HUMANITAS
CANCER CENTER

PHASE II STUDY OF TIVANTINIB (ARQ 197) IN COMBINATION WITH CETUXIMAB IN EGFR INHIBITOR-RESISTANT, MET-HIGH, KRAS WILD-TYPE METASTATIC COLORECTAL CANCER (NCT01892527)

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BACKGROUND

- MET overexpression has been found in 30-70% CRC, plays an important role in CRC progression and metastasis, and can be associated to resistance to anti-EGFR therapy[1]
- EGFR inhibitors may have a role beyond progression in mCRC[2-4]
- Tivantinib (ARQ 197) is a non-ATP-competitive, oral inhibitor of the MET receptor tyrosine kinase with activity on different cancer cell lines, including MET-High CRC lines[5-7]
- In 4 randomized, placebo controlled studies in lung, hepatocellular, colorectal and prostate carcinomas evidence of benefit from tivantinib was observed in MET-High patients only[8-11]
- Tivantinib in combination with cetuximab and irinotecan was well-tolerated and active in MET-High, second/third line CRC patients[10]
- The combination of tivantinib and cetuximab in MET-High patients in this setting appears attractive, based on the above shown background

STUDY DESIGN AND CONDUCT

This is an investigator-initiated, Italian, multicenter, single-arm, Simon 2-stage, phase II study.

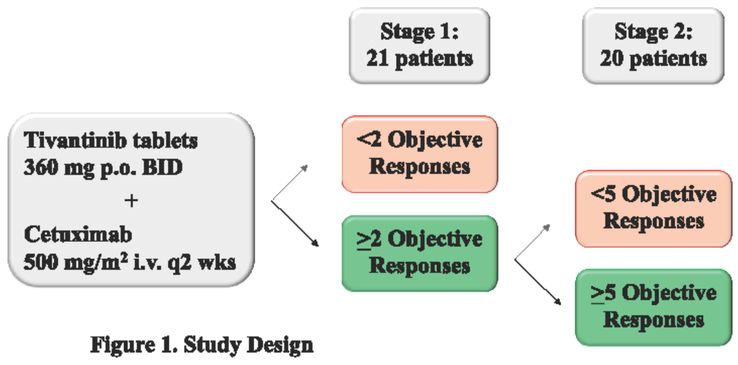

Figure 1. Study Design

The use of cetuximab beyond progression on prior anti-EGFR therapy is off-label.

Statistics: This design would reject the null hypothesis of true response rates of ≤5% with a type I error rate of 0.05 and a statistical power greater than 0.90 at the alternative hypothesis of true response rates of ≥20%.

Tumor Assessments: Computed tomography / magnetic resonance imaging scans are performed every 8 weeks. Complete (CR) and partial response (PR) must be confirmed no sooner than 4 weeks after the initial observation.
Safety Assessments: Hematology weekly in the first 2 cycles, every 2 weeks in following cycles. Chemistry, physical examination and AEs collection every 2 weeks.

Patients continue in the study until disease progression, unacceptable toxicity, or withdrawal from the study for other reasons. Patients discontinued from study treatment are followed for survival.

OBJECTIVES

Primary Endpoint:
- Objective Response Rate (ORR)

Secondary Endpoints:
- Progression-free Survival, Overall Survival, Safety

Exploratory Endpoints:
- Efficacy correlation with baseline tumor PTEN, *BRAF*, EGFR status

KEY ELIGIBILITY CRITERIA

- Surgically unresectable locally advanced or metastatic CRC
- ≥1 prior line of systemic therapies for advanced or metastatic disease
- Stable disease (SD) or better response to last treatment regimen containing cetuximab or panitumumab
- Progression on cetuximab or panitumumab within 3 months from enrollment
- Wild-type form of the gene *KRAS*
- MET-High tumors tested by IHC (IHC 2+ or 3+ in ≥50% of tumor cells) using the SP44 antibody at a central lab
- Measurable disease according to RECIST criteria, version 1.1
- Eastern Cooperative Oncology Group (ECOG) performance Status ≤2

RESULTS

Table 1. Patients Disposition and Treatment

	N (%)
Consented	**42 (100)**
MET-High*	**22 (52.4)**
Screen Failure	**1 (4.5)**
Enrolled	**21 (95.5)**
Treatment Discontinuation	**20 (95.2)**
Progressive Disease	15 (75)
Adverse Events	4 (20)
Death	1 (5)
Treatment Ongoing	**1 (4.8)**
Dose Reductions due to AEs	**8 (38.1)**
Dose Delays due to AEs	**6 (28.6)**
Median Time on Treatment, mos (range)	**2.8 (1.6-19.8)**

