ERK1/2 Inhibitor Ulixertinib Demonstrates Activity in Atypical (non-V600) BRAF Mutant Models

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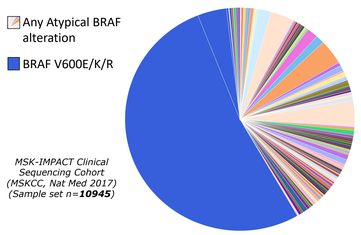
BioMed Valley Discoveries

Abstract #4022

Background

- Atypical BRAF (non-V600) alterations comprise approximately 50% of all BRAF mutations in cancer and can be categorized according to characteristics of molecular signaling (either Class II or III).
- Atypical BRAF alterations are rare (approximately 3% across all human cancers) and there are currently no approved therapies for this indication.
- As next-generation sequencing becomes standard clinical practice, oncologists are frequently identifying atypical BRAF alterations in their patients' tumors.
- The efficacy of the first-in-class ERK1/2 inhibitor, ulixertinib (BVD-523), was assessed across 10 patient-derived xenograft (PDX) models, which harbored class II or III BRAF alterations.
- RNA-sequencing was performed on tumors from the vehicle-treated and ulixertinib-treated groups to identify potential proctors of ulixertinib response.

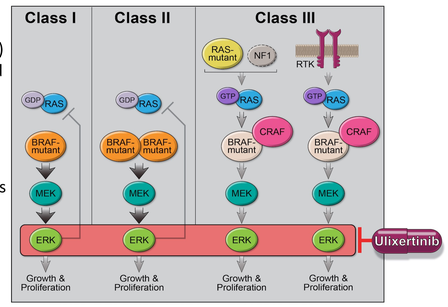
1. Atypical BRAF alterations comprise ~ 50% of all BRAF cancer associated aberrations



- The MSK-IMPACT Clinical Sequencing Cohort was utilized to investigate incidence of BRAF alterations across cancer types (sample n=10945).
- Approximately half of all BRAF alterations were non-V600.
- There are approximately 180 non-V600 BRAF alterations within this dataset.
- There are currently no approved targeting agents for patients with tumors harboring atypical BRAF alterations.

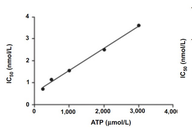
2. Molecular characteristics define BRAF alterations into classes

- BRAF alterations can be categorized based on characteristics of signaling[1-2].
- Class I BRAF alterations (V600 point mutations) signal in a RAS independent manner. Approved therapies are available for this class of BRAF alteration.
- Class II signal as RAS independent, mutant-mutant BRAF dimers.
- Class III favor binding CRAF and RAS to signal as mutant-BRAF plus wild-type CRAF dimers.
- Ulixertinib (ERK1/2 inhibitor) inhibits signaling downstream of all classes of BRAF alterations.
- Driven by high-unmet medical need, these studies are focused on Class II and III BRAF alterations.

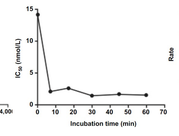


3. Ulixertinib is a potent and selective ERK1/2 inhibitor

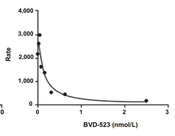
ATP-Competitive



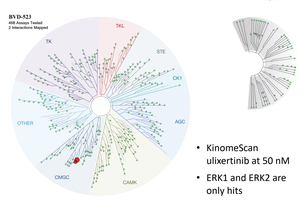
Rapid Onset



Potent

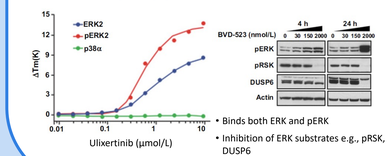


Highly Selective



- KinomeScan ulixertinib at 50 nM
- ERK1 and ERK2 are only hits

Target Engagement and Inhibition (pRSK)



- Binds both ERK and pERK
- Inhibition of ERK substrates e.g., pRSK, DUSP6
- Inhibited ERK is hyperphosphorylated

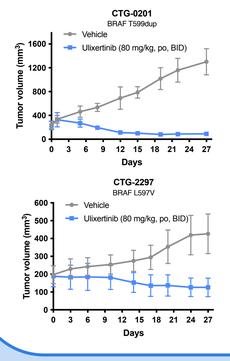
- Ulixertinib is a potent and selective ATP-competitive inhibitor of ERK1/2[3].
- Ulixertinib activity in patients with tumors harboring alterations within the MAPK pathway has been previously described[4].

