Abstract #5086: Tipifarnib, a farnesyltransferase inhibitor, for metastatic urothelial carcinoma harboring HRAS mutations

Authors: Jiyun Lee,1 Hana Kim,1 Antonio Gualberto,2 Catherine Scholz,2 Se Hoon Park1

1 Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, 2 Kura Oncology, Inc., Cambridge, MA, USA

BACKGROUND

- In urothelial carcinoma (UC), RAS somatic mutation, which leads to constitutive activation of cell growth stimulating signals and controlled cell proliferation is highly prevalent with HRAS being most prominent.
- Tipifarnib (Kura Oncology) is an orally administered, highly potent and selective non-peptide farnesyl transferase inhibitor (FTI).
- This is a phase II trial to assess antitumor and safety of tipifarnib in UC patients with missense HRAS mutation.

METHODS

- Metastatic UC patients with no available systemic therapy.
- Molecular criteria for eligibility:
  - Missense, non-synonymous HRAS mutation
  - STK11: rs2075606 (T>C) single nucleotide variant
- Tipifarnib 900 mg twice daily P.O. on D1-7, D15-21 of 28-day cycle

RESULTS

- Consort diagram of the study
- Eligible and received treatment (n = 21)
- Discontinued treatment (n = 19)
  - Disease progression (n = 14)
  - Consent withdrawal (n = 4)
  - Death (n = 2)
- Excluded due to unavailable / insufficient tumor tissues (n = 25)
- Screened for HRAS mutations and STK11: rs2075606 (n = 224)

- Patients screened for eligibility (n = 245)

- Patient characteristics
  - Age: 64 (range: 51–77)
  - Prior systemic chemotherapy: 2 (range: 1–4)

- Safety
  - The most frequently observed AE were fatigue (86%) and hematologic toxicities.
  - All grades | Grade 3 or 4
  - Neutropenia | 14 (67%) | 4 (19%)
  - Febrile neutropenia | 3 (14%)
  - Anemia | 16 (76%) | 8 (38%)
  - Thrombocytopenia | 10 (48%) | 6 (30%)
  - Anorexia | 9 (43%) | 1 (5%)
  - Nausea | 7 (33%) | 2 (10%)
  - Vomiting | 5 (24%) | 0
  - Stomatitis | 3 (14%) | 0
  - Constipation | 3 (14%) | 0
  - Diarrhea | 3 (14%) | 0
  - Fatigue | 18 (86%) | 3 (14%)
  - Pruritus | 2 (10%) | 0
  - Rash | 3 (14%) | 0
  - Pain | 6 (30%) | 0
  - Transaminase increase | 1 (5%) | 0
  - Creatinine increase | 3 (14%) | 1 (5%)  

- Efficacy
  - Median F/U duration: 28 months
  - Median PFS: 4.7 months, OS: 6.1 months
  - PFS rate at 6 months (PFS6): 19% (95% CI: 2–36%)
  - ORR: 24% (95% CI: 6–42%)

- Tipifarnib showed a manageable safety profile and encouraging efficacy in pretreated, metastatic UC patients with HRAS mutations.
- Further studies for potential combinations with other agents, e.g. immune checkpoint inhibitors, should be considered.

DISCUSSION

- Tipifarnib is not effective in patients with wildtype HRAS but polymorphism rs2075606 (T>C) in STK11 intron

Correspondence: Se Hoon Park, MD, PhD.
Division of Hematology-oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Email: hematoma@sckku.edu