration. However, the interpretation of this trial is challenging and as such, one year of trastuzumab should remain the standard for now.

METASTATIC BREAST CANCER

IMPASSION 130: IMPROVED OUTCOME WITH ADDITION OF ATEZOLIZUMAB TO NAB-PACLITAXEL IN TRIPLE NEGATIVE BREAST CANCER

Unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) is an aggressive breast cancer subtype with poor outcomes. Currently, there are no targeted treatment options for patients with TNBC and guidelines on treatment selection and sequence are scarce. The phase III IMpassion 130 trial, randomly assigned 902 patients with untreated metastatic TNBC (1:1) to receive atezolizumab plus nab-paclitaxel or placebo plus nab-paclitaxel. Patients continued therapy until disease progression or unacceptable toxicity. The two primary endpoints were progression-free (PFS) and overall survival (OS).[1,2] In the intention-to-treat analysis, the median PFS was 7.2 months with atezolizumab plus nab-paclitaxel, which was significantly longer than the 5.5 months median PFS with placebo plus nab-paclitaxel (HR[95%CI]: 0.80[0.69-0.92]; p= 0.002). This PFS benefit was more pronounced in the subgroup of patients with PD-L1-positive tumours where the median PFS was 7.5 months with atezolizumab and nab-paclitaxel as compared to 5.0 months in the control arm (HR[95%CI]: 0.62[0.49-0.78]; p< 0.001) (*Figure 1*). In the intention-to-treat analysis, the median OS was 21.3 months with atezolizumab plus nab-paclitaxel and 17.6 months with placebo plus nab-paclitaxel (HR[95%CI]: 0.84[0.69-1.02; p= 0.08). In patients with PD-L1-positive tumours, the difference in OS was more pronounced (median OS: 25.0 *vs.* 15.5 months, HR[95%CI]: 0.62[0.45-0.86]). The overall response rate was 56% with atezolizumab plus nab-

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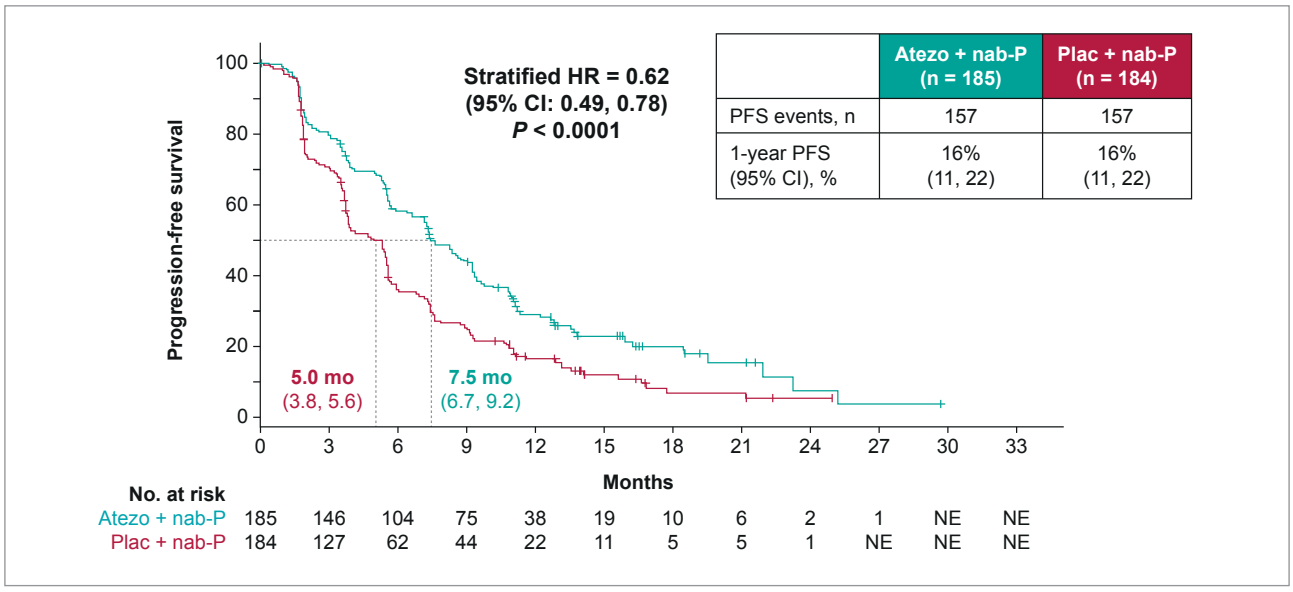


