Avutometinib/Defactinib and Gemcitabine/Nab-Paclitaxel Combination in First-Line Metastatic Pancreatic Ductal Adenocarcinoma: Initial Safety and Efficacy of Phase 1b/2 Study (RAMP 205)

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PANCREATIC CANCER ACTION NETWORK

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ABSTRACT # 4140

BACKGROUND

Pancreatic Ductal Adenocarcinoma (PDAC)

- The majority of PDAC (52%) is diagnosed with advanced/inoperable disease.[1-3]
- More than 90% of PDAC cases harbor an activating *KRAS* mutation.[4]
- The desmoplastic tumor microenvironment of PDAC is known to limit drug penetration and contributes to chemo- and immunoresistance.[5-6]
- First line therapy for metastatic PDAC offer limited efficacy (median overall survival <12 mo) and result in high rates of grade ≥3 adverse events.[7-10]

Avutometinib + Defactinib

- **Avutometinib** is a first-in-class oral RAF/MEK clamp that potently inhibits MEK kinase activity while also blocking the compensatory reactivation of MEK by upstream RAF. [11-14]
- **Defactinib** is a selective oral inhibitor of focal adhesion kinase (FAK), a signaling target which has been shown to mediate resistance to multiple anticancer agents.[15]
- Avutometinib + FAK inhibition combined with chemotherapy induced 1) tumor regression and improved survival, and 2) stromal reprogramming in preclinical models of PDAC.[16-17]

RAMP 205 Study Design

- **RAMP 205 (NCT05669482)** is a multi-center, open-label, single arm Phase 1b/2a study of gemcitabine and nab-paclitaxel (GnP) in combination with avutometinib and defactinib in patients with previously untreated metastatic PDAC (**Figure 1**)
  - **Part A**: Dose evaluation and dose limiting toxicity (DLT) assessment (standard 3+3 design) to select the maximum-tolerated dose (MTD)/recommended phase 2 dose (RP2D) for expansion in Part B (**Table 1**)
  - **Part B**: Dose expansion at RP2D
- Key eligibility criteria include histologically confirmed newly diagnosed metastatic PDAC with measurable disease, ECOG performance status ≤1, adequate organ function, and no prior treatment for advanced or metastatic disease.

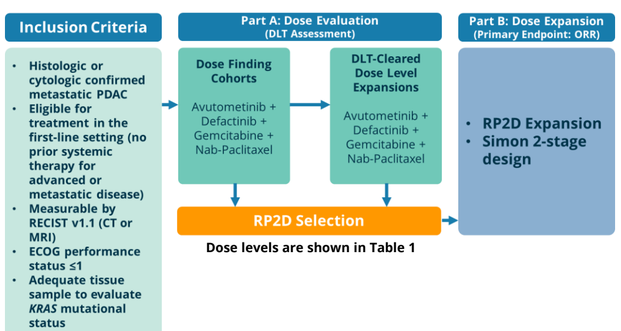


Figure 1: RAMP 205 Study Design. *CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; DLT, dose-limiting toxicity; KRAS, Kirsten Rat Sarcoma Virus; MRI, magnetic resonance imaging; ORR, objective response rate; PDAC, pancreatic ductal adenocarcinoma; RECIST v1.1, Response Evaluation Criteria In Solid Tumours version 1.1; RP2D, recommend phase 2 dose.*

RESULTS

RAMP 205 Dose Levels

Table 1: RAMP 205 Dose Levels.

Dose Level	Avutometinib PO BIW 3/4 weeks (mg)	Defactinib PO BID 3/4 weeks (mg)	Gemcitabine IV (mg/m²)	Nab-Paclitaxel IV (mg/m²)	Chemotherapy Schedule (Day)
-1	2.4	200	800	100	D1, 8, 15
1	2.4	200	800	125	D1, 8, 15
1a	3.2	200	800	125	D1, 15
2a	3.2	200	1000	125	D1, 15

All drugs dosed on 28 day cycle.
3/4 weeks, 3 out of every 4 weeks; BID, twice daily; BIW, twice weekly; D, day; IV, intravenous; mg, milligrams; mg/m², milligrams per square meter; PO, orally

Patient Demographics and Baseline Characteristics

- **All analyses reported from data cutoff, May 14, 2024.**
- Forty-one patients were enrolled to DL-1 (n=11), DL1 (n=6), DL1a (n=12), and DL2a (n=12) (**Table 2**).

Table 2: Patient demographics and baseline characteristics.

