The PLK1 Inhibitor Onvansertib is Active as Monotherapy and in Combination with Cetuximab in RAS Wild-type Colorectal Cancer Patient-derived Xenografts.

AACR 2024
Poster #1934

Maya Ridinger[1,3], Preeti Kanikarla[2,3], Fengqin Gao[2], Zhensheng Liu[2], Giulia Maddalena[2], David Menter[2], Alexey Sorokin[2], Tod Smeal[1], Scott Kopetz[2]

1. Cardiff Oncology, San Diego, CA, USA; 2. Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; 3. equal contribution

Background and Aims

Current therapies for metastatic colorectal cancer (mCRC):

- include cytotoxic chemotherapy combined with targeted therapy against the epidermal growth factor receptor (EGFR, cetuximab and panitumumab) or the vascular endothelial growth factor (VEGF, bevacizumab).
- EGFR inhibitors (EGFRi) have shown to provide clinical benefit to mCRC patients with *RAS* wild-type (RAS^{WT}) tumors[1,2]. However, their clinical benefit are limited due to intrinsic resistance or development of resistance.
- New therapeutic strategies are needed to prolong the clinical benefit of EGFRi and overcome resistance.

Polo-like kinase 1:

- Serine/threonine protein kinase, key regulator of the cell cycle.
- Overexpressed in CRC and associated with poor prognosis[3,4].
- PLK1 inhibition has been shown to sensitize non-small lung cancer to EGFRi in preclinical models[5-7].

Onvansertib:

- An oral small molecule, selective inhibitor of PLK1.
- Showed robust antitumor activity in combination with irinotecan and bevacizumab in *RAS*-mutant CRC xenograft models[8-10].
- Currently under clinical development in combination with chemotherapy + bevacizumab for *RAS*-mutant mCRC (NCT03829410, NCT06106308) – see posters #2031 and #CT275 for more details.

This study aimed at assessing the efficacy of onvansertib as monotherapy and in combination with cetuximab in RAS^{WT} CRC patient-derived xenograft (PDX) models, sensitive or resistant to cetuximab.

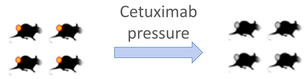
Methods

Generation of RAS^{WT} CRC PDX models → **Determination of cetuximab sensitivity**

Treatment with cetuximab (20mg/kg, BIW) for 15 days

Tumor stasis/regression → Cetuximab sensitive
Tumor progression → Cetuximab resistant

Generation of cetuximab-acquired resistance



Development of resistance → Cetuximab acquired resistance

Assessment of onvansertib and cetuximab (cetux) antitumor activity

Models:

- 7 PDXs sensitive to cetux
- 7 PDXs with intrinsic resistance to cetux
- 6 PDXs with acquired resistance to cetux

Treatment (n=5-7 mice/arm) for 18-19 days

- Vehicle
- Cetuximab (IP, 20mg/kg, twice per week)
- Onvansertib (oral, 60mg/kg, daily)
- Onv + Cetux as monotherapies

Results

1. PDXs Sensitive to Cetuximab

- As expected, all models responded to cetuximab.
- Onvansertib induced tumor stasis or regression in 5 models and tumor growth inhibition in 2 models.
- Combination treatment resulted in tumor regression in the 7 models. Antitumor activity of the combination was slightly increased compared to cetuximab single agent in 5/7 models.

2. PDXs with Intrinsic Resistance to Cetuximab

- Cetuximab resistance was confirmed in 6 of the 7 models.
- Onvansertib induced tumor stasis or regression in 5/7 models and tumor growth inhibition in 2 models.
- Combination treatment resulted in tumor regression in 6 models and tumor growth inhibition in 1 model. Antitumor activity of the combination was significantly greater compared to monotherapies in 4/7 models.

3. PDXs with Acquired Resistance to Cetuximab

- 4 models were resistant to cetuximab, 2 showed partial response.
- Onvansertib induced tumor stasis or regression in 4/6 models and tumor growth inhibition in 1 model.
- The combination treatment resulted in tumor stasis or regression in 5/6 models, and superior antitumor activity compared to single agents in 2 models.

