World Conference on Lung Cancer 2021 Highlights

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Conquering Thoracic Cancers Worldwide

CME ACCREDITED

Housekeeping Notes

- Please submit all questions through the Zoom Q and A function at the bottom of the screen
  - You can use the chat for other discussions
- We will track your questions and share them with the panel for the live Q&A at the end of the session

Disclosures

David Harpole, MD discloses he is on a Scientific Advisory Board for AstraZeneca and Medtronic

Kristin Higgins, MD discloses she is on an advisory board and a consultant for Astra Zeneca, has funded research and is on an advisory board for RefleXion Medical and receives honorarium from Ultimate Opinions in Medicine

Tom Stinchcome, MD discloses the following:

Advisory board: Takeda, AstraZeneca, Genentech/Roche, Foundation Medicine, Pfizer, EMD Serono, Novartis, Daiichi Sankyo, Lilly, Medtronic, Puma Biotechnology, Janssen Oncology, Regeneron, Turning Point Therapeutics, Sanofi/Aventis

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All other planners, reviewers and staff reported no relevant financial relationships.

All relevant financial relationships have been mitigated.

Highlights of WCLC 2021

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PL01.02 - Disparities in Lung Cancer Care Across the Population

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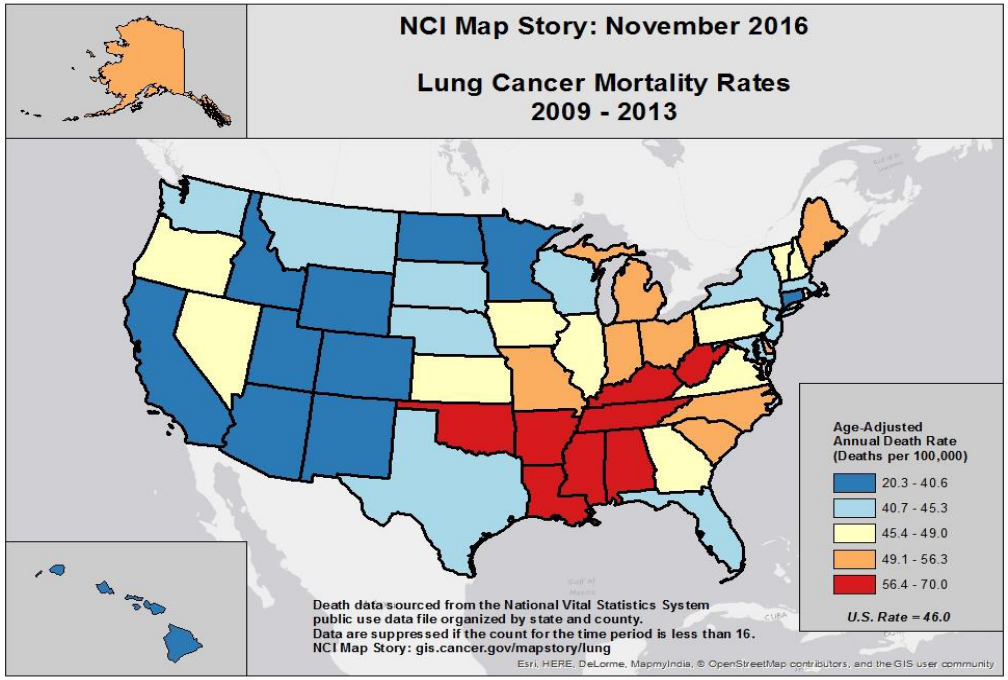
Presenter DISCLOSURES

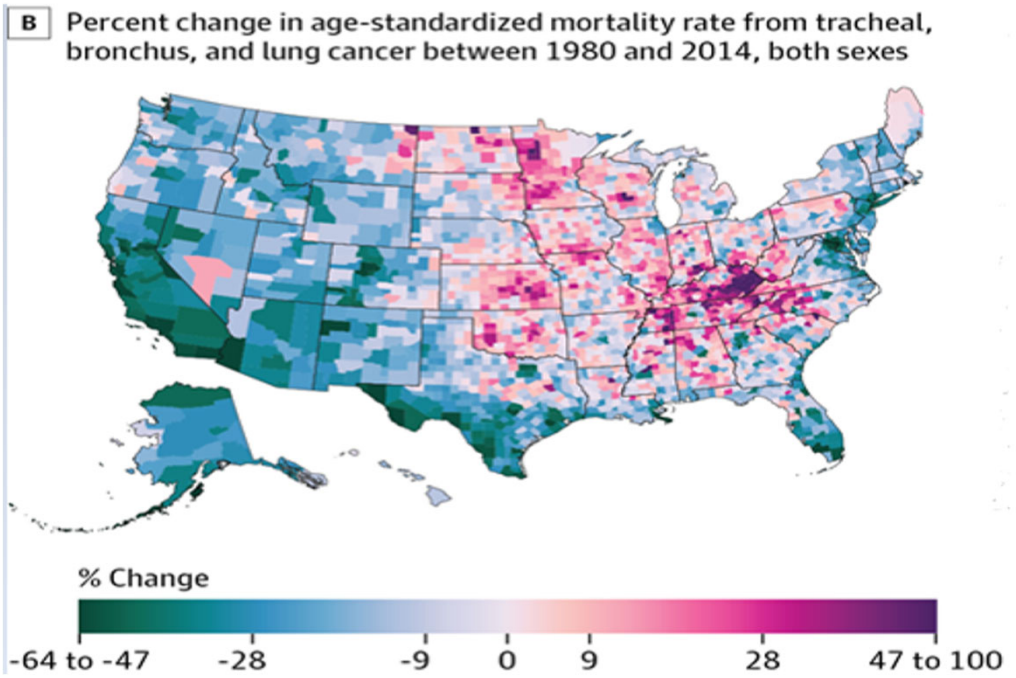
Commercial Interest	Relationship(s)
American Cancer Society	Consultant
Association of Community Cancer Centers	Consultant
AstraZeneca	Consultant
Biodesix	Speaker
Eli Lilly	Stock Ownership
Genentech/Roche	Consultant
Gilead Sciences	Stock Ownership
GO2 Foundation	Scientific Leadership Board
Lungevity Foundation	Consultant
Pfizer	Stock Ownership
Triptych Healthcare Partners	Consultant
Oncobox Devices, Inc	Founder; Patent Holder

Objectives

- Describe the multi-level framework of healthcare disparities.
- Emphasize the need for a comprehensive, proactive approach to corrective interventions.
- Exemplify innovative programmatic solutions to the problem of inequitable lung cancer care delivery.
- Highlight social policy interventions as the greatest levers.

Lung Cancer In the United States:
A Tale of Geographic Disparity





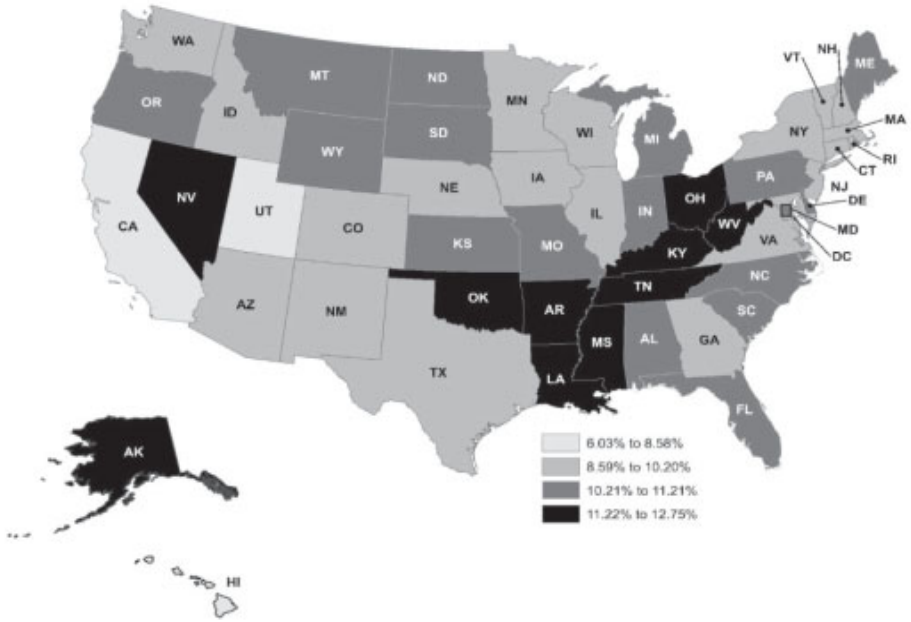
Mokdad AH, et al. JAMA. 2017. PMID: 28118455

Overview of disparities

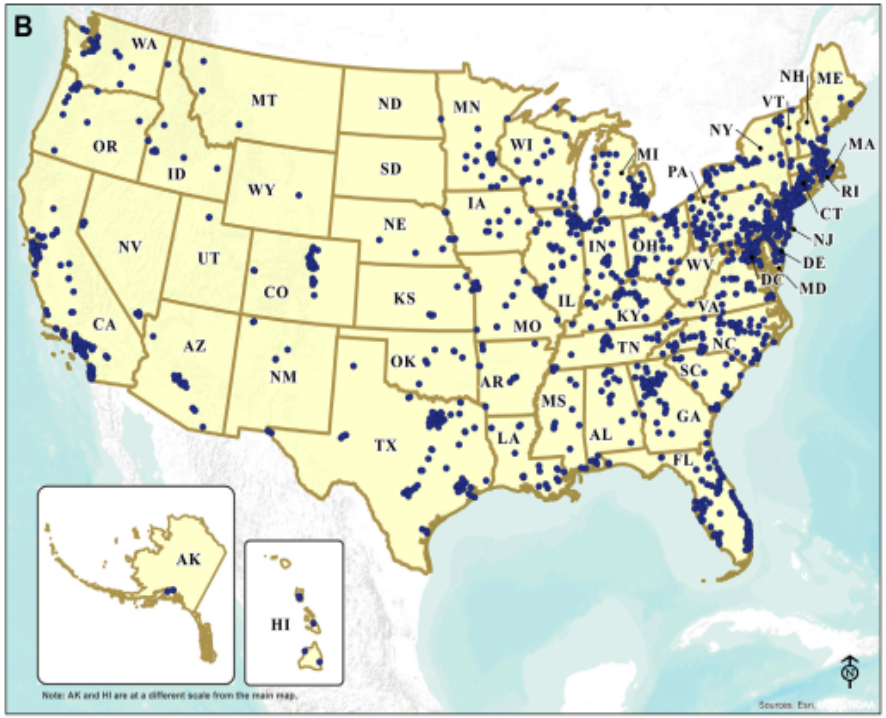
- **Health disparities:** *'differences in the incidence, prevalence, mortality, and burden of disease, and other adverse health conditions that exist among specific population groups….' (NIH, 2014).**
- **'Avoidable (preventable) difference'**
  - Patterns are predictable and similar;
  - Emerge or worsen with discovery and innovation;
  - Multi-level etiology- patient, provider, organizational and social policy.
- **Multi-level clustering leads to geographic disparities.**
- **Overcoming (preventing, eliminating, narrowing) them requires active intervention**

*https://www.nhlbi.nih.gov/health/educational/healthdisp/ Accessed on July 12, 2021.

Lung Cancer Burden v CT Screening: State-Level

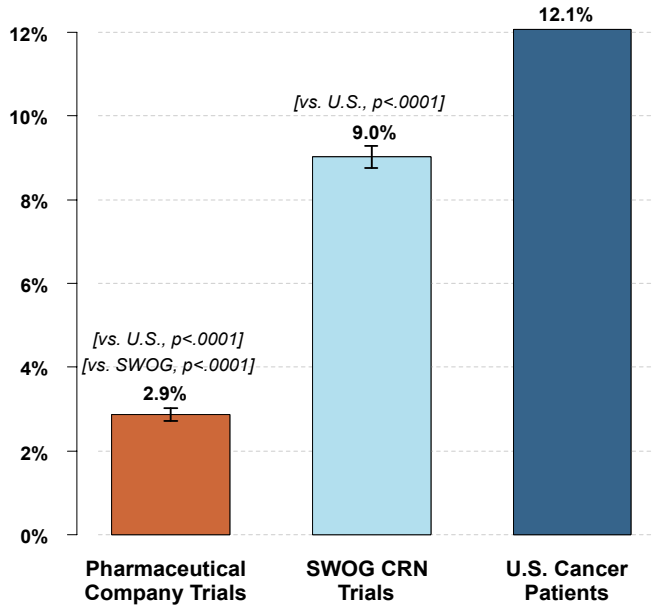


Fedewa SA, et al. J Natl Cancer Inst. 2020. PMID: 33176362.

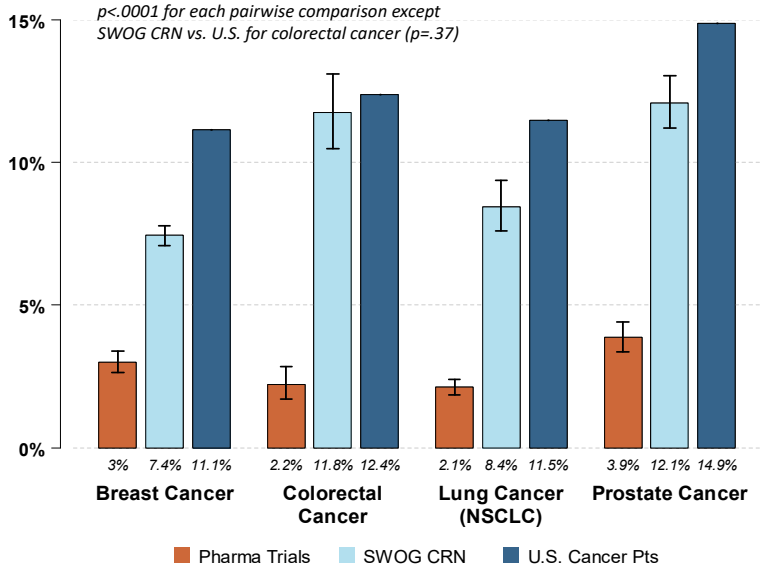


Sahar L, et al. Chest. 2021. PMID: 32888933.

If ‘the best treatment is a clinical trial’….



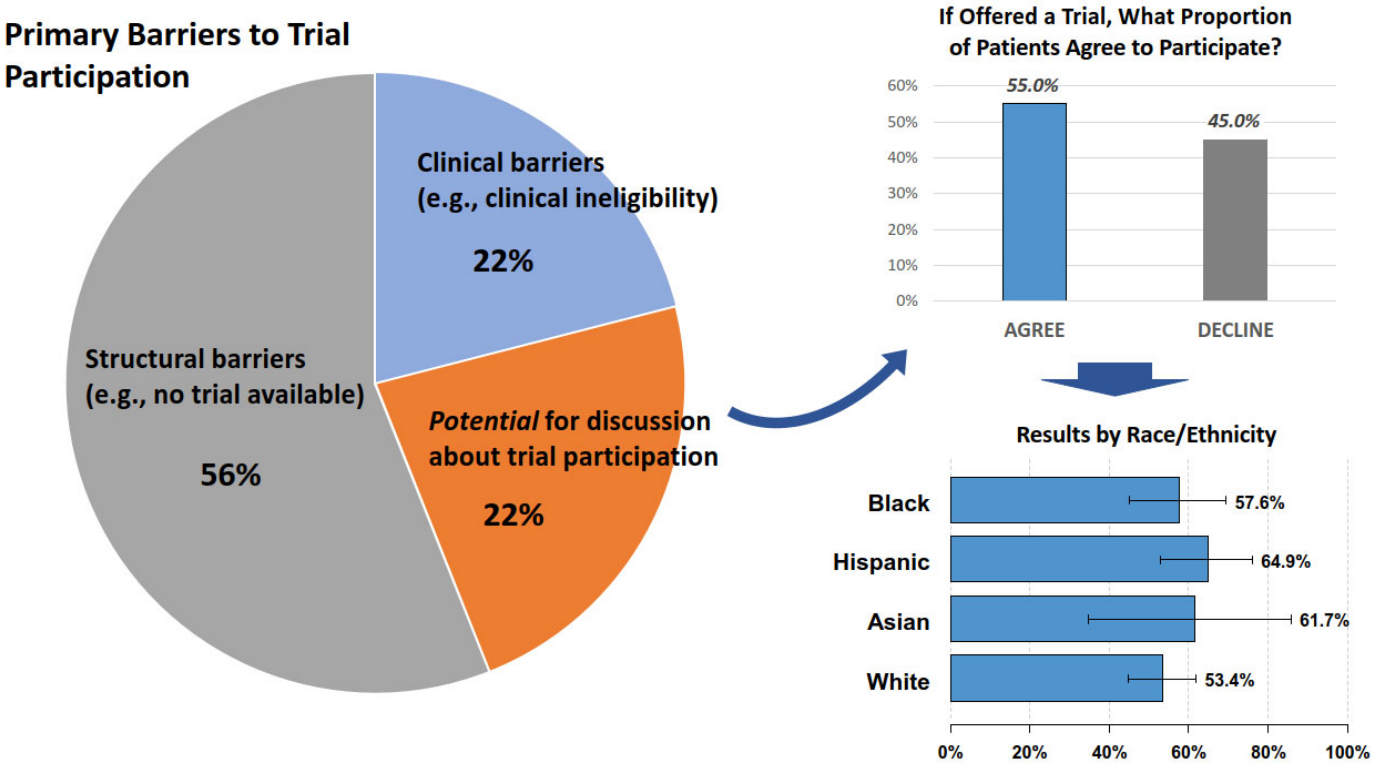
Proportion of Black patients by setting



Proportion of Black patients by setting for common cancers

Unger JM, Hershman DL, Osarogiagbon RU, et al. Representativeness of Black Patients in Cancer Clinical Trials Sponsored by the National Cancer Institute Compared With Pharmaceutical Companies. JNCI Cancer Spectr. 2020.

