BioMed Valley Discoveries

A phase 2 basket trial of ulixertinib (BVD-523) in combination with hydroxychloroquine in patients with advanced gastrointestinal malignancies harboring MAPK pathway mutations (BVD-523-HCQ)

Abstract TPS4174

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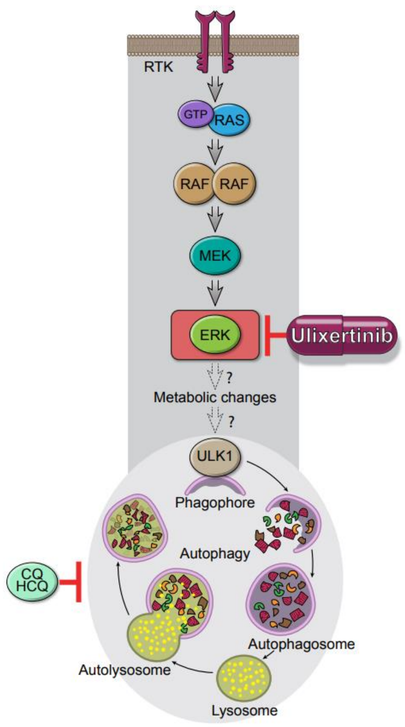
1. Background

- RAS-induced signaling through the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway plays an important role in the pathogenesis of many solid tumors.
- Ulixertinib (BVD-523) is a first-in-class and best-in-class small molecule inhibitor of ERK 1/2 that is currently being investigated in multiple cancer clinical trials, both as a single agent and as part of combination therapy.[1]
- Preclinical studies have demonstrated that inhibition of the RAS/MAPK/ERK signaling cascade leads to upregulation of autophagy, a catabolic pathway that includes the lysosomal degradation of proteins to support cellular metabolism during times of cellular stress.
- Given cancer cells' increased reliance on autophagy to enhance their survival in this context, this study seeks to evaluate the combination of ulixertinib with hydroxychloroquine, an antimalarial drug known to suppress autophagy, in patients with advanced gastrointestinal malignancies harboring mutations in genes involved in MAPK signaling.

2. Rationale

A. Preclinical

- A new understanding of the connection between the autophagy and the MAPK pathways has been developing over the past 5-10 years.
- By recycling cellular components during autophagy, the cancer cell manages to continue to fuel its high metabolic needs despite the potentially cytotoxic effects of pathway inhibition.
- Not only do MAPK mutated cells rely on a higher level of baseline autophagy, but it has also been demonstrated that cells with higher levels of resistance also have increased levels of autophagy.[2,3]
- Kinsey et al. have shown that inhibition of KRAS – RAF – MEK – ERK signaling in pancreatic ductal adenocarcinoma (PDAC) cell lines elicits autophagy.[4]
- Combining ulixertinib with chloroquine in PDAC organoid and PDX models demonstrated synergistic antitumor activity.[5]



