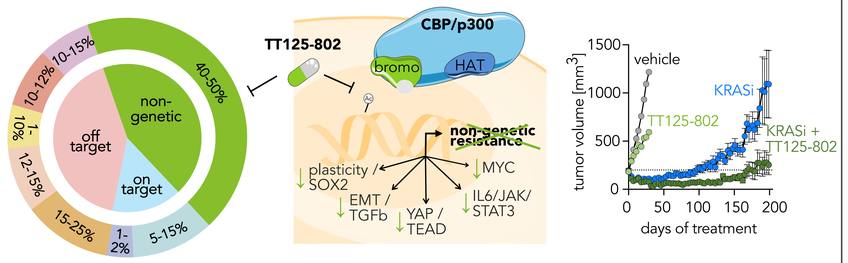
P3.204: TT125-802, a Selective Clinical Bromodomain Inhibitor of CBP/p300, Targeting Transcriptional Resistance Mechanisms in NSCLC

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The epigenetic inhibitor TT125-802 targets cancer cell plasticity, a hallmark of cancer and drug resistance

Preclinical POC: TT125-802 prevents CBP/p300 mediated non-genetic resistance to oncogene-targeting therapies in NSCLC



Resistance mechanisms to osimertinib; left panel adapted from Fu et al., 2022

- Non-genetic
- EGFR mutations
- EGFR amplification
- MET & HER2 amplification
- Bypass & downstream alterations
- Oncogene fusion
- Cell cycle alterations
- Histologic transformation

TT125-802, a bromodomain inhibitor of CBP/p300, is a novel epigenetic modulator designed to inhibit transcriptional pathways that drive cancer cell plasticity and drug resistance. It has clinical potential as monotherapy and in combination with other cancer drugs for durable therapeutic responses.

FIH monotherapy study: dose escalation in solid tumor all-comers and enrichment in NSCLC cohorts

FIH design (NCT06403436)
- Solid tumor all-comers
- Bayesian logistic regression model
- 3 - 6 patients per escalation cohort
- One cycle = 21 days

Primary endpoints
- Safety and tolerability
- Estimation of MTD and/or RDE

Secondary endpoints
- Characterization of PK
- ORR by RECIST v1.1
- DCR, DoR and PFS

Exploratory endpoints
- Exploration of PK/PD relationship and biomarkers

Dose escalation in solid tumors (fasted)
- 5 cohorts: 15 mg, 30 mg, 60 mg, 100 mg QD, 60 mg BID
- n=24

→

Food effect cohorts enriched for NSCLC
- 2 cohorts: 30 mg, 60 mg QD
- Enriched for NSCLC independent of histology or mutational status
- intra-patient food effect evaluation
- n=10

→

Monotherapy enrichment in selected NSCLC
- 3 cohorts at 60 mg QD: Selected NSCLC from EGFR ex19/21, KRAS-G12C, or squamous NSCLC
- no food constraints
- n=11

Monotherapy dose escalation results:
- PK parameters increased with doses up to 60 mg QD
- Exposures at 60 mg QD covered the pre-clinically defined efficacy threshold for 24 hours while remaining below exposures which inhibit off-target BET proteins
- 60 mg QD without fasting requirements was selected as RDE
- Target engagement was confirmed by RNA sequencing of hair follicles
- Data were previously presented by Saveedra *et al.* at ESMO2025

TT125-802 is safe and well-tolerated at biologically relevant doses

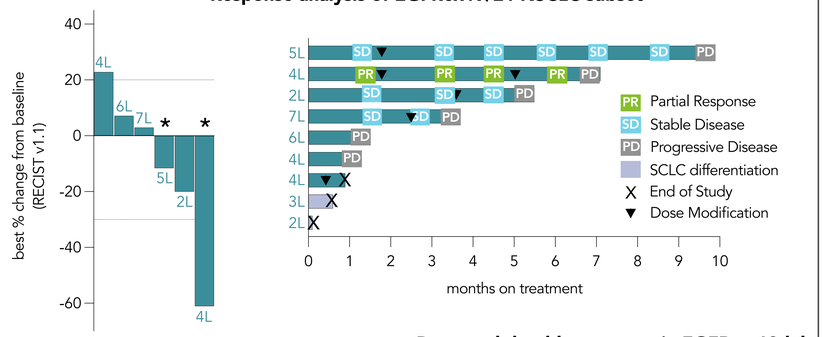
TRAEs by Preferred Term by Grade (≥15% patients or ≥ Grade 3) considering all 45 study patients

