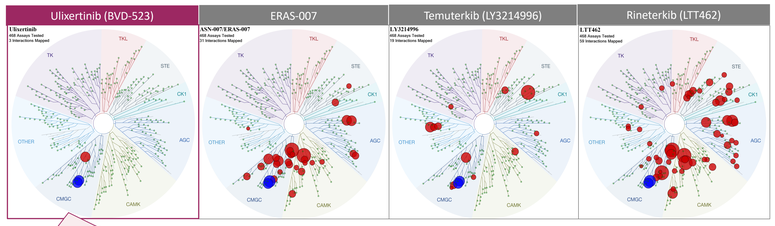
Ulixertinib, a first-in-class ERK1/2 inhibitor, as an effective combination agent in RAS mutated malignancies

Caroline M. Emery[1], Deborah Knoerzer[1], Anupama Reddy[2], Jessica Box[1], Anna Groover[1], Martin Teresk[1], Brent Kreider[1]
[1]BioMed Valley Discoveries, Inc., Kansas City, Missouri, USA, [2]Vindhya Data Science Inc., Morrisville, NC, USA.

Background

- Ulixertinib is a highly potent and selective ERK1/2 inhibitor poised for clinical differentiation in multiple indications[1,2].
- To date, over 500 patients have been treated with ulixertinib. Confirmed responses have been observed in patients harboring alterations within the RAS-MAPK pathway.
- Ongoing and planned clinical trials cover both ulixertinib monotherapy and combination settings across a variety of tumor types and mutational drivers.
- As emerging resistance mechanisms to KRAS^{G12C} inhibitors continue to be dominated by MAPK pathway re-activation, blockade with an ERK inhibitor at the terminal node of the MAPK pathway should provide durable intervention.

1. Ulixertinib is a selective ERK1/2 inhibitor



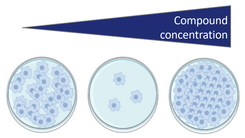
Ulixertinib binds ERK1/2 with minimal off-target effects while other compounds bind to numerous additional kinases.

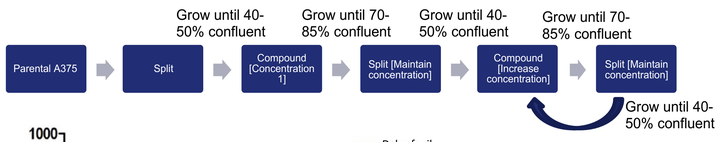
- Each inhibitor assayed at 2 μM concentration
- TREEspot Spot cut-off = 10 % ≥ control

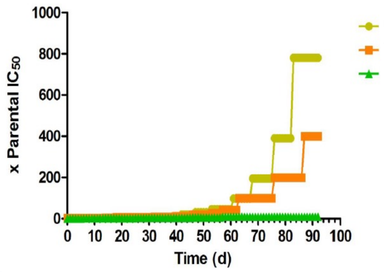
- Ulixertinib, in addition to other ERK1/2 inhibitors, were assayed against the KINOMEscan®, an active site directed competition binding assay against 468 kinases. Results for ulixertinib, ERAS-007, temuterkib, and rineterkib shown.
- Ulixertinib demonstrated a superior selectivity profile compared to the other ERK1/2 inhibitors.
- In addition to binding to ERK1/2, ulixertinib binds to ERK8 in this assay; 0.15, 0.3 and 0.45 % control, respectively.

2. Resistance to ulixertinib is delayed compared to other MAPK pathway inhibitors

- *In vitro* models of ulixertinib resistance were generated in an endeavor to characterize and predict potential mechanisms of resistance and guide rational combination therapies.
- The BRAF^{V600E} mutant melanoma cell line, A375, was cultured in progressively increasing concentrations of ulixertinib or other MAPK pathway inhibitors (dabrafenib and/or trametinib).





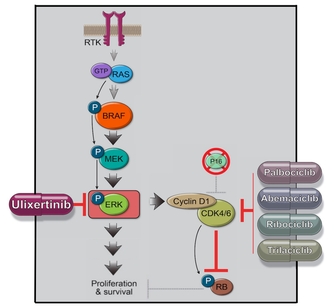


- Dabrafenib (BRAFi) or Trametinib (MEKi) culturing achieved 100x parental cell IC50 within 2 months.
- > 3 months of ulixertinib culturing was required to achieve growth in 15x parental IC50.
- This may translate to improved durability of response to ulixertinib in the clinic, especially in the setting of an optimal combination regimen.