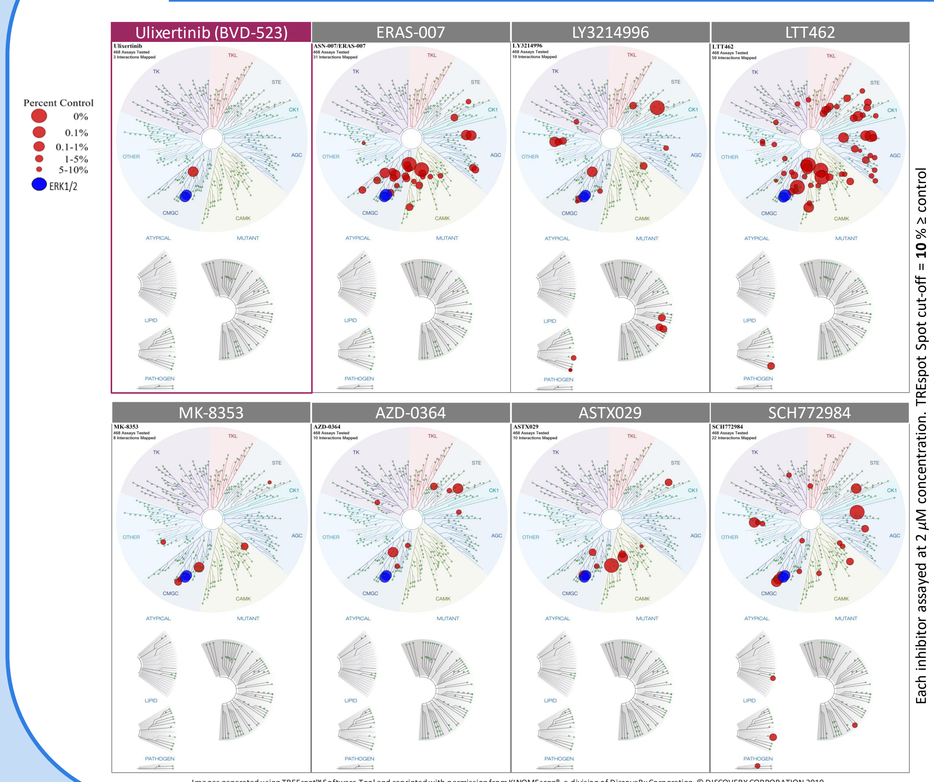
B. Clinical

- Multiple case reports have been published demonstrating the promising efficacy of combining MAPKi and hydroxychloroquine for treatment of KRAS-mutated colon and pancreatic cancers.[4,6,7]

Additional clinical trials:

- Trametinib and Hydroxychloroquine in Treating Patients With Pancreatic Cancer (THREAD) (NCT038252589)
- Phase II Study of Combination of Trametinib (MEK Inhibitor) and Hydroxychloroquine (HCQ) (Autophagy Inhibitor) in Patients With KRAS Mutation Refractory Bile Tract Carcinoma (BTC) (NCT04566133)
- Ulixertinib (BVD-523) and Hydroxychloroquine in Patients with Advanced MAPK-Mutated Gastrointestinal Adenocarcinomas (UTAH) (NCT04145297)
  - Phase 1 – Set dose of 450mg BID ulixertinib in combination with 600mg BID hydroxychloroquine

3. Ulixertinib is a potent and highly selective ERK1/2 inhibitor



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

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- Ulixertinib inhibits ERK1/2, the terminal master regulator kinase in the MAPK pathway.
- Ulixertinib, in addition to 7 other ERK1/2 inhibitors, were assayed against the KINOMEscan®, an active site directed competition binding assay against 468 kinases.
- Ulixertinib demonstrated a superior selectively profile compared to the other ERK1/2 inhibitors.

Acknowledgments

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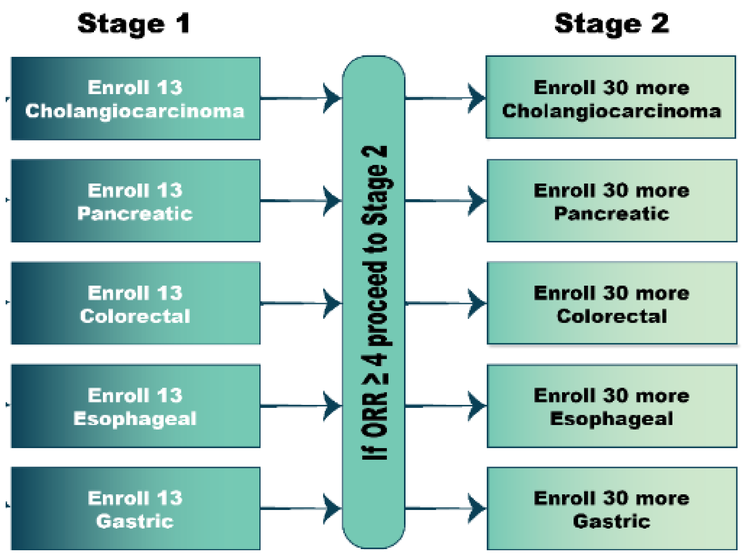
- BioMed Valley Discoveries for activities related to ulixertinib development (Lisa Lassise and Corey Burton).
- Cmed for the clinical operations of the BVD-523-HCQ phase II clinical trial.
- Mark Miller (Stowers Institute for Medical Research, Kansas City, MO) for pathway illustrations.

4. BVD-523-HCQ trial design



- This is an open-label, multicenter, phase II basket study of ulixertinib in combination with hydroxychloroquine in patients with advanced GI malignancies harboring mutations in one of the following MAPK signaling-associated genes: KRAS, NRAS, HRAS, BRAF (non-V600), MEK1/2, or ERK1/2.
- The trial has five baskets based on primary disease: cholangiocarcinoma, pancreatic adenocarcinoma, colorectal adenocarcinoma, esophageal adenocarcinoma, and gastric adenocarcinoma.
- If a basket in stage 1 achieves the ORR to proceed to stage 2, an additional 30 patients will be added.
- Planned correlative analyses include pharmacokinetics, reverse phase protein array, and transcriptomics of tumor tissue.