The *Real* Barriers to Clinical Trials Participation



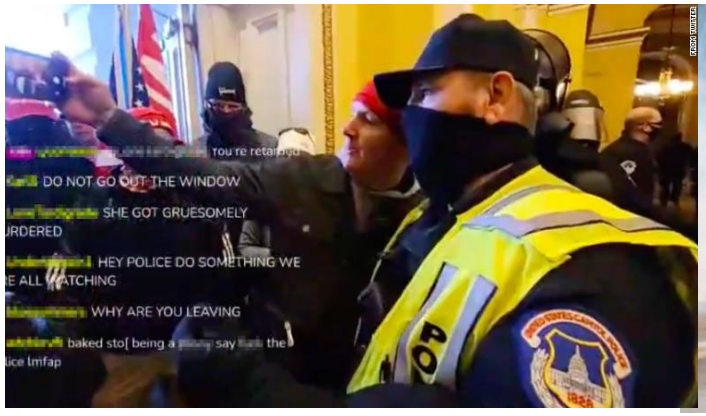
Osarogiagbon RU, Sineshaw HM, Unger JM, Acuña-Villaorduña A, Goel S. Am Soc Clin Oncol Educ Book. 2021 Mar;41:1-13. PMID: 33830825.

TAKE HOME MESSAGE

1. Healthcare (justice, and other) disparities are a reversible sociopolitical construct;

2. For corrective intervention: social policy> organization> provider> individual.

June 2, 2020: National Guard troops deployed to the Lincoln Memorial during protests over the murder of George Floyd



January 6, 2021: inside the Capitol, selfie with an insurrectionist.

June 2, 2020 / January 6, 2021.

IMpower010: Characterization of Stage IB-IIIA NSCLC Patients by Type and Extent of Therapy Prior to Adjuvant Atezolizumab

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[1] New York-Presbyterian Hospital, Weill Cornell Medicine, New York, NY; [2] Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [3] Tongji University Affiliated Shanghai Pulmonary Hospital, Shanghai, China; [4] Swedish Cancer Institute, Seattle, WA; [5] GBUZ Saint Petersburg Clinical Research Center of Specialized Types of Care (Oncology), Saint Petersburg, Russia; [6] Principal Military Clinical Hospital n.a. N.N. Burdenko, Moscow, Russia; [7] Lungenfachklinik Immenhausen, Immenhausen, Germany; [8] Kyiv Railway Clinical Hospital #3 of Branch Health Center of the PJSC Ukrainian Railway, Kyiv, Ukraine; [9] Centre Léon Bérard, Lyon, France; [10] Krankenhaus Martha-Maria; Halle-Dolau gGmbH, Halle, Germany; [11] Beijing Cancer Hospital, Beijing, China; [12] First Affiliated Hospital of Soochow University, Jiangsu, China; [13] Centro Hospitalar de Lisboa Norte E.P.E – Hospital Pulido Valente, Lisbon, Portugal; [14] Chonnam National University Medical School, and CNU Hwasun Hospital, Jeollanam-do, South Korea; [15] F. Hoffmann-La Roche Ltd., Basel, Switzerland; [16] Roche (China) Holding Ltd, Shanghai, China; [17] Genentech Inc, South San Francisco, CA; [18] Stanford University School of Medicine/Stanford Cancer Institute, Stanford, CA

IASLC 2021 World Conference on Lung Cancer
SEPTEMBER 8 - 14, 2021 I WORLDWIDE VIRTUAL EVENT

Disclosures

Ineligible company (formerly: Commercial interest)	**Relationship(s)**
NCI Moonshoot Grant 1 UG3 CA244697-01	Research grant
DoD LC200388	Research grant
Johnson & Johnson, Lung Cancer Initiative	Contracted/support research
SUS Polyethnic-1000 Initiative New York Genome Center	Contracted/support research
AstraZeneca	Investigator-initiated clinical trial, advisory board
Merck	Investigator-initiated clinical trial

Introduction

- In stage II-III NSCLC, surgical resection followed by adjuvant chemotherapy is a standard of care[1]
- The Phase III IMpower010 trial (NCT02486718) is evaluating atezolizumab (anti–PD-L1) vs BSC after adjuvant chemotherapy in patients with completely resected NSCLC and, at the DFS interim analysis, met its primary endpoint
  - Adjuvant atezolizumab showed significant DFS benefit vs BSC in the PD-L1 TC ≥1% (per SP263) stage II-IIIA and the all-randomized stage II-IIIA populations[2]
  - The statistical significance boundary for DFS was not crossed in the ITT (all-randomized stage IB-IIIA) population
  - OS data were immature at this DFS interim analysis
- **Here we explored prior therapies, including surgery type, and their potential impact on DFS outcomes in patients receiving adjuvant atezolizumab or BSC in IMpower010**

BSC, best supportive care; DFS, disease-free survival; ITT, intent to treat; TC, tumor cells.

1. Hellyer JA, Wakelee H. *Thorac Surg Clin*. 2020;30:179-185; 2. Wakelee H, et al. *J Clin Oncol*. 2021;39(suppl 15):8500.

IMpower010 study design

Completely resected stage IB-IIIA NSCLC per UICC/AJCC v7

- Stage IB tumors ≥4 cm
- ECOG PS 0-1
- Lobectomy/pneumonectomy
- Tumor tissue for PD-L1 analysis

1-4 cycles cisplatin + pemetrexed, gemcitabine, docetaxel or vinorelbine

N=1280

R 1:1

No crossover

Atezolizumab *1200 mg q21d 16 cycles*

N=1005

BSC

Survival follow-up

Stratification factors

- Male vs female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

Primary endpoints

- Investigator-assessed DFS tested hierarchically:
  1. PD-L1 TC ≥1% (SP263) stage II-IIIA population
  2. All-randomized stage II-IIIA population
  3. ITT (all-randomized stage IB-IIIA) population

Both arms included observation and regular scans for disease recurrence on the same schedule.
IC, tumor-infiltrating immune cells. [a] Per SP142 assay. [b] Two-sided α=0.05.

Hierarchical statistical testing

DFS in PD-L1 TC ≥1% stage II-IIIA population[b]

If positive:

DFS in all-randomized stage II-IIIA population[b]

If positive:

DFS in ITT population[b] (all-randomized stage IB-IIIA)

If positive:

OS in ITT population[b] (all-randomized stage IB-IIIA)

- Endpoint was met at DFS IA
- Endpoint was not met at DFS IA, and follow-up is ongoing
- OS data were immature, and endpoint was not formally tested

Patient disposition and reasons for discontinuation prior to randomization

- A total of 1280 patients were enrolled
  - 1269 patients received chemotherapy
  - 275 patients discontinued prior to randomization
  - 1005 patients were subsequently randomized to atezolizumab or BSC

Study discontinuation reason, n (%)	Patients (n=275)
Withdrawal by subject	86 (31.3)
Disease relapse	54 (19.6)
Other	41 (14.9)
Adverse event	34 (12.4)
Death	19 (6.9)
Physician decision	18 (6.5)
Protocol deviation	18 (6.5)
Lost to follow-up	4 (1.5)
Symptomatic deterioration	1 (<1)

Clinical cutoff: January 21, 2021.

Patient, disease and treatment characteristics (ITT) Well Balanced

Characteristic	Atezolizumab (n=507)	BSC (n=498)	All patients (n=1005)
Median age (range), y	62 (33-83)	62 (26-84)	62 (26-84)
Sex, male, n (%)	337 (66.5)	335 (67.3)	672 (66.9)
ECOG PS 0 / 1, n (%)	273 (53.8) / 232 (45.8)	283 (56.8) / 214 (43.0)	556 (55.3) / 446 (44.4)
Histology, non-squamous, n (%)	328 (64.7)	331 (66.5)	659 (65.6)
PD-L1 by SP263, TC ≥1%, n (%)[a]	283 (57.4)	252 (51.9)	535 (54.6)
Stage, n (%)			
IB	65 (12.8)	58 (11.6)	123 (12.2)
IIA	147 (29.0)	148 (29.7)	295 (29.4)
IIB	90 (17.8)	84 (16.9)	174 (17.3)
IIIA	205 (40.4)	208 (41.8)	413 (41.1)
Mediastinal lymph node dissection, n (%)	402 (79.3)	409 (82.1)	811 (80.7)
Mediastinal lymph node sampling, n (%)	93 (18.3)	88 (17.7)	181 (18.0)
Regional lymph node status (pN), n (%)			
N0	183 (36.1)	169 (33.9)	352 (35.0)
N1	170 (33.5)	178 (35.7)	348 (34.6)
N2	154 (30.4)	151 (30.3)	305 (30.3)
Type of surgery, n (%)[b]			
Lobectomy	394 (77.7)	391 (78.5)	785 (78.1)
Pneumonectomy	77 (15.2)	83 (16.7)	160 (15.9)
Bilobectomy	31 (6.1)	19 (3.8)	50 (5.0)
Median (range) time from surgery to first atezolizumab treatment or BSC, mo	5.2 (2.4-7.7)	5.1 (2.3-8.0)	5.2 (2.3-8.0)
Chemotherapy treatment, n (%)			
Cisplatin-docetaxel	77 (15.2)	75 (15.1)	152 (15.1)
Cisplatin-gemcitabine	88 (17.4)	77 (15.5)	165 (16.4)
Cisplatin-vinorelbine	152 (30.0)	151 (30.3)	303 (30.1)
Cisplatin-pemetrexed	190 (37.5)	195 (39.2)	385 (38.3)

Clinical cutoff: January 21, 2021. [a] 26 patients in the ITT population had unknown PD-L1 status as assessed by SP263. [b] Subgroups with ≤10 patients are not shown.

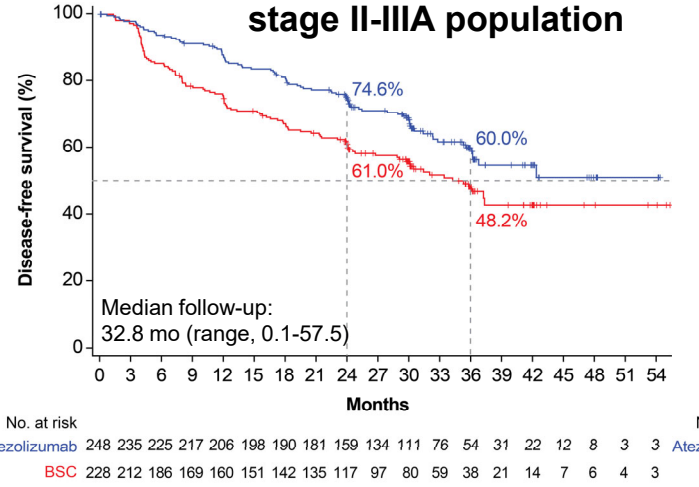
Chemotherapy treatment (randomized ITT population[a])

Chemotherapy treatment	All patients (n=1005)
Cisplatin-docetaxel	**n=152**
Received 4 cycles cisplatin, n (%)	**145 (95.4)**
Received 4 cycles docetaxel, n (%)	**144 (94.7)**
Cisplatin-gemcitabine	**n=165**
Received 4 cycles cisplatin, n (%)	**130 (78.8)**
Received 4 cycles gemcitabine, n (%)	**126 (76.4)**
Cisplatin-vinorelbine	**n=303**
Received 4 cycles cisplatin, n (%)	245 (80.9)
Received 4 cycles vinorelbine, n (%)	243 (80.2)
Cisplatin-pemetrexed	**n=385**
Received 4 cycles cisplatin, n (%)	341 (88.6)
Received 4 cycles pemetrexed, n (%)	344 (89.4)

Clinical cutoff: January 21, 2021. [a] Defined as all eligible patients enrolled in the enrollment phase who received ≥1 dose of chemotherapy (cisplatin, vinorelbine, docetaxel, gemcitabine, pemetrexed) and were subsequently randomized to atezolizumab or BSC.

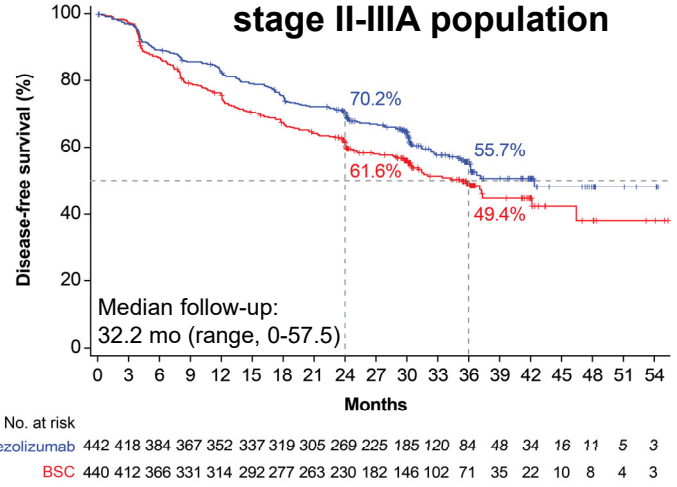
DFS in the PD-L1 TC ≥1%[a] stage II-IIIA, all-randomized stage II-IIIA and ITT populations (primary endpoint)

PD-L1 TC ≥1% stage II-IIIA population



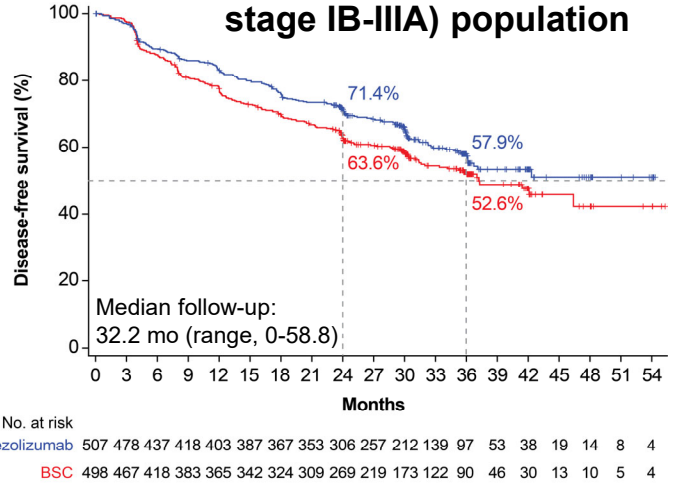
	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

All-randomized stage II-IIIA population



	Atezolizumab (n=442)	BSC (n=440)
Median DFS (95% CI), mo	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.79 (0.64, 0.96)	
P value[b]	0.02[c]	

ITT (randomized stage IB-IIIA) population



	Atezolizumab (n=507)	BSC (n=498)
Median DFS (95% CI), mo	NE (36.1, NE)	37.2 (31.6, NE)
Stratified HR (95% CI)	0.81 (0.67, 0.99)	
P value[b]	0.04[d]	

Clinical cutoff: January 21, 2021. [a] Per SP263 assay. [b] Stratified log-rank. [c] Crossed the significance boundary for DFS. [d] The statistical significance boundary for DFS was not crossed.

All-randomized stage II-IIIA population: DFS by disease and treatment characteristics

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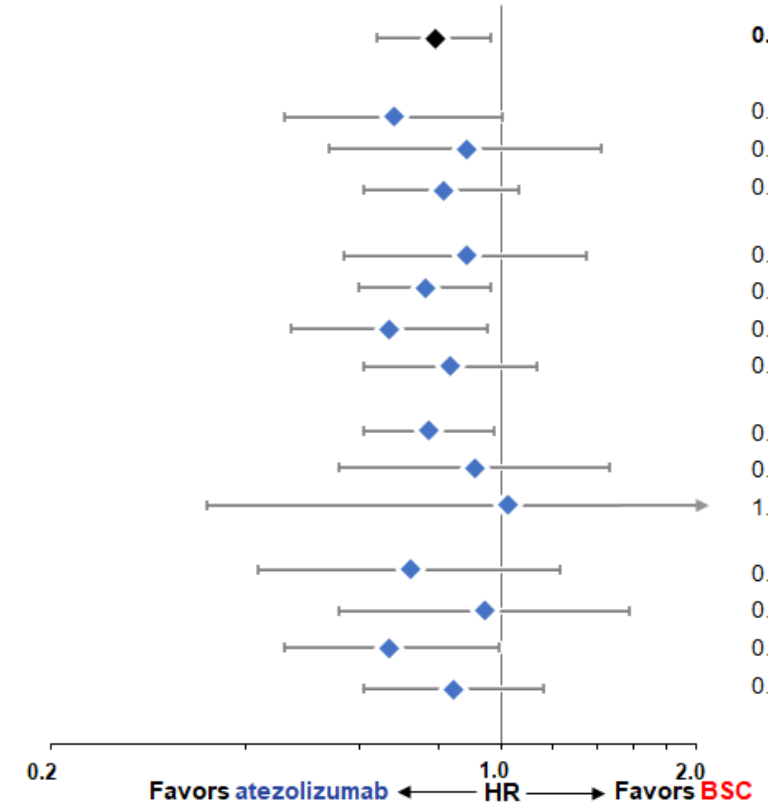
Subgroup	n	HR (95% CI)[a]	Median DFS, mo: Atezolizumab	Median DFS, mo: BSC
All patients	**882**	**0.79 (0.64, 0.96)**	**42.3**	**35.3**
Disease stage				
Stage IIA	295	0.68 (0.46, 1.00)	NE	NE
Stage IIB	174	0.88 (0.54, 1.42)	37.1	46.4
Stage IIIA	413	0.81 (0.61, 1.06)	32.3	29.7
Regional lymph node status (pN)				
N0	229	0.88 (0.57, 1.35)	NE	46.4
N+	653	0.76 (0.60, 0.96)	42.3	31.4
N1	348	0.67 (0.47, 0.95)	NE	36.0
N2	305	0.83 (0.61, 1.13)	30.2	24.1
Type of surgery[b]				
Lobectomy	675	0.77 (0.61, 0.97)	42.3	32.0
Pneumonectomy	150	0.91 (0.56, 1.47)	36.1	42.1
Bilobectomy	47	1.02 (0.35, 2.98)	36.7	NE
Chemotherapy regimen				
Cisplatin-docetaxel	124	0.72 (0.42, 1.23)	36.1	37.3
Cisplatin-gemcitabine	138	0.94 (0.56, 1.57)	36.1	46.4
Cisplatin-vinorelbine	271	0.67 (0.46, 0.99)	NE	37.0
Cisplatin-pemetrexed	349	0.84 (0.61, 1.16)	42.3	31.4



Clinical cutoff: January 21, 2021.
[a] Stratified for all patients; unstratified for all other subgroups.
[b] Subgroups with ≤10 patients are not shown.

