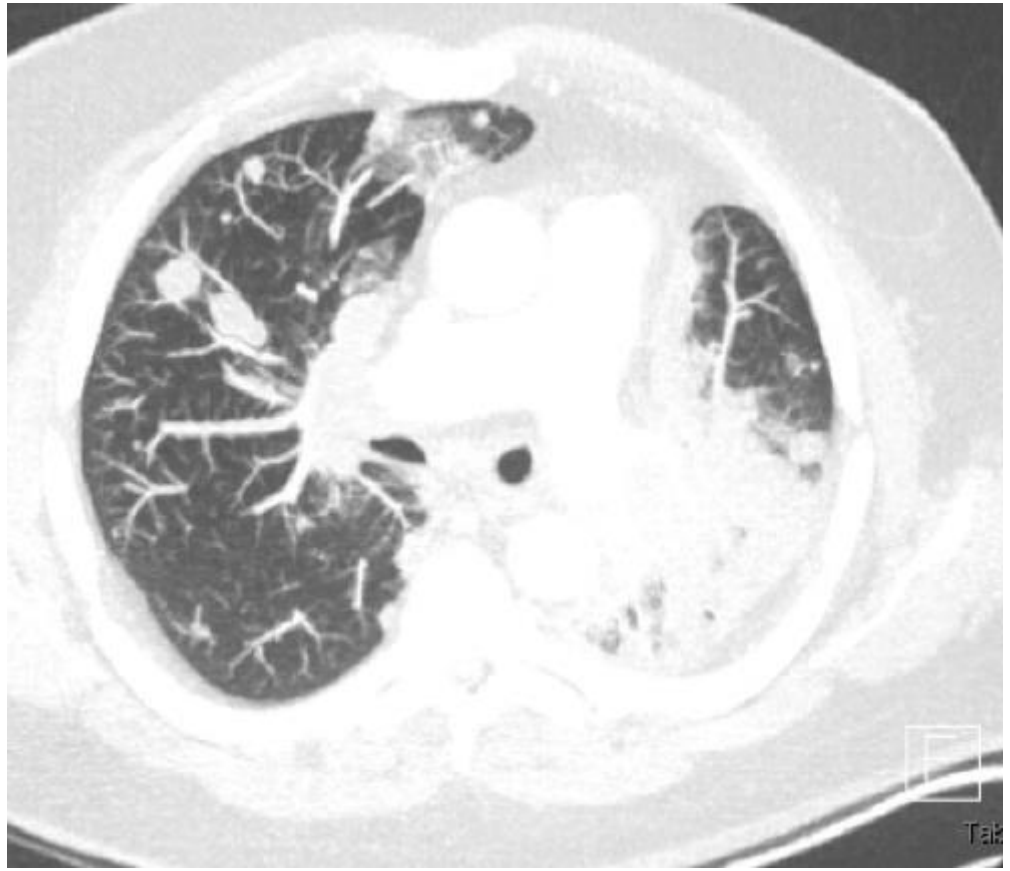
KRAS-Mutated NSCLC, Advanced Stage

Case*

- 63-year-old male with prior 40 pack-year smoking history, presents with cough & SOB
- CT scan: Imaging with LUL primary, mediastinal & hilar adenopathy, plus bilateral lung & bone metastases.
- Fine Needle Biopsy: NSCLC-adenocarcinoma (TTF1+)
- Brain MRI: no metastatic disease



*Cases may have been modified for educational purposes

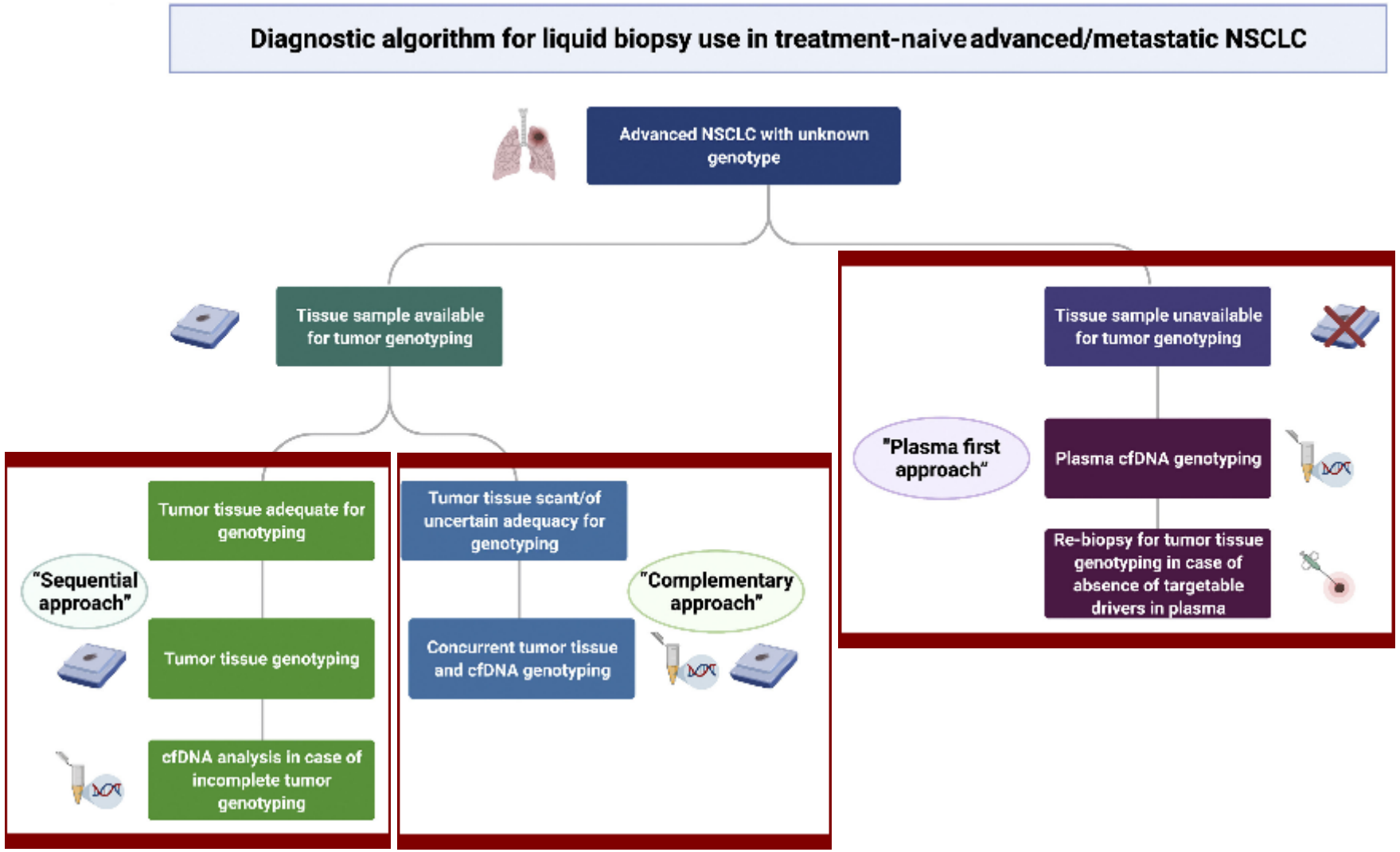
Question

63-year-old male with new diagnosis of stage IV lung adenocarcinoma with bilateral lung and bone metastases. PS=1.
You decide to perform broad comprehensive genomic profiling (CGP) for actionable molecular alterations. There is adequate tissue for next-generation sequencing (NGS).

