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A Phase 1 study of XMT-1536 in patients with solid tumors likely to express NaPi2b: A summary of dose escalation

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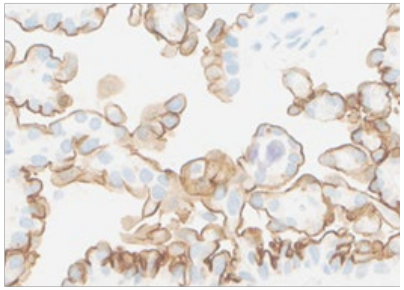
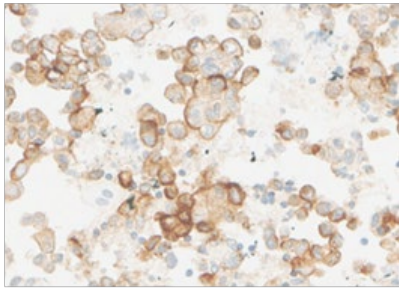
NaPi2b is an Ideal Antibody-Drug Conjugate (ADC) Target
Assay Developed to Measure Antigen Expression

- ADC internalizing sodium phosphate transporter; not an oncogene
- Broadly expressed in ovarian cancer and NSCLC adenocarcinoma
- Limited expression in normal tissues
- IHC assay calibrated to distinguish wide range of expression

Epithelial ovarian cancer
H score = 293

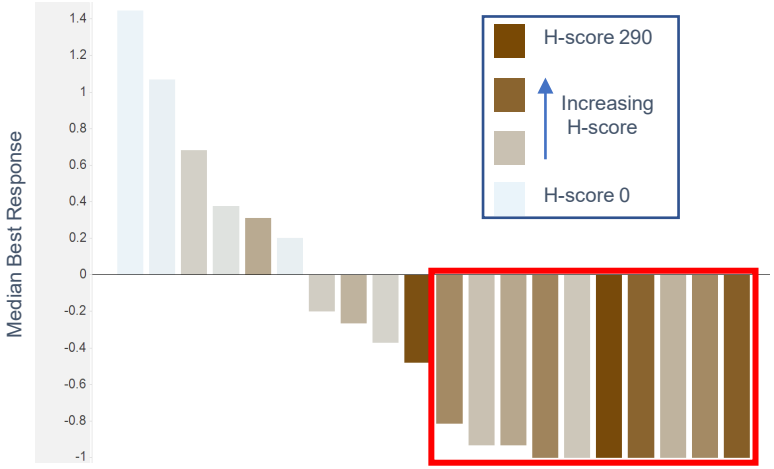


Lung adenocarcinoma
H score = 265



Ovarian Cancer Patient-Derived Xenograft Models

Response correlated with NaPi2b Expression

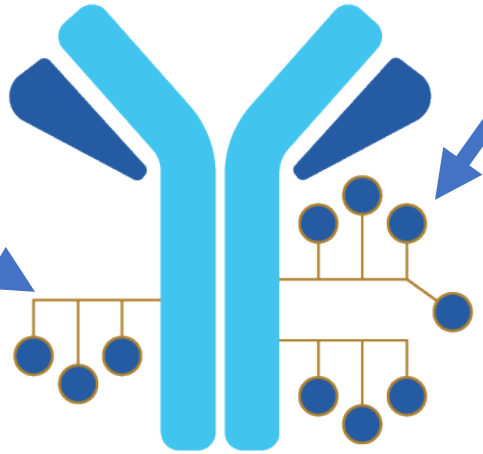


H-score measures the percentage of cells staining multiplied by their intensity (0, 1+, 2+, 3+) for a range of 0 - 300

XMT-1536 is a First-in-Class Dolaflexin ADC
Targets NaPi2b with Controlled Bystander Effect

Hydrophilic Polymer Scaffold

- High drug-to-antibody ratio (DAR) with ~10-12 payloads
- Excellent drug like properties
- Highly stable in circulation
- Dose-proportional exposure
- Very low exposure of free payload



DolaLock Payload with Controlled Bystander Effect

- Selectively toxic to rapidly dividing cells
- Initially released molecule (Auristatin F-HPA) freely cell permeable and bystander capable
- Intracellular conversion to Auristatin F diminishes permeability and controls bystander effect
- Accumulates in tumor, not a PgP substrate
- Induces immunogenic cell death

