2021 ESMO congress

658MO

Cisplatin (cis)-related immunomodulation and efficacy with atezolizumab (atezo) + cis- vs carboplatin (carbo)-based chemotherapy (chemo) in metastatic urothelial cancer (mUC)

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Background

Cis- but not carbo-based chemo leads to durable disease control in a subset of pts with mUC, but the underlying mechanisms remain elusive. Exploratory data from the randomised Ph III IMvigor130 study suggested improved OS with the addition of atezo to cis- but not carbo-based chemo (Galsky AACR 2021). Here we tested the hypothesis that cis may induce immunomodulatory effects.

Methods

Single-cell RNA sequencing (scRNA-seq) was performed on peripheral blood mononuclear cells (PBMCs) obtained at Cycle (C) 1 Day (D) 1 and C3D1 from 70 IMvigor130 pts receiving atezo + platinum and gemcitabine (plt [cis or carbo]/gem; Arm A) or placebo + plt/gem (Arm C). Gene expression profiling of paired pre-/post- neoadjuvant gem + cis samples was used to study cis-related changes in the tumour microenvironment (TME; n=113).

Results

The impact of pre-treatment tumour PD-L1 immune cell expression on OS with cis vs carbo in Arms A and C is shown (Table). In IMvigor130 Arm C cis- vs carbo-treated pts, on-treatment enrichment of Hallmark TNFα signalling via NF_KB and inflammatory response gene sets was observed across all immune cell clusters; trends were even more pronounced in Arm A. Among top-ranked genes enriched in PBMCs post-cis vs -carbo was *NINJ1*, which mediates plasma membrane rupture during lytic cell death, releasing damage-associated molecular patterns (eg, HMGB1). In a separate cohort in the neoadjuvant setting, TNFα signalling via NF_KB was also enriched in paired tumour samples post- vs pre-gem + cis chemo.Table: 658MO

IMvigor130: treatment subgroups	IC0/1		IC2/3		HR (95% CI)
	n	Median OS, mo	n	Median OS, mo	
Arm A (atezo + cis/gem)	102	19.5	35	Not reached	0.46 (0.25, 0.83)
Arm A (atezo + carbo/gem)	241	13.9	73	16.6	0.85 (0.61, 1.17)
Arm C (placebo + cis/gem)	102	12.8	34	27.9	0.51 (0.30, 0.86)
Arm C (placebo + carbo/gem)	207	13.0	57	14.0	1.00 (0.71, 1.42)

PD-L1 expression on tumour-infiltrating immune cells assessed from archival pre-treatment tumour samples (VENTANA SP142 assay). CI, confidence interval; HR, hazard ratio; IC0/1, presence of programmed death-ligand 1 (PD-L1)–expressing immune cells on <5% of the tumour area; IC2/3, presence of PD-L1–expressing immune cells on ≥5% of the tumour area; OS, overall survival.

Conclusions

PD-L1 IC 2/3 status is associated with longer OS in cis- but not carbo-treated pts with mUC. Cis, vs carbo, is associated with increased TNFα-mediated proinflammatory signalling in circulating immune cells and the TME. Together these data suggest that cis/gem induces immunogenic cell death and enhances antitumour immunity, particularly when combined with atezo.

Clinical trial identification

NCT02807636.

Editorial acknowledgement

Medical writing assistance for this abstract was provided by Bena Lim, PhD, of Health Interactions, Inc., and funded by F. Hoffmann-La Roche Ltd.

Legal entity responsible for the study

F. Hoffmann-La Roche Ltd.

Funding

F. Hoffmann-La Roche Ltd.

Disclosure

M.D. Galsky: Financial Interests, Advisory Role: Merck; Financial Interests, Advisory Role: Pfizer; Financial Interests, Advisory Role: EMD/Serono; Financial Interests, Advisory Role: BMS; Financial Interests, Advisory Role: AstraZeneca; Financial Interests, Advisory Role: Seattle Genetics; Financial Interests, Advisory Role: Astellas; Financial Interests, Advisory Role: Genentech; Financial Interests, Institutional, Research Grant: Genentech; Financial Interests, Institutional, Research Grant: BMS; Financial Interests, Institutional, Research Grant: AstraZeneca. X. Guan: Financial Interests, Personal, Full or part-time Employment: Genentech; Financial Interests, Personal, Stocks/Shares, RSU: Genentech. R. Banchereau: Financial Interests, Personal, Full or part-time Employment: Genentech; Financial Interests, Personal, Stocks/Shares: Genentech. L. Wang: Financial Interests, Personal, Full or part-time Employment: Sema4. J. 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