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First-line Olomorasib + Chemoimmunotherapy in *KRAS* G12C-Mutant NSCLC: Updated Results from the LOXO-RAS-20001 and SUNRAY-01 Trials

Marcelo V. Negrao, MD
Department of Thoracic Medical Oncology
UT MD Anderson Cancer Center, Houston, TX, USA



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Authors & Affiliations

Marcelo V. Negrao[1], James V. Uyeki[2], Irfan Cicin[3], Yuanbin Chen[4], Byoung Y. Shim[5], Masafumi Yamaguchi[6], Timothy F. Burns[7,8], Garrett Sherwood[9], Jun Sakakibara-Konishi[10], Konstantin Dragnev[11], Natraj R. Ammakkanavar[12], Victor T. G. Lin[13], So Yeon Kim[14], Yanhong Zhou[15], Nicolas Fasnacht[15], Aaron A. Fink[15], Melinda D. Willard[15], Alyson Merced[15], Carla Visseren-Grul[15], Solange Peters[16]

[1]Department of Thoracic Medical Oncology, UT MD Anderson Cancer Center, Houston, TX, USA; [2]Texas Oncology–Austin Midtown, Austin, TX, USA; [3]Medical Oncology Department, Trakya University, Edirne, Turkey; [4]Cancer and Hematology Centers of Western Michigan, Grand Rapids, MI, USA; [5]Department of Medical Oncology, St. Vincent's Hospital, The Catholic University of Korea, Seoul, Republic of Korea; [6]Department of Thoracic Oncology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan; [7]Department of Medicine, Division of Hematology Oncology, University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, PA, USA; [8]The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH, USA; [9]Novant Health Cancer Institute, Winston-Salem, NC, USA; [10]Hokkaido University Hospital, Hokkaido University, Sapporo, Japan; [11]Dartmouth Hitchcock Medical Center, Lebanon, NH, USA; [12]Community Health Network, Indianapolis, IN, USA; [13]Mary Bird Perkins Cancer Center, Baton Rouge, LA, USA; [14]Department of Internal Medicine, Yale Cancer Center, Yale School of Medicine, New Haven, CT, USA; [15]Eli Lilly and Company, Indianapolis, IN, USA; [16]Oncology Department, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.

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Declaration of Interests

Dr. Negrao reports grants to their institution from Alaunos Therapeutics, AstraZeneca, Bristol Myers Squibb (BMS), Eli Lilly and Company, Frontier Medicines, Genentech, Mirati Therapeutics, Navire Pharma, Novartis, Pfizer, and Verastem Oncology; advisory board/committee participation for AstraZeneca, BMS, Eli Lilly and Company, Genentech, Guardant Health, Pfizer, Sanofi, and Verastem Oncology; speakers bureau participation for BioBrasil, DAVA Oncology, IDEOlogy Health, Medscape, OncLive, and Targeted Oncology; and travel support from DAVA Oncology, Frontier Medicines, IDEOlogy Health, and Targeted Oncology.

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Background and Methods

- Patients with *KRAS* G12C-mutant NSCLC generally have high-risk clinical characteristics and more comorbidities.[1]
- There are no approved targeted therapies for the 1L treatment of *KRAS* G12C-mutant NSCLC. Toxicity has been a persistent challenge for some KRAS G12C inhibitor-immunotherapy combinations, limiting their development in the 1L setting.[2]
- Olomorasib, a potent, selective next-generation KRAS G12C inhibitor with intracranial activity, can be combined with immunotherapy with or without chemotherapy and previously showed promising 1L efficacy and durability across PD-L1 levels.[1,3-6]
- Here, with an additional 9 months of follow-up, we report updated results in 1L patients from the integrated analysis of LOXO-RAS-20001 and the safety lead-in for SUNRAY-01.

Olomorasib + pembrolizumab + pemetrexed + platinum[a]

LOXO-RAS-20001	SUNRAY-01
Cohort B9: 1L NSCLC (n=37)	Safety Lead-in: 1L NSCLC (n=40)

Eligibility

- Confirmed stage IIIB-IIIC or stage IV non-squamous *KRAS* G12C-mutant NSCLC
- No prior therapy for advanced or metastatic NSCLC
  - Patients may have received up to one cycle of SOC prior to enrollment (defined as one cycle of either pemetrexed-platinum +/- pembrolizumab, or pembrolizumab monotherapy)
- PD-L1 expression 0-100%[b]
- ECOG PS of 0 or 1
- Small (≤1.5 cm)[c], asymptomatic untreated or treated stable brain metastases