HPA: Hydroxypropylamide

XMT-1536 Phase 1 Dose Escalation Trial Design

Dosing: Q3 weeks

- DL 6 40 mg/m²
- DL 5 30 mg/m²
- DL 4 20 mg/m²
- DL 3 12 mg/m²
- DL 2 6 mg/m²
- DL 1 3 mg/m²

Dosing: Q4 weeks

- DL 8A 52 mg/m² Evaluation Ongoing
- DL 7A 43 mg/m²
- DL 6A 36 mg/m²
- DL 5A 30 mg/m²
- DL 4A 20 mg/m²

Objectives: Evaluate safety and tolerability; determine MTD and identify RP2D; assess preliminary antitumor activity

Patient population: Platinum-resistant, serous ovarian cancer and NSCLC adenocarcinoma progressing after standard treatments*

- Measurable disease per RECIST 1.1
- ECOG 0 or 1
- Archived tissue for retrospective assessment of NaPi2b expression

Dosing: IV initially every 3 weeks, amended to every 4 weeks, until disease progression or unacceptable toxicity

Assessments: Tumor imaging (MRI or CT): baseline and every 2nd cycle; response assessed per RECIST 1.1

MTD = maximum tolerated dose; RP2D = recommended Phase 2 dose
* Dose escalation cohort (DL 3-5/A) also included endometrial, papillary renal, salivary duct, and papillary thyroid cancers

Patient Demographics and Disease Characteristics

N=59 Patients Dosed at 3 mg/m^2 to 43 mg/m^2					
Age, years; Median (range)			65 (39-93)		
Sex Female Male			 48 (81%) 11 (19%)		
ECOG performance status; n (%) 0 1			 21 (36%) 38 (64%)		
Primary Tumor Type; n (%) Ovarian NSCLC Endometrial Papillary Renal Cancer Salivary Duct			 37 (64%) 11 (18%) 8 (13%) 2 (3%) 1 (2%)		
Prior lines of Therapy, Median (range) All patients Ovarian NSCLC			 5 (1 to 10) 5 (1 to 10) 4 (2 to 6)		
Prior Therapies Ovarian, N=36* * One patient prior treatment data not reported yet		**n (%)**	**Prior Therapies NSCLC, N=10*** * One patient prior treatment data not reported yet		**n (%)**
	Platinum	36 (100)		Platinum	10 (100)
	Taxane	33 (92)		Pemetrexed	10 (100)
	Bevacizumab	23 (64)		I/O	10 (100)
	PARPi	20 (56)		Taxane	7 (70)
	Investigational	14 (39)		TKI	1 (10)
				Investigational	7 (70)

Data cut-off: 03 Feb 2020

Treatment-Related Adverse Events (TRAEs) Reported in ≥10% of Patients

- 76% (45/59) of Patients experienced a TRAE
- No severe neutropenia, peripheral neuropathy or ocular toxicity
- No G4 or G5 TRAEs
- 4 Treatment-Related SAEs: G1 Pyrexia (possibly), G2 Pyrexia (probably), G3 congestive cardiac failure (possibly), G3 Vomiting (possibly)

	Patients dosed 3 to 40 mg/m^2 N=52				Patients dosed 43 mg/m^2 N=7			
Preferred Term	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Total – All Grades n (%)**	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Total – All Grades n (%)**
NAUSEA	16 (31)	5 (10)	0	21 (40)	1 (14)	1 (14)	0	2 (29)
FATIGUE	7 (13)	13 (25)	0	20 (38)	1 (14)	3 (43)	0	4 (57)
ASPARTATE AMINOTRANSFERASE INCREASED	5 (10)	5 (10)	6 (12)	16 (32)	2 (29)	1 (14)	0	3 (43)
HEADACHE	7 (13)	5 (10)	0	12 (23)	1 (14)	0	0	1 (14)
VOMITING	8 (15)	2 (4)	1 (2)	11 (21)	0	0	0	0
PYREXIA	8 (15)	1 (2)	0	9 (17)	2 (29)	0	0	2 (29)
BLOOD ALKALINE PHOSPHATASE INCREASED	7 (13)	1 (2)	0	8 (15)	0	0	0	0
DECREASED APPETITE	1 (2)	7 (13)	0	8 (15)	0	1 (14)	0	1 (14)
DIARRHOEA	5 (10)	1 (2)	1 (2)	7 (13)	1 (14)	0	0	1 (14)
ALANINE AMINOTRANSFERASE INCREASED	5 (10)	1 (2)	0	6 (12)	1 (14)	0	0	1 (14)
ANAEMIA	0	3 (6)	2 (4)	5 (10)	1 (14)	1 (14)	0	2 (29)
THROMBOCYTOPENIA	2 (4)	1 (2)	0	3 (6)	2 (29)	1 (14)	0	3 (43)