Question 1: How would you proceed with testing, given anticipated turn-around-times (TRT)?

1. **Send plasma only for GCP by ctDNA NGS (~7-day TRT)**
2. **Send tumor tissue only for CGP by NGS (~14-day TRT)**
3. **Send both plasma ctDNA + repeat tissue biopsy for CGP by NGS (~14-day total TRT)**

IASLC Consensus Statement on Liquid Biopsy in NSCLC: 2021



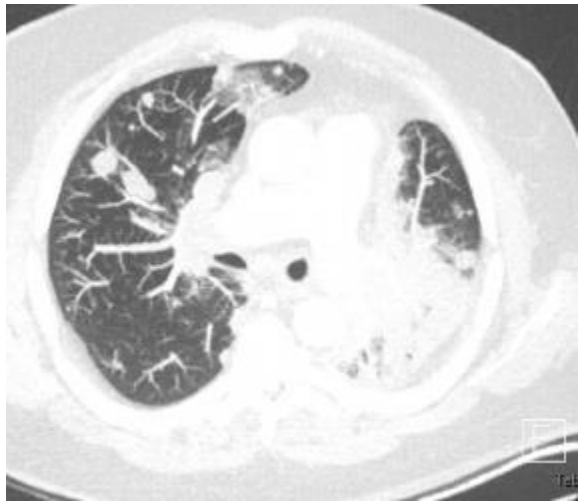
Rolfo, Gandara et al. JTO 2021

Case

- **Molecular testing by plasma NGS comprehensive genomic profiling reveals: KRAS G12C mutation + STK11 mutations. These findings are duplicated in subsequent tissue NGS analysis.**
- **PD-L1 (22C3) TPS = 1%.**

Question

For this 63-year-old patient with stage IV lung adenocarcinoma, former smoker.
PS=1. Testing: KRAS G12C/STK11-mutated & PD-L1 TPS = 1%



Question 2: What do you recommend for first-line therapy?

1. Sotorasib or adagrasib

2. Pemetrexed/carboplatin/pembrolizumab (KN 189)

3. Nivolumab + ipilimumab (CM 227)

4. Paclitaxel/carboplatin/bevacizumab/atezolizumab (IM 150)

5. Platinum chemotherapy X 2 cycles + nivolumab/ipilimumab (CM 9LA)

Immunotherapy therapeutic landscape in advanced NSCLC: Phase III Trials in 1st Line Therapy

Study	Drug (vs CT)	PD-L1 selection	Control	Primary endpoint	HR primary endpoint	Result	Publication
KN-024	Pembro	≥50%	Platinum CT	PFS	0.50	Positive	Reck et al. *NEJM* 2016
CM026	Nivo	≥5%	Platinum CT	PFS	1.15	Negative	Carbone et al. *NEJM* 2017
KN-042	Pembro	≥1%	Platinum CT	OS	0.81 0.69 (50%)	Positive	Mok et al. *Lancet* 2019
IMpower110	Atezo	≥1%	Platinum CT	OS in TC3/IC3	0.59	Positive	Herbst et al. *NEJM* 2020
EMPOWER-Lung 1	Cemi	≥50%	Platinum CT	PFS, OS	0.54 (PFS) 0.57 (OS)	Positive	Sezer et al. *Lancet* 2021
MYSTIC	Durva or Durva/Treme	≥25%	Platinum CT	PFS, OS	0.87 (PFS) durva 0.76 (OS) durva	Negative	Rizvi et al. *JAMA Oncol* 2020
CM227	Nivo or Nivo-Ipi	<1%/≥1% & TMB ≥10	Platinum CT	PFS, OS	0.58 (PFS) in TMB-H 0.62 (OS) in <1% 0.79 (OS) in ≥1%	Positive	Hellmann et al. *NEJM* 2018 Hellman et al. *NEJM* 2019
CM9LA	Nivo-Ipi-CT	≥1%	Platinum CT	OS	0.66	Positive	Paz Ares et al. *Lancet Oncol* 2021
KN-189 (NSQ)	Pembro-CT	≥1%	Platinum CT	PFS	0.52	Positive	Ghandi et al. *NEJM* 2018
KN-407 (SQ)	Pembro-CT	None	Platinum-Nab Pac	PFS, OS	0.56 (PFS) 0.64 (OS)	Positive	Paz Ares et al. *NEJM* 2018
IMpower150 (NSQ)	Atezo + Bev/Pac/Carbo	None	Bev/Pac/Carbo	PFS, OS	ACBP 0.71 (PFS) ACBP 0.78 (OS)	Positive	Socinski et al. *NEJM.* 2018
IMpower131 (SQ)	Atezo + nab Pac/Carbo	None	Pac/Carbo	PFS, OS	0.71 (PFS) 0.88 (OS)	Positive (PFS)	Jotte et al. *J Thorac Oncol* 2020
EMPOWER-Lung 3	Cemi-CT	None	Platinum CT	PFS, OS	0.56 (PFS) 0.71 (OS)	Positive	Gogishvili et al. Nat Med 2022
POSEIDON	Durva+Treme-CT	None	Platinum CT	PFS, OS	0.77 (OS)	Positive	Johnson et al. JCO 2022

