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

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## BACKGROUND

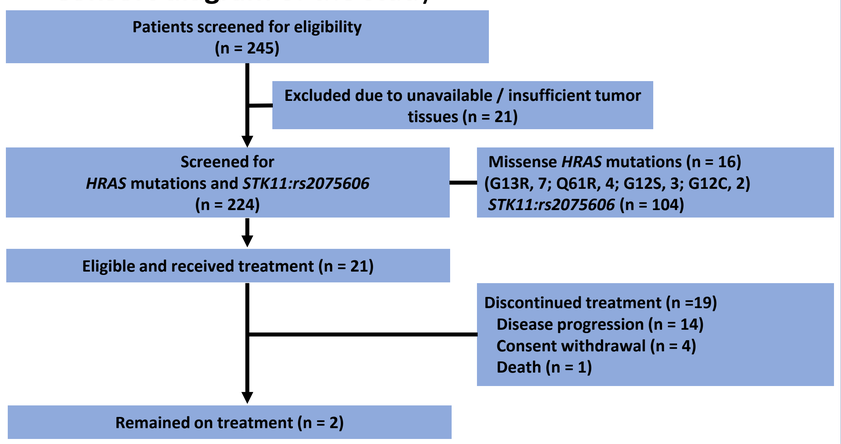
- In urothelial carcinoma (UC), RAS somatic mutation, which leads to constitutive activation of cell growth stimulating signals and controlled cell proliferation is highly prevalent with HRAS being most prominent.
- Tipifarnib (Kura Oncology) is an orally administered, highly potent and selective non-peptide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

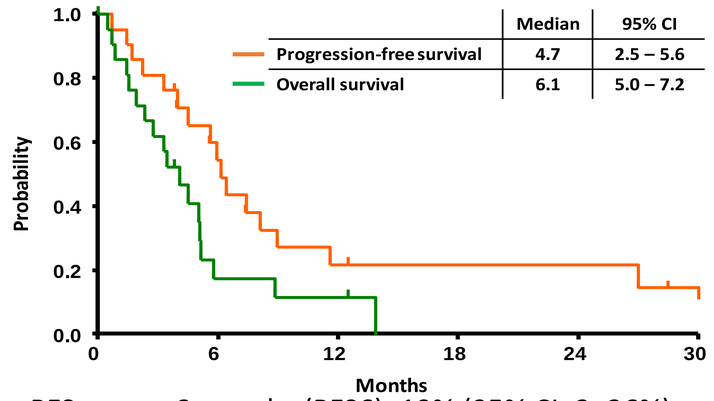
- **Consort diagram** of the study



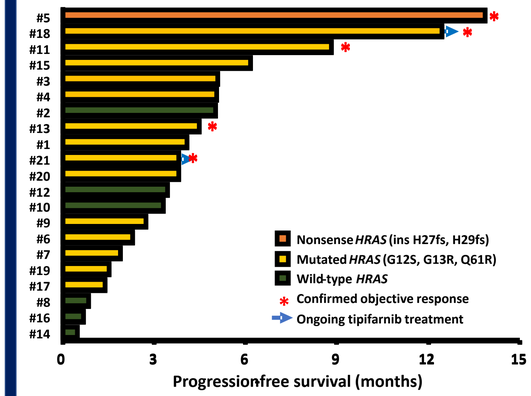

- **Patient characteristics**
  - Age: 64 (range: 51–77)
  - Prior systemic chemotherapy: 2 (range: 1–4)
- **Safety**
  - The most frequently observed AE were fatigue (86%) and hematologic toxicities.

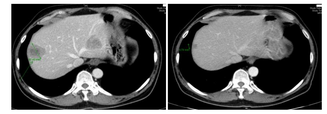
| | All grades | Grade 3 or 4 |
|---|---|---|
| Neutropenia | 14 (67%) | 4 (19%) |
| Febrile neutropenia | | 3 (14%) |
| Anemia | 16 (76%) | 8 (38%) |
| Thrombocytopenia | 10 (48%) | 6 (30%) |
| Anorexia | 9 (43%) | 1 (5%) |
| Nausea | 7 (33%) | 2 (10%) |
| Vomiting | 5 (24%) | 0 |
| Stomatitis | 3 (14%) | 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

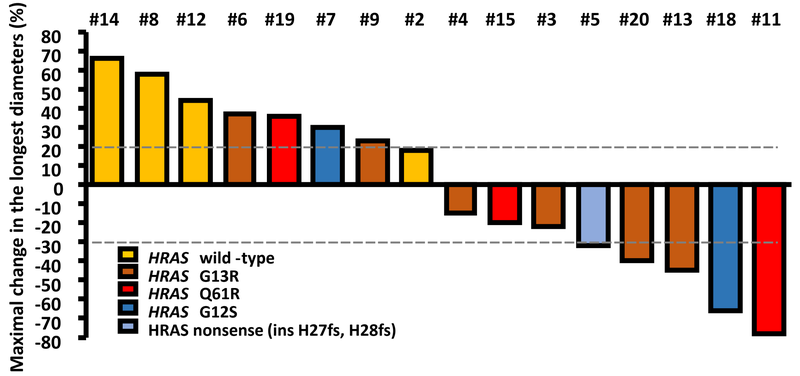



  - PFS rate at 6 months (PFS6): 19% (95% CI: 2–36%)
  - ORR: 24% (95% CI: 6–42%)
- Swimmer plot for treatment duration



- Waterfall plot for maximal change in tumor size




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

## DISCUSSION

- 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.

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