Conclusions

- At the DFS interim analysis of IMpower010, atezolizumab showed statistically significant DFS benefit vs BSC in the PD-L1 TC ≥1% stage II-IIIA (HR, 0.66; 95% CI: 0.50, 0.88) and all-randomized stage II-IIIA (HR, 0.79; 95% CI: 0.64, 0.96) populations
- The main reasons patients were not randomized after enrollment were patient withdrawal and disease progression
- In the ITT population:
  - Study arms were well balanced with regard to disease stage, regional lymph node status, surgical intervention and chemotherapy regimen
  - The majority of patients had lobectomy, lymph node dissection and 4 cycles of adjuvant chemotherapy
  - The median time from surgery to start of randomized treatment or BSC was similar between study arms
- In this exploratory analysis, improved DFS was observed with adjuvant atezolizumab vs BSC in the PD-L1 TC ≥1% stage II-IIIA and all-randomized stage II-IIIA populations – across most disease stages, in patients with nodal involvement, and across most surgery types and chemotherapy regimens

S1619 A trial of neoadjuvant cisplatin-pemetrexed with atezolizumab in combination and maintenance for resectable pleural mesothelioma

Anne Tsao, M.D.[1], Lu Qian, MS[2], Jeremy Cetnar, M.D. M.S.[3], Boris Sepesi, M.D.[1], Daniel R. Gomez, M.D.[1], John M. Wrangle, M.D.[4], George R. Simon, M.D.[5,6], Frank E. Mott, M.D.[1], Richard D. Hall, M.D.[7], Rafael Santana-Davila, MD[8], Marianna Koczywas, MD[9], Mary W. Redman, Ph.D.[2], Karen Kelly, MD10

[1]MD Anderson Cancer Center, Houston, TX; [2]SWOG Statistics and Data Management Center, Seattle, WA; [3]Oregon Health & Science University, Portland, OR; [4]Medical University of South Carolina/MUSC MU-NCORP, Charleston, SC; [5]MD Anderson Cancer Center, Houston, TX (during conduct of trial) and [6]Moffitt Cancer Center, Morsani School of Medicine, Celebration, FL (current); [7]University of Virginia Cancer Center, Charlottesville, VA/ECOG-ACRIN; [8]Fred Hutchinson Cancer Research Center, Seattle, WA; [9]City of Hope Comprehensive Cancer Center, Duarte, CA; [10]UC Davis Comprehensive Cancer Center, Sacramento, CA

Funding: NIH/NCI grant awards U10CA180888, U10CA180819 and U10CA180820

Anne Tsao DISCLOSURES

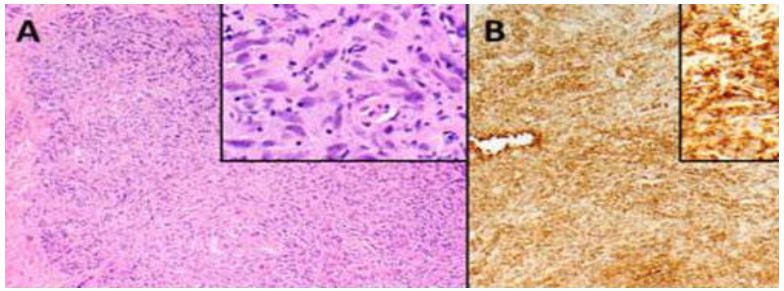
Ineligible Company (formerly: Commercial Interest)	**Relationship(s)**
BMS, Eli Lilly, Genentech, Roche, Novartis, Ariad, EMD Serono, Merck, Seattle Genetics, Astra-Zeneca, Boehringer-Ingelheim, Sellas Life Science, Daichi Sanyo, Takeda,	Advisory Boards
Eli Lilly, Millennium, Polaris, Genentech, Merck, Boehringer-Ingelheim, BMS, Ariad, Epizyme, Seattle Genetics	Research Grants

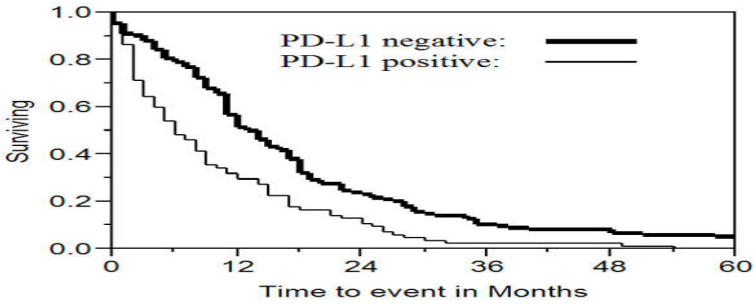
Background

- Malignant pleural mesothelioma (MPM) is an orphan disease with limited treatment options.

In the curable population, neoadjuvant chemotherapy, surgical, resection, and adjuvant radiation yield median OS 17-25 months.

- MPM is an immunogenic disease and the PD-L1 target has been identified in mesothelioma tumor cells and associated as a negative prognostic biomarker.[1]
- Mansfield et al. reports 40% PD-L1 expression in MPM (n=224) anti-human B7-H1 (clone 5H1-A3) antibody and associates IHC expression with more disease burden and worse survival (6 months vs 14 months, p<0.0001)





Rationale: We propose that adding anti-PD-L1 inhibitor to neoadjuvant cisplatin-pemetrexed and then maintenance immunotherapy after surgical resection and adjuvant radiation will enhance T-cell activation against microscopic disease and potentially increase overall survival outcomes.

[1]*Mansfield et al. Journal of Thoracic Oncology 9 S7-S52, 2014*

S1619 Neoadjuvant Mesothelioma Trial Schema

Resectable

Mesothelioma

Chemo-naïve

ESS – tissue and serum collection

N=24

Cisplatin
Pemetrexed*
+
Atezolizumab

If no progression = Resection

P/D or EPP depending on surgeon's decision

and then optional XRT

Maintenance Atezolizumab** (1200 mg IV Q3wk) x 1 year, monitor Q9 weeks x 1 year

*Cisplatin 75 mg/m^2 , Pemetrexed 500 mg/m^2 IV + Atezolizumab 1200 mg IV Q3wk

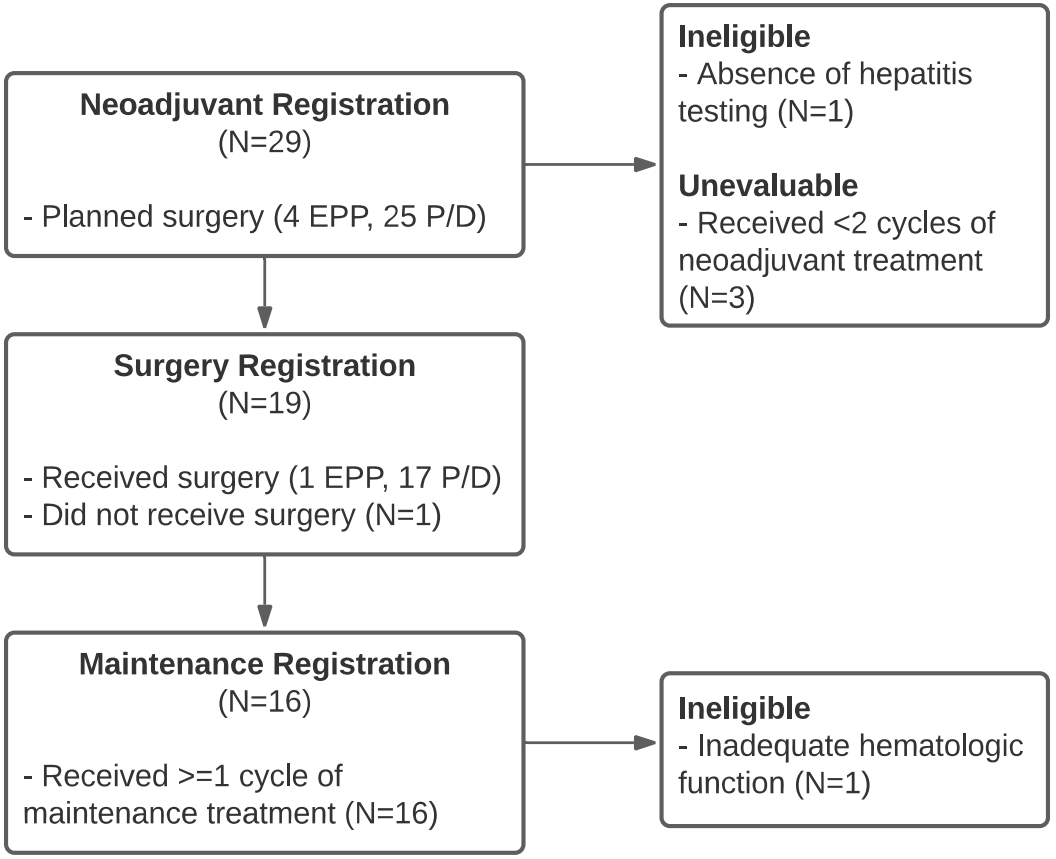
Serum blood for translational correlates obtained baseline, cycle 1-4, post-op, then prior to maintenance therapy, at time of PD

Primary endpoint: Evaluate the safety/tolerability and feasibility of neoadjuvant cisplatin-pemetrexed-atezolizumab, followed by surgery +/- radiation, followed by adjuvant maintenance atezolizumab.

- **Accrual goal**: 24 evaluable patients (12 EPP, 12 P/D)
  - Evaluable is defined as if they receive at least two cycles of the triplet neoadjuvant therapy (all three drugs). Patients who are not evaluable will be replaced. Both cohorts will be open in parallel.
- Regimen considered safe/tolerable if no patients experience a Grade 4-5 immune-related adverse event.
- Feasible/safety was defined as no Grade 4-5 immune-related adverse event; feasible if 18/24 (75%) received at least one dose of maintenance therapy.
- Analyses will separately evaluate patients who receive P/D and those who receive an EPP for their surgical procedure.
- It was anticipated that a total of 28 patients will need to be registered in order to accrue 24 eligible and evaluable patients.

Consort Diagram Enrollment

28 eligible patients (Nov 2017 - May 2020)
25 received at least 2 cycles of CPA
18 underwent surgery
15 received maintenance atezolizumab



Preliminary Outcomes

- 21 patients completed neoadjuvant therapy but seven patients did not proceed to resection.
  - 2 toxicity, 4 disease progression, 1 death (sepsis associated with non-immune related renal and respiratory failure)
- 18 patients with SD or PR proceeded to surgical resection
  - 17 received a P/D and 1 EPP.
  - 1 patient did not receive protocol-specified surgery due to PD.
  - Post-operatively, 1 patient had a fatal CVA.
- 16 patients registered to receive maintenance atezolizumab for 1 year
  - 1 patient was ineligible due to inadequate hematologic function.
- Three patients remain ongoing with maintenance atezolizumab therapy.

Neoadjuvant therapy common TRAE and AE of interest

AE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acute Renal Injury*				1	
Anemia	5	5	2		
Anorexia	7	4			
Constipation	5	2			
Creatinine increase	5	1			
Diarrhea			1		
Dysgeusia	3	2			
Fatigue	10	5			
Febrile Neutropenia			1		
Hyponatremia	4		1		
Infusion related reaction		3			
Nausea	9	10	1		
Neutropenia	4	4	3		
Pneumonitis*				1	
Respiratory failure*				1	
Sepsis*					1
Vomiting	4	2	1		

*same patient

Maintenance therapy common TRAE and AE of interest

AE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Adrenal insufficiency		1			
Anemia	1				
Anorexia	2	1			
Constipation	2				
Creatinine increase	1	1			
Diarrhea	1				
Fatigue	5	1			
Hypotension			1		
Hypothyroidism	1	1			
Infusion related reaction		1			
Nausea	2	1			
Rash	2				
Vomiting	1				

S1619 Preliminary Take Home Message

- 4 cycles of neoadjuvant cisplatin-pemetrexed-atezolizumab successfully delivered in 21 eligible and evaluable patients.
  - 18 patients with radiographic SD or PR proceeded to surgical resection
  - 16 patients were able to proceed to maintenance atezolizumab
- To date, no delayed treatment related adverse events > grade 3 have been reported.
- There was no new safety signal from the CPA regimen nor atezolizumab maintenance therapy.
- Three patients remain ongoing with maintenance atezolizumab therapy.
- Additional efficacy data will be updated at time of Sept presentation.
- This trial highlights the challenging nature of neoadjuvant therapy trials in this patient population.

Highlights of WCLC 2021

Kristin Higgins, MD
Department of Radiation Oncology
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IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

International Association for the Study of Lung Cancer (IASLC) Study of the Impacts of COVID-19 on International Lung Cancer Clinical Trials

Matthew P. Smeltzer PhD, Paul A. Bunn MD, Russ Clark, Renee Arndt, Clayton Pruett*, Upal Basu Roy PhD MPH, Fred R. Hirsch MD PhD, Tetsuya Mitsudomi MD, Heather A. Wakelee MD, Giorgio V. Scagliotti MD PhD

Matthew P. Smeltzer
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IASLC Global Clinical Trial Survey: Introduction

Clinical trials are vitally important for advancing novel therapies and improving care for persons with lung cancer.

The COVID-19 pandemic created major barriers to enrollment and completion of clinical trials.

We surveyed investigators and collected enrollment data for worldwide lung cancer trials before (2019) and during (2020-2021) the pandemic.

IASLC Global Clinical Trial Survey Methods

Data Collection Survey evaluated aggregate monthly enrollment for international lung cancer trials from 2019-2020.

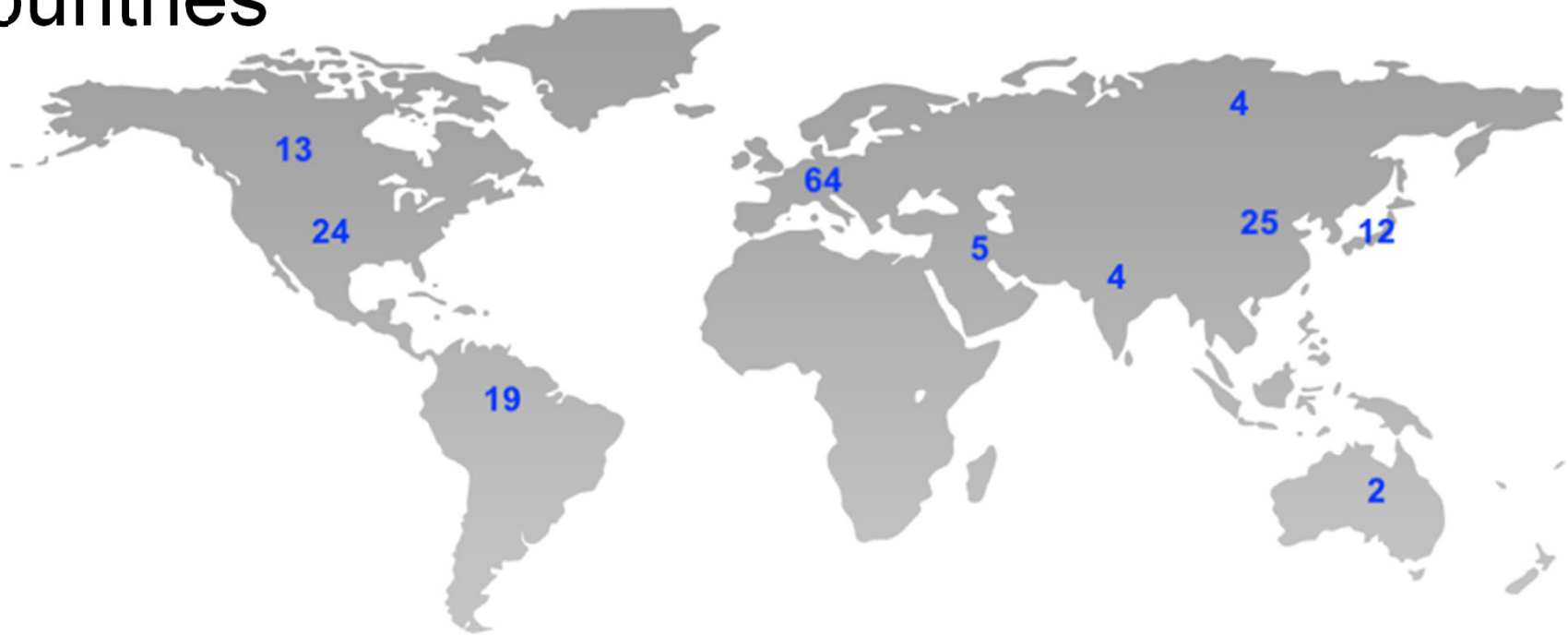
- We estimated Incidence Rate Ratios (IRR) with 95% confidence intervals (CI) by Generalized Estimating Equations.

Action Survey to assess the impact of COVID-19 on the conduct of clinical trials and identified mitigation strategies used.

