ATLANTA
LUNG CANCER SYMPOSIUM

KRAS G12C Inhibitors Should Not Be Given With Immunotherapy

Gregory J. Riely October 2025

When should we combine drugs?

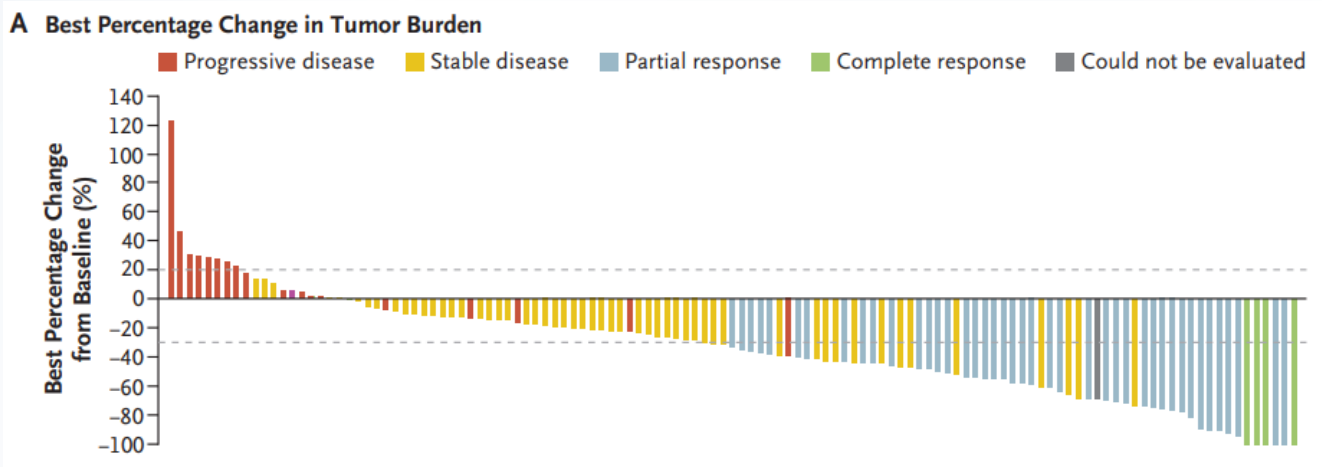
- pre-clinical evidence to support greater efficacy
- safe when given in combination
- there is clinical evidence of synergy

Sotorasib for Lung Cancers with *KRAS* p.G12C Mutation

F. Skoulidis, B.T. Li, G.K. Dy, T.J. Price, G.S. Falchook, J. Wolf, A. Italiano, M. Schuler, H. Borghaei, F. Barlesi, T. Kato, A. Curioni-Fontecedro, A. Sacher, A. Spira, S.S. Ramalingam, T. Takahashi, B. Besse, A. Anderson, A. Ang, Q. Tran, O. Mather, H. Henary, G. Ngarmchamnanrith, G. Friberg, V. Velcheti, and R. Govindan

Table 2. Tumor Response to Sotorasib Therapy According to Independent Central Review.*

Variable	Patients (N = 124)
Objective response — % (95% CI)†	37.1 (28.6–46.2)
Disease control — % (95% CI)‡	80.6 (72.6–87.2)
Best response — no. (%)	
Complete response	4 (3.2)
Partial response	42 (33.9)
Stable disease	54 (43.5)
Progressive disease	20 (16.1)
Could not be evaluated	2 (1.6)
Missing scan	2 (1.6)
Median duration of objective response (95% CI) — mo§	11.1 (6.9–NE)
Kaplan–Meier estimate of objective response (95% CI) — %	
At 3 mo	90.5 (76.7–96.3)
At 6 mo	70.8 (54.3–82.2)
At 9 mo	57.3 (40.4–71.0)



FDA grants accelerated approval to sotorasib for KRAS G12C mutated NSCLC

Skoulidis et al, NEJM 2021

Sotorasib + Immune Checkpoint Inhibitors

	Soto+Atezo Concurrent (N=10)	Soto+Pembro Concurrent (N=19)
Safety, n (%)		
TRAE, any grade	9 (90)	17 (89)
TRAE, grade 3-4	6 (60)	15 (79)
Hepatotoxicity, Gr 3-4[a]	5 (50)	9 (47)
ALT increased	4 (40)	7 (37)
AST increased	5 (50)	5 (26)
TRAE leading to discontinuation of Sotorasib and/or IO	5 (50)	10 (53)
Number of treatment doses, max)		
Sotorasib	115.0 (22, 422)	82.0 (35, 791)
IO	3.5 (2, 21)	3.0 (2, 12)
Efficacy		
ORR, % (95% CI)	20[b] (3, 56)	32[d] (13, 57)
DCR, % (95% CI)	80 (44, 98)	90 (67, 99)
Median OS, (95% CI), months	11.5 (5.0, NE)	14.1 (6.2, 17.8)

