Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™ Webinar: Clinical Updates from ESMO Immuno-Oncology Congress 2019

June 9, 2020

1:00-2:00 p.m. EST

Webinar Agenda

1:00-1:05 p.m. ET Overview: Welcome and Introductions

1:05-1:40 p.m. ET Presentation

1:40-1:55 p.m. ET Question and Answer Session

1:55-2:00 p.m. ET Closing Remarks

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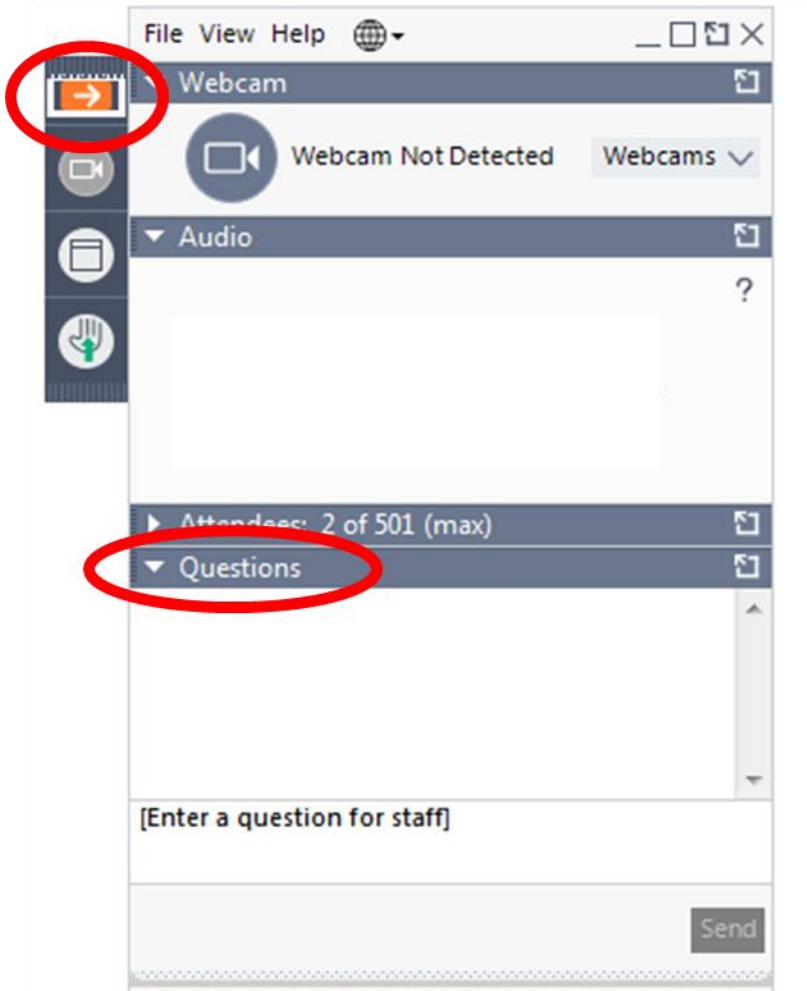
How to Submit Questions

Computer



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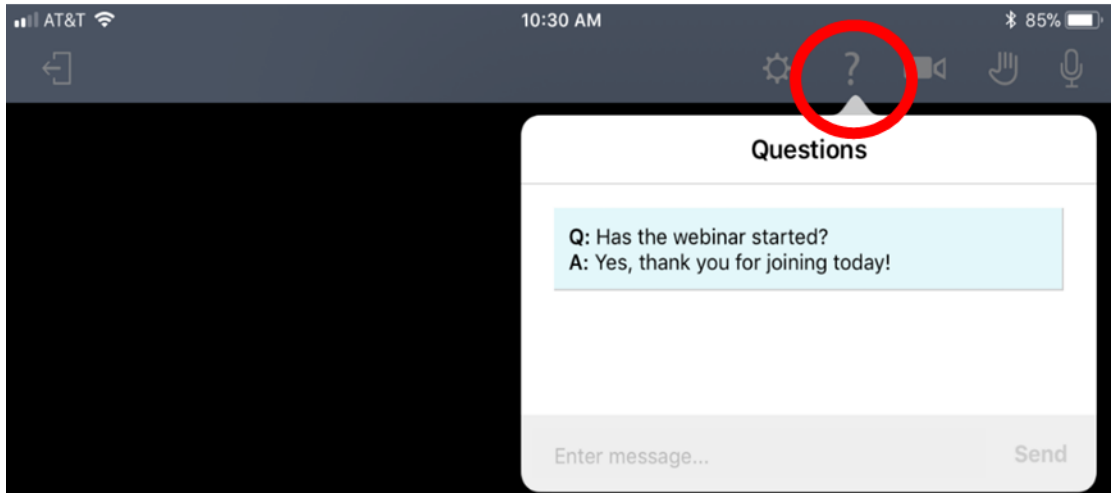

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Webinar Faculty

Joshua Brody, MD –
Icahn School of Medicine at Mount Sinai

Ezra Cohen, MD –
University of California San Diego

Tanja de Gruijl, PhD –
Amsterdam University Medical Centers

Geoffrey Gibney, MD –
Georgetown Lombardi Comprehensive Cancer Center

heads the Immunotherapy and Immune monitoring Lab at the Cancer Center of the VU University medical center (VUmc) in Amsterdam

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Tanja de Gruijl, PhD

- Department of Medical Oncology, Amsterdam University medical centers, VUmc – Cancer Center Amsterdam, Amsterdam, The Netherlands
- Heads the Immunotherapy and Immune monitoring Lab at the Cancer Center for the VU University medical center
- Professor of Translational Tumour Immunology
- Primary research: *in vivo* targeting and modulation of dendritic cells in tumour-draining lymph nodes and the tumour microenvironment

Learning objectives

Upon completion of this webinar, participants will be able to:

- Describe the latest advances in biomarkers for immune checkpoint inhibitor therapy.
- Explain the impact of adverse event management on cancer outcomes with immune checkpoint inhibitor treatments.
- Summarize emerging therapeutic approaches to increase the efficacy of cancer immunotherapy.

Outline

- Lung cancer clinical trials
- Novel agents and settings
- Biomarker studies
- Adverse event management

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- Lung cancer clinical trials
- Novel agents and settings
- Biomarker studies
- Adverse event management

Ezra Cohen, MD, FRCPSC, FASCO

- Chief, Division of Hematology-Oncology

- Associate Director, Translational Science, Moores Cancer Center
- Professor of Medicine

- Specialty: Head & Neck Cancers, Immunotherapy

Nivolumab plus low-dose ipilimumab as first-line treatment of advanced NSCLC: Overall survival analysis of checkmate 817

Fabrice Barlesi,[1] Clarisse Audigier-Valette,[2] Enriqueta Felip,[3] Tudor-Eliade Ciuleanu,[4] Kevin Jao,[5] Erika Rijavec,[6] Laszlo Urban,[7] Jean-Sébastien Aucoin,[8] Cristina Zannori,[9] Karim Vermaelen,[10] Osvaldo Arén Frontera,[11] Neal Ready,[12] Alessandra Curioni Fontecedro,[13] Helena Linardou,[14] Elena Poddubskaya,[15] Jürgen R. Fischer,[16] Rathi Pillai,[17] Sunney Li,[18] Angelic Acevedo,[18] Luis Paz-Ares[19]

[1]Aix-Marseille Université; CNRS, INSERM, CRCM; Assistance Publique-Hôpitaux de Marseille (APHM), Marseille, France; [2]Hôpital Sainte-Musse,Toulon, France; [3]Vall d'Hebron University Hospital, Barcelona, Spain; [4]The Oncology Institute Ion Chiricuta and University of Medicine and Pharmacy Iuliu Hatieganu, Cluj-Napoca, Romania; [5]Hôpital du Sacré-Cœur de Montréal, Montreal, QC, Canada; [6]Ospedale Policlinico San Martino, Genova, Italy; [7]Matrahaza University and Teaching Hospital, Matrahaza, Hungary; [8]Centre Intégré Universitaire de Santé et de Services Sociaux de la Mauricie-et-du-Centre-du-Québec, Trois-Rivières, QC, Canada; [9]Azienda Ospedaliera Santa Maria di Terni, Terni, Italy; [10]Ghent University Hospital, Ghent, Belgium; [11]Centro Internacional de Estudios Clinicos, Santiago, Chile; [12]Duke Cancer Center, Durham, NC, USA; [13]University Hospital Zurich, Zurich, Switzerland; [14]Oncology Unit, Metropolitan Hospital, Athens, Greece; [15]VitaMed LLC, Moscow, Russian Federation; [16]Löwenstein Clinic gGmbH, Löwenstein, Germany; [17]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [18]Bristol-Myers Squibb, Princeton, NJ, USA; [19]Hospital Universitario 12 de Octubre, Madrid, Spain

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Methods

Key eligibility criteria
- Stage IV/recurrent NSCLC
- No prior systemic therapy
- No known sensitizing *EGFR* or *ALK* alterations

Cohort A (n = 391)
- ECOG PS 0–1

Special populations (Cohort A1; n = 198)
- ECOG PS 2 or
- ECOG PS 0–1 and one of the following: asymptomatic untreated brain metastases, hepatic[b] or renal[c] impairment, HIV+[d]

→ **Nivolumab** Flat dose 240 mg IV Q2W + **Ipilimumab** 1 mg/kg IV Q6W →

Treat until disease progression or unacceptable toxicity for up to 2 years

Primary endpoints: Safety in Cohort A | **Secondary endpoints:** Efficacy (including OS) in Cohort A
Exploratory endpoints: Efficacy by PD-L1 and TMB in Cohort A; safety and efficacy (including OS) in Cohort A1

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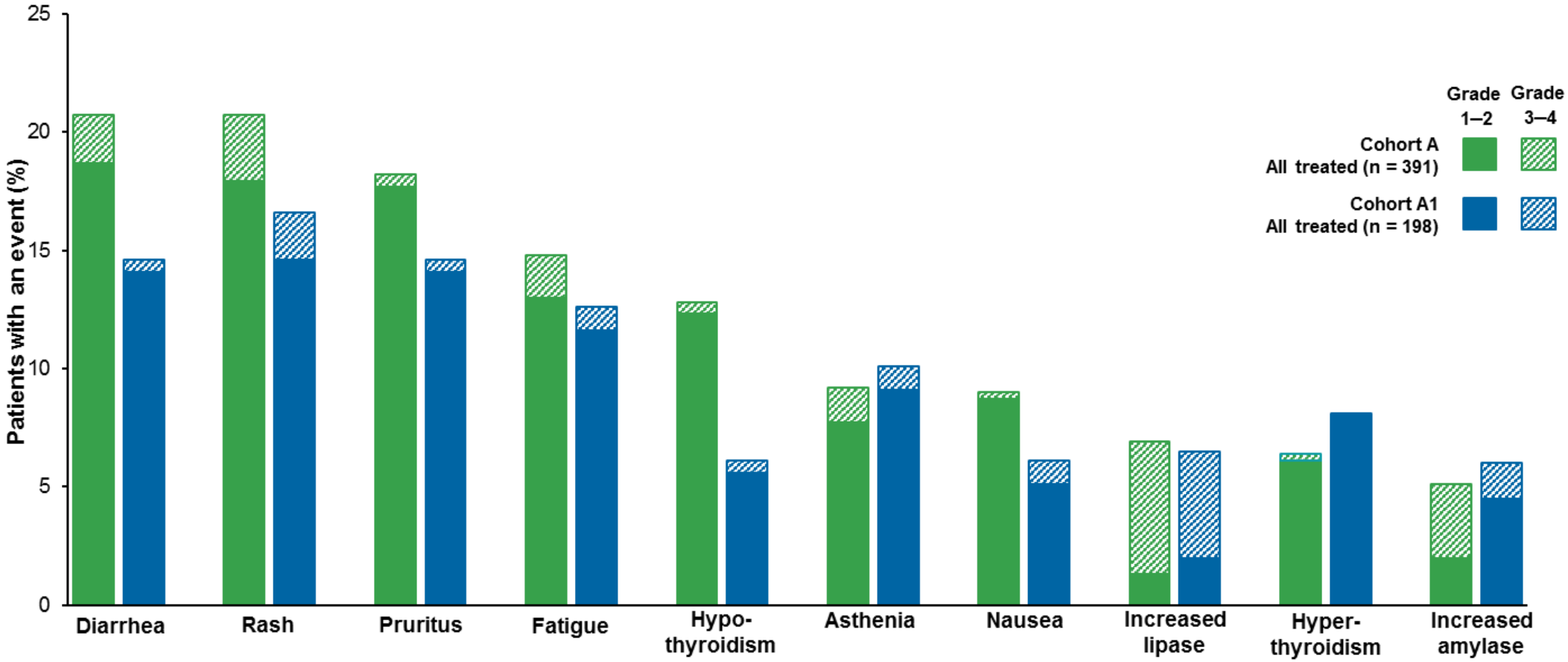
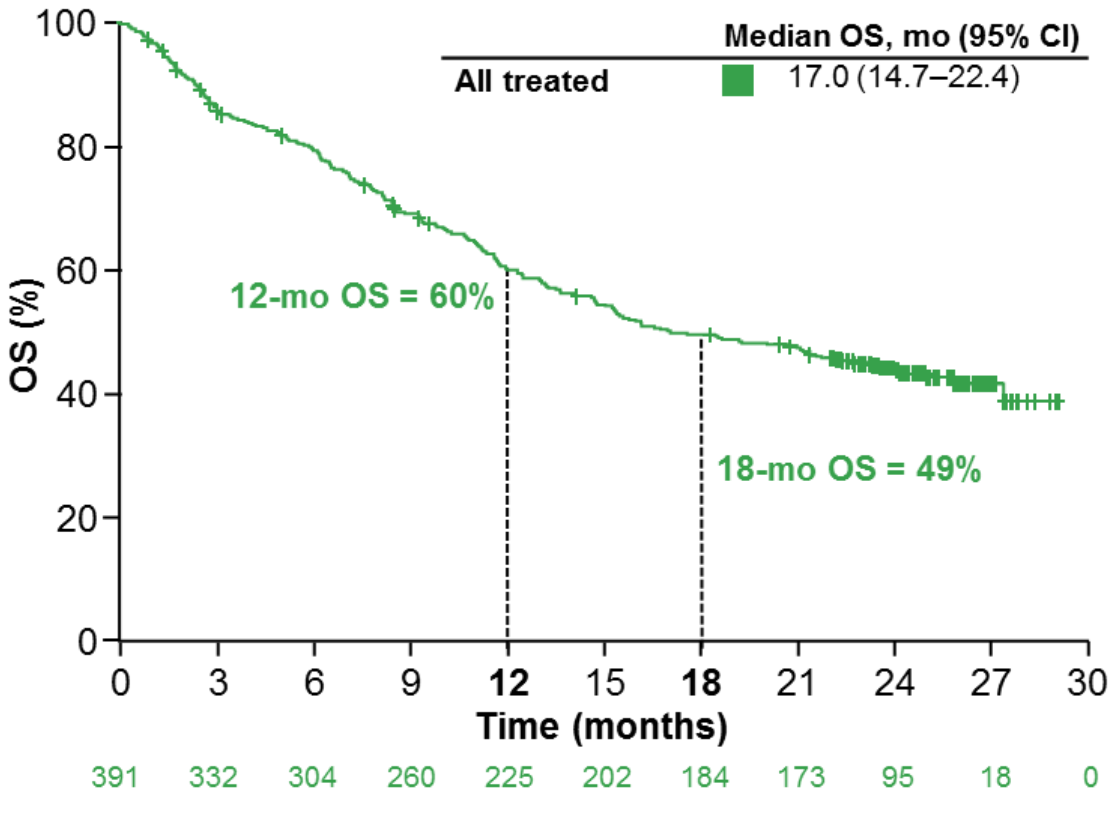
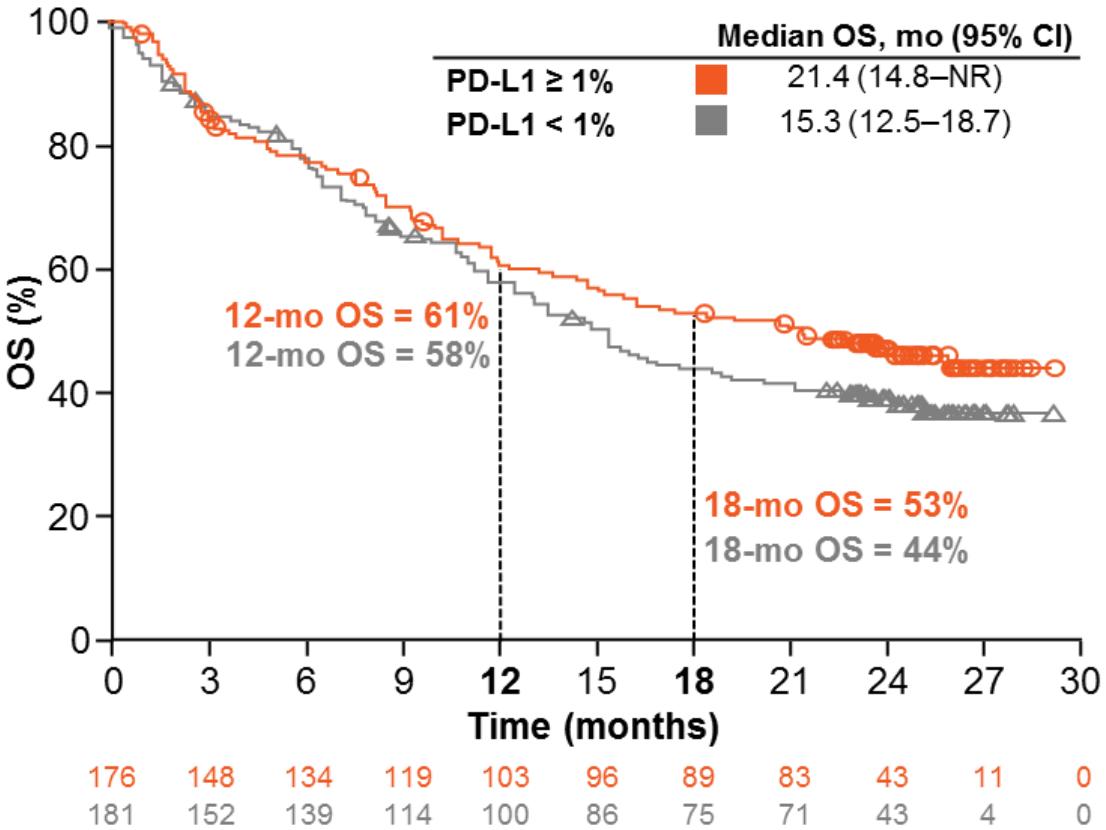
Results - Safety



[a]Patients in Cohort A had ECOG PS 0–1; Median (95% CI) treatment duration: 4.0 (3.7–4.9) months NIVO; 3.0 (2.8–4.1) months IPI; [b]Patients in Cohort A1 had ECOG PS 2, or ECOG PS 0–1 and comorbidities; Median (95% CI) treatment duration: 2.8 (2.3–3.8) months NIVO; 2.3 (1.4–2.8) months IPI; [c]Includes treatment-related AEs ≥ 5% in both cohorts; Database lock: June 28, 2019.