4. Characteristics of Class II and III PDX models

Model	Tumor type	Patient Prior Treatment (Response)	Disease Stage	Mutations	BRAF Alteration Class
CTG-0201	Melanoma	Temozolomide (not available)	IV	BRAF T599dup	II
CTG-0282	Pancreatic	Erlotinib, Sorafenib, Oxaliplatin, Carboplatin/Paclitaxel, Gemcitabine, Irinotecan (not available)	IV	BRAF G469A	II
CTG-0362	Melanoma	Not available	IV	BRAF K601E	II
CTG-0370	Hepatocellular carcinoma (HCC)	Not available	Not Available	BRAF G469A	II
CTG-2297	Endometrial	Carboplatin/Paclitaxel (responded; 8 months), Lurbinectedin/Paclitaxel (Mixed response), Docetaxel (No response), Topotecan/Bevacizumab (Responded; 4 months), Trametinib (not available)	I	BRAF L597V	II
CTG-0064	Colorectal	5-Fluorouracil/Oxaliplatin (not available)	II	BRAF G469E	III
CTG-0165	NSCLC	Carboplatin/Docetaxel (no response)	IV	BRAF N581I	III
CTG-1444	NSCLC	Carboplatin/Nab-paclitaxel (responded; duration 3 months)	IV	BRAF G466V	III
CTG-1684	Breast	Gemcitabine (not available)	Not Available	BRAF D594N	III
CTG-1501	Melanoma	Not available	III	BRAF G469E	III
				BRAF P367L	II

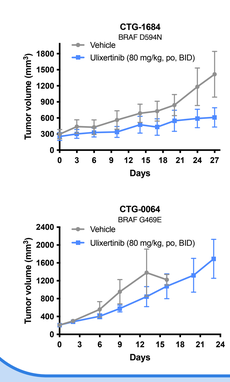
- 10 Patient Derived Xenograft (PDX) models selected representing a range of tumor types.
- Each model harbors an atypical BRAF (non-V600) alteration.
- Five models with Class II alterations, 4 with Class III, and 1 with both a Class II and Class III.
- Presence of mutant BRAF alleles was readily confirmed from RNA-seq data in all PDX models.

5. Ulixertinib efficacy in Class II BRAF mutant PDX models



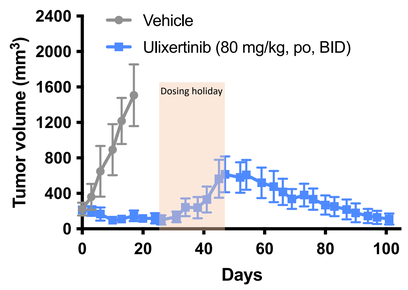
- Ulixertinib resulted in tumor regression in CTG-0201 (melanoma), and CTG-2297 (Endometrial).
- Ulixertinib resulted in overall response of statis in 3 models: CTG-0370 (HCC), CTG-0282 (pancreatic), CTG-0362 (melanoma).