Preferred Term	Grade any	Grade 1	Grade 2	Grade 3	Grade 4
Dysgeusia	29 (64%)	16 (36%)	13 (29%)	-	-
Hyperglycaemia	18 (40%)	10 (22%)	7 (16%)	1 (2%)	-
Fatigue	14 (31%)	3 (7%)	10 (22%)	1 (2%)	-
Decreased appetite	12 (27%)	8 (18%)	4 (9%)	-	-
Weight decreased	11 (24%)	5 (11%)	6 (13%)	-	-
Stomatitis	10 (22%)	8 (18%)	2 (4%)	-	-
Amylase increased	9 (20%)	2 (4%)	7 (16%)	-	-
Dry eye	8 (18%)	4 (9%)	4 (9%)	-	-
Nausea	8 (18%)	5 (11%)	3 (7%)	-	-
Aspartate aminotransferase increased	7 (16%)	7 (16%)	-	-	-
Lipase increased	7 (16%)	3 (7%)	4 (9%)	-	-
Anaemia	6 (13%)	2 (4%)	3 (7%)	1 (2%)	-
Atrial fibrillation	1 (2%)	-	-	1 (2%)	-
Lymphopenia	1 (2%)	-	-	1 (2%)	-

- No MTD was reached
- No thrombocytopenia was observed
- The two most common TRAEs: dysgeusia did not correlate with exposure; hyperglycemia correlated with exposure
- The safety profile supports a continuous dosing regimen
- 22% of patients had a dose reduction due to a TRAE
- 7% (3/45) patients discontinued treatment at 60 mg QD or higher due to dysgeusia (G2, n=1) or hyperglycemia (G2/G3, n=2)

TT125-802 has monotherapy activity in EGFR ex19/21 NSCLC, including in patients with primary resistance to osimertinib

Response analysis of EGFRex19/21 NSCLC subset

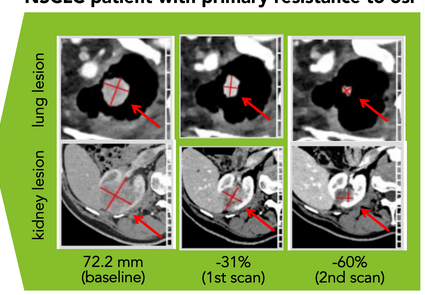


★ ≥ 6 months
L = therapy line of TT125-802

Tumor characteristics & treatment history (ranked by treatment duration)

	histology	target lesion: diameter sum (#)	EGFR mutation	response to osimertinib
5L	adeno	57.9 mm (3)	ex19del	CR (8 mo)
4L	adeno	72.2 mm (2)	ex19del	SD (3 mo)
2L	adeno	50.2 mm (2)	ex19del	PR (23 mo)
7L	adeno	33 mm (2)	ex19del	CR (9 mo)
6L	adeno	153 mm (4)	ex21mut	PR (11 mo)
4L	adeno	66.5 mm (1)	ex21mut	SD (15 mo)
4L	adeno	83.6 mm (4)	ex19delins	PR (48 mo)
3L	SCLC	69.4 mm (2)	ex19del	PR (10 mo)
2L	SCLC	174.5 mm (4)	ex19del	PR (11 mo)

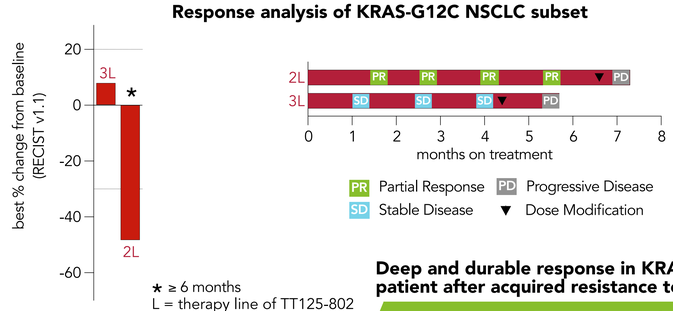
Deep and durable response in EGFR ex19del NSCLC patient with primary resistance to osi



Patient from **vignette:** primary resistance to 1L osimertinib (SD; 3 months), PR in 2L on platinum doublet (4 months), PD in 3L on atezolizumab (subsequent washout of 5 weeks prior TT125-802 start), PR to TT125-802 in 4L (7 months). Rapid and durable PR to TT125-802 confirms CBP/p300 dependence in primary resistant setting.

