head and neck cancer

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CLINICAL ACTIVITY OF THE ORAL SELECTIVE INHIBITOR OF NUCLEAR EXPORT (SINE) SELINEXOR (KPT-330) IN PATIENTS WITH HEAD & NECK SQUAMOUS CELL CARCINOMA (HN-SCC)


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Aim: The nuclear export of most tumor suppressor proteins (TSPs) inactivates their anti-cancer functions. Exportin 1 (XPO1) is the exclusive nuclear exporter of nearly all TSPs. Multiple TSP pathways are altered in HN-SCC including p53, CDKN2A, pRB and others. Selinexor (KPT-330) is a novel, orally bioavailable, selective inhibitor of nuclear export (SINE) that blocks XPO1, leading to the nuclear accumulation and re-activation of TSPs. Selinexor has shown potent in vitro and in vivo activity in numerous models of solid tumors with squamous histology.

Methods: Oral selinexor was given at 8-10 doses (2-3 times/week)/28-day cycle as part of an ongoing Phase 1 study in advanced solid tumors (KCP-330-002, NCT01607905). Response evaluation was done every 2 cycles (RECIST 1.1). Over 130 patients (pts) were enrolled, including 17 pts with heavily pretreated HN-SCC with objectively progressive disease (PD) on study entry.

Results: Seventeen pts with HN-SCC (14 M, 3 F; median age 56 yrs; ECOG PS 0/1: 4/13; median prior regimens: 2.6 (range 1-4)) received selinexor across 6 dose levels (23 to 65 mg/m²). Grade 4 AEs included thrombocytopenia without bleeding in 3 pts. The most common AEs (Grade 1/2/3) include: fatigue (12%/41%/6%), nausea (41%/6%/6%), anorexia (12%/41%/0%), diarrhea (35%/12%/0%), weight loss (18%/24%/0%) and thrombocytopenia (18%/0%/12%). Supportive care with glucocorticoids, appetite stimulants and anti-emetics improved constitutional symptoms. Pharmacokinetics and pharmacodynamics showed dose-dependent increases in Cmax/AUC0-inf and in XPO1 mRNA. Tumor biopsies showed nuclear localization of TSPs (p53, FOXO3A, IκB) and apoptosis induction. Fourteen pts with PD on study entry were evaluable for efficacy. Nine patients (64%) had stable disease and 5 pts (36%) had progressive disease. 5 pts have remained on therapy for ≥4 months (4-13).

Conclusions: Oral selinexor is generally well tolerated and can be administered over prolonged periods. Durable single agent disease control was observed in heavily pretreated HN-SCC pts. The recommended dose is 65 mg/m² twice weekly and a Phase 2 study in patients with HN-SCC is expected to begin in mid 2014.

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