LBA12 PALLAS: A randomized phase III trial of adjuvant palbociclib with endocrine therapy versus endocrine therapy alone for HR+/HER2- early breast cancer

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Background: Palbociclib (P) added to endocrine therapy (ET) improves progression-free survival in hormone receptor positive (HR+)/HER-2 negative (HER2-) metastatic breast cancer. The global PALLAS trial (NCT02513394) was designed to determine if the addition of two years of P to adjuvant ET improves invasive disease-free survival (iDFS) over ET alone in patients (pts) with HR+/HER2- early-stage breast cancer.

Methods: In this phase III open-label trial, pts with stage II-III HR+/HER2- breast cancer were randomized to receive either 2 years of P with adjuvant ET, or ET alone. Eligible pts were within 12 months of diagnosis and 6 months of initiating adjuvant ET. The primary objective was to compare invasive disease-free survival (iDFS) between arms; secondary objectives include other recurrence endpoints and safety, as well as quality of life, adherence, and translational science. The study had 85% power to detect a 25% improvement in iDFS (0.75 hazard ratio [HR]). Interim analyses (IA) were predefined in the protocol; IA2 was triggered when 67% of events were observed.

Results: 5,760 pts (median age 52 years) were randomized and included in the analysis; 1,013 (17.6%) had stage IIA disease and 4,729 (82.1%) stages IIB/III. 4,754 (82.5%) had received prior chemotherapy. At IA2, after a median follow-up of 23.7 months (351 events), iDFS was similar between the two arms, with 3-year iDFS of 88.2% for P and ET, and 88.5% for ET alone (HR 0.93, 95% confidence interval 0.76-1.15), crossing a pre-specified futility boundary. No benefit from P was observed within clinicopathologic subgroups. Grade 3 or 4 neutropenia was more common with P (61.3% vs 0.4%) but febrile neutropenia was uncommon (1.0%). Other all-grade toxicities occurring more often with P included leukopenia, fatigue, thrombocytopenia, anemia, upper respiratory tract infection, and alopecia. 42.2% of pts discontinued P prior to the planned 2 year duration, primarily due to adverse events.

Conclusions: Within the PALLAS trial, at IA2, two years of adjuvant palbociclib with ET did not improve iDFS compared to ET alone. Ongoing long-term follow-up and additional clinical and translational analyses will explore the effect of P in this patient population.

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Legal entity responsible for the study: Alliance Foundation Trials, LLC; Austrian Breast and Colorectal Cancer Study Group (ABCSG).

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LBA13 Tumour infiltrating lymphocytes (TILs), PD-L1 expression and their dynamics in the NeoTRIPaPDL1 trial

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Background: NeoTRIP, randomized 280 pts to 8 cycles of nab-paclitaxel/carbo (CT) or with atezolizumab (CT/A). 260 pts were evaluable for pCR as Per-Protocol Population.

Methods: We collected samples at baseline (n=260/260; 100%), on day 1 cycle 2 (d1c2) (n=228/260; 87.7%], and at surgery (SX) [n=231/260; 88.8%]. We assessed stromal and intratumoral TILs (sTILs, iTILs), and PD-L1 expression (SP142) on immune (IC) and tumor (TC) cells, their dynamics and association with pCR. We also aim to validate sTILs≥40% at d1c2 as predictive of pCR (Bianchini G ASCO 2020).

