A Phase 1/2 study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of TNG260 in combination with pembrolizumab in patients with STK11-mutated advanced solid tumors

Poster #561

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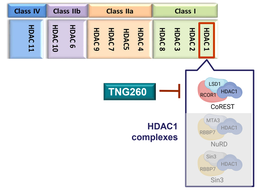
Key Points

- STK11 loss-of-function mutations occur in ~20% of NSCLC and are associated with reduced T cell infiltration, primary resistance to immune checkpoint blockade, and poor prognosis.
- Patients with STK11-mutant lung adenocarcinoma have markedly inferior responses to anti-PD-(L)1 therapy as compared to STK11-WT (mPFS: 10 weeks in KRAS WT, 8 weeks in KRAS mutant; Ricciuti et al., JTO, 2022).
- TNG260 is an orally-administered CoREST inhibitor that sensitizes preclinical models to anti-PD1 by increasing expression of specific immunomodulatory genes in STK11-mut cancer cells (See poster 681).
- TNG260 is being evaluated in combination with pembrolizumab in a phase 1/2 clinical trial (NCT05887492) to evaluate pharmacokinetics, safety, tolerability, and efficacy.
- The safety profile of TNG260 is on-target and consistent with HDAC1/2 inhibition, including cytopenias and fatigue. The selected go-forward dose 80 mg QD is well tolerated.
- Paired on treatment tumor biopsies show that TNG260 alters expression of key immunomodulatory genes in STK11-mut NSCLC, leading to remodeling of the tumor microenvironment via increased T cell infiltration
- TNG260 is clinically active in STK11-mut, KRAS wild-type NSCLC. There is no evidence of activity STK11 mut KRAS-mut NSCLC or non-lung histologies.
- Patients with STK11 mut/KRAS wild-type NSCLC (~ 50% of STK11 mut NSCLC) receiving clinically active doses of TNG260 plus pembrolizumab had a median PFS of 29 weeks in dose escalation (n=5), a marked improvement over the SOC PFS.

TNG260, a novel small-molecule CoREST inhibitor, sensitizes STK11-mutant tumors to anti-PD-1 therapy

See poster 681 for preclinical rationale for TNG260

A



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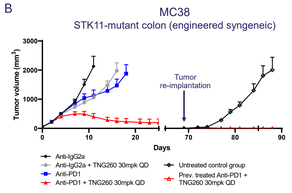


- 5/8 mice with complete tumor regression at day 34
- 5/5 mice with complete regression rejected tumor re-implantation

(A) TNG260 selectively inhibits CoREST, one of several deacetylase complexes containing HDAC1. (B) STK11-deficient tumors respond poorly to anti-PD1. TNG260 sensitizes these tumors to anti-PD1 treatment. In mice that were cured by TNG260 + anti-PD1, re-implantation of tumor cells was rejected, indicating the formation of immune memory for that tumor type.