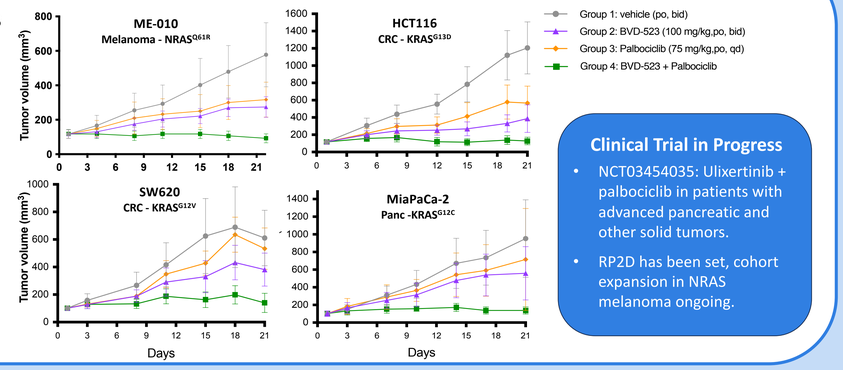
3. Combination of ulixertinib and palbociclib demonstrate significant efficacy in vivo

- It has been well established that ERK activation increases cyclin D1 levels and entry into the cell cycle[3]. The combination of MEKi with CDK4/6i has been shown to be beneficial[4] and has since been tested in the clinic.
- We hypothesized that the combination of ERK1/2 and CDK4/6 inhibitors (A) would have synergistic antitumor activity in RAS mutated tumors.
- Four xenograft models were utilized to assess the combination of ulixertinib and palbociclib, each xenograft harboring a RAS mutation (B).
- Ulixertinib monotherapy across all models showed modest tumor growth inhibition (TGI) while palbociclib monotherapy showed limited TGI across all models.
- The combination groups demonstrated significant responses ranging from 75% - 90% TGIs. All treatment regimens were well tolerated across all models.

A



B



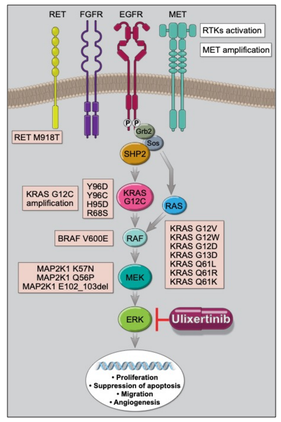
Clinical Trial in Progress

- NCT03454035: Ulixertinib + palbociclib in patients with advanced pancreatic and other solid tumors.
- RP2D has been set, cohort expansion in NRAS melanoma ongoing.

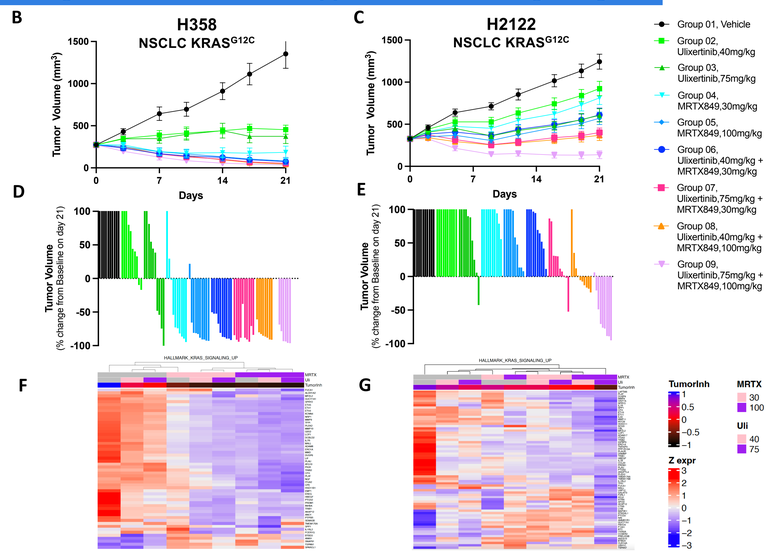
4. Ulixertinib plus KRAS^{G12C} inhibitor resulted in superior tumor growth inhibition and suppression of KRAS signaling