Data cut-off: 03 Feb 2020

Well Tolerated to Date. No DLT at Highest Completed Dose Level of 43 mg/m^2 q4w

Dose Level (DL)	Dose	Tumor Types	Pts / DL	DLT Description, Number of Patients with Event
1	3 mg/m^2 q3w	Ovarian	1	
2	6 mg/m^2 q3w	Ovarian	1	
3	12 mg/m^2 q3w	Ovarian (1) NSCLC (2) Endometrial (3) Papillary Renal (1)	7	
4/4A	20 mg/m^2 q3w/q4w	Ovarian (11) NSCLC (1) Endometrial (1) Salivary Duct (1) Papillary renal (1)	15	
5/5A	30 mg/m^2 q3w/q4w	Ovarian (12) NSCLC (3) Endometrial (4)	19	Transient G3 AST; resolved to G1 within 21 days; n=1
6	40 mg/m^2 q3w	Ovarian (1)	1	Transient G3 AST; resolved to G1 within 21 days; n=1
6A	36 mg/m^2 q4w	Ovarian (7) NSCLC (1)	8	G2 AST/G1 ALT preventing 2nd dose & causing study discontinuation; n=1
7A	43 mg/m^2 q4w	Ovarian (3) NSCLC (4)	7	

Data cut-off: 03 Feb 2020

Favorable Dose- and Biomarker-Response Relationship

Emerging Data Will Define Biomarker Cut-Off for Patient Selection in Future Studies

Response - Ovarian Cancer and NSCLC adenocarcinoma N=39*		
		All
20 mg/m²	N	10
	PR	**1 (10%)**
	SD	6 (60%)
	DCR (PR+SD)	**7 (70%)**
	PD	3 (30%)
30, 36, 40 mg/m²	N	22
	PR	**3 (14%)**
	SD	10 (45%)
	DCR (PR+SD)	**13 (59%)**
	PD	9 (41%)
43 mg/m²	N	7
	PR	**2 (29%)**
	SD	4 (57%)
	DCR (PR+SD)	**6 (86%)**
	PD	1 (14%)

[O] Higher NaPi2b Expression: at/above lowest H-score at which response observed (≥110)
[OO] Lower NaPi2b Expression: below the lowest H-score at which response observed (<110)

*Excludes 3 patients discontinued due to investigator/patient choice and 1 without RECIST scan
**Hypocellular specimen/indeterminate for H-score or not determined yet

Data cut-off: 03 Feb 2020

Favorable Dose- and Biomarker-Response Relationship

Emerging Data Will Define Biomarker Cut-Off for Patient Selection in Future Studies

Response - Ovarian Cancer and NSCLC adenocarcinoma N=39*		N (%)			
		All	**Higher NaPi2b ᵒ**	**Lower NaPi2b ᵒᵒ**	**Indeterm NaPi2b ****
20 mg/m²	N	10	7	2	1
	PR	**1 (10%)**	**0**	**0**	**1 (100%)**
	SD	6 (60%)	4 (57%)	2 (100%)	0
	DCR (PR+SD)	**7 (70%)**	**4 (57%)**	**2 (100%)**	**1 (100%)**
	PD	3 (30%)	3 (43%)	0	0
30, 36, 40 mg/m²	N	22	12	7	3
	PR	**3 (14%)**	**3 (25%)**	**0**	**0**
	SD	10 (45%)	6 (50%)	3 (43%)	1 (33%)
	DCR (PR+SD)	**13 (59%)**	**9 (75%)**	**3 (43%)**	**1 (33%)**
	PD	9 (41%)	3 (25%)	4 (57%)	2 (67%)
43 mg/m²	N	7	3	2	2
	PR	**2 (29%)**	**2 (67%)**	**0**	**0**
	SD	4 (57%)	0	2 (100%)	2 (100%)
	DCR (PR+SD)	**6 (86%)**	**2 (67%)**	**2 (100%)**	**2 (100%)**
	PD	1 (14%)	1 (33%)	0	0

