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POSTER SESSION ABSTRACTS | MAY 02 2024

Abstract PO3-13-02: Genomic and intrinsic subtype correlates of serum thymidine kinase activity in patients with metastatic breast cancer treated with palbociclib and fulvestrant in the PYTHIA trial FREE

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Abstract

Background: Serum thymidine kinase activity (sTKa) is a novel non-invasive proliferation biomarker providing prognostic, predictive and monitoring information in patients (pts) with metastatic breast cancer (MBC). We have shown in PYTHIA that high baseline sTKa and lack of sTKa clearance at day 15 of the first cycle of treatment with palbociclib (P)+ fulvestrant (F) are poor prognostic factors in terms of PFS. Here we characterized the molecular features of tumor samples from PYTHIA, and their relation with sTKa.
Methods: PYTHIA (IBCSG 53- 14/BIG 14-04; NCT02536742) is a phase II biomarker discovery trial downstream of the AURORA molecular program (BIG 14-01; NCT02102165) which enrolled 122 pts with endocrine-resistant, ER+ and HER2 - MBC receiving P+F. Intrinsic subtypes of metastatic samples from 24 pts were estimated using RNA-Seq. Somatic mutations (mut) from 66 pts were identified using an NGSpanel of 411 cancer-related genes (36 primary and 48 metastatic samples). sTKa was measured using

DiviTum® TKa (Biovica International) before treatment (D0) and at day 15 (D15) of cycle 1 of P+F. sTKa clearance at D15 was defined as sTKa below the limit of detection (LOD). Intrinsic subtypes and ESR1 mut were assessed in metastatic samples, PIK3CA and TP53 mut were derived from a combined cohort, wheremetastatic samples were used when available and primary samples otherwise. Association of mut and continuous sTKa with PFS was assessed using Cox regression. **Results:** In metastatic samples, sTKa levels at D0 tended to be higher in luminal B and HER2-enriched subtypes. Lack of sTKa clearance at D15 was observed in 14% of the cases, all classified as luminal B. PIK3CA and TP53 were the most frequently altered genes (38% and 27%, respectively). ESR1 mut were found in 8% of primary and 25% of metastatic samples. Only TP53 was associated with worse PFS. sTKa levels at D0 tended to be higher in pts with TP53 mut vs wild-type (wt) and lower in PIK3CA mut vs wt. Interestingly, lack of sTKa clearance at D15 was more frequent in TP53 mut vs wt and less frequent in PIK3CA mut vs wt. Levels of sTKa were similar in pts with ESR1 mut vs wt both at D0 and at D15 (**Table 1**). The inclusion of TP53 as a predictor of PFS in bivariate Cox models with sTKa at either D0 (likelihood ratio test p=0.44) or D15 (p=0.21) did not add to the prognostic value provided by sTKa alone. **Conclusions:** Tumors with high proliferation and poor prognostic features (luminal B, HER2-enriched and TP53 mut) tend to have higher baseline sTKa and less sTKa response on-treatment, in line with sTKa being a circulating dynamic biomarker of tumor cell proliferation. After accounting for sTKa values, TP53mutational status did not contribute to prognosis. This suggests that high sTKa at D0 and lack of sTKa clearance at D15 might be associated with a worse prognosis independently of TP53 status. Further validation in larger datasets is warranted.

Table 1:

Results summary

	D0, N (%)	sTKa D0 (Du/L)^ median (IQR)	P-val*	D15 N (%)	Lack of sTKa D15 clearance	P-val**	Univariate association with PFS: HR (95% CI), P-val
Intrinsic subtype							
Lum A	3 (12.5%)	<LOD (<LOD, 56)		3 (14%)	0 (0%)		Not assessed
Lum B	12 (50%)	224 (81, 402)		11 (52%)	3 (27%)		
HER2e	7 (29%)	87 (81, 211)		5 (24%)	0 (0%)		
Basal	2 (8.5%)	49 (33, 64)		2 (10%)	0 (0%)		
total	24 (100%)	94 (42, 252)		21 (100%)	3 (14%)		
TP53 mut	18 (27%)	158 (87, 919)	0.07	15 (26%)	5 (33%)	0.13	1.82 (1.02, 3.24), P 0.04
TP53 wt	48 (63%)	84 (21, 270)		43 (74%)	6 (14%)		
total	66 (100%)			58 (100%)			
PIK3CA mut	25 (38%)	75 (33, 220)	0.15	21 (36%)	0 (0%)	0.004	0.77 (0.44-0.1.34), P 0.37
PIK3CA wt	41 (62%)	144 (36, 1035)		37 (64%)	11 (30%)		
total	66 (100%)			58 (100%)			
ESR1 mut	12 (25%)	149 (79, 1041)	0.4	10 (24%)	2 (20%)	1	1.31 (0.66-2.65), P 0.44
ESR1 wt	36 (75%)	91 (37, 315)		32 (76%)	7 (22%)		
total	48 (100%)			42 (100%)			
*-Wilcoxon test; **-Fisher's exact test. ^ LOD: 20 Divitum unit (Du)/L							

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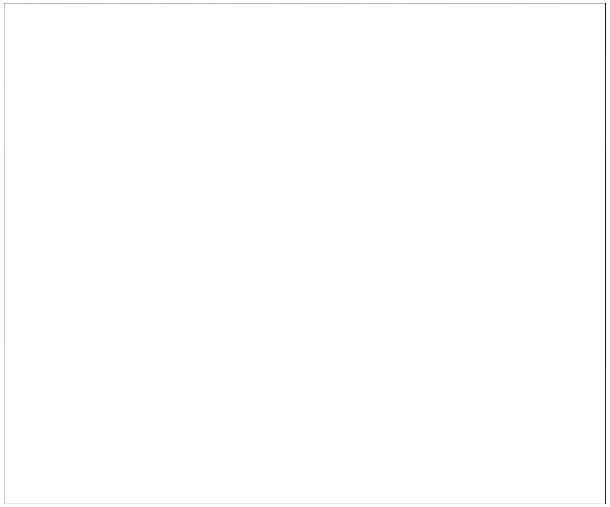

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