# KRAS mutant NSCLC: What is the Standard of Care Now?

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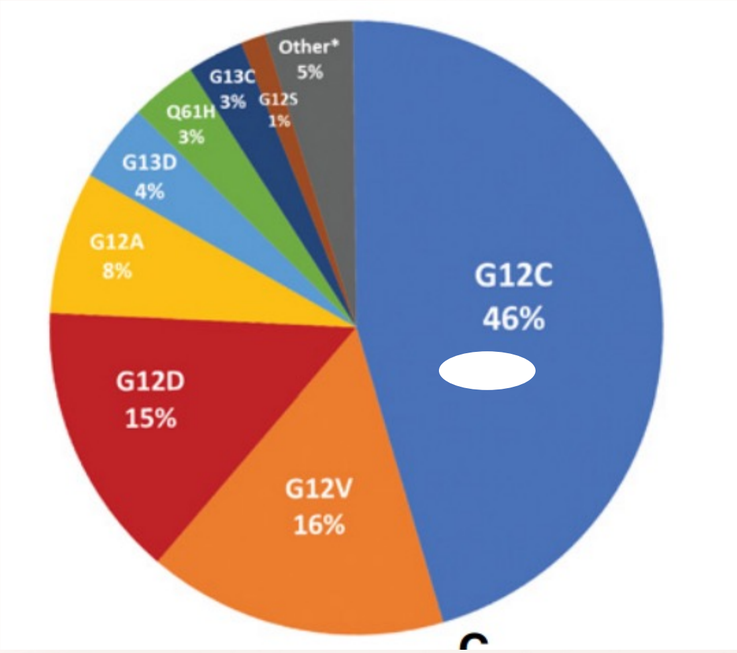
# Agenda

- ❑Front line treatment strategies
- ❑Available second line targeted agents
- ❑Potential targeted-IO combinations

# First Line Therapy

# Subtypes of KRAS mutations

1194 patients with NGS and KRAS mutation 772 with stage IV disease:




Armour K CCR 2021

# Front Line therapy

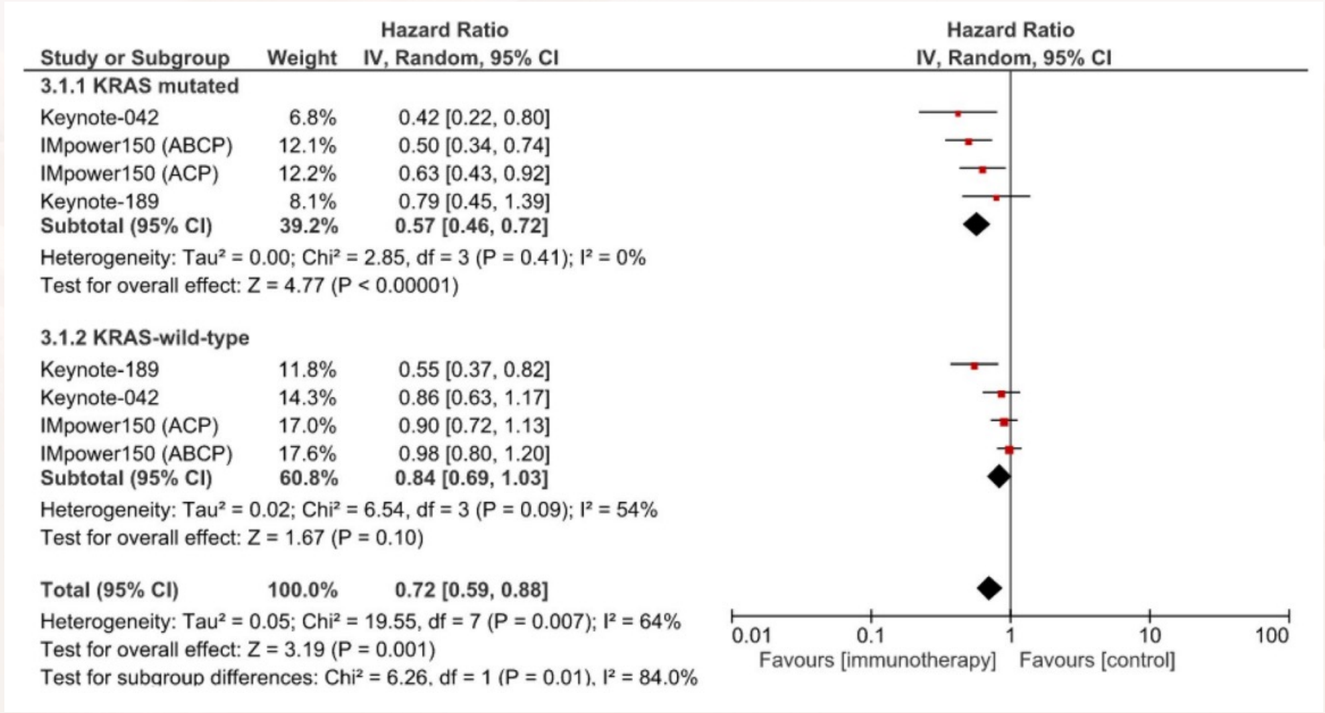
- Phase II or III trials on anti-PD-(L)1 with or without chemotherapy and published KRAS subsets

