A Phase 1/2 study of vopimetostat in combination with daraxonrasib or zoldonrasib in patients with MTAP deleted RAS mutant (MTAPdel/RASmut) metastatic PDAC and NSCLC

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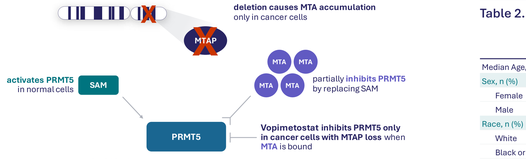
Poster Number: 3149P

Introduction

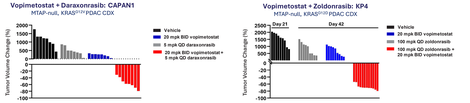
- In a pan-solid tumor analysis of more than 400,000 tumor tissue biopsies, 11.4% of solid tumors demonstrated MTAP loss.[1] Increased prevalence has been observed among patients with PDAC (30-40%) and NSCLC (15%).[1–5]
- RAS mutations frequently co-occur with MTAP loss, occurring in >90% of PDAC cases with MTAP loss[6] and approximately 30% of NSCLC cases with MTAP loss.[4]
- MTAP is an essential enzyme in the methionine salvage pathway, responsible for metabolization of MTA, a SAM-competitive inhibitor of PRMT5. In tumor cells with MTAP loss, MTA accumulates and binds PRMT5, locking it in an inactive conformation.[7]
- Vopimetostat (TNG462) is a selective, oral, MTA-cooperative PRMT5 inhibitor. Vopimetostat selectively binds MTA-bound PRMT5, resulting in preferential PRMT5 inhibition in tumor cells with MTAP-loss, supporting selective antitumor activity in preclinical models (**Figure 1**).[8]

Figure 1. Vopimetostat Mechanism of Action



- Daraxonrasib is an oral, RAS(ON) multi-selective, noncovalent tri-complex inhibitor that directly targets mutant and wild-type RAS signaling. In metastatic PDAC, daraxonrasib has demonstrated an overall response rate of 31.6% (95% CI, 25.8-38.0), PFS of 7.2 months, and OS of 13.2 months in a phase 3 study of patients with 2L PDAC.[9]
- Zoldonrasib is an oral, RAS(ON) G12D-selective, covalent tri-complex inhibitor. Preliminary results from an ongoing Phase 1/1b first-in-human trial of zoldonrasib in metastatic RAS G12D-mutant PDAC demonstrated an ORR of 30%.[10]
- Preclinical studies have demonstrated synergy with combination RAS and PRMT5 inhibition (**Figure 2**).[11–13]

Figure 2. Tumor regression in Murine Models of PDAC with MTAP-Loss Treated with Vopimetostat and the RAS(ON) Inhibitors Daraxonrasib or Zoldonrasib[13]



Vopimetostat and daraxonrasib dosed sub-therapeutically. Percent tumor volume change at the indicated time points in CAPAN1 or KP4 tumor-bearing mice following oral administration of vopimetostat, daraxonrasib, zoldonrasib, combination treatments, or vehicle (n=9/group for vehicle and single agent groups, n=12/group for combination group for KP4; n=8/group for CAPAN1). Data: Tango Therapeutics, data on file.

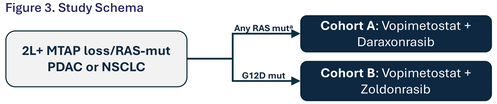
- TNG462-C102 is a phase 1/2 study evaluating vopimetostat in combination with a RAS(ON) inhibitor in patients with MTAP-loss, RAS-mutant PDAC or NSCLC. Here we report efficacy and safety findings.

Methods

Study Design

- TNG462-C102 is a dose escalation and expansion trial evaluating safety, tolerability, and antitumor activity of combination treatment with vopimetostat and daraxonrasib or zoldonrasib in PDAC and NSCLC with RAS mutation and MTAP loss (NCT06922591; **Figure 3**).
- The primary objective in the dose escalation phase was MTD determination. Secondary objectives included antitumor activity, pharmacokinetics, and safety.
- Patients were treated until PD, with the option to continue beyond PD if the investigator determined continuing treatment beneficial.
- Dose escalation was guided by BLRM.