Key Objectives

- Safety, tolerability, and pharmacokinetics
- ORR, DOR, DCR, and PFS per RECIST v1.1

References: 1. Peters S, et al. *Future Oncol.* 2026;22(9):1073–1082; 2. Li BT, et al. *J Thorac Oncol* 2022; 17(9, Suppl.): S10–S11. 3. Burns TF, et al. *J Thorac Oncol.* 2026;21(4):103528; 4. Murciano-Goroff YR, et al. *Nat Commun.* 2026;17(1):3834; 5. Johnson ML, et al. *J Thorac Oncol.* 2025;20(10 suppl 1):S59 [abstr MA02.06]; 6. Negrao MV, et al. *J Thorac Oncol*. 2025;20(10 suppl 1):S26–S27 [abstr OA08.02].

[a]Doses: Olomorasib 50 or 100 mg BID; Pembrolizumab 200 mg IV Q3W; Pemetrexed 500 mg/m^2, Q3W, Platinum - cisplatin 75 mg/m^2 or carboplatin AUC 5 mg/mL/min, Q3W (max dose = 750 mg). [b]PD-L1 status was assessed using various clones to determine PD-L1 expression locally, and the antibody clone used for testing was at the discretion of the site. [c]Small defined as ≤1.5 cm in SUNRAY-01 only.

Abbreviations: 1L, first-line; BID, twice daily; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, every three weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SOC, standard of care. LOXO-RAS-20001: NCT04956640, SUNRAY-01: NCT06119581.

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Demographics and Baseline Characteristics

Characteristics	Olomorasib + chemoimmunotherapy (N=77)
Age, years, median (range)	66 (45-83)
Sex, n (%)	
Male / Female	45 (58.4) / 32 (41.6)
Race, n (%)	
White / Asian / Black / Not reported	42 (54.5) / 23 (29.9) / 5 (6.5) / 7 (9.1)
Smoking status, n (%)	
Former or current / Never / Not reported	69 (89.6) / 6 (7.8) / 2 (2.6)
ECOG PS, n (%)[a]	
0 / 1 / 2	27 (35.1) / 49 (63.6) / 1 (1.3)
PD-L1 expression, n (%)[b]	
<1%	26 (33.8)
1-49%	31 (40.3)
≥50%	18 (23.4)
Unknown	2 (2.6)
Metastases at baseline, n (%)	
Brain	16 (20.8)
Liver	9 (11.7)
Bone	22 (28.6)
Received 1 cycle of SOC prior to enrollment, n (%)[c]	25 (32.5)