ᵒ Higher NaPi2b Expression: at/above lowest H-score at which response observed (≥110)
ᵒᵒ Lower NaPi2b Expression: below the lowest H-score at which response observed (<110)

*Excludes 3 patients discontinued due to investigator/patient choice and 1 without RECIST scan
**Hypocellular specimen/indeterminate for H-score or not determined yet

Data cut-off: 03 Feb 2020

Favorable Dose- and Biomarker-Response Relationship

Emerging Data Will Define Biomarker Cut-Off for Patient Selection in Future Studies

Response - Ovarian Cancer and NSCLC adenocarcinoma N=39*		N (%)			
		All	Higher NaPi2b °	Lower NaPi2b °°	Indeterm NaPi2b **
20 mg/m²	N	10	7	2	1
	PR	**1 (10%)**	**0**	**0**	**1 (100%)**
	SD	6 (60%)	4 (57%)	2 (100%)	0
	DCR (PR+SD)	**7 (70%)**	**4 (57%)**	**2 (100%)**	**1 (100%)**
	PD	3 (30%)	3 (43%)	0	0
30, 36, 40 mg/m²	N	22	12	7	3
	PR	**3 (14%)**	**3 (25%)**	**0**	**0**
	SD	10 (4	6 (50%)	3 (43%)	%)
	DCR (PR+SD)	**13 (5**	**9 (75%)**	**3 (43%)**	**%)**
	PD	9 (4	3 (25%)	4 (57%)	%)
43 mg/m²	N	7	3	2	2
	PR	**2 (29%)**	**2 (67%)**	**0**	**0**
	SD	4 (57%)	0	2 (100%)	2 (100%)
	DCR (PR+SD)	**6 (86%)**	**2 (67%)**	**2 (100%)**	**2 (100%)**
	PD	1 (14%)	1 (33%)	0	0

