Advances in Small Cell Lung Cancer

Ravi Salgia, MD, PhD

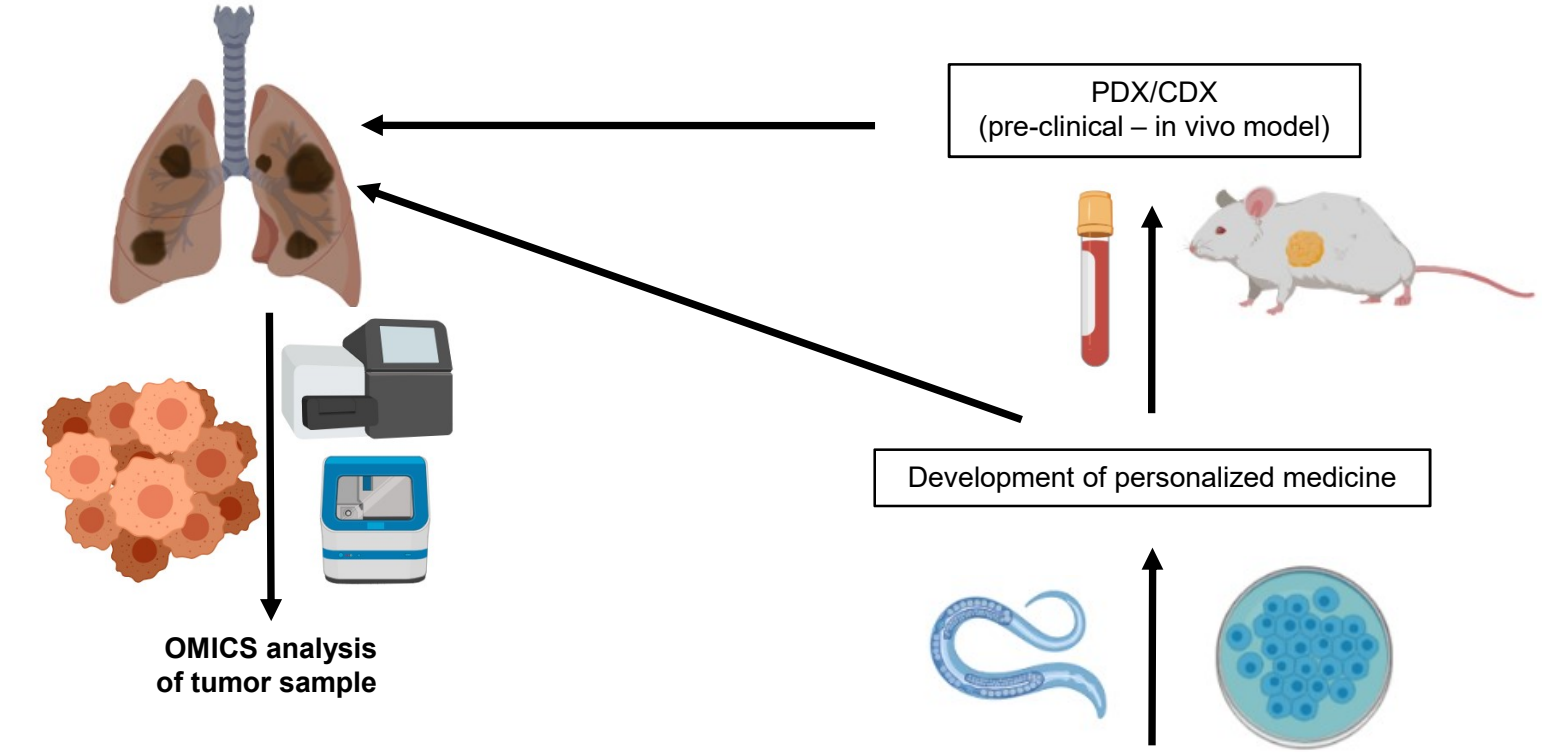
Professor and Chair, Medical Oncology
and Therapeutics Research

10-30-2020

Objectives--SCLC

- Research and Pipeline
  - Models
  - Therapeutic Targets
- Immunotherapy
- Potential for Future

SCLC Research Pipeline



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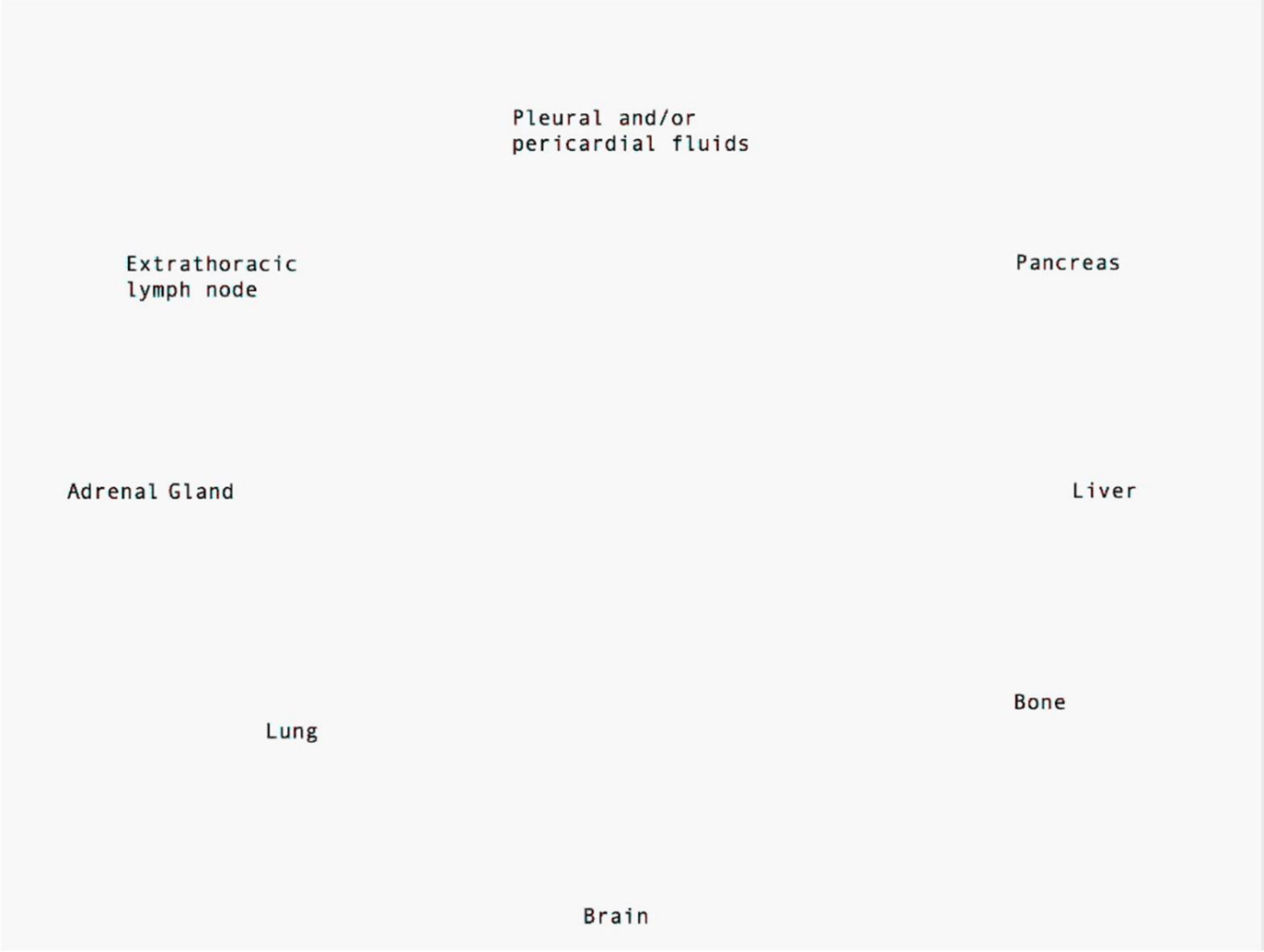
Small Cell Lung Cancer Metastasis