Patient demographics

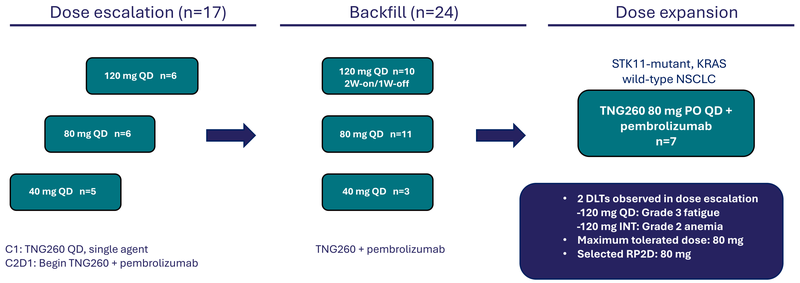
		TNG260 40mg n=8	TNG260 80mg Dose escalation n=17	TNG260 120mg n=6	TNG260 120mg INT n=10	TNG260 80mg Dose expansion n=7	Total n=48
Age Group (Years), n(%)	25-44	0	1 (6)	0	2 (20)	1 (14)	4 (8)
	45-64	2 (25)	6 (35)	4 (67)	7 (70)	2 (29)	21 (44)
	>=65	6 (75)	10 (59)	2 (33)	1 (10)	4 (57)	23 (48)
	Age, Median	68	67	60	60	66	63.5
Sex (%)	Female	1 (13)	8 (47)	3 (50)	6 (60)	3 (43)	21 (44)
	Male	7 (88)	9 (53)	3 (50)	4 (40)	4 (57)	27 (56)
Tumor Type (%)	NSCLC	6 (75)	10 (59)	4 (66)	10 (100)	7 (100)	37 (77)
	Pancreatic	2 (25)	1 (6)	0	0	0	3 (6)
	Other	0	6 (35)	2 (33)	0	0	8 (17)
Number of Prior Systemic Regimens (%)	0	1 (13)	1 (6)	0	1 (10)	0	3 (6)
	1	2 (25)	5 (29)	1 (17)	1 (10)	4 (57)	13 (27)
	2	3 (38)	4 (24)	1 (17)	2 (20)	1 (14)	11 (23)
	≥3	2 (25)	7 (41)	4 (67)	6 (60)	2 (29)	21 (44)
	Median	2.0	2.0	3.0	3	1	2.0
Prior PD-1/PD-L1 inhibitor (%)	Yes	5 (63)	14 (82)	5 (83)	8 (80)	7 (100)	39 (81)
	No	3 (38)	3 (18)	1 (17)	2 (20)	0.0	9 (19)
Prior PD-1/PD-L1 inhibitor in NSCLC (%)	Yes	5 (83)	9 (90)	4 (100)	8 (80)	7 (100)	33 (89)
	No	1 (17)	1 (10)	0	2 (20)	0	4 (11)
KRAS mutation (%)	Yes	2 (25)	8 (47)	2 (33)	1 (10)	0	13 (27)
	No	6 (75)	9 (53)	4 (67)	9 (90)	7 (100)	35 (73)

Other tumor types included anal, cervical, endometrial, head and neck, melanoma, ovarian, rectal, and carcinoma of unknown primary. One patient was enrolled with each of the prior tumor types.

TNG260 first-in-human trial design

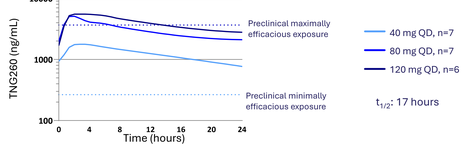
Key eligibility criteria
- Adv or metastatic solid tumor
- STK11-loss of function mutation
- Measurable or evaluable disease
- Underwent prior approved treatment for actionable alterations
- No prior line limit

Endpoints
Pharmacokinetics, safety, tolerability, and preliminary efficacy



DOSE AND SCHEDULE. Patients in escalation received re-baseline scans after 3 weeks of TNG260 single agent. After 3 weeks of single agent treatment, dose escalation patients received pembrolizumab which was then dosed every 3 weeks. The DLT review period encompassed 3 weeks of single agent treatment and combination treatment at each dose· Patients enrolled to backfill cohort initiated pembrolizumab * TNG260 on C1D1. An additional cohort was opened to assess an intermittent (INT) administration of TNG260 (2 weeks-on/1 week-off) in combination with pembrolizumab. Both 40mg QD dose level and the 120mg intermittent dose level were clinically inactive. Data cutoff: Sept 22, 2025

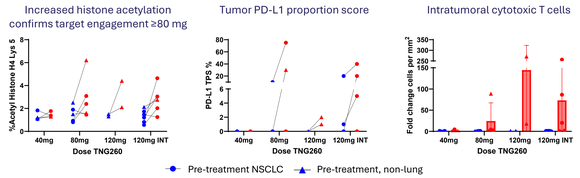
TNG260 exposures at 80 mg PO QD meet the maximally efficacious exposure identified in preclinical models