RESULTS

Table 2. Baseline Patients Characteristics

	N=21
Median Age, yrs (range)	**66.7 (50.9-78.1)**
Gender, N (%)	
Male / Female	**12 (57.1) / 9 (42.9)**
ECOG PS Score, N (%)	**20 (95.23)***
0 / 1	13 (65) / 7 (35)
Number of Metastatic Sites, median (range)	**2 (1-4)**
Prior Treatment, N (%)	
Surgery	17 (81)
Radiation	4 (19)
Prior Systemic Treatment, median (range)	**2 (1-4)**
Prior Systemic Treatment, N (%)	**20 (95.23)***
Irinotecan	19 (95)
Oxaliplatin	15 (75)
Bevacizumab	8 (40)
Median Time between anti-EGFR and Enrollment, mos (range)	**1.94 (0.76-8.6)****
Median CEA Value, ng/ml (range)	**50 (2-604)*****

*Data available for 20 pts. **1 protocol violation.
***Data available for 13 pts

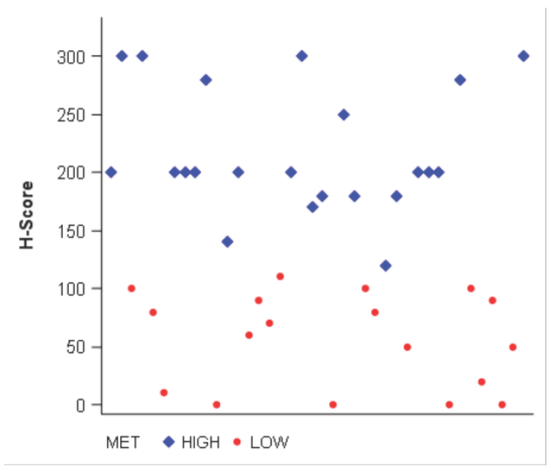

Figure 2. Patient distribution by MET H-Score

No correlation was found between MET-status and timing of biopsy (before/after anti-EGFR therapy). However, since data collection is not completed, no analysis is possible in terms of relation between MET-status and prior chemotherapy, surgery, or biopsy site.

Table 3. Adverse Events Summary

Preferred Term	All Grades, N (%)	Grade ≥3, N (%)
Most Common (≥10%) AEs:		
Skin Toxicity	**13 (61.9)**	**2 (9.5)**
Fatigue	**8 (38.1)**	**3 (14.3)**
Neutropenia	**9 (42.9)**	**8 (38.1)***
Anemia	**6 (28.6)**	**4 (19.0)**
Nausea/Vomiting	**5 (23.8)**	**-**
Hypomagnesemia	**3 (14.3)**	**1 (4.8)**
Diarrhea	**3 (14.3)**	**-**
Less Common AEs of Interest:		
Thrombocytopenia	**1 (4.8)**	**1 (4.8)**

*Including 2 patients with febrile neutropenia and 1 toxic death

Table 4. Best Overall Response

	N=21 (%)	Median duration, mos (range)
Best Response		
Complete Response	1 (4.8)	1+*
Partial Response	2 (9.5)	2.6; 19.8
Stable Disease	8 (38.1)**	4.6 (3.6-5.0)
Progressive Disease	9 (42.9)	-
Not Evaluable	1 (4.8)	-
Objective Response Rate (CR + PR)	**3 (14.3)**	**5.5 (2.6-19.8)**
Disease Control Rate (CR + PR + SD)	**11 (52.4)**	**4.6 (2.6-19.8)**

* This patient obtained PR at week 8, and CR at week 32
**Including 2 PR for which confirmatory CT scan was not performed