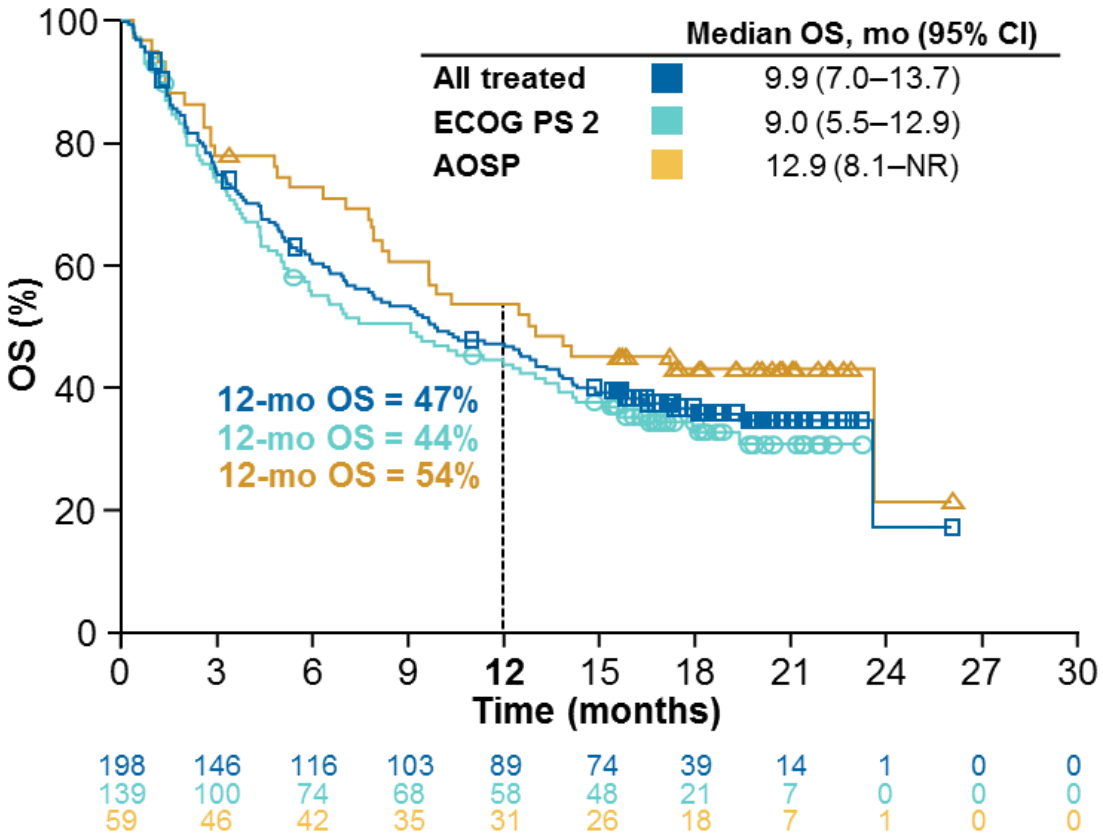
Results – Overall survival

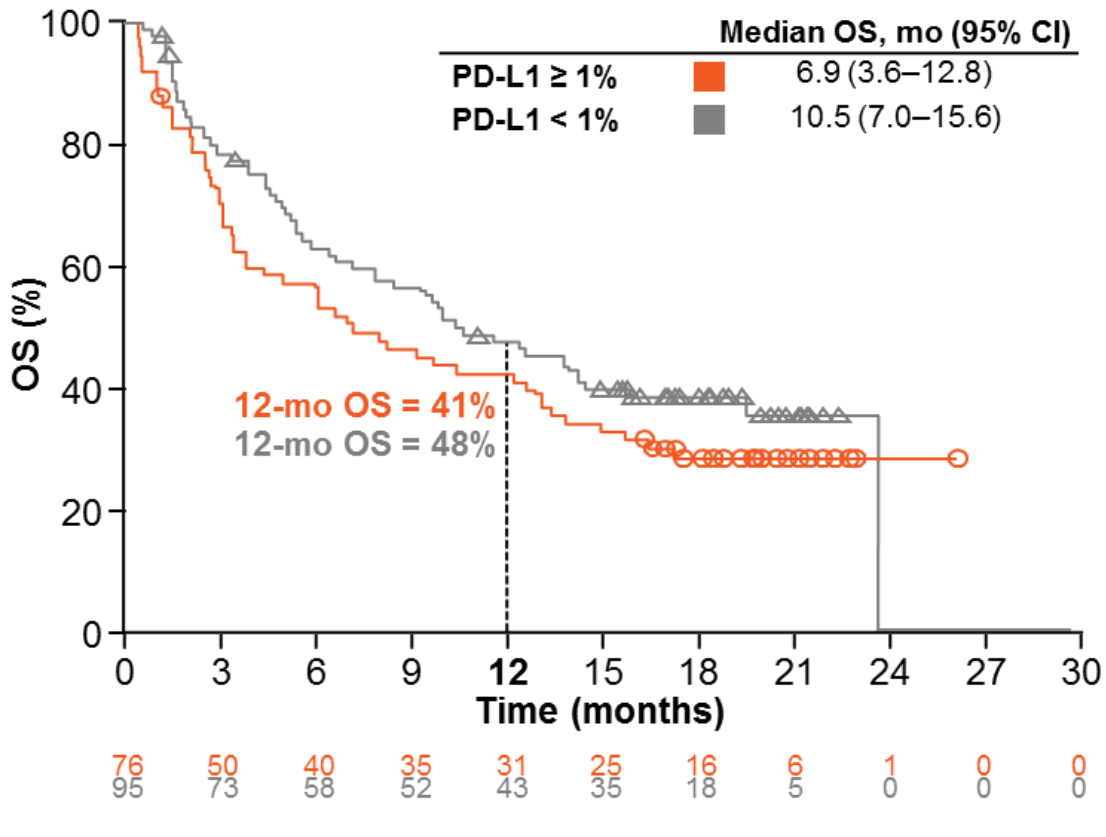




[a]Patients in Cohort A had ECOG PS 0–1; Minimum follow-up: 21.0 months; Database lock: June 28, 2019.

Results – Overall survival





- The 12 month OS rates were 33% (PD-L1 ≥ 1%; n = 52) and 49% (PD-L1 < 1%; n = 67) in patients with ECOG PS 2; 58% (PD-L1 ≥ 1%; n = 24) and 45% (PD-L1 < 1%; n = 28) among AOSP

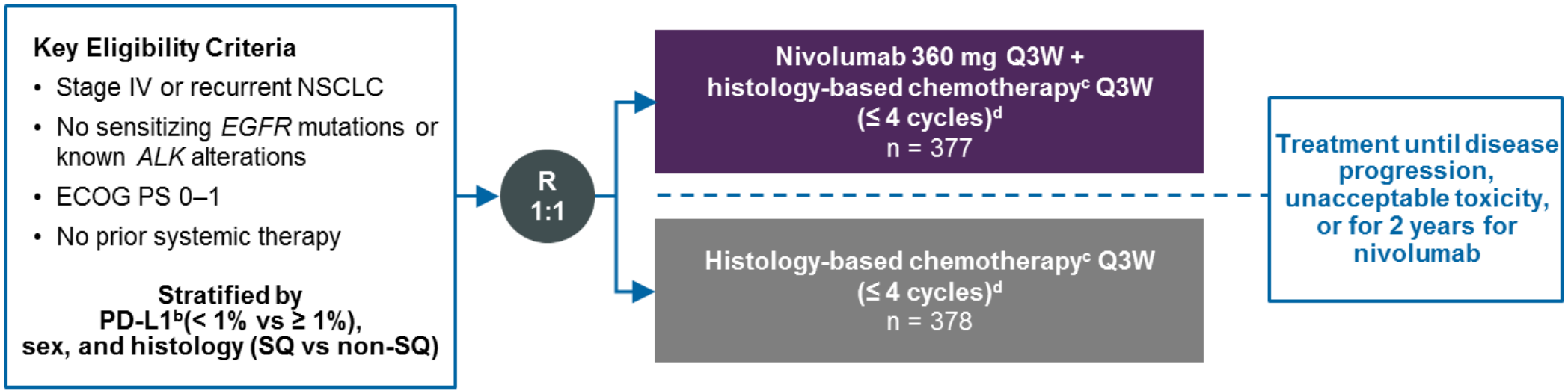
[a]Patients in Cohort A1 had ECOG PS 2, or ECOG PS 0–1 and comorbidities; Minimum follow-up: 14.1 months; Database lock: June 28, 2019.

Nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo as first-line (1L) treatment (tx) for advanced non-small cell lung cancer (aNSCLC): CheckMate 227 Part 2 final analysis

Luis Paz-Ares,[1] Tudor E. Ciuleanu,[2] Xinmin Yu,[3] Pamela Salman,[4] Adam Pluzanski,[5] Adnan Nagrial,[6] Libor Havel,[7] Ruben Kowalyszyn,[8] Clarisse Audigier-Valette,[9] Yi-Long Wu,[10] Hossein Borghaei,[11] Matthew D. Hellmann,[12] Julie Brahmer,[13] Martin Reck,[14] Suresh Ramalingam,[15] Li Zhang,[16] Faith E. Nathan,[17] Kenneth J. O'Byrne[18]

[1]University Hospital 12 De Octubre and Universidad Complutense & CiberOnc, Madrid, Spain; [2]Prof. Dr. Ion Chiricuta Institute of Oncology and UMF Iuliu Hatieganu, Cluj-napoca, Romania; [3]Zhejiang Cancer Hospital, Zhejiang, China; [4]Fundacion Arturo Lopez Perez, Santigo de Chile, Chile; [5]Klinika Nowotworow Pluca i Klatki Piersiowej, Warszawa, Poland; [6]Blacktown Hospital, Blacktown, NSW, Australia; [7]Charles University, Thomayer Hospital, Prague, Czech Republic; [8]Clinica Viedma S.A., Rio Negro, Argentina; [9]Hôpital Sainte Musse, Toulon, France; [10]Guangdong General Hospital, Guangzhou, Guangdong, China; [11]Fox Chase Cancer Center, Philadelphia, PA, USA; [12]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [13]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [14]Lung Clinic Grosshansdorf, German Center for Lung Research, Grosshansdorf, Germany; [15]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [16]Sun Yat-Sen University Cancer Center, Guangzhou, Guangdong, China; [17]Bristol-Myers Squibb, Princeton, NJ, USA; [18]Princess Alexandra Hospital, Brisbane, Woolloongabba, QLD, Australia

Methods



Primary endpoint:
- OS in non-SQ NSCLC

Secondary endpoints:
- OS in all randomized patients (hierarchically tested)
- PFS (non-SQ and all randomized patients)
- ORR (non-SQ and all randomized patients)
- OS, PFS, and ORR in PD-L1 selected populations

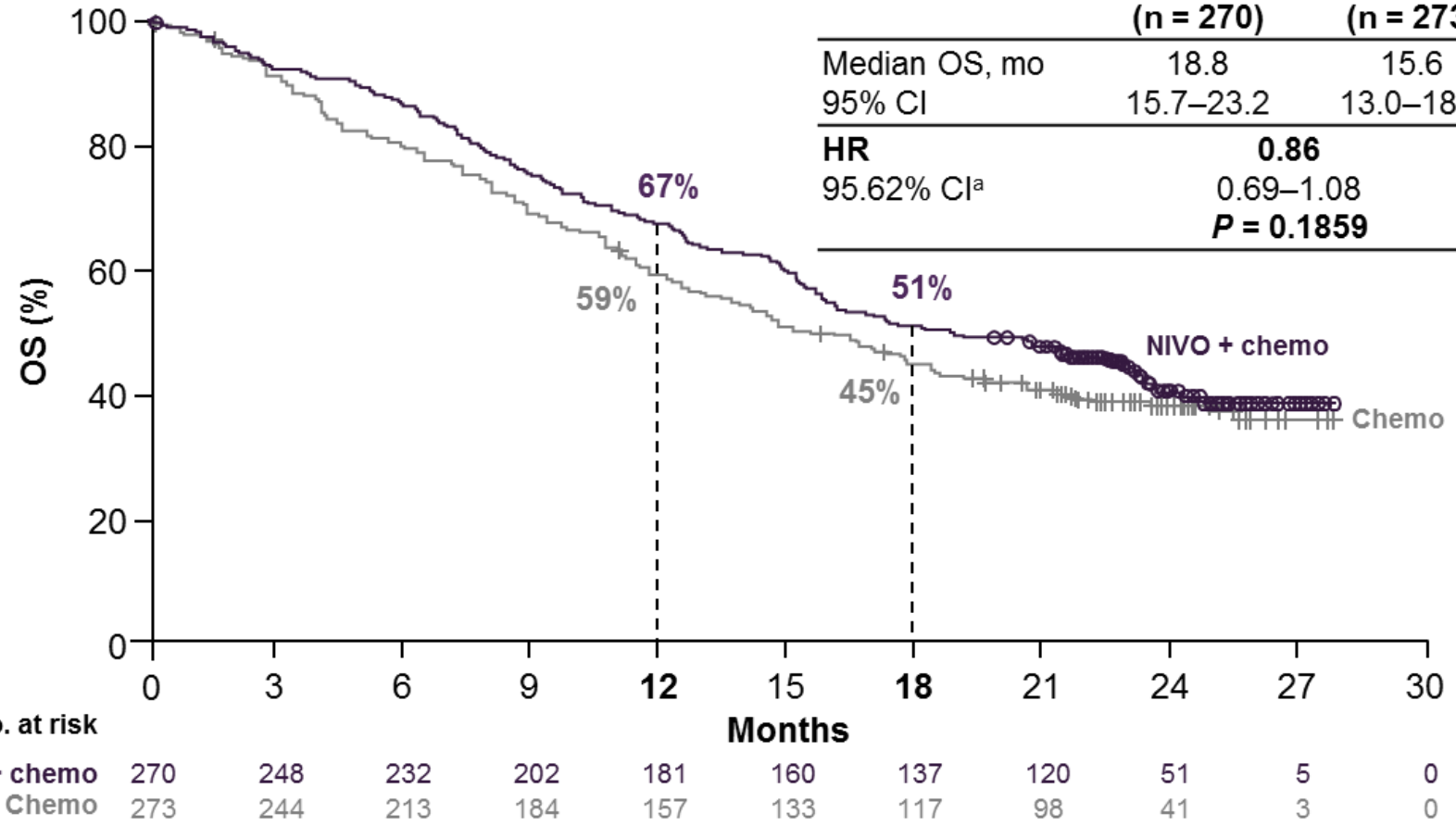
Exploratory endpoint:
- Safety and tolerability

Database lock: July 2, 2019; minimum follow-up for primary endpoint: 19.5 months.

[a]NCT02477826; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]**Non-SQ**: pemetrexed + cisplatin or carboplatin; **SQ**: paclitaxel + carboplatin; [d]After 4 cycles patients with non-SQ NSCLC could receive optional pemetrexed maintenance.

Results – Overall survival

	NIVO + chemo (n = 270)	Chemo (n = 273)
Median OS, mo	18.8	15.6
95% CI	15.7–23.2	13.0–18.4
HR	**0.86**	
95.62% CI[a]	0.69–1.08	
	***P* = 0.1859**	

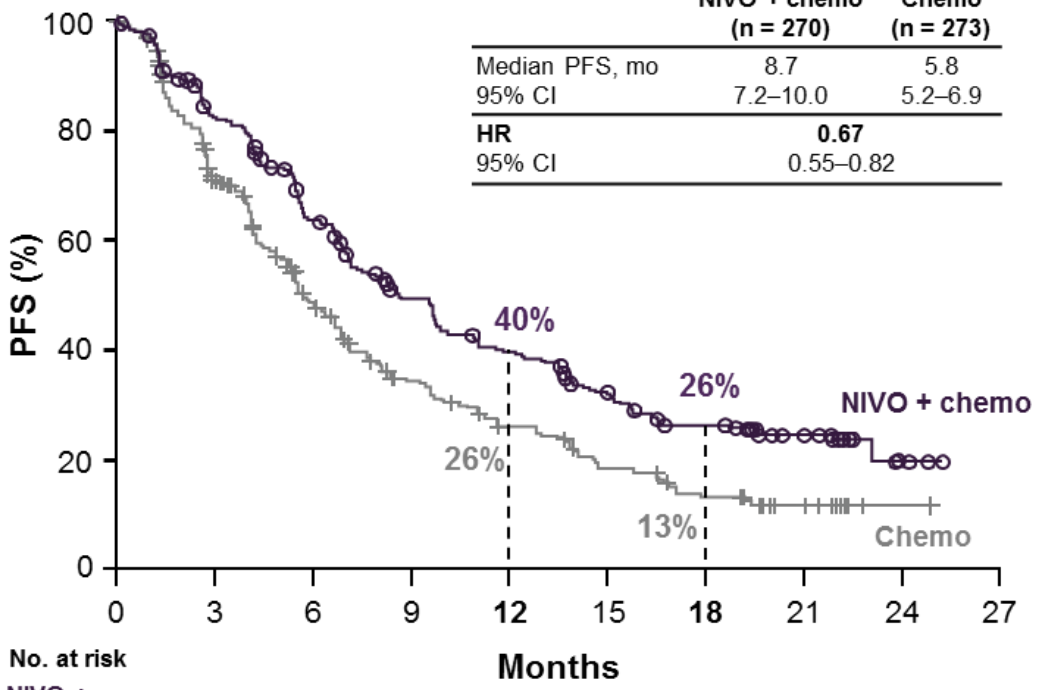


Minimum follow-up for primary endpoint: 19.5 months.
Events occurred in 57.8% of NIVO + chemo patients and 60.1% of chemo patients.
[a]95% CI, 0.69–1.07.

Results – PFS and DOR

PFS per BICR

	NIVO + chemo (n = 270)	Chemo (n = 273)
Median PFS, mo	8.7	5.8
95% CI	7.2–10.0	5.2–6.9
HR	**0.67**	
95% CI	0.55–0.82	

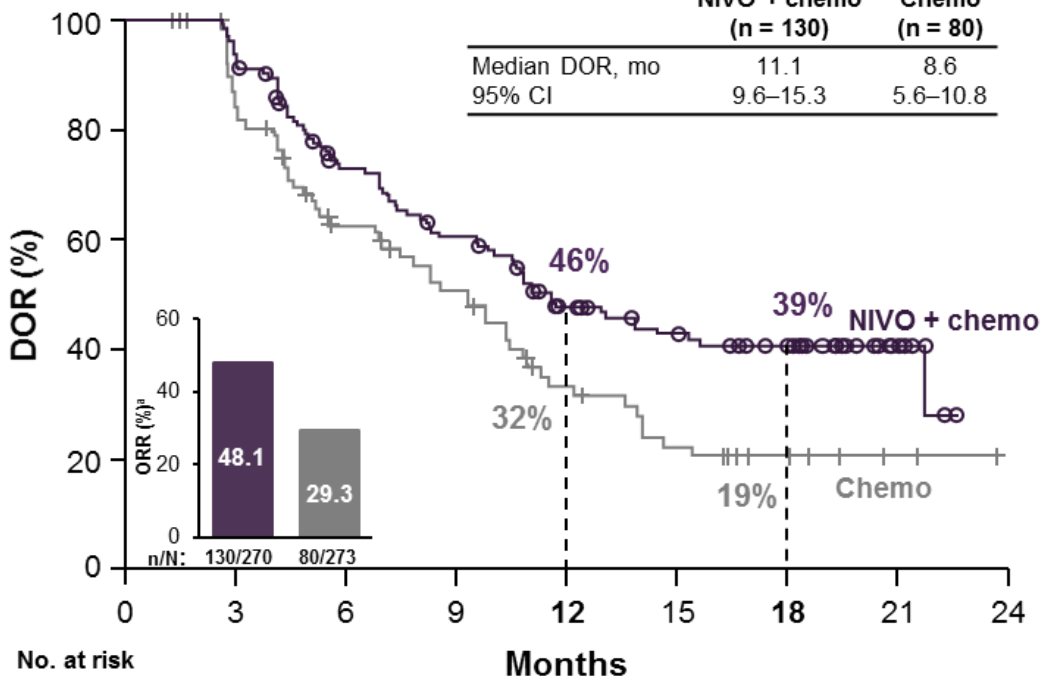


No. at risk

NIVO + chemo	270	214	159	117	93	71	53	35	4	0
Chemo	273	176	106	69	49	33	22	13	1	0

DOR per BICR

	NIVO + chemo (n = 130)	Chemo (n = 80)
Median DOR, mo	11.1	8.6
95% CI	9.6–15.3	5.6–10.8



No. at risk

	130	121	86	70	49	38	30	6	0
	80	63	42	32	18	11	6	2	0

Minimum follow-up: 18.4 months.
[a]With NIVO + chemo, CR rate was 3.7%, PR rate was 44.4%; with chemo, CR rate was 1.8%, PR rate was 27.5%.