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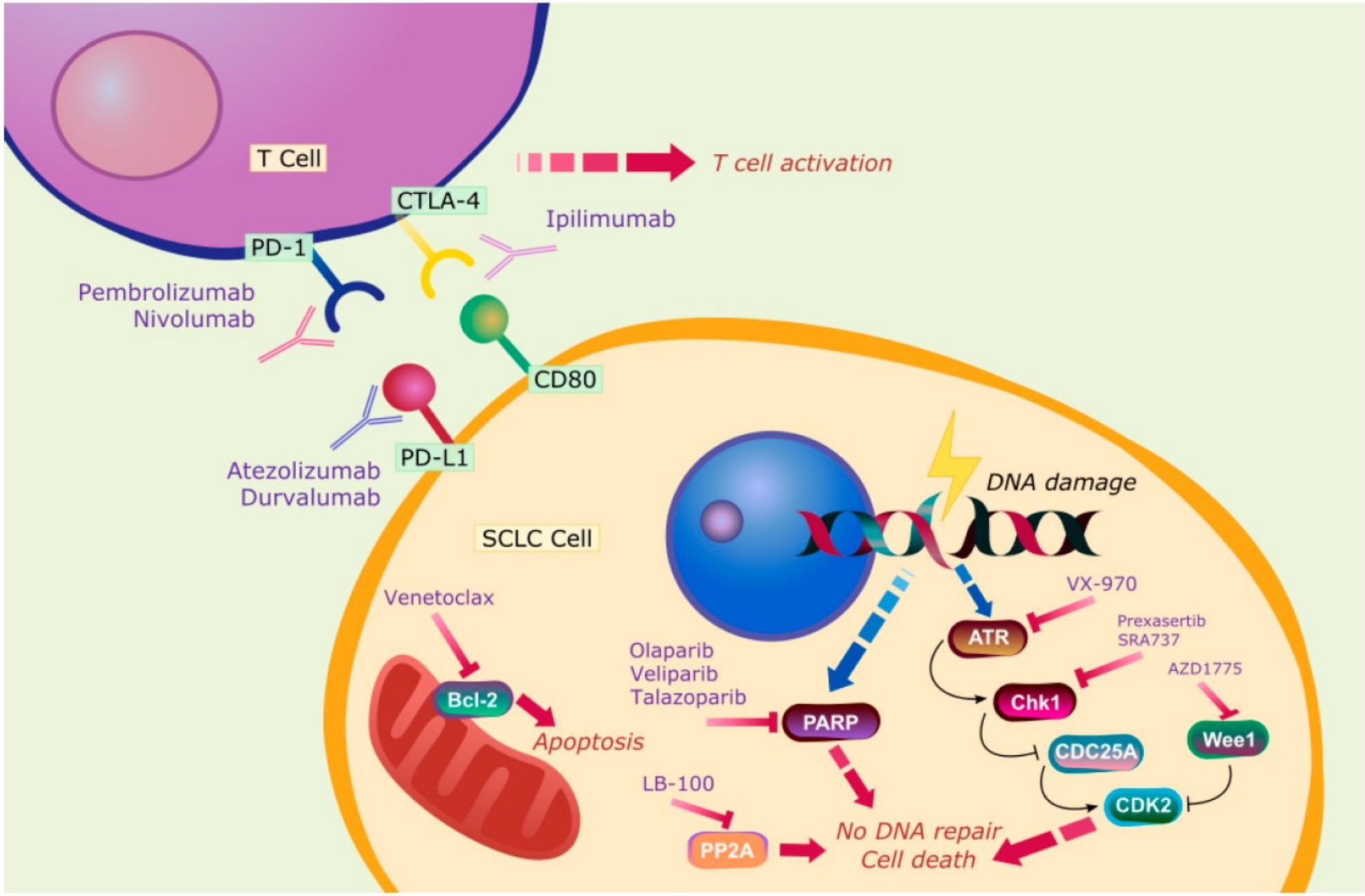
Potential Therapeutic Targets for SCLC



