Abstract Details

Session title: Late Breaking and Best Proffered Papers
Session type: Plenary Session 1
Track: LIVE - pre-rec and live Q&A
Catalog number: 5
Presentation number: ORAL-005

Abstract title:
Intermittent dosing of RMC-4630, a potent, selective inhibitor of SHP2, combined with the MEK inhibitor cobimetinib, in a phase 1b/2 clinical trial for advanced solid tumors with activating mutations of RAS signaling

1Sarah Cannon Research Institute/Tennessee Oncology, Drug Development Unit, Nashville, USA.
2Sarah Cannon Research Institute/University of Oklahoma, Oklahoma TSET Phase I Program, Oklahoma City, USA.
3City of Hope Medical Center, Department of Medical Oncology & Therapeutics Research, Duarte, USA.
4Johns Hopkins University, Upper Aerodigestive Department, Baltimore, USA.
5University of Texas, Department of Oncology, Austin, USA.
6Honor Health, Department of Hematology and Oncology, Scottsdale, USA.
7University of California, Thoracic Oncology, San Francisco, USA.
8Karmanos Cancer Center, Department of Oncology, Detroit, USA.
9Dana-Farber Cancer Institute, Department of Medical Oncology, Boston, USA.
10University of Colorado, Department of Oncology, Denver, USA.
11University of California, Department of Hematology and Oncology, Davis, USA.
12US Oncology, Department of Oncology, Fairfax, USA.
13Emory University, Department of Hematology and Medical Oncology, Atlanta, USA.
14Revolution Medicines- Inc., Medical Director, Redwood City, USA.
15Revolution Medicines- Inc., Oncology, Redwood City, USA.
16Sanofi, Oncology, Cambridge, USA.
17Revolution Medicines- Inc., Non-clinical Development and Pharmacology, Redwood City, USA.
18Revolution Medicines- Inc., Clinical Development, Redwood City, USA.
19University of California, Department of Hematology and Oncology, Irvine, USA.

Background

Single agent MEK inhibition has been disappointing in clinical trials of RAS mutant tumors, probably due to the induction of resistance through upstream activation of receptor tyrosine kinases (RTKs). RMC-4630 is a potent, selective inhibitor of SHP2, a convergent signaling node for many RTKs. RMC-4630 monotherapy has shown anti-tumor activity against RAS-mutant NSCLC in an ongoing phase 1 clinical trial (NCT03634982). RMC-4630 has combinatorial activity with MEK inhibitors in preclinical models of RAS-mutant cancers and tumors harboring loss of neurofibromin 1 (NF1LOF) and BRAFclass3mutations. Intermittent dosing of RMC-4630, to provide discontinuous SHP2 inhibition above the EC50 for RAS pathway inhibition, retains anti-tumor activity and is better tolerated than daily continuous dosing.

Methods

In this phase 1b/2 study (NCT03989115), RMC-4630 and cobimetinib were both sequentially dose-escalated in patients with tumors harboring RAS pathway alterations (KRASG12x, KRASamp, NF1LOF, BRAFclass3). RMC-4630 was administered twice weekly (D1,D4 or D1,D2); cobimetinib was dosed either daily (21 days on, 7 off) or twice weekly on D1,D2.

Results
The study is ongoing and the recommended phase 2 dose and schedule (RP2DS) is currently being refined. As of 18 May 2020, 33 patients have been treated across four different dose cohorts/schedules. The highest dose level of RMC-4630 tested to date is 140 mg (D1,D2 or D1,D4 twice weekly); the highest dose level of cobimetinib tested is 40 mg daily or 60 mg D1,D2. The most common treatment-related adverse events (TRAEs) were diarrhea (63.6%), edema (33.3%), and thrombocytopenia (24.2%). Grade 3-4 TRAEs were diarrhea (9.1%) and thrombocytopenia (6.1%). Blurred vision and retinopathy were reported in 4 patients (1 with Grade 2; 1 with Grade 3 AEs), reversible on holding cobimetinib dosing. The observed safety profile is consistent with an ‘on-pathway’ effect of the combination and with previous clinical experience of both RMC-4630 and MEK inhibitors. The pharmacokinetic profiles of both RMC-4630 and cobimetinib were generally consistent with monotherapies and no pharmacokinetic interaction has been detected. At all dose levels and schedules tested, exposure was within the range that induced tumor regressions in preclinical models. Preliminary evidence of anti-tumor activity has been observed in KRASmut colorectal cancer with tumor reduction in 3 of 8 patients including, at data cut-off, 1 unconfirmed PR (range of tumor reduction 10-30%; time on treatment 1.9-5.1 months).

Conclusions

The interim data suggest that the combination of intermittent RMC-4630 plus daily or intermittent cobimetinib has acceptable tolerability at doses that exceed ‘target’ plasma exposure based on preclinical models of RAS-pathway driven cancers. Further evaluation of anti-tumor activity in RAS-activated tumors will occur at the RP2DS.

Conflict of interest:
Conflict of interest:
Advisory Board:
J. Bendell: Consulting /Advisory Role -All to Institution
•Gilead
•Genentech / Roche
•BMS
•Five Prime
•Lilly
•Merck
•MedImmune
•Celgene
•Taiho
•Macrogenics
•GSK
•Novartis
•OncoMed
•LEAP
•TG Therapeutics
•AstraZeneca
•BI
•Daiichi Sankyo
•Bayer
•Incyte
•Apexigen
•Array
•Sanofi
•ARMO
•Ipsen
•Merrimack
•Oncogenex
•FORMA
•Arch Oncology
•Prelude Therapeutics
•Phoenix Bio
•Cyteir
•Molecular Partners
•Innate
•Torque
•Tizona