1st Line trials included

| | | |
|---|---|---|
| Keynote-042 | Pembrolizumab | 1,274 |
| Keynote-189 | Pembrolizumab + ChT | 616 |
| IMpower-150 | Atezoli- zumab + ChT + bev- | 1,200 |

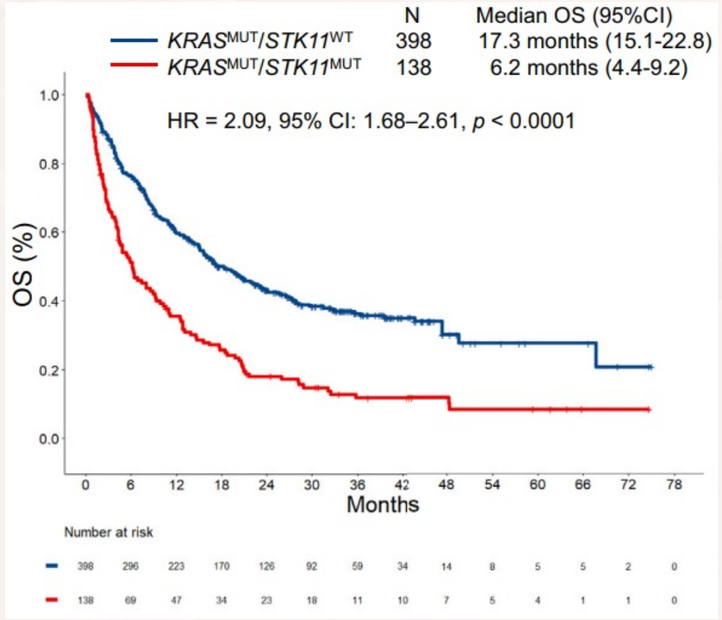
Landre Cancer Immunology, Immunotherapy (2022) 71:719–726

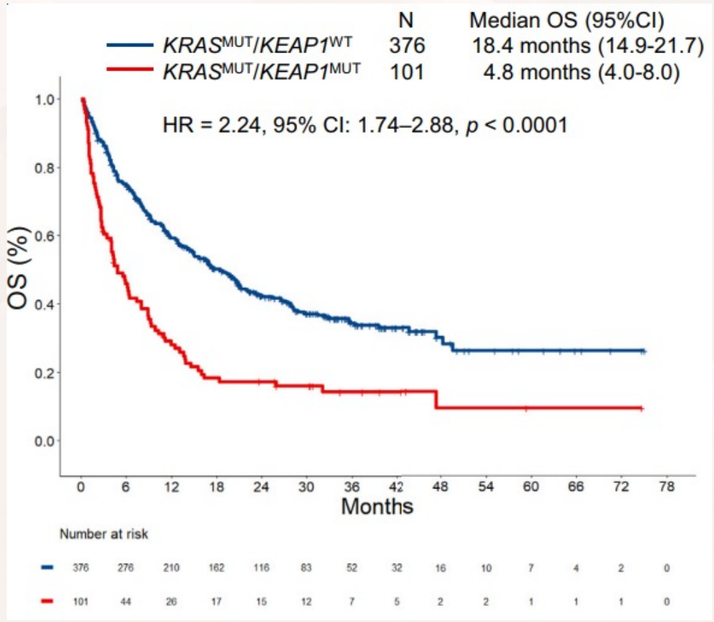
# KRAS mutated vs KRAS non-mutated-front line therapy



# KRAS IO and co-mutations

Two independent academic based cohorts that received PDL1/PD1 IO and had KRAS with comprehensive genomic profiling