TT125-802 showed monotherapy activity in secondary resistant KRAS-G12C NSCLC

Response analysis of KRAS-G12C NSCLC subset

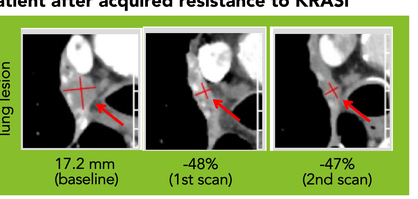


★ ≥ 6 months
L = therapy line of TT125-802

Tumor characteristics & treatment history (ranked by treatment duration)

	target lesions: diameter sum (#)	prior KRAS inhibitor	response to KRASi
2L	17.2 mm (1)	elironrasib (1L)	SD (12 mo)
3L	37 mm (2)	sotorasib (2L)	PR (24 mo)

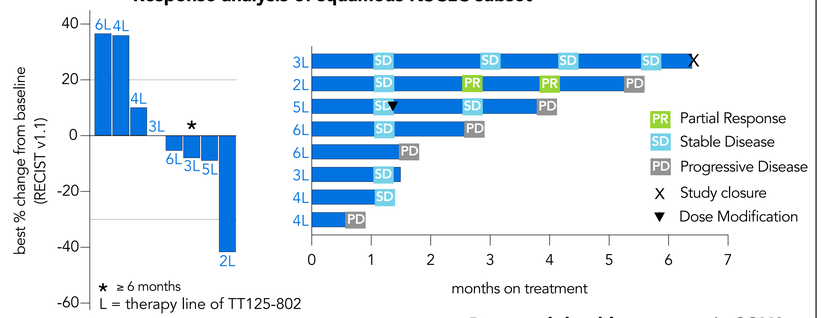
Deep and durable response in KRAS-G12C NSCLC patient after acquired resistance to KRASi



Patient from **vignette:** acquired resistance to 1L elironrasib (SD, 12 months), PR to TT125-802 in 2L (7 months). Rapid and durable PR to TT125-802 confirms CBP/p300 dependence in acquired resistant setting.

TT125-802 shows durable anti-tumor activity in SOX2-amplified squamous NSCLC

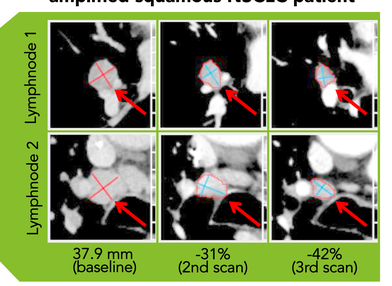
Response analysis of squamous NSCLC subset



Tumor characteristics & treatment history (ranked by treatment duration)

	target lesion: diameter sum (#)
3L	87 mm (2)
2L	37.9 mm (2)
5L	76.6 mm (3)
6L	103 mm (1)
6L	64 mm (1)
3L	21 mm (1)
4L	20.6 mm (1)
4L	55 mm (1)

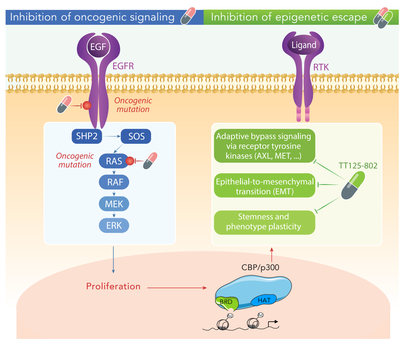
Deep and durable response in SOX2-amplified squamous NSCLC patient



Patient from **vignette:** acquired resistance to 1L carbo/pacli/pembro (14 months); PR to TT125-802 in 2L (5.5 months) Durable PR to TT125-802 confirms CBP/p300 dependence in SOX2-amplified NSCLC. Transcriptional SOX2 repression was the primary screening readout used in the phenotypic development of TT125-802.

Conclusion: CBP/p300 is a driver of drug resistance in NSCLC

- Various resistance mechanisms lead to relapse to oncogene targeting therapies including many without known genetic driver.
- Non-genetic resistance mechanisms via cancer cell plasticity have so-far been hard to target.
- The epigenetic modulators CBP/p300 mediate non-genetic escape mechanisms that run in parallel to oncogenic signaling.
- TT125-802 is a small molecule inhibitor of CBP/p300 that targets transcriptional resistance mechanisms including EMT and plasticity.
- Its favourable safety profile (no thrombocytopenia) in the clinic makes TT125-802 a versatile combination partner.
- In preclinical studies TT125-802 demonstrated synergistic effects when combined with oncogene targeting therapies (eg. KRASi, EGFRi).
- In a separate study TT125-802 will be assesses in combination with osimertinib in EGFR ex19/21 NSCLC.



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- No AI tools were used to generate this poster.