- 64-questions, distributed by email to select international clinical trial sites

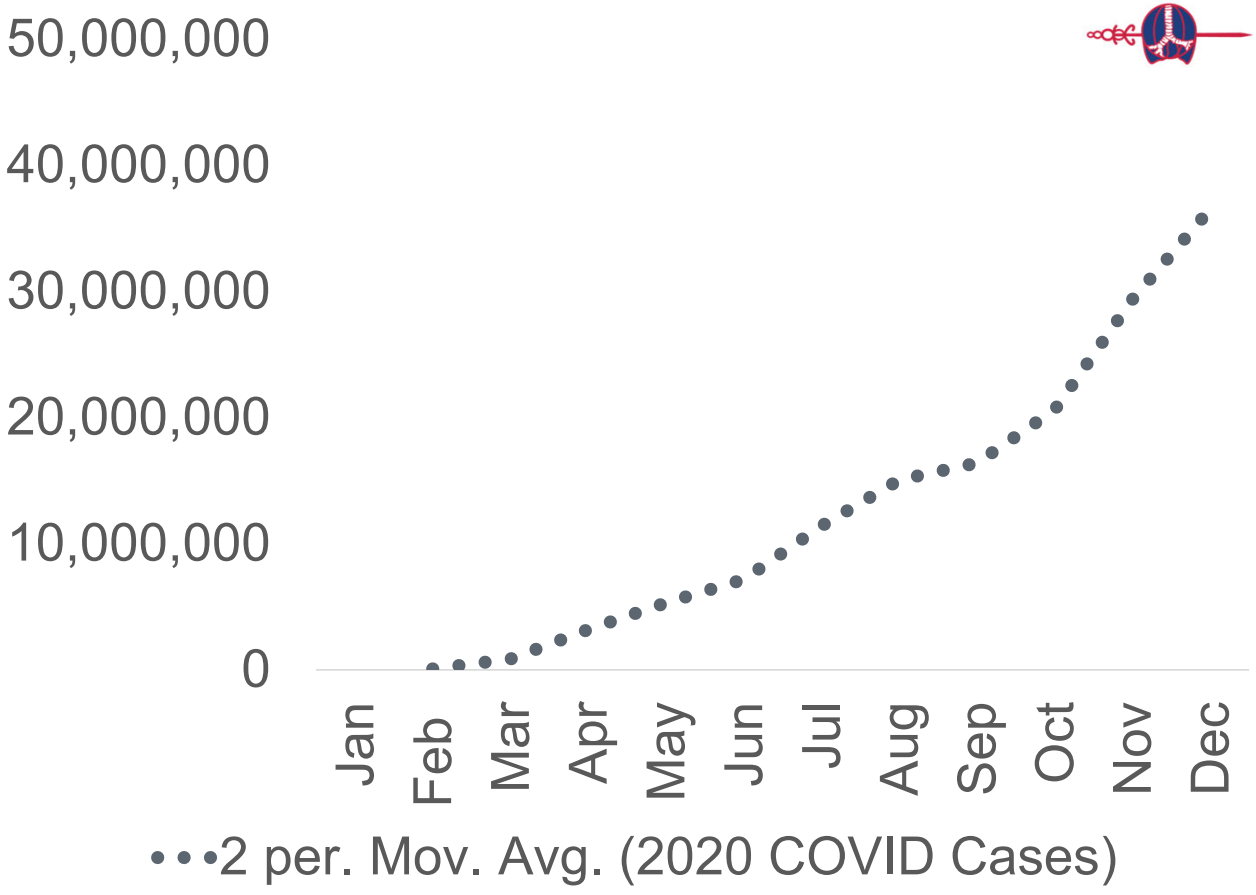
Global Lung Cancer Clinical Trial Enrollment Results

173 Clinical Sites 171 Trials 45 Countries

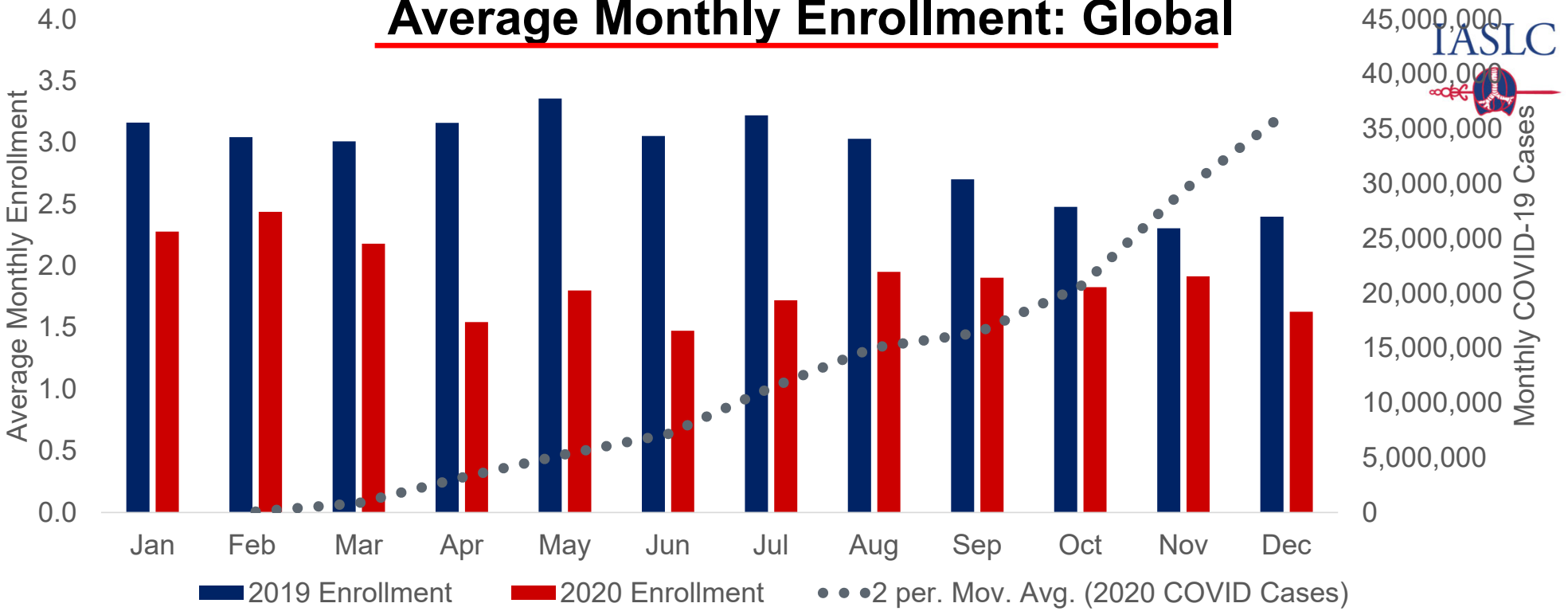


How did the Pandemic Impact Trial Enrollment?

- **Monthly COVID-19 cases increased for all of 2020**
- **We compared monthly enrollment in 2019 vs. 2020 from the 171 clinical trials.**

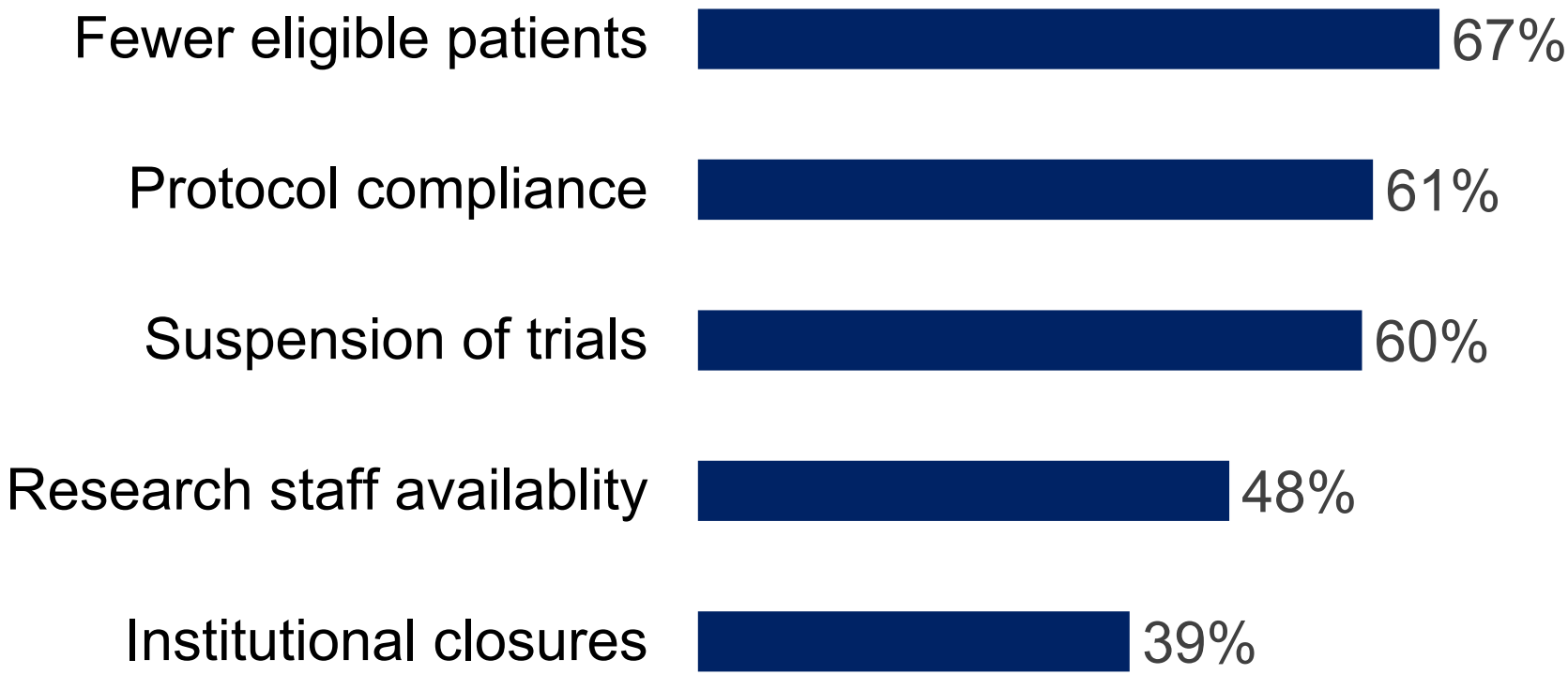


Average Monthly Enrollment: Global



- **COVID-19 cases increased consistently for all of 2020,** Enrollment declined by 43% from 2019 to 2020 (IRR: 0.57 [CI: 0.37, 0.88]) p=0.0115), with the most dramatic decrease April-August.
- **however the impact on trial enrollment was significantly less in October-December (p=0.0160).**

Most Frequent Challenges Faced by Sites



Patient Challenges and Concerns

IASLC

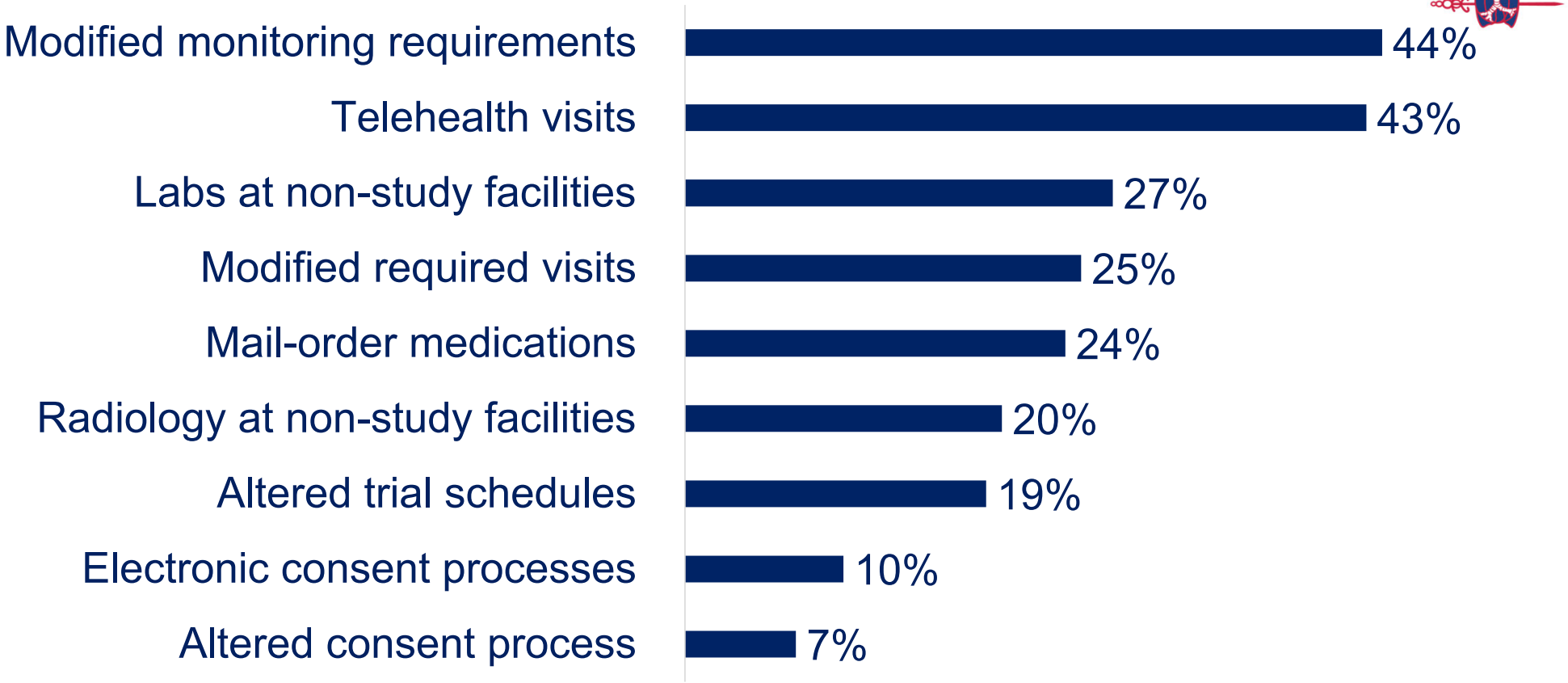
Challenges

- Willingness to visit site - 63%
- Ability to travel - 60%
- Access to trial site - 52%
- Exposure-related quarantine - 40%
- COVID-19 infection - 26%

Concerns

- Fear of COVID-19 infection - 83%
- Travel restrictions - 47%
- Securing transportation - 38%
- Lab/radiology access - 14%

Most Frequent Mitigation Strategies



Sites felt the most effective mitigation strategies were

Remote monitoring (64%)
Remote diagnostics (59%)
Telehealth visits (59%)
Modified Symptom monitoring (59%)

→ **Flexibility in "Place"**

Delayed visits (65%)
Delayed assessment (62%)
IRB changes (62%)

→ **Flexibility in "Time"**

Conclusions from the IASLC COVID-19 Clinical Trial Survey

- **The COVID-19 pandemic created many challenges causing reductions in lung cancer clinical trial enrollment.**
- **Mitigation strategies were employed, removing barriers**
- **Although the pandemic worsened, trial enrollment began to improve due in part to these strategies.**

Conclusions from the IASLC COVID-19 Clinical Trial Survey

More flexible approaches should be approved by sponsors, trial sites, and global regulatory bodies and should include at least:

- **Allowing telehealth visits (research staff & physicians)**
- **Allowing local testing including labs and scans**
- **Mailing experimental agents where possible**
- **Flexible alterations in trial schedules**

IASLC COVID-19 Clinical Trial Survey Take-Home Message

- **A more flexible approach -removing unnecessary barriers- may improve enrollment and access to clinical trials, even beyond the pandemic.**

Death from intercurrent disease after proton- versus photon-based chemoradiotherapy for NSCLC

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Proton therapy for LA-NSCLC

- Potential to reduce normal tissue exposure for a patient population with significant pre-existing comorbidities
- Clinical benefit remains uncertain

Objective

- To determine if proton therapy is associated with a reduced risk of death from intercurrent disease (DID), defined as death in the absence of disease progression

Methods

- Single institution retrospective review of patients with LA-NSCLC receiving either proton- (n=98) or photon- (n=89) based chemoradiation
- DID compared between groups using CIF and modelled with Fine-Gray method
- Overall survival (OS) assessed with Kaplan Meier method and Cox regression

Baseline

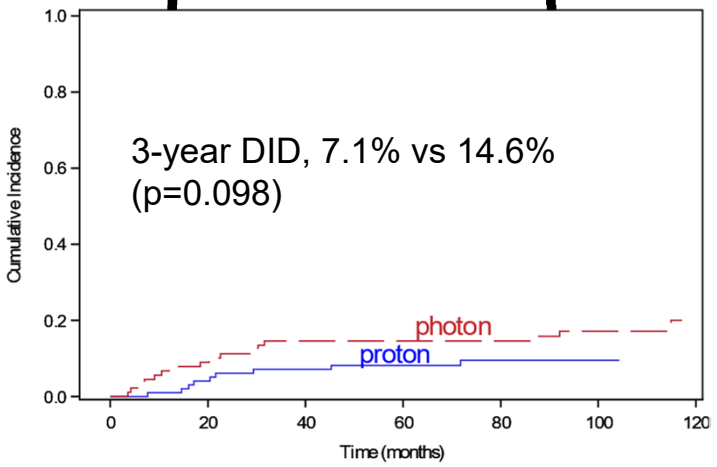
	Proton (n=98)	Photon (n=89)	P
Age (median, IQR)	69 (65-75)	62 (56-70)	**<0.001**
Women	51 (52%)	48 (53.9%)	0.80
ECOG PS			0.35
0	33 (33.7%)	37 (41.6%)	
1	55 (56.1%)	47 (52.8%)	
2	10 (10.2%)	5 (5.6%)	
Cardiovascular comorbidity	53 (54.1%)	31 (34.8%)	**0.008**
Pulmonary comorbidity	42 (42.9%)	39 (43.8%)	0.78
Smoking, pack-years (median, IQR)	40 (19-55)	30 (10-47)	**0.043**
AJCC Stage			0.15
IIA-B	1 (1%)	3 (3.4%)	
IIIA	67 (68.4%)	52 (58.4%)	
IIIB	28 (28.6%)	34 (38.2%)	
IV	2 (2%)	0 (0%)	
Year of treatment			**<0.001**
2008-2011	4 (4.1%)	42 (47.2%)	
2012-2016	94 (95.9%)	47 (52.8%)	
Radiation dose, Gy (median, IQR)	66.6 (66.6-66.6)	66.6 (66.6-70.2)	0.59
Radiation technique			-
IMPT (vs PSPT)	9 (9.2%)		
IMRT (vs 3DCRT)		68 (76.4%)	

Dose to organs at risk

Median, IQR	Proton (n=98)	Photon (n=89)	P
Heart			
Mean (Gy)	6.7 (4-11.2)	15 (6.2-22.5)	**<0.001**
V5 (%)	18.8 (12.8-30.2)	42.8 (23.5-72)	**<0.001**
V30 (%)	9.6 (5-15.8)	18.7 (6.1-31.7)	**0.001**
Total Lung			
Mean (Gy)	16.5 (12.9-19.1)	17.4 (14.5-19.7)	0.18
V5 (%)	35.9 (29.5-43.1)	48.2 (41.5-57.6)	**<0.001**
V20 (%)	29.7 (23.5-34.2)	28.7 (24.6-32.5)	0.51
Contralateral lung			
Mean (Gy)	0.97 (0.2-3.3)	5.9 (4.2-8.4)	**<0.001**
Esophagus			
Mean (Gy)	22.1 (16-30)	26.5 (21.4-34.2)	**0.003**
V50 (%)	25.7 (13.2-37.9)	27.7 (18.7-38.5)	0.15