Figure 3. Study Schema



*Nonsynonymous mutation of KRAS, NRAS, or HRAS at codons 12, 13, or 61 (G12, G13, or Q61)

Treatment Cohorts

- Doses were administered orally QD; treatment cycles were 21 days in length.

Table 1. Dose Levels

Dose Level	Vopimetostat + Daraxonrasib	Vopimetostat + Zoldonrasib
DL1	Vopimetostat 200 mg + Daraxonrasib 100 mg	Vopimetostat 200 mg + Zoldonrasib 600 mg
DL2	Vopimetostat 250 mg + Daraxonrasib 100 mg	Vopimetostat 250 mg + Zoldonrasib 600 mg
DL3	-	Vopimetostat 250 mg + Zoldonrasib 1200 mg
DL4	-	Vopimetostat 200 mg + Zoldonrasib 1200 mg

Patients

- Eligible patients were adults with metastatic PDAC or locally advanced, recurrent, or metastatic NSCLC, an ECOG PS of 0-1, confirmed MTAP loss (IHC or NGS), measurable disease by RECIST v1.1, and sufficient washout from prior lines of therapy.
  - PDAC: no more than 2 prior systemic lines of therapy; NSCLC: no more than 3 prior lines of therapy
- Patients were ineligible if they had received prior therapies targeting RAS, PRMT5, or MAT2A.

Methods

Assessments and Statistical Considerations

- Objective response was assessed by investigators according to RECIST v1.1 criteria.
  - Responses required confirmation by subsequent imaging. To ensure all responses had sufficient time for confirmation, ORR is reported in patients who received their first dose ≥14 weeks prior to the data extract.
  - Reported ORRs include unconfirmed responses, pending confirmation.
- PFS was summarized using Kaplan-Meier estimates and 95% CIs.
- Adverse events were reported according to CTCAE v5.0.

Results

Patients

Table 2. Demographics and Baseline Characteristics

	Vopimetostat + Daraxonrasib n=34		Vopimetostat + Zoldonrasib n=40[a]
	PDAC (n=29)	NSCLC (n=5)	PDAC (n=39)
Median Age, (range), years	66.0 (44, 74)	55.0 (38, 71)	66.0 (37, 81)
Sex, n (%)			
Female	17 (58.6)	2 (40.0)	18 (46.2)
Male	12 (41.4)	3 (60.0)	21 (53.8)
Race, n (%)			
White	18 (62.1)	2 (40.0)	22 (56.4)
Black or African American	3 (10.3)	-	2 (5.1)
Asian	3 (10.3)	1 (20.0)	3 (7.7)
Other	-	2 (40.0)	3 (7.7)
NR	5 (17.2)	-	9 (23.1)
Ethnicity, n (%)			
Not Hispanic/Latino	21 (72.4)	4 (80.0)	26 (66.7)
Hispanic/Latino	4 (13.8)	1 (20.0)	6 (15.4)
NR	4 (13.8)	-	7 (17.9)
Baseline ECOG, n (%)			
0	17 (58.6)	2 (40.0)	13 (33.3)
1	11 (37.9)	3 (60.0)	26 (66.7)
Missing	1 (3.4)	-	-
Prior anti-cancer therapies, n (%)			
0	2 (6.9)[b]	-	-
1	10 (34.5)	1 (20.0)	18 (46.2)
2	17 (58.6)	3 (60.0)	21 (53.8)
3+	-	1 (20.0)	-
KRAS mutation variant, n (%)			
G12V	15 (51.7)	1 (20.0)	-
G12R	6 (20.7)	-	-
Q61H/K/R	4 (13.8)	1 (20.0)	-
G12A	2 (6.9)	-	-
G12D	-	2 (40.0)	39 (100.0)
G13C	-	1 (20.0)	-
Missing	2 (6.9)	-	-
Liver metastases at baseline, n (%)	21 (72.4)	1 (20.0)	31 (79.5)

[a]One patient treated with vopimetostat+zoldonrasib had NSCLC and is omitted from this table.
[b]Treatment in the 1L setting was permitted in cases where standard of care was not appropriate.