Parameters

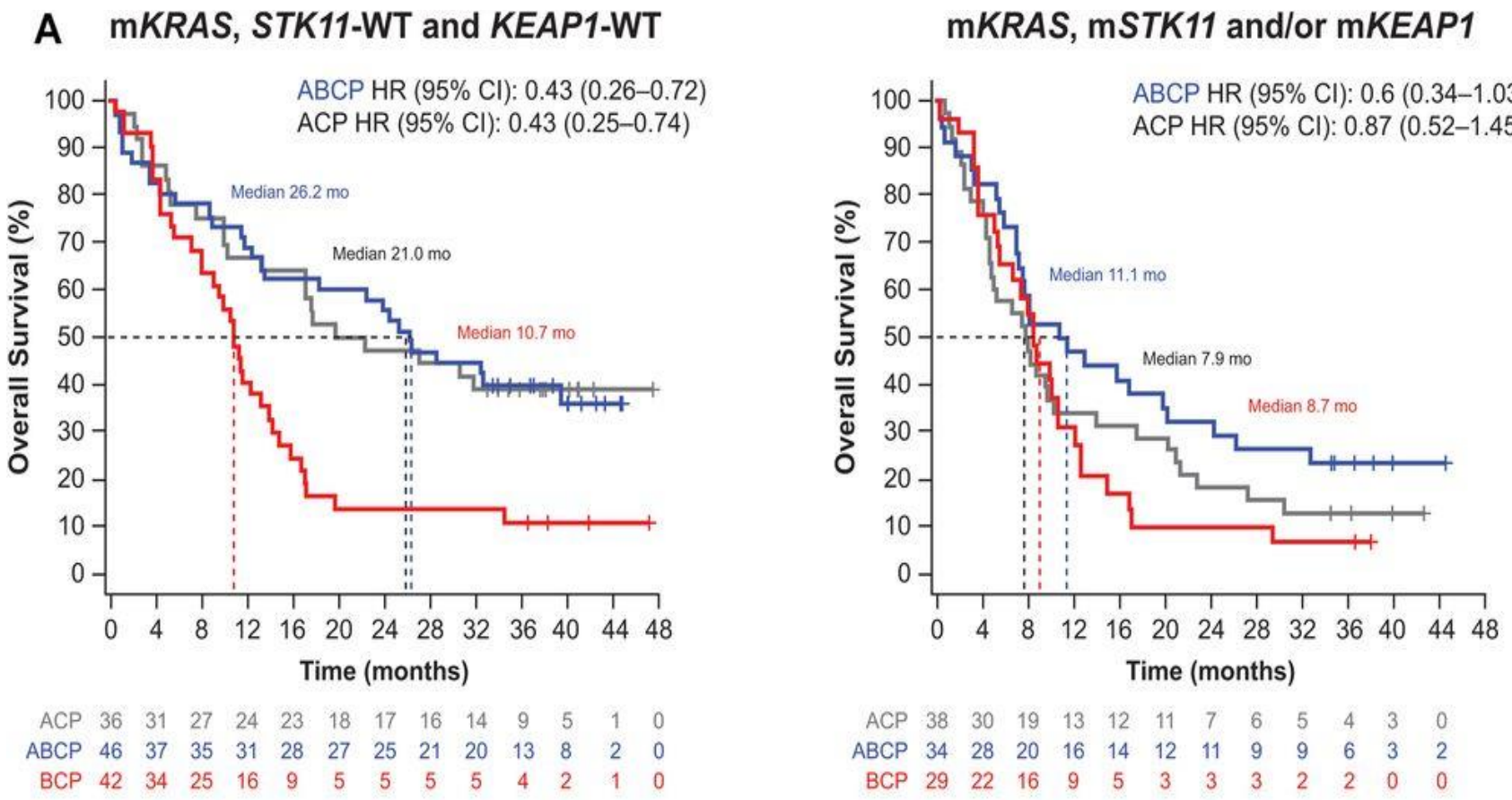
Test Regimen
ICI Monotherapy
ICI+CT
ICI+CT+Bev
ICI + CTLA-4

Biomarker
None
PD-L1
TMB

Histology
All
SQ
NSQ

Primary Endpoint
PFS
OS
Both

IMpower150: Decreased Survival in KRAS Pts with Co-mutations



- **ACP-Atezo/chemo mOS**
  - **21 mo for mKRAS and wt STK11/KEAP1**
  - **7.9 for mSTK11/KEAP1**
- **ABCP: Atezo/bev/chemo mOS**
  - **26.2 mo for mKRAS and wt STK11/KEAP1**
  - **11.1 mo for mKRAS and m STK11/KEAP1**
- **BCP: Bev/chemo mOS**
  - **10.7 mo for mKRAS and wtSTK11/KEAP1**
  - **8.7 mo for mKRAS and mSTK11/KEAP1**

West et al. J Immunother Cancer 2022;10:e003027

Question

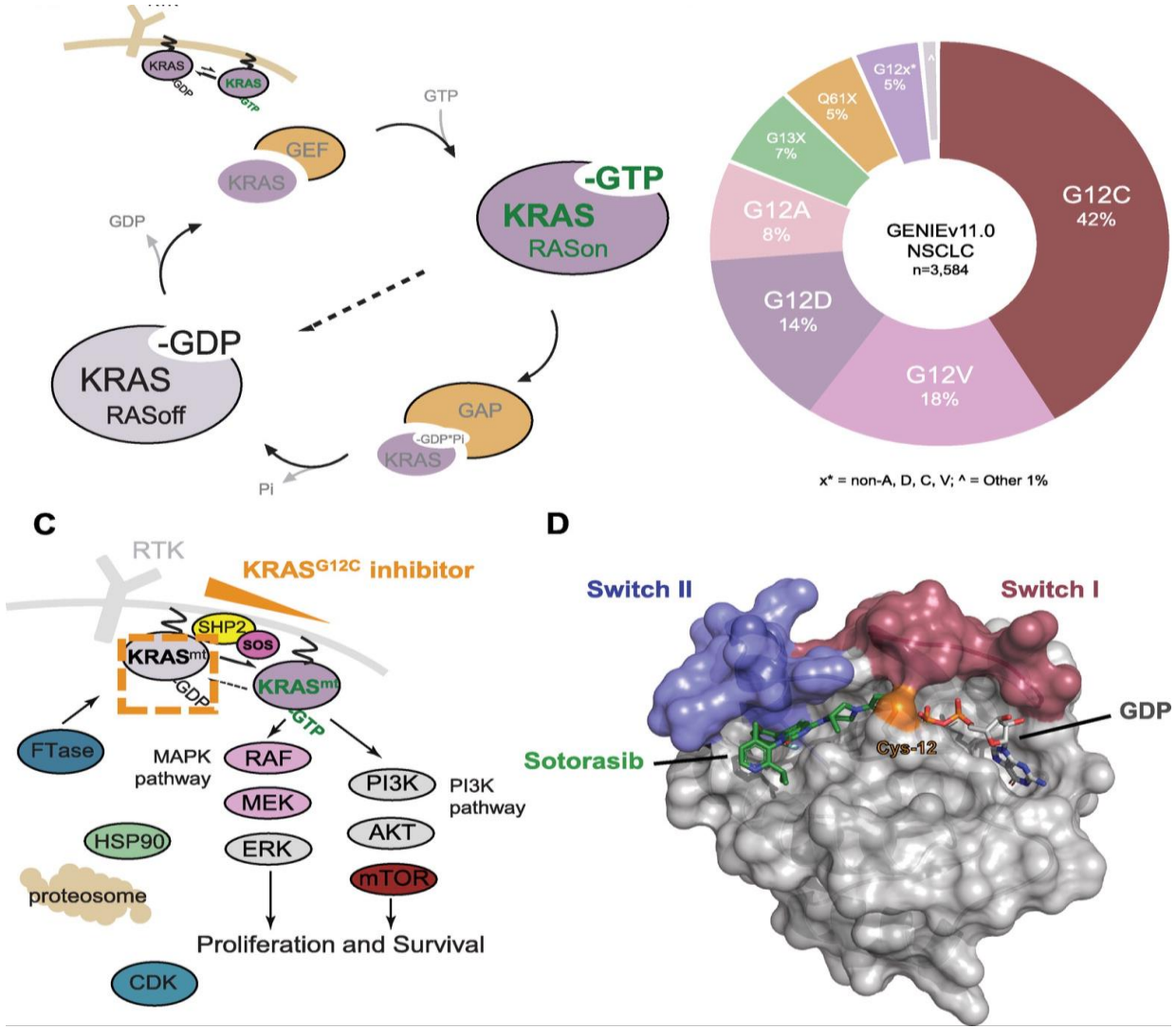
The patient is treated initially with pemetrexed/carboplatin/pembrolizumab & achieves a partial response.

However, at 6 months there is progressive disease in 3 sites (2 new bone lesions & growth of a pulmonary nodule from 2 to 5 cm.