Riciutti B JTO 2022

# Potential rescue with CTLA4 + PDL1+ platinum doublet

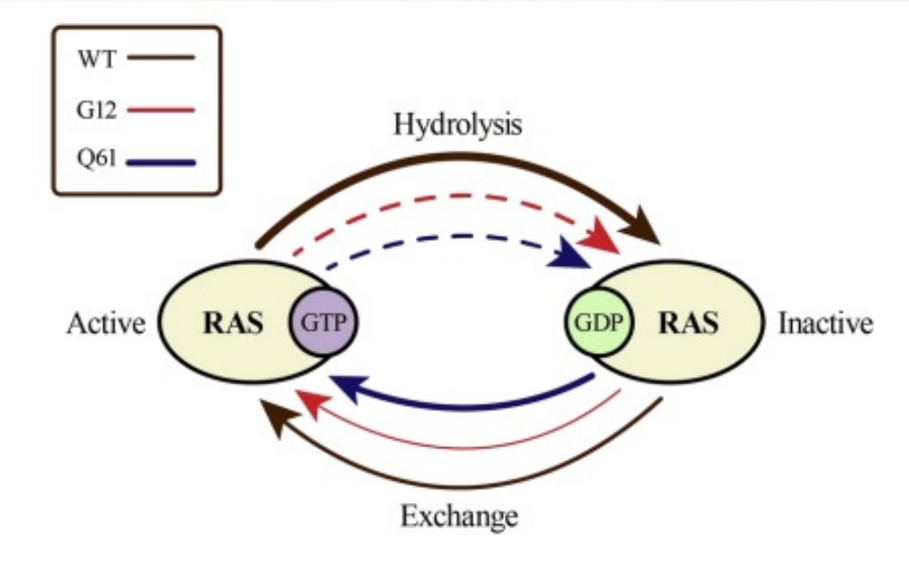
- POSEIDON trial: chemo+ tremelimumab + durvalumab vs chemo + durvalumab vs chemo
- Overall response rates: 45.2%, 45.5%, and 55.0% for *STK11*-, *KEAP1*-, and *KRAS*-mutated subgroups in 4 drug regimen
- HR of 0.56 (95% CI 0.30-1.03) for STK11-mutated non-squamous NSCLC, an HR of 0.43 (95% CI 0.16-1.25) for KEAP1-mutated NSCLC, and 0.56 (95% CI 0.36-0.88) for KRAS-mutated non-squamous NSCLC.

Peters S 2022 World Conference on Lung Cancer. Abstract OA15.04

# Second line therapy

# KRAS12C available tyrosine kinase inhibitors

- “Off” binders targeting GDP-bound inactive state
- High affinity of the RAS for cytoplasmic GTP renders competitive inhibition difficult to achieve
- Codon 12 mutation in KRAS leads to impaired return to inactive state