- As of 20 August 2026, 74 patients have received treatment, including 34 receiving vopimetostat+daraxonrasib and 40 receiving vopimetostat+zoldonrasib (**Table 2**).

Combination Vopimetostat + Daraxonrasib

Figure 4. Pharmacokinetics of Combination Vopimetostat + Daraxonrasib (DL1)

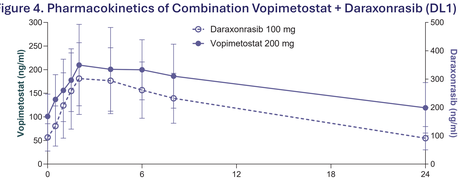


Table 3. Summary of Steady-state Pharmacokinetic Parameters of Combination Vopimetostat + Daraxonrasib

Analyte	Dose Level	Cmax (ng/ml) Mean ± s.d.	Tmax (h) Median (Range)	AUC0-24h (ng*h/mL) Mean ± s.d.
Vopimetostat	DL1 (n=18)	242.6 ± 84.5	2.0 (0.5-24.0)	3,814.7 ± 1443.8
	DL2 (n=3)	476.7 ± 321.2	4.0 (1.5-6.0)	7933.7 ± 7036.0
Daraxonrasib	DL1 (n=20)	362.0 ± 99.4	4.0 (1.5-8.0)	4303.1 ± 1720.7
	DL2 (n=3)	485.7 ± 38.5	2.0 (2.0-2.0)	6800.8 ± 3430.1

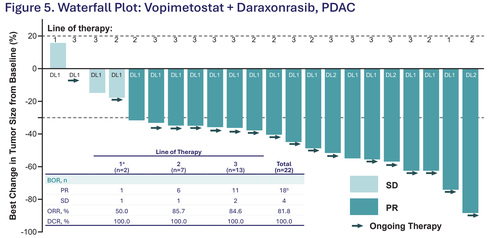
DL1, vopimetostat 200 mg+daraxonrasib 100 mg; DL2, vopimetostat 250 mg+daraxonrasib 100 mg.

- At DL1, vopimetostat + daraxonrasib increased steady-state daraxonrasib exposure to 4303 ng.h/mL (CV%, 40.0), with daraxonrasib 100 mg QD exposure in the combination comparable to that observed with daraxonrasib monotherapy at 300 mg QD (**Figure 4 & Table 3**).[14]
  - Vopimetostat exposure in the combination DL1 arm was not affected by concomitant administration of daraxonrasib.

Results

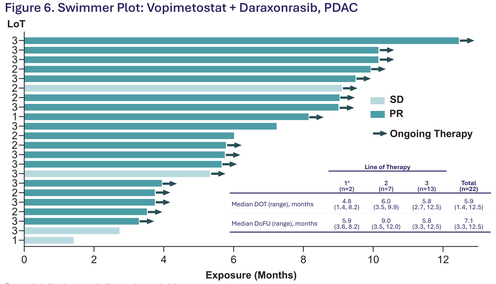
Combination Vopimetostat + Daraxonrasib

Figure 5. Waterfall Plot: Vopimetostat + Daraxonrasib, PDAC



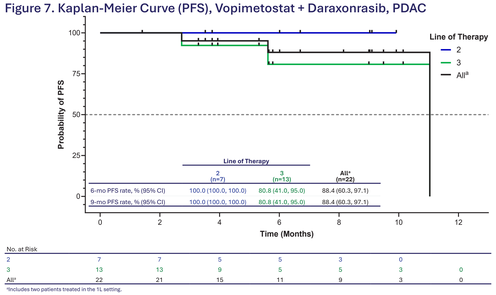
DL1, vopimetostat 200 mg+daraxonrasib 100 mg; DL2, vopimetostat 250 mg+daraxonrasib 100 mg.
*Treatment in the 1L setting was permitted in cases where standard of care was not appropriate.
[a]Includes 11 confirmed PRs and seven PRs awaiting confirmation.

