First-in-man dose escalation and pharmacokinetic study of CAP7.1, a novel etoposide prodrug in adults with heavily pretreated solid tumors.

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CAP7.1 is a new chemical entity that releases etoposide in the presence of carboxylesterases, leading to higher intra-tumor etoposide (E) concentration than conventional E, improved safety and efficacy in animals including activity in E-resistant models.

A phase I study in patients (pt) with heavily pretreated solid tumors was performed to define dose limiting toxicities (DLT), safety, recommended phase II dose (RP2D) and pharmacokinetics of CAP7.1.

CAP7.1 was given i.v. day 1-5 in 3-week cycles (cy). Safety was assessed with CTCAE v 3.0, efficacy with RECIST 1.0. Dose escalation based on DLTs followed a 3+3 design and a modified Fibonacci schema. Nineteen pt were treated, in 4 successive dose levels: 45 (3 pt), 90 (3 pt), 150 (6 pt) and 200 (7 pt) mg/ m^2/dailyx5. Overall, 62 cy were administered (8 at 45, 10 at 90, 16 at 150 and 28 at 200 mg/m^2/day x 5).

Non-hematological adverse events (AE) were mild or moderate. Most frequent AE were nausea, vomiting, fatigue and diarrhea (in 24, 17, 16, 9 pt respectively). Three pt presented DLTs including 1 febrile neutropenia (FN) at 150 mg, 1 sepsis and 1 FN at 200mg/ m^2/d. G3-4 neutropenia in Cy1 occurred in 3 pt at 150 and in all pt at 200 mg/ m^2/d; uncomplicated g 3-4 thrombocytopenia occurred in 3/7 pt at 200 and in 1/6 at 150 mg/ m^2/d.

Plasma pharmacokinetic samples for evaluation of CAP7.1 and E levels were drawn on day 1-5 pre- and 15 minutes post- end of infusion (EOI); on day 1 samples were also taken 30 minutes prior to EOI and up to 10 hour after EOI. CAP7.1 was rapidly cleared (t1/2 = 30-45min) whereas the mean t1/2 of E was 5.47, 8.23, 7.84 and 5.88 in dose levels 1 – 4, respectively.

A pt with Merkel tumor and prior E achieved a partial response lasting 4 months (mo). Other 13/19 pt had stable disease (SD). At 200mg/ m^2/d 4 pt had SD for $\geq$ 6 mo. Ten pt survived > 6 months, with longest OS 25 mo (gallbladder carcinoma) and 20 mo (carcinoma of unknown origin).

CAP7.1 presents manageable toxicity (mainly hematological) at dose levels 750-1000 mg/m^2/cycle, nearly a 2-3fold increase of conventional etoposide dose (360 mg/m2/cycle) without organ toxicity. Interestingly, CAP7.1 has no hematological toxicities at doses 360mg/m2/cy used for conventional E. Phase II studies are warranted and will include neoplasms known to be susceptible and resistant to etoposide.