First-line durvalumab plus platinum-etoposide in extensive-stage (ES)-SCLC: safety, pharmacokinetics (PK) and immunogenicity in CASPIAN

Mustafa Özgüroğlu,[1] Jonathan W Goldman,[2] Niels Reinmuth,[3] Yuanbin Chen,[4] Mikhail Dvorkin,[5] Dmytro Trukhin,[6] Galina Statsenko,[7] Katsuyuki Hotta,[8] Jun Ho Ji,[9] Maximilian J Hochmair,[10] Oleksandr Voitko,[11] Libor Havel,[12] Artem Poltoratskiy,[13] György Losonczy,[14] Francesco Verderame,[15] Maggie Thomas,[16] Yanan Zheng,[17] Andrew Lloyd,[18] Haiyi Jiang,[16] Luis Paz-Ares[19]

[1]Istanbul University–Cerrahpaşa, Cerrahpaşa School of Medicine, Istanbul, Turkey; [2]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [3]Asklepios Lung Clinic, Munich-Gauting, Germany; [4]Cancer & Hematology Centers of Western Michigan, Grand Rapids, MI, USA; [5]BHI of Omsk Region Clinical Oncology Dispensary, Omsk, Russian Federation; [6]Odessa National Medical University, Odessa, Ukraine; [7]Omsk Regional Cancer Center, Omsk, Russian Federation; [8]Okayama University Hospital, Okayama, Japan; [9]Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, South Korea; [10]Karl Landsteiner Institute of Lung Research and Pulmonary Oncology, Krankenhaus Nord, Vienna, Austria; [11]Kyiv City Clinical Oncological Centre, Kiev, Ukraine; [12]Thomayer Hospital, First Faculty of Medicine, Charles University, Prague, Czech Republic; [13]Petrov Research Institute of Oncology, St Petersburg, Russian Federation; [14]Semmelweis University, Budapest, Hungary; [15]AO Ospedali Riuniti PO Vincenzo Cervello, Palermo, Italy; [16]AstraZeneca, Gaithersburg, MD, USA; [17]AstraZeneca, Mountain View, CA, USA; [18]AstraZeneca, Alderley Park, UK; [19]Department of Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain

Methods

- Treatment-naïve ES-SCLC
- WHO PS 0 or 1
- Asymptomatic or treated and stable brain metastases permitted
- Life expectancy ≥12 weeks
- Measurable disease per RECIST v1.1

N=805 (randomised)

1:1:1

R

Stratified by planned platinum agent (carboplatin vs cisplatin)

Durvalumab + EP*
Durvalumab 1500 mg + EP q3w for up to 4 cycles

→ **Durvalumab**
1500 mg q4w until disease progression

EP*
q3w for up to 6 cycles†

→ **Optional PCI†**

Durvalumab + tremelimumab + EP*
Durvalumab 1500 mg + tremelimumab 75 mg + EP q3w for up to 4 cycles

→ **Durvalumab‡**
1500 mg q4w until disease progression

Primary endpoint
- OS

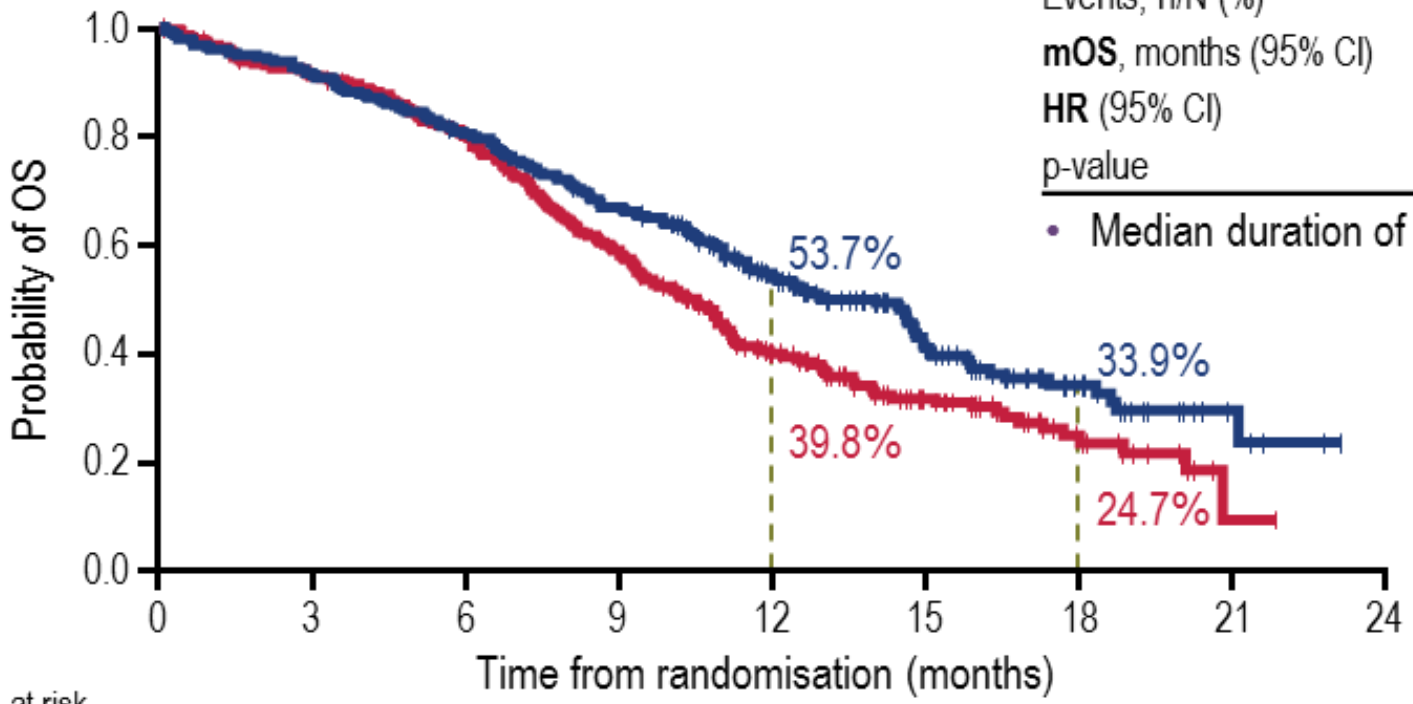
Secondary endpoints
- PFS; ORR
- Safety & tolerability
- Pharmacokinetics
- Immunogenicity

Following pre-planned interim analysis by the IDMC, the durvalumab + tremelimumab + EP arm remains sponsor-blind and continues to final analysis

*EP consists of etoposide 80–100 mg/m^2 with either carboplatin AUC 5–6 or cisplatin 75–80 mg/m^2; †Patients could receive an additional 2 cycles of EP (up to 6 cycles total) and PCI at the investigator's discretion; ‡Patients received an additional dose of tremelimumab post-EP

AUC, area under the curve; ES-SCLC, extensive-stage small-cell lung cancer; EP, platinum-etoposide; IDMC, Independent Data Monitoring Committee; ORR, objective response rate; OS, overall survival; PCI, prophylactic cranial irradiation; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; q4w, every 4 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; WHO, World Health Organization

Results: Overall survival



No. at risk									
Durvalumab + EP	268	244	214	177	116	57	25	5	0
EP	269	242	209	153	82	44	17	1	0

	Durvalumab + EP	EP
Events, n/N (%)	155/268 (57.8)	181/269 (67.3)
mOS, months (95% CI)	**13.0** (11.5–14.8)	**10.3** (9.3–11.2)
HR (95% CI)	**0.73** (0.59–0.91)	
p-value	0.0047	

- Median duration of follow-up: 14.2 months (range 0.1–23.1)

HR, hazard ratio; mOS, median overall survival

Paz-Ares L, et al. Lancet 2019;394:1929–39

Results: Safety

	Durvalumab + EP (n=265)	EP – all cycles (n=266)	EP – cycles 1–4 only (n=266)
Any grade all-cause AEs, n (%)	260 (98)	258 (97)	252 (95)
Grade 3 or 4	163 (62)	166 (62)	154 (58)
Serious AEs	82 (31)	96 (36)	80 (30)
AEs leading to discontinuation*	25 (9)	25 (9)	21 (8)
AEs leading to death	13 (5)	15 (6)	10 (4)
Treatment-related deaths†	5 (2)	2 (1)	0

*Includes patients who permanently discontinued at least one study drug

†AEs assessed by the investigator as possibly related to any study treatment. Causes of death were cardiac arrest, dehydration, hepatotoxicity, pancytopenia, and sepsis (one patient each) in the durvalumab + EP arm; pancytopenia and thrombocytopenia/haemorrhage (one patient each) in the EP arm

Conclusions – Lung Cancer

- Several options exist for the treatment of metastatic NSCLC depending on genomics and PDL1 expression
- anti-PD1 plus anti-CTLA4 is now an option for NSCLC
- anti-PD1/PDL1 plus chemotherapy is an option for SCLC

Outline

- Lung cancer clinical trials
- Novel agents and settings
- Biomarker studies
- Adverse event management

Geoffrey Gibney, MD

- Associate Professor of Medicine and Co-Leader of the Melanoma Group
- Medical Director, Adult Outpatient Infusion Services
- Lombardi Comprehensive Cancer Center
- Medstar Georgetown University Hospital

- Specialty: Medical Oncology, Melanoma, Non-Melanoma Skin Cancers, Renal Cell Carcinoma

- Research Focus: Novel immunotherapy strategies, prognostic biomarker development in advanced melanoma and basal cell carcinoma

A multi-center phase IIa trial to assess the safety and efficacy of BL-8040 (a CXCR4 inhibitor) in combination with pembrolizumab and chemotherapy in patients with metastatic pancreatic adenocarcinoma (PDAC)

Manuel Hidalgo[1,2,3], Valerya Semenisty[4], Bruno Bockorny[1], Erkut Borazanci[6], Daniel Von Hoff[6], Jamie Feliu[7], Mariano Ponz-Sarvise[8], David Gutierrez Abad[9], Amnon Peled[10,11], Osnat Bohana Kashtan[12], Yosi Vainstein-Haras[12], Teresa Macarulla[5]

[1]Division Hematology Oncology, Beth Israel Deaconess Medical Center, Boston, MA, US; [2]Harvard Medical School, Boston, MA, US; [3]Weill Cornell Medical College, New York, NY, US; [4]Rambam Health Care Campus, Haifa, Israel; [5]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [6]Honor-Health/TGen, Scottsdale, AZ, US; [7]Hospital Universitario La Paz, Madrid, Spain; [8]Clinica Universidad de Navarra, Pamplona, Spain; [9]Grupo Oncologia Fuenlabrada, Madrid, Spain; [10]Biokine Therapeutics Ltd, Ness Ziona, Israel; [11]Goldyne Savad Institute of Gene Therapy, Hebrew University Hospital, Jerusalem, Israel; [12] BioLineRx, Modi'in, Israel; [13]Early Development Oncology, Merck & Co., Inc., Kenilworth, NJ, US; [14]StatExcellence Ltd, Nesher, Israel

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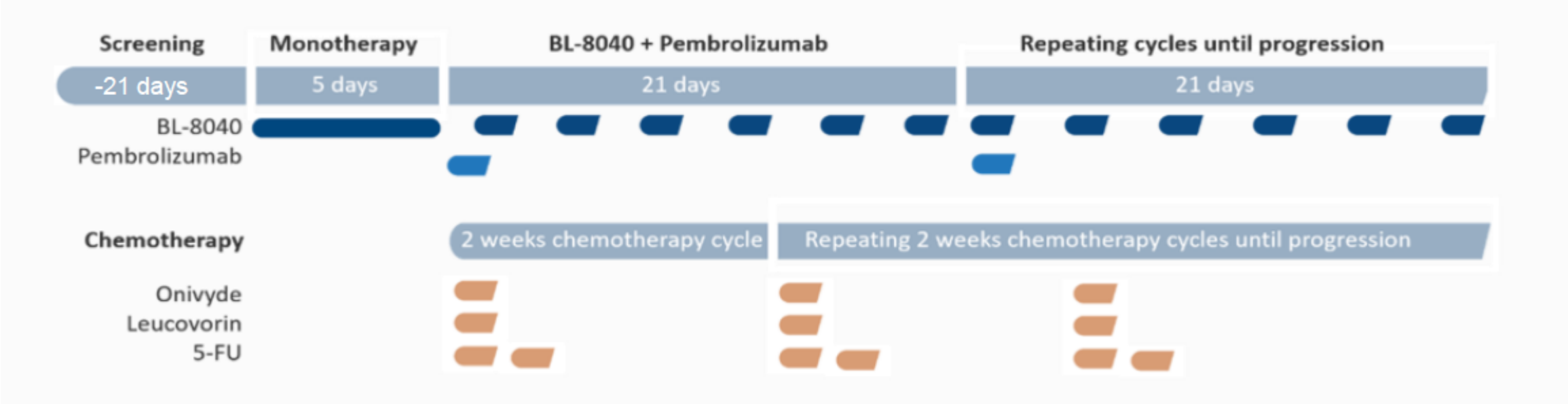
Methods



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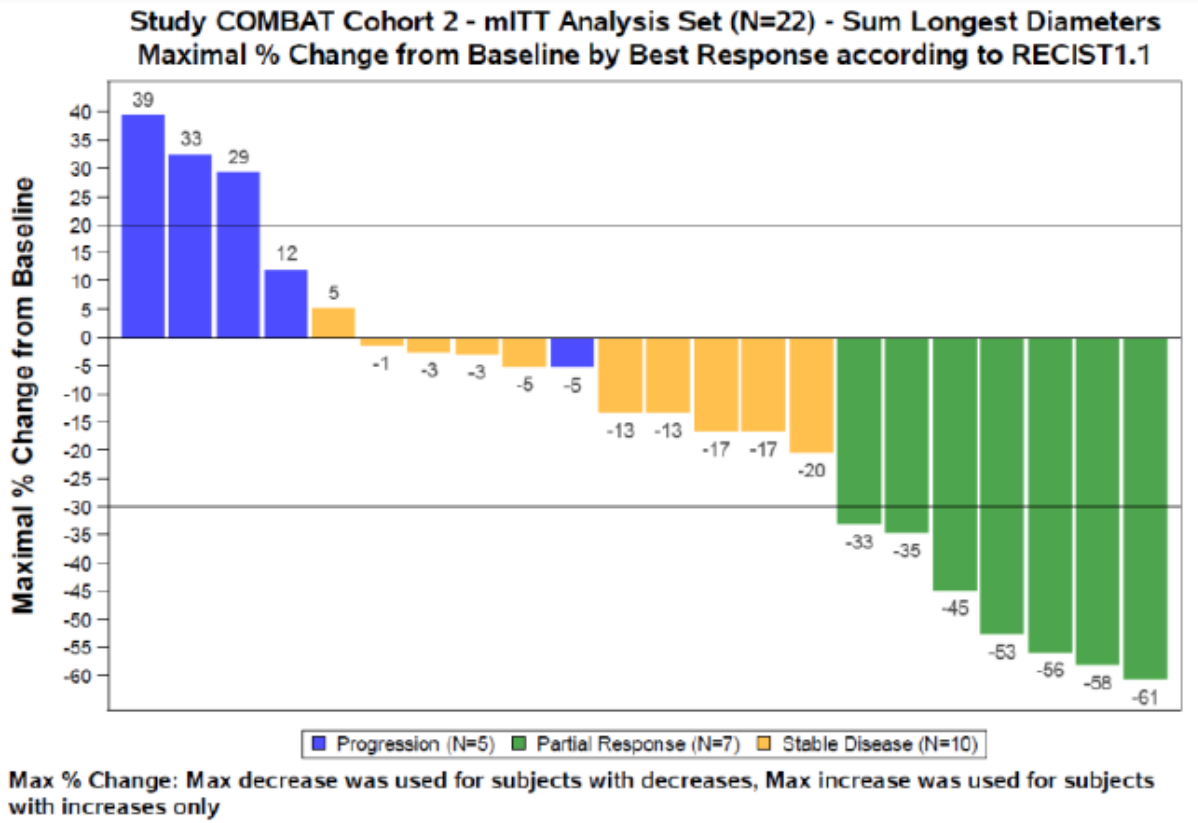
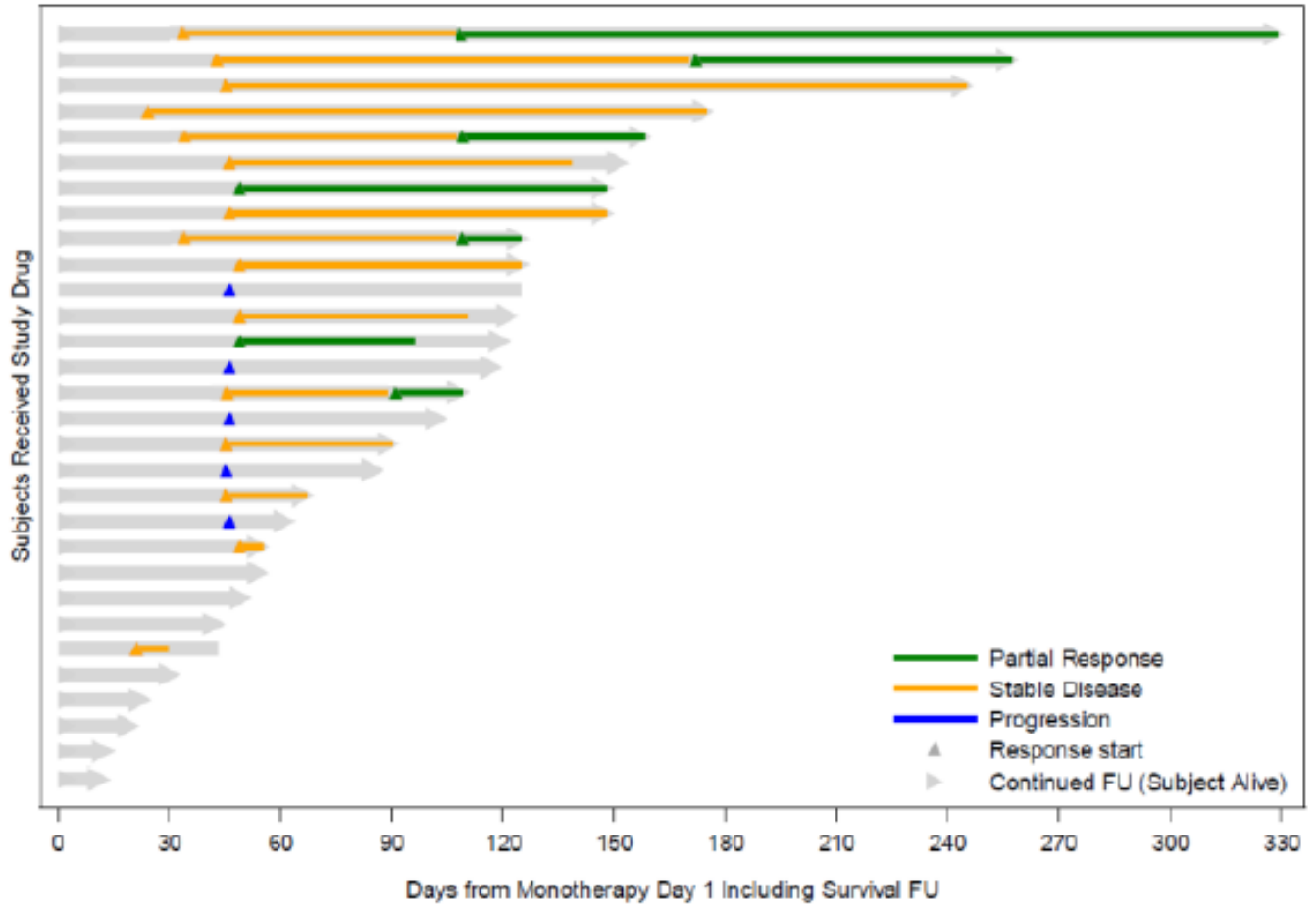
Results

Safety cohort N=30	Any grade, n (%)	Grade 3–4,n (%)
All Adverse events (AEs) Related to any of the study drugs	87.5%	
Adverse events reported in >15% of the patients		
Vomiting	14(47%)	2 (7%)
Diarrhea	13 (43%)	4 (13%)
Asthenia	13 (43%)	3 (10%)
Injection site pain	12 (40%)	1 (3%)
Nausea	12 (40%)	--
Anemia	8 (27%)	1 (3%)
Pruritus	8 (27%)	1 (3%)
Generalized pruritus	7 (23%)	--
Skin Hyperpigmentation	7 (23%)	--
Rash	5 (17%)	--
Decrease Appetite	5 (17%)	2 (7%)



Max % Change: Max decrease was used for subjects with decreases, Max increase was used for subjects with increases only

Results



Subjects with no response category are Non-Evaluable Subjects

Conclusions – Targeting CXCR4

- Inhibition of CXCR4 with BL-8040 may overcome the stromal CXCL12 mediated immune exclusion phenotype seen in pancreatic adenocarcinoma as demonstrated in preclinical models.
- *Cohort 1 BL-8040 plus pembrolizumab had modest clinical activity (1 PR and 9 SD out of 29 subjects).*
- Cohort 2 BL-8040 plus pembrolizumab plus liposomal irinotecan/5-FU/LV had more promising clinical activity (35%) compared to historical data (16%, NAPOLI-1 study).
- Longer follow up and a future randomized study with a control arm are needed
- CXCR4 inhibition strategies could be important in other tumor types with desmoplasia/cancer-associate fibroblast mediated T-cell exclusion (e.g. breast cancer)

First results of phase I/II studies evaluating viral vector-based heterologous prime/boost immunotherapy against predicted HLA class I neoantigens demonstrate CD8 T cell responses in patients with advanced cancers

