IASLC 2022 World Conference on Lung Cancer

AUGUST 6-9, 2022 | VIENNA, AUSTRIA

PD-1/PD-L1 Directed IO for Advanced NSCLC

UCDAVIS COMPREHENSIVE CANCER CENTER

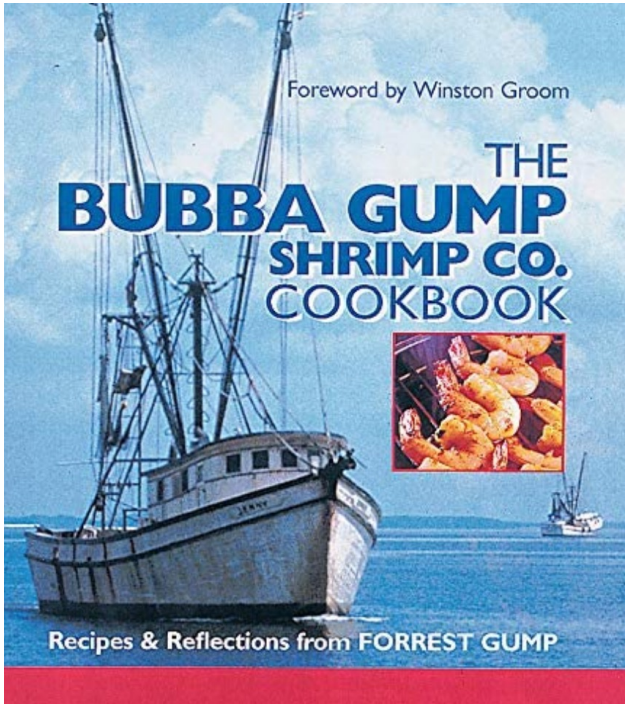
Jonathan Riess, M.D. M.S.
Associate Professor of Medicine
Medical Director Thoracic Oncology
University of California Davis School of Medicine
UC Davis Comprehensive Cancer Center

NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

DISCLOSURES

Company	Relationship(s)
Blueprint, Beigene, Daiichi Sankyo, EMD Serano, Janssen, Regeneron, Sanofi, Biodesix, Bayer, Turning Point, Bristol Myers Squibb, Jazz Pharmaceuticals, Novartis, Roche/Genentech, Boehringer Ingelheim	Consulting/Advisory Board
Merck, Boehringer Ingelheim, Novartis, AstraZeneca, Spectrum, Revolution Medicines	Research Funding (To Institution)

IO Combinations in NSCLC



- Targeted therapy + IO (KRAS G12Ci)
- Hudson (ATR inhibitor – among others)
- ADC + IO (Dato-DxD – Trop2 ADC)

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CodeBreaK 100/101: First report of safety and efficacy of sotorasib in combination with pembrolizumab or atezolizumab in advanced *KRAS* p.G12C NSCLC

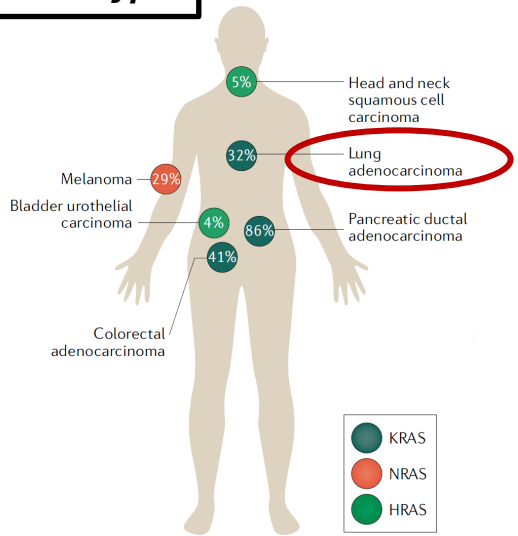
Bob T. Li,[1] Gerald S. Falchook,[2] Gregory A. Durm,[3] Timothy F. Burns,[4] Ferdinandos Skoulidis,[5] Suresh S. Ramalingam,[6] Alexander Spira,[7] Christine M. Bestvina,[8] Sarah B. Goldberg,[9] Rajwanth Veluswamy,[10] Wade T. Iams,[11] Alberto A. Chiappori,[12] Charlotte R. Lemech,[13] Alison R. Meloni,[14] Victoria A. Ebiana,[14] Tian Dai,[14] Diana M. Gauto,[14] Tracy L. Varrieur,[14] Wendy J. Snyder,[14] Ramaswamy Govindan[15]

[1]Memorial Sloan Kettering Cancer Center, Weill Cornell Medicine, New York, NY, USA; [2]Sarah Cannon Research Institute at HealthONE, Denver, CO, USA [3]Indiana University School of Medicine, Indianapolis, IN, USA; [4]University of Pittsburgh Medical Center (UPMC) Hillman Cancer Center, Pittsburgh, PA, USA; [5]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [6]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [7]US Oncology Research, The Woodlands, TX, USA; [8]The University of Chicago Medicine, Chicago, IL, USA; [9]Yale School of Medicine, New Haven, CT, USA; [10]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [11]Vanderbilt University Medical Center, Nashville, TN, USA; [12]Moffitt Cancer Center, Tampa, FL, USA; [13]Scientia Clinical Research, Randwick, Australia; [14]Amgen Inc., Thousand Oaks, CA, USA; [15]Washington University School of Medicine, St Louis, MO, USA

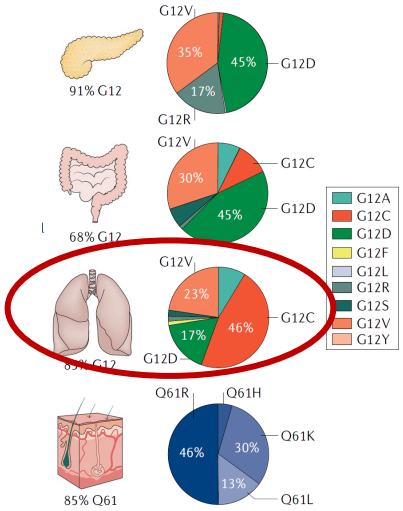
Bob T. Li, MD, PhD, MPH, Memorial Sloan Kettering Cancer Center, New York, NY, USA

KRAS mutations in cancer – Focus on NSCLC

Frequency of KRAS Mutations by Tumor Type



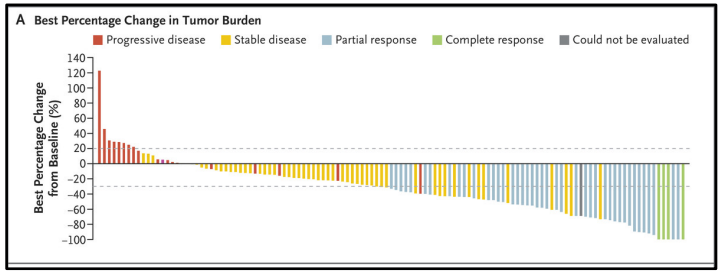
KRAS Mutation Subtypes By Tumor Tupe



Figures from Moore AR et al. Nat Rev Drug Discov 19, 533–552 (2020).