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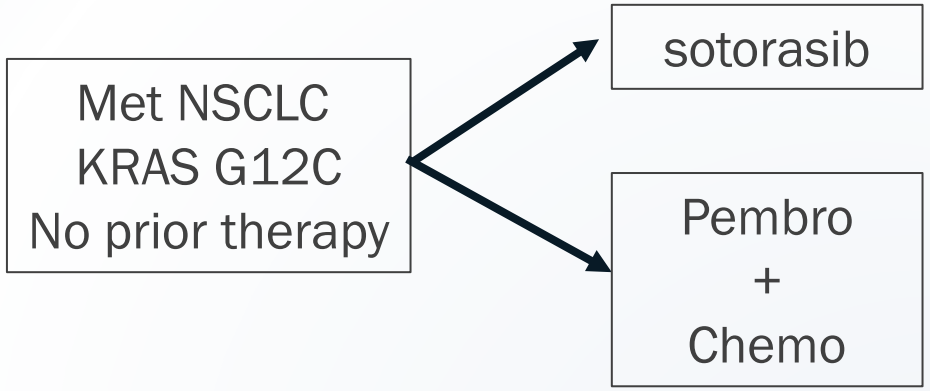


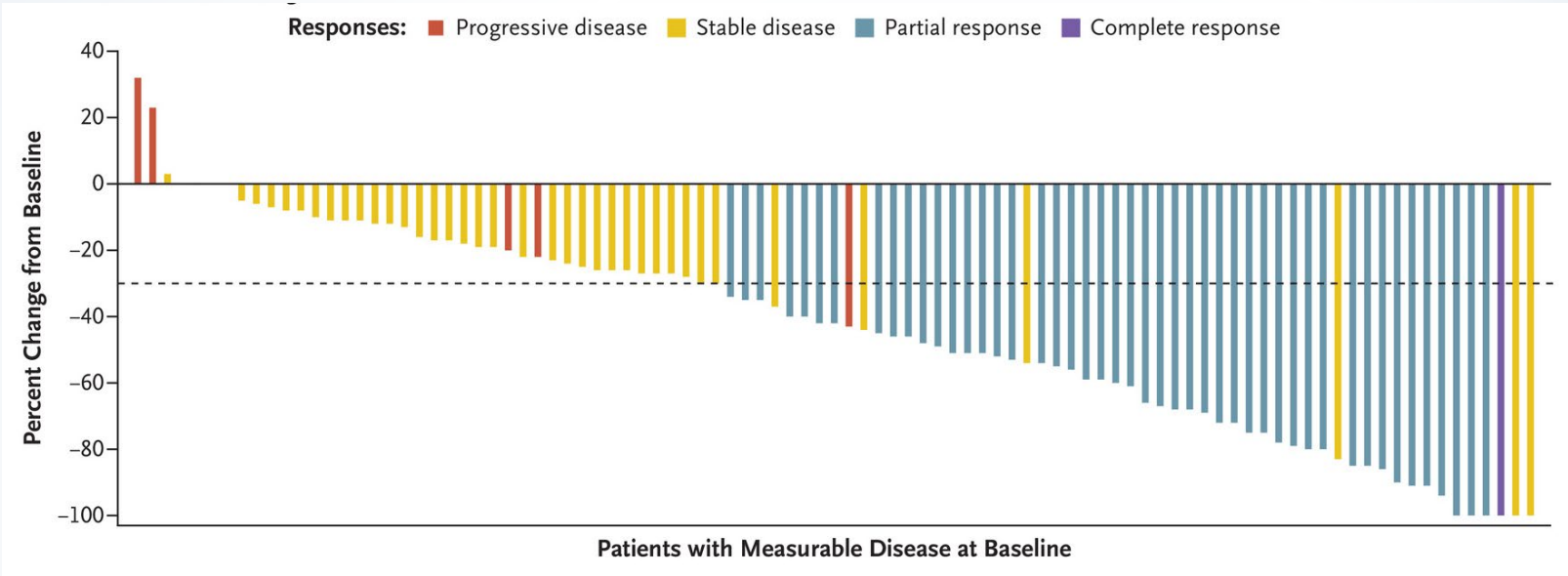
Modified from Li et al, WCLC 2022, Vienna

Adagrasib in Non–Small-Cell Lung Cancer Harboring a $KRAS^{G12C}$ Mutation

Pasi A. Jänne, M.D., Ph.D., Gregory J. Riely, M.D., Ph.D., Shirish M. Gadgeel, M.D., Rebecca S. Heist, M.D., M.P.H., Sai-Hong I. Ou, M.D., Ph.D., Jose M. Pacheco, M.D., Melissa L. Johnson, M.D., Joshua K. Sabari, M.D., Konstantinos Leventakos, M.D., Ph.D., Edwin Yau, M.D., Ph.D., Lyudmila Bazhenova, M.D., Marcelo V. Negrao, M.D., et al.