Results: Baseline PD-L1 IC was balanced (IC0 43.4%; IC1 37.6%; IC2/3 18.5%), but sTILs and iTILs were higher in CT arm (p=0.046, p=0.005). All baseline biomarkers were significantly associated with pCR in CT/A, but only PD-L1 was in CT arm. Considering log PD-L1 IC (to correct skewness) as continuous variable, OR were 3.42 [1.93-6.07] (p=0.00003) and 1.51 [1.04-2.21], (p=0.032) in CT/A and CT, respectively (interaction p=0.02). pCR for CT/A vs CT (and ΔpCR) by PD-L1 IC groups were 87.0% vs 72.0% [Δ15%] (IC2/3), 56.2% vs 44.0% [Δ12.2%] (IC1) and 35.1% vs 41.1% [Δ-6.0%] (IC0). After 1 cycle of treatment (d1c2), tumor cells were not found in 28.8% (CT/A) and 13.6% (CT) (p=0.003), which was predictive of pCR (78.2% vs 42.5%, p<0.0001). TILs increased at d1c2 in both arms (p<0.0001). PD-L1 IC+ did however increase from 45.4% to 74.7% in CT/A (p=0.03) (65.8% change to pos), but decreased from 52.7% to 37.9% in CT (p=0.0001) (44.0% change to neg). In CT/A, also PD-L1 TC+ increased for 2.7% to 36.5%. In both arms, sTILs at d1c2 were more informative than baseline sTILs and ΔTILs, e.g. in CT/A, sTILs≥40% had 71.4% pCR (OR 6.38 [2.24-20.9], p=0.0007). Conversion rate of PD-L1 IC baseline to surgery (SX) was 42.9% (- to + 28.6% and + to − 14.3%) and 30.3% (- to + 9.1% and + to − 21.2%) in CT/A and CT arms, respectively.

Conclusions: Baseline imbalance in sTILs and iTILs might have resulted in smaller differences of pCR between arms. Atezo increased pCR by more than 10% in

"immune-rich" groups (PDL1 IC+, high sTILs/iTILs). PD-L1 dynamic is strong and divergent by arm, with atezo turning most PD-L1 neg to pos. D1c2 assessment provides an early surrogate of pCR, and high rate of tumor absence may suggests that shorter therapy may be enough for some cases.

Clinical trial identification: Neoadjuvant Therapy in TRIPle Negative Breast Cancer With antiPDL1 (NeoTRIPaPDL1) (NCT02620280).

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LBA14 De-escalated neoadjuvant T-DM1 with or without endocrine therapy (ET) vs trastuzumab+ET in early HR+/HER2+ breast cancer (BC): ADAPT-TP survival results

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Background: HR+/HER2+ BC is a distinct entity associated with different molecular and therapeutic features compared to HR-/HER2+ BC. The HER2 antibody drug conjugate T-DM1 is highly effective in metastatic and early HER2+ BC. So far, no survival data for de-escalated T-DM1-based (neo)adjuvant regimens without systemic chemotherapy (CT) are available. Here, we present first survival data from ADAPT-TP.

Methods: The prospective WSG-ADAPT-TP phase II-trial is part of the ADAPT-umbrella protocol (NCT NCT01779206): 375 patients (pts) with HR+/HER2+ BC were randomized to 12 weeks of T-DM1 +/- standard ET and trastuzumab+ET q3w (ratio 1:1:1). Primary endpoint was pCR (ypT0/is/ypN0) (previously published: T-DM1/T-DM1+ET/T+ET: 41%/42%/15%). Secondary endpoints: safety, 5-y DFS, OS, translational research. Omission of further CT was allowed in all pts with pCR after 12-weeks study therapy.

Results: After median follow-up of 5 years, no significant differences between study arms were observed regarding DFS (T-DM1/T-DM1+ET/T+ET 5-y rate: 88.9%, 85.3%, and 84.6%) and OS (97.2%, 96.4% and 96.3%). pCR (vs. non-pCR) after the 12-week study treatment was strongly associated with improved DFS (5y DFS 92.7% vs. 82.7, HR=0.40, 95% CI 0.18-0.85). Among 117 pts with pCR, no further CT was given in 41 pts (35%). Significant differences between CT-treated vs. non-treated pCR pts regarding baseline characteristics were only observed for age (median 50y vs. 56y, p=0.005); similar 5y DFS was observed in both groups (92.1% (95%-CI: 78-97%) vs. 93% (84-97%)). Only 3 deaths occurred in pts with pCR.

Conclusions: Early pCR after 12 weeks of therapy was strongly associated with improved outcome in ADAPT TP and may serve as a predictive marker for CT treatment (de)-escalation. Despite substantially higher pCR rates, T-DM1 +/- ET was not associated with different DFS or OS vs. T+ET, most likely due to standard CT, given to all non-pCR pts and most pCR pts or small sample size of study. Excellent 93% 5y DFS in pts with pCR after only 12 weeks of T-DM1 +/- ET (even w/o further CT) is promising and may serve as a basis for further prospective trials addressing omission of CT overtreatment in carefully selected patients with HER2+ early BC.

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