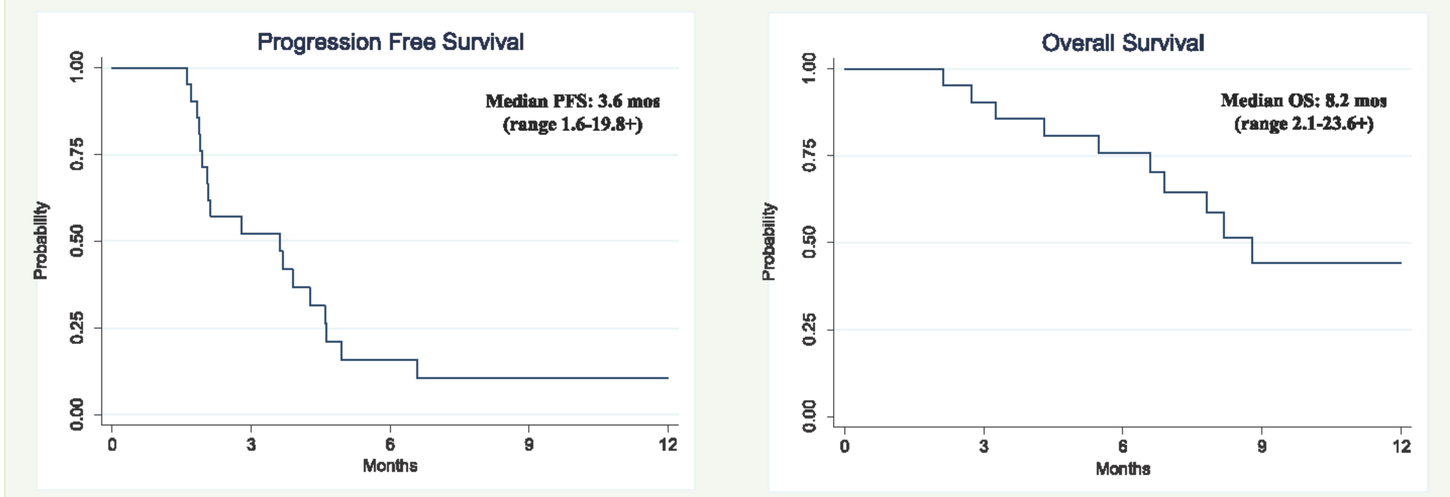

Figure 3. Progression-free and Overall Survival - Median Follow-up: 12.8 mos (range 2.1-23.6)

Table 5. Responding Patients Characteristics

Characteristics	Pt # 001007	Pt # 001001	Pt # 001013
Gender, Age (yrs)	**F, 74**	**F, 60**	**M, 67**
Prior Therapies	**FOLFIRI + Cet**	**FOLFOX, FOLFIRI + Bev, CPT11 + Cet**	**XELOX + Bev, CPT11 + Cet, FOLFIRI + Cet**
Disease Sites	**Colon, Liver, Lung, Abd Nodes**	**Liver, Lung, Abd Nodes**	**Liver, Lung**
CEA (ug/L)	**604**	**61**	**8**
MET H-Score	**200**	**200**	**200**
Objective Response	**PR (-49%)**	**PR (-36%)**	**CR**
CEA Response (ug/L)	**168**	**57**	**2**
Time on Therapy (mos)	**6.6**	**18.4**	**8.3+**
Dose reduction	**Yes**	**No**	**Yes**

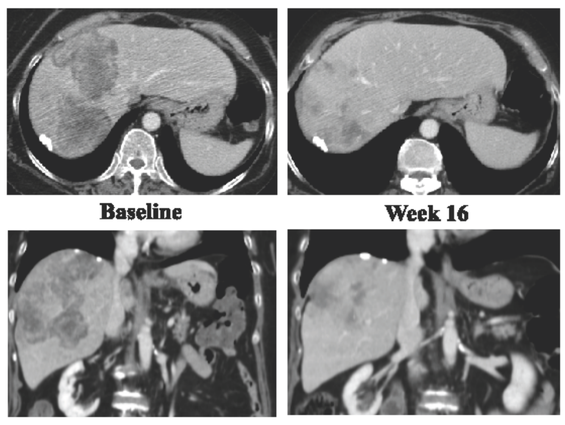

Figure 4. Patient #001007 CT scan

CONCLUSIONS

- This study tests the hypothesis that MET inhibition can revert resistance to EGFR inhibitors, and yields encouraging initial results in this population
- These data are consistent with the tivantinib activity shown in MET-High patients in 4 previous randomized studies
- The 360mg BID tablet tivantinib dose is associated with relatively frequent AEs when combined with full cetuximab dose. Neutropenia is frequent but lasts few days when promptly treated with growth factors
- The first dose reduction level of 240mg BID is well tolerated, equally active, and should be used in future studies in this patient population (tablets provide higher exposure than the previous capsule formulation)
- Enrolment in stage 2 of this clinical trial has recently completed, with final results and analysis expected by year end

REFERENCES / AKNOWLEDGMENTS

[1]Krumbach R et al. Eur J Cancer 2011. [2]Saif MW et al. Clin Colorectal Cancer 2010. [3]Metges J et al. J Clin Oncol 2010;28 suppl, abstr e14000. [4]Santini D et al. Ann Oncol 2012. [5]Eathiraj S et al. J Biol Chem 2011. [6]Munshi N et al. Mol Cancer Ther 2010. [7]Lu S et al. Z Gastroenterol 2012. [8]Scagliotti G et al. J Clin Oncol 2015. [9]Santoro A et al. Lancet Oncol 2013. [10]Eng C et al. J Clin Oncol 2013;31 suppl, abstr 3508. [11]Monk P et al. J Clin Oncol 2015;33 suppl 7, abstr 146.

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