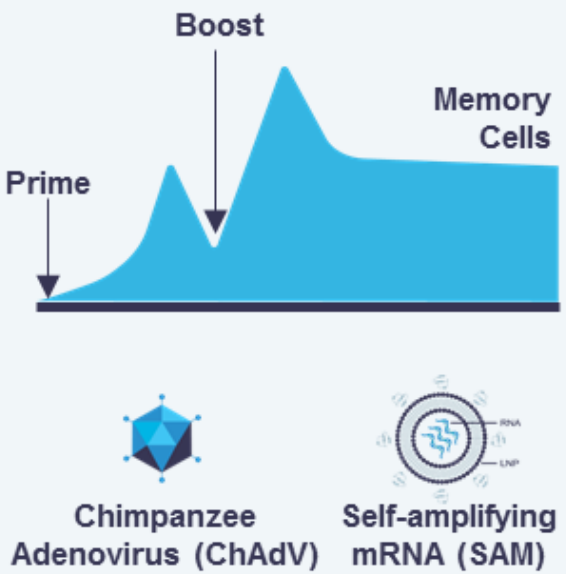
Melissa Johnson[1], Alex Spira[2], David Carbone[3], Charles Drake[4], Brian Henick[4], Matthew Ingram[4], Kamilah Caldwell[5], Shawn Chan[5] Meghan Hart[5], Ashley Malloy[5], Elizabeth Maloney[5], Christine Palmer[5], Aaron Yang[5], Mike Zhong[5], Paul Basciano[6], Eirini Bournazou[6], Andrew Ferguson[5], Daniel Catenacci[7]

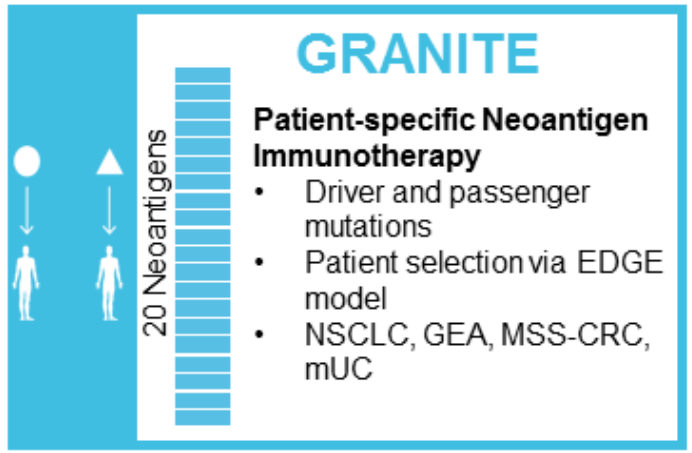
1 Sarah Cannon Research Institute, Tennessee Oncology PLLC, Nashville, Tennessee, USA; 2 Virginia Health Specialists, Fairfax, Virginia, USA; 3 The Ohio State University Medical Center, Columbus, Ohio, USA; 4 Columbia University Medical Center, New York, New York, USA; 5 Gritstone Oncology, Emeryville, California, USA; 6 Bristol-Myers Squibb, Lawrenceville, New Jersey, USA; 7 University of Chicago Comprehensive Cancer Center, Chicago, IL, USA

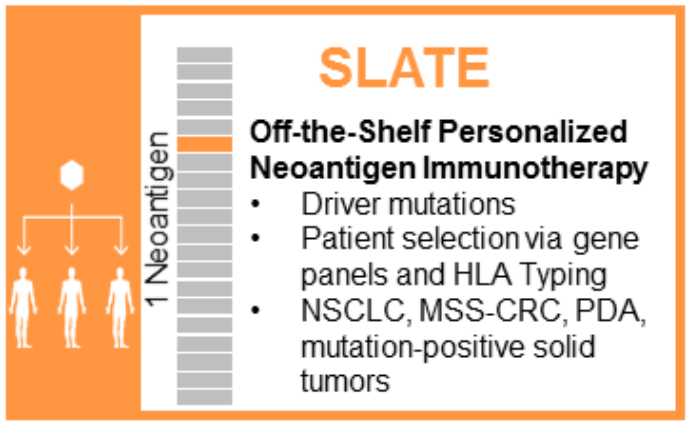
Methods

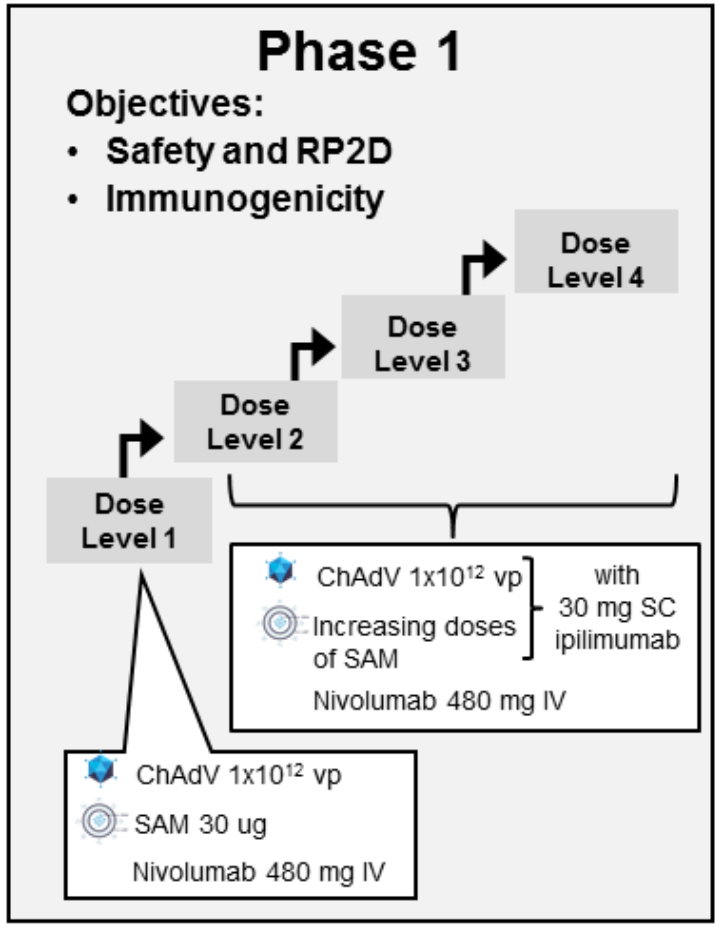
1. Neoantigen Prediction via EDGE

2. Heterologous Prime/Boost









EDGE = Epitope Discovery in Cancer Genomes; SC = subcutaneous; vp = viral particles

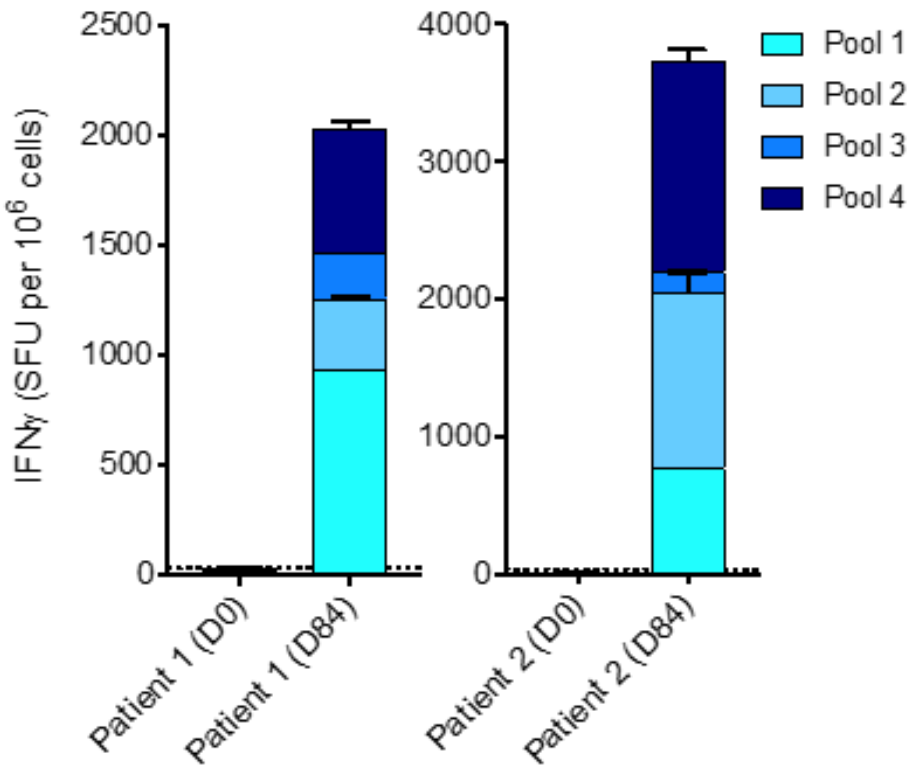
Results

	GRANITE (n=5)		SLATE (n=3)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Treatment-related adverse events				
Fever	6	0	0	0
Skin rash	2	0	0	0
Diarrhea	2	0	0	0
Fatigue	2	0	0	0
CK Elevation	0	1[a]	0	0
Injection-site reactions	1	0	0	0
Myalgia	0	0	1	0
Pruritus	0	0	1	0
SAEs				
Fever	2[b]	0	0	0
Cervical Fracture	0	0	0	1[c]
Heart Failure	0	1[c]	0	0

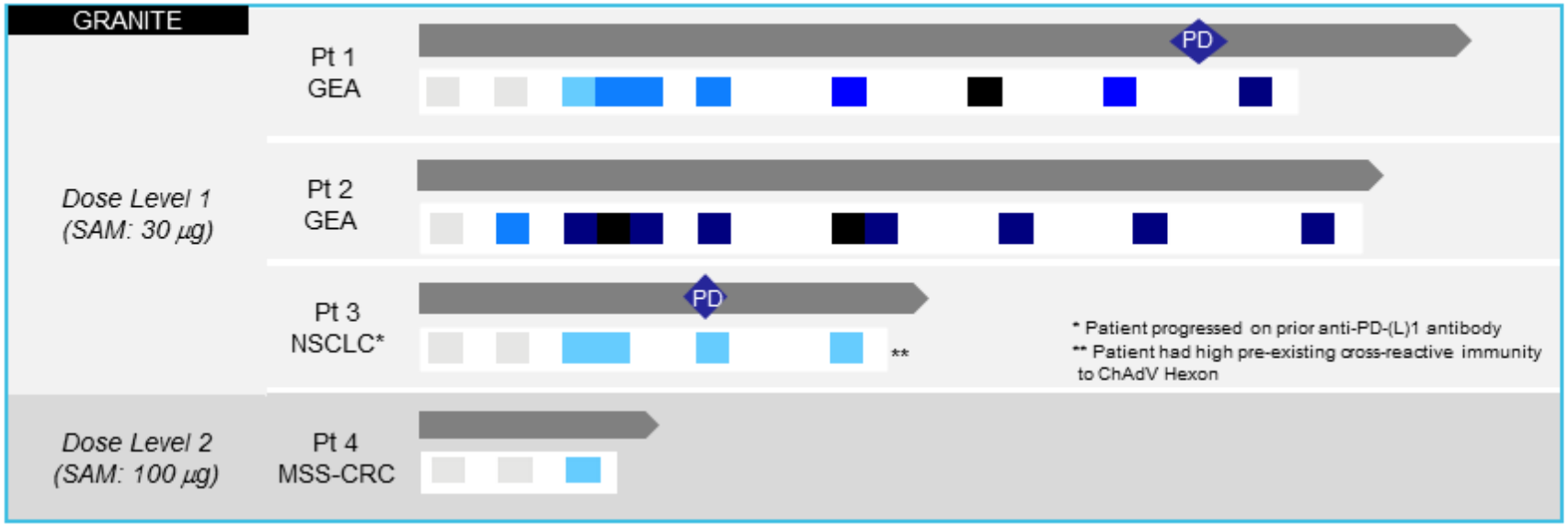
No DLTs have been observed to date

a Self-limiting, asymptomatic increase in creatine kinase
b Both SAEs of fever occurring in the same patient
c Not treatment-related

Ex vivo ELISpot responses to 4 different peptide pools show polyclonal responses



Results

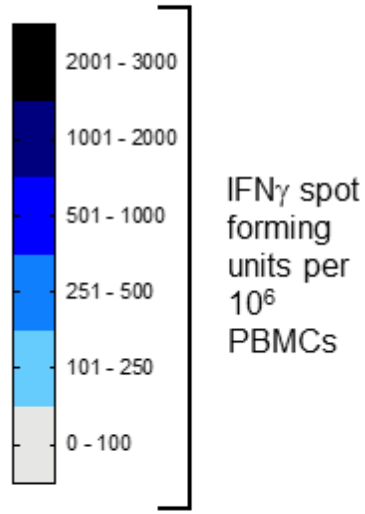


ChAdV $1x10^{12}$ vp

SAM 30 / 100 µg

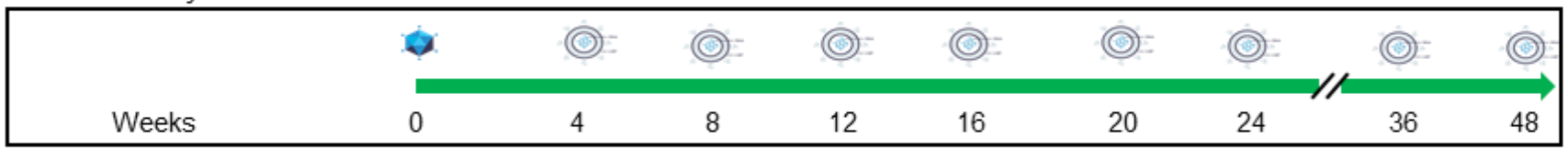
Nivolumab 480 mg Q4W IV

Ex vivo (overnight) ELISpot for $CD8^+$ T cell responses



IFNγ spot forming units per 10^6 PBMCs

Planned study treatment



PD = progressive disease based on RECIST v1.1; both patients treated beyond PD

Conclusions – mRNA Neoantigen Vaccination

- One of the first neoantigen mRNA viral vector based/self-amplifying vaccination strategies to treat patients with active malignancies.
- The GRANITE and SLATE vaccination strategies with nivolumab were well tolerated with primarily grade 1-2 adverse events and limited injection site reactions in the first reported 8 patients.
- ELISA spot assays have demonstrated T-cell responses against the neoantigen vaccine sequences.
- No efficacy data presented yet.
- In past vaccine oncology studies, T-cell reactivity to vaccines has not necessarily translated to clinical efficacy. Need follow up data for this study!

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Outline

- Lung cancer clinical trials
- Novel agents and settings
- Biomarker studies
- Adverse event management

Association of KRAS mutational status with response to pembrolizumab monotherapy given as first-line therapy for PD-L1-positive advanced nonsquamous NSCLC in KEYNOTE-042

Roy S. Herbst,[1] **Gilberto Lopes**,[2] Dariusz M. Kowalski,[3] Kazuo Kasahara,[4] Yi-Long Wu,[5] Gilberto Castro Jr,[6] Byoung Chul Cho,[7] Hande Z. Turna,[8] Razvan Cristescu,[9] Deepti Aurora-Garg,[9] Jared Lunceford,[9] Julie Kobie,[9] Mark Ayers,[9] M. Catherine Pietanza,[9] Bilal Piperdi,[9] Tony S.K. Mok[10]

[1]Yale University School of Medicine, Yale Cancer Center, New Haven, CT, USA; [2]Sylvester Comprehensive Cancer Center at the University of Miami, Miami, FL, USA; [3]Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland; [4]Kanazawa University Hospital, Kanazawa, Japan; [5]Guangdong Lung Cancer Institute, Guangdong, China; [6]Instituto do Cancer do Estado de Sao Paulo, Sao Paulo, Brazil; [7]Yonsei Cancer Center, Seoul, South Korea; [8]Instanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey; [9]Merck & Co., Inc., Kenilworth, NJ, USA; [10]State Key Laboratory of South China, Chinese University of Hong Kong, Shatin, Hong Kong Special Administrative Region, China

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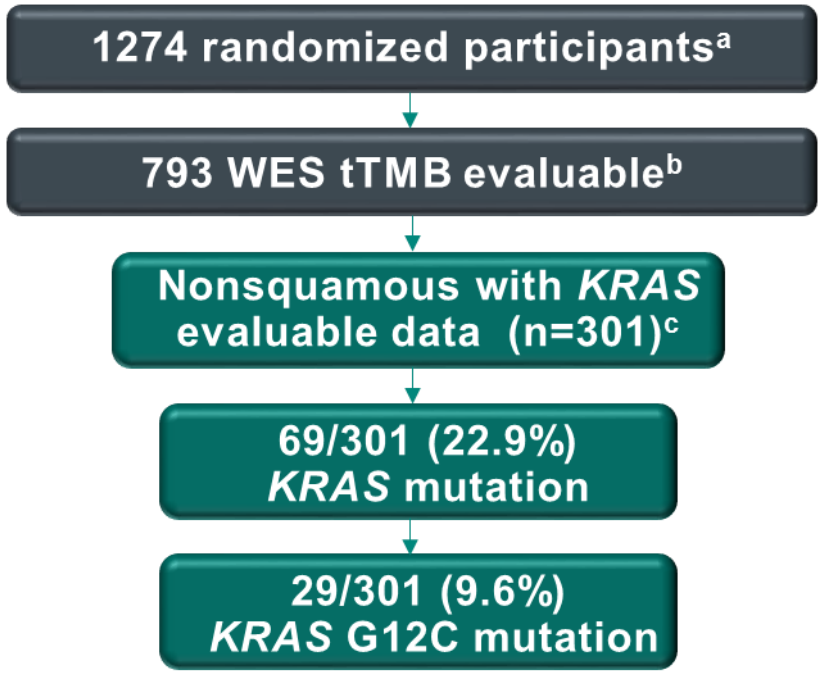
Methods

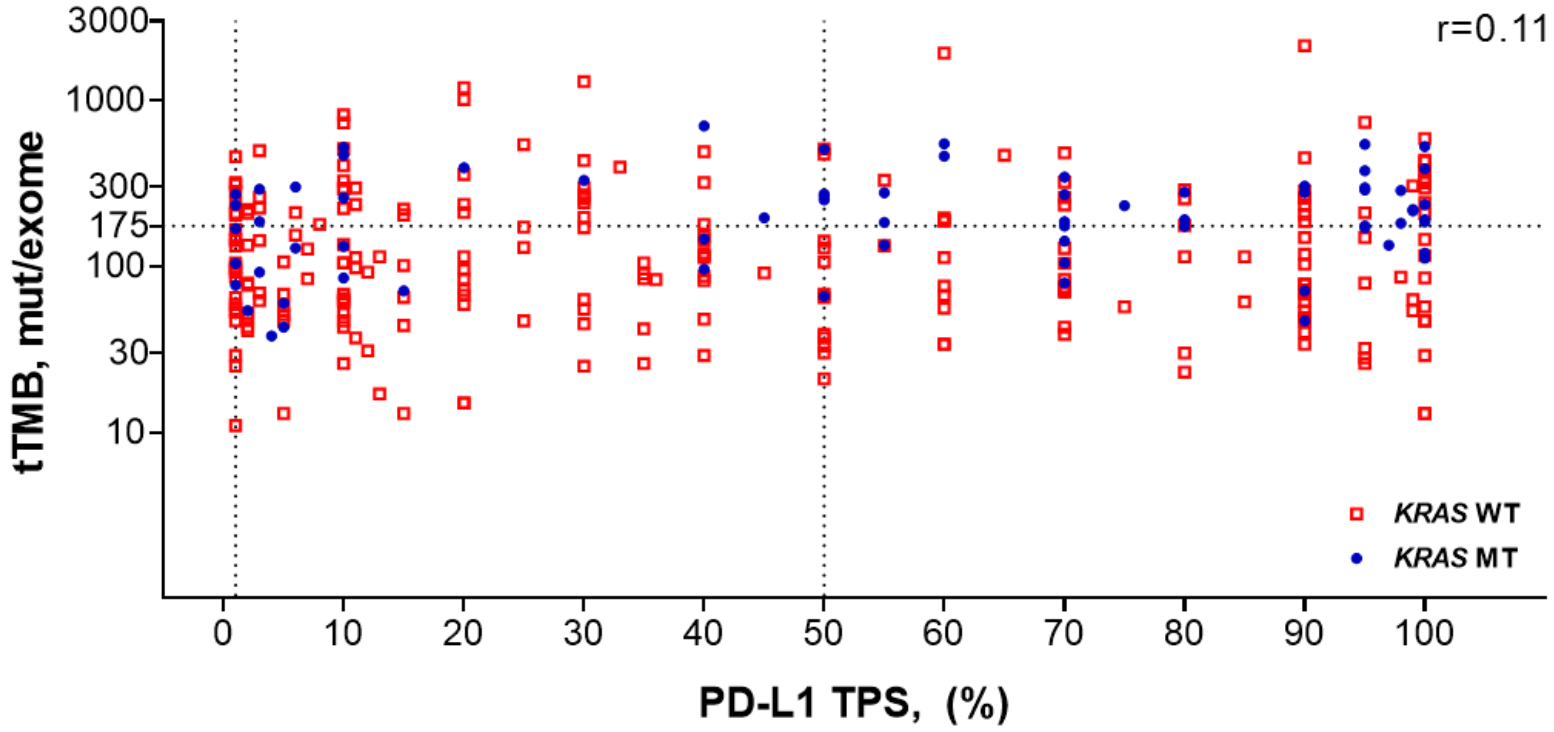
KEYNOTE-042

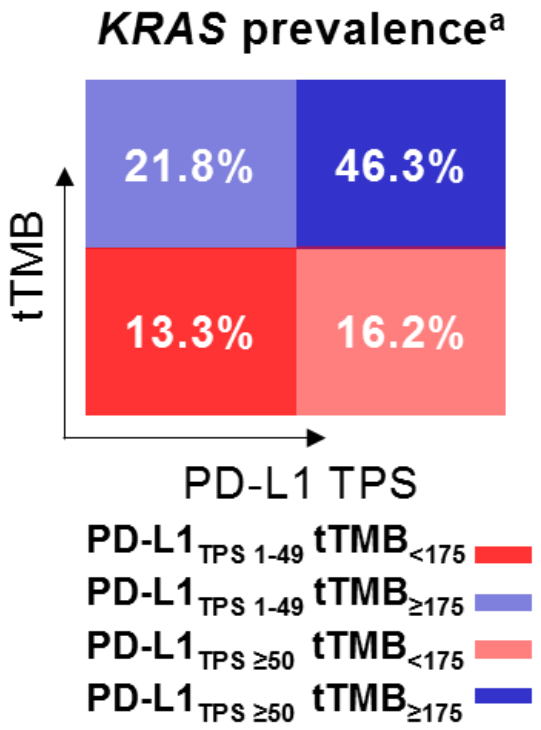
- Study design
  - Open label phase 3 trial
  - Untreated locally advanced or metastatic NSCLC of any histology
  - Treatment-naïve, PD-L1-positive (TPS ≥1%), without sensitizing *EGFR* or *ALK* alterations
- Randomization (N=1274)
  - 1:1 to pembrolizumab 200 mg (Q3W) or platinum-based chemotherapy[a]
  - Stratified by region (east Asia vs rest of world), ECOG PS (0 vs 1), Histology (squamous vs nonsquamous), PD-L1 TPS (≥50% vs 1-49%)
- End points
  - Primary: OS
  - Secondary: PFS and ORR, and safety



[a]Carboplatin AUC 5 or 6 Q3W + Paclitaxel 200 mg/m2 Q3W OR Carboplatin AUC 5 or 6 Q3W + Pemetrexed 500 mg/m2 Q3W; Pemetrexed maintenance therapy was optional but strongly encouraged for patients with nonsquamous histology.