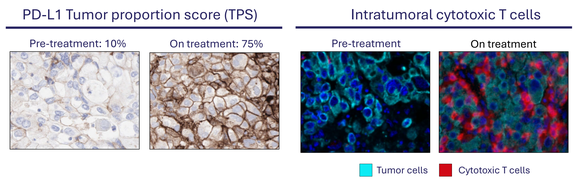


PK Parameters – C1D15
Arithmetic mean (Standard deviation)

QD Cohort	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-}tau}$ (h*ng/mL)	C_{trough} (ng/mL)	$RacAUC_{0\text{-}tau}$
40 mg (n=7)	2000 (980)	1.5 – 4.0	30500 (15500)	770 (477)	1.61 (0.648)
80 mg (n=7)	5240 (1420)	1.5 – 4.0	76500 (18100)	2110 (917)	1.45 (0.280)
120 mg (n=6)	6840 (3600)	1.5 – 4.0	92300 (79800)	2090 (2550)	1.09 (0.318)

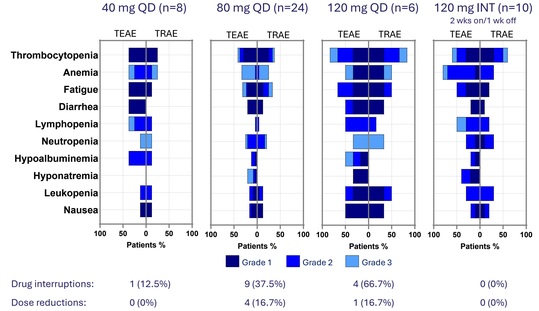
TNG260 alters the microenvironment of STK11-mutant cancer, reversing immune evasion





Biopsies were collected prior to treatment with TNG260 and on-treatment after one cycle of combination treatment. For the 120 mg INT group, biopsies were collected while patient was on combination treatment. (**A**) Histone H4 Lys 5 acetylation was determined by mass spectrometry of FFPE tissue. (**B**) PD-L1 TPS was determined by IHC with PD-L1 (22C3). (**C**) CD3+, CD8+ T cells were quantified in tumor regions defined by H&E. (**D**) NSCLC patient treated with 80 mg TNG260. Tissue was profiled for PD-L1 and T cell infiltration by multiplex immunofluorescence.

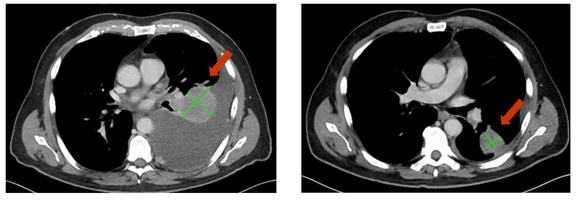
TNG260 80 mg QD is well tolerated



	40 mg QD (n=8)	80 mg QD (n=24)	120 mg QD (n=6)	120 mg INT (n=10)
Drug interruptions:	1 (12.5%)	9 (37.5%)	4 (66.7%)	0 (0%)
Dose reductions:	0 (0%)	4 (16.7%)	1 (16.7%)	0 (0%)
Drug withdrawals:	0 (0%)	1 (4.2%)	1 (16.7%)	0 (0%)

Figure representing 10 most frequent treatment emergent adverse events from all patients on study.

NSCLC with confirmed RECIST PR (-69%)