Table 2. Overall Efficacy Summary According to Blinded Independent Central Review.*

Variable	Cohort A (N=112)†
Objective response‡	
No. of patients	48
Percent (95% CI)	42.9 (33.5–52.6)
Best overall response — no. (%)	
Complete response	1 (0.9)
Partial response	47 (42.0)
Stable disease	41 (36.6)
Progressive disease	6 (5.4)
Not evaluable	17 (15.2)
Disease control	
No. of patients	89
Percent (95% CI)	79.5 (70.8–86.5)
Median duration of response (95% CI) — mo	8.5 (6.2–13.8)
Median progression-free survival (95% CI) — mo	6.5 (4.7–8.4)
Median overall survival (95% CI) — mo§	12.6 (9.2–19.2)



FDA grants accelerated approval to adagrasib for KRAS G12C-mutated NSCLC

Jänne PA et al. N Engl J Med 2022;387(2):120-31.

Combining Adagrasib + Pembrolizumab

KRYSTAL-7[a] phase 2

Key eligibility criteria

- Advanced, unresectable or metastatic NSCLC with *KRAS*^{G12C} mutation[b]
- No prior systemic therapy for locally advanced/metastatic disease[c]
- Known PD-L1 TPS (local or central testing)[d]
- Treated, neurologically stable brain metastases allowed

ADA 400 mg PO BID +
PEMBRO 200 mg IV Q3W[e,f]

Primary endpoint

- ORR per investigator assessment (RECIST v1.1)

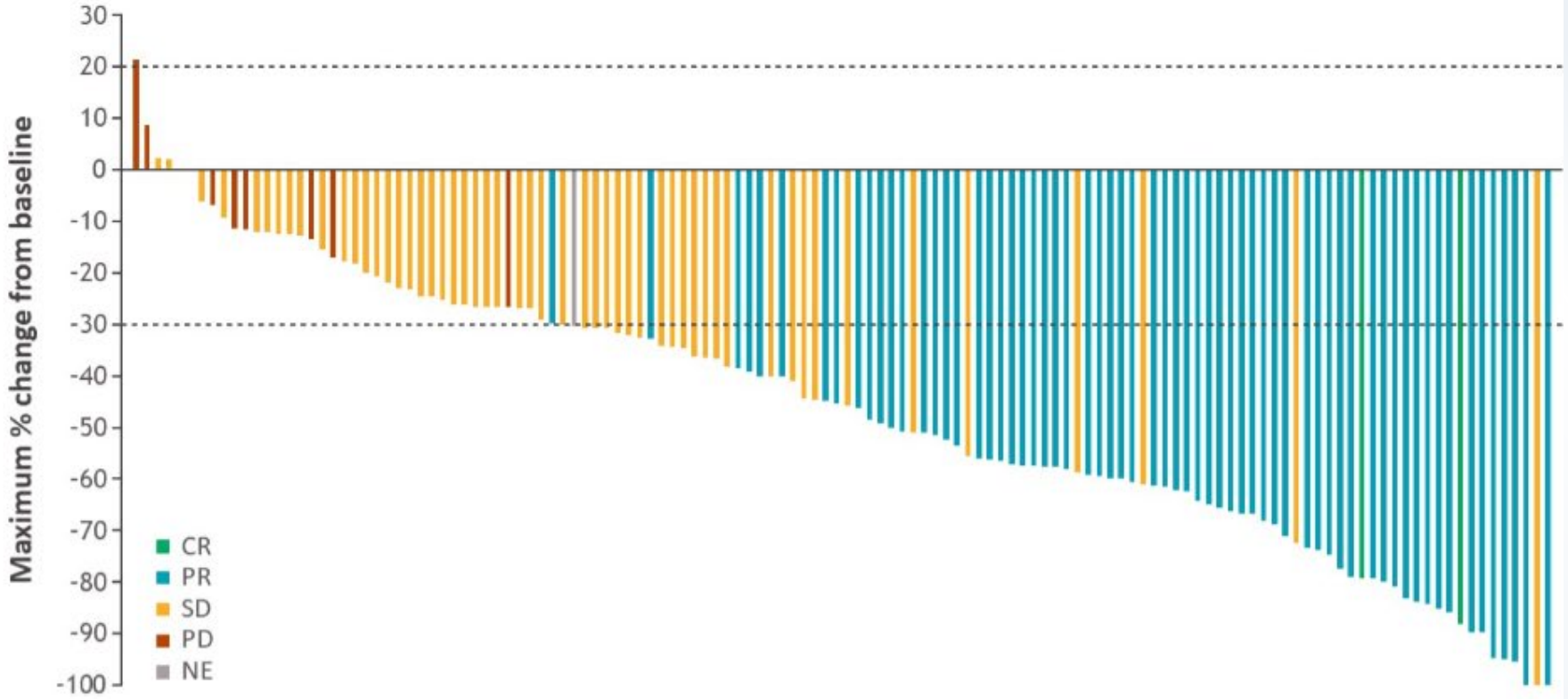
Secondary endpoints

- DOR and PFS per investigator assessment
- OS
- Safety

Janne et al, ASCO 2025

Response Rate of 1st line Adagrasib + Pembrolizumab

	All patients (N = 149)
ORR,[a] n (%)	**66 (44)**
95% CI	36-53
BOR, n (%)	
CR	2 (1)
PR	64 (43)
SD	55 (37)
PD	12 (8)
NE	16 (11)[b]
DCR,[c] n (%)	**121 (81)**
95% CI	74-87

