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PErioperative PEmbrolizumab (P) plus metastasis-directed therapy (MDT) versus MDT alone in patients (pts) with oligometastatic renal cell carcinoma (omRCC): The randomized phase II PE-PE trial

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Background

Adjuvant P is the standard of care for pts with intermediate-high/high risk of relapse after nephrectomy (Nx), as well as for those with M1NED within 1y of previous Nx. Although omRCC pts may receive anti-PD-1-based combos, the optimal management of those eligible for MDT remains uncertain.

Methods

The PE-PE trial (NCT05578664) is a randomized, open-label, multicenter phase II study evaluating the efficacy of P in delaying tumor progression for omRCC pts candidates for MDT, including surgery or SABR to all metastatic sites. Eligible pts had undergone prior Nx and presented with ≤3 metastases within 5 years of Nx or previous metastasectomy. Pts were randomized 2:1 to receive P 400 mg every 6 weeks for 9 cycles (1 year) plus MDT (P+MDT) or MDT alone. The first dose of P was administered before MDT. The primary endpoint was relapse-free survival (RFS), while others included distant RFS, local relapse, OS, and safety.

Results

85 pts were randomized between March 2023 and February 2026: 56 to the P+MDT arm and 29 to the MDT-alone arm. Baseline characteristics were well balanced between treatment groups. SABR was selected in 73% vs. 72% of pts, while surgery was performed in 23% vs. 28%, respectively. The median number of P cycles administered was 6.6. The most frequent reasons for P discontinuation were disease progression (11 pts) and adverse events (AE, 4 pts). After a median follow-up of 17.5 mos, 35 RFS events were observed (19 vs.16), with two deaths (one in each arm). Median RFS was 25.4 mos in the P+MDT arm vs. 11.0 mos in the MDT-alone arm (HR 0.47; 95% CI, 0.24-0.92; p=0.024). Regarding safety, 80% vs. 21% of pts experienced at least one AE, while G3 AEs occurred in 7% vs. 3% of pts in the P+MDT and MDT-alone arms, respectively. P-related AEs of any G occurred in 59%, the most common being hypothyroidism (23%), fatigue (18%), and diarrhea (16%). Two pts experienced G3 toxicity without G4 or 5.

Conclusions

The PE-PE trial supports the use of 1 year of perioperative P in pts with omRCC eligible for MDT, demonstrating a statistically significant and clinically meaningful improvement in RFS with a manageable and consistent safety profile.

Clinical trial identification

NCT05578664.

Legal entity responsible for the study

Clinical Research Technology. Via San Leonardo trav. Migliaro 84131 Salerno (Italy).

Funding

MSD.

Disclosure

R. Iacovelli: Financial Interests, Personal, Advisory Board: BMS, MSD, Janssen, Astellas, Ipsen, Pfizer, Bayer, Sanofi, Eisai, Merck, GENENTA, GSK, AstraZeneca; Financial Interests, Personal, Invited Speaker: Recordati; Financial Interests, Institutional, Research Grant: BMS; Financial Interests, Institutional, Local PI: MSD, Pfizer, Aveo; Non-Financial Interests, Member: AIOM; Non-Financial Interests, Advisory Board, Italian Society of Uro-Oncology: SIUrO. D. Bimbatti: Financial Interests, Personal, Invited Speaker: Ipsen, Astellas, Janssen, Bayer; Financial Interests, Personal, Advisory Board: MSD, Eisai. F. Massari: Financial Interests, Personal, Advisory Board: Astellas, AstraZeneca, Bayer, Janssen, MSD, Pfizer, Eisai, Advanced Accelerator Applications, Merck; Financial Interests, Personal, Invited Speaker: BMS, Ipsen. L. Bonomi: Financial Interests, Personal, Invited Speaker: BMS, AstraZeneca, MSD; Financial Interests, Personal, Advisory Board: Ipsen; Financial Interests, Institutional, Local PI: Roche, AstraZeneca; Other, Other, travel and accomodation fees for scientific meetings: Ipsen, Janssen. M. Rizzo: Financial Interests, Personal, Advisory Board: Astellas, AstraZeneca, Merck Serono, MSD; Financial Interests, Personal, Invited Speaker: Johnson and Johnson, Ipsen; Financial Interests, Institutional, Local PI: BMS, Roche, AstraZeneca, Astellas, MSD, Pfizer; Non-Financial Interests, Institutional, Product Samples: Astellas, AstraZeneca. E. Zanardi: Financial Interests, Personal, Invited Speaker: Astellas, Johnson and Johnson, Bayer; Financial Interests, Personal, Advisory Board: Johnson and Johnson, Ipsen, Novartis. F. Nolè: Financial Interests, Personal, Advisory Board: Astellas, Janssen; Financial Interests, Personal, Invited Speaker: Bayer, Novartis, AstraZeneca. H. Lipari: Financial Interests, Personal, Invited Speaker, Advisory Board: AstraZeneca; Financial Interests, Personal, Writing Engagement, reviewer: Bristol Myers Squibb; Financial Interests, Personal, Invited Speaker, Honoraria per speaker bureau: Johnson e Johnson; Financial Interests, Personal and Institutional, Other, Sub Investigator in studi finanziati da MSD: Ms. E. Verzoni: Financial Interests, Personal, Advisory Board: MSD, Janssen, AstraZeneca, Eisai; Financial Interests, Personal, Invited Speaker: BMS, Astellas, Ipsen, Pfizer, Novartis; Non-Financial Interests, Principal Investigator: MSD, Ipsen, Astellas, Janssen, Lilly, Pfizer. M. Santoni: Financial Interests, Personal, Invited Speaker: Bayer, Novartis, MSD, Janssen, Astellas, AstraZeneca. C. Ciccarese: Financial Interests, Personal, Advisory Board: MSD, BMS, AstraZeneca; Financial Interests, Personal, Invited Speaker: Astellas, Ipsen, Johnson and Johnson, Novartis; Financial Interests, Personal, Other, travel grant: Pfizer. All other authors have declared no conflicts of interest.

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