Question 3: In this case with KRAS G12C/STK11-mutated & PD-L1 TPS = 1%, which do you recommend at this point?

1. **SBRT to all sites of PD & continue pemetrexed & pembrolizumab maintenance therapy**
2. **Switch to sotorasib or adagrasib**
3. **Switch to docetaxel/ramucirumab**
4. **Switch to nivolumab/ipilimumab**

Direct KRAS^{G12C} inhibitors form a covalent bond with cysteine 12 in a binding pocket to lock KRAS^{G12C} in the GDP-bound off state



Sotorasib: FDA Approved 5/2021
Skoulidis et al, NEJM 2021

Adagrasib: FDA Approved 12/2022
Janne et al, NEJM 2022

Luo et al, ASCO Ed Book 2022 DOI: 10.1200/EDBK_360354

RESEARCH SUMMARY

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

Skoulidis F et al. DOI: 10.1056/NEJMoa2103695

CLINICAL PROBLEM

The prognosis in patients receiving second or subsequent lines of therapy for advanced non–small-cell lung cancer, including patients with the molecularly diverse and clinically heterogeneous group of cancers with *KRAS* mutations, is unsatisfactory. A treatment that inhibits the KRAS protein may improve outcomes in patients with these mutations.

CLINICAL TRIAL

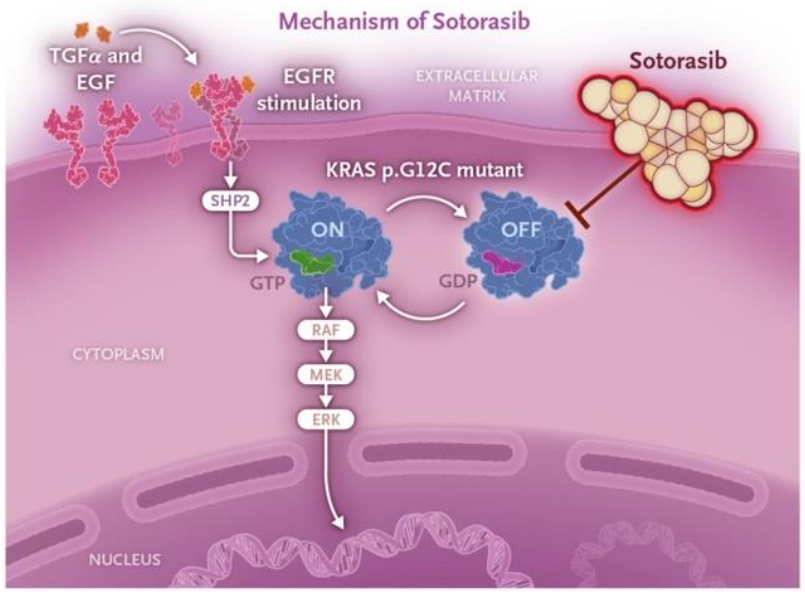
Design: A multicenter, single-group, open-label, phase 2 trial to evaluate the efficacy and safety of sotorasib, a selective irreversible inhibitor of the G12C-activated *KRAS* oncogene.

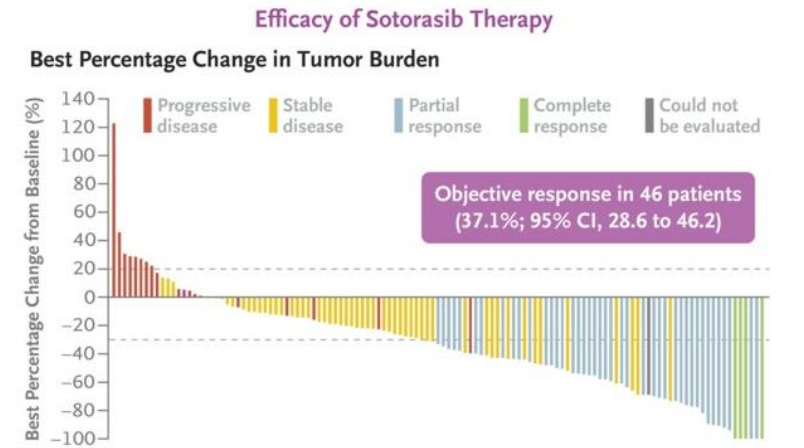
Intervention: 126 patients with *KRAS* p.G12C–mutated advanced non–small-cell lung cancer previously treated with standard therapies received an oral dose of 960 mg of sotorasib once daily. The primary end point was objective response as assessed by radiologic review.

RESULTS

Efficacy: Among 124 patients with measurable lesions at baseline, 3.2% had a complete response to sotorasib and 33.9% had a partial response. Median progression-free survival was nearly 7 months.

Safety: Grade 4 adverse events deemed to be related to treatment (pneumonitis and dyspnea) were noted





CodeBreaK100

- Ph2 open label trial with n=126 previously treated KRAS G12C NSCLC pts receiving 960 mg sotorasib daily
- Primary endpoint:
  - 37% RR
  - DCR 81%, mPFS: 6.8 mos
- Excluded active untreated brain mets, >3 prior lines of therapy

CodeBreaK 100 Long Term Update in NSCLC

CodeBreaK 100 Long term Update in NSCLC

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Response by Central Review	Phase 1/2 NSCLC N = 172*
Objective response rate, % (95% CI)	40.7 (33.3, 48.4)
Best overall response, n (%)	
Complete response	5 (2.9)
Partial response	65 (37.8)
Stable disease	74 (43.0)
Progressive disease	23 (13.4)
Not evaluable or missing scan	5 (2.9)
Disease control rate, % (95% CI)	83.7 (77.3, 88.9)
Median progression-free survival, months (95% CI)	6.3 (5.3, 8.2)

- Median follow-up 24.9 months
- Median DOR 12.3 months (95 CI 7.1-15.0)

Dy, GK et al, AACR 2022

CodeBreaK 100 Long term Update in NSCLC: Overall Survival

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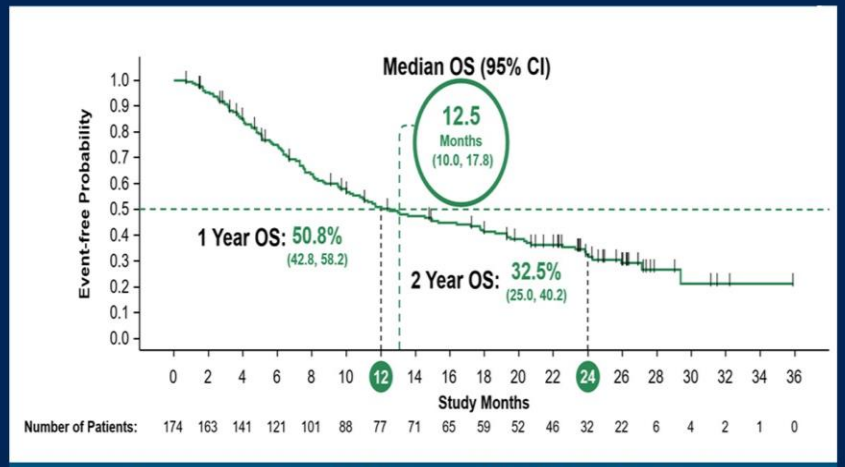