Subbiah, et int. Salgia, J. Clin. Med. 2020

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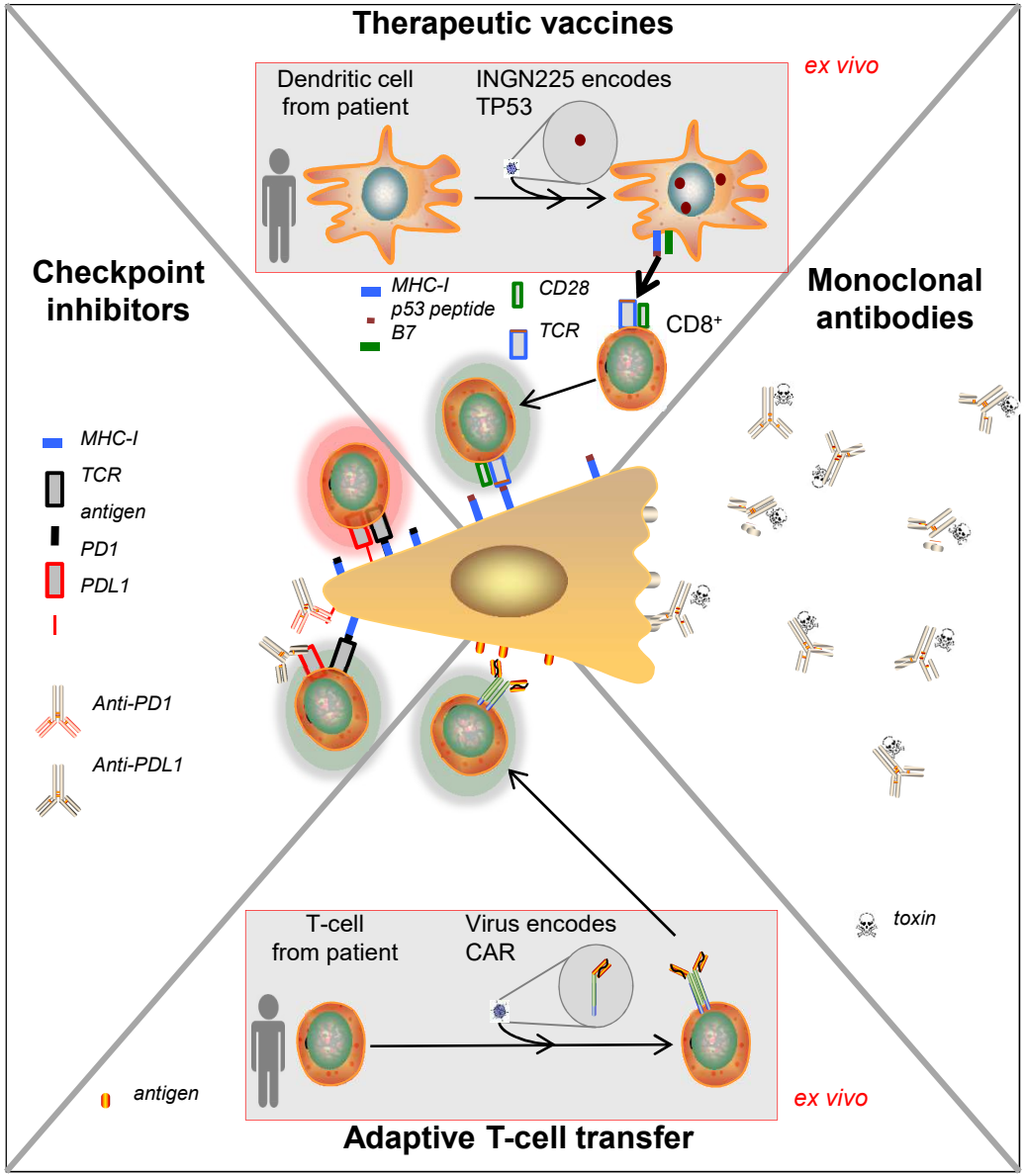
Immunotherapy in SCLC



Sattler and Salgia, 2016

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New First-Line Treatment for ED SCLC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer

L. Horn, A.S. Mansfield, A. Szczęsna, L. Havel, M. Krzakowski, M.J. Hochmair, F. Huemer, G. Losonczy, M.L. Johnson, M. Nishio, M. Reck, T. Mok, S. Lam, D.S. Shames, J. Liu, B. Ding, A. Lopez-Chavez, F. Kabbinavar, W. Lin, A. Sandler, and S.V. Liu, for the IMpower133 Study Group*

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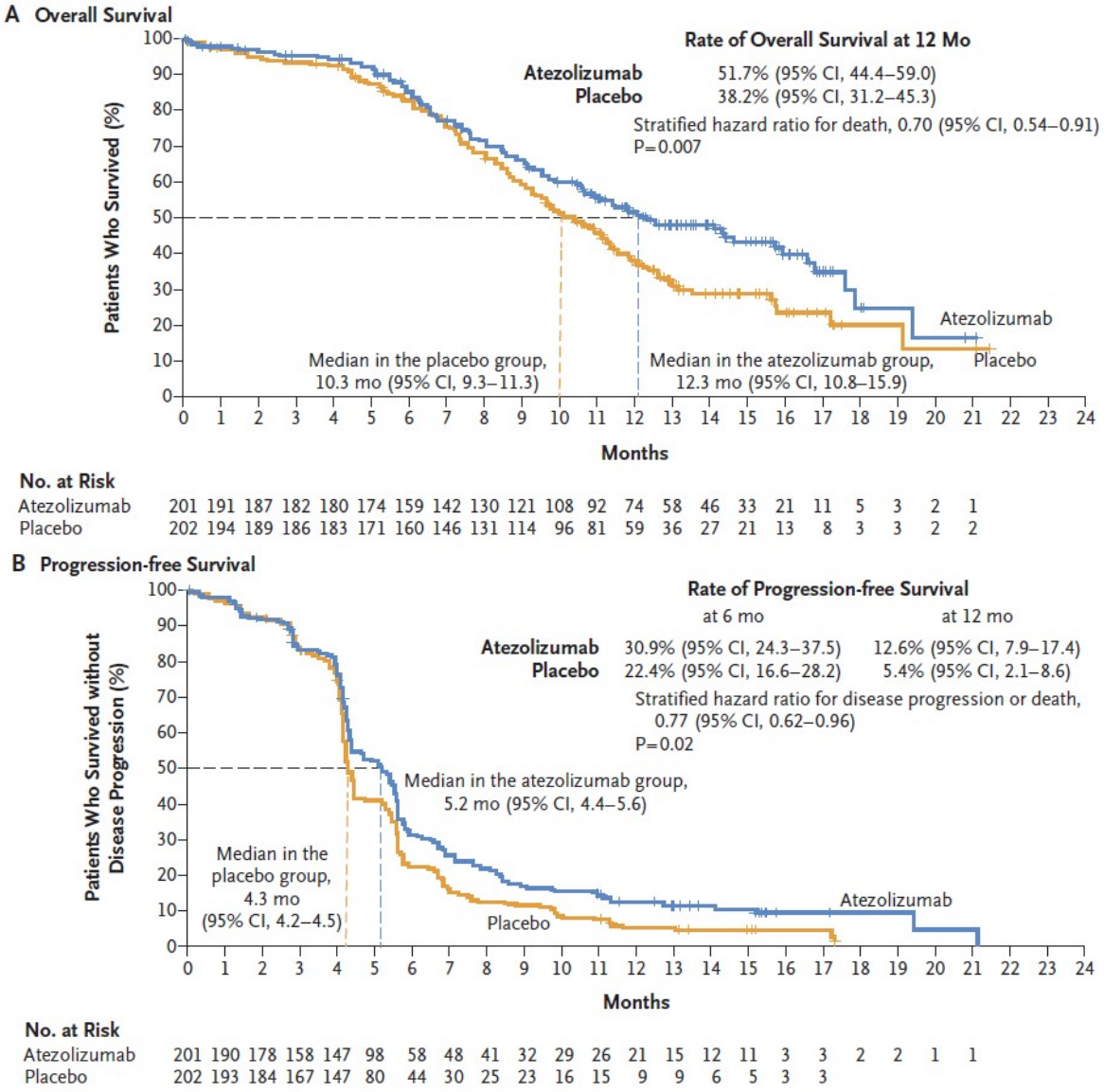
OS and PFS Atezolizumab + Chemotherapy



