Table: 3MO

Germline mutations

	Total biomarker cohort (n=1173)	Abemaciclib + ET (n=580)		ET Alone (n=593)	
Altered Gene	N (%)	N	IDFS Events (%)	N	IDFS Events (%)
gBRCA1	6 (0.5%)	3	0 (0.0%)	3	3 (100.0%)
gBRCA2	35 (3.0%)	17	1 (5.9%)	18	6 (33.3%)
gBRCA1/2	41 (3.5%)	20	1 (5.0%)	21	9 (42.9%)

Uncommon somatic alterations

	Prevalence	Abemaciclib + ET		ET Alone	
Altered Gene	N (%)	N	IDFS Events (%)	N	IDFS Events (%)
CCNE2	97 (8.3%)	49	18 (36.7%)	48	18 (37.5%)
PTEN	95 (8.1%)	40	14 (35.0%)	55	17 (30.9%)
AKT1	70 (6.0%)	32	8 (25.0%)	38	12 (31.6%)
RB1	66 (5.6%)	34	12 (35.3%)	32	7 (21.9%)
NF1	65 (5.5%)	35	8 (22.9%)	30	12 (40.0%)
BRCA2	49 (4.2%)	22	7 (31.8%)	27	8 (29.6%)

Conclusions: In these exploratory analyses from an IDFS-event-enriched cohort of monarchE, fewer IDFS events occurred in pts with germline *BRCA1/2* mutations receiving adjuvant abemaciclib + ET compared to ET alone; however, small pt numbers limit the evaluation of statistical significance for both *gBRCA1/2* and uncommon somatic alterations.

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4MO Neoadjuvant letrozole and palbociclib versus chemotherapy in the NeoPAL study: A translational analysis

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Background: The randomised phase II NeoPAL study (NCT02400567) compared neoadjuvant letrozole-palbociclib (LP) to chemo (CT) in 103 patients with early high-risk PAM50-defined luminal BC. Clinical activity was similar in both arms. We report the pre-specified translational analysis.

Methods: We compared baseline (BL) and surgical tumor samples expression of Ki67, cell cycle proteins and immune cell markers by central IHC, DNAseq, gene expression by the Nanostring nCounter BC360™ panel, and 3'mRNA sequencing (RNA-Seq) with BayesPrism cell type deconvolution.

Results: By IHC, BC360 signatures and RNA-Seq, no difference was observed between the BL samples of both arms. Median Ki67 was significantly reduced at surgery in both arms [LP: 27.5% (IQR 20-40) to 1% (IQR 0-5), p<.0001) and was lower in the LP than in the CT arm (median 1% (IQR 0-5) vs 5% (IQR 2-15), p=.0001). Similar reductions were seen in pRb and CCND1 Hscores in each arm. At surgery, the BC360 proliferation signature was reduced in both arms along most of the initially upregulated pathways, while the upregulated BC360 signatures were almost all immune-related (all p<.01). Active immune cell recruitment was confirmed by IHC after both therapies. No DNAseq changes were observed with LP therapy. Deconvolution of bulk RNA-Seq data using a finely annotated single-cell cellular atlas revealed enrichment of cancer cells, immunosuppressive cancer-associated fibroblasts, FOXP3+ CD4+ regulatory T cells and TREM2+ macrophages at BL. In contrast, myoepithelial cells, normal-like fibroblasts, FOLR2+ macrophages and SELL+ CD4+ T cells accumulate after treatment (p values: .046 to 7.2e-07). Strikingly, all these changes were almost identical between the LP and CT arms. Finally, a low ROR score was observed at surgery in 60% and 40% of patients in the LP and CT arms, respectively (p=.064). In these patients, no 3-year breast cancer-specific survival event was observed.

Conclusions: This comprehensive analysis strongly suggests that LP has as profound an effect on luminal tumours as chemotherapy, with regard to proliferation decrease, immune attraction and stromal changes associated with tumor response. These results provide rationale for future chemo-sparing studies in high-risk luminal breast cancer.

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