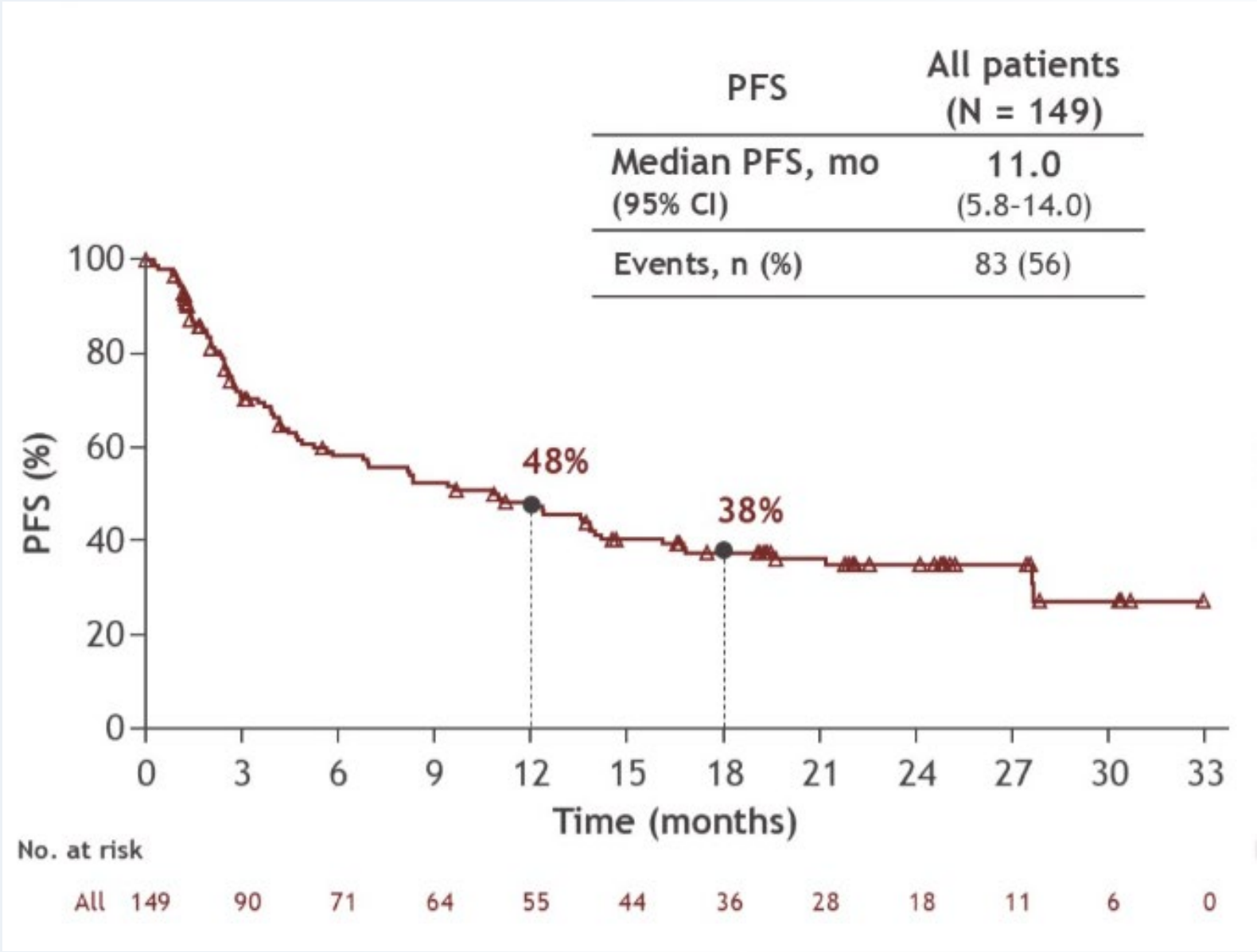


- ORR in the biomarker-evaluable population was 36% (90% CI, 23-50) for PD-L1 TPS < 1%, 41% (90% CI, 25-58) for PD-L1 TPS 1-49%, and 61% (90% CI, 46-74) for PD-L1 TPS ≥ 50%

Waterfall plot includes evaluable patients with at least one target lesion at baseline and at least one post-baseline tumor assessment.
[a]ORR is defined as the proportion of patients with a confirmed CR/PR according to RECIST v1.1. [b]Reasons for no post-baseline imaging assessment were: non-treatment-related deaths (n = 5), withdrawal from the study (n = 2), non-compliant/lost to follow-up (n = 2), discontinuation due to TRAEs (n = 3) or non-TRAEs (n = 2), and global deterioration of health/clinical progression (n = 2). [c]DCR is defined as the proportion of patients with a confirmed CR/PR/SD according to RECIST v1.1.