Wu X Frontiers in Immunology 2023

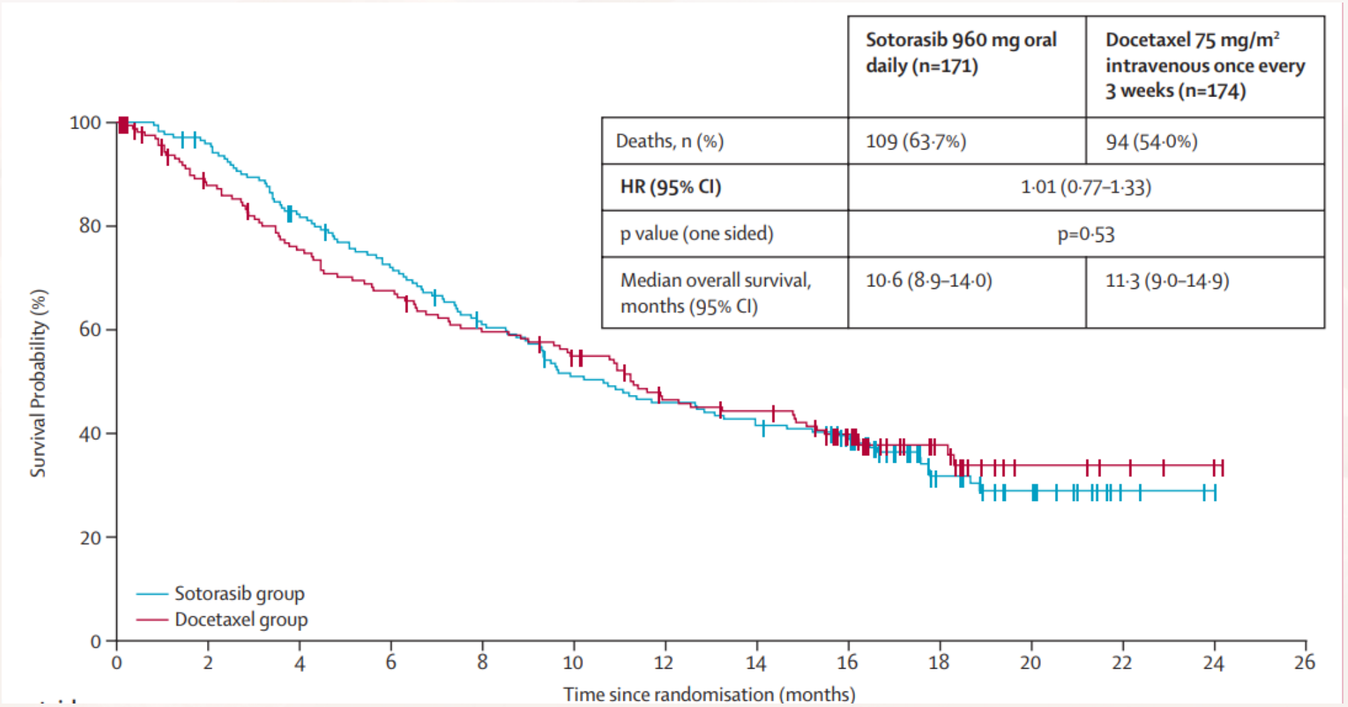
# Sotorasib and Adagrasib

| | Ph I CodeBreaK 100 | Ph II CodeBreaK 100 | CodeBreaK 200 | KRYSTAL-1 |
|---|---|---|---|---|
| Phase | I | II | III | I–II |
| Drug | Sotorasib | Sotorasib | Sotorasib vs Docetaxel | Adagrasib |
| N for NSCLC | 59 | 126 | 171 vs 174 | 112 |
| RR for NSCLC | 32.2% | 37.1% | 28.1% vs 13.2% | 43% |
| DOR (months) | 10.9 | 11.1 | 8.36 vs 6.8 | 8.5 |
| PFS (months) | 6.3 | 6.8 | 5.6 vs 4.5 | 6.5 |
| OS (months) | NA | 12.5 | 10.6 vs 11.3 | 12.6 |

Zhang S Lung Cancer Targets and Therapy 2023;

# CodeBreaK-200 Overall Survival

| | Sotorasib 960 mg oral daily (n=171) | Docetaxel 75 mg/m² intravenous once every 3 weeks (n=174) |
|---|---|---|
| Deaths, n (%) | 109 (63·7%) | 94 (54·0%) |
| **HR (95% CI)** | 1·01 (0·77–1·33) | |
| p value (one sided) | p=0·53 | |
| Median overall survival, months (95% CI) | 10·6 (8·9–14·0) | 11·3 (9·0–14·9) |




Johannes de Langen, Lancet 2023

# Sotorasib toxicity vs. docetaxel

| | Sotorasib (n=169) | | Docetaxel (n=151) | |
|---|---|---|---|---|
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Diarrhoea | 57 (34%) | 20 (12%) | 28 (19%) | 3 (2%) |
| Fatigue | 11 (7%) | 1 (1%) | 38 (25%) | 9 (6%) |
| Alopecia | 2 (1%) | 0 | 31 (21%) | 0 |
| Nausea | 24 (14%) | 2 (1%) | 30 (20%) | 1 (1%) |
| Anaemia | 5 (3%) | 1 (1%) | 27 (18%) | 5 (3%) |
| Decreased appetite | 18 (11%) | 3 (2%) | 21 (14%) | 0 |
| Stomatitis | 1 (1%) | 0 | 17 (11%) | 2 (1%) |
| Constipation | 5 (3%) | 0 | 16 (11%) | 0 |
| Asthenia | 7 (4%) | 1 (1%) | 16 (11%) | 4 (3%) |
| Alanine aminotransferase increased | 17 (10%) | 13 (8%) | 0 | 0 |
| Aspartate aminotransferase increased | 17 (10%) | 9 (5%) | 0 | 0 |
| Neutropenia | 2 (1%) | 0 | 20 (13%) | 18 (12%) |
| Neuropathy peripheral | 0 | 0 | 15 (10%) | 1 (1%) |
| Oedema peripheral | 0 | 0 | 14 (9%) | 1 (1%) |
| Dysgeusia | 4 (2%) | 0 | 13 (9%) | 0 |
| Myalgia | 3 (2%) | 0 | 13 (9%) | 2 (1%) |
| Vomiting | 8 (5%) | 0 | 10 (7%) | 0 |
| Arthralgia | 2 (1%) | 0 | 10 (7%) | 1 (1%) |
| Mucositis | 1 (1%) | 0 | 10 (7%) | 2 (1%) |
| Alkaline phosphatase increased | 11 (7%) | 5 (3%) | 1 (1%) | 0 |
| Malaise | 2 (1%) | 1 (1%) | 9 (6%) | 1 (1%) |
| Febrile neutropenia | 0 | 0 | 8 (5%) | 8 (5%) |
| Abdominal pain | 9 (5%) | 2 (1%) | 6 (4%) | 0 |
| Pyrexia | 1 (1%) | 0 | 8 (5%) | 0 |
| Pneumonia | 0 | 0 | 7 (5%) | 5 (3%) |