	Atezo + nab-P (n = 185)	Plac + nab-P (n = 184)
PFS events, n	157	157
1-year PFS (95% CI), %	16% (11, 22)	16% (11, 22)

FIGURE 1. Progression-free survival in PD-L1 expressing TNBC patients enrolled in Impassion 130.[1,2]

paclitaxel and 46% with nab-paclitaxel alone (59% *vs.* 43% in the PD-L1 positive subgroup). The incidence of all-cause grade 3/4 adverse events was only slightly raised in the combination arm (49% *vs.* 42%). Adverse events that led to the discontinuation of any agent occurred in 15.9% of the patients who received atezolizumab plus nab-paclitaxel and in 8.2% of those who received placebo plus nab-paclitaxel.[1,2]

This is the first targeted treatment to show a clinical meaningful improvement in OS in metastatic PD-L1 positive TNBC, and also represents the first proof of immune therapy being able to improve outcome in breast cancer. Importantly, the benefit in the intent-to-treat population was mainly driven by the activity in the PD-L1 positive tumours, which represented about 40% of the target population. This study represents a major step forward defining a new optimal regimen in the first-line treatment of metastatic TNBC, but several questions arise: do all triple negative tumours benefit from immune therapy, or can we identify/validate biomarkers (like PD-L1) to better select patients? Is nab-paclitaxel the best chemotherapy partner? How does this compare to platinum, certainly in patients with a *BRCA* mutations or signs of homologous recombination deficiency (HRD)? What is the place of checkpoint inhibitors in TNBC patients with short disease-free interval after primary breast cancer, who are rare in trials but far too common in practice? Are I/O-combinations capable of improving the benefit in the biomarker-negative patients?

PALOMA 3: LONGER OS WITH PALBOCICLIB PLUS FULVESTRANT IN HORMONE-RESISTANT ADVANCED BREAST CANCER

The vast majority of patients with hormone receptor positive (HR+) breast cancer become resistant to hormonal therapies over time and CDK4/6-inhibition can temporarily overcome and delay resistance to endocrine therapy in advanced HR+/HER2- breast cancer. The prospective, randomised phase 3 PALOMA-3 trial previously demonstrated that the CDK4/6 inhibitor palbociclib in combination with fulvestrant significantly improved the PFS in 521 women with HR+/HER2- metastatic breast cancer that had progressed on previous hormonal therapy.[3] During ESMO 2018, Cristofanilli *et al.* presented the OS results of this study. Patients in PALOMA3 had relapsed or progressed on prior endocrine therapy +/- 1 prior chemotherapy regimen for advanced disease before being randomised to palbociclib (125mg/day orally, schedule 3/1) plus fulvestrant (500mg per standard of care) or placebo plus fulvestrant. The presented OS analysis was performed when approximately 60% (N≈310) of the 521 patients in the study had died. The median OS improved by 6.9 months with palbociclib plus fulvestrant compared to placebo plus fulvestrant (median OS 34.9 *vs.* 28.0 months; stratified HR[95%CI]: 0.814[0.644-1.029]; 1-sided p= 0.09).[4,5]Among 410 patients with sensitivity to previous endocrine therapy, the median OS was 39.7 months in the palbociclib-fulvestrant group and 29.7 months with placebo-fulvestrant (HR[95%CI]: 0.72[0.55-0.94]). The median duration of subsequent therapy was similar in the two groups, and the median time to the receipt of chemotherapy was 17.6 months in the palbociclib-fulvestrant group, as compared with 8.8 months in the placebo-fulvestrant group (HR[95%CI]: 0.58[0.47-0.73]; p< 0.001).[4,5]

This study is the first to show that CDK4/6 inhibitors in luminal metastatic breast cancer not only improve the PFS, but that they also achieve a clinically meaningful improvement

in OS in those with sensitivity to prior endocrine treatment. The numerical difference of 6,9 months in OS in the whole study population only showed a statistical trend (p 0.09), but we should acknowledge that OS was a secondary endpoint. As such, the study was not powered for a survival analysis, and the OS analysis was also significantly influenced by post-progression treatments in both arms. Moreover, the survival data presented were originating from the PALOMA-3 population, which included more heavily pre-treated patients than the patients that are currently considered for treatment with CDK4/6-inhibitors (e.g. 35 % of patients received chemotherapy for advanced disease prior to inclusion). From a clinical point of view, survival data of the Phase III trials investigating CDK4/6-inhibitors in first line may have more impact on decision-making. Longer follow-up, and results from other trials with CDK4/6 inhibitors will contribute to confirm the estimate of the OS benefit in this population.