Results

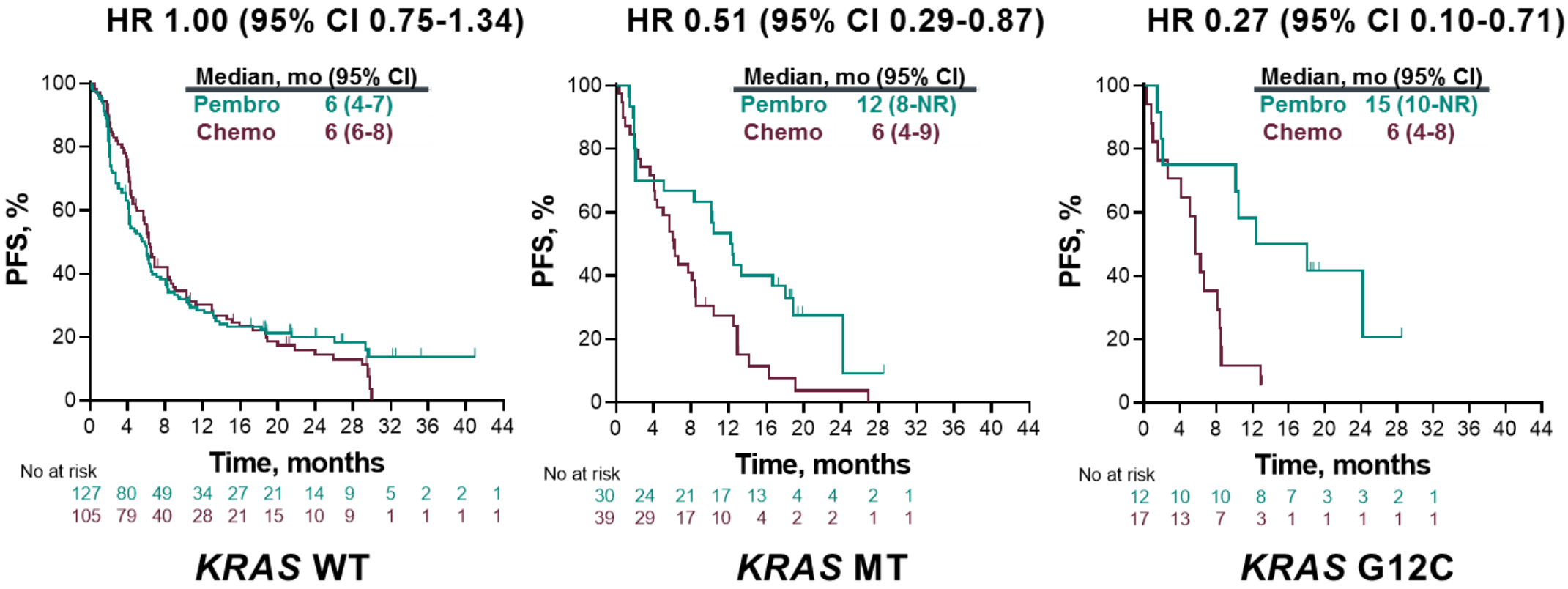




Prevalence of *KRAS* mutations was higher among patients with higher vs lower levels of PD-L1 expression and tTMB

All patients were PD-L1-positive (TPS ≥1%). tTMB was graphed on a $\log_{10}$ scale and PD-L1 TPS on a linear scale. Dotted horizontal line denotes tTMB at 175 mutations/exome and vertical lines denote PD-L1 at TPS 1% and 50%. [a]Prevalence of *KRAS* mutations at indicated tTMB (< and ≥175 mutations/exome) and PD-L1 (TPS 1-49% and ≥50%) levels.
Data cutoff date: Sep 4, 2018.

Results



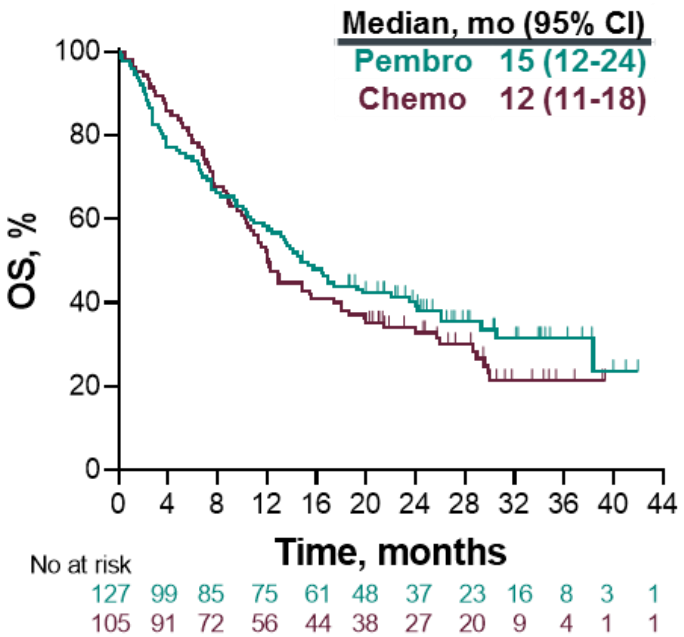
Total ITT Population (N=1274): HR 1.05 (95% CI 0.93-1.19)

All patients were PD-L1-positive (TPS ≥1%).

Data cutoff date: Sep 4, 2018.

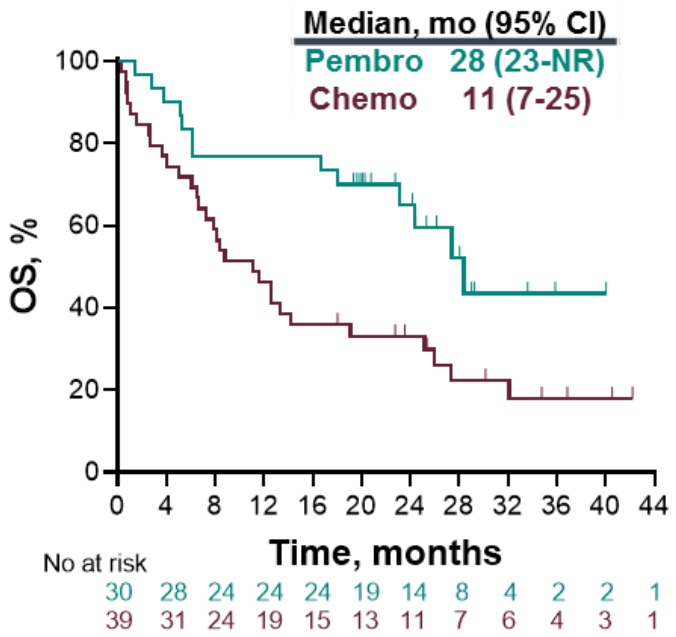
Results

HR 0.86 (95% CI 0.63-1.18)



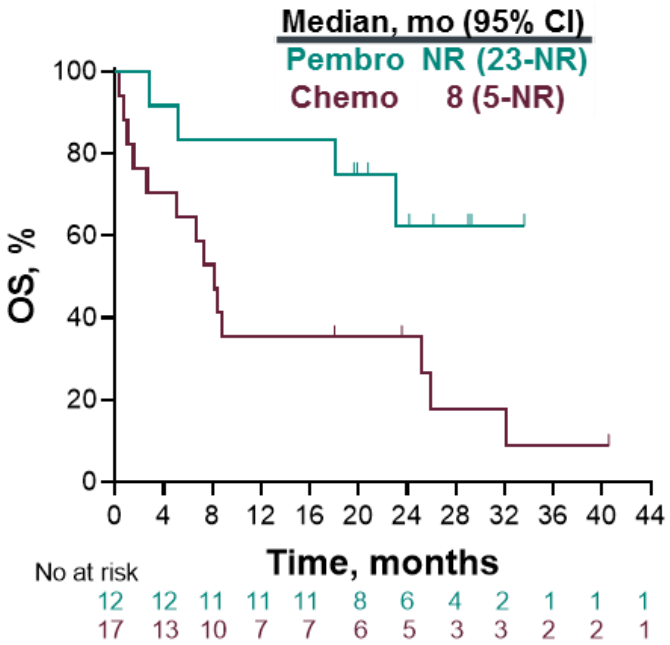
KRAS WT

HR 0.42 (95% CI 0.22-0.81)



KRAS MT

HR 0.28 (95% CI 0.09-0.86)



KRAS G12C

Total ITT Population (N=1274): HR 0.82 (95% CI 0.71-0.93)

All patients were PD-L1-positive (TPS ≥1%).

Data cutoff date: Sep 4, 2018.

KRAS mutational status and efficacy in KEYNOTE-189: pembrolizumab (pembro) plus chemotherapy (chemo) vs placebo plus chemo as first-line therapy for metastatic non-squamous NSCLC

Shirish M. Gadgeel[1], Delvys Rodriguez-Abreu[2], Enriqueta Felip[3],Emilio Esteban[4], Giovanna Speranza[5], Martin Reck[6], Rina Hui[7], Michael Boyer[8], Edward B. Garon[9], Hidehito Horinouchi[10], Razvan Cristescu[11], Deepti Aurora-Garg[11], Jared Lunceford[11], Julie Kobie[11], Mark Ayers[11], Bilal Piperdi[11], M. Catherine Pietanza[11], Marina C. Garassino[12]

[1]Karmanos Cancer Institute, Detroit, MI, USA; [2]Complejo Hospitalario Universitario Insular Materno-Infantil de Gran Carnaria, Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain; [3]Hospital Universitario Central de Asturias, Oviedo, Spain; [4]Vall d'Hebron University, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [5]Centre inegre de cancerologie de la Monteregie, Universite de Sherbrooke, Greenfield Park QC, Canada; [6]LungenClinic, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany; [7]Westmead Hospital and University of Sydney, Sydney, NSW, Australia; [8]Chris O'Brien Lifehouse, Camperdown, NSW, Australia; [9]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [10]National Cancer Center Hospital, Tokyo, Japan; [11]Merck & Co., Inc., Kenilworth, NJ, USA; [12]Fondazione IRCCS Instituto Nazionale dei Tumori, Milan, Italy

Society for Immunotherapy of Cancer

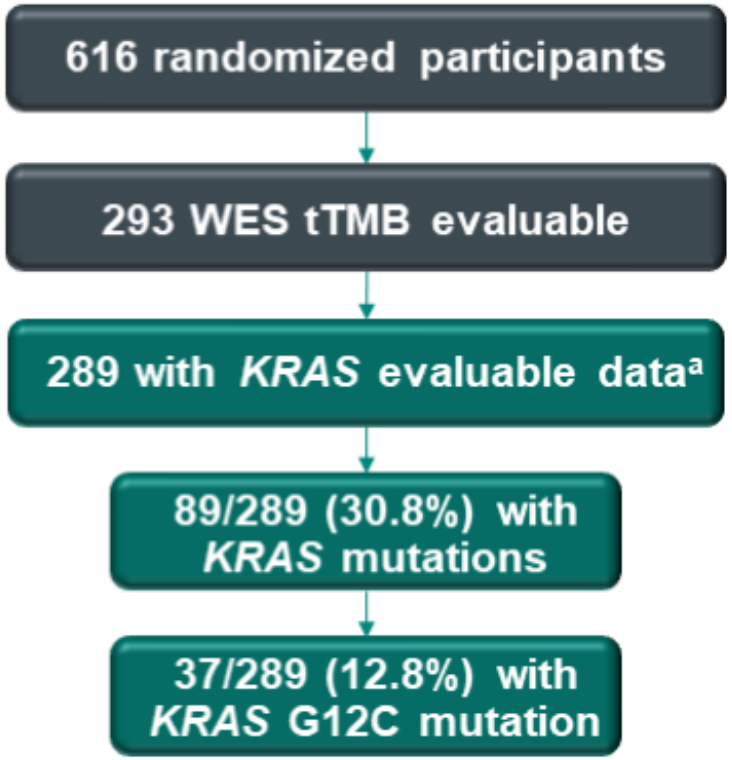
Methods

KEYNOTE-189 (NCT02578680)[1]

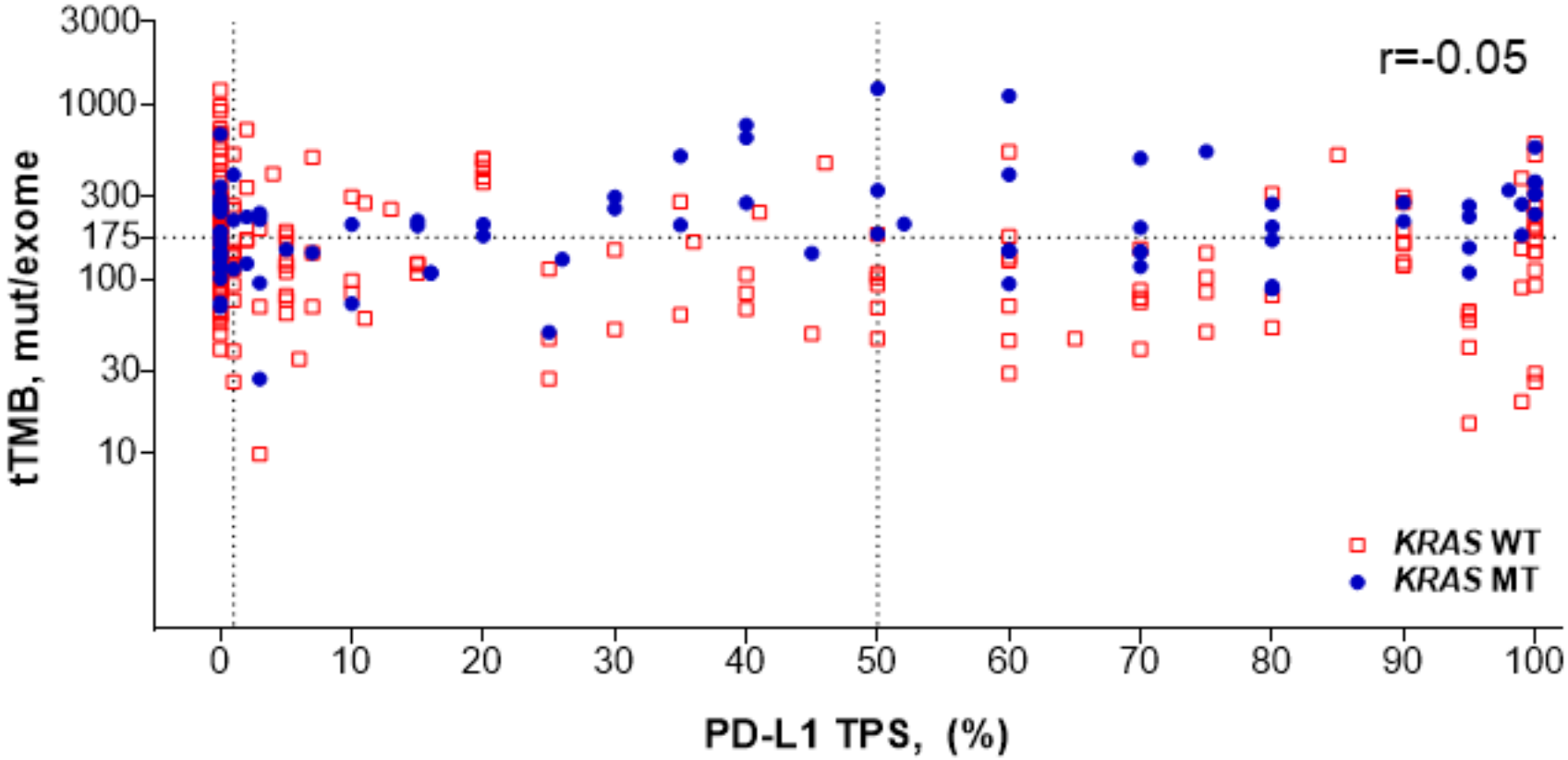
- Phase 3, double-blind trial
- 2:1 randomization to pembrolizumab + pemetrexed + platinum or placebo + pemetrexed + platinum

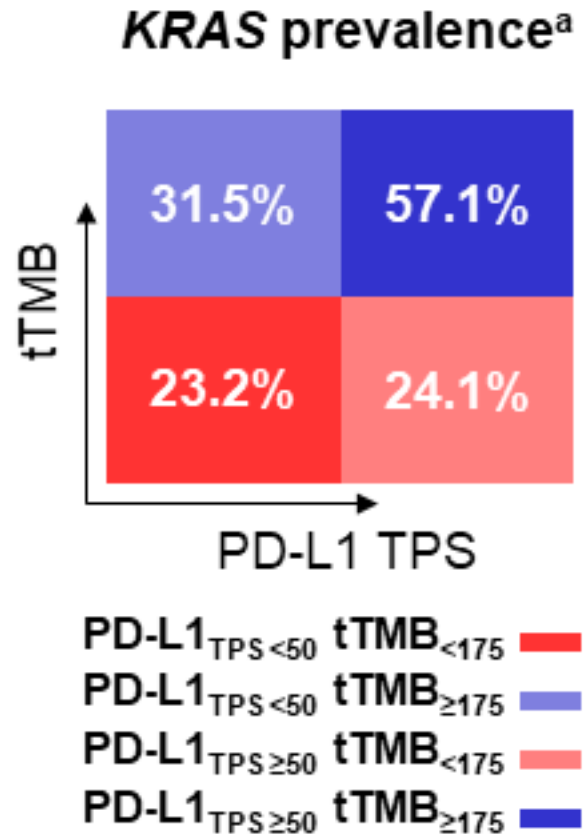
Association of *KRAS* Mutations with Outcomes

- Whole-exome sequencing (WES) of tumor tissue and matched normal DNA (blood) were performed[2]
- Prevalence of *KRAS* mutations (including G12C) and associations of *KRAS* mutations with tTMB and PD-L1 as well as with clinical efficacy were explored
- Due to limited size of the subgroups, data are summarized descriptively