PR: 33%
DCR: 73%

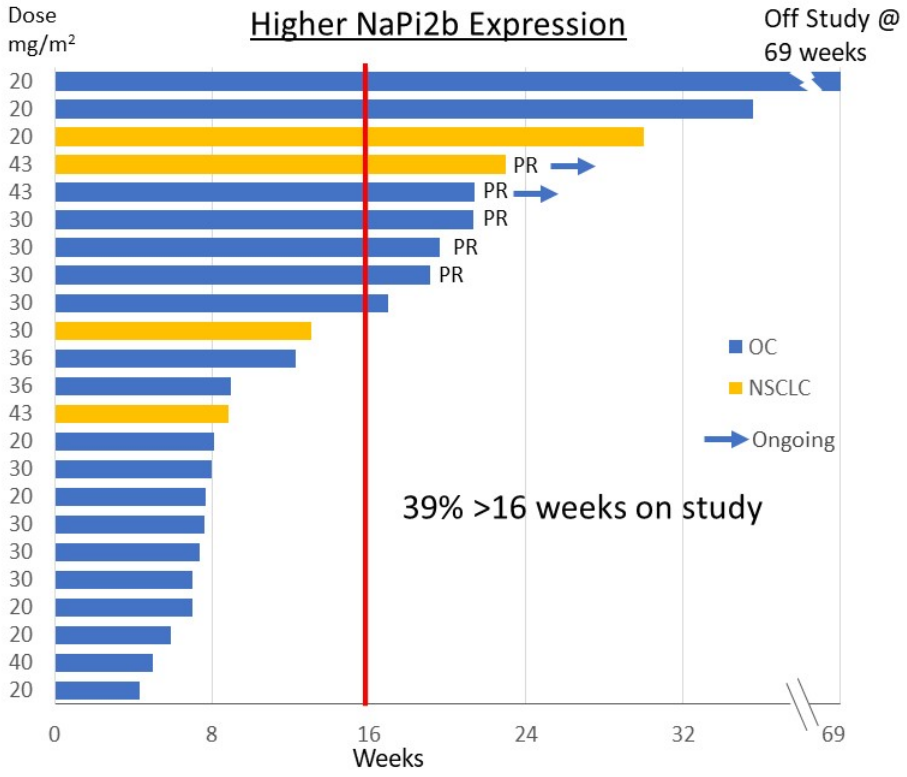
PR: 0%
DCR: 55%

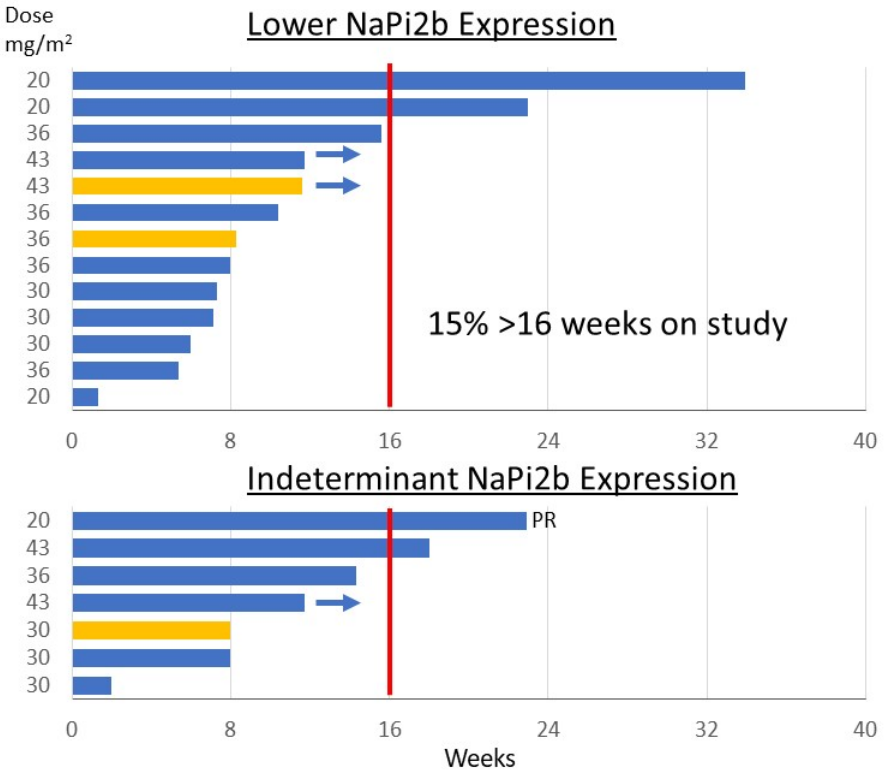
° Higher NaPi2b Expression: at/above lowest H-score at which response observed (≥110)
°° Lower NaPi2b Expression: below the lowest H-score at which response observed (<110)

*Excludes 3 patients discontinued due to investigator/patient choice and 1 without RECIST scan
**Hypocellular specimen/indeterminate for H-score or not determined yet

Data cut-off: 03 Feb 2020

Durations at ≥ 20mg/m² - Longer Treatment Duration Observed in Patients with Higher NaPi2b Expression