Johannes de Langen, Lancet 2023

# Divarasib

- Also a covalent KRAS G12C inhibitor that binds to the cysteine residue and irreversibly locks the protein into its inactive state
- Phase I data, multiple tumor types

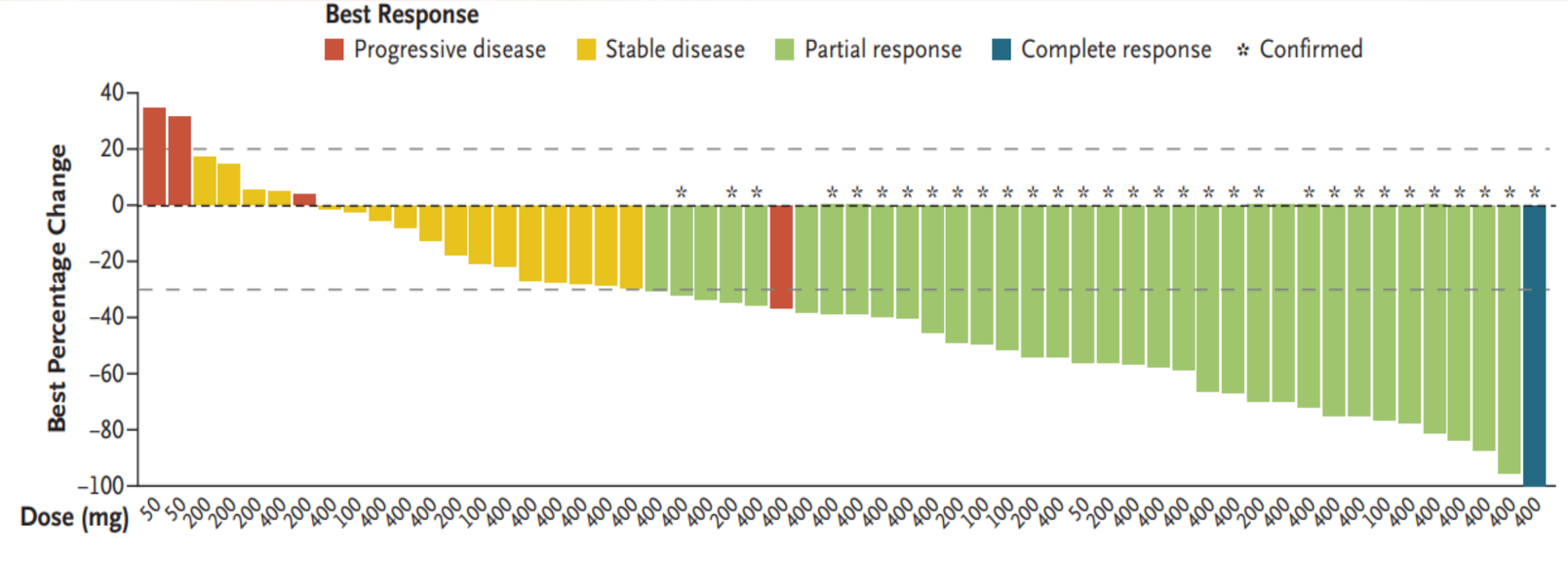
Sacher A NEJM 2023

# Divarasib

| Treatment-Related Adverse Event | NSCLC (N = 60) | |
|---|---|---|
| | Any Grade | Grade 3–5* |
| At least one event | 56 (93) | 11 (18) |
| Nausea | 47 (78) | 1 (2) |
| Diarrhea | 36 (60) | 2 (3) |
| Vomiting | 38 (63) | 0 |
| Fatigue | 16 (27) | 1 (2) |
| Decreased appetite | 11 (18) | 0 |
| Aspartate aminotransferase level increased | 9 (15) | 4 (7) |

Sacher A NEJM 2023

# Lung cancer response rate 61%
# Median PFS 13.7 months




Sacher A NEJM 2023

# JDQ443

- Also covenlant binder in inactive off state
- 7% grade 3 adverse events
  - –fatigue (17.9%), edema (14.3%), diarrhea (16.1%), nausea (16.1%), vomiting (10.7%), and peripheral neuropathy (10.7%).
- Confirmed response rate similar 41%

Cassier JCO.2023.41.16_suppl.9007

# Intracranial activity

- Incidence of brain metastases about 40%
- Delayed CNS with sotorasib compared with docetaxel, 9.6 months versus 5.4 months (HR 0.84 [95% CI: 0.32, 2.19], P=0.37).
- KRYSTAL-1 Trial had 25 patients with untreated brain metastases
  - Intracranial objective response rate of 42%, disease control rate of 90%, progression-free survival of 5.4 months