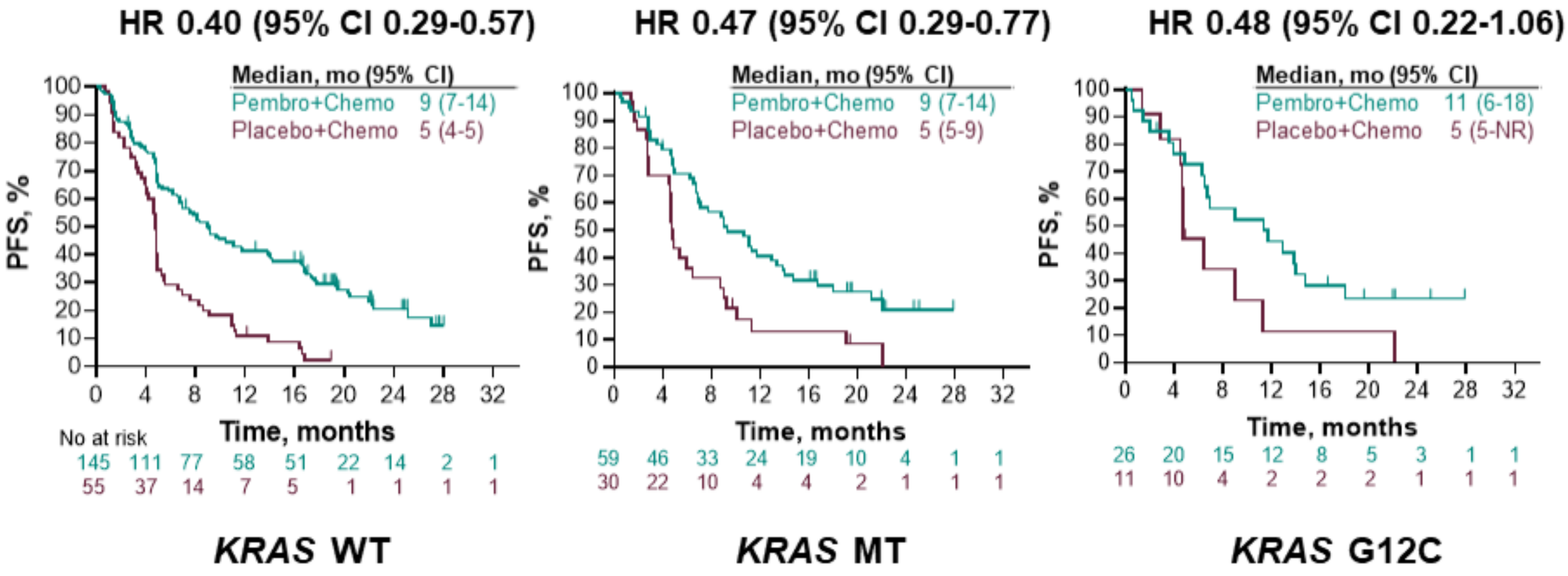
Results





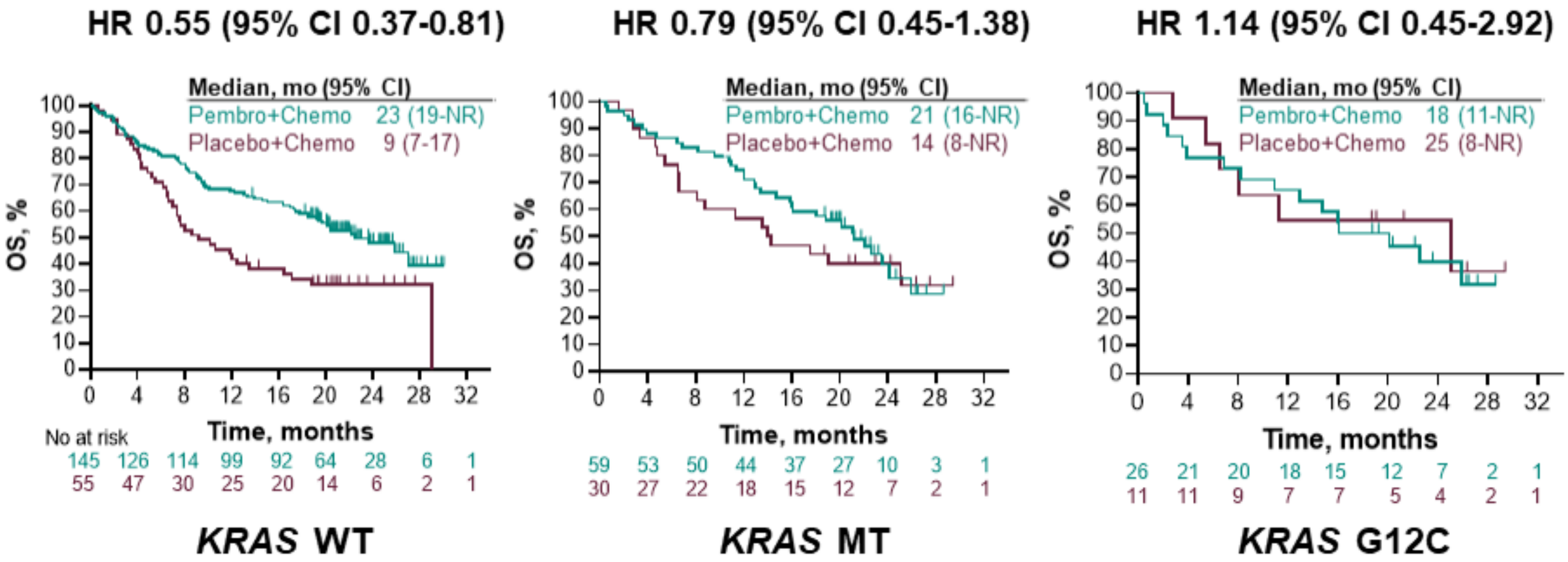
Prevalence of *KRAS* mutations was higher among patients with higher vs lower levels of PD-L1 expression and tTMB

Results



Total ITT Population (N=616): HR 0.48 (95% CI, 0.40-0.58)[1]

Results



Total ITT Population (N=616): HR 0.56 (95% CI, 0.45-0.70)[1]

Conclusions – KRAS and Anti-PD-1 activity

- Prior studies have implicated PD-L1 expression in higher and longer PFS with anti-PD-1 therapy in advanced KRAS mut vs wt NSCLC. *Dong ZY, et al, Clin Cancer Res, 2017*
- Unclear if KRAS mutation is directly related to immune mechanisms or is a surrogate marker (such as higher TMB related to chronic tobacco exposure)
- In these two studies, KRAS mutations in NSCLC were associated with higher TMB and positive PD-L1 status, *but 13-23% have low-negative TMB/PD-L1 status*.
- Presence of KRAS mutation generally enriches for greater clinical activity with anti-PD-1 therapies than chemotherapy alone.

Joshua Brody, MD

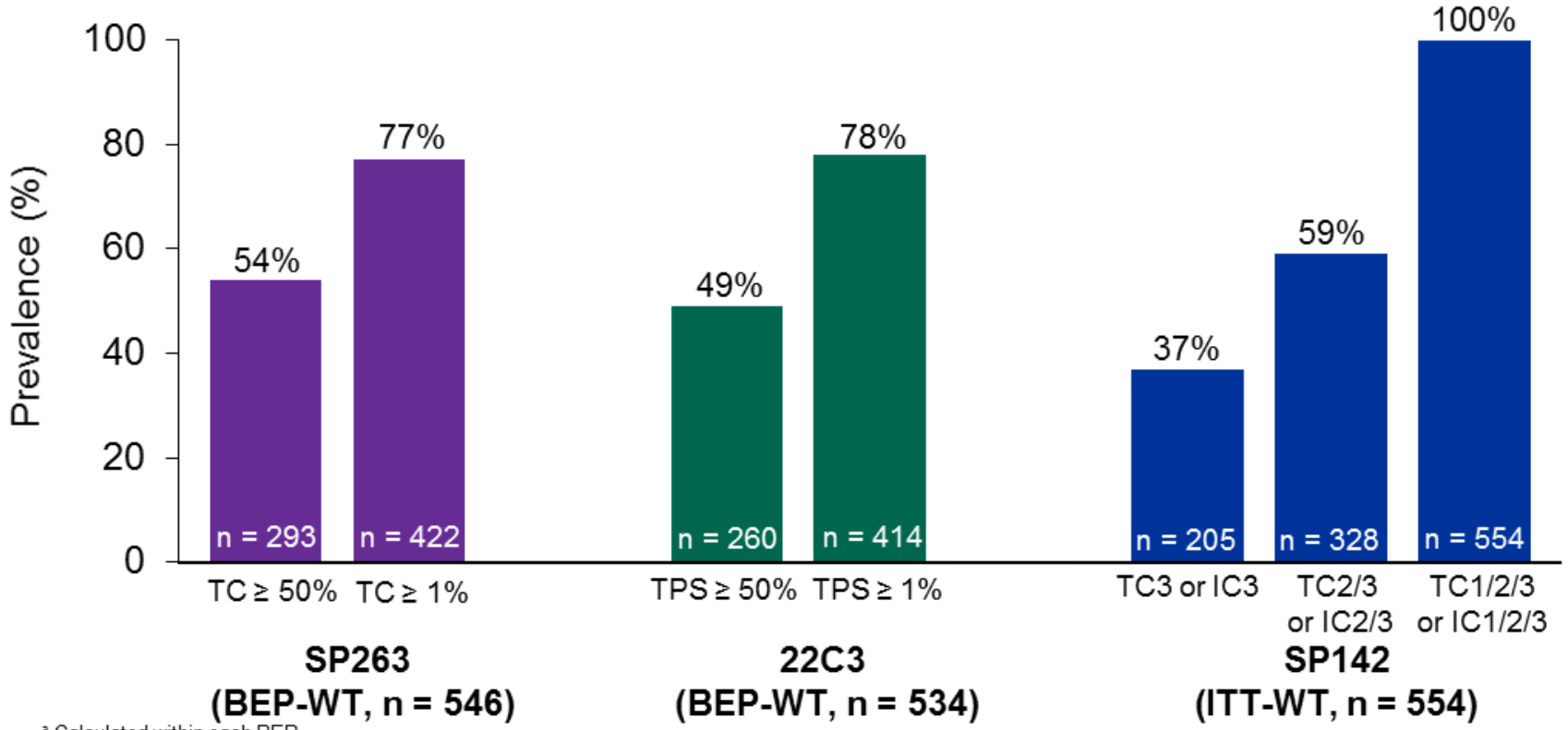
- Associate Professor of Medicine, Hematology and Medical Oncology
- Director of the Lymphoma Immunotherapy Program at the Icahn School of Medicine at Mount Sinai
- Specialty: Hematology-Oncology

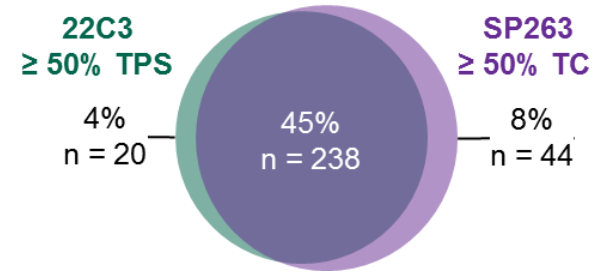
Clinical efficacy of atezolizumab in biomarker subgroups by SP142, SP263 and 22C3 PD-L1 immunohistochemistry assays and by blood tumour mutational burden: Results from the IMpower110 study

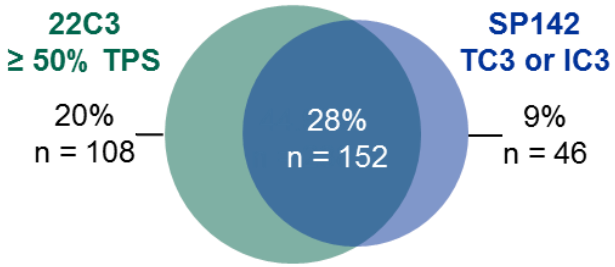
Roy S. Herbst,[1] Filippo De Marinis,[2] Giuseppe Giaccone,[3] Niels Reinmuth,[4] Alain Vergnenegre,[5] Carlos Henrique Barrios,[6] Masahiro Morise,[7] Enriqueta Felip,[8] Zoran Andric,[9] Sarayut Geater,[10] Mustafa Özgüroğlu,[11] Simonetta Mocci,[12] Mark McCleland,[12] Wei Zou,[12] Ida Enquist,[12] Kimberly Komatsubara,[12] Yu Deng,[12] Hiroshi Kuriki,[12] David Spigel,[13] Jacek Jassem[14]

[1]Yale School of Medicine, New Haven, CT, USA; [2]European Institute of Oncology, Milan, Italy; [3]Weill Cornell Medical Center, New York, NY, USA; [4]Asklepios Lung Clinic, Munich-Gauting, Germany; [5]Limoges University Hospital, Limoges, France; [6]Centro de Pesquisa Clínica, Hospital São Lucas, PUCRS, Porto Alegre, Brazil; [7]Nagoya University Graduate School of Medicine, Aichi, Japan; [8]Vall d'Hebron University Hospital, Barcelona, Spain; [9]Clinical Hospital Center Bezanijska Kosa, Belgrade, Serbia; [10]Prince of Songkla University - Hat Yai, Songkhla, Thailand; [11]Istanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine, Istanbul, Turkey; [12]Genentech, Inc, South San Francisco, CA, USA; [13]Sarah Cannon Research Institute, Nashville, TN, USA; [14]Medical University of Gdańsk, Gdańsk, Poland

Results – PD-L1 expression



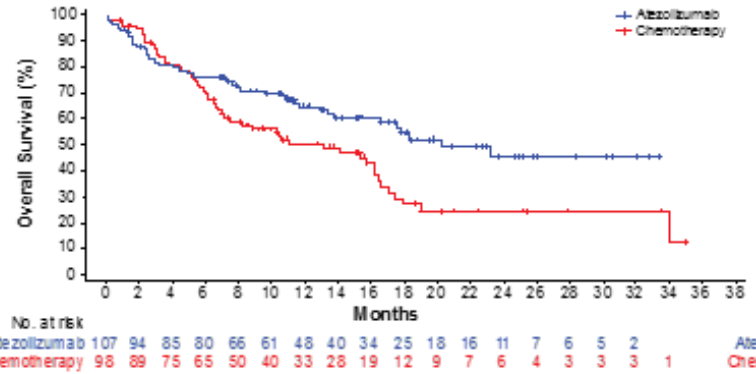




[a] Calculated within each BEP.
TC3 or IC3 = PD-L1 expression ≥ 50% TC or ≥ 10% IC;
TC2/3 or IC2/3 = PD-L1 expression ≥ 5% TC or IC; TC1/2/3 or IC1/2/3 = PD-L1 expression ≥ 1% TC or IC.

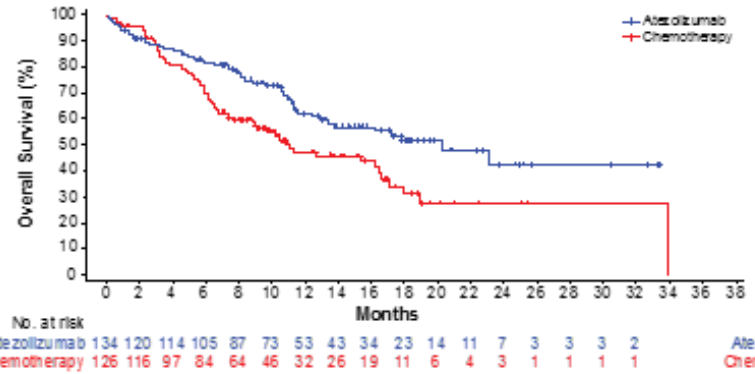
Results – OS in PD-L1-high subgroups

SP142 (TC3 or IC3-WT)[a]



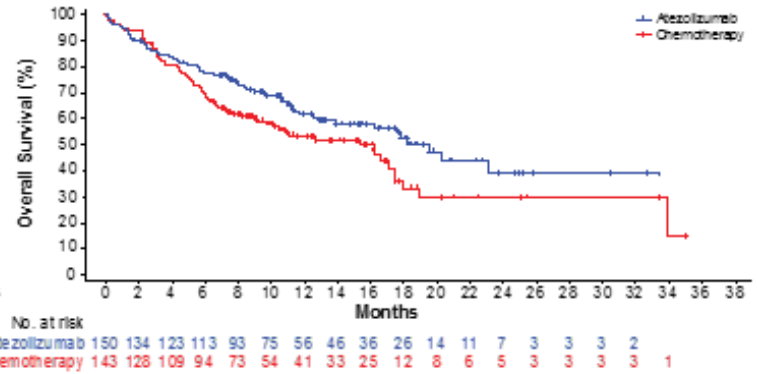
	Atezo (n = 107)	Chemo (n = 98)
mOS, mo	20.2	13.1
HR[b] (95% CI)	0.59 (0.40, 0.89)	

22C3 BEP-WT (TPS ≥ 50%)[a]



	Atezo (n = 134)	Chemo (n = 126)
mOS, mo	20.2	11.0
HR[c] (95% CI)	0.60 (0.41, 0.86)	

SP263 BEP-WT (TC ≥ 50%)[a]

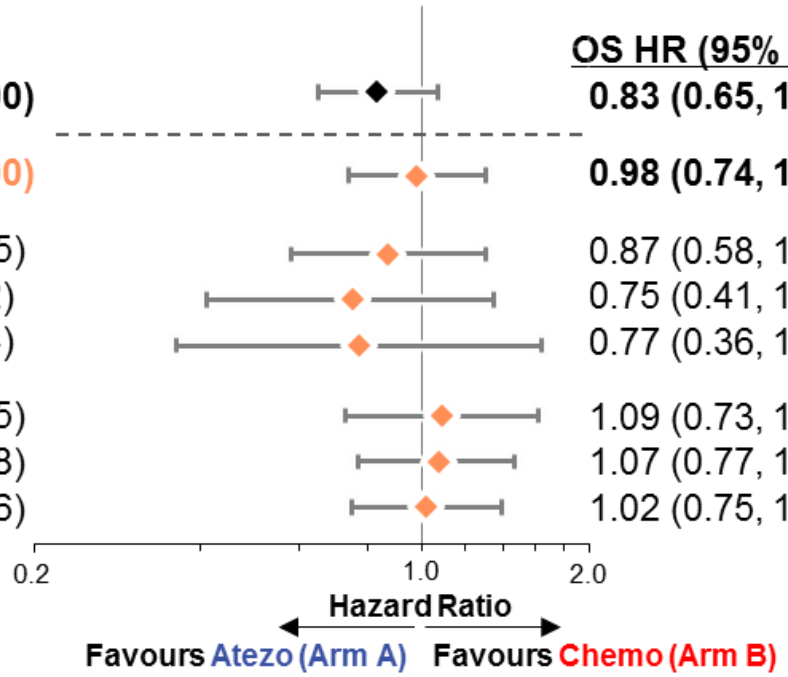


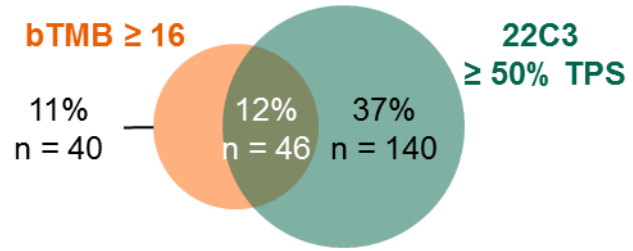
	Atezo (n = 150)	Chemo (n = 143)
mOS, mo	19.5	16.1
HR[c] (95% CI)	0.71 (0.50, 1.00)	

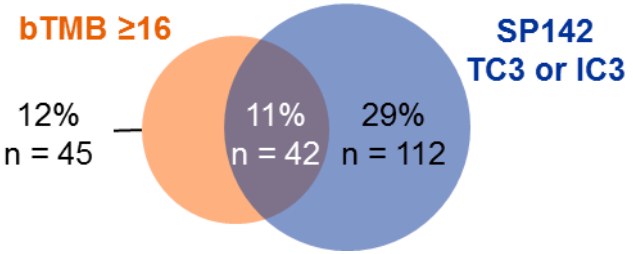
[a] SP142 TC1/2/3 or IC1/2/3-WT (n = 554); 22C3 BEP-WT (n = 534); SP263 BEP-WT (n = 546). [b] Stratified. [c] Unstratified.

Results - bTMB

Subgroup	n (%)	OS HR (95% CI)[a]	Median OS, mo Atezo	Median OS, mo Chemo
TC1/2/3 or IC1/2/3-WT	554 (100)	0.83 (0.65, 1.07)	17.5	14.1
bTMB BEP-WT	389 (100)	0.98 (0.74, 1.30)	13.3	15.3
bTMB ≥ 10	175 (45)	0.87 (0.58, 1.30)	11.2	10.3
bTMB ≥ 16	87 (22)	0.75 (0.41, 1.35)	13.9	8.5
bTMB ≥ 20	56 (14)	0.77 (0.36, 1.64)	17.2	10.5
bTMB < 10	214 (55)	1.09 (0.73, 1.62)	16.2	16.2
bTMB < 16	302 (78)	1.07 (0.77, 1.47)	12.9	15.3
bTMB < 20	333 (86)	1.02 (0.75, 1.39)	13.3	15.3







[a] Stratified HRs for SP142; unstratified HRs for bTMB.