2-year overall survival observed in 32.5% of patients

- TRAE leading to dose modification: 22%
- TRAE leading to treatment discontinuation: 7%
- Most common treatment related TRAEs: Diarrhea (32% all grade, 4% grade 3), nausea (19% all grade, 0% grade 3), ALT/AST increase (15% all grade, 0% grade 3), fatigue (11% all grade, 0%), Vomiting (8% all grade, 0% grade 3)

Skoulidis, F et al, N Engl J Med 2021; Dy, GK et al, AACR 2022

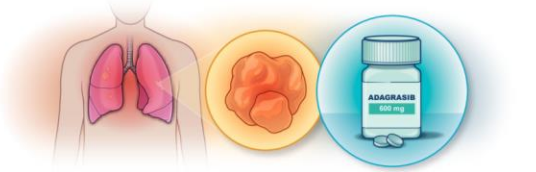
RESEARCH SUMMARY

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

Jänne PA et al. DOI: 10.1056/NEJMoa2204619

CLINICAL PROBLEM

KRAS is the most frequently mutated oncogene in human cancer, with mutations occurring in roughly one fourth of non–small-cell lung cancers (NSCLCs). The KRAS^{G12C} inhibitor adagrasib showed promising antitumor activity and had an acceptable adverse-event profile in a phase 1–1b study, but additional data are needed.



CLINICAL TRIAL

Design: A phase 2 trial examined the efficacy and safety of adagrasib in adults with unresectable or metastatic NSCLC with a *KRAS*^{G12C} mutation who had previously received platinum-based chemotherapy and checkpoint inhibitor therapy.

Intervention: 116 patients received 600 mg of oral adagrasib twice daily until disease progression, unacceptable adverse events, withdrawal of consent, or death occurred. The primary efficacy end point was objective response. Secondary end points included safety.

RESULTS

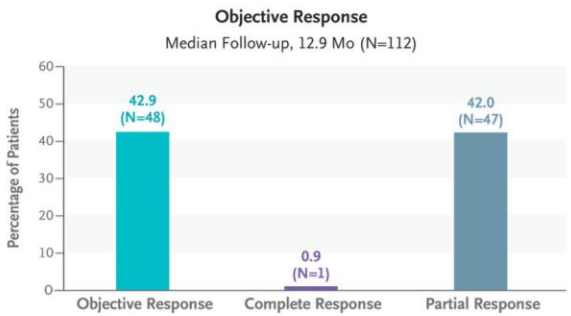
Efficacy: Over 40% of patients with measurable disease at baseline had a confirmed objective response; tumor shrinkage of any magnitude was observed in 79% of patients.

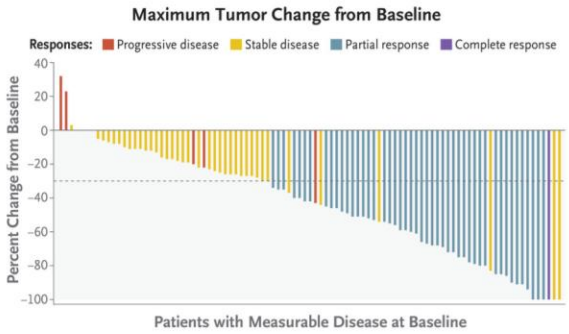
Safety: Treatment-related adverse events occurred in nearly all patients; the most common adverse events were diarrhea, nausea, vomiting, and fatigue. Most of the frequently observed treatment-related adverse events were grade 1 or 2; grade 3 or higher events occurred in 44.8% of the patients, including two grade 5 events.

LIMITATIONS AND REMAINING QUESTIONS

Further study is required to understand the following:

- How adagrasib compares with other treatments.
- The efficacy and safety of different doses of adagrasib; a dose of 400 mg twice daily is currently under investigation.
- Whether objective response would be more likely among previously untreated patients.
- The long-term efficacy of adagrasib against central nervous system metastases.



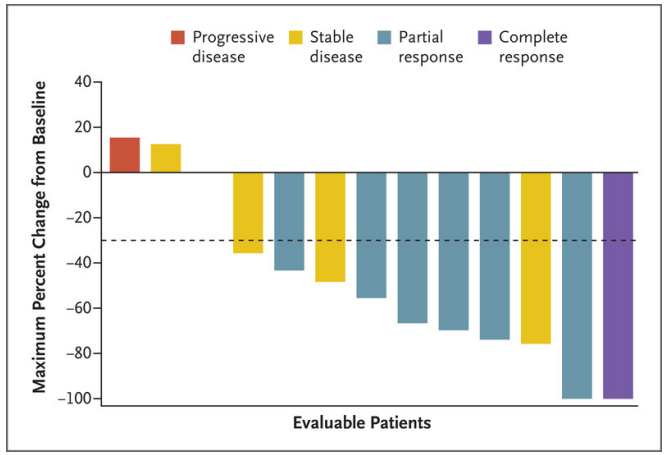


CONCLUSIONS

Use of the KRAS^{G12C} inhibitor adagrasib led to an objective response in more than 40% of patients with previously treated, advanced *KRAS*^{G12C}-mutated NSCLC.

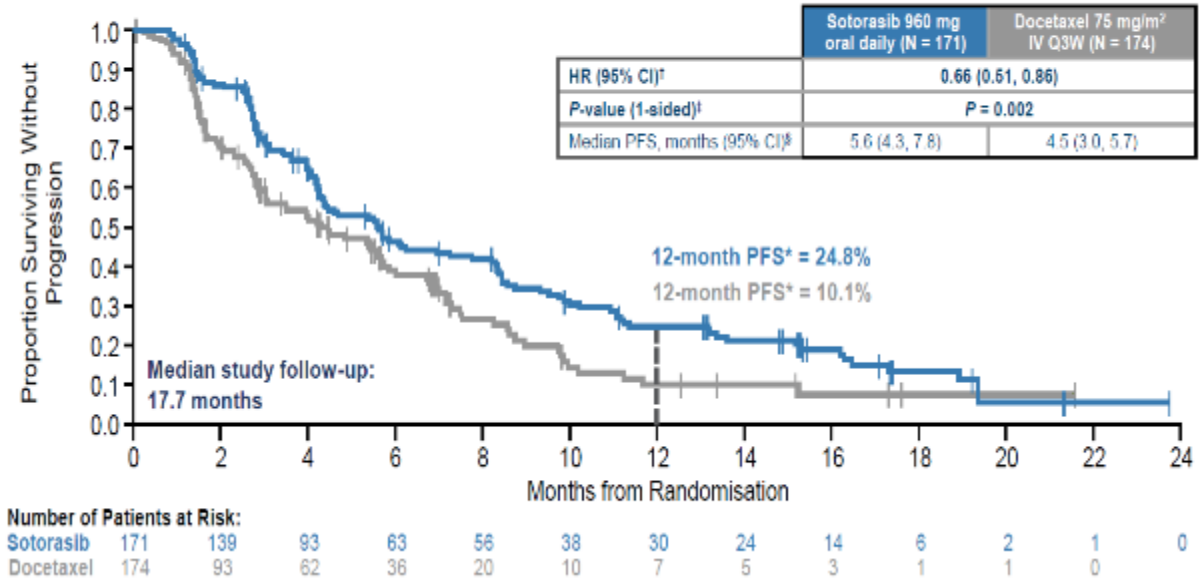
KRYSTAL-1

- Ph2 trial with n=116 previously treated KRAS G12C NSCLC pts receiving 600 mg adagrasib daily
- Primary endpoint:
  - 43% RR
  - DCR 79.5%, mPFS: 6.5 mos
- N=33 pts with treated, stable brain mets, IC ORR 33.3%