Cui W Lung Cancer 2020;146:310-7; Dingemans JCO.2023.41.17_suppl.LBA9016 Negrao JCO 2023

# TKI-IO combinations

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# KRYSTAL-7 (849-007) Phase 2 Cohorts

## Key Eligibility Criteria

- Advanced, unresectable or metastatic NSCLC with KRAS$^{G12C}$ mutation[a]
- No prior systemic therapy for locally advanced/ metastatic disease[b]
- Stable brain metastases allowed
- Known PD-L1 TPS score[c]

**Cohorts 1a and 2[c]**
Adagrasib 400 mg BID +
Pembrolizumab 200 mg Q3W
N=148

## Key Study Objectives

- Primary endpoint: ORR (RECIST v1.1 per investigator assessment)
- Secondary endpoints: DOR and PFS (per investigator assessment), OS, safety, PK

- We report safety in all treated patients (N=148) and efficacy in patients with PD-L1 TPS ≥50% (n=51[d]) from the KRYSTAL-7 study evaluating adagrasib[e] + pembrolizumab (200 mg IV Q3W) in treatment-naïve patients with NSCLC harboring a KRAS$^{G12C}$ mutation
- Median follow-up for all treated patients, 8.7 months; PD-L1 TPS ≥50%, 10.1 months

- [a]KRAS$^{G12C}$ mutation detected in tumor tissue and/or ctDNA by sponsor-approved local laboratory testing. [b]Prior systemic therapy or chemoradiation in the (neo)adjuvant setting were allowed if >1 year prior to the first dose of study treatment, and no TRAE of grade ≥2 while on (neo)adjuvant CPI (exceptions for clinically stable vitiligo and psoriasis regardless of grade, and hyper- or hypothyroidism that was adequately controlled). [c]Cohort 1a enrolled patients with PD-L1 TPS <1%; Cohort 2 enrolled patients with PD-L1 TPS ≥1%. Molecular testing for PD-L1 TPS was performed locally or centrally, with a sponsor-approved laboratory test (PD-L1 IHC 22C3 pharmDx, PD-L1 IHC 28-8 pharmDx or Ventana PD-L1 [SP142] assay). An additional cohort (1b) is enrolling patients with PD-L1 TPS <1% to receive adagrasib monotherapy, 600 mg BID. [d]Three patients excluded due to protocol deviations, including one each of atrial fibrillation, stroke within 6 months of enrollment, and presence of KRAS$^{G13C}$ mutation. [e]KRYSTAL-7 was initiated using the capsule (fasted) form of adagrasib but switched to the tablet (fed or fasted) form during study conduct

# Treatment-Related Adverse Events

| Most Frequent TRAEs[a], % | Concurrent 400 mg BID Adagrasib + Pembrolizumab (N=148) | | | | |
|---|---|---|---|---|---|
| | Any grade | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Nausea | 51 | 28 | 20 | 3 | 0 |
| Diarrhea | 44 | 33 | 7 | 3 | 0 |
| ALT increase | 38 | 15 | 13 | 9 | 1 |
| AST increase | 32 | 10 | 8 | 13 | 1 |
| Vomiting | 29 | 17 | 11 | 1 | 0 |
| Fatigue | 26 | 12 | 10 | 4 | 0 |
| Decreased appetite | 24 | 14 | 9 | 1 | 0 |
| Lipase increased | 24 | 3 | 9 | 10 | 1 |

- There were two Grade 5 TRAEs, one each of pneumonitis and pneumonia
- Immune-related TRAEs[b] of any grade occurred in 18% of patients (26/148) and grade ≥3 occurred in 5% (8/148)
- TRAEs led to adagrasib dose reduction in 46% of patients (68/148) and temporary dose interruption in 59% of patients (88/148)
- TRAEs led to permanent discontinuation of adagrasib only in 6% of patients (9/148) and pembrolizumab only in 11% of patients (16/148); 4% of patients (6/148) discontinued both drugs due to TRAEs

- [a]Any grade TRAEs occurring in ≥20% of patients. [b]Includes all TRAEs of colitis, hepatitis, adrenal insufficiency, hypophysitis, hypothyroidism, hyperthyroidism, type 1 diabetes mellitus, nephritis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and pneumonitis
- Data as of 19 June 2023. Median follow-up 8.7 months

