800P - A Phase 1b Study of Oraxol in Combination with Ramucirumab in Patients with Gastric or Esophageal Cancers Who Failed Previous Chemotherapy

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BACKGROUND

- Oraxol consists of oral paclitaxel administered with the novel P-glycoprotein inhibitor encequidar (HM30181A) (15mg) which enables the oral absorption of paclitaxel. Ramucirumab (RAM) + intravenous paclitaxel is FDA approved 2nd line treatment of gastric cancer. Oraxol 200mg/m^2 days 1-3, weekly has similar exposure to weekly paclitaxel 80/m2 intravenously.
- This study was to determine the maximum tolerated dose (MTD) of Oraxol + RAM

METHODS

- 17 patients with gastric or esophageal cancers who failed prior fluoropyrimidine or platinum containing chemotherapies were studied.
- Dose escalation followed the standard 3+3 design:
  - Cohort 1: oral paclitaxel and encequidar 200mg/m^2 days 1-3, weekly.
  - Cohort 2: oral paclitaxel and encequidar 250mg/m^2 days 1-3, weekly.
  - Cohort 3: oral paclitaxel and encequidar 300mg/m^2 days 1-3, weekly.
  - RAM 8 mg/kg IV every 2 weeks was co-administered in all patients.
- Dose limiting toxicity (DLT) were assessed by week 4.
- Adverse events (AEs) were assessed per CTCAE v4.03 and response by RECIST v1.1.

RESULTS

- **Table 1** shows patient demographics and cancer diagnosis
- **Table 2** summarises the AE, DLT data and reason for discontinuation
- **Figure 1** shows waterfall plots of tumour response data
- **Cohort 1:** One grade-4 febrile neutropenia (DLT) occurred in 6 patients. Partial response (PR)=2/6, stable disease (SD)=1/6 and progressive disease (PD)=3/6.
- **Cohort 2:** One grade-3 neutropenia with treatment delay (DLT) occurred in 7 patients. PR=3/6 and PD=3/6 in 6 evaluable patients.
- **Cohort 3:** Two DLT (grade-3 febrile neutropenia and grade-3 gastric hemorrhage) occurred in 4 patients.
- **MTD of Oraxol & RAM:** Oraxol 300mg/m^2 days 1-3, weekly in combination with RAM 8 mg/kg IV every 2 weeks.
- All patients in this study had complete recovery of their DLT.
- Oral paclitaxel PK did not increase significantly in Cohort-2 and Cohort-3. (See Table 3)

Patient demographics and cancer diagnosis		
N		17
Age (year)	Mean+-SD	63.6 +- 12.0
Sex	Male	10 (59%)
	Female	7 (41%)
Race	Asian	14 (82%)
	White	3 (18%)
Ethnicity	Not Hispanic or Latino	15 (88%)
	Hispanic or Latino	2 (12%)
Primary Cancer Diagnosis	Gastric	15 (88%)
	Esophageal	1 (6%)
	Gastro-esophageal	1 (6%)
Number of Metastatic Site	0	0 (0%)
	1	8 (47%)
	2	4 (24%)
	>=3	5 (29%)

Table 1: Demographic and Cancer Diagnosis

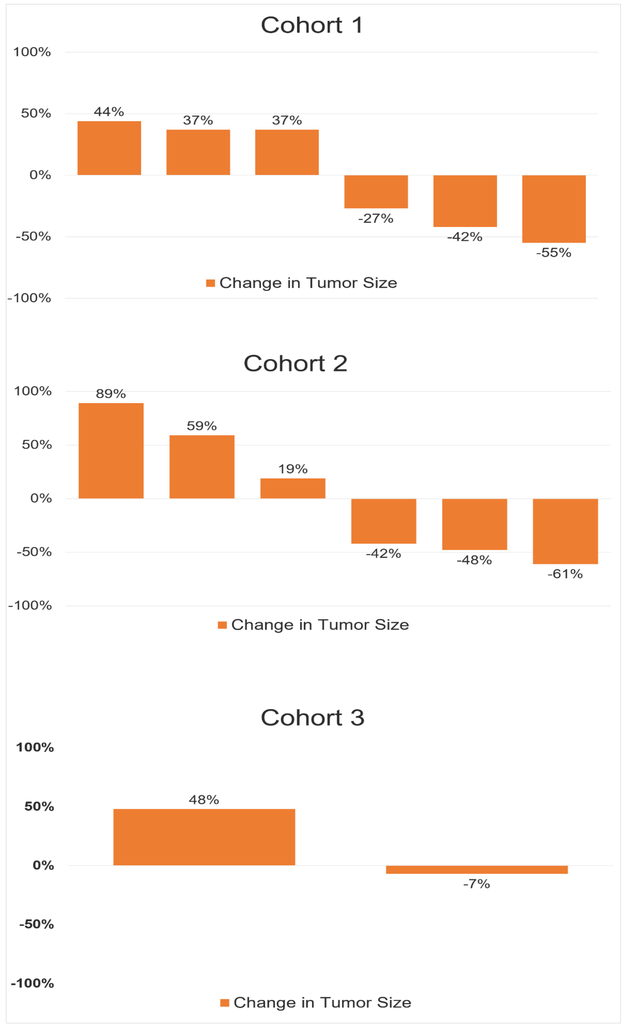

Figure 1: Waterfall Plots of Tumour Response Data

	Cohort 1	Cohort 2	Cohort 3
N (evaluable patients)	6 (6)	7 (6)	4 (3)
Discontinuation due to PD	6	4	1
Discontinuation due to AE	0	2 (1G3 neutropenia, 1G3 vomiting)	3 (1G3 neutropenia, 1G3 gastric haemorrhage, 1G3 FN)
DLT	1 (G4 febrile neutropenia (FN))	1 (G3 neutropenia)	2 (1G3 gastric haemorrhage, 1G3 FN)
Drug related SAE	2 in 1 subject (G4 FN, G4 neutropenia)	1 in 1 subject (G4 neutropenia)	5 in 3 subjects (2 x G4 neutropenia, 2 x G3 FN, 1x G3 gastric haemorrhage)
Most comment AE	Vomiting (70%), neutropenia (59%), decreased appetite (53%), nausea (24%), mucositis (24%),		

Table 2: Adverse Event & Discontinuation Data

Oral Paclitaxel PK Parameters Day 1						
Dose (mg/m^2)		T_{max} (h)	C_{max} (ng/ml)	AUC_{0-23h} (h*ng/ml)	$AUC_{0-\infty}$ (h*ng/ml)	$t_{1/2}$ (h)
200	N	6	6	6	6	6
	Mean	-	245	718	821	10.6
	CV%	-	54	62	61	20.2
	Median	1.0	236	581	659	9.88
250	N	7	7	7	4	6
	Mean	-	247	844	1120	12.0
	CV%	-	89	72	69	31.7
	Median	1.00	278	761	988	10.1
300	N	4	4	4	2	2
	Mean	-	140	698	651	7.36
	CV%	-	51	41	76	21.4
	Median	2.5	154	806	651	7.36

Table 3: Summary of Preliminary Paclitaxel Pharmacokinetic Parameters Across Cohorts.

CONCLUSION

Based on the lack of significant increase in exposure to Oraxol at higher doses, with similar efficacy and DLT in Cohorts 1 and 2, the stage 2 of this study using Oraxol 200mg/m^2 Days 1-3, weekly + Ramucirumab 8 mg/kg every 2 weeks as in Cohort-1 has been initiated.

Clinicaltrials.gov: NCT02970539

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