A phase 1 study of the APE1 protein inhibitor APX3330 in patients with advanced solid tumors

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Introduction

APX3330 is an orally-administered agent targeting the APE1 protein. APE1 maintains NFkB, STAT3, AP-1 and HIF-1α in a reduced form, acting as a regulator of transcription factors. APE1 plays a key role in a variety of inflammatory disorders and tumorigenesis, including cancers of the colon, pancreas, skin, blood, diabetic macular edema, inflammatory bowel disorders and others. APX3330 selectively binds to APE1, inhibiting its redox signaling activity.

The Importance of the APE1 protein in cancer cells

We report on study NCT03375086 evaluating APX3330 in patients with incurable malignancies.

• Eligibility required adequate organ function, PS 0-2 and tumors not amenable to curative therapy.
• Primary and secondary objectives included determining the recommended phase 2 dose (RP2D), the safety and PK/PD profiles of APX3330 and reporting any RECIST anti-tumor activity.
• Patients received APX3330 b.i.d. in 21-day cycles.
• AE evaluation included pt/pcohort until the occurrence of ≥ G2 toxicity at which time the study proceeded in a 3+3 design.
• Additional patient were also recruited in cohorts in order to attain PK/PD and biopsy samples.

Results

Between 2/18 and 8/18, 19 subjects (13M, 6F) with median age of 67 y started therapy. Dose (mg/d) escalation and number of patients treated (n) per each cohort proceeded as follows: 240 mg (1), 360 (4), 480 (2), 600 (6) and 720 (6).

APX3330 was well tolerated at dose levels from 240-600 mg/d. The most frequent treatment-related adverse events (all grades) included G1 nausea (16%) and fatigue (16%). A G3 rash occurred in two subjects at the 720 mg level defining 600 mg/d as the RP2D for further development. Six subjects had disease stabilization for >4 cycles, and of these, four subjects with the following diagnosis, RECIST response and days on study included: (CRC, PR, 357), (Endometrial, SD, 421d), (Melanoma, SD, 337d), (Prostate, SD, 252d).

Duration of study participation

All study objectives completed, APX3330...

• Is safe for chronic dosing at 600 mg/d
• Provides clinical benefit to patients with a variety of tumor types (e.g., endometrial, colorectal, prostate and melanoma cancer)
• Patient biopsy evaluation indicates APX3330-mediated effect upon cancer cells, including decrease in transcription factors regulated by the APE1 protein
• Circulating tumor cell analysis indicates APX3330-mediated decrease in tumor cells
• All results consistently show that APX3330 mediates activity of APE1 target as expected
• Pharmacodynamic data indicate confirmation of pre-clinical data

Pharmacodynamic Analyses

Confirmed target engagement:
Proteins altered downstream of APE1 regulated transcription factors

Heatmap of differentially-expressed proteins (DEPs) obtained by comparing pre-treatment and on-treatment tumor biopsies from 3 patients receiving APX3330.

Heatmap of APE1 protein levels which were reduced following APX3330 treatment in the melanoma patient with SD > 1 year.

Pharmacokinetic analyses

Distribution of fold changes (FC) of protein expression levels on-treatment vs pre-treatment

Paired biopsy analysis pre-treatment and while on-treatment. Melanoma patient with disease stabilization > 1 year (red line) with lower APE1-regulated protein expression than patients with mPca and mCRC with best response of PD. FCs in the scale of log2.

Serum levels of APE1 are elevated in patients with aggressive tumors

APE1 serum levels were determined using a standard ELISA assay. Statistical comparisons were done between two groups (patients with SD vs PD) using two-sample t-test. p-value 0.028 and statistically significant. SD patients are defined as those on treatment past 4 cycles.

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