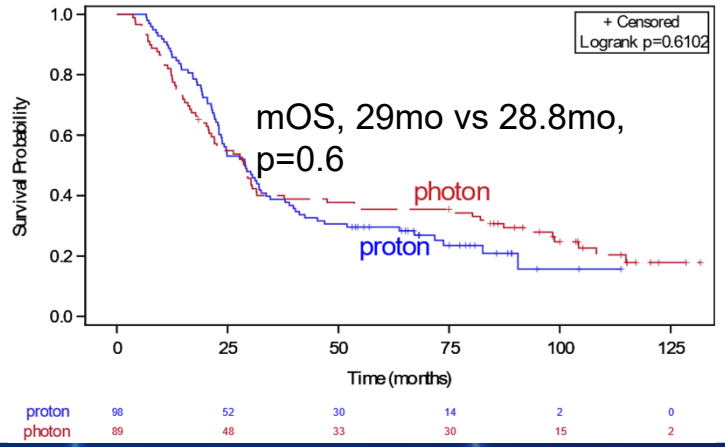
Death from intercurrent disease – protons vs photons

	Proton (n=98)	Photon (n=89)
Total Events	9	16
Respiratory failure (unrelated to cancer/toxicity)	3	7
OOH cardiopulm arrest	2	2
Undifferentiated sepsis	1	1
CRT toxicity	0	2
Unknown	3	4



No difference in OS or disease progression

- Disease progression: 3-yr cumulative incidence 68.4% vs 67.4%, p=0.9



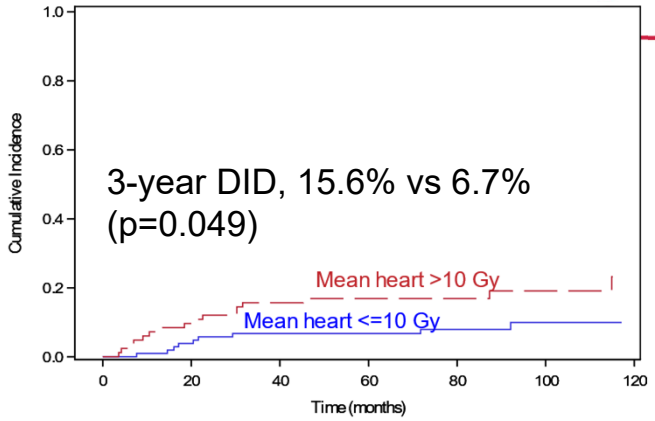
Death from intercurrent disease – UVA and MVA

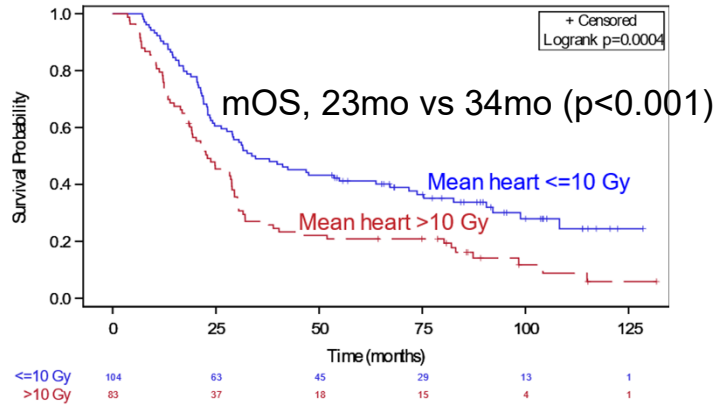
	Univariate		Multivariate	
	sHR (95% CI)	P	sHR (95% CI)	P
Age (y)	1.07 (1.03-1.11)	<0.001		
ECOG PS (stratum)	2.16 (1.21-3.85)	0.009		
Pulm comorbidity	1.80 (0.83-3.92)	0.14		
Year ('12-'16 vs '08-'11)	0.69 (0.3-1.58)	0.38		
Proton (vs photon)	0.50 (0.22-1.1)	0.09	0.25 (0.1-0.65) [1]	0.004
Mean heart dose (Gy)	1.05 (1.01-1.08)	0.007	1.06 (1.02-1.10) [1]	0.002
Mean esophageal dose (Gy)	1.04 (1.01-1.08)	0.015	1.05 (1.01-1.09)	0.019
Mean lung dose (Gy)				

[1] Paired with age and ECOG PS; 3 separate models

OS

	HR (95% CI)	P
Age (y)	1.04 (1.02-1.06)	<0.001
ECOG PS (stratum)	1.52 (1.1-2.08)	0.01
Pulm comorbidity	1.48 (1.05-2.09)	0.026
Gross tumor volume (cc)	1.001 (1.000-1.002)	0.033
Mean heart dose (Gy)	1.03 (1.01-1.04)	0.013





Summary

- Proton therapy associated with reduced normal tissue exposure and reduced risk of death from intercurrent disease after adjusting for age
- Endpoint may become more clinically relevant as risk of disease progression decreases with immunotherapy

Global Lung Cancer Deaths Attributable to Air Pollution

Oncologists United for Climate and Health

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Former Deputy Director of Inova Schar Cancer Institute and
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Air Pollution and Lung Cancer

Estimated Deaths

Globally (2017)

- 1.88 million total deaths
- 265,267 deaths attributable to air pollution
- 14.1 % of all lung cancer deaths
- One in seven lung cancer deaths

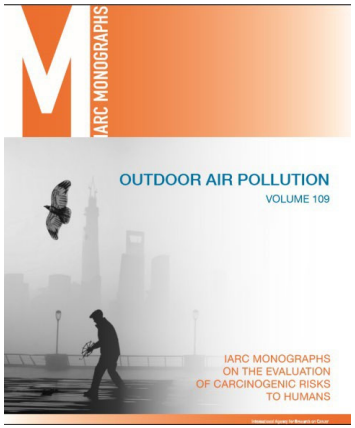
United States (2020)

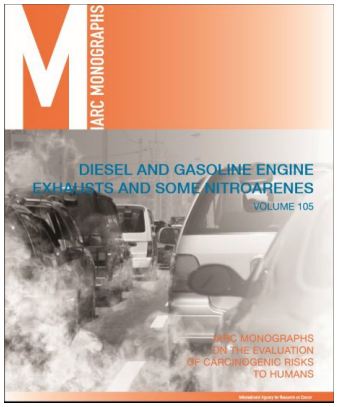
- 136,000 total deaths
- 6392 deaths attributable to air pollution
- 4.7% of all lung cancer deaths
- One in twenty lung cancer deaths

Turner, C. CA CANCER J CLIN 2020; 70:460-479

Air Pollution and Lung Cancer

IARC Hazard Assessment Group 1 Carcinogens





Volume 109 (2016)

Outdoor air pollution classified as human carcinogen Particulate matter in outdoor air pollution classified as human carcinogen

- Sufficient evidence for lung cancer
- Positive associations with urinary bladder cancer

Data includes general population studies/environmental levels of exposures.

Volume 105 (2014)

Diesel engine exhaust classified as human carcinogen

- Sufficient evidence for lung cancer
-Positive associations with urinary bladder cancer Data mostly from occupational exposure settings.

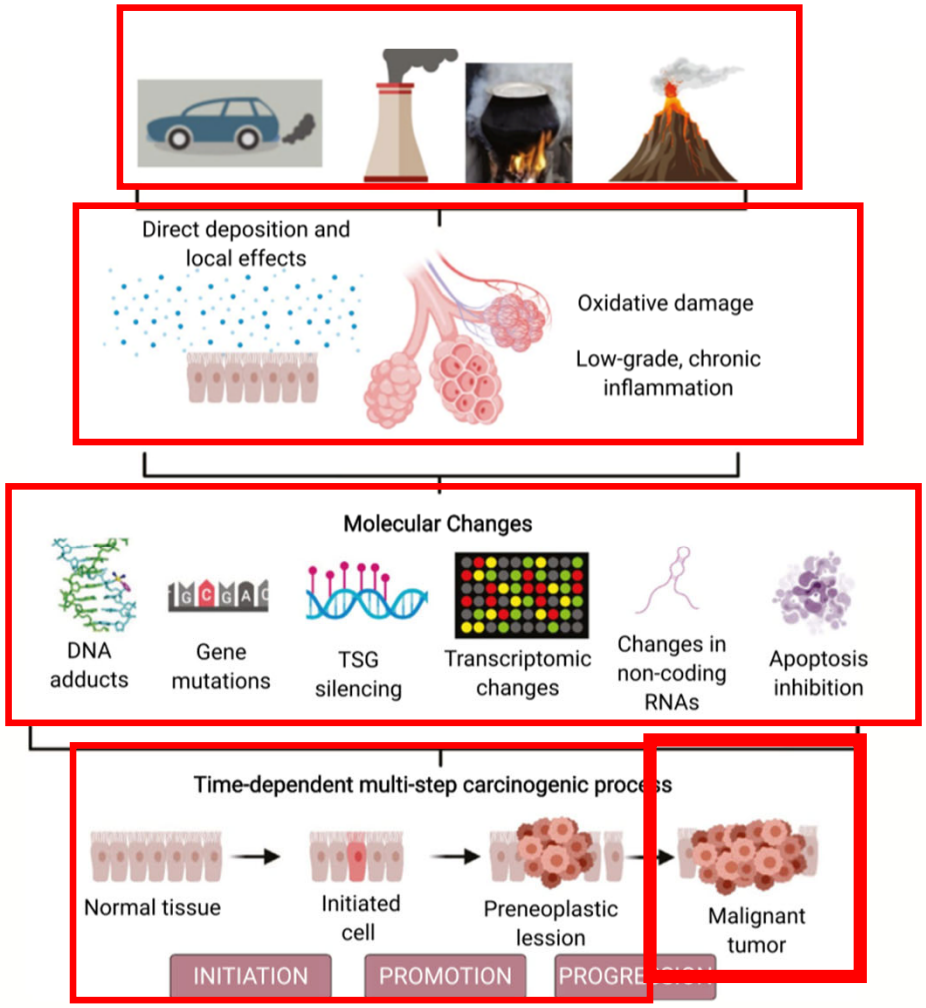
Uncertainty of effect at low dose environmental exposure levels. Less data for other cancers.

Volume 100e (2012)

Indoor emissions from household combustion of coal classified as human carcinogen (lung cancer)

International Agency for Research on Cancer

World Health Organization



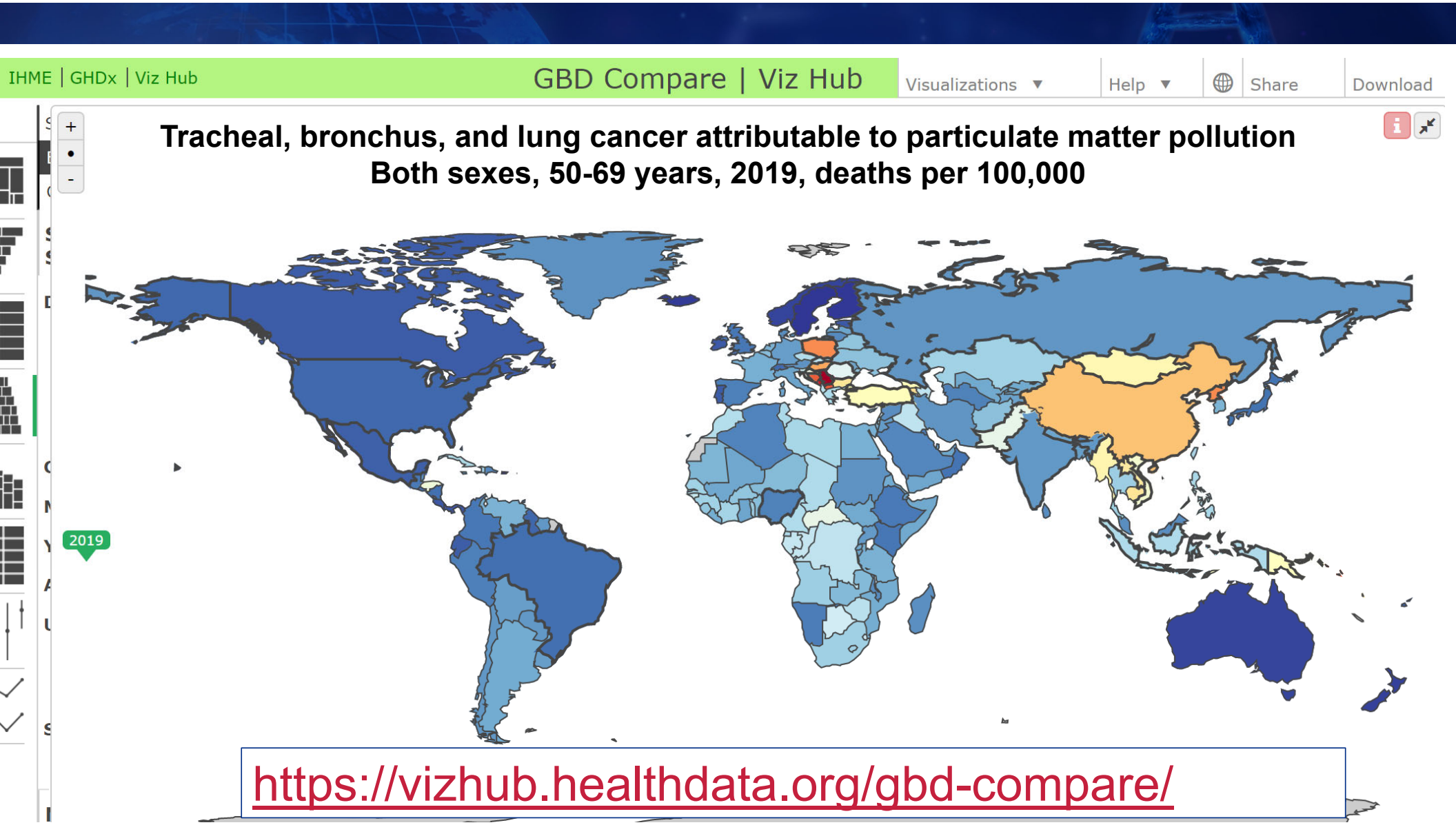
CANCER

FIGURE 4. Air Pollution-Related Cancer: Potential Pathways and Mechanisms. TSG indicates tumor-suppressor genes.

Turner, C. CA CANCER J CLIN 2020; 70:460–4

METHODOLOGY

- Estimates of deaths from lung cancer in countries across the globe
- Estimation of Particulate Matter (PM ≤ 2.5 microns) exposure
  - Satellite measurements and surface measurements used
  - Transport and geographical data
  - Aggregated gridded exposure concentrations to national-level population-weighted means
- Risk estimates were from studies of ambient air pollution, household air pollution, second-hand smoke exposure and active smoking
- Population-attributable fraction then estimated with combination of estimates of exposure and relative risk


IHME | GHDx | Viz Hub
GBD Compare | Viz Hub
Visualizations
Help
Share
Download
Tracheal, bronchus, and lung cancer attributable to particulate matter pollution
Both sexes, 50-69 years, 2019, deaths per 100,000
2019
https://vizhub.healthdata.org/gbd-compare/

Results

	Rank	Attributable Deaths/100,000 Ages 50 – 69 (Uncertainty Interval)	Adult smoking (%)	Particulate Matter 2.5 µm (µg/m³)
Serbia	1	36.88 (25.04-51.61)	41.7 %	24.3
Poland	5	27.97 (19.74-38.3)	28.0 %	16.9
China	8	24.63 (17.89-32.95)	24.7 %	34.7
Mongolia	13	19.71 (12.78-29.14)	26.5 %	46.4
Turkey	15	19.2 (12.93-27.08)	26.0 %	18.7
India	81	6.88 (4.9 -8.89)	11.1 %	51.9
United States	176	3.91 (1.89 – 6.58)	17.3 %	9.6

Sources of Particulate Matter Pollution

- Transportation
- Indoor cooking
- Energy sources: % of energy production from coal
  - Serbia 70%
  - Poland 74%
  - China 65%
  - Mongolia 80%
  - Turkey 35%
  - India 57%
  - US 19%

https://www.statista.com/statistics/689572/share-of-coal-energy-in-global-generation-by-country-and-type/

Conclusions

- Fourteen percent of all lung cancer deaths worldwide are attributable to air pollution and risk varies worldwide
- Sources of air pollution include fossil fuel plants, transit and indoor cooking modules
- Both smoking and air pollution are important causes of lung cancer
- Both need to be eliminated to help prevent lung cancer and save lives
- As lung cancer professionals, we can mitigate the effects of air pollution on causing lung cancer by speaking out for clean energy standards

Highlights from WCLC in advanced disease NSCLC and SCLC

Tom Stinchcombe

Duke Cancer Institute

IASLC

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

Conquering Thoracic Cancers Worldwide

CME ACCREDITED

Topics

- First-line non-small cell lung cancer: Poseidon
- Second-line small cell lung cancer: Atlantis
- Treatment of patients with brain metastases with chemotherapy and immunotherapy
  - Retrospective analysis of Checkmate 9LA
  - Prospective single arm phase 2 trial of chemotherapy and atezolizumab

Durvalumab ± Tremelimumab + Chemotherapy as First-Line Treatment for mNSCLC: Results from the Phase 3 POSEIDON Study