- Clinically described mechanisms of acquired resistance to KRAS^{G12C} inhibitors converge on reactivation of the *RAS-MAPK* pathway (A)[5-8].
- The efficacy of ulixertinib, in combination with KRAS^{G12C} inhibitor, adagrasib (MRTX849), was assessed in cell line-derived xenograft models harboring *KRAS*^{G12C} mutations. Models were selected based on response to single agent adagrasib, ranging from sensitive (H358) to partially responsive (H2122)[7].

A



- Combining ulixertinib with MRTX849 (MRTX) resulted in superior tumor growth inhibition compared to dosing of either single agent alone in both models (B-E). In H2122 high-dose combination treatment (Groups 8 and 9) yielded robust regression compared to all other treatment groups.
- Tumor volume over time is shown for groups dosed to day 21 for H359 (B) and H2122 (C). Tumor volume percent change from baseline at day 21 is shown for H359 (D) and H2122 (E). Visualization of growth is capped at 100% (D, E).
- Differential expression analysis was performed on tumors collected on day 21 to identify pathways associated with tumor growth inhibition (F,G). Consistent with previous studies by others[9], significantly enriched genesets related to KRAS signaling, apoptosis, mTOR, MYC, and cell cycle were revealed. Combination treatment further enriched each of these pathways compared to single agent MRTX849.
- The KRAS signaling up geneset was robustly down-regulated by the MRTX + uli combination groups compared to vehicle in H358 (F), and in H2122 (G).
- **These data provide a robust rationale for combining ulixertinib with KRAS^{G12C} inhibition in the clinic. Discussions are ongoing regarding clinical deployment.**



5. Ulixertinib clinical trials underway and in development

	Pre-clinical / Protocol Development	Phase 1	Phase 2
Monotherapy			
Expanded Access Protocol (EAP)	NCT04566393		
Adult low-grade glioma	NCT05804227		
Histiocytosis	Q4 / 2023		
Pediatric low-grade glioma (pLGG)	Q1 / 2024		
Combinations			
+ Hydroxychloroquine (HCQ)	NCT05221320 (Multiple GI Cancers)		
+ Palbociclib	NCT03454035 (NRAS Melanoma)		
+ multiple combinations (EAP)	NCT04566393 (Solid Tumors)		
+ EGFRi, +/- BRAFi	Q4 / 2023 (CRC)		
Pediatric low-grade glioma (pLGG) + RAF / Senolytics TBD	Q1 / 2024		
POC combinations of interest: + RAFi, KRASi, JAKi, STATi, MDM2i	TBD		

Conclusions

- Ulixertinib demonstrates tumor regression in multiple RAS driven models as monotherapy, in combination with CDK4/6 inhibitors, and in combination with KRAS^{G12C} inhibitors.
- By targeting the last node in the MAPK pathway with ulixertinib, we believe that more durable MAPK inhibition will be possible and that the pathway reactivation resistance mechanisms will be addressed.
- Ulixertinib has established tolerable BID doses in both adult and pediatric patient populations, with 500+ patients treated to date. Multiple clinical efforts are underway in RAS/MAPK activated patient populations.

References

1. Germann et al. Mol Cancer Ther. 2017 Nov;16(11):2351-2363.
2. Sullivan et al. Cancer Discov. 2018;8(2):184-195.
3. Ravenhall C, et al. Br J Pharmacol. 2000 Sep;131(1):17-28.
4. Kwong LA et al. Nat Med. 2012 Oct;18(10): 1503-1510.
5. Tanaka N, et al. Cancer Discov. 2021 Aug;11(8):1913-1922.
6. Zhao Y et al. Nature. 2021 Nov;599(7886):679-683.
7. Awad MM et al. N Engl J Med. 2021 Jun 24;384(25):2382-2393.
8. Blaquier JB, Cardona AF, Recondo G. Front Oncol. 2021 Dec 24;11:787585.
9. Hallin J et al. Cancer Discov. 2020 Jan;10(1):54-71.

For poster PDF scan the QR code