Cyclin E1 overexpression (O/E) drives premature S-phase entry and overloads the DNA replication machinery, resulting in genome instability; with no approved therapies, this is an area of high unmet need in the clinic. Lunresertib monotherapy inhibits xenograft growth across doses and schedules. Proof of mechanism established, and preliminary antitumor activity observed.

Lunresertib + camonsertib is well tolerated with promising anti-tumor activity across schedules. At preliminary RP2D (n=10): 3/Y likely due to synergy and ATRi effect. Unselected OR: 33.3% (n=18). Other endpoints: Rash did not lead to discontinuations. cPR* -70.2 21.4+ at the preliminary RP2D: Weekly or 2 weeks on / 1 week off. Best % change in TL. Dose of camonsertib is ~50% lower than the monotherapy RP2D.

Mutations that are essential for fitness in resistant/intolerant to standard therapy. Inactivation of FBXW7 (RPE1 WT cells) increase cyclin E levels and replication stress.

Meaningful tumor reductions and clinical benefit observed across all lunresertib-sensitizing genotypes. Conclusions: First clinical proof-of-concept for a synthetic lethal strategy with a PKMYT1 inhibitor in patients with molecularly selected cancers. Lunresertib, trial-in-class, potent PKMYT1 inhibitor, in cancers with CCNE1 amplification, PPP2R1A and FBXW7 deleterious mutations.

Deleterious mutations of FBXW7, CCNE1, and PPP2R1A are enriched in triple-negative breast cancers. Mutations in FBXW7 (Homozygous deletion or nonsense/frameshift mutation) are associated with increased cyclin E1 protein levels and increased tumorigenicity in breast cancer xenograft models. Lunresertib and camonsertib: TRAEs

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