Poster session 1: Clinical studies

P1.14 A DOSE ESCALATION SINGLE ARM PHASE IB COMBINATION STUDY OF BEZ235 WITH EVEROLIMUS IN PATIENTS WITH ADVANCED SOLID MALIGNANCIES

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Background/Purpose: The dual phosphatidylinositol 3-kinase (PI3K) and mammalian target of rapamycin (mTOR) inhibitor, BEZ235, was shown to be efficacious as an inhibitor of cancer cell proliferation in combination with the mTOR-allosteric inhibitor, RAD001 or everolimus, in a preclinical model over everolimus alone. We hypothesized that the combinatorial effect on the mTOR and PI3K pathway would result in a synergistic anti-tumor effect in humans. Therefore, we designed a first in human, phase 1b trial, in order to study the safety and pharmacokinetics of the combination of BEZ235 and everolimus in patients with solid tumor malignancies.

Methods: Nineteen patients with solid tumor malignancies that had progressed on standard of care treatment were enrolled. The experimental medication, BEZ235, was provided to us by Novartis. BEZ235 was administered orally once a day at escalating doses of 200, 400, and 800mg and everolimus was administered orally once a day at 2.5mg in 28 day cycles.

Results: The most common toxicities observed included fatigue (68%), diarrhea (74%), nausea (63%), mucositis (42%) and elevated liver enzymes (63%). The maximum tolerated dose (MTD) was not reached due to toxicity resulting in early discontinuation of the trial. BEZ235 serum levels were inconsistent suggesting poor absorption. Everolimus exposure was increased over what would be expected for administration alone, likely due to the previously postulated drug interaction between BEZ235 and everolimus. Of the twelve patients evaluated for response, one had SD at 5 weeks and no PR or CR was observed.

Conclusion: The combination therapy of BEZ235 and everolimus was shown to be poorly tolerated in our patient population likely due to poor absorption, drug interaction, and inter-patient variability leading to inconsistent drug levels. Although, there were no confirmed responses, one patient did respond clinically for a brief period. We expect that the combination of everolimus with new dual inhibitors with improved toxicity profiles and increased absorption will be more promising.