Figure 6. Swimmer Plot: Vopimetostat + Daraxonrasib, PDAC



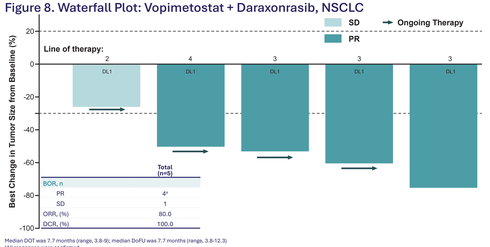
*Treatment in the 1L setting was permitted in cases where standard of care was not appropriate.

Figure 7. Kaplan-Meier Curve (PFS), Vopimetostat + Daraxonrasib, PDAC



*Includes two patients treated in the 1L setting.

Figure 8. Waterfall Plot: Vopimetostat + Daraxonrasib, NSCLC



Median DOT was 7.7 months (range, 3.8-9); median DoFU was 7.7 months (range, 3.8-12.3)
*All responses were confirmed.

Results

Combination Vopimetostat + Zoldonrasib

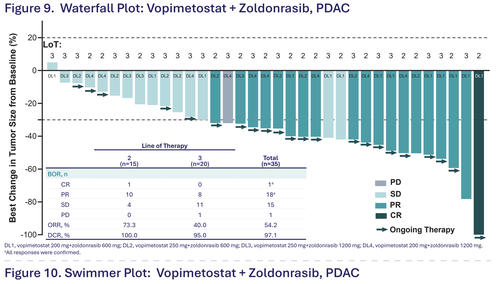
Table 4. Treatment Exposure: Vopimetostat + Zoldonrasib

	DL1	DL2	DL3	DL4
Vopimetostat AUC, mean (s.d.), ng·h/mL (n)	3946.6 ± 2161.3 (13)	7778.2 ± 4900.3 (8)	6407.8 ± 3967.4 (4)	4040.4 ± 1458.8 (12)
Zoldonrasib AUC, mean (s.d.), ng·h/mL (n)	7838.6 ± 4362.5 (13)	14174.7 ± 9458.3 (8)	24697.8 ± 9407.2 (3)	16362.9 ± 11160.0 (11)

DL1, vopimetostat 200 mg+zoldonrasib 600 mg; DL2, vopimetostat 250 mg+zoldonrasib 600 mg; DL3, vopimetostat 250 mg+zoldonrasib 1200 mg; DL4, vopimetostat 200 mg+zoldonrasib 1200 mg.

- Combination treatment with vopimetostat and zoldonrasib increased zoldonrasib exposure by ~1.5-fold at 200 mg and ~2.4-fold at 250 mg (**Table 4**).
  - Vopimetostat exposure was not affected by concomitant administration of zoldonrasib.

Figure 9. Waterfall Plot: Vopimetostat + Zoldonrasib, PDAC



DL1, vopimetostat 200 mg+zoldonrasib 600 mg; DL2, vopimetostat 250 mg+zoldonrasib 600 mg; DL3, vopimetostat 250 mg+zoldonrasib 1200 mg; DL4, vopimetostat 200 mg+zoldonrasib 1200 mg.
*All responses were confirmed.

