Clinical Activity of the Oral Selective Inhibitor of Nuclear Export (SINE™) Selinexor (KPT-330) in Patients with Head & Neck Squamous Cell Carcinoma (HN-SCC)

Abstract 6980


1. Moffitt Cancer Center, Tampa, FL, USA; 2. Gabriel Cancer Center, Canton, OH, USA; 3. Karmanos Cancer Institute, Detroit, MI, USA; 4. Department of Oncology, Rigshospitalet, Copenhagen, Denmark; 5. Karyopharm Therapeutics Inc., Newton, MA, USA; 6. Olimex Research Inc., Toronto, Canada (Drug Development Program, Princess Margaret Cancer Center, Toronto, Ontario)

Selinexor Inhibits XPO1

Major Eligibility Criteria:
- XPO1 is the sole nuclear exporter among major tumor-suppressor proteins (TSPs)
- XPO1 is overexpressed in esophageal SCC and many other solid tumors and its loss often correlates with poor outcomes

Selinexor Inhibits XPO1

Selinexor (KPT-330) is a covalent, slowly-reversible, selective inhibitor of nuclear export (SINE™) that inhibits XPO1

HPV infection is associated with 14% of HN-SCC overall and 53% of head and neck squamous cell carcinomas

Selinexor single agent can stabilize tumour suppressors like p53 and pRb, leading to disruption of HPV-dependent and HN-SCC cell survival

Selinexor is tolerated with manageable side effects of fatigue, anorexia, nausea and weight loss

Selinexor single agent can stabilize disease progression with tumor shrinkage in different types of head and neck squamous cell carcinomas

Selinexor (35 mg/m²) is an XPO1 antagonist, is rational therapy for HN-SCC based upon an MDA that involves forced nuclear retention of the tumor suppressors p53 and pRb, leading to disruption of HPV dependence and tumor cell survival

Conclusions

Primary: Safety, tolerability and Recommended Phase 2 Dose (RP2D)
Secondary: Pharmacokinetics (PK), pharmacodynamics (PD), anti-tumor response and confirmation of EOC of selinexor

Selinexor Mechanism of Action

Effect of XPO1 inhibition on the transcription of TSPs

• Inhibits XPO1

Selinexor PK/PD

• Plasma concentration

• PK/PD

• XPO1 inhibition

• Median AUC and T1/2

• Sinephosphatidyl

• Disruption of p53-pRb-PTEN Pathway

Pathway A: p53-pRb-PTEN Pathway
- Prevents p53 from leaving the nucleus
- Selinexor induces nuclear retention of Fbxw7 and degradation of Notch
- Export

Pathway B: XPO1 Pathway
- Prevents pRb from leaving the nucleus
- Selinexor induces nuclear retention and stabilization of pRb

Safety & Pharmacokinetics

• PK/PD

• Median AUC and T1/2

• Cmax and AUC in plasma are proportional to dose and t1/2

• Disruption of p53-pRb-PTEN Pathway

Pathway A: p53-pRb-PTEN Pathway
- Prevents p53 from leaving the nucleus
- Selinexor induces nuclear retention of Fbxw7 and degradation of Notch
- Export

Pathway B: XPO1 Pathway
- Prevents pRb from leaving the nucleus
- Selinexor induces nuclear retention and stabilization of pRb

Safety & Pharmacokinetics

• PK/PD

• Median AUC and T1/2

• Cmax and AUC in plasma are proportional to dose and t1/2

• Disruption of p53-pRb-PTEN Pathway

Pathway A: p53-pRb-PTEN Pathway
- Prevents p53 from leaving the nucleus
- Selinexor induces nuclear retention of Fbxw7 and degradation of Notch
- Export

Pathway B: XPO1 Pathway
- Prevents pRb from leaving the nucleus
- Selinexor induces nuclear retention and stabilization of pRb

Summary data are presented here from the ongoing first in human phase 1 study of oral selinexor and focused on patients with advanced head and neck solid tumors

Safety & Pharmacokinetics

• PK/PD

• Median AUC and T1/2

• Cmax and AUC in plasma are proportional to dose and t1/2

• Disruption of p53-pRb-PTEN Pathway

Pathway A: p53-pRb-PTEN Pathway
- Prevents p53 from leaving the nucleus
- Selinexor induces nuclear retention of Fbxw7 and degradation of Notch
- Export

Pathway B: XPO1 Pathway
- Prevents pRb from leaving the nucleus
- Selinexor induces nuclear retention and stabilization of pRb

Summary data are presented here from the ongoing first in human phase 1 study of oral selinexor and focused on patients with advanced head and neck solid tumors

Safety & Pharmacokinetics

• PK/PD

• Median AUC and T1/2

• Cmax and AUC in plasma are proportional to dose and t1/2

• Disruption of p53-pRb-PTEN Pathway

Pathway A: p53-pRb-PTEN Pathway
- Prevents p53 from leaving the nucleus
- Selinexor induces nuclear retention of Fbxw7 and degradation of Notch
- Export

Pathway B: XPO1 Pathway
- Prevents pRb from leaving the nucleus
- Selinexor induces nuclear retention and stabilization of pRb

Clinical Activity of the Oral Selective Inhibitor of Nuclear Export (SINE™) Selinexor (KPT-330) in Patients with Head & Neck Squamous Cell Carcinoma (HN-SCC)

Clinical Activity of the Oral Selective Inhibitor of Nuclear Export (SINE™) Selinexor (KPT-330) in Patients with Head & Neck Squamous Cell Carcinoma (HN-SCC)

Clinical Activity of the Oral Selective Inhibitor of Nuclear Export (SINE™) Selinexor (KPT-330) in Patients with Head & Neck Squamous Cell Carcinoma (HN-SCC)

Clinical Activity of the Oral Selective Inhibitor of Nuclear Export (SINE™) Selinexor (KPT-330) in Patients with Head & Neck Squamous Cell Carcinoma (HN-SCC)