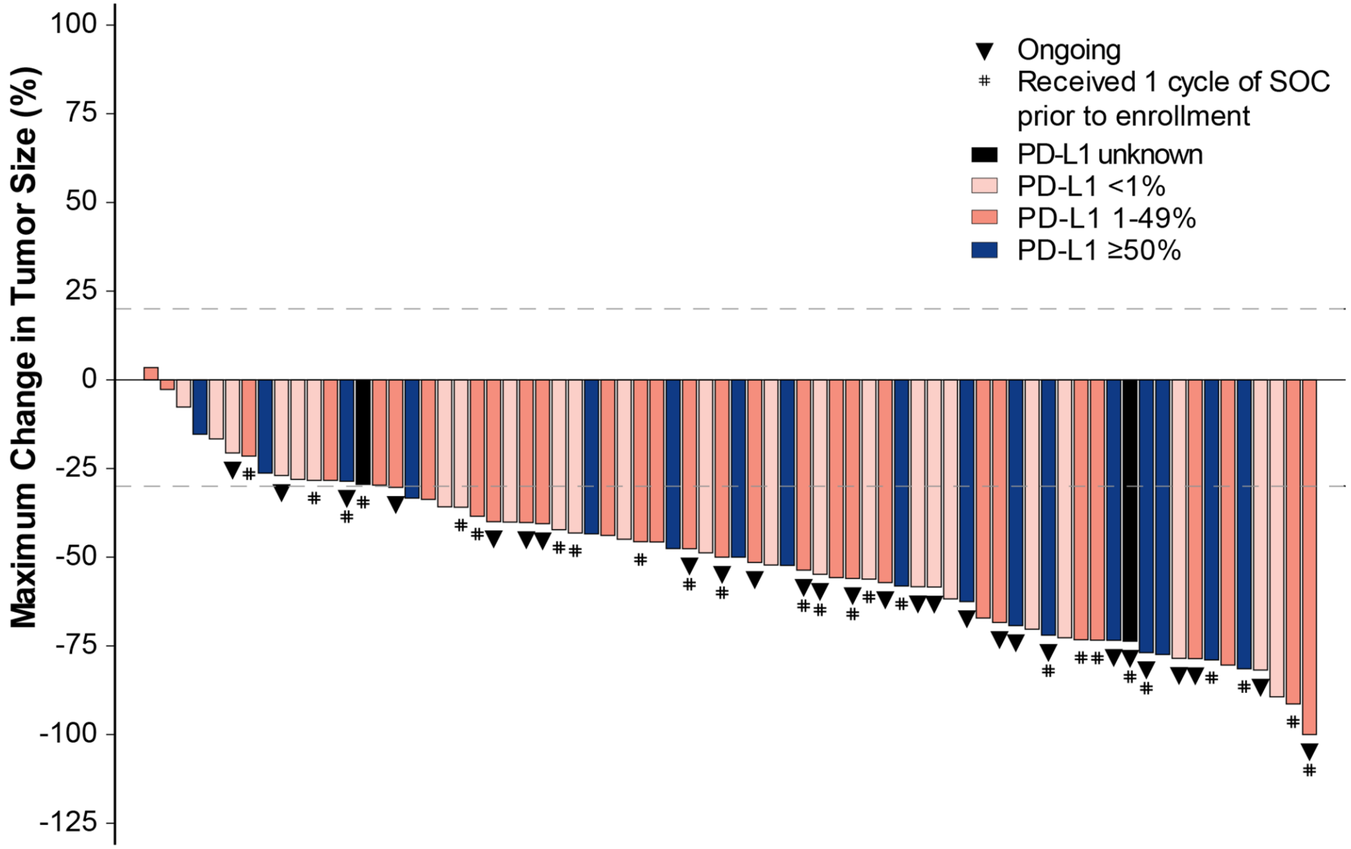
Data cutoff: 05 Mar 2026. [a]One patient had a change in ECOG PS from 1 at screening to 2 by Cycle 1 Day 1. [b]PD-L1 status was assessed using various clones to determine PD-L1 expression locally, and the antibody clone used for testing was at the discretion of the site. [c]Defined as a single cycle of either pemetrexed-platinum +/- pembrolizumab, or pembrolizumab monotherapy. Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death-ligand 1; SOC, standard of care.

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Efficacy of 1L Olomorasib + Chemoimmunotherapy

Outcomes	Olomorasib + chemoimmunotherapy			
	All patients PD-L1 0-100% (N=77)[a]	PD-L1 <1% (n=26)	PD-L1 1-49% (n=31)	PD-L1 ≥50% (n=18)
cORR[b], % (n/N)	**62 (48/77)**	54 (14/26)	68 (21/31)	67 (12/18)
BOR, n (%)				
cPR	48 (62)	14 (54)	21 (68)	12 (67)
SD	21 (27)	8 (31)	8 (26)	5 (28)
PD	3 (4)	2 (8)	0	0
NE	5 (6)	2 (8)	2 (6)	1 (6)
DCR, % (n/N)	**90 (69/77)**	85 (22/26)	94 (29/31)	94 (17/18)
mDOR[b], mo (95% CI)	**14.5 (8.5–NE)**	**10.5 (5.4–NE)**	**NE (8.5–NE)**	**NE (6.1–NE)**
12-mo DOR rate, % (95% CI)	55.7 (39.5–69.1)	49.0 (21.6–71.7)	60.3 (34.0–78.9)	54.5 (22.9–78.0)
mPFS[b], mo (95% CI)	**11.6 (9.5–21.5)**	**9.7 (5.9–15.9)**	**12.1 (5.9–NE)**	**NE (7.7–NE)**

Median follow-up time: 18.7 months (IQR: 16.8–20.3)
Median treatment duration: 9.7 months (IQR: 3.8–18.7)



Data cutoff: 05 Mar 2026. Efficacy analyses done in efficacy evaluable patients who were those with ≥1 post-baseline response assessment or had discontinued treatment before the first post-baseline response assessment. Patients with not evaluable response values were not included in the plot. Median time to response was 1.4 months (95% CI: 1.3–2.9). [a]PD-L1 status was unknown for 2 patients. [b]ORR, DOR, and PFS were investigator assessed. Abbreviations: BOR, best overall response; cORR, confirmed overall response rate; cPR, confirmed partial response; DCR, disease control rate; IQR, interquartile range; mDOR, median duration of response; mPFS, median progression-free survival; NE, not evaluable; PD, progressive disease; PD-L1, programmed death-ligand 1; SD, stable disease.