	DL-1 (n=11)	DL1 (n=6)	DL1a (n=12)	DL2a (n=12)	Total (N=41)
Age, median, yrs (range)	63 (42-70)	65 (58-75)	67 (36-79)	65 (47-73)	**64 (36-79)**
Male sex, n (%)	3 (27.2)	3 (50.0)	5 (41.7)	8 (66.7)	**19 (46.3)**
Race, n (%)					
White	4 (36.4)	4 (66.7)	9 (75.0)	8 (66.7)	**25 (61.0)**
Other	3 (27.3)	1 (16.7)	3 (25.0)	1 (8.3)	**8 (19.5)**
Asian	3 (27.3)	0 (0)	0 (0)	3 (25.0)	**6 (14.6)**
Black	1 (9.1)	1 (16.7)	0 (0)	0 (0)	**2 (4.9)**
ECOG PS, n (%)					
0	4 (36.4)	3 (50.0)	5 (41.7)	5 (41.7)	**17 (41.5)**
1	6 (54.5)	3 (50.0)	6 (50.0)	5 (41.7)	**20 (48.8)**
Unknown[a]	1 (9.1)	0 (0)	1 (8.3)	2 (16.7)	**4 (9.8)**
No. of sites of metastatic disease[b], n (%)					
1	1 (9.1)	0 (0)	1 (8.3)	1 (8.3)	**3 (7.3)**
2	3 (27.3)	2 (33.3)	2 (16.7)	2 (16.7)	**9 (21.4)**
≥3	7 (63.6)	4 (66.7)	9 (75.0)	8 (75.0)	**28 (68.3)**

[a]Patients with unknown ECOG PS have not yet been reported in EDC at time of data cutoff.
[b]RECIST v1.1 data from one DL2a patient was not available at the time of data cutoff.
DL, dose level; ECOG PS, Eastern Cooperative Oncology Group performance status; EDC, electronic data capture; RECIST v1.1, Response Evaluation Criteria In Solid Tumours version 1.1.

Preliminary Efficacy

- Median time to response: 4.6 mo (range 1.9-6.1)
- With mature follow up (all patients enrolled ≥6 mo prior to data cutoff): **83% ORR observed in DL1 (5/6 PR, 1 SD confirmed per RECIST v1.1) (Figure 2)**
- DL-1, DL1a, and DL2a follow up is immature with most patients recently enrolled and treatment ongoing (**Figure 3**)
- All (5/5) patients from DL1 with an elevated CA19-9 at baseline experienced a ≥60% CA 19-9 reduction, with 60% (3/5) of these patients achieving this decrease by week 8 of treatment(**Figure 4**)

Preliminary Efficacy

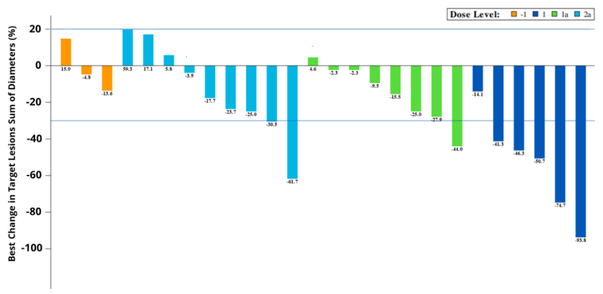
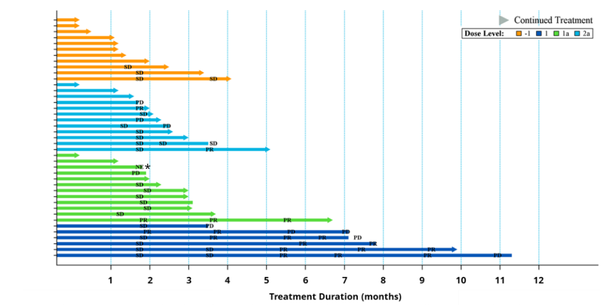
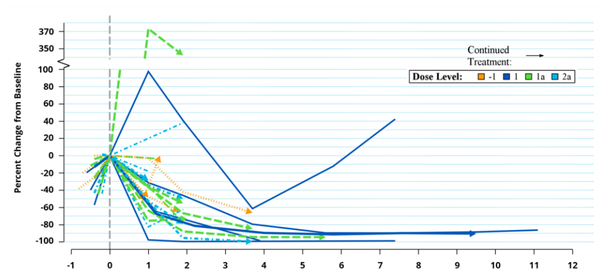


Figure 2: Best change in target lesions, in patients with at least one post-baseline assessment.