DELAYED DISEASE PROGRESSION WITH ALPELISIB IN PATIENTS WITH *PIK3CA*-MUTATED HR+/HER2- ADVANCED BREAST CANCER

About 40% of patients with HR-positive breast cancer harbour *PIK3CA* mutations, that activate the PI3K pathway leading to cancer progression and resistance to endocrine therapy. Alpelisib (BYL719) is an oral PI3K inhibitor that specifically targets the PI3K alpha isoform, leading to less toxicity than what was seen with pan-PI3K inhibitors. In a previous phase I trial alpelisib showed promising preliminary efficacy and a manageable safety profile in patients with HR+/HER2- metastatic breast cancer.[6]

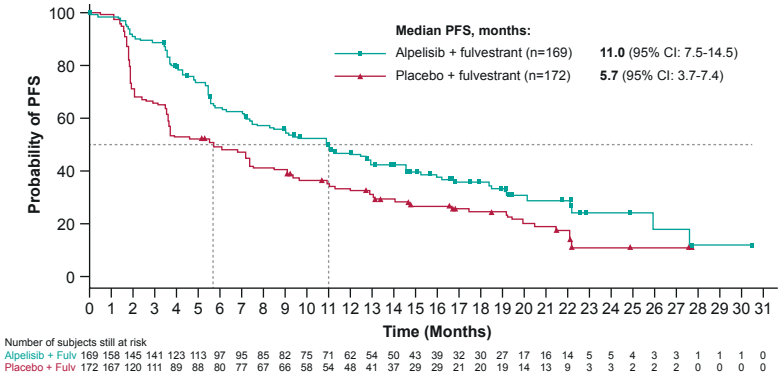
The phase III SOLAR-1 trial randomised 572 postmenopausal women or men with HR+/HER2- advanced breast cancer. The patients had a good Eastern Cooperative Oncology Group performance status (ECOG PS) (≤ 1) and had received one or more prior lines of hormonal therapy but no chemotherapy for advanced breast cancer. They had not previously received fulvestrant or any PI3K, AKT, or mTOR inhibitor, and were not on concurrent anticancer therapy. Patients were randomly assigned to receive oral alpelisib (300 mg/d) or placebo plus intramuscular fulvestrant (500 mg every 28 days and on days 1 and 15 of treatment cycle 1). The primary endpoint of the trial was locally assessed PFS in patients with *PIK3CA* mutations (N= 341). Results showed the PFS was nearly twice as long in patients with *PIK3CA* mutations randomly assigned to receive alpelisib compared to the placebo group. The median PFS was 11.0 months in the alpelisib arm compared to 5.7 months in the placebo group (HR[95%CI]: 0.65[0.50–0.85], p= 0.00065) at a median follow-up of 20.0 months (*Figure 2*). Just over one-third (35.7%) of patients with measurable *PIK3CA*-mutated advanced breast cancer (N= 262) had a RECIST partial response to alpelisib plus fulvestrant, whereas the ORR in the placebo/fulvestrant group was 16% (p= 0.0002). The secondary endpoint of locally assessed PFS in patients without *PIK3CA* mutations did not meet the predefined proof of concept endpoint (median PFS: 7.4 *vs.* 5.6 months; HR[95%CI]: 0.85[0.58–1.25]).[7]

The most frequent side effects with alpelisib were hyperglycaemia (63.7% *vs.* 9.8%); nausea (44.7% *vs.* 22.3%), decreased appetite (35.6% *vs.* 10.5%), and rash (35.6% *vs.* 5.9%). About a quarter of patients on alpelisib had dose discontinuations due to adverse events as compared to approximately 4% in the placebo/fulvestrant arm.[7]

As such, this is the first study in metastatic luminal breast cancer showing that targeted treatment in a genomic subgroup of breast cancer patients can induce clinically significant PFS improvements. The *PIK3CA* mutation is relatively frequent in this population (around 40%) and targeting the alpha isoform of PI3K allows reduced toxicity compared to inhibition of all PI3K isoforms. The major drawback in the interpretation in current practice is that only 6% of the trial population received prior CDK4/6-inhibitors. The efficacy of alpelisib and endocrine therapy after CDK4/6-inhibitors is being evaluated in an ongoing phase III trial (BYLieve, NCT03056755).