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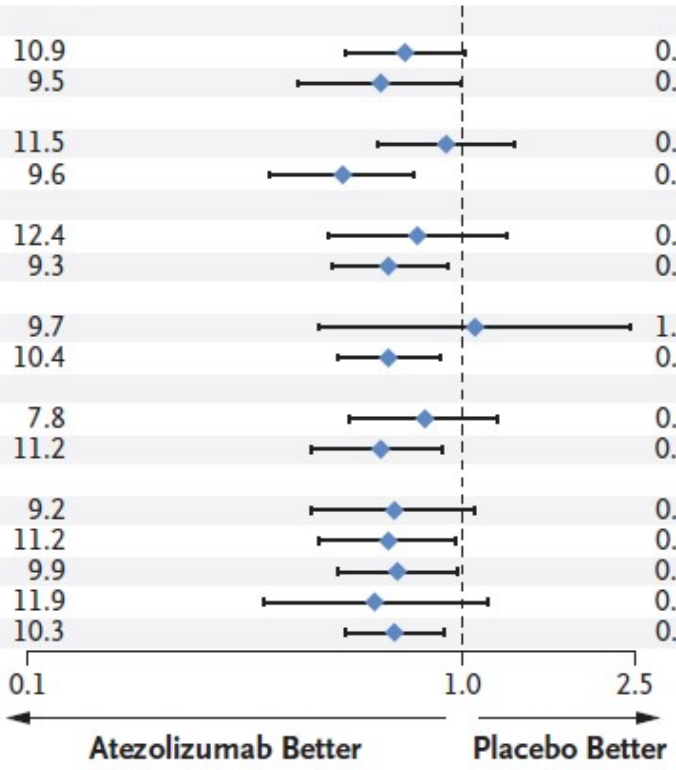
OS By Baseline Characteristics (Atezo)

C Overall Survival According to Baseline Characteristics

Subgroup	No. of Patients (%)	Median Overall Survival (mo)		Hazard Ratio for Death (95% CI)
		Atezolizumab	Placebo	
Sex				
Male	261 (65)	12.3	10.9	0.74 (0.54–1.02)
Female	142 (35)	12.5	9.5	0.65 (0.42–1.00)
Age				
<65 yr	217 (54)	12.1	11.5	0.92 (0.64–1.32)
≥65 yr	186 (46)	12.5	9.6	0.53 (0.36–0.77)
ECOG score				
0	140 (35)	16.6	12.4	0.79 (0.49–1.27)
1	263 (65)	11.4	9.3	0.68 (0.50–0.93)
Brain metastases				
Yes	35 (9)	8.5	9.7	1.07 (0.47–2.43)
No	368 (91)	12.6	10.4	0.68 (0.52–0.89)
Liver metastases				
Yes	149 (37)	9.3	7.8	0.81 (0.55–1.20)
No	254 (63)	16.8	11.2	0.64 (0.45–0.90)
Tumor mutational burden				
<10 mutations/Mb	139 (34)	11.8	9.2	0.70 (0.45–1.07)
≥10 mutations/Mb	212 (53)	14.6	11.2	0.68 (0.47–0.97)
<16 mutations/Mb	271 (67)	12.5	9.9	0.71 (0.52–0.98)
≥16 mutations/Mb	80 (20)	17.8	11.9	0.63 (0.35–1.15)
Intention-to-treat population	403 (100)	12.3	10.3	0.70 (0.54–0.91)



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Atezolizumab + Chemotherapy Summary

- **IMpower133** is the first study in over 20 years to show a clinically meaningful improvement in OS over the current standard-of-care in 1L ES-SCLC
- The addition of atezolizumab to carboplatin and etoposide provided a significant improvement in OS and PFS, compared with carboplatin and etoposide alone in 1L ES-SCLC
  - mOS: 12.3 vs. 10.3 months; HR: 0.70 (p = 0.0069); 12-month OS: 51.7% vs. 38.2%
  - mPFS: 5.2 vs. 4.3 months; HR: 0.77 (p = 0.017); 12-month PFS: 12.6% vs. 5.4%
- The safety profile of atezolizumab plus carboplatin and etoposide was as expected with no new findings
- Rates of hematologic side effects were similar between treatment groups
- Administration of atezolizumab did not compromise the ability to deliver standard carboplatin plus etoposide
- The incidence and types of immune-related AEs were similar to those seen with atezolizumab monotherapy
- **These data suggest that atezolizumab plus carboplatin and etoposide is a new standard of care for the first-line treatment of ES-SCLC**