KRAS G12C inhibitors have activity in *KRAS* G12C NSCLC

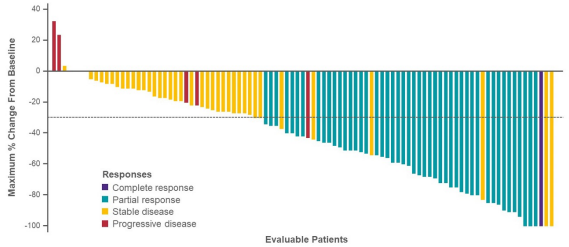
Sotorasib
CodeBreaK100 (Ph 2)



N=124 pts at 960 mg po qd
Median 2 prior lines of therapy
81% received both platinum and anti-PD-(L)1
ORR 37.1% (95% CI 28.6-46.2) // **DCR 80.6%** (95% CI 72.6-87.2)
mDOR 11.1 mo (95% CI 6.9-NE); **mPFS 6.8 mo** (95% CI 5.1-8.2)
mOS 12.5 mo (95% CI 10.0-NE)*

*median f/u 15.3 months F Skoulidis et al. N Engl J Med 2021;384:2371-2381.

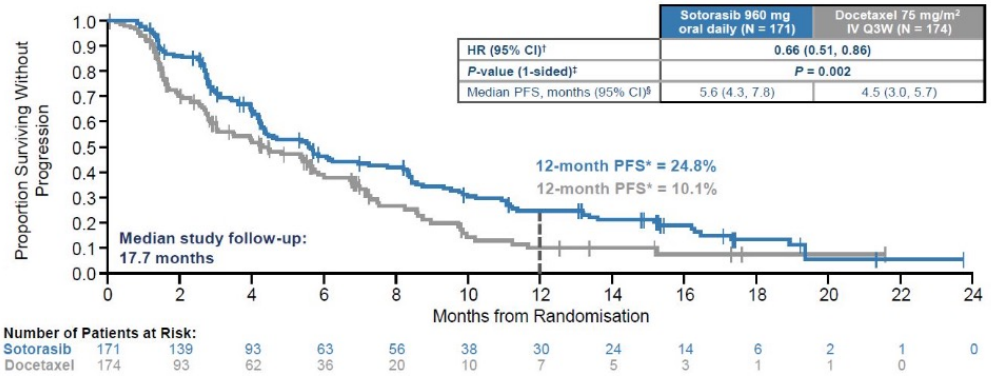
Adagrasib
KRYSTAL-1 study (Ph 1/1b & 2)



N=112 pts at 600 mg po bid
98% received both chemo and anti-PD-(L)1
ORR 43% // DCR 80% // mPFS 6.5 months (95% CI 4.7-8.4)
mOS 12.6 months (95% CI 9.2-19.2)

Spira A. ASCO 2022

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)

CodeBreaK 200 met its primary endpoint with sotorasib demonstrating superior PFS over docetaxel (HR 0.66, *P* = 0.002); 12-month PFS rate was 24.8% for sotorasib and 10.1% for docetaxel

ORR 28.1% vs. 13.2%
mOS 10.6 (soto) vs. 11.3 months (doce). No difference in OS.
34% crossover in docetaxel arm

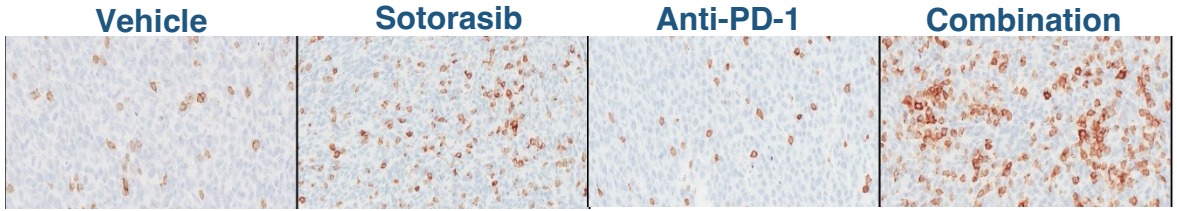
M. Johnson et al ESMO 2022

Introduction

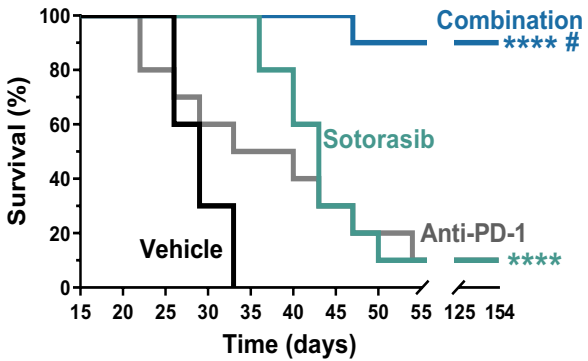
- Sotorasib, a first-in-class KRAS^{G12C} inhibitor, is approved as a monotherapy in the US, EU, and other countries for patients with previously treated *KRAS* p.G12C-mutated advanced NSCLC[1-4]

CodeBreaK 100[5]	ORR	DOR	Median OS	Grade 3-4 TRAE	TRAE leading to discontinuation
Pooled Phase 1/2 (N=174)	41%	12.3 months	12.5 months	21%	6%

- Sotorasib synergizes with anti-PD-1 to inhibit tumor growth in mice and enhances CD8+ T cell infiltration[1]



Figures adapted from Canon J, et al. *Nature*. 2019;575:217-223.



****P<0.0001 vs vehicle; $^{\#}P$<0.001 combination vs sotorasib or anti-PD-1 alone by 2-sided Mantel-Cox test

DOR, duration of response; KRAS, Kirsten rat sarcoma virus; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed death 1; TRAE, treatment-related adverse event.

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CodeBreaK 100/101 Study Design

- Phase 1b multicenter, open-label studies

Key Eligibility
- Advanced *KRAS* p.G12C-mutated NSCLC
- Received (or refused) prior standard therapies
- No prior $KRAS^{G12C}$ inhibitor
- No active brain mets

Screening/Enrollment →

Sotorasib* (oral daily) at:	Sotorasib lead-in 21d or 42d then combination (N = 29)	Concurrent treatment (N = 29)
960 mg	Atezolizumab 1200 mg Q3W (N = 10)	Atezolizumab 1200 mg Q3W (N = 10)
720 mg		
360 mg	*OR*	*OR*
240 mg	Pembrolizumab 200 mg Q3W (N = 19)	Pembrolizumab 200 mg Q3W (N = 19)
120 mg		

Primary endpoints: safety
Key secondary endpoints: ORR, DOR, DCR, PK

*Not all doses were tested for each cohort.
DCR, disease control rate; PK, pharmacokinetics; Q3W, every 3 weeks.