Janne et al, ASCO 2025

PFS of 1st line Adagrasib + Pembrolizumab



Janne et al, ASCO 2025

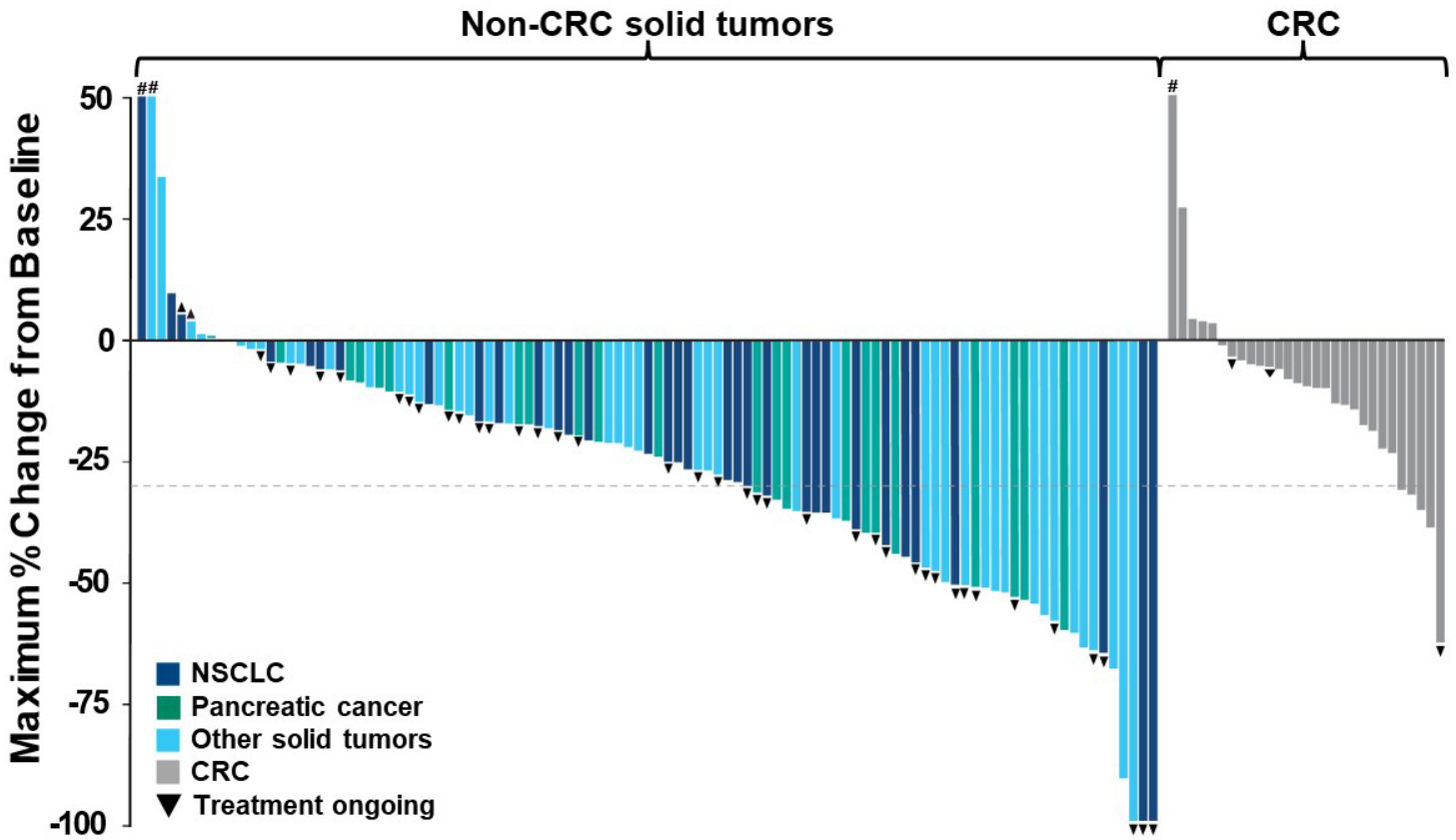
NCI definition of ***synergy***: interaction of two or more drugs when their combined effect is greater than the sum of the effects seen when each drug is given alone

	Adagrasib (2nd line)	**Pembrolizumab** (2nd line, PD-L1 positive)	**Adagrasib + Pembrolizumab** (1st line)
Response Rate	43%	33%	44%
mPFS	6.5 months	5.3 months	11 months