KEYNOTE-604 From ASCO 2020

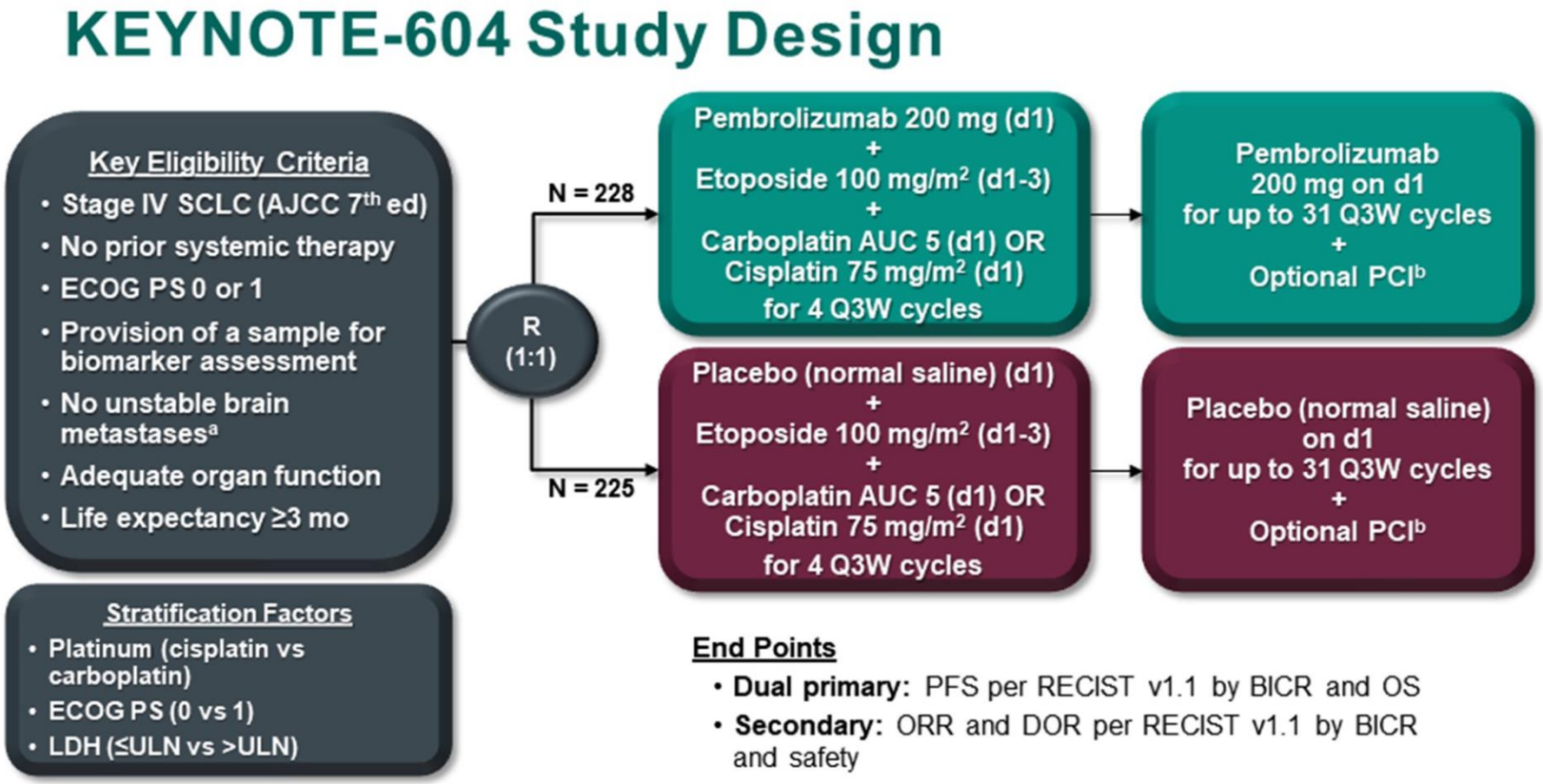
KEYNOTE-604: Pembrolizumab or Placebo plus Etoposide and Platinum as First-Line Therapy for Extensive-Stage Small-Cell Lung Cancer

Charles M. Rudin,[1] Mark M. Awad,[2] Alejandro Navarro,[3] Maya Gottfried,[4] Solange Peters,[5] Tibor Csőszi,[6] Parneet K. Cheema,[7] Delvys Rodriguez-Abreu,[8] Mirjana Wollner,[9] Grzegorz Czyżewicz,[10] James Chih-Hsin Yang,[11] Julien Mazieres,[12] Francisco J. Orlandi,[13] Alexander Luft,[14] Mahmut Gümüş,[15] Terufumi Kato,[16] Gregory P. Kalemkerian,[17] Yiwen Luo,[18] M. Catherine Pietanza,[18] Hye Ryun Kim[19]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]Vall d'Hebron University Hospital, Barcelona, Spain; [4]Meir Medical Center, Kfar-Saba, Israel; [5]Lausanne University Hospital, Lausanne, Switzerland; [6]Hetenyi G Korhaz Onkologiai Kozpont, Szolnok, Hungary; [7]William Osler Health System, University of Toronto, Brampton, ON, Canada; [8]Complejo Hospitalario Universitario Insular Materno-Infantil de Gran Canaria, Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain; [9]Rambam Medical Center, Haifa, Israel; [10]John Paul II Hospital, Cracow, Poland; [11]National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei, Taiwan; [12]Centre Hospitalier Universitaire de Toulouse, Université Paul Sabatier, Toulouse, France; [13]Oncología-Health and Care, Santiago, Chile; [14]Leningrad Regional Clinical Hospital, St. Petersburg, Russia; [15]Istanbul Medeniyet University Hospital, Istanbul, Turkey; [16]Kanagawa Cancer Center, Yokohama, Japan; [17]University of Michigan, Ann Arbor, MI, USA; [18]Merck & Co., Inc., Kenilworth, NJ, USA; [19]Yonsei Cancer Center, Seoul, South Korea

KEYNOTE-604 From ASCO 2020

Rudin KN604 ASCO 2020



[a]All brain-targeted treatment completed ≥14 d before starting study, no new or enlarging brain lesions, and neurologically stable without steroids for ≥7 d before starting study.
[b]Participants with CR or PR after cycle 4 could receive up to 25 Gy of PCI in 10 fractions at investigator's discretion; PCI was to begin within 2-4 wk and no later than 6 wk after last dose of cycle 4; study treatment could continue during PCI. KEYNOTE-604 ClinicalTrials.gov identifier, NCT03066778. BICR, blinded independent central review.