Figure 10. Swimmer Plot: Vopimetostat + Zoldonrasib, PDAC

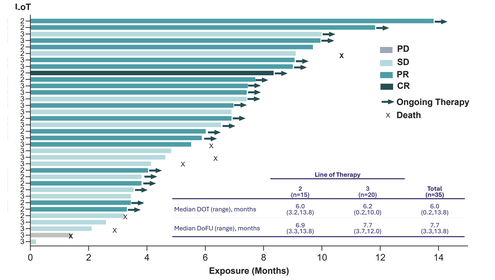
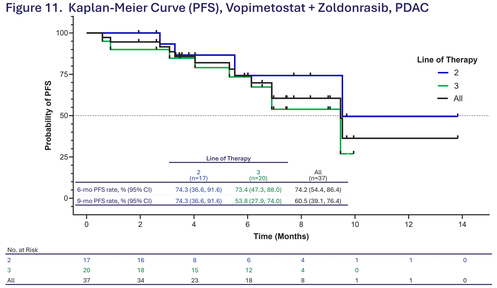


Figure 11. Kaplan-Meier Curve (PFS), Vopimetostat + Zoldonrasib, PDAC



Abbreviations
1L, first line; 2L, second line; 3L, third line; AST, aspartate aminotransferase; AUC, area under the concentration-time curve; AUC0-24h, area under the concentration-time curve from 0 to 24 hours; BID, twice daily; BOR, best overall response; CDX, cell line derived xenograft; CI, confidence interval; CL, clearance; Cmax, maximum plasma concentration; CO, cohort; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; CV%, coefficient of variation; D, daraxonrasib; DCR, disease control rate; DL, dose level; DLT, dose-limiting toxicity; DoFU, duration of follow-up; DOT, duration of treatment; ECOG PS, Eastern Cooperative Oncology Group performance status; EDC, electronic data capture; IHC, immunohistochemistry; LoT, line of therapy; MAT2A, methionine adenosyltransferase 2A; MTA, methylthioadenosine; MTAP, methylthioadenosine phosphorylase; NGS, next-generation sequencing; NR, not reported; NSCLC, non-small cell lung cancer; ORR, overall response rate (CR+PR); OS, overall survival; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; PR, partial response; PRMT5, protein arginine methyltransferase 5; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; SAM, S-adenosylmethionine; s.d., standard deviation; SD, stable disease; Tmax, time to maximum observed plasma concentration; TRAE, treatment-related adverse event; V, vopimetostat; Z, zoldonrasib.

Acknowledgments
The authors thank the patients and their families, participating clinical trial sites, and co-investigators for their contributions to this study. The authors also thank Glenn Ritz, Bradley Atkinson, Josh Chen, Fatima Ocak, and other colleagues at Tango Therapeutics for their contributions to the conduct and reporting of the study. Revolution Medicines is acknowledged for providing daraxonrasib and zoldonrasib under a clinical trial supply agreement. Medical writing and editorial support were provided by Meghan Sullivan, PhD, CHPP, an employee of Tango Therapeutics.

Disclosures
AS, JH, EMO'R, CW, SS, CP, JMM, JR, and KS have received research funding from Tango Therapeutics. DS and TL are employees of and have stock ownership in Revolution Medicines. RM, AT, AC, KB, KW, DF, and MP are employees of and have stock ownership in Tango Therapeutics.

References (1) Pavlick et al. *JCO Precis Oncol.* 2026;10:(Suppl e2600037); (2) Ngo et al. *Oncol.* 2024;29:(6):493-503; (3) Hustin et al. *Cancer Biol Ther.* 2006;4:(1):90-93; (4) Mavrakis et al. *Science.* 2016;351:(6278):1208-1213; (5) Kumar et al. *Cancer Med.* 2023;12:(2):1157-1166; (6) O'Kane et al. *Cancer Res.* 2024; 83:(7_suppl):PR-177; (7) Kryukov et al. *Science.* 2016;351:(6278):1214-1218; (8) Cottrell et al. *J Med Chem.* 2025;68:(5):5097-5116; (9) O'Reilly et al. *N Engl J Med.* 2026;395:(4):325-337; (10) Spira et al. *J Clin Oncol.* 2025;43:(4_suppl):724-724; (11) Knott et al. *Cancer Res.* 2025;85:(16):3540-3557; (12) Zhang et al. *Cancer Res.* 2025;85 (8_Supplement_1):2996–2996; (13) RAS2NQUE® (daraxonrasib). Prescribing information. Revolution Medicines; 2026. Revised 10/29/2026, post presentation.