Snapshot: April 15, 2022

Here we present first data of lead-in and concurrent sotorasib with pembrolizumab or atezolizumab from CodeBreaK 100/101 with median follow-up time of 12.8 months (range: 1.6, 29.9)

Safety by Dose: Pembrolizumab Concurrent

TRAE, n (%)	Sotorasib 120 mg (N = 5)		Sotorasib 360 mg (N = 8)		Sotorasib 720 mg (N = 2)		Sotorasib 960 mg (N = 4)	
	Any	Grade ≥ 3	Any	Grade ≥ 3	Any	Grade ≥ 3	Any	Grade ≥ 3
All TRAEs	5 (100)	4 (80)	7 (88)	6 (75)	2 (100)	2 (100)	3 (75)	3 (75)
Hepatotoxicity	2 (40)	2 (40)	3 (38)	2 (25)	2 (100)	2 (100)	3 (75)	3 (75)
ALT increased	2 (40)	1 (20)	3 (38)	1 (13)	2 (100)	2 (100)	3 (75)	3 (75)
AST increased	2 (40)	2 (40)	3 (38)	0	2 (100)	2 (100)	3 (75)	1 (25)

- Higher rate of TRAEs than with either monotherapy[6–8], with no fatal TRAEs
- At lower doses of sotorasib, there was a trend towards less liver enzyme elevations, although sample sizes were limited
- Given the safety data for this combination, sotorasib lead-in was explored

Hepatotoxicity included autoimmune hepatitis, ALT increased, AST increased, ALP increased, bilirubin increased, and GGT increased.
ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase.

Safety Summary: Lead-in versus Concurrent

	Sotorasib + Atezolizumab Lead-In (N = 10)	Sotorasib + Atezolizumab Concurrent (N = 10)	Sotorasib + Pembrolizumab Lead-In (N = 19)	Sotorasib + Pembrolizumab Concurrent (N = 19)
TRAE, any grade, n (%)	10 (100)	9 (90)	15 (79)	17 (89)
Grade 3	3 (30)	5 (50)	10 (53)	14 (74)
Grade 4*	0	1 (10)	0	1 (5)
TRAE leading to sotorasib and/or IO discontinuation, n (%)	1 (10)	5 (50)	6 (32)	10 (53)
Median duration of sotorasib, months (min, max)	6.5 (1, 18)	4.4 (1, 14)	2.8 (1, 15)	4.9 (2, 30)
Median duration of combination, months (min, max)‡	1.5 (0, 18)	2.5 (1, 14)	0.7 (1, 15)	2.3 (1, 9)
Hepatotoxicity grade ≥ 3, median onset, days (range)	50 (28, 93)	67 (36, 147)	73 (45, 127)	51 (29, 190)

- **Lead-in had lower incidence of Grade 3-4 TRAEs and TRAEs leading to discontinuation than concurrent**
- **Grade 3-4 hepatotoxicity first occurrence was outside DLT window† in 88% of patients; 97% of events resolved with corticosteroids, treatment modification, and/or discontinuation**
- **The incidence of hepatotoxicity TRAEs was similar in IO-naïve versus IO-pretreated patients**

Hepatotoxicity included ALT increased, AST increased, ALP increased, bilirubin increased, GGT increased; also hepatitis, liver function test increased, drug-induced liver injury, transaminases increased for sotorasib+atezolizumab; also hepatic enzyme increased, immune-mediated hepatitis for sotorasib lead-in+pembrolizumab; also autoimmune hepatitis for sotorasib+pembrolizumab concurrent.
*Grade 4 TRAEs were ALT increased (n = 1; related to sotorasib and atezolizumab), and AST increased (n = 1; related to sotorasib).
‡Duration of combination calculated for patients receiving both sotorasib and IO; one patient in a lead-in cohort did not receive IO and not included
†DLT window was 21 days following initiation of combination treatment. IO, immune-oncology

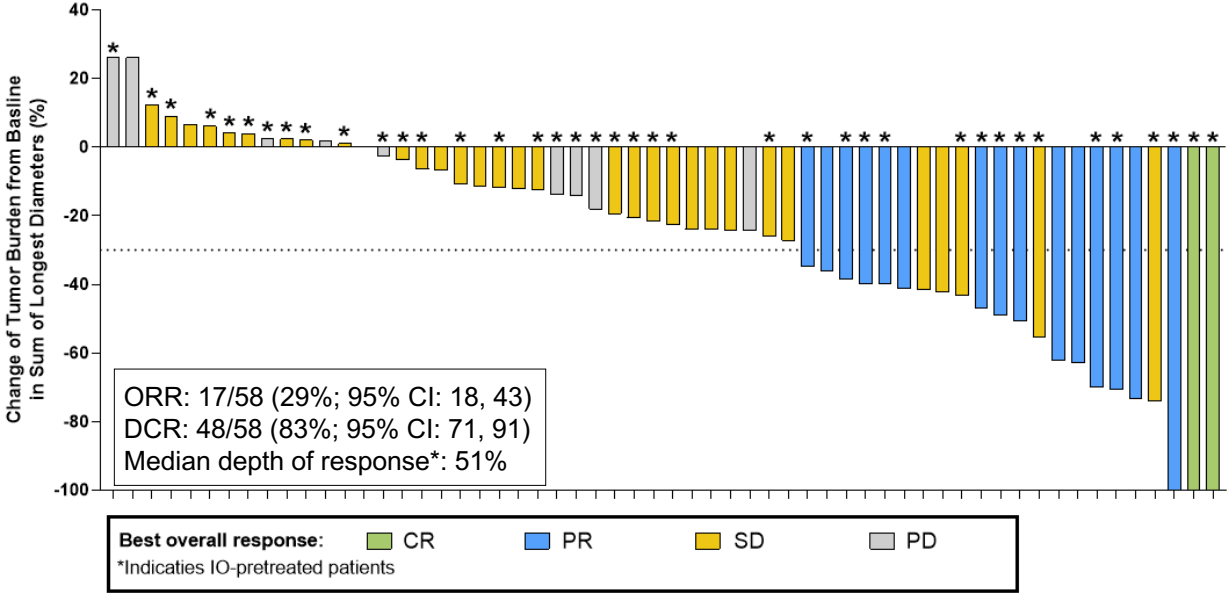
Safety for Sotorasib Lead-in + Pembrolizumab

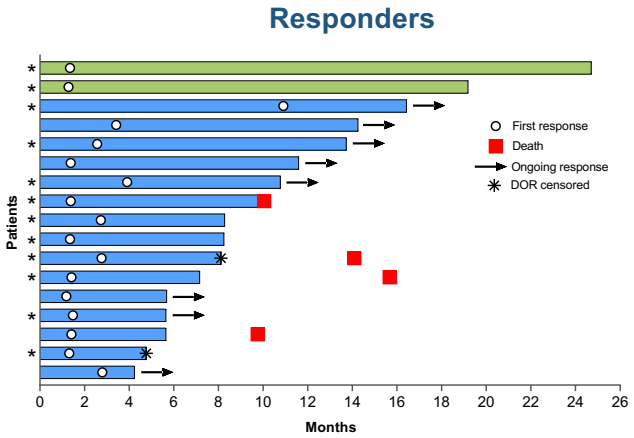
TRAE*, n (%)	Sotorasib 120 mg (N = 3)		Sotorasib 240 mg (N = 5)		Sotorasib 360 mg (N = 11)	
	Any	Grade ≥ 3	Any	Grade ≥ 3	Any	Grade ≥ 3
All TRAEs	**3 (100)**	**3 (100)**	**3 (60)**	**1 (20)**	**9 (82)**	**6 (55)**
ALT increased	2 (67)	2 (67)	1 (20)	1 (20)	6 (55)	3 (27)
AST increased	2 (67)	2 (67)	1 (20)	1 (20)	6 (55)	2 (18)
ALP increased	2 (67)	0	0	0	3 (27)	2 (18)
Diarrhea	1 (33)	0	1 (20)	0	6 (55)	1 (9)
Arthralgia	1 (33)	0	0	0	2 (18)	0
Nausea	0	0	0	0	4 (36)	0
Fatigue	0	0	0	0	4 (36)	0
Hypokalemia	0	0	0	0	3 (27)	2 (18)
Decreased appetite	0	0	0	0	3 (27)	0
Headache	0	0	0	0	2 (18)	0
Hepatotoxicity	**2 (67)**	**2 (67)**	**2 (40)**	**1 (20)**	**6 (55)**	**5 (45)**