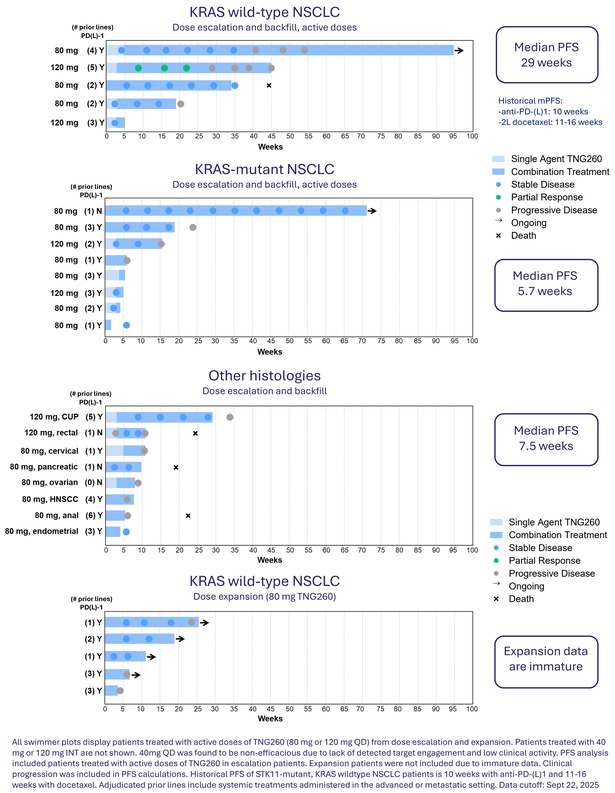


C3D1 (after 3 weeks of single agent TNG260) (+130% from baseline)

After 6 weeks of TNG260 + pembrolizumab (-64% from re-baseline)

Confirmed PR in heavily pretreated patient including prior pembrolizumab failure
Patient: 70-year-old male with stage IV NSCLC (diagnosed May 2022)
Prior Treatment: 5 prior lines of therapy, including carboplatin/pemetrexed/pembrolizumab
Treatment Regimen: TNG260 120 mg monotherapy (3 weeks) → TNG260 120 mg + pembrolizumab
Tumor response:
C2D1 (3 weeks TNG260 monotherapy): +130% with new lesions (PD)
C4D1 (6 weeks TNG260 + pembrolizumab): -64% (PR)
Best overall response: -69% with complete response in 2 target lesions (confirmed PR)
Treatment Duration: 44.8 weeks total
Treated through radiographic progression at C10D1 (26 weeks) with continued clinical benefit
Key Takeaway: Single-agent TNG260 showed initial progression, but combination with pembrolizumab achieved durable response in a pembrolizumab-refractory patient

TNG260 + pembrolizumab is active in STK11-mutant KRAS wild-type NSCLC



All swimmer plots display patients treated with active doses of TNG260 (80 mg or 120 mg QD) from dose escalation and expansion. Patients treated with 40 mg or 120 mg INT are not shown. 40mg QD was found to be non-efficacious due to lack of detected target engagement and low clinical activity. PFS analysis included patients treated with active doses of TNG260 in escalation patients. Expansion patients were not included due to immature data. Clinical progression was included in PFS calculations. Historical PFS of STK11-mutant, KRAS wildtype NSCLC patients is 10 weeks with anti-PD-(L)1 and 11-16 weeks with docetaxel. Adjudicated prior lines include systemic treatments administered in the advanced or metastatic setting. Data cutoff: Sept 22, 2025

Summary

- **80 mg QD selected as RP2D**
- **Dose escalation**
  - mPFS 29 weeks in STK11mut/KRAS WT NSCLC at active doses
  - Efficacy observed in all patients with prior anti-PD-(L)1 treatment failure
  - No evidence of activity in STK11mut/KRASmut NSCLC or non-NSCLC histologies
  - 1 partial response in KRASwt NSCLC (ORR: 20% at active doses). No PRs were observed in KRAS-mutant NSCLC or non-lung histologies.
- **mPFS 29 wks compares favorably to SOC docetaxel (11-16 wks)**
- **TNG260 80 mg QD is well tolerated with on-target AEs including cytopenia and fatigue.**
- **TNG260 modulates the microenvironment of STK11-mutant tumors through cytokine regulation and increased T cell infiltration, demonstrating clinical proof-of-mechanism**
- **Currently enrolling STK11mut/KRASwt patients with no limitation on number of prior lines of therapy**

Acknowledgements

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References

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