Synergy? …I think not

Janne et al, NEJM 2022; Herbst et al, JTO 2021; Janne et al ASCO 2025

Olomorasib – single-agent



Efficacy Evaluable Patients[a]	Non-CRC solid tumors (N=105)	CRC (N=32)
Objective Response Rate[b], % (n/N)	**35% (37/105)**	**9% (3/32)**
Best overall response		
CR, n (%)	2 (2)	-
PR, n (%)	35 (33)[c]	3 (9)
SD, n (%)	56 (53)	24 (75)
PD, n (%)	10 (10)	3 (9)
NE, n (%)	2 (2)	2 (6)
DCR, % (n/N)	**89% (93/105)**	**84% (27/32)**

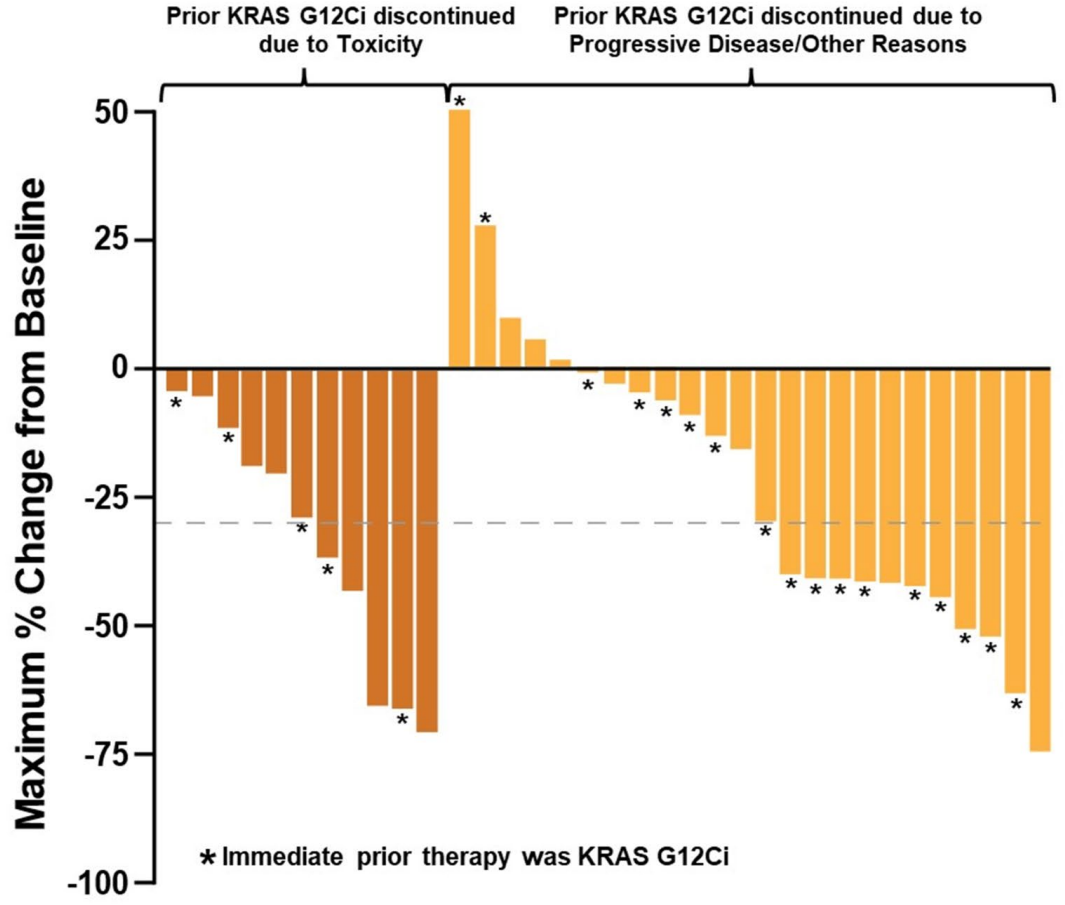
- Consistent activity was seen across a range of cancer types including NSCLC, pancreatic cancer, and other solid tumors
- As anticipated, monotherapy activity was lower in CRC
- Responses seen in 14 unique tumor types

Data cutoff date of 18 Mar 2024. #Indicates patient with >50% increase in sum of diameters. [a]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment before the first post-baseline response assessment. Data for 5 patients are not shown in the waterfall plot due to discontinuation prior to first response assessment, or incomplete target lesion assessment in the context of overall non-target PD. 6 NSCLC patients with active brain metastases are not included in this analysis. [b]ORR includes patients with a best response of CR and PR (confirmed, and pending confirmation and ongoing). [c]2 patients had unconfirmed PRs, pending confirmation and ongoing. Investigator assessed response per RECIST v1.1. Total % may be different from the individual components due to rounding.