Results

Safety

Table 5. Summary of TRAEs: Vopimetostat + Daraxonrasib, PDAC and NSCLC

n, (%)	V (200mg) + D (100 mg) DL1: PDAC (n=25)	V (200mg) + D (100mg) DL1: NSCLC (n=5)	V (250mg) + D (100mg) DL2: PDAC (n=4)	Total (n=34)
Any TRAE	19 (76.0)	5 (100.0)	4 (100.0)	28 (82.3)
Grade 1-2	9 (36.0)	4 (80.0)	1 (25.0)	14 (41.2)
Grade 3	10 (40.0)	1 (20.0)	3 (75.0)	14 (41.2)
Grade 4	-	-	-	-
Grade 5	-	-	-	-
SAE	-	-	-	-
Leading to Dose Modification	11 (44.0)	3 (60.0)	4 (100.0)	18 (52.9)
Interruption	10 (40.0)	2 (40.0)	4 (100.0)	16 (47.1)
Dose Reduction	5 (20.0)	2 (40.0)	1 (25.0)	8 (23.5)
Leading to Withdrawal	-	-	1 (25.0)	1 (2.9)
Leading to DLT	-	-[a]	2 (50.0)[b]	2 (5.9)

TRAEs occurring in ≥15% of Patients	All Grades	Grade 3	All Grades	Grade 3	All Grades	Grade 3	All Grades	Grade 3
Rash[c]	11 (44.0)	-	5 (100.0)	-	4 (100.0)	1 (25.0)	20 (58.8)	1 (2.9)
Stomatitis/Mucositis	12 (48.0)	-	2 (40.0)	-	2 (50.0)	1 (25.0)	16 (47.1)	1 (2.9)
Diarrhea	7 (28.0)	-	4 (80.0)	-	2 (50.0)	-	13 (38.2)	-
Fatigue	4 (16.0)	-	2 (40.0)	-	3 (75.0)	1 (25.0)	9 (26.5)	1 (2.9)
Anemia	6 (24.0)	3 (12.0)	1 (20.0)	1 (20.0)	-	-	7 (20.6)	4 (11.8)
Nausea	3 (12.0)	-	2 (40.0)	-	1 (25.0)	-	6 (17.6)	-
Edema peripheral	4 (16.0)	-	-	-	2 (50.0)	-	6 (17.6)	-
Thrombocytopenia	4 (16.0)	2 (8.0)	1 (20.0)	-	1 (25.0)	-	6 (17.6)	2 (5.9)
Vomiting	4 (16.0)	-	1 (20.0)	-	1 (25.0)	-	6 (17.6)	-

[a]At the time of the datacut, an event (Grade 2 anemia) was incorrectly captured in the EDC as a DLT; this has since been corrected.
[b]Grade 3 acneiform rash (resulting in dose reduction and continued treatment) and Grade 3 stomatitis and fatigue (withdrawn consent).
[c]Includes TRAEs of rash, rash maculo-papular and dermatitis acneiform.

Table 6. Summary of TRAEs: Vopimetostat + Zoldonrasib, PDAC[a]