CodeBreaK 200: Sotorasib vs Docetaxel

Primary Endpoint: PFS by BICR

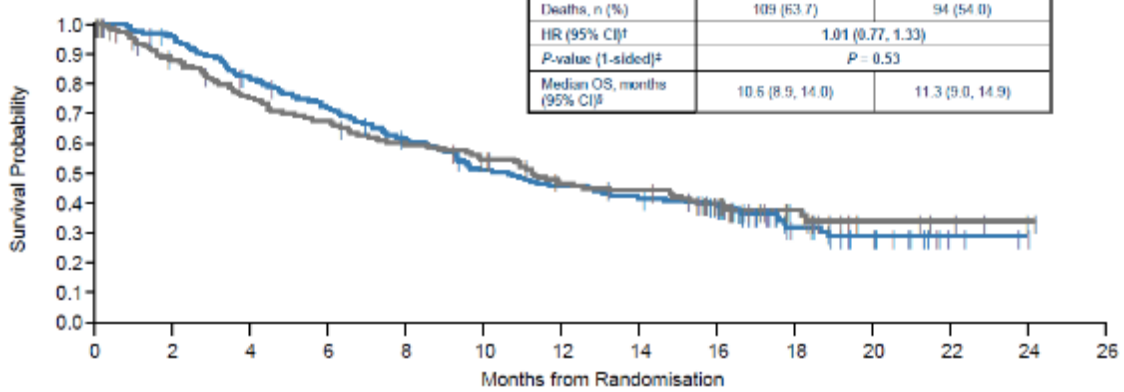


	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
HR (95% CI)†	0.66 (0.51, 0.86)	
P-value (1-sided)‡	*P* = 0.002	
Median PFS, months (95% CI)§	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)

Number of Patients at Risk:

Sotorasib	171	139	93	63	56	38	30	24	14	6	2	1	0
Docetaxel	174	93	62	36	20	10	7	5	3	1	1	0	

OS: Sotorasib vs Docetaxel



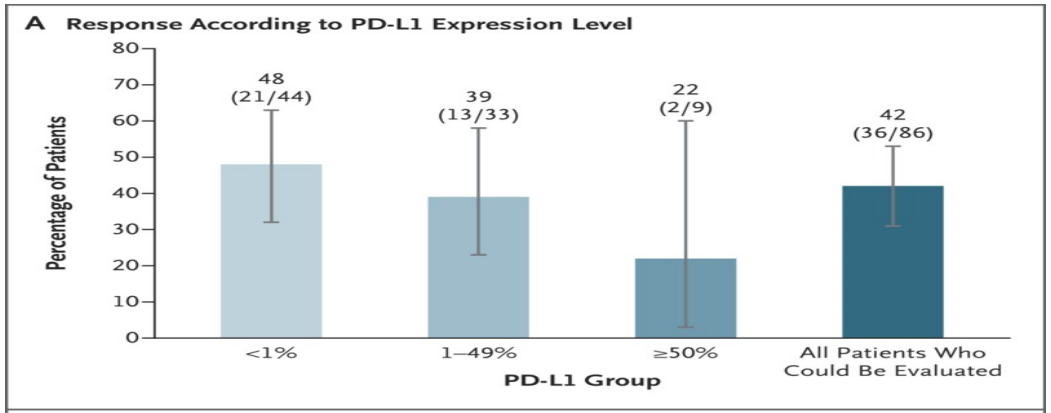
	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
Deaths, n (%)	109 (63.7)	94 (54.0)
HR (95% CI)†	1.01 (0.77, 1.33)	
P-value (1-sided)‡	*P* = 0.53	
Median OS, months (95% CI)§	10.6 (8.9, 14.0)	11.3 (9.0, 14.9)

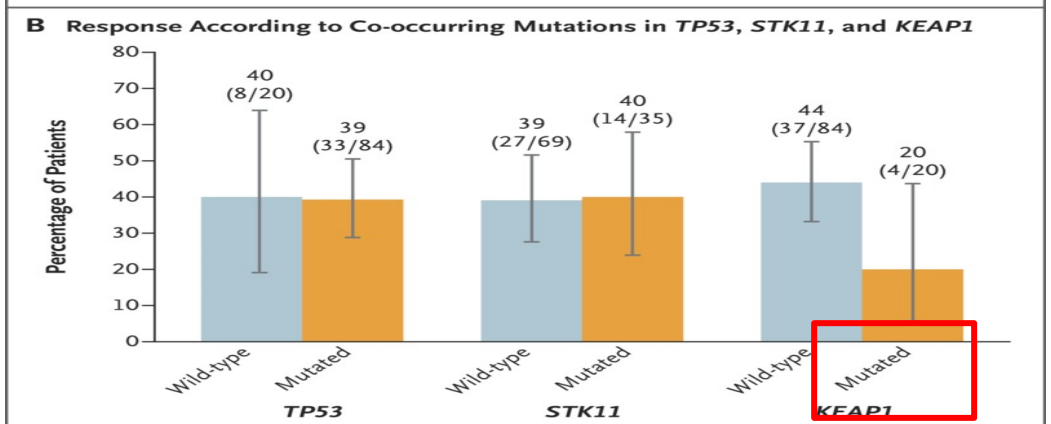
Number of Patients at Risk:

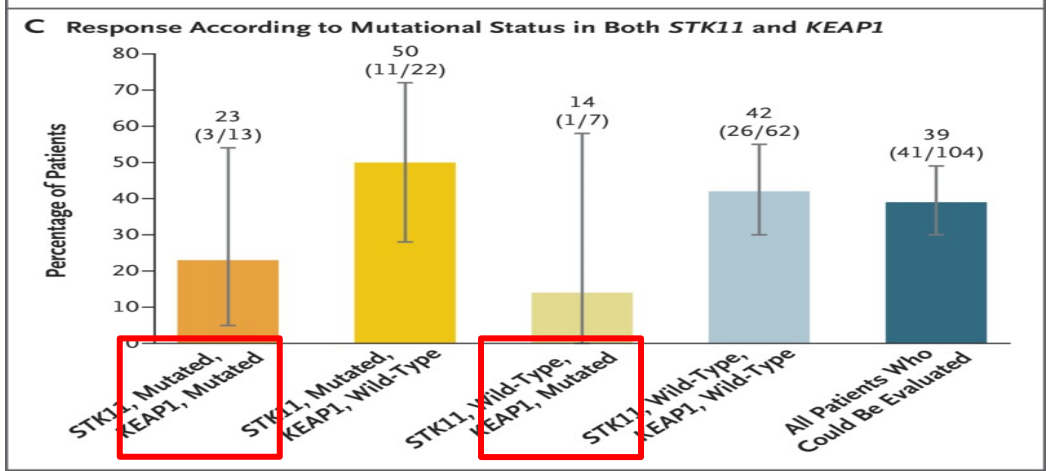
Sotorasib	171	162	137	119	98	81	73	66	56	25	15	3	0
Docetaxel	174	135	115	103	90	81	65	61	44	20	7	4	1	0