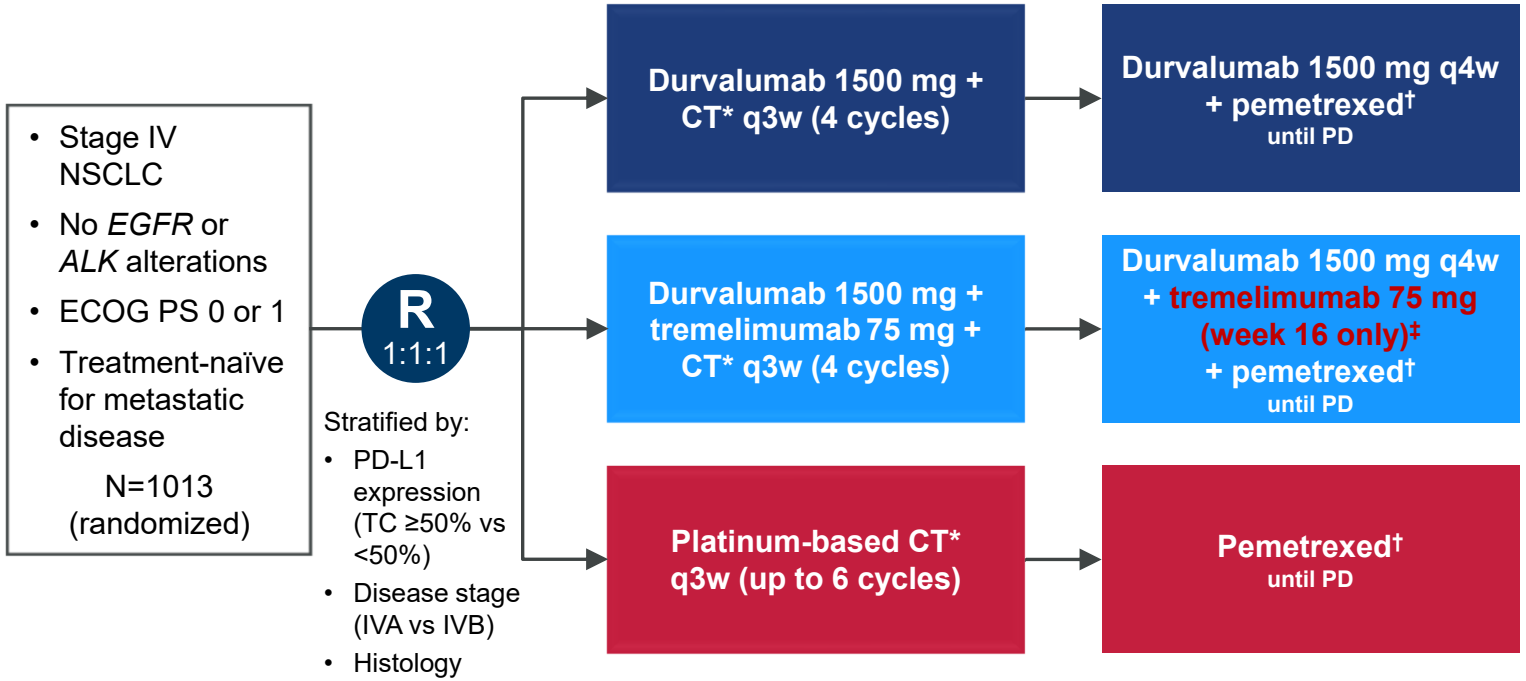
Melissa L Johnson,[1] Byoung Chul Cho,[2] Alexander Luft,[3] Jorge Alatorre-Alexander,[4] Sarayut Lucien Geater,[5] Konstantin Laktionov,[6] Aleksandr Vasiliev,[7] Dmytro Trukhin,[8] Sang-We Kim,[9] Grygorii Ursol,[10] Maen Hussein,[11] Farah Louise Lim,[12] Cheng-Ta Yang,[13] Luiz Henrique Araujo,[14] Haruhiro Saito,[15] Niels Reinmuth,[16] Xiaojin Shi,[17] Lynne Poole,[18] Solange Peters,[19] Edward B Garon,[20] Tony Mok[21]

[1]Sarah Cannon Research Institute, Tennessee Oncology, PLLCC, Nashville, TN, USA; [2]Yonsei Cancer Center, Seoul, Korea; [3]Leningrad Regional Clinical Hospital, St Petersburg, Russia; [4]Health Pharma Professional Research, Mexico City, Mexico; [5]Prince of Songkla University, Songkhla, Thailand; [6]Federal State Budgetary Institution "N.N. Blokhin National Medical Research Center of Oncology" of the Ministry of Health of the Russian Federation (N.N. Blokhin NMRCO), Moscow, Russia; [7]"Private Health Institution "Clinical Hospital" RZD-Medicine", St Petersburg, Russia; [8]Odessa Regional Oncological Dispensary, Odessa, Ukraine; [9]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [10]Acinus, Kropyvnytskyi, Ukraine; [11]Florida Cancer Specialists – Sarah Cannon Research Institute, Leesburg, FL, USA; [12]Queen Mary University of London, London, United Kingdom; [13]Chang Gung Memorial Hospital, Taoyuan City, Taiwan; [14]Instituto Nacional de Cancer-INCA, Rio de Janeiro, Brazil; [15]Kanagawa Cancer Center, Yokohama, Japan; [16]Asklepios Lung Clinic, Munich-Gauting, Germany; [17]AstraZeneca, Gaithersburg, MD, USA; [18]AstraZeneca, Cambridge, UK; [19]Centre Hospitalier Universitaire Vaudois, Lausanne University, Lausanne, Switzerland; [20]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [21]Chinese University of Hong Kong, Hong Kong, China

IASLC 2021 World Conference on Lung Cancer
SEPTEMBER 8 - 14, 2021 I WORLDWIDE VIRTUAL EVENT

POSEIDON Study Design

Phase 3, global, randomized, open-label, multicenter study



Primary endpoints
- PFS by BICR (D+CT vs CT)
- OS (D+CT vs CT)

Key secondary endpoints
- PFS by BICR (D+T+CT vs CT)
- OS (D+T+CT vs CT)
- OS in patients with bTMB ≥20 mut/Mb (D+T+CT vs CT)

Additional secondary endpoints
- ORR, DoR, and BOR by BICR
- PFS at 12 months
- HRQoL
- Safety and tolerability

*CT options: gemcitabine + carboplatin/cisplatin (squamous), pemetrexed + carboplatin/cisplatin (non-squamous), or nab-paclitaxel + carboplatin (either histology);
†Patients with non-squamous histology who initially received pemetrexed during first-line treatment only (if eligible); ‡Patients received an additional dose of tremelimumab post CT (5th dose)

BICR, blinded independent central review; BOR, best objective response; bTMB, blood tumor mutational burden; D, durvalumab; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; Mb, megabase; mut, mutations; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; q4w, every 4 weeks; T, tremelimumab; TC, tumor cell

Baseline Characteristics

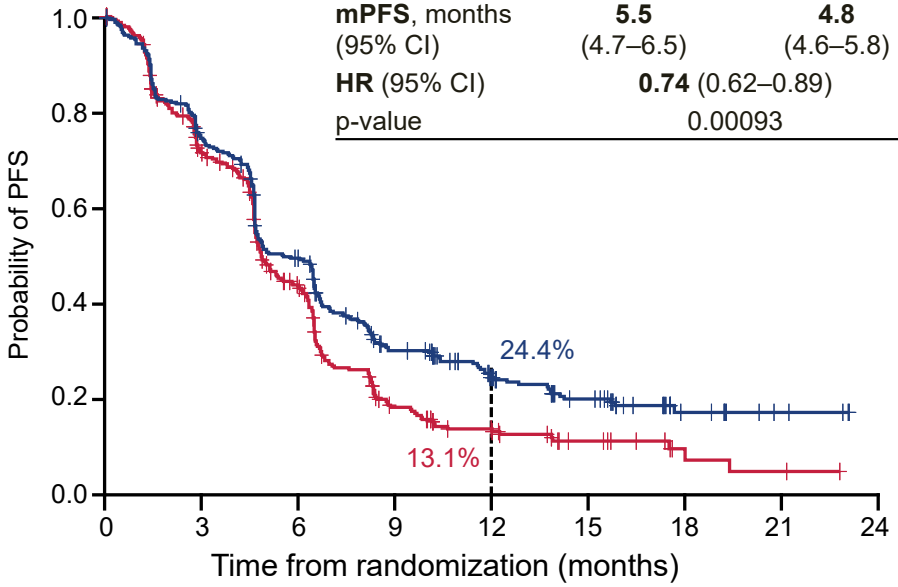
	D+CT (n=338)	D+T+CT (n=338)	CT (n=337)
Median age (range), years	64.5 (32–87)	63.0 (27–87)	64.0 (32–84)
Male, %	74.9	79.6	73.6
White / Asian / Other, %	53.8 / 36.4 / 9.8	60.7 / 29.3 / 10.1	53.1 / 38.0 / 8.9
Eastern Europe / Asia / North America / Western Europe / Other region, %	30.5 / 35.5 / 13.6 / 7.7 / 12.7	36.1 / 28.4 / 13.0 / 8.6 / 13.9	28.2 / 36.8 / 11.9 / 8.3 / 14.8
ECOG PS 0 / 1, %	32.2 / 67.8	32.5 / 67.5	35.3 / 64.4
Squamous / Non-squamous histology*, %	37.9 / 61.8	36.7 / 63.3	36.2 / 63.5
AJCC disease stage IVA / IVB*, %	50.3 / 49.4	50.6 / 48.8	49.3 / 50.4
Current or former / Never smoker, %	75.1 / 24.9	82.5 / 17.5	76.3 / 23.4
PD-L1 TC ≥50%* / TC ≥1%, %	27.8 / 66.3	29.9 / 63.0	28.8 / 61.4
CNS metastases, %	8.3	9.8	13.4
Liver metastases, %	18.3	20.4	23.7

*Stratification factors
AJCC, American Joint Committee on Cancer; CNS, central nervous system

Durvalumab + CT vs CT: PFS and OS

PFS

	D+CT	CT
Events, n/N (%)	253/338 (74.9)	258/337 (76.6)
mPFS, months (95% CI)	**5.5** (4.7–6.5)	**4.8** (4.6–5.8)
HR (95% CI)	**0.74** (0.62–0.89)	
p-value	0.00093	

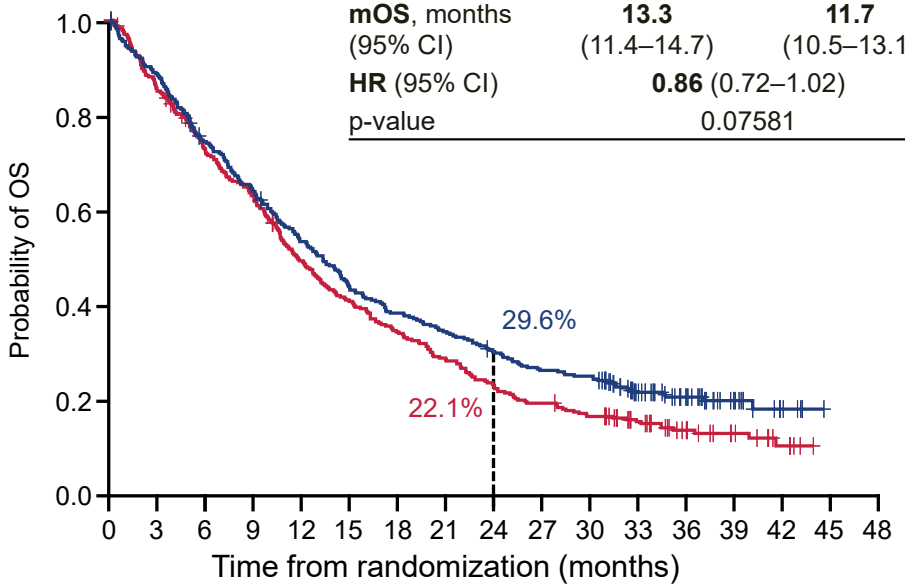


No. at risk									
D+CT	338	246	158	88	53	35	11	4	0
CT	337	219	121	43	23	12	3	2	0

- Median follow-up in censored patients at DCO: 10.3 months (range 0–23.1)

OS

	D+CT	CT
Events, n/N (%)	264/338 (78.1)	285/337 (84.6)
mOS, months (95% CI)	**13.3** (11.4–14.7)	**11.7** (10.5–13.1)
HR (95% CI)	**0.86** (0.72–1.02)	
p-value	0.07581	



No. at risk																	
D+CT	338	296	247	212	176	142	126	112	97	85	81	51	33	15	5	0	0
CT	337	284	236	204	160	132	111	91	72	62	52	38	21	13	6	0	0

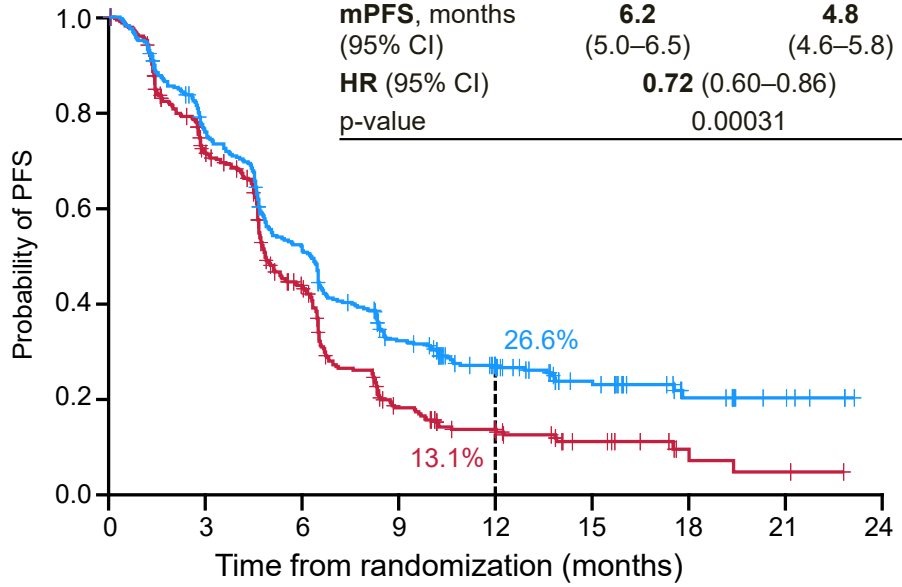
- Median follow-up in censored patients at DCO: 34.9 months (range 0–44.5)

DCO PFS FA: Jul 24, 2019; DCO OS FA: Mar 12, 2021
DCO, data cut-off; FA, final analysis; mOS, median OS; mPFS, median PFS

Durvalumab + Tremelimumab + CT vs CT: PFS and OS

PFS

	D+T+CT	CT
Events, n/N (%)	238/338 (70.4)	258/337 (76.6)
mPFS, months (95% CI)	**6.2** (5.0–6.5)	**4.8** (4.6–5.8)
HR (95% CI)	**0.72** (0.60–0.86)	
p-value	0.00031	

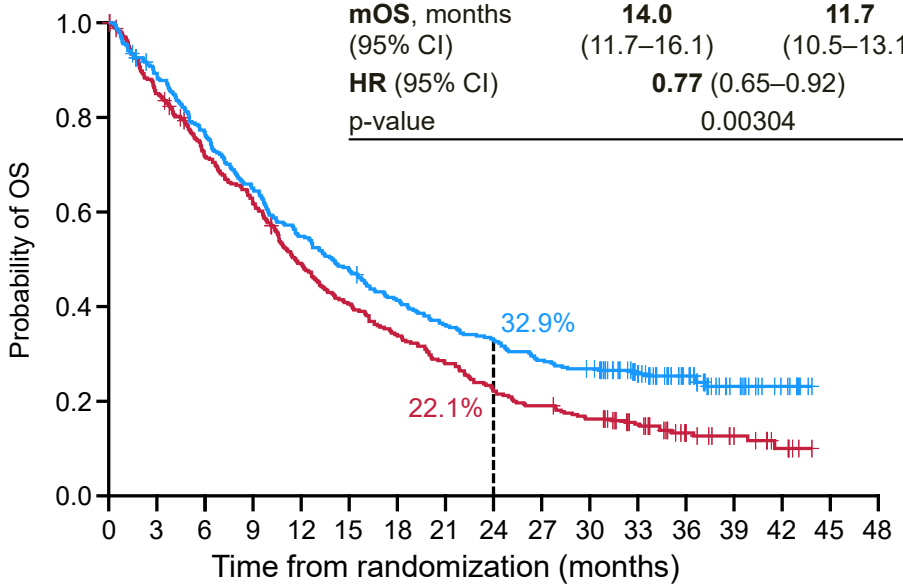


No. at risk									
D+T+CT	338	243	161	94	56	32	13	5	0
CT	337	219	121	43	23	12	3	2	0

- Median follow-up in censored patients at DCO: 10.3 months (range 0–23.1)

OS

	D+T+CT	CT
Events, n/N (%)	251/338 (74.3)	285/337 (84.6)
mOS, months (95% CI)	**14.0** (11.7–16.1)	**11.7** (10.5–13.1)
HR (95% CI)	**0.77** (0.65–0.92)	
p-value	0.00304	



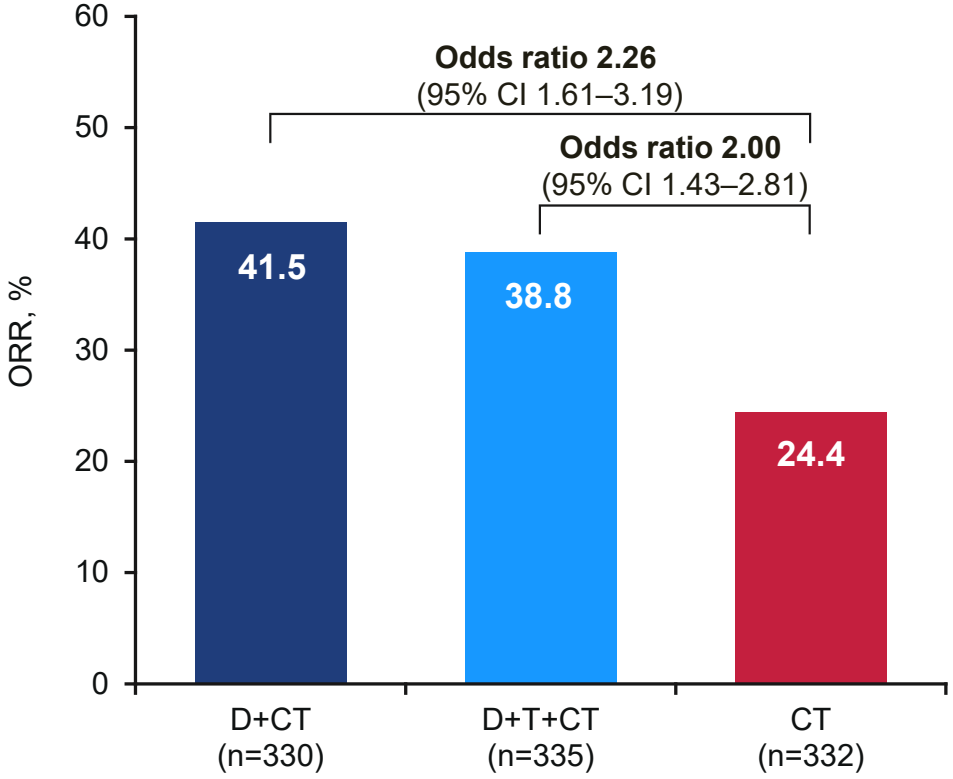
No. at risk																		
D+T+CT	338	298	256	217	183	159	137	120	109	95	88	64	41	20	9	0	0
CT	337	284	236	204	160	132	111	91	72	62	52	38	21	13	6	0	0