POSITIVE PHASE III RESULTS WITH A HISTONE DEACETYLASE (HDAC) INHIBITOR IN PATIENTS WITH HR+ ADVANCED BREAST CANCER

Previous studies demonstrated that_histone deacetylase (HDAC) inhibitors can overcome resistance to endocrine therapy (Munster *et al*, British Journal of Cancer),[8] but no randomised trial so far has demonstrated superiority with an HDAC inhibitor over existing treatments in advanced breast cancer. During ESMO 2018, Jiang *et al.* presented data from a phase III trial evaluating the addition of the HDAC inhibitor chidamide to exemestane in HR+/HER2- advanced breast cancer patients who progressed on previous endocrine therapy (tamoxifen and/or an aromatase inhibitor).[9] In total, 365 postmenopausal women were randomised (2:1) to the combination of chidamide (30mg twice a week) plus exemestane (25mg daily) or placebo plus exemestane. The median PFS was reported at 7.4 months with chidamide plus exemestane and 3.8 months with placebo plus exemestane (HR[95%CI]: 0.755[0.582–0.978]; p= 0.0336). The addition of chidamide also doubled the ORR from 9.1% with placebo/exemestane to 18.4% with chidamide/exemestane (p= 0.0260). Data for OS were not mature at the time of the analysis. Serious adverse events occurred in 51 (20.9%) patients in the chidamide group and in 7 patients (5.8%) on placebo/exemestane. The most common adverse events were haematological and included reduced blood levels of neutrophils



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

• The primary endpoint crossed the prespecified Haybittle-Peto boundary (one-sided p≤0.0199)

FIGURE 2. Progression free survival in *PIK3CA*-mutant patients enrolled in SOLAR-1.[7]

(50.8% *vs.* 2.5%), platelets (27.5% *vs.* 2.5%), and leukocytes (18.8% *vs.* 2.5%). There were no treatment-related deaths in the experimental arm.[9]

This Chinese study is the first phase III trial to demonstrate that a HDAC inhibitor added to endocrine therapy improves PFS in luminal breast tumours who were progressive after prior endocrine therapy. The exact place of this new class of epigenetic therapy remains to be defined.

EARLY BREAST CANCER

SERUM ASSESSMENT OF NON-ADHERENCE TO ADJUVANT ENDOCRINE THERAPY IN PREMENOPAUSAL WOMEN

Adjuvant endocrine therapy is recommended for five to ten years in all patients with HR+ breast cancer, but previous research has shown that many discontinue long-term therapy. Non-adherence to endocrine therapy (i.e. taking less than 80% of prescribed treatment) is a serious problem and can be associated with a higher risk of mortality and a shorter time to breast cancer recurrence. At ESMO 2018, Pistilli *et al.* presented results of a study in which treatment adherence was assessed by measuring serum levels of tamoxifen rather than simply asking patients about how they take their treatment.[10] The study included patients recently diagnosed with early (stage I-III) breast cancer in the CANTO cohort, which is a French prospective study investigating the long-term impact of side-effects with breast cancer treatments in around 12,000 participants. The researchers focused on the sub-group of 1,799 (16%) premenopausal women prescribed adjuvant hormonal therapy, assessing their adherence to tamoxifen by measuring serum levels at one, three and five years and comparing this with patients' self-reports of adherence. Results showed that nearly one in five (16.0%; 188/1,177) of the premenopausal women prescribed tamoxifen were not adequately adherent at one year based on serum assessment of tamoxifen (defined as <60 ng/ml). Just over one in ten (10.7%) were non-adherent, with undetectable levels of tamoxifen. A further 5.3% of patients were poorly adherent, with serum levels of tamoxifen below the steady-state concentration expected after 3 months of treatment. An analysis of patients' self-reports showed that at least 50% of patients with undetectable/low tamoxifen levels did not declare that they were not taking their tamoxifen as prescribed.[10]

ZOLEDRONIC ACID IN PREMENOPAUSAL HR+ EARLY BREAST CANCER

Studies previously demonstrated reduced recurrence and breast cancer mortality with zoledronic acid plus hormonal therapy in HR+ breast cancer in postmenopausal women,[11] but the benefit in premenopausal women was less clear. The phase III HOBOE-2 trial included 1,065 patients with HR+ early breast cancer who had their last menstruation within 1 year of randomization. They were treated with the gonadotrophin-releasing hormone agonist triptorelin (3.75 mg every 4 weeks) for 5 years up to the age of 55 to suppress ovarian function, and nearly two-thirds (63%) received chemotherapy before randomization. Patients were randomly assigned to hormonal therapy with tamoxifen (20 mg/d) or letrozole (2.5 mg/d) or to combination therapy with zoledronic acid (4 mg intravenously every 6 months) plus letrozole (2.5 mg/d) for a planned treatment duration of 5 years. The study was stopped early in May 2018 after a median follow-up of 65 months. There were 32 disease-free survival (DFS) events