Overall safety data from lead-in and concurrent cohorts support lower dose sotorasib and lead-in administration for better tolerability

*Any grade TRAE or grade ≥ 3 TRAE occurring in ≥ 1 patient in any dose cohort.

Efficacy

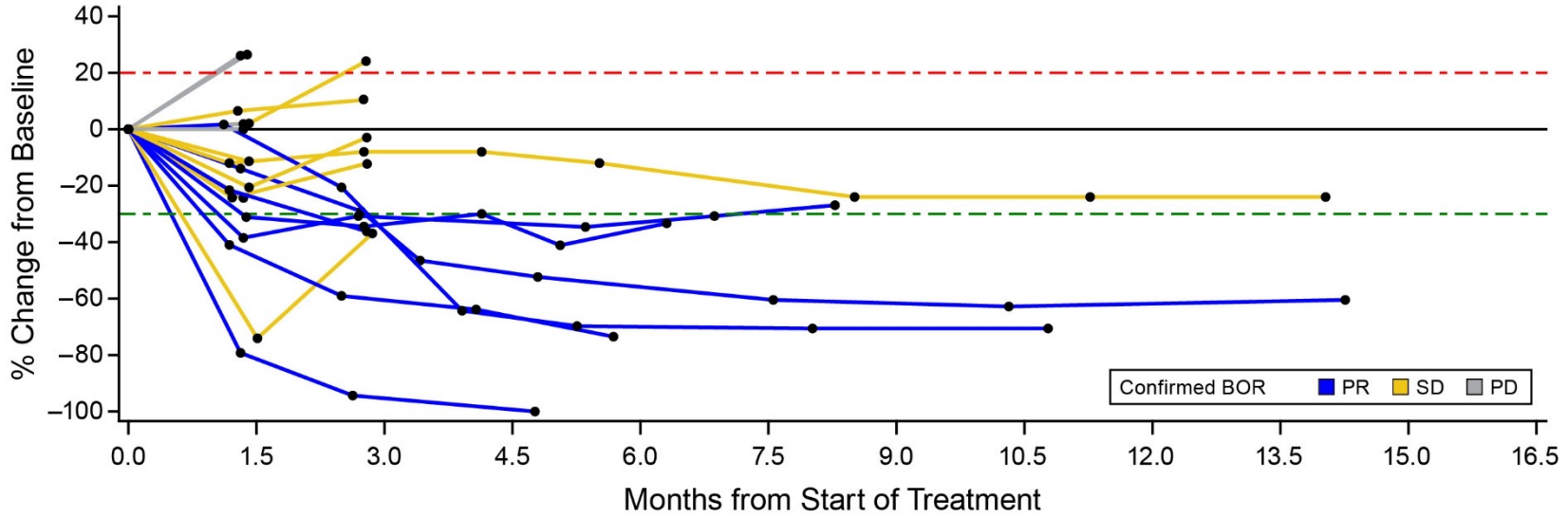




- **Deep and durable responses were observed for this combination across all cohorts, including at low doses**
- **Among the 17 responders, median duration of response was 17.9 months (95% CI: 5.6, NE)**
- **Response was similar in IO-naïve and IO-pretreated patients**

*Median depth of response among responders. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Efficacy for Sotorasib Lead-In + Pembrolizumab



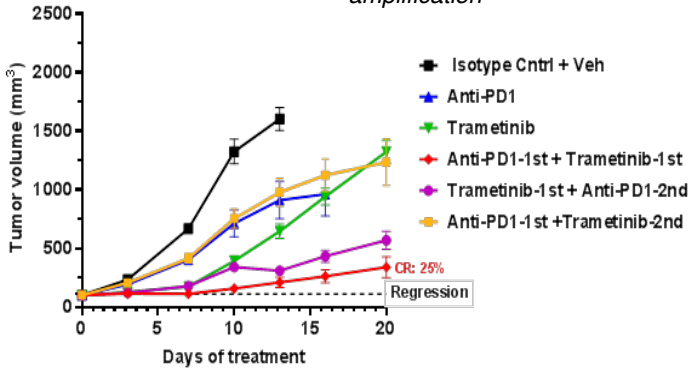
- Durable clinical benefit observed with sotorasib lead-in + pembrolizumab, with deep responses
- Low dose sotorasib lead-in + pembrolizumab is being pursued given its safety and efficacy profile

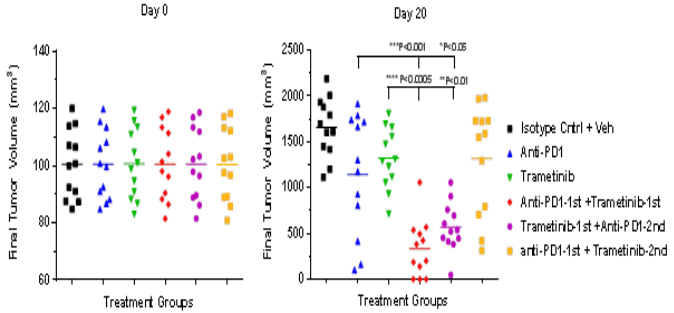
BOR, best overall response. PD, progressive disease; PR, partial response; SD, stable disease

Lead in TT + IO Rationale

1. Three regimens tested in syngeneic CT26 engrafted BALB/C mice
   - Trametinib+anti-PD1 concurrently
   - In sequence trametinib 1st then anti-PD1 2nd
   - In sequence anti-PD1 1st then trametinib 2nd
   - All inhibited tumor growth more effectively than their single agent controls during the initial 2-3 weeks of treatment
2. Two treatments produced profound TGD
   - Concurrent treatment
   - Trametinib 1st then anti-PD1 2nd
3. Combination increased tumor infiltrating CD8+ T cells *in vivo*. No significant alterations in the numbers and expression levels of CD3, CD4, CD25, CD69, PD1.