- Median follow-up in censored patients at DCO: 34.9 months (range 0–44.5)

DCO PFS FA: Jul 24, 2019; DCO OS FA: Mar 12, 2021

Confirmed Objective Response Rate and Duration of Response

ORR*



Duration of Response

	D+CT	D+T+CT	CT
Responders*, n	137	130	81
Median DoR, months (95% CI)	**7.0** (5.7–9.9)	**9.5** (7.2–NE)	**5.1** (4.4–6.0)
Remaining in response at 12 months, %	**38.9**	**49.7**	**21.4**

*Confirmed objective response by BICR assessed in patients with measurable disease at baseline; confirmation was not required per protocol (post-hoc analysis)
DCO PFS FA: Jul 24, 2019
NE, not estimable

Immune-Mediated Adverse Events (Grouped Terms)

	D+CT (n=334)		D+T+CT (n=330)		CT (n=333)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any imAE*, n (%)	64 (19.2)	23 (6.9)	111 (33.6)	33 (10.0)	17 (5.1)	5 (1.5)
Hypothyroid events	20 (6.0)	0	27 (8.2)	0	3 (0.9)	0
Pneumonitis	10 (3.0)	4 (1.2)	12 (3.6)	3 (0.9)	2 (0.6)	2 (0.6)
Rash	5 (1.5)	2 (0.6)	13 (3.9)	3 (0.9)	6 (1.8)	2 (0.6)
Hepatic events	11 (3.3)	8 (2.4)	12 (3.6)	7 (2.1)	0	0
Dermatitis	4 (1.2)	1 (0.3)	14 (4.2)	1 (0.3)	1 (0.3)	0
Colitis	4 (1.2)	1 (0.3)	13 (3.9)	5 (1.5)	0	0
Hyperthyroid events	4 (1.2)	1 (0.3)	9 (2.7)	0	1 (0.3)	0
Adrenal insufficiency	4 (1.2)	1 (0.3)	8 (2.4)	2 (0.6)	0	0
Rare/miscellaneous	1 (0.3)	1 (0.3)	11 (3.3)	3 (0.9)	2 (0.6)	1 (0.3)

imAEs leading to death occurred in 1 patient receiving D+CT (myocarditis) and in 2 patients receiving D+T+CT (pneumonitis in 1 patient; and hepatic, renal, and pancreatic events and myocarditis in 1 patient)

*imAEs with an incidence >2% in any treatment arm; an imAE was defined as an AE of special interest consistent with an immune-mediated mechanism of action, where there is no clear alternate etiology, and requiring the use of systemic steroids or other immunosuppressants and/or, for specific endocrine events, endocrine therapy. DCO OS FA: Mar 12, 2021
imAE, immune-mediated AE

Lurbinectedin/doxorubicin *versus* CAV or topotecan in relapsed SCLC patients: Phase III randomized ATLANTIS trial

Luis Paz-Ares[1]

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Tudor Eliade Ciuleanu[2], Alejandro Navarro[3], Andrea Fulop[4], Sophie Cousin[5], Laura Bonanno[6], Egbert Smit[7], Alberto Chiappori[8], Mª Eugenia Olmedo[9], Ildiko Horvath[10], Christian Gröhé[11], José Antonio López-Vilariño[12], Rafael Núñez[12], Antonio Nieto[12], Martin Cullell-Young[12], Noelia Vasco[12], Carmen Kahatt[12], Ali Zeaiter[12], Enric Carcereny[13], Jaromir Roubec[14], Konstantios Syrigos[15], Gregory Lo[16], Isidoro Barneto[17].

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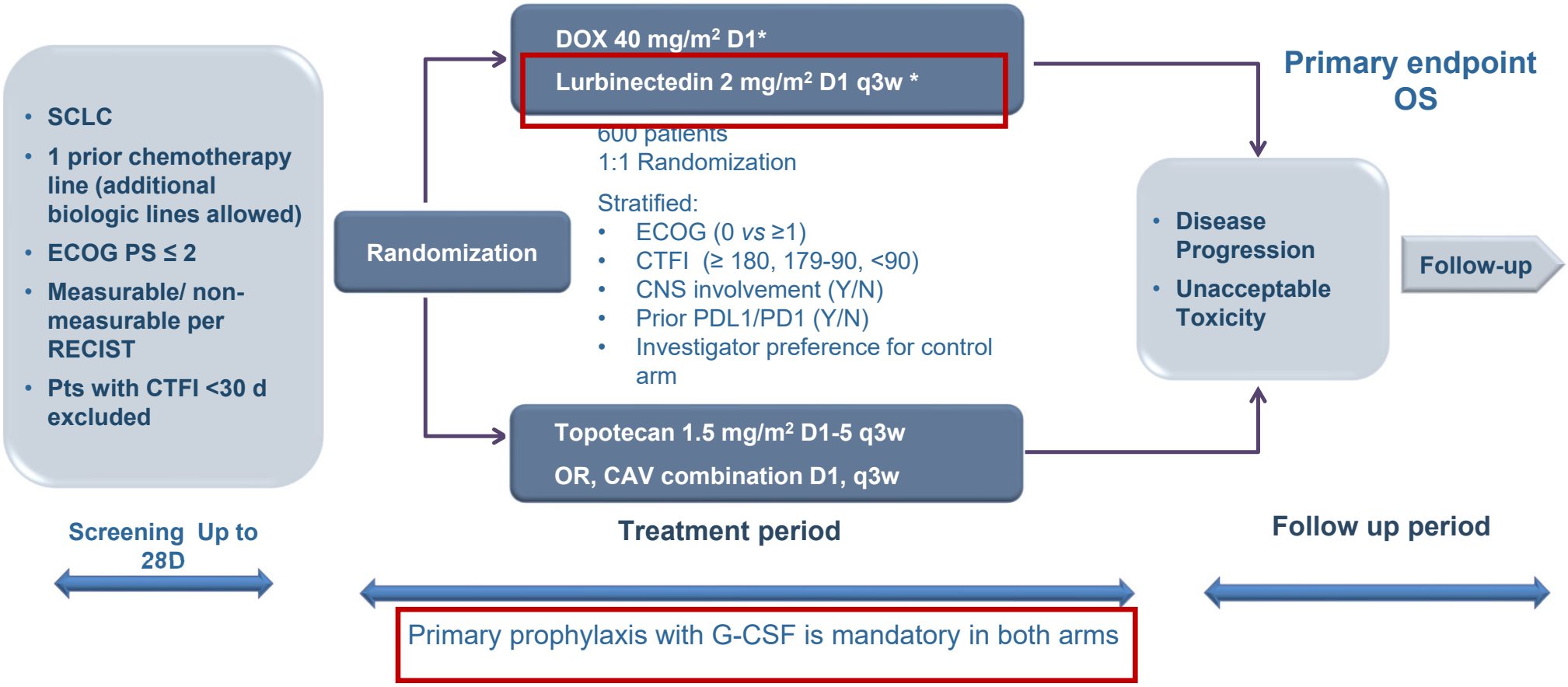
ATLANTIS: Study design

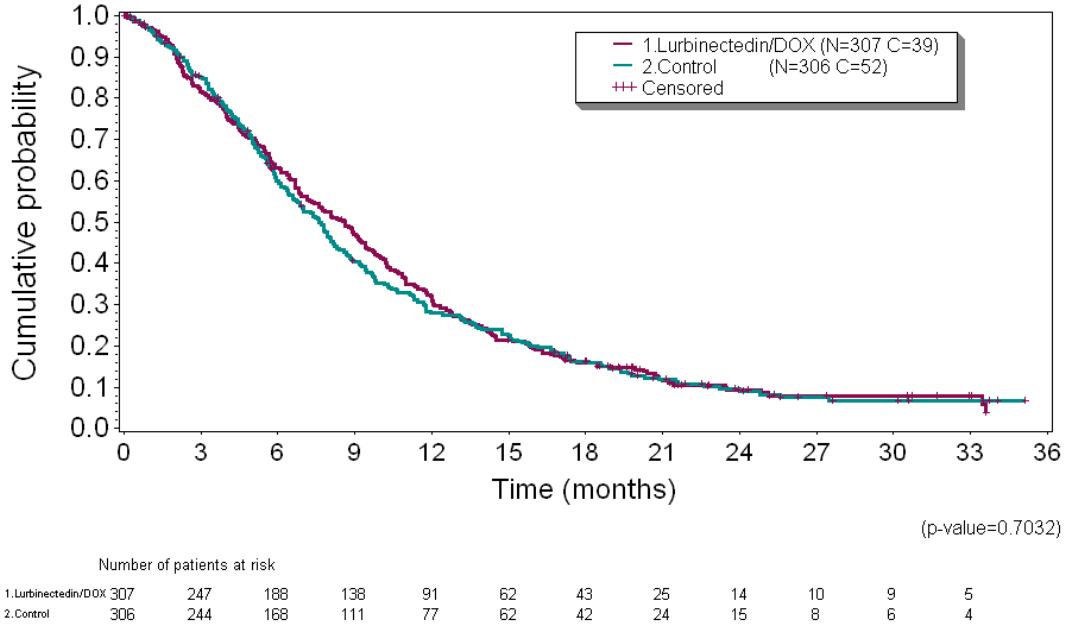


* Maximum 10 cycles, lurbinectedin to be continued at 3.2 mg/m² D1 q3w

Baseline Characteristics (II)

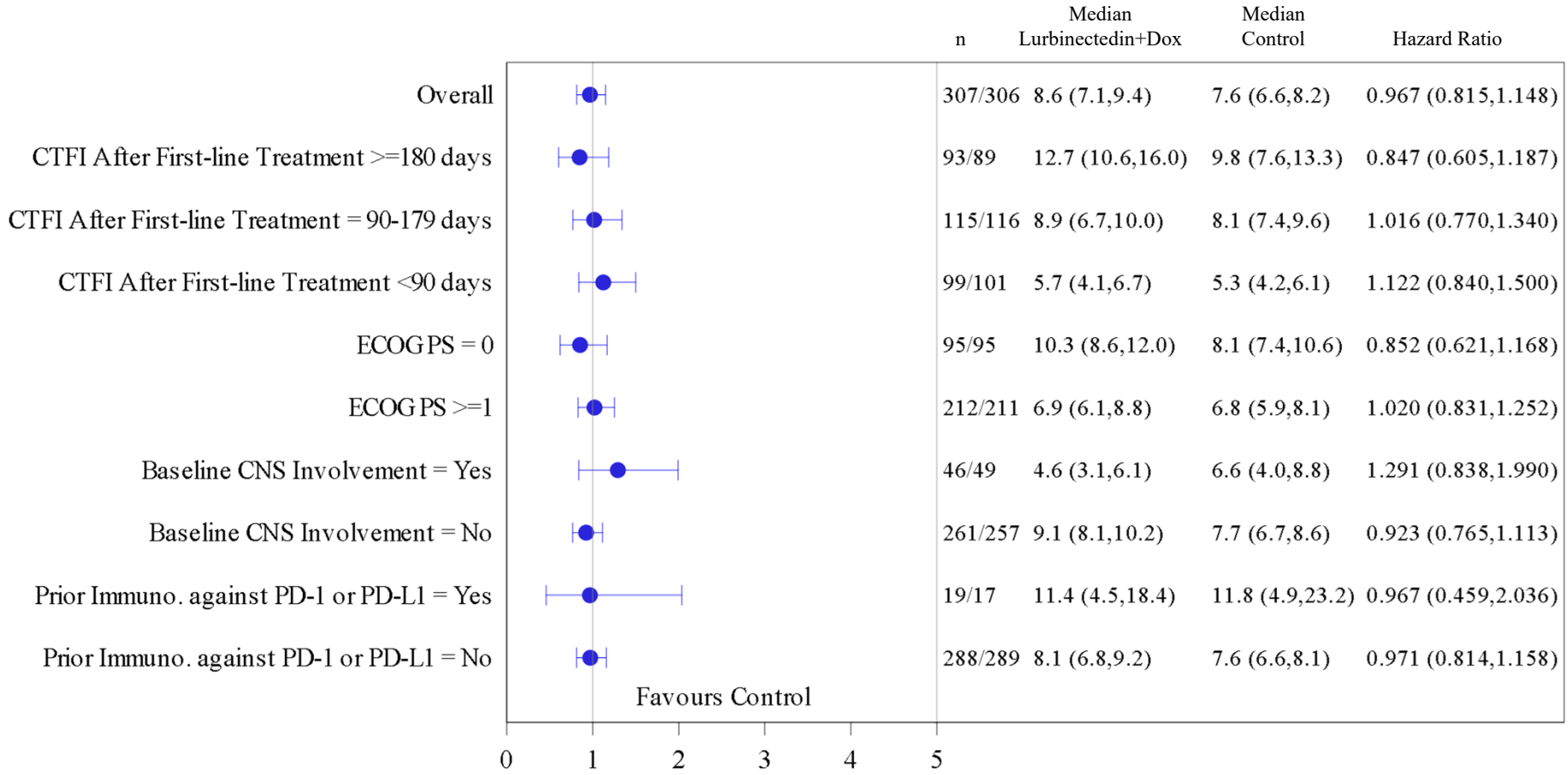
		Experimental Arm Lurbinectedin+DOX (n=307)	Control Arm Topotecan/CAV (n=306)
Bulky disease, %	**one lesion ≥50mm**	**46.9**	**41.5**
CNS Involvement , %		**15.0**	**16.0**
Prior lines of therapy (#), %	**# median (range)**	1.0 (1-2)	1.0 (1-2)
	1 line	97.1	98.7
	2 lines	2.9	1.3
Best response to prior chemotherapy, %	**CR**	**5.5**	**4.9**
	PR	**62.5**	**62.4**
	SD	23.1	20.6
	PD	5.5	6.9
	NE/UK/NA	3.3	5.2
Prior anti PD-1 or PD-L1, %		6.2	5.6
TTP to prior chemotherapy, months	**median (range)**	7.4 (0.8-40.2)	7.4 (1.6-33.7)
CTFI (days), %	**median (range)**	115.0 (0-1094)	120.5 (13-960)
	<90	**32.2**	**33.0**
	90-179	**37.5**	**37.9**
	≥180	**30.3**	**29.1**

Overall Survival (ITT population)



	Lurbinectedin+DOX (N=307)	Control (N=306)	Parameter	p-value
Events, n (%)	268 (87.3)	254 (83.0)		
Censored, n (%)	39 (12.7)	52 (17.0)		
Median OS (95% CI), months	**8.6 (7.1, 9.4)**	**7.6 (6.6, 8.2)**	**HR : 0.967 (0.815, 1.148)**	**0.7032**
Mean OS, months	10.6	9.9		

Overall Survival – Stratification factors



Safety Summary

Hematological	Lurbinectedin+DOX (n=303)	Control (n=289)	
	Grade ≥3	Grade ≥3	p-value
Anaemia	44 (14.5)	90 (31.1)	<0.0001
Neutropenia	112 (37.0)	200 (69.2)	<0.0001
Febrile neutropenia	12 (4.0)	24 (8.3)	0.0377
Thrombocytopenia	42 (13.9)	90 (31.1)	<0.0001

Non hematological	Lurbinectedin+DOX (n=303)	Control (n=289)	
	Grade ≥3	Grade ≥3	p-value
ALT increased	6 (2.0)	3 (1.0)	0.5057
AP increased	2 (0.7)	3 (1.0)	0.6783
AST increased	7 (2.3)	4 (1.4)	0.5463
Fatigue	26 (8.6)	31 (10.7)	0.4051
Nausea	6 (2.0)	4 (1.4)	0.7525
Vomiting	4 (1.3)	0	0.1242

	Lurbinectedin+DOX (n=303) n (%)	Control (n=289) n (%)
Any AE treatment-related	268 (88.4)	266 (92.0)
Any grade ≥3 AE	**143 (47.2)**	**218 (75.4)**
Any grade 4 AE	**49 (16.2)**	**158 (54.7)**
Any grade ≥3 SAE	38 (12.5)	83 (28.7)
Death associated with AEs	**1 (0.3)**	**10 (3.5)**
Treatment discontinuations associated with AEs	23 (7.6)	45 (15.6)
Delays associated with AEs	79 (26.1)	99 (34.3)
Reductions associated with AEs	66 (21.8)	138 (47.8)

First-line nivolumab + ipilimumab + chemotherapy in patients with advanced NSCLC and brain metastases: results from CheckMate 9LA

David Paul Carbone,[1] Tudor-Eliade Ciuleanu,[2] Manuel Cobo,[3] Michael Schenker,[4] Bogdan Zurawski,[5] Juliana Menezes,[6] Eduardo Richardet,[7] Jaafar Bennouna,[8] Enriqueta Felip,[9] Oscar Juan-Vidal,[10] Aurelia Alexandru,[11] Hiroshi Sakai,[12] Emmanuel de la Mora Jimenez,[13] Luis Paz-Ares[14], Martin Reck,[15] Thomas John,[16] Nan Hu,[17] Xiaoqing Zhang,[17] Phuong Tran,[17] Diederik Grootendorst,[17] Shun Lu[18]