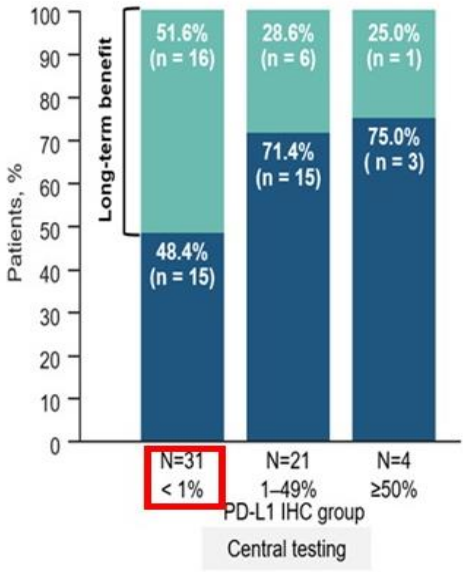
Johnson ML, et al. ESMO 2022. Abstract LBA10

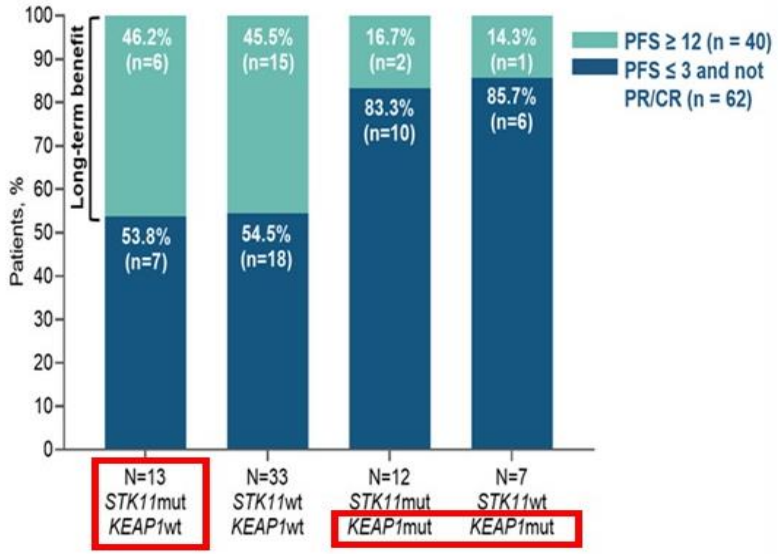
CodeBreaK100: Subgroup Exploratory Analysis







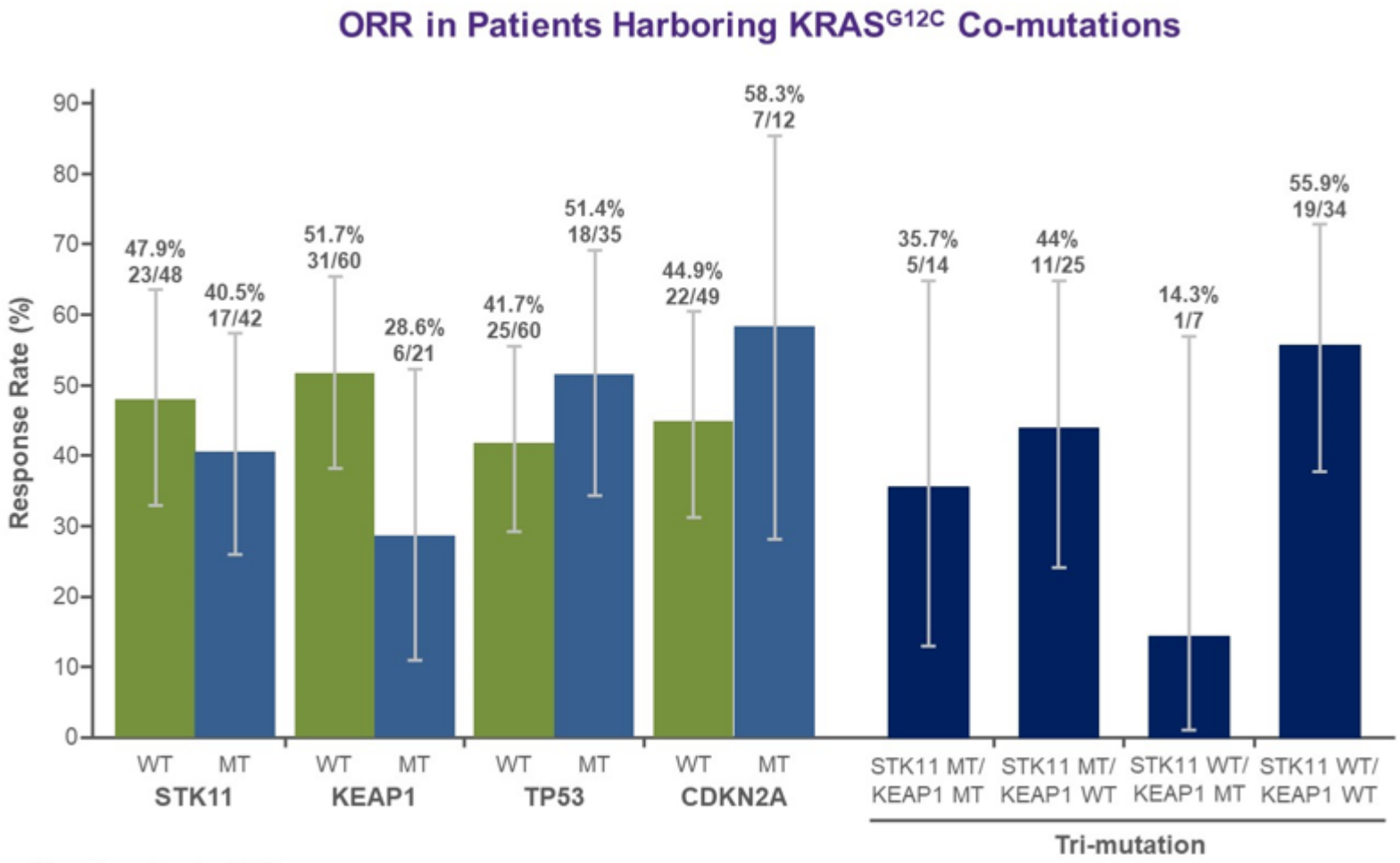




- Response and long-term clinical benefit across PDL1 expression groups
- Response and clinical benefit seen for STK11 co-mutation
- Less response and long-term benefit with KEAP1 co-mutation

Skoulidis, et al, NEJM 2021 DOI:10.1056/NEJMoa2103695
Dy, GK et al, AACR 2022

Preliminary Exploratory Correlative Analysis of Co-Mutations with KRASG12C and Response Rate in Patients with NSCLC treated with Adagrasib



Spira AI, et al. ASCO 2022. Abstract 9002

Question

This patient with KRAS G12C-mutated NSCLC and now progressive disease is treated with sotorasib as 2nd line therapy.

