Final results of phase I/II trial of fractionated dose 177Lu-PSMA-617 for metastatic castration-resistant prostate cancer (mCRPC)

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Background
Safety and initial efficacy results of a phase I dose-escalation study of a fractionated (dose-dense) regimen were previously described, without short-term dose-limiting toxicity [ESMO 2019]. Here, we report results of the complete phase I/II study.

Methods
Men with progressive mCRPC following at least 1 AR-pathway inhibitor (ARPI) and taxane chemo (or ineligible/refuse), intact organ function, and ECOG PS 0-2. Treatment: a single fractionated cycle of 177Lu-PSMA-617 on days 1 and 15 (7.4 to 22 GBq in dose-escalation cohort, followed by Simon 2-stage phase II study at 22GBq). PSMA expression was not a prerequisite for treatment, but baseline and post-treatment 68Ga-PSMA11 PET/CT and/or 177Lu-PSMA-617 SPECT performed. Follow up with serial PSA measurements, CT/bone scans, and circulating tumor cell (CTC; CellSearch) counts.

Results
50 men with median PSA 173.8, 35 (70%) CALGB (Halabi) poor risk. 47 (94%) with bone, 38 (76%) LN, 12 (24%) lung, 11 (22%) liver mets. 29 (58%) with ≥2 prior ARPI, 29 (58%) chemo, 14 (28%) radium-223, 2 (4%) 177Lu-J591. 27 (54%) treated at 22 GBq. 40 (80%) with any PSA decline, 27 (54%) with >50% PSA decline. Median PFS 5.6 mo [95%CI 3.9-8.0], radiographic PFS 9.6 mo [5.6-14.9], and OS 15.2 mo [10.8-27.0]. Of 31 with paired CTC counts, 16 (52%) decreased, 5 (16%) stable; 10 (32.3%) converted to favorable/undetectable. Adverse events included 38 (76%) pain flare, 27 (54%) xerostomia, 24 (48%) nausea, 21 (42%) fatigue, 17 (34%) thrombocytopenia, 10 (20%) anemia, 5 (10%) neutropenia; All AEs restricted to Gr 1-2 except 4 (8%) with Gr 3 anemia. On multivariable analysis, higher PSMA uptake (p<0.005) and dose (p=0.06) associated with >50% PSA response and CALGB risk (p=0.032), prior chemo (p=0.041), higher PSMA uptake (p=0.085), and dose (p=0.072) associated with OS.

Conclusions
A single-cycle of fractionated-dose 177Lu-PSMA-617 is safe. Despite no pre-selection for PSMA expression, most have post-treatment PSA decline with favorable biochemical and radiographic progression-free survival compared to historical non-PSMA controls and similar to PSMA-selected studies administering multiple cycles in a less dose-intense fashion.

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Legal entity responsible for the study
Weill Cornell Medicine.

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Disclosure
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