Harmonization and standardization of panel-based tumour mutational burden (TMB) measurement: Real-world results and recommendations of the QuIP study

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Study methods

20 FFPE tumor samples with matched WES data
(10 NSCLC, 7 SCCHN, 3 CRC; prepared at the Institute of Pathology, Heidelberg)
6 gene panel assays; 15 testing centers

OTML	QIAseq	NEOplus	TSO500	ACADEMIC	F1
Lab 1	Lab 4	Lab 8	Lab 1	Lab 1	Lab 15
Lab 2	Lab 6	Lab 10	Lab 2	Lab 8	
Lab 3	Lab 7	Lab 11	Lab 7	Lab 11	
Lab 4	Lab 8	Lab 12	Lab 11		
Lab 5	Lab 9	Lab 13	Lab 14		

Gene panel assays

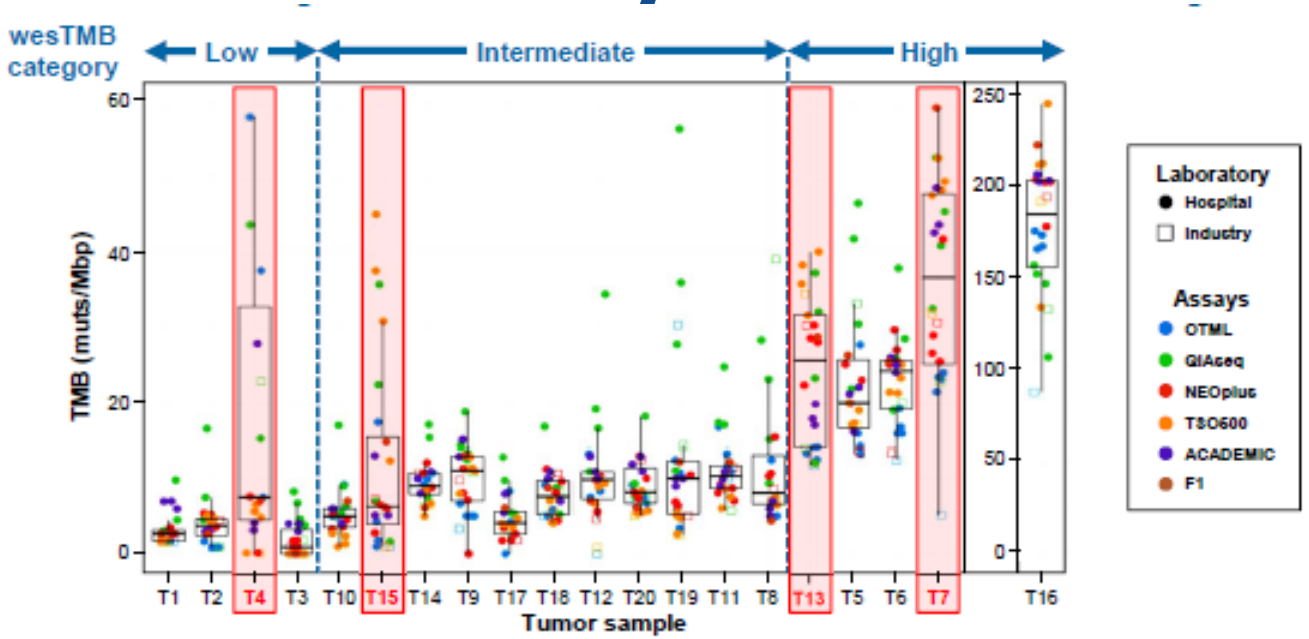
- Oncomine Tumor Mutational Load Assay (OTML; Thermo Fisher Scientific)
- QIAseq TMB panel (QIAseq; QIAGEN)
- NEOplus RUO assay (NEOplus; NEO New Oncology)
- TruSight Oncology 500 panel (TSO500; Illumina)
- A custom-designed academic panel (ACADEMIC)
- FoundationOne (F1; Foundation Medicine)

Comparative analyses

- TMB levels and correlations
- Bridging psTMB to wesTMB
- TMB classification
- Interlab comparisons
- Germline filtering

CRC, colorectal cancer; FFPE, formalin-fixed, paraffin-embedded; NSCLC, non-small cell lung cancer; SCCHN, squamous cell carcinoma of the head and neck; WES, whole exome sequencing; wesTMB, TMB derived using whole exome sequencing.

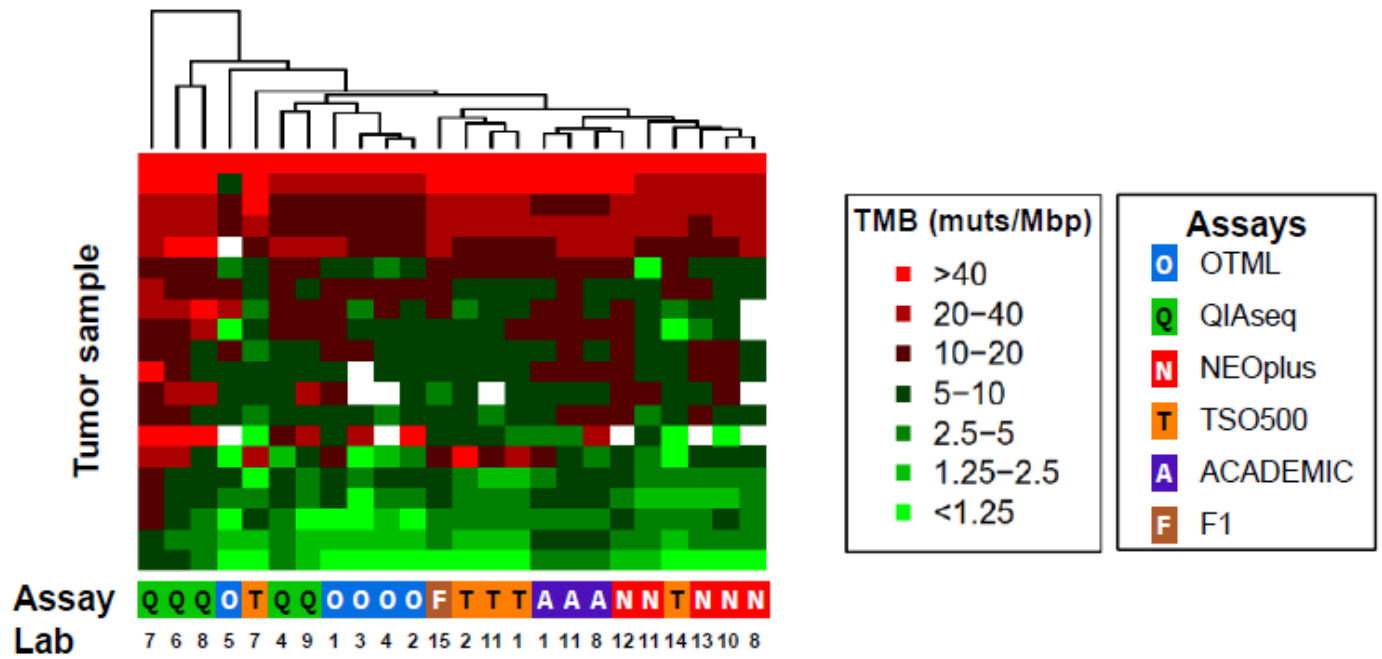
Results – psTMB of 20 tumor samples by 6 gene panel assays



psTMB ranged from 0–244 muts/Mbp (median 9.2 muts/Mbp)

Four samples showed a larger psTMB interquartile range compared with the remaining samples

Hierarchical Clustering of psTMB Levels

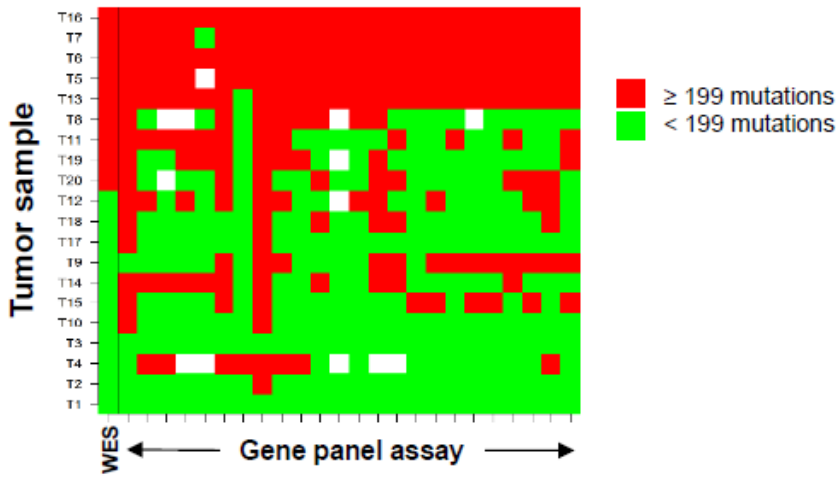


Data readouts based on the same sequencing panel often clustered together, demonstrating independence from the operating laboratory

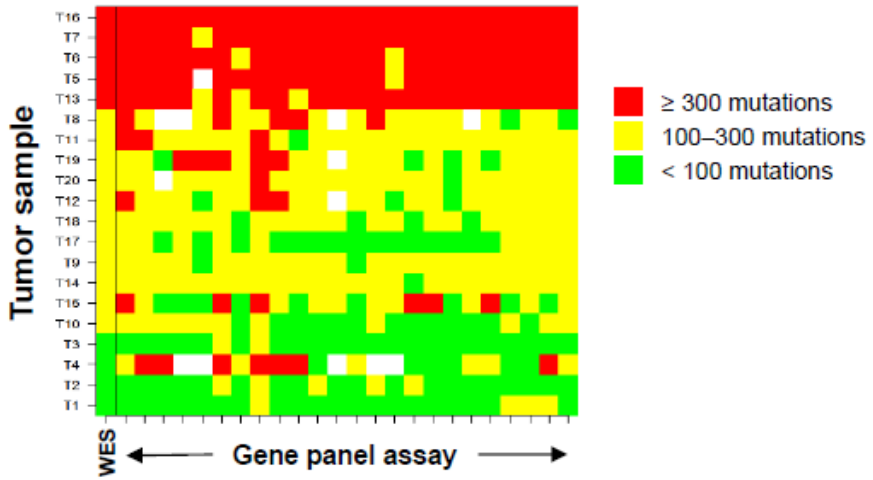
White boxes indicate insufficient DNA quality.

Evaluation of 2-Tier and 3-Tier TMB Classification Systems

2-tier classification
Cutpoint: 199 missense mutations



3-tier classification
Cutpoints: 100 and 300 missense mutations

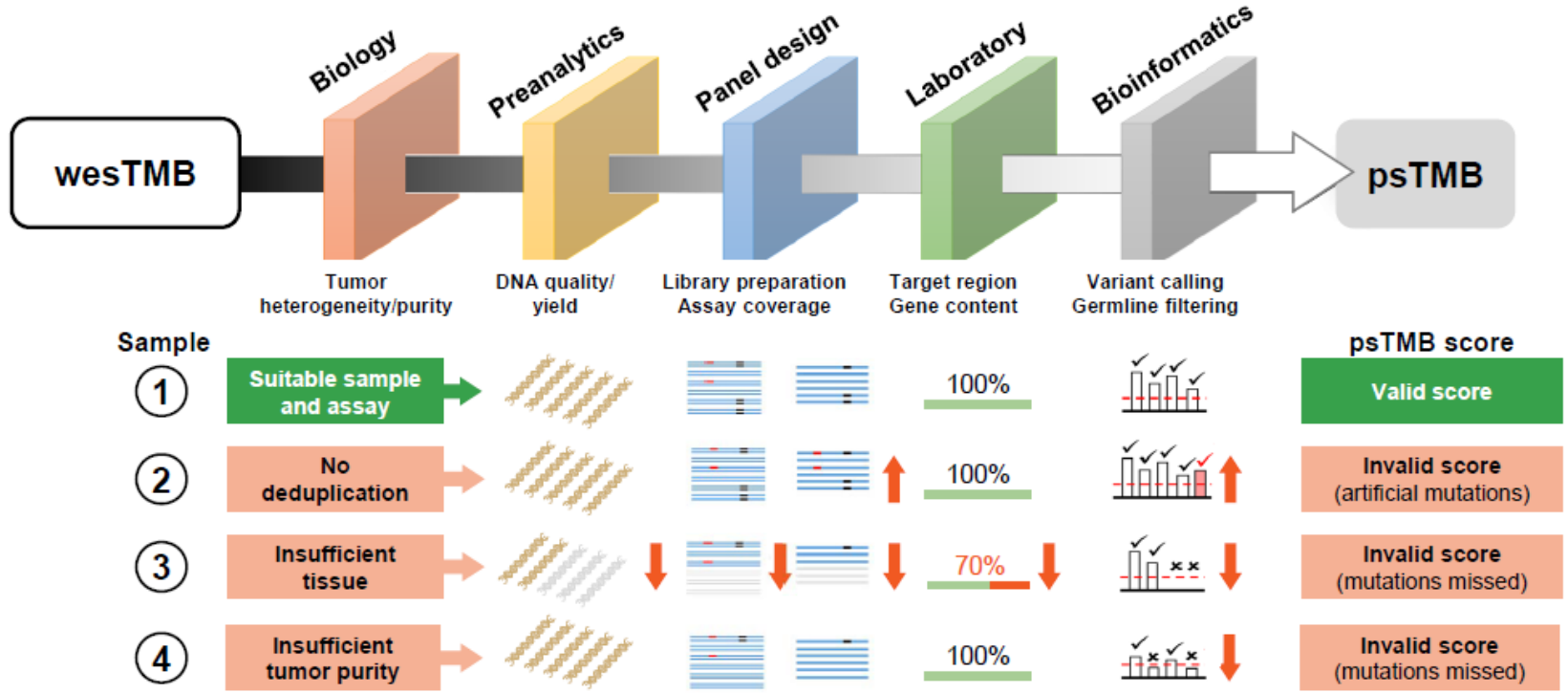


psTMB vs wesTMB agreement

74.9% (2-tier classification)

76.7% (3-tier classification)

Assay-Independent and Assay-Specific Parameters Influence the Accuracy of psTMB Scores



Confounders of psTMB estimation included fixation artefacts, DNA input, sequencing depth, genome coverage, and VAF cutpoint

VAF, variant allele frequency.

Conclusions

- There are small differences between different clinical PD-L1 assays, and moderate differences between different TMB assays

Outline

- Lung cancer clinical trials
- Novel agents and settings
- Biomarker studies
- Adverse event management

Impact of early introduction of steroid on immune-checkpoint inhibitors (ICI) in patients with advanced non-small cell lung cancer

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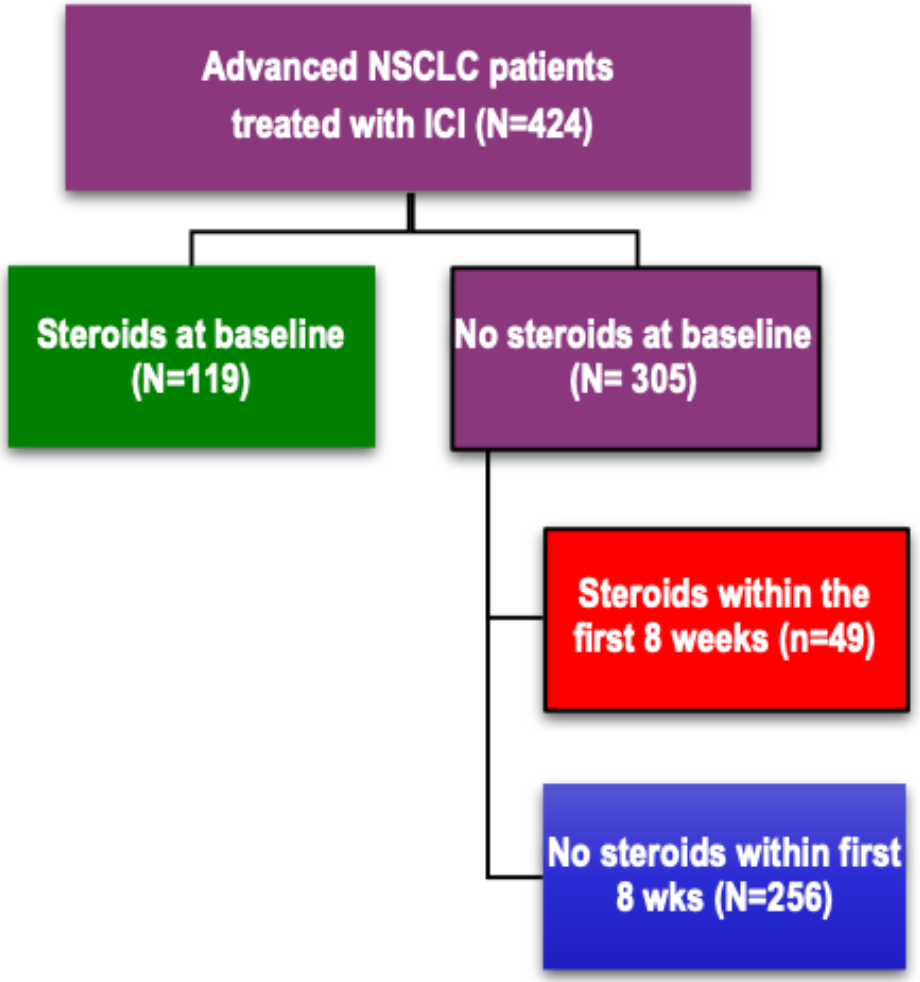
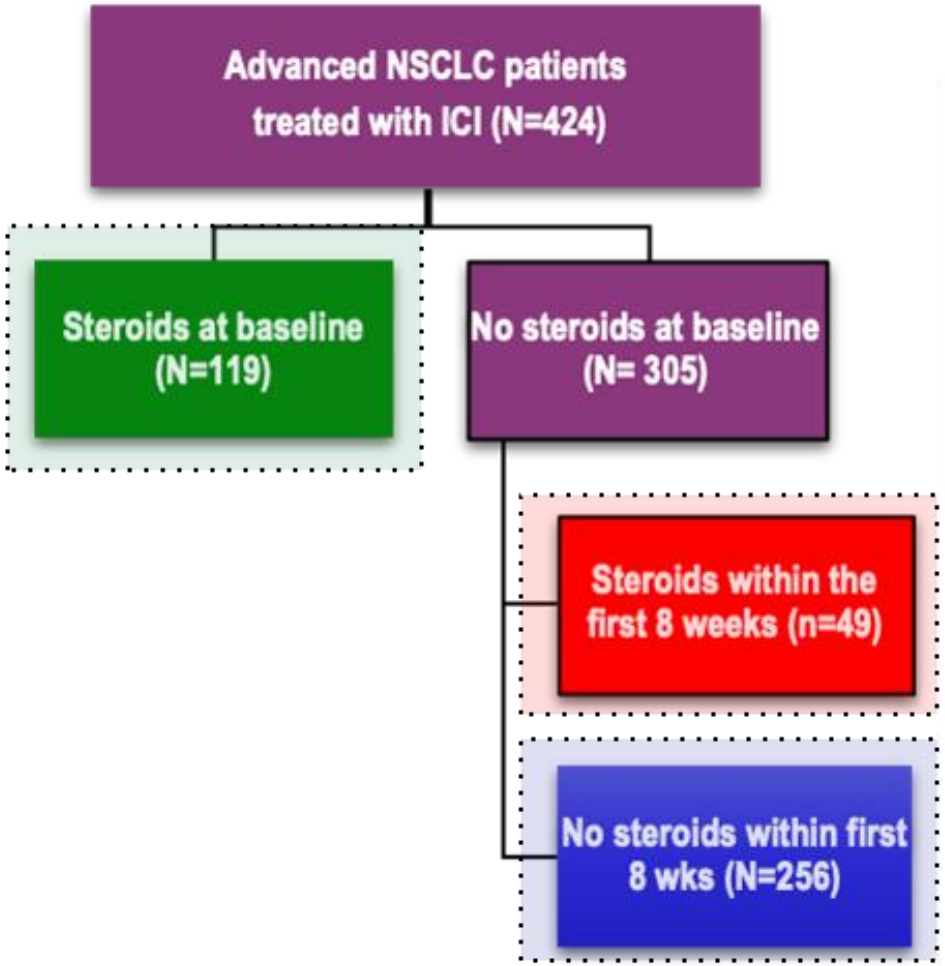
Methods