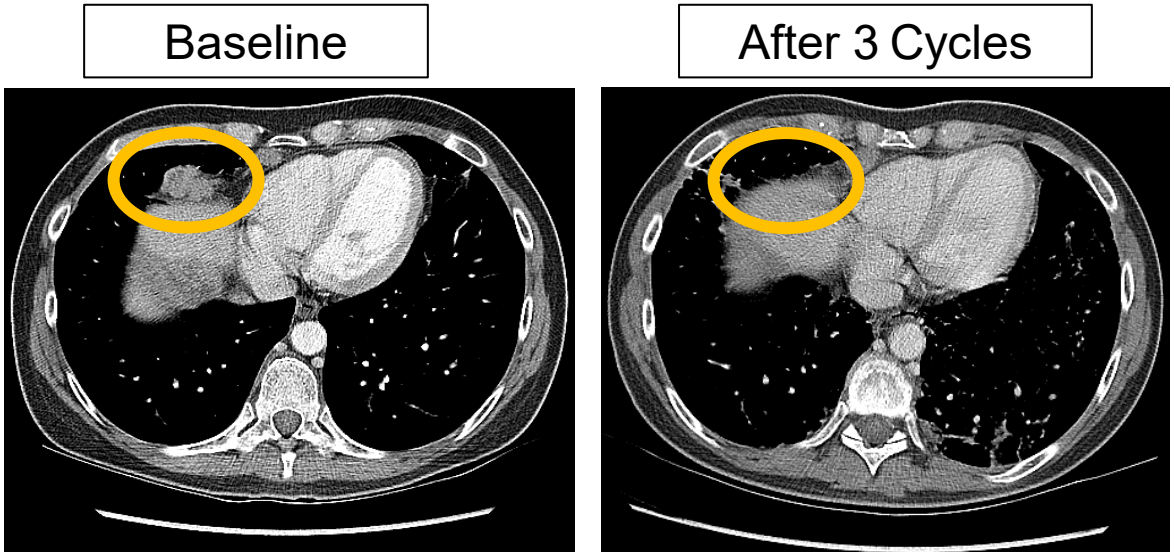




Data cut-off: 03 Feb 2020

Patient with Ovarian Cancer – Confirmed PR with 62% Tumor Reduction

Platinum Resistant Ovarian Cancer Patient Treated with 43mg/m^2	
Age	43
# prior regimens	9
CA125 Baseline (U/mL)	5409
CA125 after 3 Cycles (U/mL)	427
NaPi2b IHC, H-Score	110

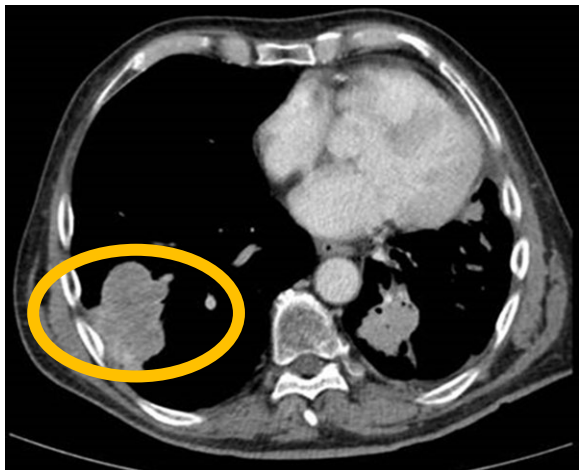


- Prior treatments with carboplatin, paclitaxel, cisplatin, liposomal doxorubicin, gemcitabine, bevacizumab, olaparib
- PR detected at Cycle 2 and confirmed at Cycle 3

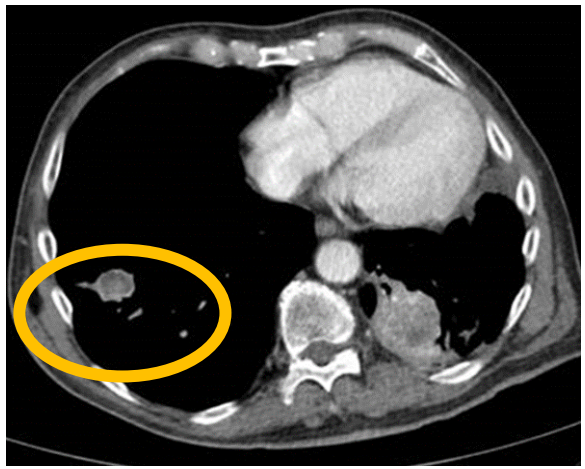
Patient with NSCLC – Confirmed PR with 34% Tumor Reduction

NSCLC Adenocarcinoma Patient Treated with 43 mg/m^2	
Age	80
# prior regimens	4
NaPi2b IHC, H-Score	245

Baseline



After 3 Cycles



- Prior treatments with carboplatin, pemetrexed, paclitaxel, nivolumab
- PR detected at Cycle 2 and confirmed at Cycle 3

Conclusions

- XMT-1536 has a favorable safety profile
  - Most treatment related adverse events (TRAEs) were Grade 1 or 2
  - Nausea, fatigue, transient increase in AST, headache, and vomiting were the most frequent TRAEs
  - No severe neutropenia, peripheral neuropathy or ocular toxicity
- 52 mg/m^2 dose escalation cohort under evaluation
- Antitumor activity observed in heavily pretreated patients with PROC and NSCLC adenocarcinoma (median of 5 prior lines of therapy)
  - Higher response rate at doses $\geq$30 mg/m^2
  - Higher response rate in patients with higher NaPi2b expression; No responses in patients with lower NaPi2b expression
  - Literature suggests low single digit response rates in platinum-resistant ovarian cancer with similar lines of therapy[1,2,3]
- Expansion at 36 and 43 mg/m^2 q 4 weeks is ongoing in PROC and NSCLC adenocarcinoma

[1]Bruchim, Eur J Obs&Gyn and Repro Biology 2013;166:94-98
[2]Griffiths, Int J Gynecol Cancer 2011;21:58-65
[3]Hoskins, Gynecologic Onc 2005;97:862-869

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