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Safety of 1L Olomorasib + Chemoimmunotherapy

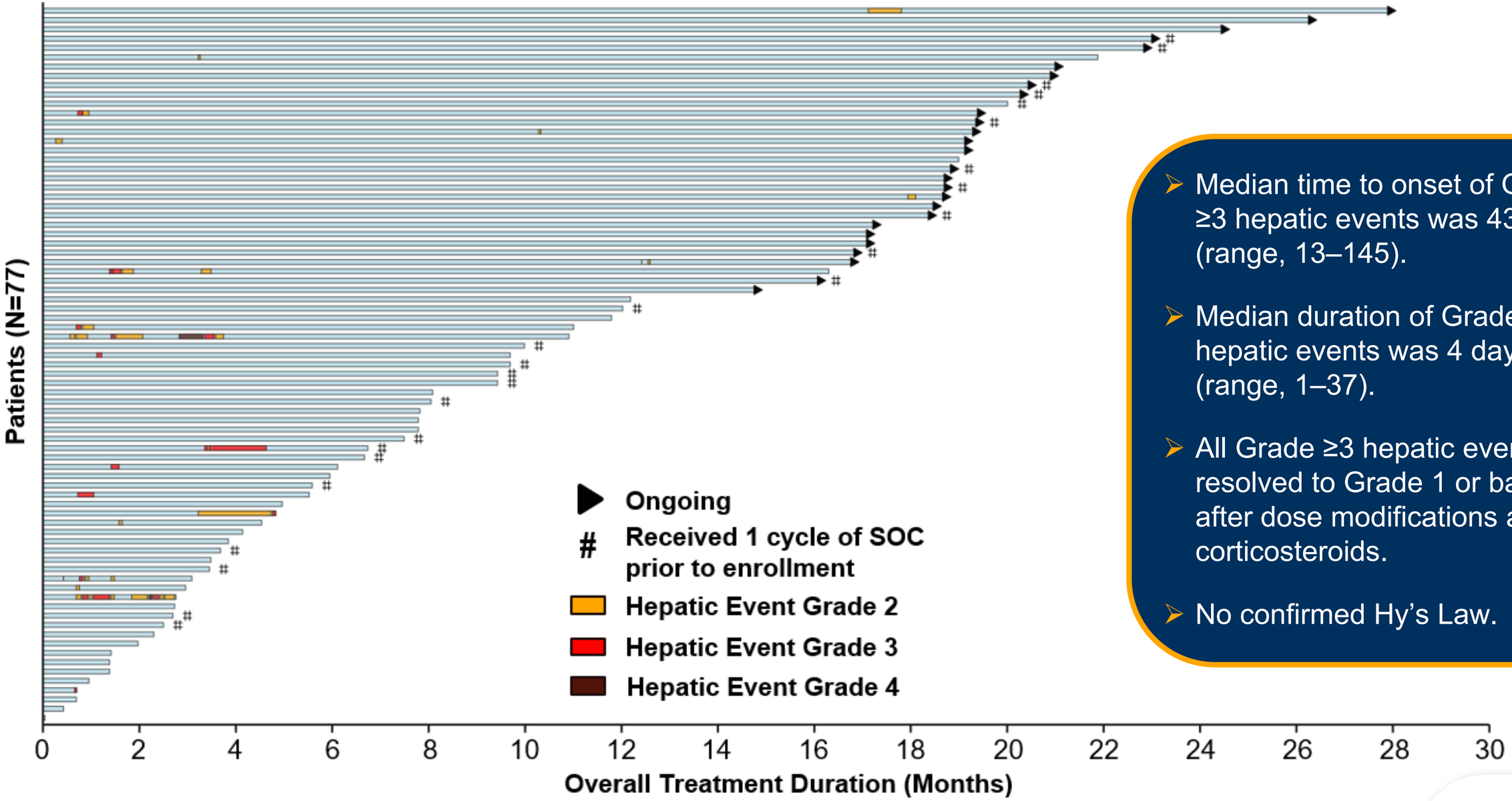
Olomorasib + chemoimmunotherapy (N=77)[a]					
Parameter, n (%)	**TRAEs (≥10%)**				
	Any grade	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Any TRAE	74 (96.1)	5 (6.5)	27 (35.1)	31 (40.3)	11 (14.3)
Nausea	34 (44.2)	16 (20.8)	15 (19.5)	3 (3.9)	0
Anemia	31 (40.3)	4 (5.2)	14 (18.2)	12 (15.6)	1 (1.3)
Fatigue	31 (40.3)	16 (20.8)	14 (18.2)	1 (1.3)	0
AST increased	25 (32.5)	11 (14.3)	6 (7.8)	7 (9.1)	1 (1.3)
Diarrhea	25 (32.5)	12 (15.6)	9 (11.7)	4 (5.2)	0
Neutropenia	24 (31.2)	3 (3.9)	5 (6.5)	8 (10.4)	8 (10.4)
ALT increased	22 (28.6)	7 (9.1)	6 (7.8)	9 (11.7)	0
Leukopenia	15 (19.5)	6 (7.8)	1 (1.3)	5 (6.5)	3 (3.9)
Blood creatinine increased	14 (18.2)	9 (11.7)	5 (6.5)	0	0
Thrombocytopenia	14 (18.2)	4 (5.2)	1 (1.3)	4 (5.2)	5 (6.5)
Vomiting	14 (18.2)	8 (10.4)	5 (6.5)	1 (1.3)	0
Decreased appetite	11 (14.3)	5 (6.5)	5 (6.5)	1 (1.3)	0
Constipation	10 (13.0)	6 (7.8)	4 (5.2)	0	0
Pruritus	10 (13.0)	4 (5.2)	6 (7.8)	0	0
Rash	9 (11.7)	5 (6.5)	3 (3.9)	1 (1.3)	0
Stomatitis	9 (11.7)	7 (9.1)	1 (1.3)	1 (1.3)	0
Pneumonitis/ILD	8 (10.4)	0	5 (6.5)	3 (3.9)	0