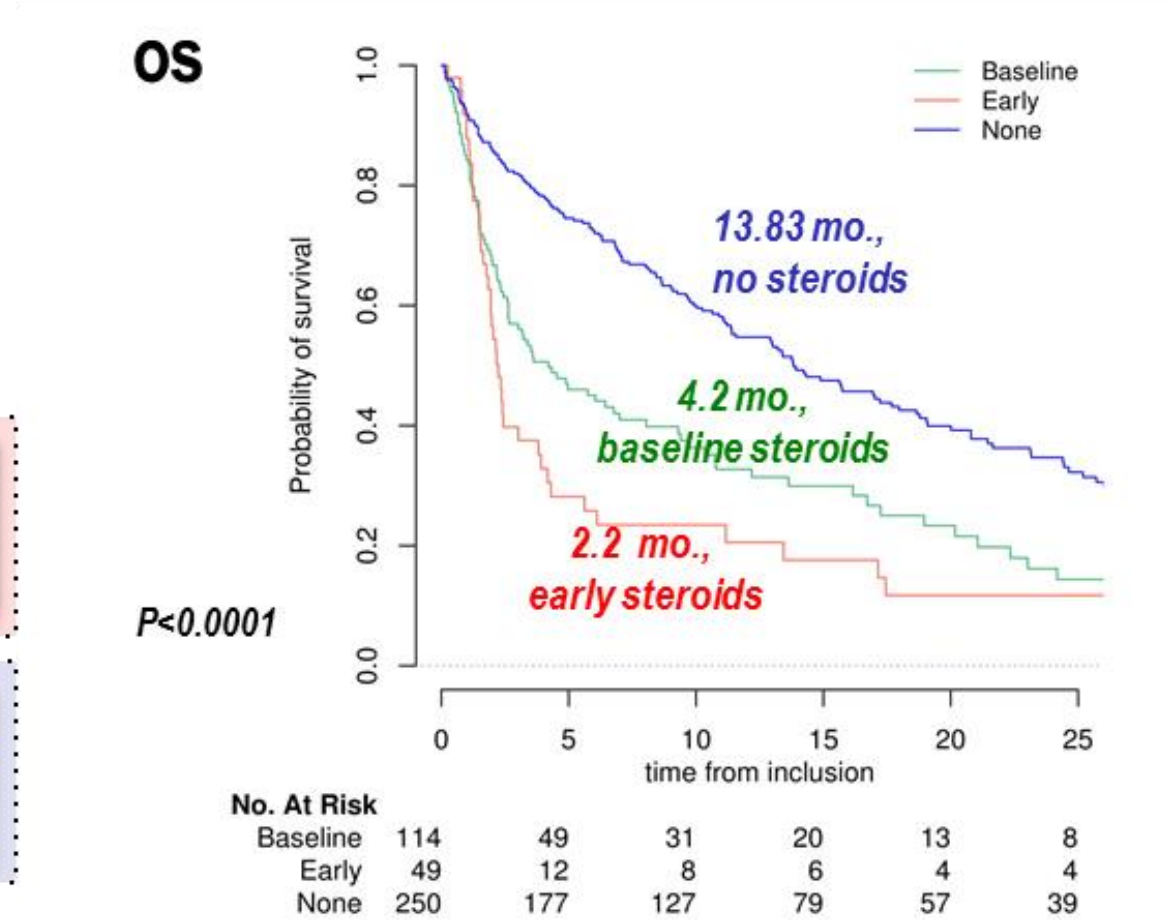


Cancer-related indications	N=38 (%)
Dyspnea cancer related	19 (50%)
Brain metastasis	6 (16%)
Superior vena cava synd.	3 (8%)
Others	10 (26%)

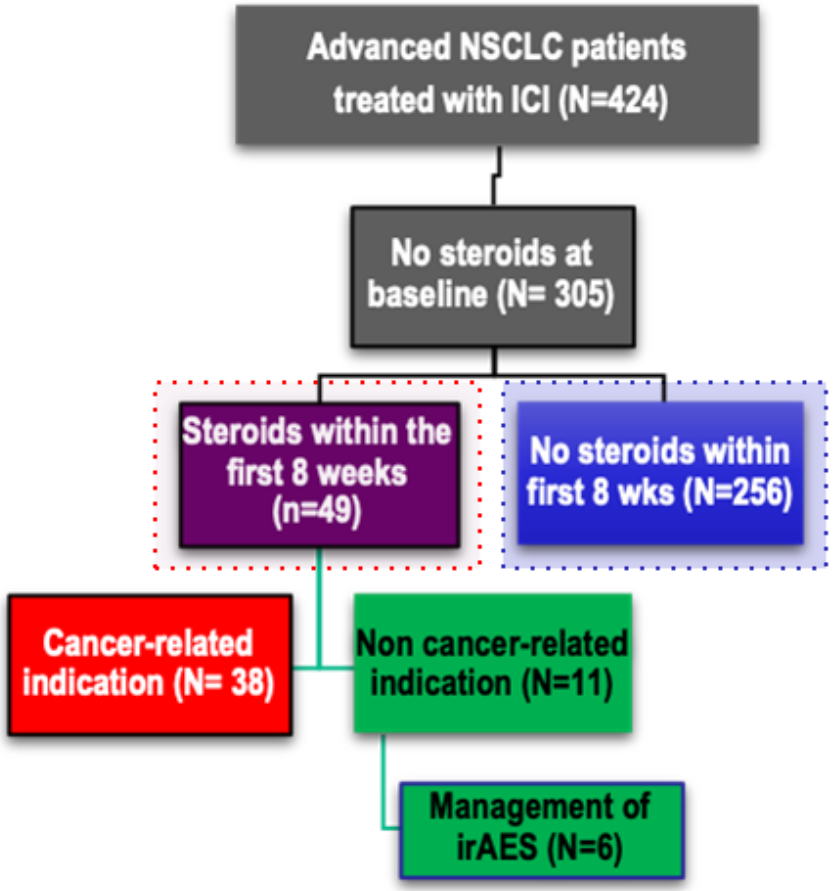
Non cancer-related	N=11 (%)
Immune related pneumonitis	3 (27%)
COPD	3 (27%)
Immune related arthritis	2 (18%)
Immune related hepatitis	1 (9%)
Others	2 (18%)

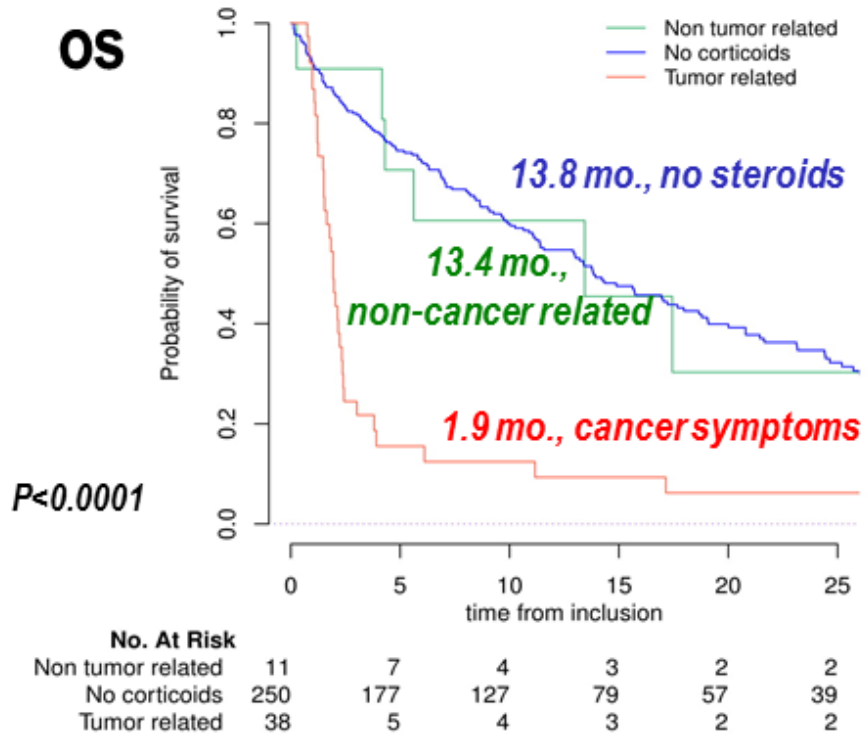
Results: Steroid therapy and OS





Results: Steroid treatment by indication and OS





Early steroids for **cancer-related symptoms** was an **independent prognostic factor** for **OS** [**HR 4.53**; 95%CI, 1.84-11.12; P<0.0001]

Association of systemic corticosteroids with overall survival in patients receiving cancer immunotherapy for advanced melanoma, non-small cell lung cancer or urothelial cancer in routine clinical practice

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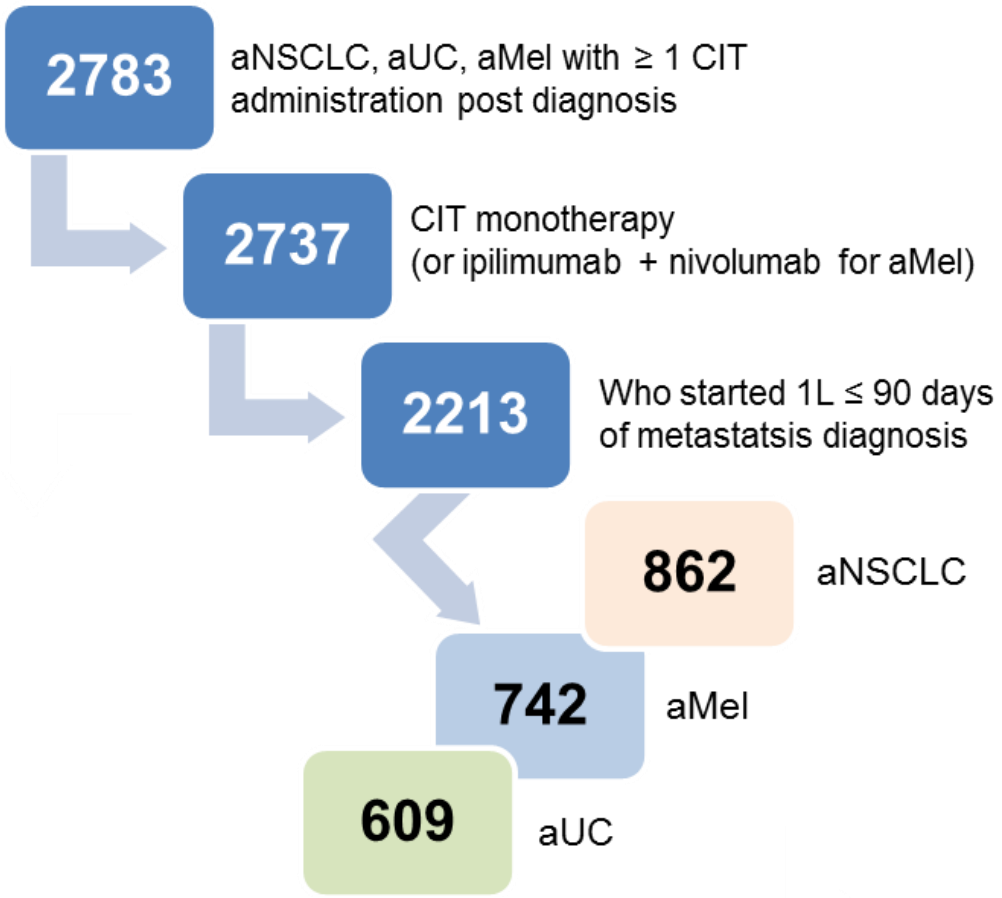
Methods

- Observational study of patients in the Flatiron Health electronic health record (EHR)–derived de-identified database
- Patients with aMel, aNSCLC or aUC diagnosed between January 2011 and June 2017 and treated with CIT (any line of therapy)
- Baseline CS use defined as ≥ 1 IV, IM or oral prescription ≤ 14 days prior to and ≤ 30 days after start of CIT
  - Baseline use was observed in 19%-30% of patients
  - Any use of CS was common (67-95%) as was prior use (80-87% for aNSCLC and aUC, 16% for aMel)
- Association of baseline CS use with OS was estimated using multivariable Cox PH models adjusted for key baseline factors

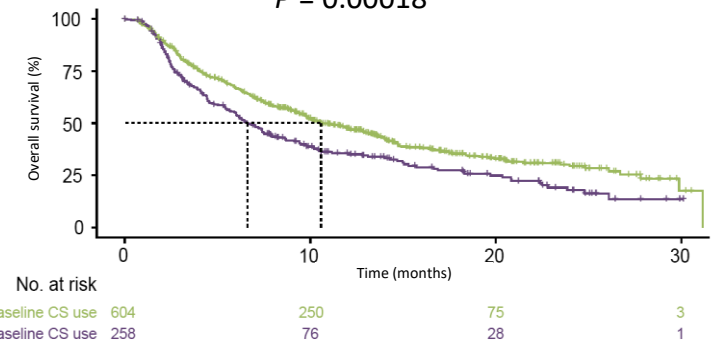


Results

OS by baseline CS use (univariate analysis)

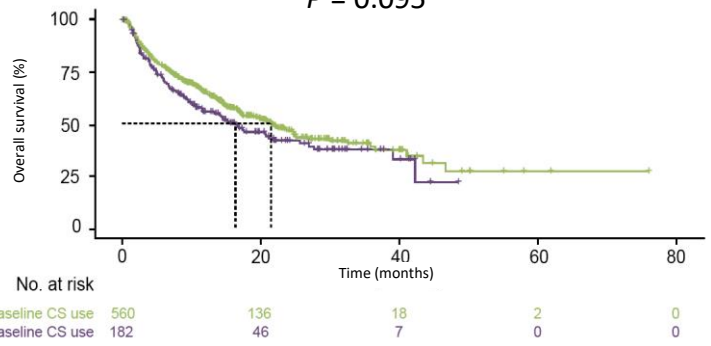
aNSCLC

P = 0.00018



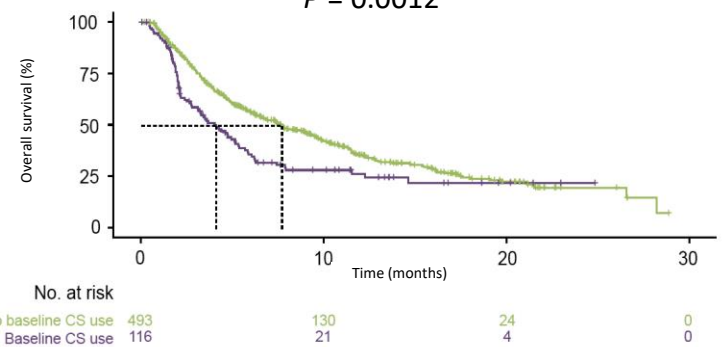
aMel

P = 0.095



aUC

P = 0.0012



Median OS (univariate analysis)

	Median OS (95% CI), months		
	aNSCLC	aMel	aUC
No baseline CS use	10.6 (9.7, 13.1)	21.5 (17.2, 25.1)	7.7 (6.4, 9.3)
Baseline CS use	6.6 (5.7, 8.2)	16.4 (11.5, 25.6)	4.1 (3.1, 5.3)

Multivariable analysis[a]

	Multivariable Cox model, HR (95% CI)		
	aNSCLC	aMel	aUC
No baseline CS use	Reference	Reference	Reference
Baseline CS use	1.34 (1.12, 1.61)	1.24 (0.97, 1.57)	1.44 (1.12, 1.87)

[a] Adjusted for key prognostic factors: age at CIT start, stage at diagnosis, race/ethnicity, sex, ECOG PS at CIT start, treatment sequence, brain metastases, smoking status (aNSCLC, aUC), histology (aNSCLC), grade (aUC) and prior steroid use.

Conclusions - irAE

Though steroid use correlates with poor outcomes in IO treated patients, this is primarily due to a priori risk of:

- baseline steroid use (i.e. co-morbidities) or
- cancer-therapy required steroid use (e.g. CNS dx)
- steroid use to treat IrAE's has not been shown to worsen outcomes and should not be withheld when needed.

ESMO-IO 2019 trends

- Continuing progress in clinical development immune checkpoint inhibitors: more combinations (chemotherapy, NSCLC), dosing (reductions), and moving into the neo-adjuvant setting (melanoma, NSCLC)
- Biomarker development (and combinatorial interventions) based on mechanisms of IT resistance and efficacy: immune exclusion and role of dendritic cells and other myeloid cells in the TME; oncogenic wiring and TME composition
- PET imaging of ongoing immune responses
- Local ablations and intratumoral IT (FLT3L/TLR-L/ICI)
- AI/computational biology in support of IT
- CAR-T, oncolytic viruses, neo-Ag vaccines

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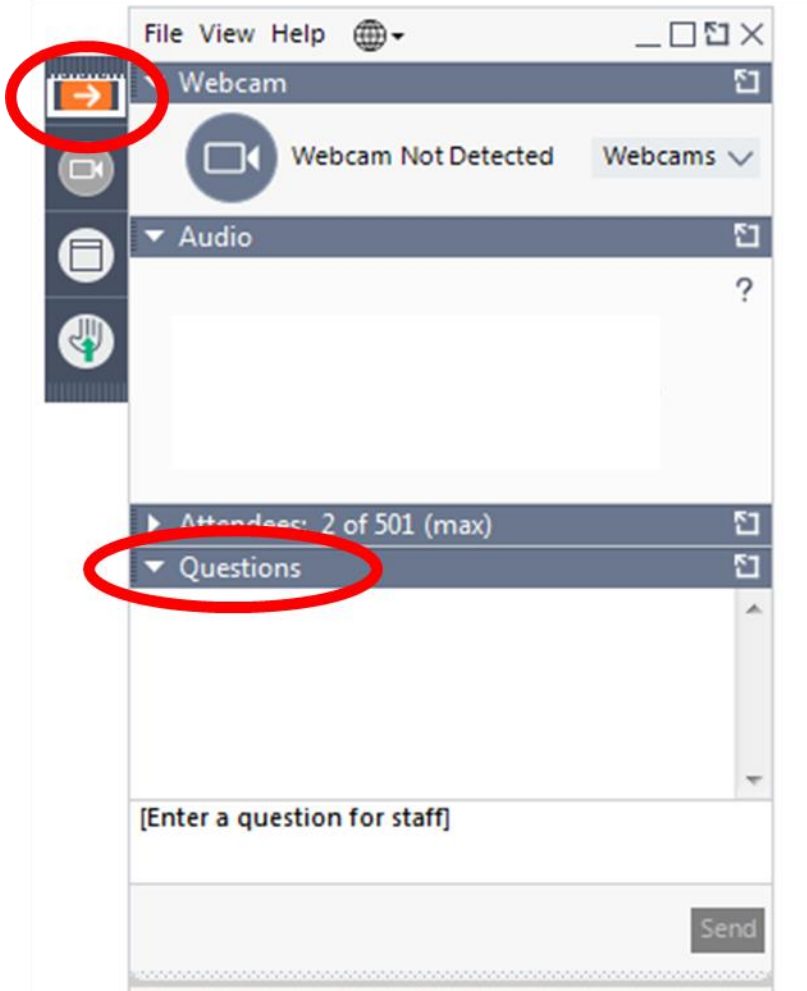
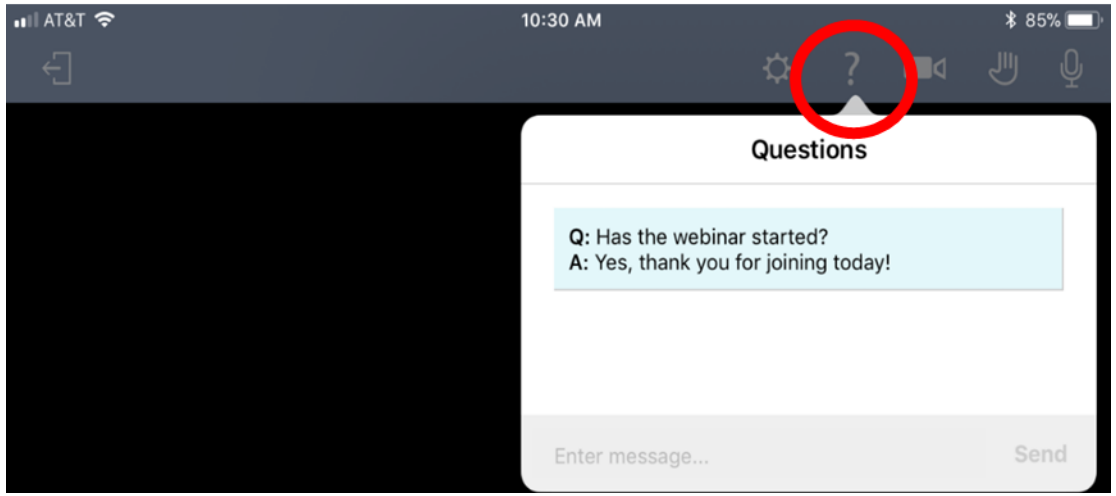
How to Submit Questions

Computer



Mobile Phone



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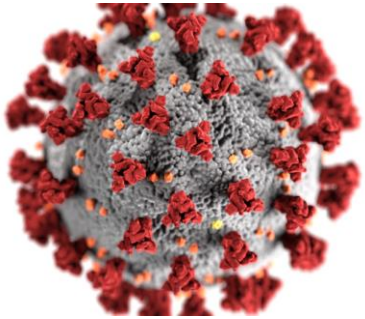

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