6. Ulixertinib efficacy in Class III BRAF mutant PDX models



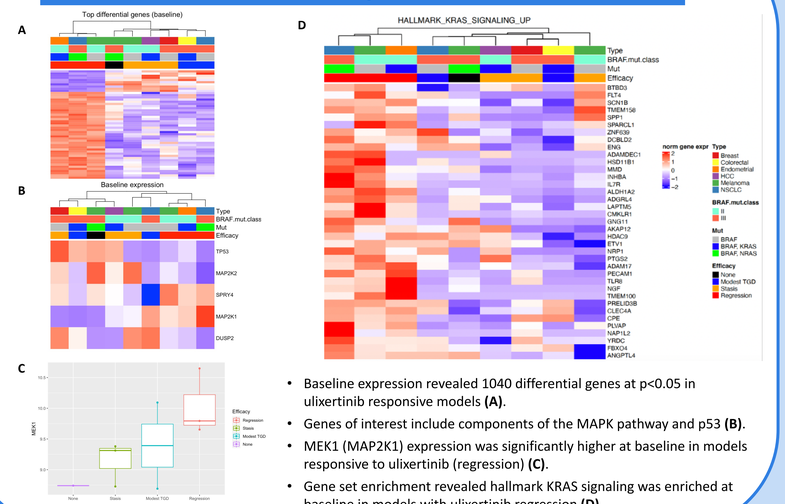
- Ulixertinib resulted in modest tumor growth delay in CTG-1684 (Breast), CTG-0165 (NSCLC) and CTG-0064 (CRC).
- Ulixertinib resulted in tumor regression in CTG-1444 (NSCLC).
- Ulixertinib demonstrated no activity in melanoma model CTG-1501 (both Class II and III BRAF mutations present).

7. Ulixertinib efficacy following dosing holiday



- CTG-1444 NSCLC PDX model with a Class III BRAF alteration responded robustly to ulixertinib treatment (TGI > 100%) compared to the vehicle control group.
- Ulixertinib treatment was stopped on day 27, tumor outgrowth occurred.
- On day 47, ulixertinib dosing was resumed. Despite the enlarged tumor volume, the tumor regressed.

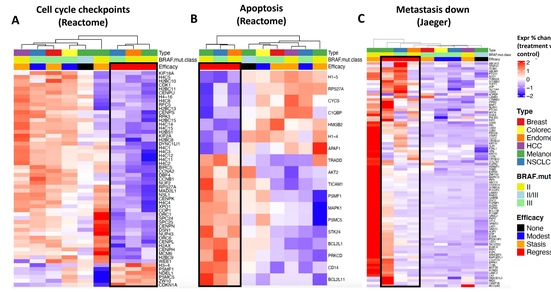
8. Enriched baseline expression of MAPK pathway genes in ulixertinib responsive models



- Baseline expression revealed 1040 differential genes at p<0.05 in ulixertinib responsive models **(A)**.
- Genes of interest include components of the MAPK pathway and p53 **(B)**.
- MEK1 (MAP2K1) expression was significantly higher at baseline in models responsive to ulixertinib (regression) **(C)**.
- Gene set enrichment revealed hallmark KRAS signaling was enriched at baseline in models with ulixertinib regression **(D)**.

9. Cell cycle, apoptosis, and metastasis gene sets are regulated in ulixertinib responsive models

- Expression levels in vehicle treated samples were compered to ulixertinib treated samples to reveal differentially expressed gene sets perturbed by treatment.
- Cell cycle gene sets were decreased in ulixertinib responsive models **(A)**. Combining ulixertinib with a CDK4/6 inhibition is hypothesize to increase magnitude and/or duration of response (**see Abstract #1057**).
- Apoptosis signaling was increased in the responsive models **(B).**
- Metastasis down-regulation **(C)** gene sets were enriched in responsive models.



Conclusions

- Monotherapy ulixertinib is efficacious in PDX models harboring atypical BRAF alterations (Class II and Class III). Robust regression to moderate tumor growth delay were observed in 9/10 models.
- Gene expression analysis showed enriched MAPK pathway expression at baseline in ulixertinib responsive models compared to the non-responders. EMT gene set was enriched in ulixertinib responsive models, conversely metastasis and cell cycle gene sets were decreased.
- Exploring rational ulixertinib combinations may increase magnitude and/or duration of response (e.g., CDK4/6 inhibition (**see Abstract #1057**); this combination is currently under clinical evaluation in a phase I trial (NCT03454035)).
- Ulixertinib has FDA Fast Track designation for patients with solid tumors, other than colorectal cancers, harboring specific atypical BRAF mutations: G469A/V, L485W, and L597Q. Ulixertinib is currently under clinical evaluation in patients with tumors harboring any atypical BRAF alteration (NCT04488003).

References

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