KEY MESSAGES FOR CLINICAL PRACTICE

1. IMpassion 130: atezolizumab plus nab-paclitaxel improves OS in metastatic PD-L1 TNBC and represents the first proof of immune therapy being able to improve outcome in breast cancer.
2. SOLAR-1: Delayed disease progression with alpelisib added to fulvestrant in patients with PIK3CA-mutated HR+/HER2- advanced breast cancer.
3. PALOMA-3: first trial to show that CDK4/6 inhibitors in luminal metastatic breast cancer not only improve the PFS, but that they also achieve a clinically meaningful improvement in OS in patients with prior sensitivity to endocrine therapy
4. Phase III data demonstrate that a HDAC inhibitor added to endocrine therapy improves PFS in luminal breast tumours who were progressive after prior endocrine therapy.
5. Non-compliance with adjuvant hormonal treatment is an under-appreciated and under-reported problem.
6. HOBOE-2 suggests that adjuvant bisphosphonates improve DFS in premenopausal luminal breast cancer patients who have received ovarian function suppression combined with an aromatase inhibitor.
7. One year of trastuzumab should remain the standard for now, but a low threshold to stop adjuvant trastuzumab after ending chemotherapy can be adapted in case of (cardiac) side effects and lower risk patients.

in patients treated with zoledronic acid/letrozole, giving a 5-year DFS probability of 0.93. In contrast, there were 58 events in patients treated with tamoxifen and 44 events in the letrozole group, giving 5-year DFS rates of 0.85 and 0.93, respectively (p= 0.008). The risk of breast cancer recurrence or non-cancer death was nearly halved in patients treated with zoledronic acid/letrozole compared to those treated with tamoxifen (HR[95%CI]: 0.52[0.34–0.80], p= 0.003). There was no statistically significant difference in disease-free survival comparing letrozole with tamoxifen (HR[95%CI]: 0.72[0.48–1.07]; p= 0.06) or comparing zoledronic acid/letrozole with letrozole alone (HR[95%CI]: 0.70[0.44–1.12]; p= 0.22). The DFS improvement with zoledronic acid/letrozole compared to tamoxifen was seen in all subgroups of patients apart from the small subgroup of women with tumours overexpressing HER2 who showed a greater benefit with tamoxifen (interaction p= 0.002).[12]

This study adds to the data that adjuvant bisphosphonates also improve DFS in premenopausal luminal breast cancer patients who have received ovarian function suppression combined with an aromatase inhibitor. It has to be mentioned that there was only a statistically significant difference between letrozole + zoledronic acid and tamoxifen arms in the study. The study was underpowered but will contribute to the ongoing meta-analyses by EBCTCG.

SHORT-TERM TRASTUZUMAB FOR SOME PATIENTS WITH HER2+ EARLY BREAST CANCER?

After the recent release of several 'adjuvant trastuzumab duration trials', ShortHER (N=1,254) is yet another large adjuvant study comparing short term (9 weeks) trastuzumab administration to the standard 1-year duration. At 6 years median follow-up, non-inferiority could not be claimed for the short trastuzumab course in this trial (5-year DFS 88% *vs.* 85% for long and short arm, respectively) (HR[90%CI]: 1.13[0.89-1.42]; with the upper limit of CI crossing the non-inferiority margin set at 1.29). During ESMO 2018, results of a subgroup analysis were presented in which researchers looked for subgroups of patients where a shorter course of trastuzumab was non-inferior to the standard longer course. They found that women with low and intermediate risk of relapse (pT < 2cm and any N category) had similar rates of relapse with the short trastuzumab duration. This population includes 89% of the patients and the 5-year DFS rate was not different in the two treatment arms (89% long, 88% short; HR[95%CI]: 1.02[0.78-1.33]). The risk of cardiac events was significantly higher in the long arm compared to the standard 1-year treatment duration (12.8% *vs.* 4.5%; RR[95%CI]: 2.88[1.85-4.47]). The interpretation of these results remains challenging since low-risk patients these days often receive paclitaxel only as

chemotherapy backbone, and short duration of trastuzumab has never been evaluated with this type of chemotherapy. One year of trastuzumab should remain the standard for now, but a low threshold to stop adjuvant trastuzumab after ending chemotherapy can be adapted in case of (cardiac) side effects and lower risk patients.

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