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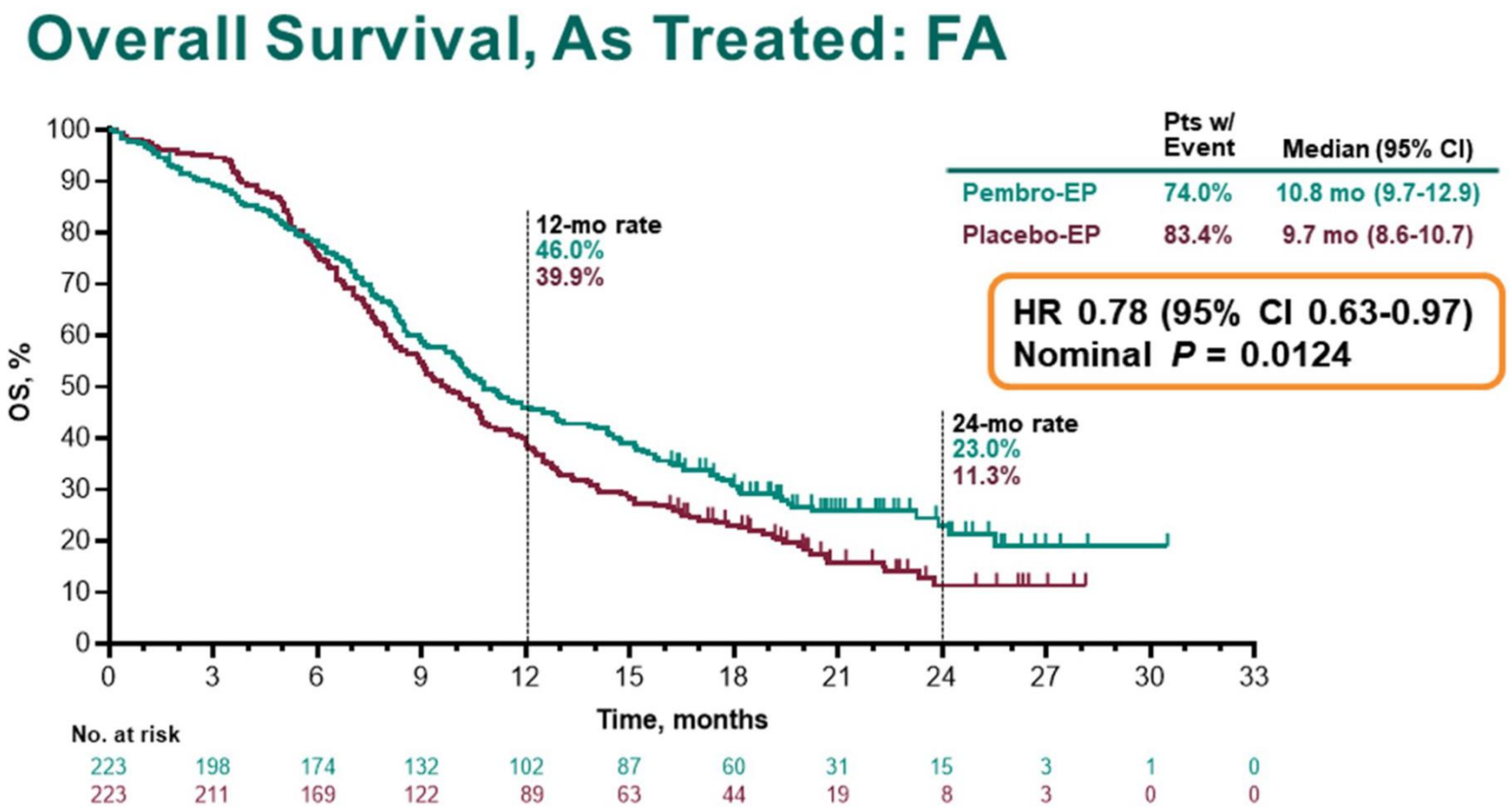
KEYNOTE-604 From ASCO 2020

Rudin KN604 ASCO 2020



Data cutoff date: Dec 2, 2019.

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KEYNOTE-604 From ASCO 2020

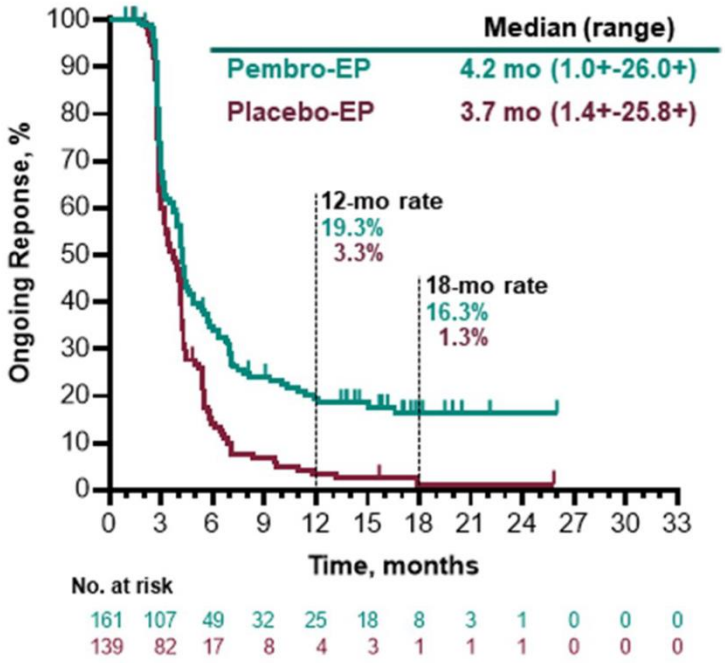
Rudin KN604 ASCO 2020

Summary of Response, ITT: FA

	Pembro-EP N = 228	Placebo-EP N = 225
ORR, % (95% CI)	70.6% (64.2-76.4)	61.8% (55.1-68.2)
Best response, n (%)		
CR	4 (1.8%)	2 (0.9%)
PR	157 (68.9%)	137 (60.9%)
SD	40 (17.5%)	56 (24.9%)
PD	8 (3.5%)	12 (5.3%)
NE[a]	6 (2.6%)	5 (2.2%)
NA[b]	13 (5.7%)	13 (5.8%)

[a]≥1 post-baseline imaging assessment, but none evaluable per RECIST v1.1 by BICR.
[b]No post-baseline imaging assessment.
Data cutoff date: Dec 2, 2019.