CT26 mouse colorectal tumor cells: homozygous KRAS G12D mutation, *MAPK1* and *MET amplification*

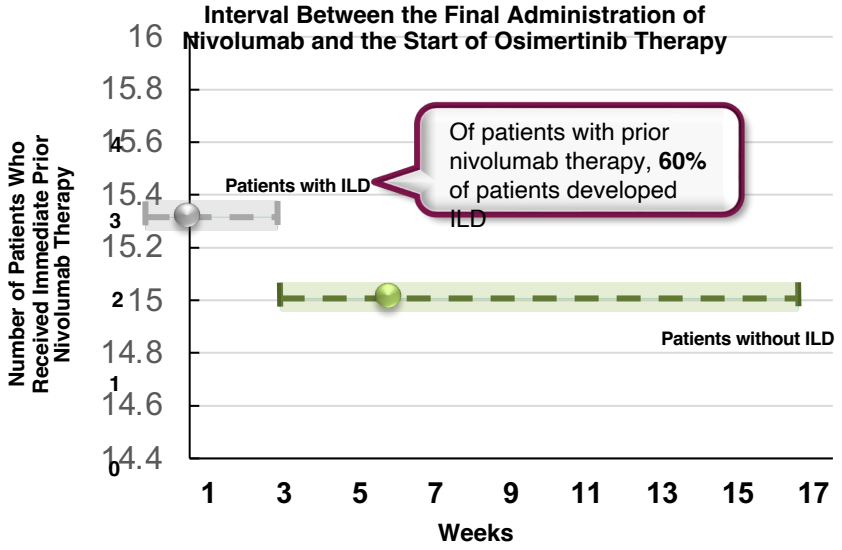




[illegible] et al, CCR 2015.

Increased Toxicity with EGFR-TKI + PD-(L)1

EGFR-TKI	PD-(L)1	Toxicity
Erlotinib	Atezolizumab	39% G3-4 trAEs (pyrexia, transaminitis)
Erlotinib	Nivolumab	10% G3 trAEs (diarrhea, transaminitis)
Osimertinib	Durvalumab	64% pneumonitis (TKI naïve); 26% (prior TKI)
Afatinib Gefitinib	Pembrolizumab Durvalumab	36% irAEs (nephritis, adrenal insuff, colitis) G3-4 irAEs (20%) transaminitis

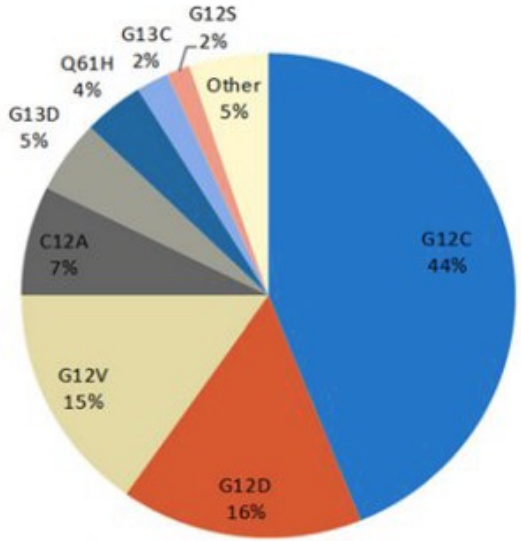


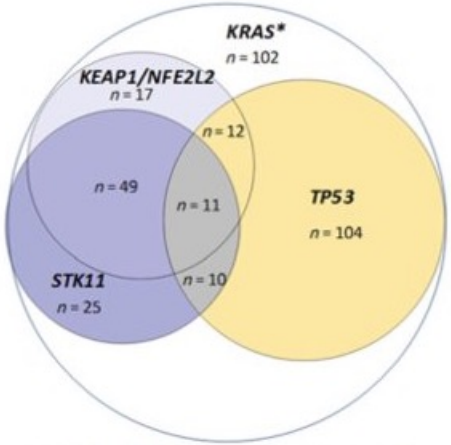
1. Kotake M, et al. *Ann Oncol.*

Conclusions

- In mostly IO-pretreated patients, sotorasib with atezolizumab or pembrolizumab led to a high incidence of grade 3-4 TRAEs
- Lower sotorasib doses trended toward less hepatotoxicity TRAEs including fewer grade ≥3 events
- Sotorasib lead-in had lower rates of grade 3-4 TRAEs and TRAEs leading to discontinuation compared with concurrent administration. ? More efficacy.
- Lead-in cohorts demonstrated durable clinical activity and depth of response
- Among 17 responders, median duration of response was 17.9 months (95% CI: 5.6, NE)
- Lower dose and lead in being pursued.
- Co-mutation status may impact response to PD-(L)1 plus KRAS G12Ci

Spectrum of KRAS mutations and Co-Mutations in NSCLC

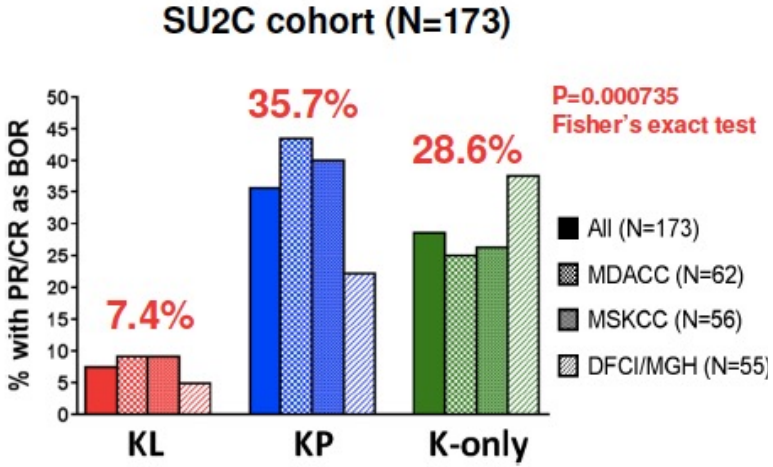




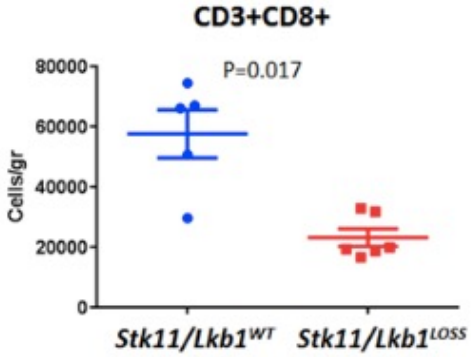
*KRAS (*n* = 102) listed above represents number of patients with *KRAS* mutations but without cooccurring mutations in *TP53*, *STK11*, *KEAP1* or *NFE2L2*

Arbour et al CCR 2018

Differential activity of PD-1 Blockade in KRAS mutant NSCLC by STK11 (LKB1) co-mutation status



Patients with KRAS;STK11(LKB1) co-mutated tumors exhibit poor clinical response to PD-1 inhibitors



"Cold" Tumor Microenvironment in Syngeneic KRAS LUAC mouse model

Skoulidis F et al, ASCO Annual Meeting, 2017
Skoulidis F et al, Cancer Discovery, 2018

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HUDSON: AN OPEN-LABEL, MULTI-DRUG, BIOMARKER-DIRECTED PHASE 2 STUDY IN NSCLC PATIENTS WHO PROGRESSED ON ANTI-PD-(L)1 THERAPY