Heist et al, ASCO 2024

Olomorasib – single-agent

Efficacy in KRAS G12Ci-pretreated NSCLC



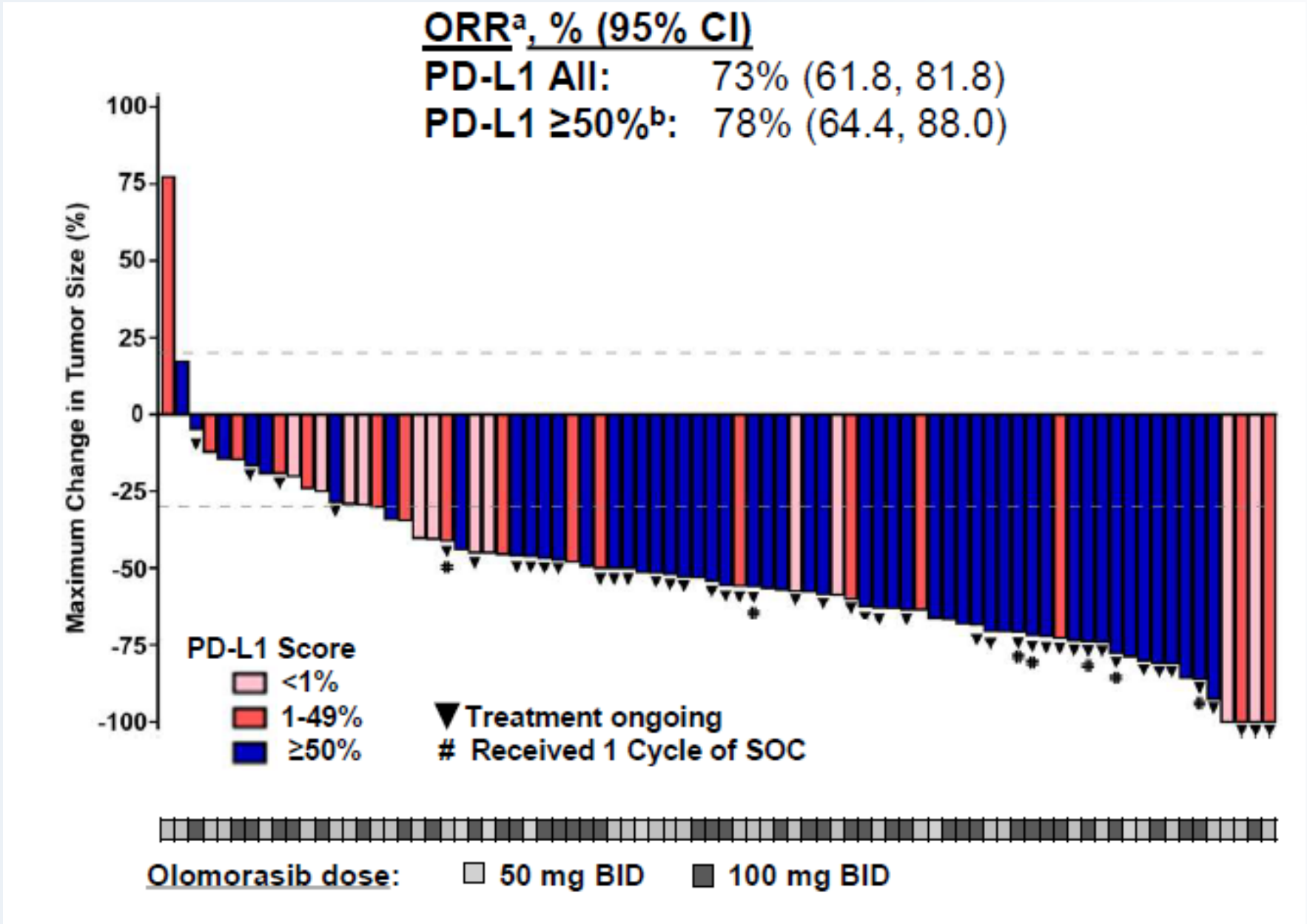
Efficacy Evaluable Patients[a]	Prior KRAS G12Ci discontinued due to toxicity (N=11)	Prior KRAS G12Ci discontinued due to PD / other reasons (N=28)
Objective Response Rate[b], % (n/N)	**46% (5/11)**	**39% (11/28)**
Best overall response		
CR, n (%)	-	-
PR, n (%)	5 (46)	11 (39)
SD, n (%)	6 (55)	10 (36)
PD, n (%)	-	5 (18)
NE, n (%)	-	2 (7)
DCR, % (n/N)	**100% (11/11)**	**75% (21/28)**

- 41% ORR overall (16/39), with responses seen after sotorasib, adagrasib, and divarasib treatment; 63% had a KRAS G12Ci as their immediate prior therapy
- Safety profile for patients who discontinued prior KRAS G12Ci due to toxicity was similar to all patients treated with monotherapy; 1 patient (9%) discontinued olomorasib due to a TRAE
- Of the 29/39 patients with pretreatment ctDNA data, only 2 had second-site KRAS resistance mutations[c]

utoff date of 18 Mar 2024. [a]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment before the first post-baseline response assessment. Data for 4 patients not shown in the waterfall due to discontinuation prior to first response assessment, or