Duration of Response



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KEYNOTE-604 From ASCO 2020

Rudin KN604 ASCO 2020

Summary and Conclusions

- Adding pembrolizumab to EP as first-line therapy for ES-SCLC significantly improved PFS (HR 0.75, $P = 0.0023$; significance threshold $P = 0.0048$)
- The HR for OS favored pembrolizumab-EP, but the significance threshold was missed (HR 0.80, $P = 0.0164$; significance threshold $P = 0.0128$)
- Pembrolizumab-EP provided durable responses in a subset of participants
- Pembrolizumab-EP safety profile was as expected and manageable
- Data support the benefit of pembrolizumab and the value of immunotherapy in SCLC

Updated CASPIAN From ASCO 2020

9002: Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC: Updated results from the phase 3 CASPIAN study

Luis Paz-Ares,[1] Mikhail Dvorkin,[2] Yuanbin Chen,[3] Niels Reinmuth,[4] Katsuyuki Hotta,[5] Dmytro Trukhin,[6] Galina Statsenko,[7] Maximilian J. Hochmair,[8] Mustafa Özgüroğlu,[9] Jun Ho Ji,[10] Oleksandr Voitko,[11] Artem Poltoratskiy,[12] Francesco Verderame,[13] Libor Havel,[14] Igor Bondarenko,[15] Jon Armstrong,[16] Natalie Byrne,[16] Haiyi Jiang,[17] Jonathan W. Goldman[18]

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

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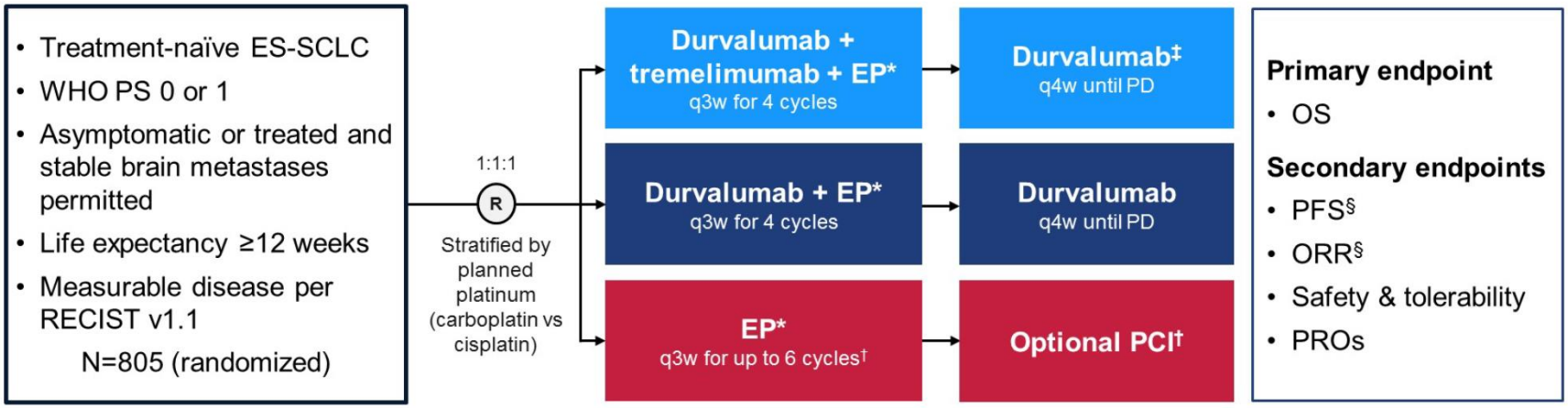
Updated CASPIAN From ASCO 2020

CASPIAN Study Design

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



*EP consists of etoposide 80–100 mg/m2 with either carboplatin AUC 5–6 or cisplatin 75–80 mg/m2, durvalumab dosed at 1500 mg, tremelimumab dosed at 75 mg
†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; §By investigator assessment per RECIST v1.1
AUC, area under the curve; ORR, objective response rate; PCI, prophylactic cranial irradiation; PD, disease progression; PFS, progression-free survival; PROs, patient-reported outcomes; PS, performance status; q3w, every 3 weeks; q4w, every 4 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1

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Updated CASPIAN From ASCO 2020

Baseline Characteristics

	D+T+EP (n=268)	D+EP (n=268)	EP (n=269)
Median age (range), years	63 (36–88)	62 (28–82)	63 (35–82)
Male, %	75.4	70.9	68.4
White / Asian / Other, %	80.2 / 17.5 / 2.4	85.4 / 13.4 / 1.1	82.2 / 15.6 / 2.2
WHO PS 0 / 1, %	40.7 / 59.3	36.9 / 63.1	33.5 / 66.5
Disease stage III / IV*, %	6.7 / 93.3	10.4 / 89.6	8.9 / 91.1
Current / Former / Never smoker, %	41.8 / 52.6 / 5.6	44.8 / 47.0 / 8.2	46.8 / 47.6 / 5.6
Brain or CNS metastases, %	14.2	10.4	10.0
Liver metastases, %	43.7	40.3	38.7