Benjamin Besse[1], Mark M. Awad[2], Patrick M. Forde[3], Michael Thomas[4], Glenwood Goss[5], Boaz Aronson[6], Rosalind Hobson[7], Emma Dean[7], Jane Peters[7], Sonia Iyer[8], James Conway[6], J. Carl Barrett[8], Jan Cosaert[7], Marlene Dressman[6], Simon T. Barry[7], John V. Heymach[9]

[1]Paris-Saclay University, Institut Gustave Roussy, Villejuif, France; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [4]Thoraxklinik am Universitätsklinikum Heidelberg, Translational Lung Research Center Heidelberg (TLRC-H), Heidelberg, Germany; [5]The Ottawa Hospital Research Institute, Ottawa, Ontario, Canada; [6]AstraZeneca, Gaithersburg, MD, USA; [7]AstraZeneca, Cambridge, UK; [8]AstraZeneca, Boston, MA, USA; [9]MD Anderson Cancer Center, Houston, TX, USA

Rationale

Combination agent	Mechanism of action	Mechanism of anti-PD-(L)1 resistance targeted	HUDSON biomarkers
Ceralasertib (AZD6738)	ATR inhibitor	Improving tumor immunogenicity and tumor immune microenvironment via DDR pathway inhibition, to sensitize cancer cells to anti-PD-L1/PD-1 therapy[1]	ATM alteration
Olaparib	PARP inhibitor	Alterations to DDR pathways affect anti-PD-(L)1 sensitivity;[2] PARP inhibition promotes DDR pathway defects[3]	HRRm *STK11/LKB1m*
Danvatirsen	STAT3 inhibitor	Interferon-γ signalling defects arising from JAK-STAT pathway mutations associated with acquired resistance[4]	Not applicable
Oleclumab	Anti-CD73 monoclonal antibody	Immunosuppressive tumor immune microenvironment due to production of adenosine, mediated by CD73[5]	High CD73 expression

:293–301;
4. Schoenfeld & Hellmann. Cancer Cell 2020;37:443–455; 5. Roh et al. Curr Opin Pharmacol 2020;53:66–76.
ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3-relatedprotein kinase; CD73, cluster of differentiation 73; DDR, DNA damage response and repair; HRRm, homologous recombination repair mutated; STK11/LKB1m, STK11/LKB1 aberration; PARP, Poly-(ADP-ribose) polymerase; PD-(L)1, programmed death (ligand)-1

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HUDSON: Phase II multi-arm umbrella study

- Locally advanced or metastatic NSCLC
- Previous platinum-based chemotherapy
- Failure of prior anti-PD-(L)1 immunotherapy
- Suitable for new tumor biopsy / biopsy post-progression on anti-PD-(L)1 therapy
- No targetable alterations in *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET*, or *RET*

Central molecular screen,‡ ***n* = 255** (Jan 26, 2018–Apr 14, 2021)

Primary endpoint: ORR
Secondary endpoints: DCR, PFS, OS, safety and tolerability

Group A: biomarker-matched, *n* = 86

HRRm	Durvalumab + olaparib (PARPi), ***n* = 21**
LKB1	Durvalumab + olaparib (PARPi), ***n* = 21**
ATM	**Durvalumab + ceralasertib (ATRi), *n* = 21***
ATM	Single-agent ceralasertib (ATRi)*
CD73h	Durvalumab + oleclumab (CD73 mAb), ***n* = 23**
HER2e	Durvalumab plus trastuzumab deruxtecan (HER2i)†
HER2m	

Group B: biomarker-non-matched, *n* = 169

Primary resistance (disease progression ≤24 weeks)§	Acquired resistance (disease progression >24 weeks)#
Durvalumab + olaparib (PARPi), ***n* = 22**	Durvalumab + olaparib (PARPi) , ***n* = 23**
Durvalumab + danvatirsen (STAT3i), ***n* = 23**	Durvalumab + danvatirsen (STAT3i), ***n* = 22**
Durvalumab + ceralasertib (ATRi), *n* = 20	**Durvalumab + ceralasertib (ATRi), *n* = 25**
Durvalumab + oleclumab (CD73 mAb), ***n* = 9**	Durvalumab + oleclumab (CD73 mAb), ***n* = 25**
	Durvalumab + cediranib (VEGFi)†

*Ongoing. †Data not mature. ‡Immunohistochemistry was also performed. §/# Progression on prior anti-PD-(L)1 therapy within 24 weeks / after > 24 weeks.
ATM, ataxia telangiectasia mutated; ATRi, ataxia telangiectasia receptor inhibitor; CD73(h), (high expression of) cluster of differentiation 73; DCR, disease control rate; HER2e/i/m, human epidermal growth factor receptor 2 expression/inhibitor/mutated; HRRm, homologous recombination repair mutated; LKB1, LKB1/STK11 aberration; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PARPi, poly ADP ribose polymerase inhibitor; PD-(L)1, programmed death (ligand)-1; PFS, progression-free survival; STAT3i, signal transducer and activator of transcription 3 inhibitor; VEGFi, vascular endothelial growth factor inhibitor.

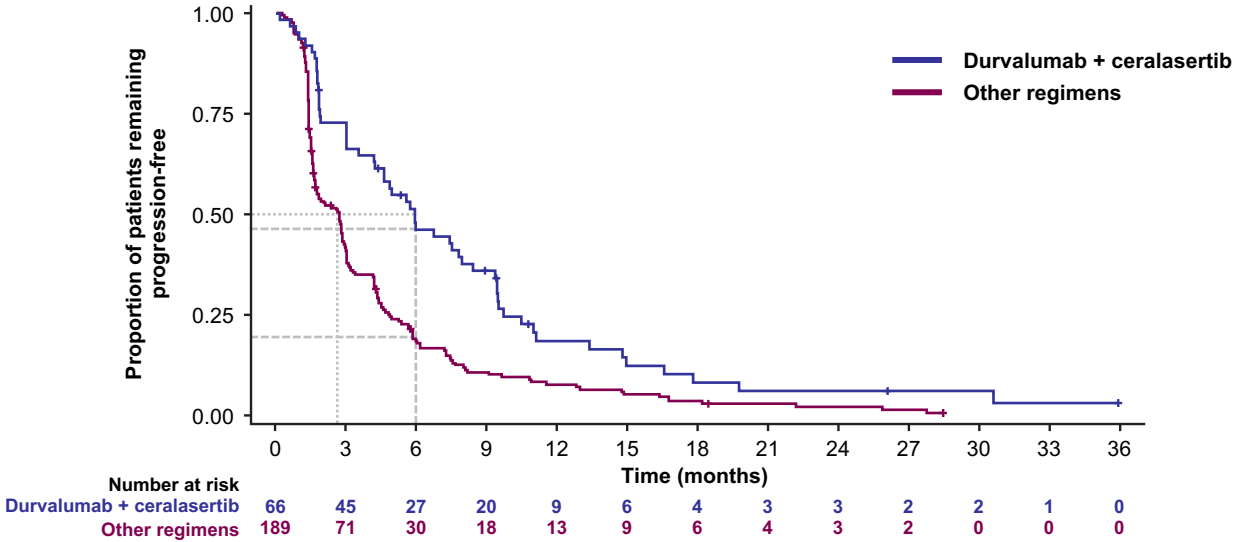
Treatment efficacy by regimen

	Durvalumab + ceralasertib n=66	Durvalumab + olaparib n=87	Durvalumab + danvatirsen n=45	Durvalumab + oleclumab n=57
Median treatment duration, months				
Durvalumab*	**7.3**	3.7	2.8	2.9
Other agent†	**6.3**	3.2	2.8	2.9
12-week disease control rate, %	**60.6**	36.8	26.7	29.8
24-week disease control rate, %	**42.4**	17.2	13.3	15.8
ORR, %	**16.7%**	4.6%	0%	1.8%