5. Endpoints, Dosing Schedule, Schedule of Assessments, and Statistics

- Primary endpoints of overall response rate (ORR), as defined by the proportion of patients achieving a confirmed PR and CR (defined by RECIST 1.1) as evaluated by the local treating investigator and safety of combination treatment.
- Secondary endpoint of progression-free survival (PFS), as defined as the time from study drug initiation to the time of documented disease progression (as assessed by RECIST 1.1) or death from any cause.
- Ulixertinib (450mg, PO) and hydroxychloroquine (600mg, PO) will be administered twice-daily on a 28-day cycle starting with cycle one day one.
- Schedule of assessments include disease assessments (CT scans) at baseline and repeated every 8 weeks regardless of dose holds or delays. Biopsies at screening and cycle three day one are required along with an optional biopsy offered at the time when the decision to discontinue treatment is made. A standard ophthalmologic exam must be completed at screening, C2D1, and every 3 cycles therafter and as clinically indicated to assess for retinopathies. A full PK curve will be conducted on cycle one day 15.
- Under Simon's optimal two-stage design with a 5% significance level and 80% power, assuming a null hypothesis for ORR ≤ 20% versus the alternate hypothesis of ORR ≥ 40%, a total of 43 evaluable patients are required for the evaluation of the primary endpoint; 13 in Stage 1 and an additional 30 in Stage 2, for each basket.

6. BVD-523-HCQ key inclusion/exclusion criteria

Key Inclusion

- Male of female patient aged ≥ 18 years.
- Histologically confirmed esophageal adenocarcinoma, esophageal squamous cell carcinoma, GEJ adenocarcinoma, gastric adenocarcinoma, pancreatic adenocarcinoma, intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma, extrahepatic cholangiocarcinoma, or colorectal adenocarcinoma harboring a MAPK-mutated GI malignancy: KRAS, NRAS, HRAS, BRAF non-V600, MEK1/2 (MAP2K1/2), or ERK1/2 (MAPK3/1).
- Patients must have been previously treated with one or more lines of anti-cancer therapy and have documented disease progression during or after their most recent line of anti-cancer treatment.
- Patients must have measurable disease by RECIST version 1.1.
- Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1.
- Willing to provide a biopsy at the time points indicated on the Schedule of Activities.
- Adequate renal function Estimated creatinine clearance (CL_{cr})≥ 50 mL/min by Cockcroft-Gault.
- Adequate hepatic function [total bilirubin ≤1.5 times ULN; AST (aspartate transaminase) and ALT (alanine transaminase) ≤3 times ULN or ≤5 times ULN if the elevation is due to liver involvement by tumor].

Key Exclusion

- Received systemic antineoplastic therapy (including unconjugated therapeutic antibodies and toxin immunoconjugates) or any investigational therapy ≤ 14 days or within five half-lives prior to starting study treatment, whichever is shorter.
- Known uncontrolled brain metastases or cranial epidural disease. Stable brain metastases/cranial epidural disease s either treated or being treated with a stable dose of steroids/anticonvulsants, with no dose change in the previous 4 weeks, can be allowed. In the event of steroid taper post-radiation therapy, taper must be complete within 2 weeks before baseline.
- History or current evidence of central serous retinopathy (CSR) or retinal vein occlusion (RVO) or current risk factors for RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyperviscosity).
- Prior stomach or duodenal resection that in the opinion of the Principal Investigator and Medical Monitor would affect the breakdown and absorption of the study medications. A patient with a feeding tube should also be excluded, as ulixertinib capsules cannot be taken apart.

Conclusion

- Ulixertinib (BVD-523) is a potent and selective small molecule inhibitor of ERK1/2. Ulixertinib has been dosed in hundreds of patients to date and has demonstrated activity in patients with a wide range of tumor types harboring molecular alterations in the MAPK pathway.
- The BVD-523-HCQ phase II clinical trial is designed to evaluate the combination of ulixertinib with hydroxychloroquine in patients with advanced gastrointestinal malignancies harboring mutations in genes involved in MAPK signaling.
- The BVD-523-HCQ phase II clinical trial (NCT05221320) is ongoing. At the time of abstract submission, 26 patients of the planned 65 patients in stage 1 had been enrolled.
- Contact for comments or questions: info@biomed-valley.com

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