770 ADU-1604, A NOVEL CTLA-4 BLOCKING ANTIBODY MODULATES PHARMACODYNAMIC MARKERS IN PD1 RELAPSE/REFRACTORY MELANOMA PATIENTS

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Background Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is a negative regulator of T-cell responses, also known as an immune checkpoint. The clinical relevance of CTLA-4 blockade was demonstrated by the approval of ipilimumab (YERVOY®) for the treatment of melanoma, both in the adjuvant as well as metastatic settings. Sairopa acquired ADU-1604, a humanized hIgG1 CTLA-4 antagonist antibody. ADU-1604 binds a unique epitope on CTLA-4 demonstrating, in contrast to ipilimumab full blockade of both CD80 and CD86 interactions. In vitro and in vivo ADU-1604 demonstrates at least as potent efficacy as compared to ipilimumab, was well tolerated in non-human primates and demonstrated enhanced immunogenicity against hepatitis B vaccine in non-human primates.[1]

Methods This is a phase 1, first-in-human (FIH), two-part, open-label clinical trial of intravenous (IV) administration of ADU-1604 given as monotherapy in subjects with advanced-stage, relapsed/refractory melanoma who relapsed or were refractory to a prior anti-PD-1/PD-L1 therapy. Main endpoints are safety of ADU-1604 monotherapy, pharmacokinetics, pharmacodynamics (upregulation of ICOS and Ki-67 on circulation CD4+ T cells and ALC, CD4+ and CD8+ T cells) as well as preliminary clinical efficacy. Up to 20 subjects will receive escalating doses of ADU-1604 IV (25, 75, 225, 450 mg flat dose) Q3W. In the dose expansion part up to 20 additional patients will be treated to determine the recommended phase 2 dose (RP2D) and safety and preliminary efficacy of ADU-1604 monotherapy in PD1 relapsed/refractory melanoma patients will be evaluated.

The study was initiated in Jun 2022. Cohort 4 (450 mg) is ongoing at time of submission of this abstract (07/2023).

Results ADU-1604 was demonstrated to have a typical pharmacokinetic behavior for a human IgG1 antibody and similar exposure was observed as described for ipilimumab.[2] Administration of ADU-1604 in cycle 1 and 2 showed a dose-dependent modulation of ICOS and Ki-67 on circulating CD4+ T cells. Similarly, in cycles 3 and 4 a dose-dependent increase of ALC and CD4+ and CD8+ T cells was detected. Notably, no DLTs across the 25, 75 and 225 mg dose level have occurred. Sofar (dose level 1–2) an ongoing durable SD lasting more than nine months has been noted in one patient, who received 8 cycles of 25 mg before continuing on 75 mg dose.

Conclusions Initial dose-escalation data supports ADU-1604 activity, as indicated by the pharmacodynamic markers. Importantly, no DLTs have been reported during the study. Updated safety, biomarker and response assessments will be reported at the meeting.

Trial Registration The clinical trial is registered with EudraCT number 2021–002623-38.

REFERENCES

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Ethics Approval All participants gave informed consent prior to study participation. Ethical Committee Approval issued by France, CPP Sud-Méditerranée on 16Mar2022, issued by Spain, CEim Hospital Clinic on 16Mar2022, issued by Italy, IRCCS Pascale on 31Mar2022, issued by Poland, Bioethics Committee of Narodowy Instytut Onkologii on 15Dec2021.

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