*NE patient treated with DL1a was determined to have squamous cell carcinoma histology.
NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease

Figure 3: Duration of Treatment (N=41, all treated patients).



Includes all patients with elevated baseline CA 19-9 and at least one post-baseline measurement (n=26).

Figure 4: Percent change in CA 19-9 from baseline.

Safety

- One DLT was observed: febrile neutropenia (DL1).
- Twelve patients experienced 19 treatment emergent serious adverse events (SAEs), 11 patients with grade ≥3. Grade ≥3 treatment emergent SAEs included blood bilirubin increased (n=2), biliary obstruction (n=2), febrile neutropenia (n=2), pulmonary embolism (n=2), sepsis (n=2), anaemia (n=1), pneumoperitoneum (n=1), septic shock (n=1), skin infection (n=1), malignant neoplasm progression (n=1), and vomiting (n=1).
- Two patients discontinued treatment due to TRAEs (febrile neutropenia, blood bilirubin increased, and detachment of retinal pigment epithelium)

Table 3: Any grade TEAEs occurring in ≥20% or grade ≥3 occurring in ≥5% of patients[a]

	DL-1 (n=11)		DL1 (n=6)		DL1a (n=12)		DL2a (n=12)		Total (N=41)	
	Any Grade, n (%)	Grade ≥3, n (%)	Any Grade, n (%)	Grade ≥3, n (%)	Any Grade, n (%)	Grade ≥3, n (%)	Any Grade, n (%)	Grade ≥3, n (%)	**Any Grade, n (%)**	**Grade ≥3, n (%)**
Nausea	6 (54.5)	0 (0)	5 (83.3)	0 (0)	7 (58.3)	0 (0)	6 (50.0)	0 (0)	**24 (58.5)**	**0 (0)**
Fatigue	5 (45.5)	0 (0)	5 (83.3)	0 (0)	5 (41.7)	1 (8.3)	7 (58.3)	0 (0)	**22 (53.7)**	**1 (2.4)**
Constipation	4 (36.4)	0 (0)	5 (83.3)	0 (0)	7 (58.3)	0 (0)	4 (33.3)	0 (0)	**20 (48.8)**	**0 (0)**
Diarrhoea	1 (9.1)	0 (0)	4 (66.7)	0 (0)	6 (50.0)	0 (0)	6 (50.0)	0 (0)	**17 (41.5)**	**0 (0)**
Alopecia	3 (27.3)	0 (0)	6 (100.0)	0 (0)	3 (25.0)	0 (0)	2 (16.7)	0 (0)	**14 (34.1)**	**0 (0)**
Neutrophil count decreased	2 (18.2)	2 (18.2)	4 (66.7)	4 (66.7)	4 (33.3)	3 (25.0)	3 (25)	2 (16.7)	**13 (31.7)**	**11 (26.8)**
Rash maculo-popular	4 (36.4)	0 (0)	5 (83.3)	0 (0)	3 (25.0)	0 (0)	1 (8.3)	0 (0)	**13 (31.7)**	**0 (0)**
Vomiting	3 (27.3)	0 (0)	4 (66.7)	0 (0)	4 (33.3)	1 (8.3)	2 (16.7)	0 (0)	**13 (31.7)**	**1 (2.4)**
Anaemia	2 (18.2)	1 (9.1)	2 (33.3)	2 (33.3)	2 (16.7)	2 (16.7)	3 (25.0)	1 (8.3)	**9 (22.0)**	**6 (14.6)**
Decreased appetite	2 (18.2)	0 (0)	3 (50.0)	0 (0)	3 (50.0)	0 (0)	1 (8.3)	0 (0)	**9 (22.0)**	**0 (0)**
Alanine aminotransferase increased	1 (9.1)	1 (9.1)	2 (33.3)	2 (33.3)	3 (25.0)	1 (8.3)	1 (8.3)	0 (0)	**7 (17.1)**	**4 (9.8)**

[a]TEAEs were graded based on guidelines provided in CTCAE v5.0.
CTCAE v5.0, Common Terminology Criteria for Adverse Events version 5.0; DL, dose level; TEAE, treatment emergent adverse event.

CONCLUSIONS

- Avutometinib/defactinib has been combined with gemcitabine/nab-paclitaxel at 4 DL cohorts, MTD has not been reached.
- One DLT has been observed in DL1, cohort cleared with additional patients.
- DL1 cohort: 5/6 pts (83%) achieved RECIST v1.1 confirmed PR with a median time to response of 4.6 mo.
- Additional cohorts recently enrolled, follow-up is ongoing, and most patients remain on treatment.

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