ORR, objective response rate.
*Treatment duration for durvalumab calculated as (the earliest of (last infusion date + 27, date of death, date of cut-off) – first infusion date + 1) / (365.25/12).
†Treatment duration for:

- Olaparib calculated as (Last dose date – first dose date + 1) / (365.25/12)
- Danvatirsen calculated as (Last infusion date – first infusion date + 1) / (365.25/12), if the last cycle is Cycle 0 and there were less than 3 doses, or (the earliest of (last infusion date + 6, death date, date of cut-off) – first infusion date + 1) / (365.25/12) for all other cases
- Ceralasertib calculated as (Last dose date – first dose date + 1) / (365.25/12)
- Oleclumab calculated as (the earliest of (last infusion date + 13, death date, date of cut-off) – first infusion date + 1) / (365.25/12) if the last cycle is Cycle 1 or 2, or as (the earliest of (last infusion date + 27, death date, date of cut-off) – first infusion date + 1) / (365.25/12), for all other cases.

PFS



	Durvalumab + ceralasertib. n=66	Other regimens n=189
Median PFS, months (80% CI)	6.0 (4.6–7.5)	2.7 (1.8–2.8)
6-month PFS, % (80% CI)	46.3 (37.9–54.2)	18.0 (14.5–21.9)

PFS, progression-free survival.

Conclusions

- Durvalumab plus ceralasertib (Module 3) demonstrated an efficacy signal across biomarker-matched and biomarker-non-matched patients with locally advanced or metastatic NSCLC following failure of prior anti-PD-1/PD-L1-containing immunotherapy and platinum-doublet regimen
  - The combination resulted in the highest ORR (16.7% vs 0–4.8%) and disease control rates (12-week: 60.6% vs 26.7–36.8%; 24-week: 42.4% vs 13.3–17.2%) among the regimens evaluated to date
  - Hypothesis generating for future studies
  - Need to match IO enhancement/resistance mechanism to combo treatment.

NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed death (ligand)-1

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TROPION-Lung02: Initial Results for Datopotamab Deruxtecan Plus Pembrolizumab and Platinum Chemotherapy in Advanced NSCLC

Benjamin Levy,[1] Luis Paz-Ares,[2] Olivier Rixe,[3,4] Wu-Chou Su,[5] Tsung-Ying Yang,[6] Anthony Tolcher,[7] Yanyan Lou,[8] Yoshitaka Zenke,[9] Panayiotis Savvides,[10] Enriqueta Felip,[11] Manuel Domine,[12] Konstantinos Leventakos,[13] Mariano Provencio Pulla,[14] Marianna Koczywas,[15] Atsushi Horiike,[16] Siddhartha Rawat,[4] Xiangfeng Wu,[4] Priyanka Basak,[4] Michael Chisamore,[17] Yasushi Goto[18]

[1]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Medicine, Baltimore, MD, USA; [2]Hospital Universitario 12 de Octubre, CNIO-H12O Lung Cancer Unit, Universidad Complutense & CiberOnc, Madrid, Spain; [3]Quantum Santa Fe, Santa Fe, NM, USA; [4]Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; [5]Department of Oncology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan [6]Division of Chest Medicine, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan; [7]NEXT Oncology, San Antonio, TX, USA; [8]Mayo Clinic, Jacksonville, FL, USA; [9]Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [10]Mayo Clinic, Phoenix, AZ, USA; [11]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [12]Department of Oncology, Hospital Universitario Fundación Jiménez Díaz (IIS-FJD), Madrid, Spain; [13]Mayo Clinic, Rochester, MN, USA; [14]Department of Medical Oncology, Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain; [15]Department of Medical Oncology & Therapeutic Research, City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [16]Department of Thoracic Medical Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; [17]Merck & Co., Inc., Rahway, NJ, USA; [18]National Cancer Center Hospital, Tokyo, Japan

Background

- Dato-DXd is an ADC composed of a humanized TROP2 IgG1 mAb covalently linked to a topoisomerase I inhibitor payload via a stable tetrapeptide-based cleavable linker
- TROPION-Lung02 is a phase 1b study evaluating Dato-DXd + pembrolizumab (pembro) ± platinum CT[a] in advanced NSCLC without actionable genomic alterations (NCT04526691)
- Study approach: safety of Dato-DXd + pembro "doublets" was established prior to evaluation of platinum-containing "triplets"
  - Safety of Dato-DXd 4-mg/kg combinations was established prior to evaluation of 6-mg/kg combinations

Key eligibility

- Advanced/metastatic NSCLC
- Dose confirmation[b]: ≤2 lines of prior therapy[c]
- Dose expansion
  - ≤1 line of platinum-based CT (cohorts 1 and 2)[c]
  - No prior therapy (cohorts 3-6)[c]

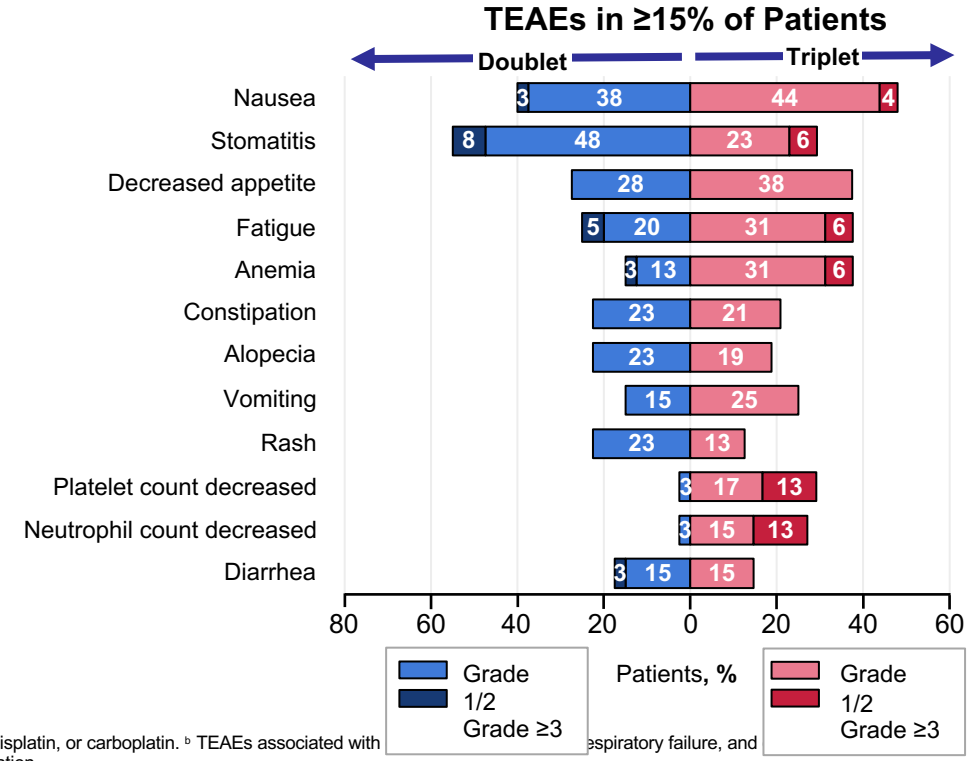
	Dato-DXd IV Q3W	+	pembro IV Q3W	+	platinum CT IV Q3W	
Cohort 1 (n=20)[d]:	4 mg/kg	+	200 mg			"Doublet"
Cohort 2 (n=20)[d]:	6 mg/kg	+	200 mg			
Cohort 3 (n=17)[d]:	4 mg/kg	+	200 mg	+	carboplatin AUC 5	"Triplet"
Cohort 4 (n=20)[d]:	6 mg/kg	+	200 mg	+	carboplatin AUC 5	
Cohort 5 (n=7)[d]:	4 mg/kg	+	200 mg	+	cisplatin 75 mg/m^2	
Cohort 6 (n=4)[d]:	6 mg/kg	+	200 mg	+	cisplatin 75 mg/m^2	