# ORR and Best Tumor Change from Baseline in Patients With PD-L1 TPS ≥50%

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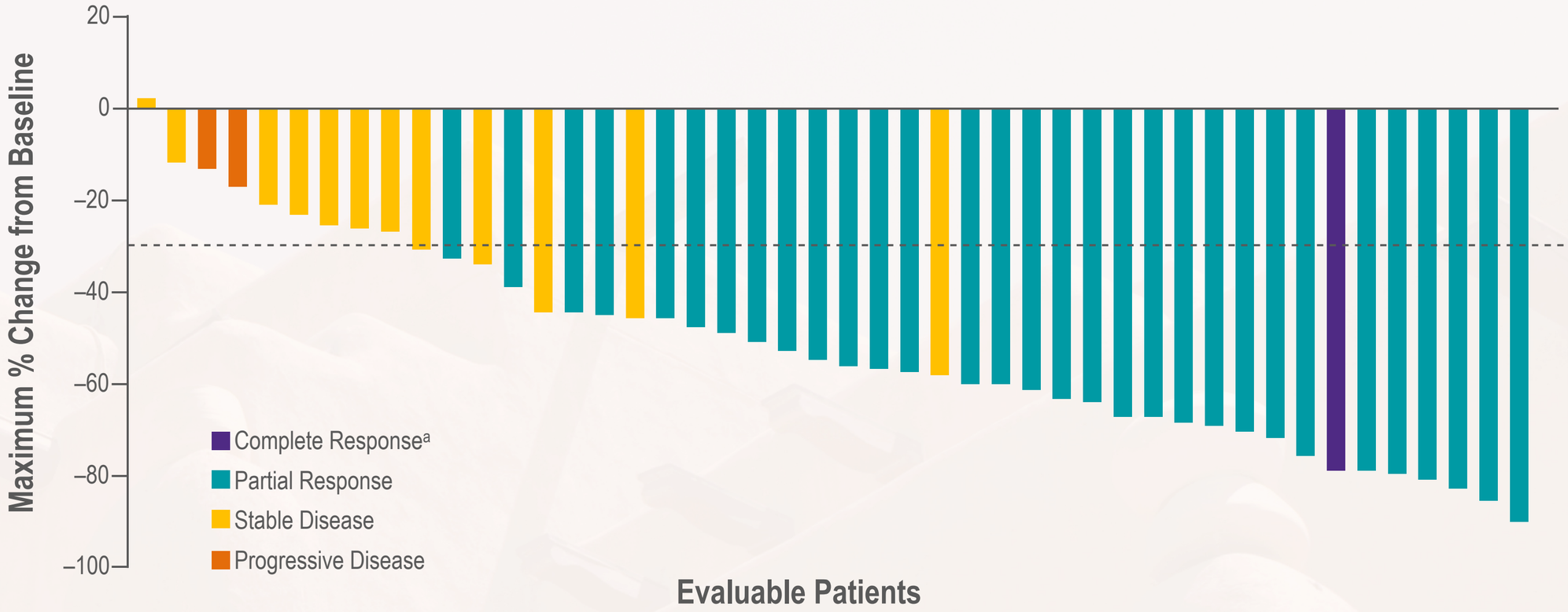


- Confirmed ORR was 63% (32/51; 95% CI, 48–76) and DCR was 84% (43/51; 95% CI, 71–93)
- Of those patients who experienced any grade hepatotoxicity[b], ORR was 70% (14/20; 95% CI, 46–88)

- Response per investigator assessment (n=51; modified full analysis set). Waterfall plot excludes three patients without post-baseline measurement and one patient without confirmatory scan (only one assessment of PR on day 28, but minimum duration requirement for SD is 42 days). [a]One patient had CR without –100% change from baseline due to lymph node as target lesion. [b]Includes AST increase, ALT increase, mixed liver injury and liver function test increase; no grade 4 hepatotoxicity was observed in patients with PD-L1 TPS ≥50%
- Data as of 19 June 2023. Median follow-up 10.1 months