n, (%)	V (200mg) + Z (600mg) DL1 (n=13)	V (250mg) + Z (600mg) DL2 (n=9)	V (200mg) + Z (1200mg) DL4 (n=13)	V (250mg) + Z (1200mg) DL3 (n=4)	Total (n=39)
Any TRAE	11 (84.6)	9 (100)	9 (69.2)	4 (100)	33 (84.6)
Grade 1-2	6 (46.2)	6 (66.7)	8 (61.5)	1 (25.0)	21 (53.8)
Grade 3	4 (30.8)	3 (33.3)	1 (7.7)	3 (75.0)	11 (28.2)
Grade 4	1 (7.7)[b]	-	-	-	1 (2.6)
Grade 5	-	-	-	-	-
SAE	1 (7.7)	1 (11.1)	0	1 (25.0)	3 (7.7)
Leading to Dose Modification	5 (38.5)	3 (33.3)	2 (15.4)	2 (50.0)	12 (30.8)
Interruption	5 (38.5)	3 (33.3)	2 (15.4)	2 (50.0)	12 (30.8)
Dose Reduction	1 (7.7)	2 (22.2)	1 (7.7)	2 (50.0)	6 (15.4)
Leading to Withdrawal	-	-	-	-	-
Leading to DLT	-	-[c]	-	-	-

TRAEs occurring in ≥15% of patients	All Grades	Grade 3	All Grades	Grade 3	All Grades	Grade 3	All Grades	Grade 3	All Grades	Grade 3
Nausea	3 (23.1)	-	5 (55.6)	-	5 (38.5)	-	2 (50)	-	15 (38.5)	-
Vomiting	4 (30.8)	-	4 (44.4)	-	5 (38.5)	-	2 (50)	-	15 (38.5)	-
Dysgeusia	3 (23.1)	-	3 (33.3)	-	4 (30.8)	-	1 (25)	-	11 (28.2)	-
Fatigue	3 (23.1)	-	2 (22.2)	-	3 (23.1)	-	2 (50)	-	10 (25.6)	-
Anemia	3 (23.1)	3 (23.1)	1 (11.1)	1 (11.1)	1 (7.7)	-	4 (100)	3 (75.0)	9 (23.1)	7 (17.9)
Diarrhea	2 (15.4)	-	3 (33.3)	1 (11.1)	-	-	3 (75)	-	8 (20.5)	1 (2.6)
Rash[d]	2 (15.4)	-	3 (33.3)	-	2 (15.4)	-	-	-	7 (17.9)	-

[a]One patient treated with vopimetostat+zoldonrasib had NSCLC and is omitted from this table.
[b]Grade 4 AST increase.
[c]At the time of the datacut, an event (Grade 1 vomiting) was incorrectly captured in the EDC as a DLT; this has since been corrected.
[d]Includes TRAEs of rash, rash maculo-papular and dermatitis acneiform.

- Treatment with both combinations was generally consistent with established toxicities of the individual agents; no unexpected safety findings were observed (**Tables 5 & 6**).
  - In both treatment arms, most TRAEs were Grade ≤3 in severity; no TRAEs resulted in death.

Conclusions

- **Pharmacokinetic analyses support concurrent delivery of clinically active exposure of both agents.**
- **Vopimetostat + daraxonrasib was well tolerated at the selected Phase 3 dose (DL1), with no DLTs, no Grade 4-5 TRAEs, and limited dose reductions.** Gastrointestinal toxicities were predominantly low grade (Grade 1-2) and only low-grade rash and stomatitis was observed.
- **Vopimetostat + daraxonrasib demonstrated encouraging clinical activity in MTAP-loss PDAC**, including an ORR of 82% and a 9-month PFS rate of 88% in heavily pretreated patients, supporting advancement into Phase 3 evaluation.
- **Vopimetostat + zoldonrasib demonstrated promising antitumor activity** (ORR, 54%; 9-month PFS, 61%) and was well tolerated, supporting continued evaluation and expansion of the 200 mg/1200 mg QD regimen in MTAP-loss, G12D-mutant PDAC.

Candidate Phase 3 Dose in PDAC:
Vopimetostat 200 mg + Daraxonrasib 100 mg (DL1)

- **Pharmacokinetics:** Daraxonrasib 100 mg achieved exposure comparable to 300 mg QD monotherapy while maintaining vopimetostat exposure
- **Efficacy:** Clinically meaningful ORR (82%) and 9-month PFS rate (88%) in second and third-line PDAC
- **Safety:** No DLTs, no Grade 4-5 TRAEs