ABSTRACT #TPS3178: An open-label study to assess the safety and efficacy of naporafenib (ERAS-254) administered with trametinib in previously treated patients with locally advanced unresectable or metastatic solid tumor malignancies with RAS Q61X mutations [SEACRAFT-1]

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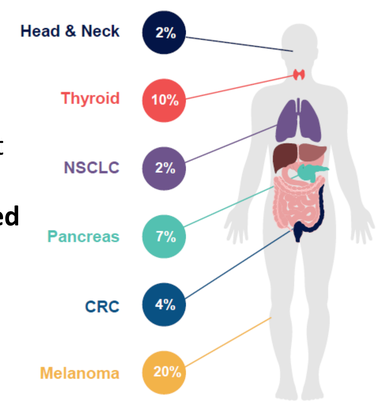
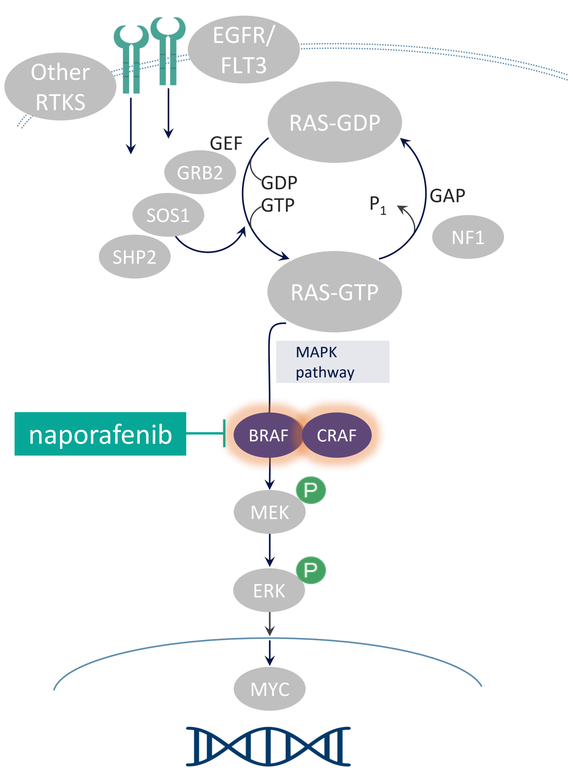
OBJECTIVE: Assess if **RAS Q61X** is a potential **predictive biomarker** for the combination of naporafenib with trametinib

NAPORAFENIB BACKGROUND

- Inappropriate activation of the **RAS/MAPK pathway drives tumorigenesis**
- Compared to other mutations in RAS, mutations at codon 61 (**RAS Q61X**) are thought to be the most oncogenic and are prevalent in tumor types with **high unmet need**
- RAS Q61X mutations drive downstream signaling via both **BRAF and CRAF**
- **Naporafenib** is a potent and selective inhibitor of **BRAF and CRAF**[1]

Incidence of RAS Q61X





- Naporafenib has been dosed as **a monotherapy or in combination** with other anticancer agents in more than **500 patients**, establishing its safety, tolerability, and preliminary **proof-of-concept** in multiple indications
- Results from studies in NRAS Q61X melanoma and KRAS Q61X non-small cell lung cancer (NSCLC) support **development in RAS Q61X tissue agnostic solid tumors** (SEACRAFT-1)

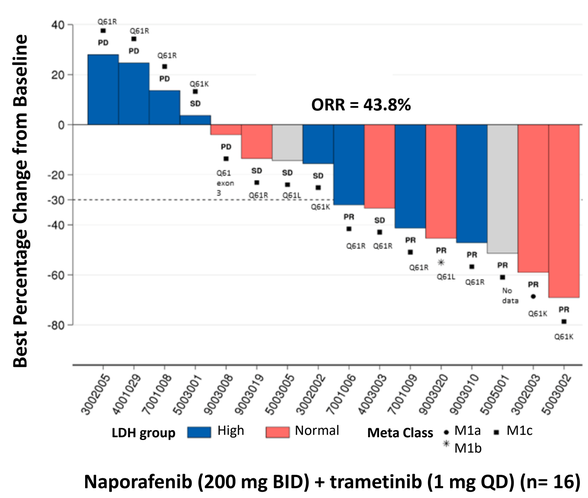
NRASm melanoma (study LXH254X2102)