Heist et al, ASCO 2024

Olomorasib + chemotherapy in first line



Johnson et al, WCLC 2025

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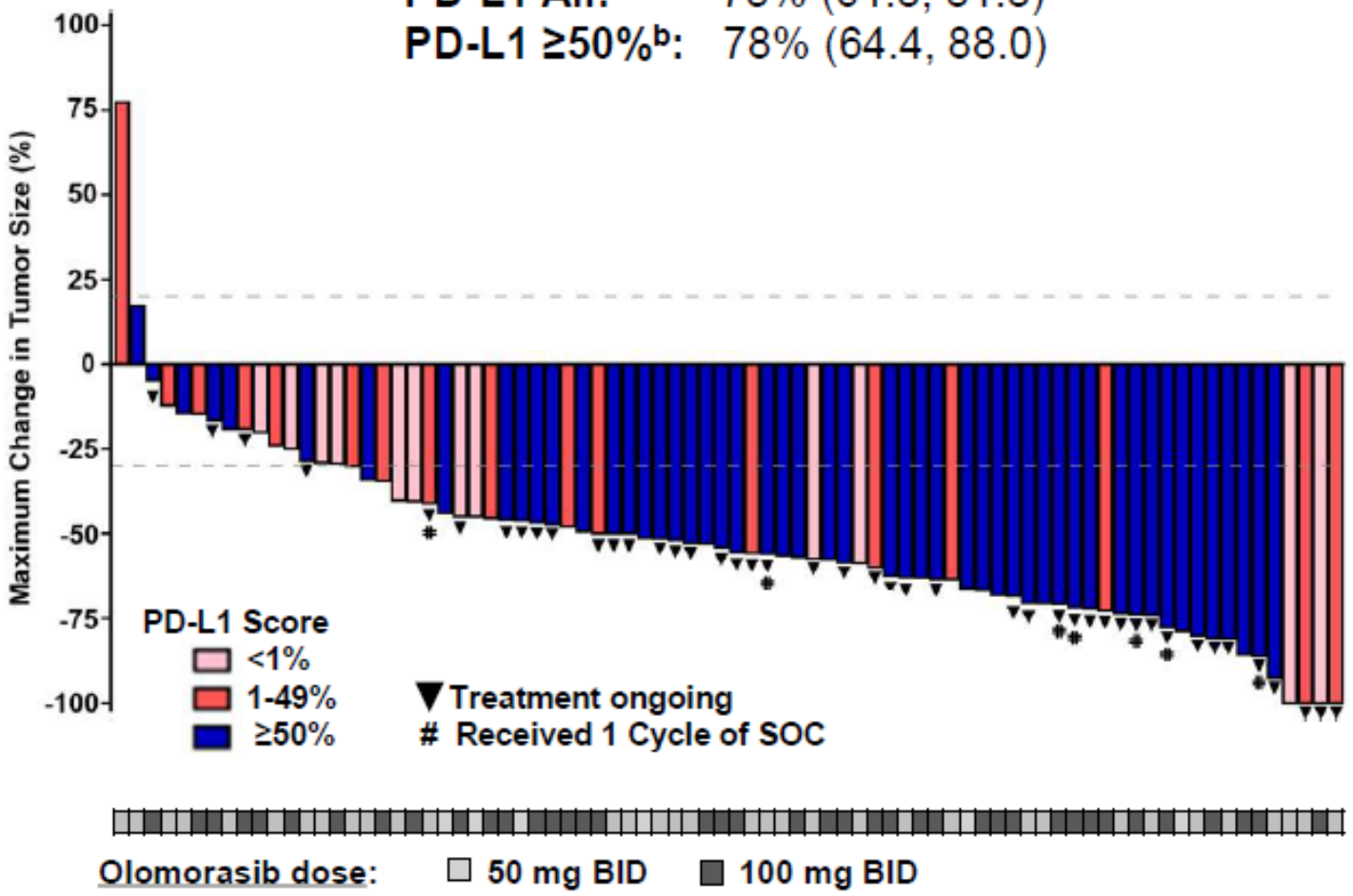

Dose modifications due to TRAEs

- TRAEs led to dose reductions of olomorasib[c] in 29 patients (34.1%)
- TRAEs led to permanent discontinuation[d] of the treatment regimen in 10 patients (11.8%)[c]

Johnson et al, WCLC 2025

Debate Conclusions

Combining KRAS G12C targeted therapies with checkpoint inhibitors increases the toxicity of these agents

There is no clear class effect showing synergy between KRAS G12C targeted therapies and immune checkpoint inhibitors

There may be individual drugs where synergy is present.

Some ongoing trials…

Krascendo 2 – pembrolizumab + divarasib vs pembrolizumab + chemo

Krystal 7 – pembrolizumab + Adagrasib vs pembrolizumab in PD-L1 ≥50%

Sunray 01 – pembrolizumab + olomorasib vs pembrolizumab in PD-L1 ≥50% and chemotherapy/pembrolizumab + olomorasib vs chemotherapy/pembrolizumab in all PD-L1 levels

“We really need to do the studies and not assume results.”

--Jennifer W. Carlisle, MD, of Emory University’s Winship Cancer