- **Primary objectives:** safety and tolerability
- **Secondary objectives:** efficacy, pharmacokinetics, and anti-drug antibodies

ADC, antibody-drug conjugate; AUC, area under the curve; CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; DLT, dose-limiting toxicity; IgG1, immunoglobulin G1; IV, intravenous; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; pembro, pembrolizumab; Q3W, every 3 weeks; TROP2, trophoblast cell-surface antigen 2.
[a] Administered sequentially at the same visit. [b] The first 3-6 patients in each cohort were enrolled to confirm acceptable safety/DLT rate; the remaining patients are considered part of "dose expansion" (for which enrollment was ongoing at time of data cutoff). [c] Prior therapy requirements are for treatment in the advanced/metastatic setting. [d] As of the May 2, 2022, data cutoff.

Safety

Events, n (%)	Doublet (n=40)	Triplet (n=48)
TEAEs	37 (93%)	47 (98%)
Study treatment-related[a]	33 (83%)	46 (96%)
Grade ≥3 TEAEs	16 (40%)	29 (60%)
Study treatment-related[a]	14 (35%)	26 (54%)
Serious TEAEs	9 (23%)	13 (27%)
Study treatment-related	4 (10%)	7 (15%)
TEAEs associated with		
Death[b]	2 (5%)	1 (2%)
Discontinuation due to any drug	9 (22%)	9 (19%)
Discontinuation due to Dato-DXd	6 (15%)	5 (10%)
ILD adjudicated as drug related[c]		
Grade 1/2	2 (5%)	0
Grade 3	1 (3%)	1 (2%)



cisplatin, or carboplatin. [b] TEAEs associated with espiratory failure, and ation.

Antitumor Activity

In the overall population:

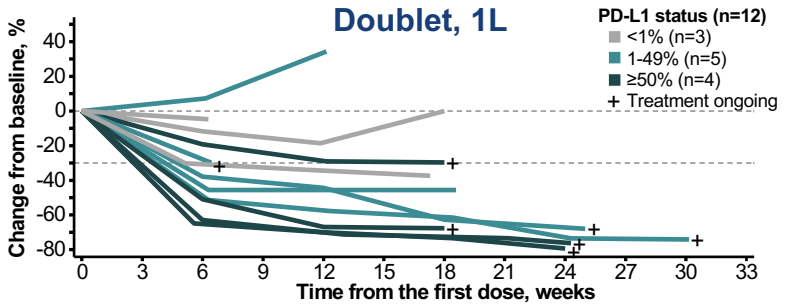
ORRs (confirmed + pending) of 37% and 41% were seen with doublet (n=38) and triplet (n=37) therapy, respectively; both groups had 84% DCR

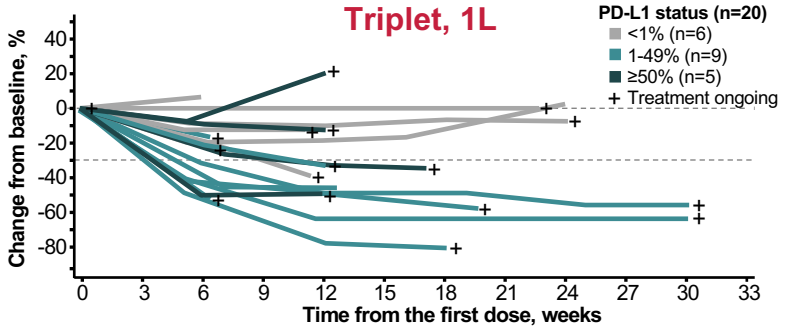
BOR With 1L Therapy For Advanced NSCLC[a,b]

Response, n (%)	Doublet (n=13)	Triplet (n=20)
ORR confirmed + pending	**8 (62%)**	**10 (50%)**
CR	0	0
PR confirmed	8 (62%)	7 (35%)
PR pending	0	3 (15%)
SD	5 (39%)	8 (40%)
DCR	13 (100%)	18 (90%)

- As 1L therapy, the doublet and triplet yielded ORRs (confirmed + pending) of 62% and 50%, respectively
- As 2L+ therapy, respective ORRs (confirmed + pending) were 24% and 29%

Percent Change in Sum of Diameters[a]





Data cutoff: May 2, 2022.
BOR, best overall response; CR, complete response; DCR, disease control rate; ORR, overall response rate; PR, partial response; SD, stable disease.
[a] By investigator. [b] BOR is based on response evaluable patients who have ≥1 postbaseline tumor assessment or discontinued.

Summary

- This first reported clinical experience of a TROP2 ADC + a checkpoint inhibitor ± platinum CT in metastatic NSCLC demonstrated a tolerable safety profile and supported further evaluation of the 6-mg/kg dose of Dato-DXd in immunotherapy combination regimens[a]

- Stomatitis and nausea, mostly grade 1/2, were the most frequent TEAEs in patients receiving doublet and triplet therapy, respectively

Interim efficacy results in the overall population and in patients receiving 1L therapy

  – Responses were observed across all PD-L1 expression levels

  – The study is ongoing, and additional analyses with longer follow-up and more patients are pending

- The phase 3 TROPION-Lung08 trial (NCT05215340) is evaluating Dato-DXd + pembro vs pembro alone as 1L therapy in advanced/metastatic NSCLC with PD-L1 TPS >50%[1]

TPS, tumor proportion score.
[a] The Dato-DXd 6-mg/kg dose is also being evaluated as monotherapy in ongoing, global, phase 3 studies.
1. Levy B, et al. Poster presented at: American Society for Clinical Oncology; June 3-7, 2022. Abstract TPS3162.

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