- Encouraging **antitumor activity**, with confirmed ORR = 44%
- 15 out of 16 patients had confirmed **codon Q61X melanoma** (1 patient had no data)

KRASm NSCLC (study LXH254X2102)

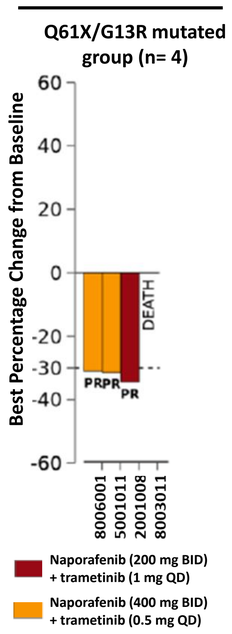
- **2 confirmed partial responses (PRs)** out of 3 patients with Q61X mutation
- **1 unconfirmed PR** in the patient with G13R mutation

NRASm Melanoma



Naporafenib (200 mg BID) + trametinib (1 mg QD) (n= 16)

KRASm NSCLC



Source: LXH254X2102 Ph 1b combination data from Novartis Non-Confidential Materials

PATIENT ELIGIBILITY

Key Inclusion Criteria

- Locally advanced or metastatic tumor that has progressed on or is intolerant to standard therapy, or for which no standard therapy exists, or is not a candidate for standard therapy
- Documentation of a RAS Q61X mutation (tumor tissue or blood)
- ANC ≥1.5, plt >75, Hgb ≥9, total bili ≤ULN, ALT/AST ≤3x ULN (≤5x ULN w/liver metastases)
  - Adolescents: ANC ≥1.0, plt >75, Hgb ≥8, total bili ≤ULN for age, ALT/AST ≤3x ULN for age (≤5x ULN w/liver metastases)
- LDH ≤2.5x ULN (patients with melanoma only)
- Estimated creatinine clearance per institutional standards ≥30 mL/min
- Eastern Cooperative Oncology Group (ECOG) status 0, 1, or 2
  - Adolescents ≥70 (Lansky or Karnofsky, age dependent)
- Pts with controlled central nervous system metastases are eligible

Key Exclusion Criteria

- Prior therapy with an ERK, MEK, RAF, or RAS inhibitor
- Treatment with prior anti-cancer therapy ≤2-4 weeks (or 5 half-lives) prior to first dose of study treatment Timing based on type of therapy
- QTcF at screening >450 ms
- Left ventricular ejection fraction (LVEF) <50%
  - Adolescents <LLN
- Uncontrolled HTN (≥150/100)
  - Adolescents: elevated blood pressure (above 95% of the age-specific percentile)[2]

STUDY DESIGN AND ENDPOINTS

Screening

Pts with solid tumors (Age 12+)

Post-available therapy

Confirm RAS Q61Xm

Add QR code

Treatment

naporafenib (200 mg, oral BID) + **trametinib** (1 mg, oral QD) 28-day cycles

End of Treatment (EOT) visit

Adults (≥18 years) with tumor harboring **RAS Q61X** (n = ~15 per cohort)

- melanoma
- NSCLC
- thyroid
- CRC
- pancreatic
- other solid tumors (n= ~25)

Adolescent sub-study (≥ 12 to <18 years) with any tumor harboring RAS Q61X (n= 15)

Follow up

Safety Follow Up: 30 days after the decision to permanently discontinue study treatment

Survival Follow Up: Contact every 3 months

Endpoints

Primary

ORR (objective response rate)

Secondary

DOR (duration of response)
PFS (progression free survival)
DCR (disease control rate)
TTR (time to response)
PK of naporafenib and trametinib
OS (overall survival)

BID = twice daily; CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QD = once daily; PDX = patient-derived xenograft; PK = pharmacokinetics; Pt = patients

ENROLLMENT, STATUS, AND REGISTRATION

- A total of **up to 115 pts** will be enrolled
- Treat until disease progression, unacceptable toxicity, or withdrawal of consent
- Enrollment is **ongoing**
- Clinical trial registry number - **NCT05907304**
- **SEACRAFT-1; Protocol ERAS-254-01**
- Study Centers in USA, Canada, UK, Australia, and South Korea

REFERENCES

1. Monaco K-A, Delach S, et al. LXH254, a Potent and Selective ARAF-Sparing Inhibitor of BRAF and CRAF for the Treatment of MAPK-Driven Tumors. 2021. PMID: 33355204
2. National High Blood Pressure Education Program Working Group, 2004