## Abstract

Adenosine is a strong immunosuppressive mediator often found at high extracellular levels in the microenvironment of most tumors. Blocking $A_{2A}$ receptors, predominantly expressed on tumor-infiltrating immune cells, is aimed at reversing the immunosuppressive effect of adenosine. EOS100850 is a potent and highly selective small molecule antagonist of the $A_{2A}$ receptor that remains active even at the high adenosine concentration found in tumors and that does not cross the blood-brain barrier. This multicenter FIH Phase I clinical trial (NCT02740985) assessed the safety, pharmacokinetic (PK), pharmacodynamic (PD), and preliminary clinical activity of EOS100850 monotherapy in subjects with refractory solid tumors. Pharmacodynamic assessments were performed in peripheral blood and tumor biopsies with simultaneous determination of plasma PK. Twenty-one adult participants with advanced malignancies were treated with EOS100850 monotherapy. Cohorts of 3 participants each were evaluated at 20 and 40 mg QD or 40 mg BID administration. Six participants were subsequently tested at doses of 80 mg BID and at the maximum administered dose of 160 mg BID. All subjects had at least 1 prior regimen (median 3). PK analysis indicated dose-proportional increase of EOS100850 plasma exposures up to 80 mg BID while PD evaluations revealed prolonged and maintained $A_{2A}$R inhibition over the dosing interval. The most common adverse events (>15%) attributed to the investigational treatment included Grade 1-2 nausea, fatigue, vomiting, and liver enzyme abnormalities. No drug-related Grade 3-4 AEs and no dose-limiting toxicities were observed. As of the data cut off (15JAN20), stable disease was observed in 6 participants who remain on therapy, including head & neck cancers, endometrial cancers, and checkpoint inhibitor-refractory melanoma. Further evaluation is ongoing as monotherapy and in combination with pembrolizumab or chemotherapy in both immune checkpoint-naïve and -refractory patients.

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