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ERBB2 mutations as potential predictors of poor outcomes in patients (pts) treated with enfortumab vedotin (EV): The impact of genomic alterations (GAs) beyond NECTIN-4

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Background

EV has improved survival in metastatic UC (mUC), both as monotherapy and in combination with pembrolizumab. Retrospective evaluations have showed that GAs of *PVRL-4*, the gene that encodes NECTIN-4, may impact outcomes. Studies are currently exploring other genomic biomarkers relevant to EV response. In a real-world cohort of pts treated with EV, we present GAs associated with outcomes.

Methods

We retrospectively identified pts with mUC treated at Dana-Farber Cancer Institute who received at least 2 cycles of EV monotherapy as 2nd line or later therapy between January 2018 and March 2024. All pts underwent somatic genomic profiling with an internal targeted NGS platform (OncoPanel). The primary aim was to to explore somatic mutations and copy number alterations that correlate with response rate (ORR), progression-free survival (PFS), and overall survival (OS).

Results

Of 143 pts screened, 99 were included after excluding those with < 2 EV cycles or concurrent malignancies. Median age at EV start was 70 (interquartile range: 62–74); 72% were male. *PVRL4* gain/amplification (36.3%), was linked to numerically longer OS (14.1 vs 11.5 months; P = 0.51) with no significant PFS (P = 0.31) or ORR (P = 0.18) differences. *ERBB2* mutations (10.1%) were associated with shorter OS (6 vs 13.3 months; P = 0.002) and PFS (5.2 vs 6.6 months; P = 0.05), with similar ORR (55% vs 56%; P = 1.00). *FAT1* mutations (14.1%) correlated with worse OS (P = 0.01), *COL7A1* mutations (13.1%) with inferior PFS (P = 0.002). In multivariable analysis adjusted for Bellmunt score and relevant GAs, *ERBB2* predicted poorer OS (Hazard Ratio [HR]: 2.6, 95% Confidence Interval (CI): 1.3–5.1; P = 0.006) and trended for shorter PFS (HR: 2.2, 95% CI: 0.97–4.5; P = 0.06); *COL7A1* remained linked to worse PFS (HR: 2.3, 95% CI: 1.1–5.0; P = 0.03).

Conclusions

PVRL4 gain/amplification was associated with numerically longer OS, suggesting a potential favorable prognostic biomarker. In contrast, *ERBB2* mutations correlated with shorter OS and PFS despite comparable ORR, implying early relapse and reduced durability of EV benefit. These findings are being validated in an expanded cohort.

Legal entity responsible for the study

The authors.

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Disclosure

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Bellmunt: Financial Interests, Personal, Advisory Board, Joined the Global adboard this year: Pfizer; Financial Interests, Personal, Advisory Board, Regular GU adboard for bladder cancer: Astra-Zeneca; Financial Interests, Personal, Invited Speaker, Lectures in the setting of National meetings: Merck; Financial Interests, Personal, Advisory Board, Bladder adboard: Merck; Financial Interests, Personal, Advisory Board, For the adjuvant study CM 247: BMS; Financial Interests, Personal, Invited Speaker, For ESMO Asia Symp 2020: MSD; Financial Interests, Personal, Stocks/Shares, Holdings: Bicycle; Financial Interests, Personal, Royalties, Role as Section Editor for Bladder: UpToDate; Financial Interests, Institutional, Coordinating PI, Pi of INDUCOMAIN Study (Avelumab first line in unfit patients) Though APRO Association: MSD; Financial Interests, Institutional, Coordinating PI, Pi of Prostate Study (Avelumab + Carboplatin) Though APRO Association.: Pfizer; Non-Financial Interests, Other, Steering committee member of IMvigor 011: Genentech; Non-Financial Interests, Member: ASCO. 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