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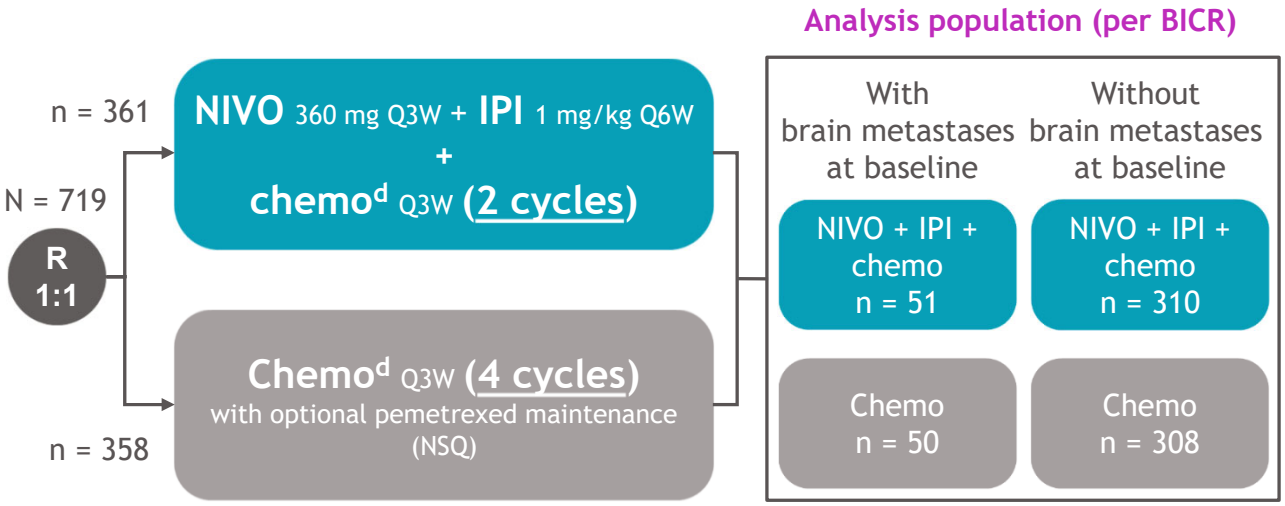
CheckMate 9LA[a,b] study design and analysis population

Key eligibility criteria

- Stage IV or recurrent NSCLC
- No prior systemic therapy
- No sensitizing *EGFR* mutations or known *ALK* alterations
- ECOG PS 0–1
- Brain MRI/CT performed at baseline
- **For patients with brain metastases:**
  - **Adequately treated and asymptomatic for ≥ 2 weeks prior to first treatment dose[c]**

Stratified by PD-L1 (< 1% vs ≥ 1%), sex, and histology (SQ vs NSQ)



Primary endpoint
- OS

Secondary endpoints
- PFS per BICR
- ORR per BICR

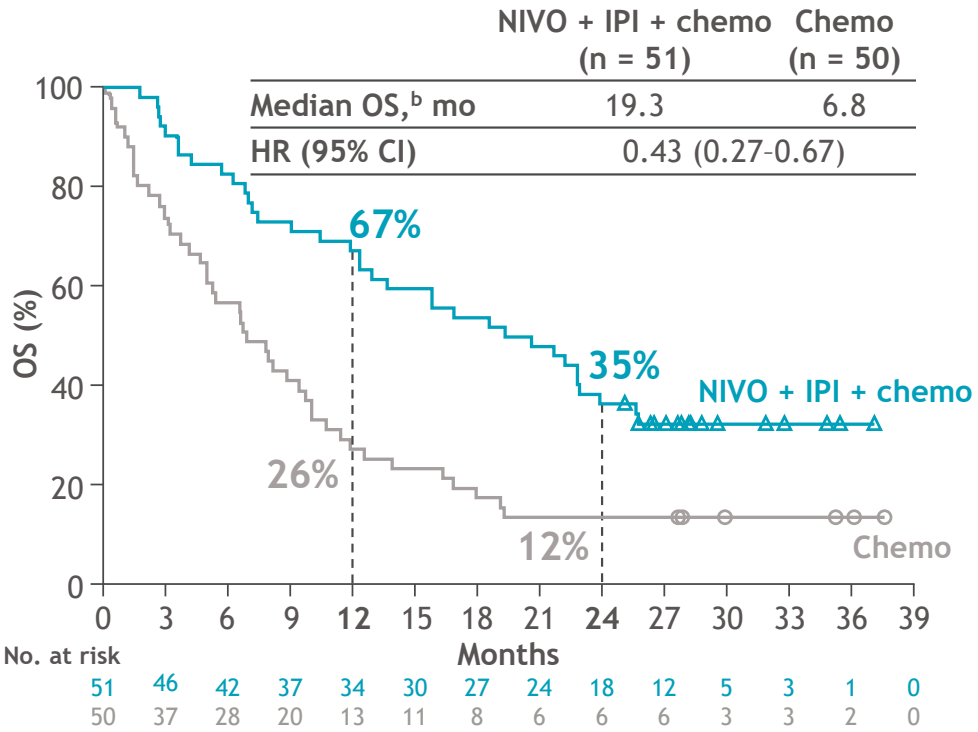
Post hoc analysis
- Systemic[e] efficacy and safety in patients with or without brain metastases at baseline
- Intracranial[f] efficacy in patients with brain metastases at baseline

Database lock: February 18, 2021; minimum / median follow-up for OS: 24.4 months / 30.7 months

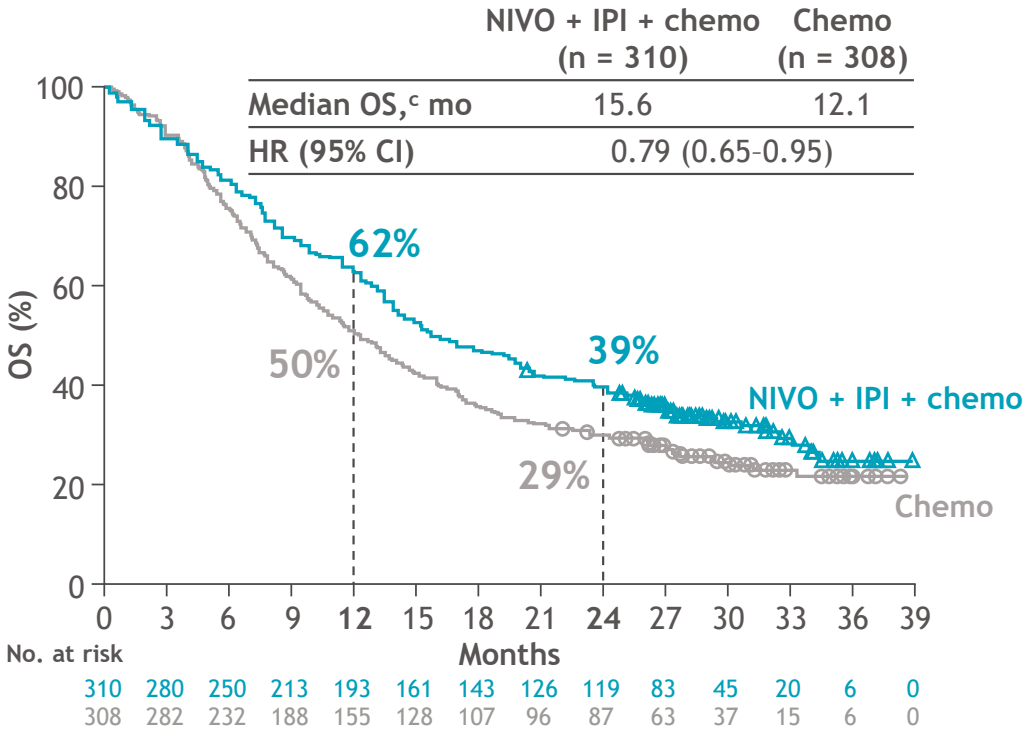
[a]NCT03215706; [b]Patients were treated until disease progression, unacceptable toxicity, or for 2 years for immunotherapy; [c]Off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for ≥ 2 weeks before first treatment; [d]NSQ: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin; [e]Systemic efficacy was assessed by BICR per RECIST v1.1 criteria based on all lesions; [f]Intracranial efficacy was assessed by BICR per modified RECIST v1.1 (adapted for brain metastases) based on brain lesions.

OS: NIVO + IPI + chemo vs chemo[a]

With baseline brain metastases



Without baseline brain metastases



Minimum follow-up: 24.4 months.

[a]Patients with brain metastases at baseline: subsequent radiotherapy was received by 18% (NIVO + IPI + chemo) and 20% (chemo); subsequent systemic therapy by 29% and 34%; subsequent immunotherapy by 4% and 26%; subsequent chemo by 29% and 14%, respectively. Patients without brain metastases at baseline: subsequent radiotherapy was received by 14% (NIVO + IPI + chemo) and 14% (chemo); subsequent systemic therapy by 34% and 47%; subsequent immunotherapy by 8% and 37%; subsequent chemo by 32% and 25%, respectively; [b]95% CI = 12.3-23.9 (NIVO + IPI + chemo) and 4.7-9.7 (chemo); [c]95% CI = 13.8-19.4 (NIVO + IPI + chemo) and 10.2-13.7 (chemo).

ATEZO-BRAIN (GECP 17/05): NON-RANDOMIZED PHASE II CLINICAL TRIAL OF ATEZOLIZUMAB COMBINED WITH CARBOPLATIN PLUS PEMETREXED IN CHEMOTHERAPY-NAÏVE PATIENTS WITH ADVANCED NON-SQUAMOUS NSCLC WITH UNTREATED BRAIN METASTASES

Ernest Nadal (1), Delvys Rodríguez-Abreu (2), Bartomeu Massutí (3), Oscar Juan (4), Gerardo Huidobro (5), Rafael López (6), Javier De Castro (7), Anna Estival (8), Rosario Garcia-Campelo (9), Ivana Sullivan (10), Enriqueta Felip (11), Ana Blasco (12), Maria Guirado (13), Marta Simó (14), Eva Pereira (15), Valentín Navarro (1), Jordi Bruna (14)

(1) Institut Català d'Oncologia – L'Hospitalet, Spain; (2) Hospital Insular de Gran Canaria, Spain; (3) Hospital General de Alicante, Spain; (4) Hospital Universitari La Fe, Spain; (5) Complejo Hospitalario Universitario de Vigo, Spain; (6) Hospital Clínico de Valladolid, Spain; (7) Hospital Universitario La Paz, Spain; (8) Institut Català d'Oncologia - Badalona, Spain; (9) Hospital Universitario A Coruña, Spain; (10) Hospital Sant Pau, Spain; (11) Hospital Universitario Vall d'Hebron, Spain; (12) Hospital General de Valencia, Spain; (13) Hospital Universitario de Elche, Spain; (14) Hospital Universitari de Bellvitge, Spain; (15) Spanish Lung Cancer Group, Spain

ATEZO-BRAIN Trial Design

Single arm phase II clinical trial

Key Elegibility Criteria:
Stage IV non-squamous NSCLC
Untreated brain metastases
Treatment naïve
EGFR/ALK negative, any PD-L1
ECOG PS 0-1
Anticonvulsivants and dexamethasone ≤ 4 mg qd allowed
Measurable systemic and brain lesion/s

Carboplatin (5 AUCs) + Pemetrexed 500mg/m^2 + Atezolizumab 1200mg Q3W for 4-6 cycles

Pemetrexed 500mg/m2 + Atezolizumab 1200mg Q3W until tumor progression (*), unacceptable toxicity or 2 years

Tumor evaluation by body CT scan and brain MRI Q6W until the 12th week and thereafter Q9W until PD

(*) If exclusive CNS PD, patients could continue on study after brain RT

Co-primary endpoint:
- Safety
- Investigator-based PFS by RECIST v1.1 & RANO-BM

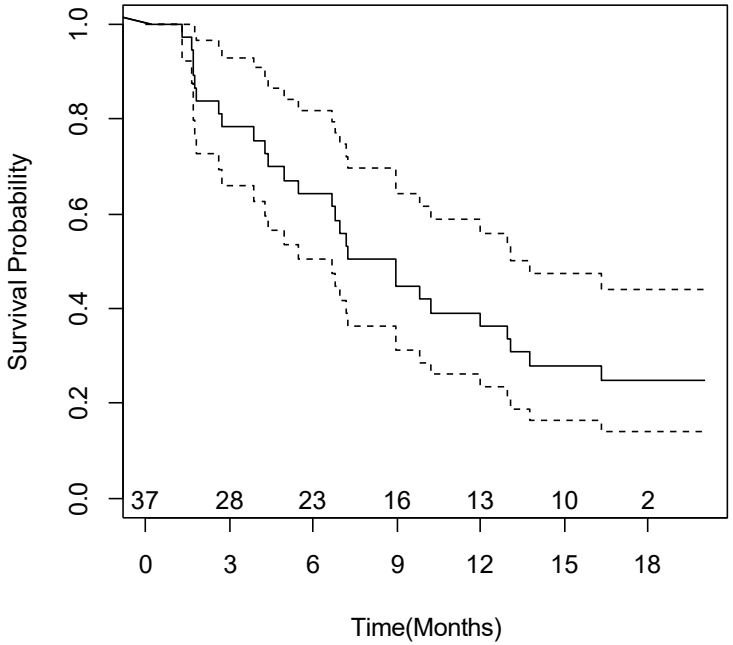
Secondary endpoint:
- Response rate, DoR
- Overall Survival
- QoL, neurocognitive function
- Time to brain radiotherapy

Exploratory endpoint:
- To identify neuroimaging (MRI) and blood biomarkers predicting response or resistance

Primary Endpoint: Systemic and Intracranial PFS

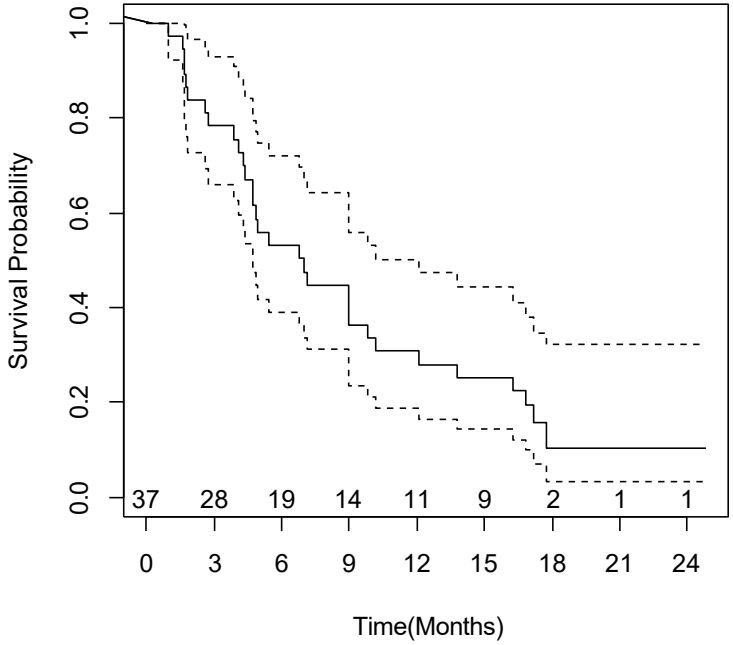
Median follow-up
17.3 months

Systemic PFS by RECIST v1.1



Median PFS = 8.9 months (95% CI 6.7- 13.8)
18 months PFS rate = 24.9%

Intracranial PFS by RANO-BM



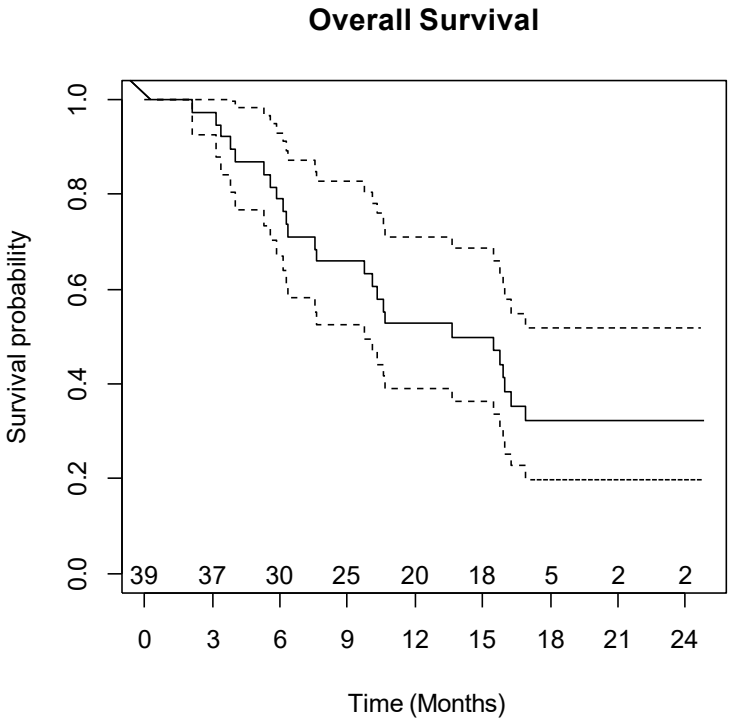
Median icPFS = 6.9 months (95% CI 4.7 – 12.1)
18 months icPFS rate = 10.4%

Secondary Endpoints: Response Rate and Overall Survival

	Best Intracranial Response (RANO-BM)	Best Systemic Response (RECIST v1.1)
CR	4 (10%)	0
PR	12 (30%)	19 (47.5%)
SD	19 (47.5%)	16 (40%)
PD	4 (10%)	3 (7.5%)
NE	1 (2.5%)	2 (5%)
ORR	**16 (40%)**	**19 (47.5%)**

Only 4 patients had discordance among systemic and CNS response:

- 2 with PD in body and SD in brain
- 2 with PD in brain and PR in body



Median OS = 13.6 (95% CI 9.7 – NR)
2y OS rate = 32%

Conclusions

- Chemotherapy with durvalumab and tremelimumab will likely become available as a first-line option
- Role of lurbinectedin in doubt
- Chemotherapy and immunotherapy safe and active in patients with brain metastases