The patient has a good response for 6 months and then develops isolated brain metastases, with 3 small (1 cm) lesions which are asymptomatic. PET/CT shows that response continues outside the brain.

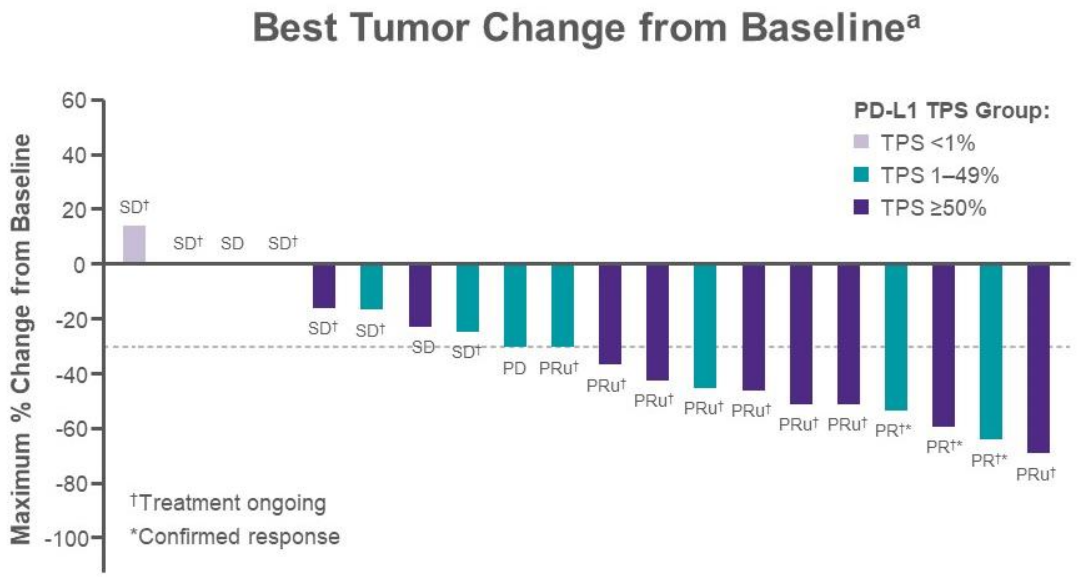
Question 4: In this case with KRAS G12C/STK11-mutated & PD-L1 TPS = 1%, which do you recommend at this point?

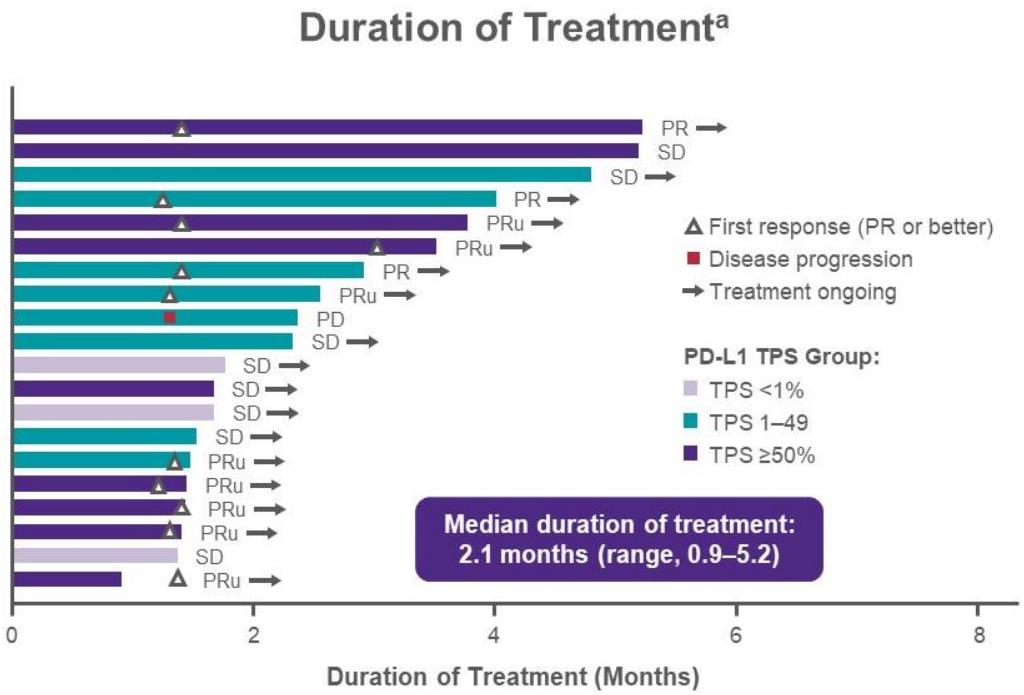
1. **SBRT to brain metastases & continue sotorasib**
2. **Switch to adagrasib**
3. **Switch to docetaxel/ramucirumab**
4. **Switch to nivolumab/ipilimumab**

Take Aways

- Sotorasib and adagrasib have clinically significant disease activity in previously treated NSCLC tumors with KRAS G12C mutations and are FDA approved
- Subgroup analysis of frontline trials show that chemo-immunotherapy is an effective approach for most KRASm patients
    - Patients with co-mutations, eg. KEAP1/STK11 may benefit from a different approach
- CodeBreaK-201, KRYSTAL-7 will inform frontline use of KRAS G12C inhibitors
- Numerous other KRAS G12C inhibitors in development alone and with other agents

First-Line Adagrasib 400 mg BID With Pembrolizumab in KRAS^{G12C}-Mutated NSCLC: Efficacy Outcomes





- ORR was 77% (7/9) in patients with PD-L1 TPS ≥50%, and 50% (4/8) in patients with PD-L1 TPS 1–49%

[a]n=20; one additional patient with a TPS score of <1% did not have post baseline scan at time of data cutoff
Data as of April 1, 2022

Data courtesy of Jamie Christiansen, 6 June 2022

First-Line Adagrasib 400 mg BID With Pembrolizumab in KRAS^{G12C}-Mutated NSCLC: Treatment-Related AEs

	Adagrasib 400 mg BID + Pembrolizumab[a]	
	Grade 1/2 (N=37)	Grade 3/4 (N=37)
Any treatment-related AE[b], n (%)	**12 (32.4%)**	**16 (43.2%)**
Diarrhea	10 (27.0%)	1 (2.7%)
Nausea	8 (21.6%)	4 (10.8%)
Amylase increased	8 (21.6%)	0
Fatigue	7 (18.9%)	1 (2.7%)
ALT increased	**6 (16.2%)**	**2 (5.4%)**
AST increased	**6 (16.2%)**	**2 (5.4%)**
Blood alkaline phosphatase increased	6 (16.2%)	0
Decreased appetite	5 (13.5%)	0
Edema peripheral	4 (10.8%)	0
Vomiting	4 (10.8%)	0
Lipase increased	3 (8.1%)	5 (13.5%)

- There were no grade 5 TRAEs
- TRAEs resulted in treatment discontinuations in 1/37 (2.7%) of patients

[a]Pooled data from Cohorts 1a and 2; [b]Occuring in >10% of patients
Data as of April 1, 2022

Data courtesy of Jamie Christiansen, 6 June 2022