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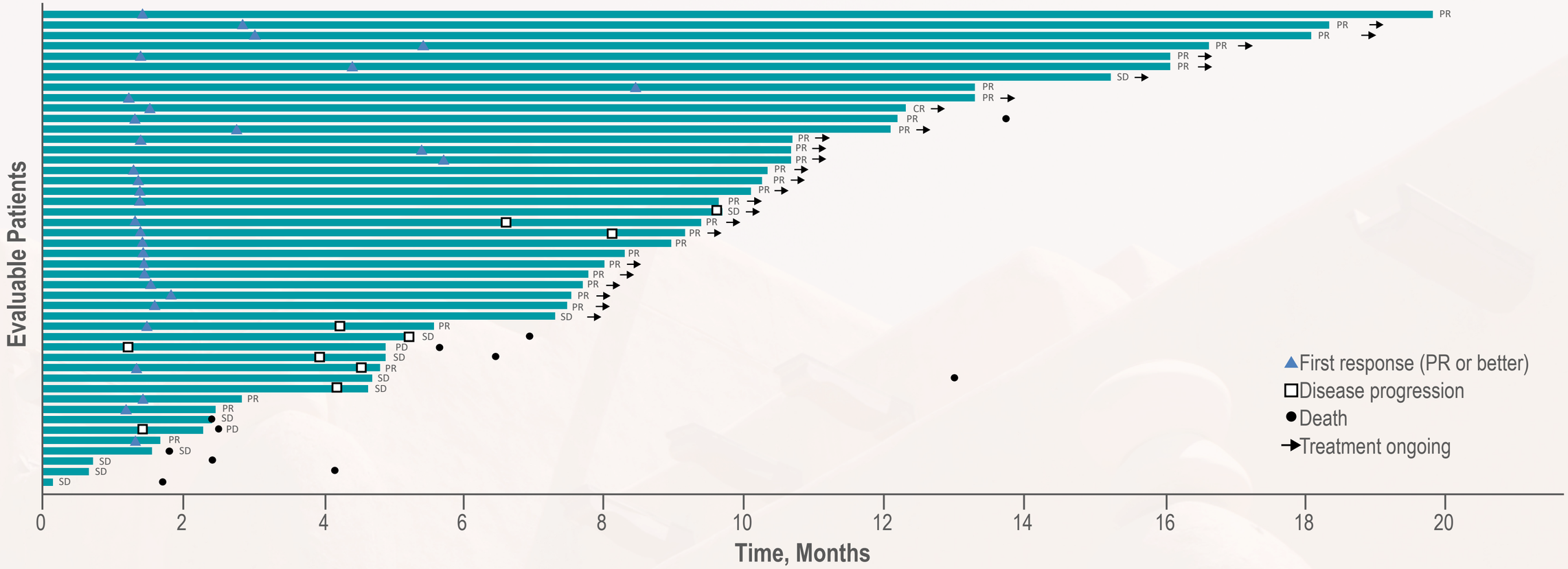
# Duration of Treatment in Patients With PD-L1 TPS ≥50%




- Median time to response was 1.4 months; median duration of response was not reached (95% CI, 12.6–NE)

- Response per investigator assessment (n=51; modified full analysis set). Swimmer plot excludes three patients without post-baseline measurement and one patient without confirmatory scan (only one assessment of PR on day 28, but minimum duration requirement for SD is 42 days)
- Data as of 19 June 2023. Median follow-up 10.1 months

# Sotorasib plus IO

| | Soto+Atezo Soto Lead-In (N=10) | Soto+Atezo Concurrent (N=10) | Soto+Pembro Soto Lead-In (N= 19) | Soto+Pembro Concurrent (N=19) |
|---|---|---|---|---|
| Safety, n (%) | | | | |
| TRAE, any grade | 10 (100) | 9 (90) | 15 (79) | 17 (89) |
| TRAE, grade 3-4 | 3 (30) | 6 (60) | 10 (53) | 15 (79) |
| Hepatotoxicity, Gr 3-4[a] | 3 (30) | 5 (50) | 8 (42) | 9 (47) |
| ALT increased | 1 (10) | 4 (40) | 6 (32) | 7 (37) |
| AST increased | 0 | 5 (50) | 5 (26) | 5 (26) |
| TRAE leading to discontinuation of Sotorasib and/or IO | 1 (10) | 5 (50) | 6 (32) | 10 (53) |
| Number of treatment doses, median (min, max) | | | | |
| Sotorasib | 129.5 (36, 562) | 115.0 (22, 422) | 73.0 (41, 426) | 82.0 (35, 791) |
| IO | 2.5 (1, 26) | 3.5 (2, 21) | 1.0 (1, 20) | 3.0 (2, 12) |
| Efficacy | | | | |
| ORR, % (95% CI) | 20 (3, 56) | 20[b] (3, 56) | 37[c] (16, 62) | 32[d] (13, 57) |
| DCR, % (95% CI) | 90 (56, 100) | 80 (44, 98) | 74 (49, 91) | 90 (67, 99) |
| Median OS, (95% CI), months | 8.1 (2.5, NE) | 11.5 (5.0, NE) | NE (10.1, NE) | 14.1 (6.2, 17.8) |

Li BT volume 17, issue 9, supplement , s10-s11, September 2022

# Conclusions

- IO based therapy remains standard of care for first line treatment of KRAS mutations including KRAS 12C
- Unfavorable co-mutations present with KRAS mutations portend to worse prognosis with IO therapy
- Available targeted agents include TKIs covelantly bonding to the ADP inactive state and have associated progression free survival benefits and  do demonstrate intracranial activity