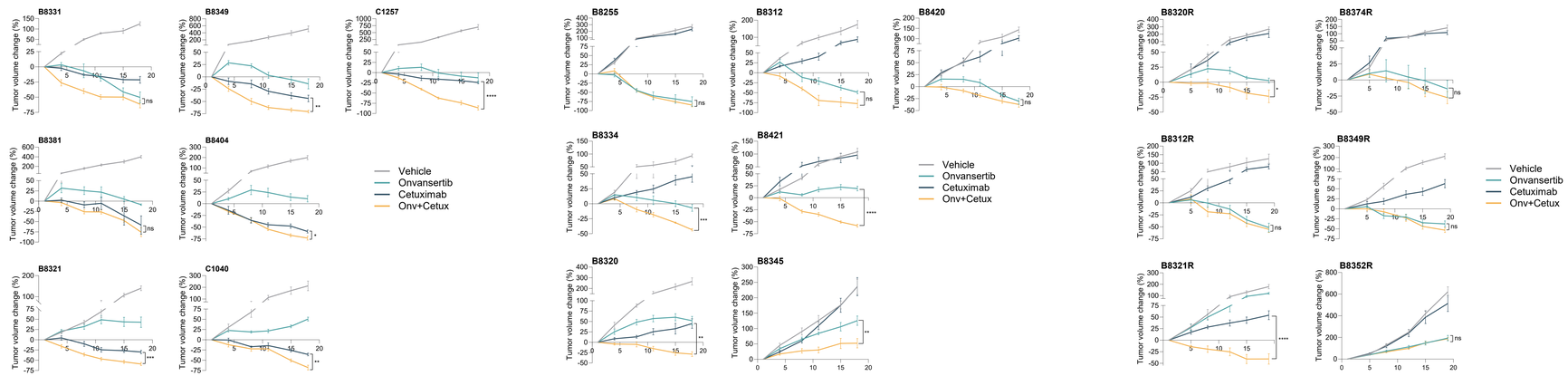


Figure 1. Antitumor activity of onvansertib and cetuximab in RAS^{WT} CRC PDX models sensitive to cetuximab (left), or with intrinsic (middle) or acquired (right) resistance to cetuximab. PDX models were treated with vehicle, onvansertib (Onv), cetuximab (Cetux) or the combination (Onv+Cetux) for 18-19 days. Tumor volumes (TV) were measured twice a week, and % tumor volume change (TVC) from baseline was calculated as follows: $(TV_i/TV_0\text{-}1)*100$. Tumor stasis defined as TVC between 0 and 20%, and tumor regression as TVC less than 0% at last measurement. Results are presented as mean ± SEM. Unpaired t-test was used to compare %TVC at last measurement between combination treatment and the most effective monotherapy ;*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

4. Onvansertib Monotherapy and in Combination with Cetuximab Across Models

- Onvansertib induced tumor regression (n=11) or stasis (n=3) in 14 (70%) of the 20 models.
- Onvansertib potent antitumor activity was observed in PDX models sensitive to cetuximab (5/7, 71%) and resistant to cetuximab (9/13, 69%).
- Onvansertib + cetuximab induced tumor regression in 18 (90%) of the 20 models.
- Overall, the antitumor activity of the combination was superior compared to monotherapies in both cetuximab sensitive and resistant models.

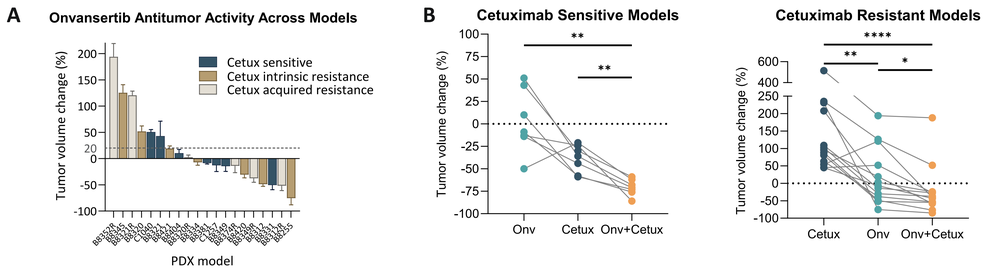


Figure 2. Antitumor activity of onvansertib monotherapy and in combination with cetuximab across all models. A. %tumor volume change (TVC) at last measurement for onvansertib group across all models (mean ± SEM). **B.** %TVC for onvansertib (Onv), cetuximab (Cetux) and combination (Onv+Cetux) groups for all models. One-way ANOVA with Tukey's multiple comparisons test was used to compare %TVC, *p<0.05, **p<0.01, ****p<0.0001.

Conclusions

- Onvansertib displayed robust antitumor activity in RAS^{WT} CRC PDXs:
  - Induced tumor stasis or regression in 70% (14/20) of the models.
  - Efficacy was independent of cetuximab sensitivity, similar antitumor activity observed in cetuximab sensitive and resistant models.
- Onvansertib + cetuximab combination was highly effective:
  - Induced tumor stasis or regression in 90% (18/20) of the models.
  - Resulted in enhanced efficacy compared to monotherapies.
- Genomic and proteomic analyses are ongoing to identify potential biomarkers of response and resistance to onvansertib.
- Collectively, these data support the clinical development of onvansertib as a potential treatment for RAS wild-type colorectal cancer.

References

1. Bokemeyer *et al.*, Eur J Cancer 2012, 48 (10)
2. Douillard *et al.*, Ann Oncol 2014, 25 (7)
3. Takahashi *et al.*, Cancer Science 2003, 94 (2)
4. Ran *et al.*, Gene 2019, 721
5. Nilsson *et al.*, Sci Transl Med 2020, 12 (559)
6. Eggermont *et al.*, Cancers (Basel) 2023, 15 (9)
7. Wang *et al.*, Oncotarget 2016, 7 (30)
8. Valsasina *et al.*, Mol. Cancer Ther. 2012, 11 (4)
9. Ahn *et al.*, Clin Cancer Res 2024
10. Kopetz *et al.*, Annals of Oncology 2022, 33, S704

Cardiff Oncology contact: Maya Ridinger PhD, mridinger@cardiffoncology.com. **MD Anderson contact**: Scott Kopetz MD PhD, skopetz@mdanderson.org. **Presented at** AACR 2024 - Experimental and Molecular Therapeutics.