347P Results of the phase Ib dose escalation study of MEN1611, a PI3K inhibitor, combined with trastuzumab (T) ± fulvestrant (F) for HER2+/PIK3CA mutant (mut) advanced or metastatic (a/m) breast cancer (BC)

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Background: MEN1611 (MEN) is an oral PI3K inhibitor active on the p110α mut and WT, β and γ isoforms, while sparing the δ. Antitumor activity of MEN combined with other agents in patient-derived xenografts and BC cell lines with different *PIK3CA* mutations, provides a strong rationale for clinical testing.

Methods: B-PRECISE-01 is an ongoing phase Ib study in patients (pts) with HER2+/*PIK3CA*mut a/m BC treated with at least 2 anti-HER2 therapies. A 3+3 design combined 3 dose levels of MEN BID and T weekly IV. HR+ postmenopausal pts also received F. Primary objectives are to determine safety and recommended phase II dose (RP2D). Dose-limiting toxicities (DLTs) were assessed during cycle 1. Secondary objectives included assessment of preliminary clinical activity, pharmacokinetics and pharmacodynamics. Here we present mature data from dose escalation cohorts.

Results: As of Oct. 2019, 12 female pts were treated: 9 MEN+T+F and 3 MEN+T. Median age: 59 years (range 39-77). Median prior metastatic regimens: 5.5 (4-12). No DLTs were observed at any dose cohort. 48 mg was selected as RP2D. Most common grade (G)1/2 treatment-related adverse events (TRAEs) were diarrhoea (n=9), anemia (n=6), nausea (n=4), asthenia (n=4), decreased appetite (n=4), hyperglycemia (n=4), and mucosal inflammation (n=3). G3/4 TRAEs were not dose-dependent and occurred in 4 pts such as hyperglycemia (n=3), pneumonitis (n=1), decreased appetite (n=1), mucosal inflammation (n=1), and AST/ALT increase (n=1). Dose was reduced in one pt at 48 mg. No deaths from toxicity occurred. There were no overt differences in the safety profile of MEN+T+F vs. MEN+T. 5 pts (42%) had partial response, 5 stable disease, 4 disease control >8 months (mo) and 2 were on treatment >11 mo. MEN exposure tends to increase with increasing doses. Tmax was reached after 0.5-8 h following administration and the terminal half-life was ~3.5 h.

Conclusions: Tolerability of MEN+T±F is acceptable; most TRAEs were reversible and manageable by supportive care. Promising antitumor activity in heavily pretreated pts, together with prolonged disease control, provide the rationale for cohort expansion at RP2D in pts with HER2+/*PIK3CA* mut a/m BC.

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348P First findings from SYNERGY, a phase I/II trial testing the addition of the anti-CD73 oleclumab (O) to the anti-PD-L1 durvalumab (D) and chemotherapy (ChT) as first line therapy for patients (pts) with metastatic triple-negative breast cancer (mTNBC)

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Background: Immunotherapy with PD-(L)1 blocking agents combined with ChT improve prognosis in mTNBC, but responses are limited to a proportion of pts and most will experience disease progression. The adenosine pathway has been demonstrated to limit anti-tumor activity in TNBC, making CD73, the adenosine generating enzyme, an attractive target to enhance the efficacy of immunotherapy in this disease.

Methods: Pts with locally-advanced unresectable or mTNBC were enrolled to the phase I, dose-finding part consisting of O, starting at 3000mg (as previously defined for use with D alone) every 2 weeks (q2w) x 5, followed by maintenance q4w, given with D 1500mg q4w plus paclitaxel 80mg/m^2 and carboplatin AUC 2, both q1w x 12, until disease progression, limiting toxicity or withdrawal of consent. The incidence of dose-limiting toxicities (DLT), i.e. any adverse event (AE) ≥ G3 occurring up to 28 days after 1st O infusion, was used to find its recommended phase II dose (RP2D) in combination with D + ChT, within a de-escalation 3+3 design. Phase II is recruiting in Belgium and France, and openly randomizes pts 1:1 to arm A (O + D + ChT) or arm B (D + ChT). The primary aim is to improve the clinical benefit rate at week 24 [complete response (CR) + partial response (PR) + stable disease (SD) rates, per RECIST] of arm A vs. arm B, from 40% to 60% (1-sided α=0.1 and 80% power with 68 pts/arm; 150 pts to be enrolled).