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Predictive value of gene-expression profiles (GEPs) and their dynamics during therapy in the NeoTRIPaPDL1 trial

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Background

GEPs may reveal pathways associated with pathological complete response (pCR) in TNBC treated with neoadjuvant immunotherapy combination.

Methods

In NeoTRIP patients with TNBC were randomized to eight cycles of nab-paclitaxel/carbo (CT) with/without atezolizumab (CTA). 258 patients were evaluable for pCR. RNA-sequencing performed pre-treatment (n=242/258; 93.8%) and on treatment on day 1 of cycle 2 (excluding samples without tumor cells) (d1c2; n=161/258; 62.4%). We evaluated the association with pCR of the 27-gene IO score, TNBCtypes (BL1, BL2, LAR, M and MSL; Ring et al 2016), and selected tumor intrinsic and extrinsic gene-signatures. Within pCR group, super-responders were those with no tumor cells at d1c2 (33.3% in CTA; 16.5% in CT). Analyses were adjusted for baseline PD-L1 and sTILs.

Results

Pre-treatment, binary IO score was predictive of pCR in CTA (OR 3.64 [1.68-7.90], p=0.001), but not in the CT arm (1.31 [0.64-2.67] (p=0.46) (interaction p=0.029). Among TNBCtypes, the LAR subtype had the lowest pCR rate (CTA 22.2%, CT 18.8%), and BL1 had the highest (CTA 70.3%, CT 54.3%) (p=0.001) (Interactions not significant). High angiogenesis and fatty acid/cholesterol were independently linked to resistance in CTA, but not CT, arm (interaction p=0.005 and p=0.02, respectively). Only in CTA arm, super-responders were also characterized by high expression of some immune-signatures. At d1c2, high expression of several immune-related signatures were similarly predictive of pCR in both arms (p<0.01), whereas glutamine metabolism was linked to resistance in CTA arm only. For instance, high CD8 (above median) was associated with 58.6% and 61.7% pCR rate in CTA and CT arm, respectively, but low CD8 with only 22% and 23.1%. Combination of both baseline value and dynamic of some biomarkers was more informative than either one alone.

Conclusions

IO score, but not TNBCtype, is predictive of atezolizumab benefit over CT alone. Angiogenesis and lipid/glutamine metabolism were linked to resistance, suggesting new potential therapeutic targets. Super-responders in atezolizumab arm have a unique biology and represent ideal candidates to treatment de-escalation. Early biomarker dynamics provide additional predictive information.

Clinical trial identification

NCT02620280.

Legal entity responsible for the study

Fondazione Michelangelo.

Funding

Roche.

Disclosure

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