- The safety profile remains consistent with an additional 9 months of follow-up time.
- TRAEs led to olomorasib[b] dose reductions in 15 (19.5%) patients.
- TRAEs led to permanent discontinuation of the treatment regimen[c] in 6 (7.8%) patients.

Data cutoff: 05 Mar 2026. Neutropenia=neutrophil count decreased/neutropenia; Leukopenia=white blood cell count decreased/leukopenia; Thrombocytopenia=platelet count decreased/thrombocytopenia. [a]Safety population consists of patients who received at least one dose of study treatment. No grade 5 TRAEs. [b]Reasons for olomorasib dose reductions: ALT/AST increased (n=10), anemia (n=4), neutropenia/neutrophil count decreased (n=3), and biliary sepsis, blood creatinine increased, diarrhea, fatigue, hypokalemia, iron deficiency anemia, lipase increased, nausea, renal failure, vomiting, and white blood cell count decreased (n=1 each). [c]Reasons for discontinuation of the treatment regimen (olomorasib + chemoimmunotherapy): pancytopenia (n=2), pneumonitis (n=1), interstitial pneumonia (n=1), neutropenia followed by diarrhea and pneumonitis (n=1) and anemia followed by declining kidney function (n=1). Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ILD, interstitial lung disease; TRAEs, treatment-related adverse events.

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Hepatic Events Over Time in the Safety Population



- Median time to onset of Grade ≥3 hepatic events was 43 days (range, 13–145).
- Median duration of Grade ≥3 hepatic events was 4 days (range, 1–37).
- All Grade ≥3 hepatic events resolved to Grade 1 or baseline after dose modifications and/or corticosteroids.
- No confirmed Hy's Law.

Hepatic events included ALT increased, AST increased, hepatitis, immune hepatitis, autoimmune hepatitis, and hepatotoxicity. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; SOC, standard of care.

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Conclusions

- Olomorasib + chemoimmunotherapy demonstrated durable efficacy in patients with PD-L1 expression 0–100%, including in higher-risk patients with PD-L1 expression 0–49%.
  - With a median follow-up of 18.7 months (IQR: 16.8–20.3), the ORR was 62% in the overall population, with a median DOR of 14.5 months and median PFS of 11.6 months.
- The safety profile of olomorasib + chemoimmunotherapy was consistent with previous reports and with the known profiles of each drug.
  - Safety was monitorable and manageable with supportive care, dose adjustments, and/or corticosteroids.
  - No prophylactic medications for olomorasib related toxicities are required by the protocol.

Part B of the ongoing Phase 3 SUNRAY-01 trial (NCT06119581) evaluating chemoimmunotherapy with olomorasib or placebo as first-line treatment in patients with advanced *KRAS* G12C-mutant NSCLC, irrespective of PD-L1 expression has completed enrollment and is expected to read out in the first half of 2027.

Abbreviations: DOR, duration of response; IQR, interquartile range; NSCLC, non–small cell lung cancer; ORR, overall response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival.

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Thank You

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