*All patients were confirmed as having ES-SCLC
CNS, central nervous system

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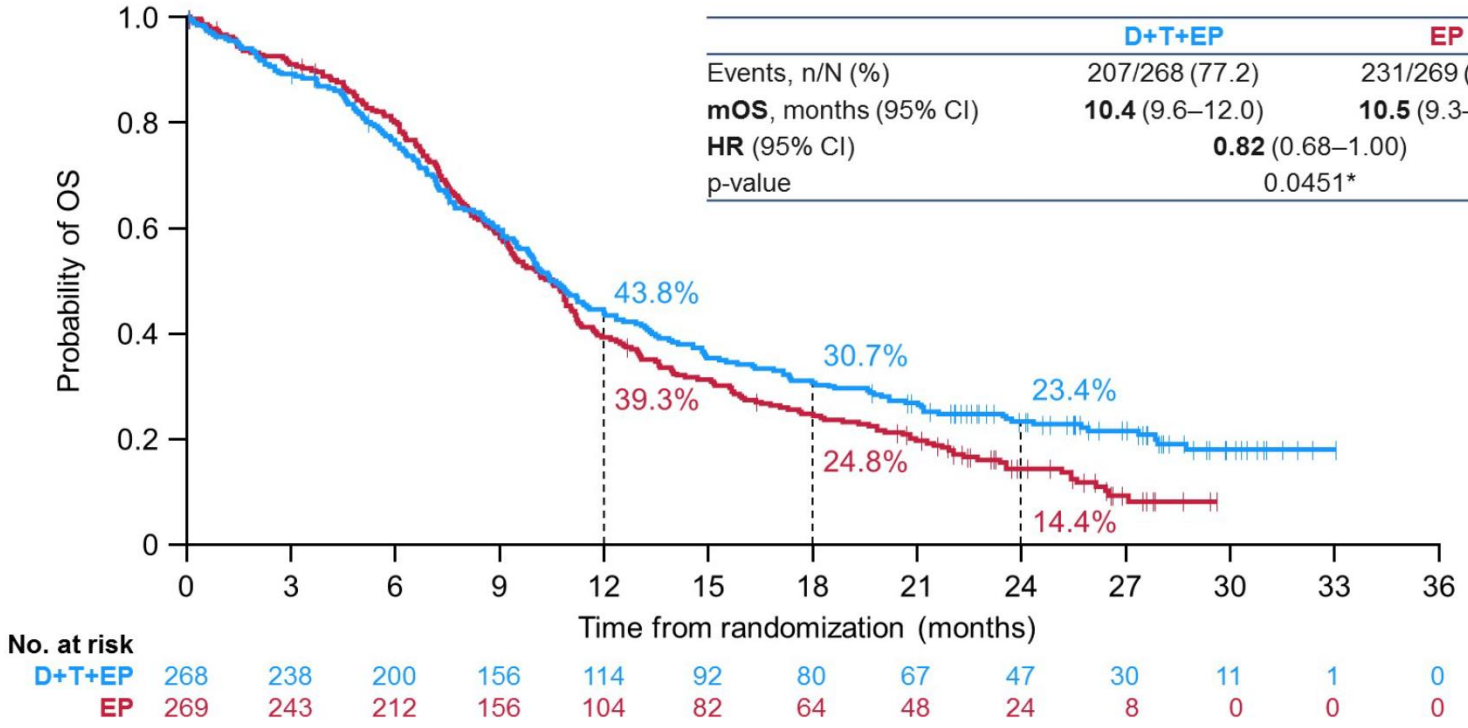
Updated CASPIAN From ASCO 2020

Overall Survival: D+T+EP vs EP (Primary Endpoint)



	D+T+EP	EP
Events, n/N (%)	207/268 (77.2)	231/269 (85.9)
mOS, months (95% CI)	**10.4** (9.6–12.0)	**10.5** (9.3–11.2)
HR (95% CI)	**0.82** (0.68–1.00)	
p-value	0.0451*	

*p≤0.0418 required for statistical significance

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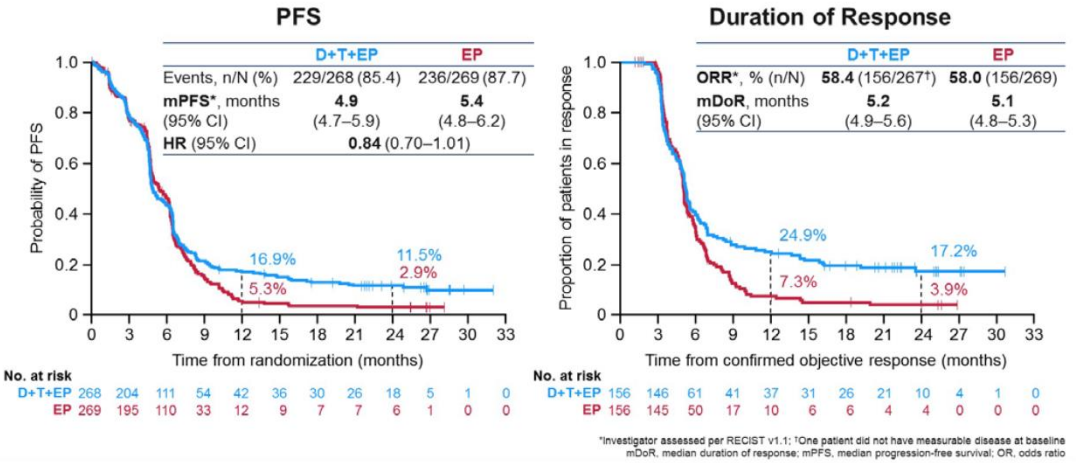
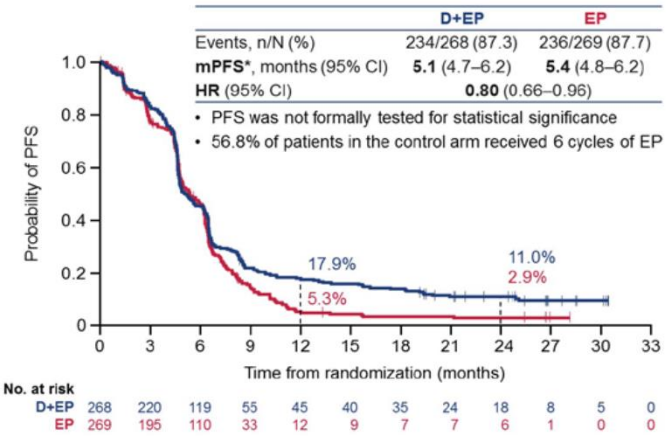
Updated CASPIAN From ASCO 2020

PFS and Confirmed Objective Response: D+T+EP vs EP



*Investigator assessed per RECIST v1.1; †One patient did not have measurable disease at baseline
mDoR, median duration of response; mPFS, median progression-free survival; OR, odds ratio

Updated Progression-free Survival: D+EP vs EP



Landmark PFS, %	D+EP (n=268)	EP (n=269)
6 months	45.4	45.8
12 months	17.9	5.3
18 months	13.9	3.4
24 months	11.0	2.9

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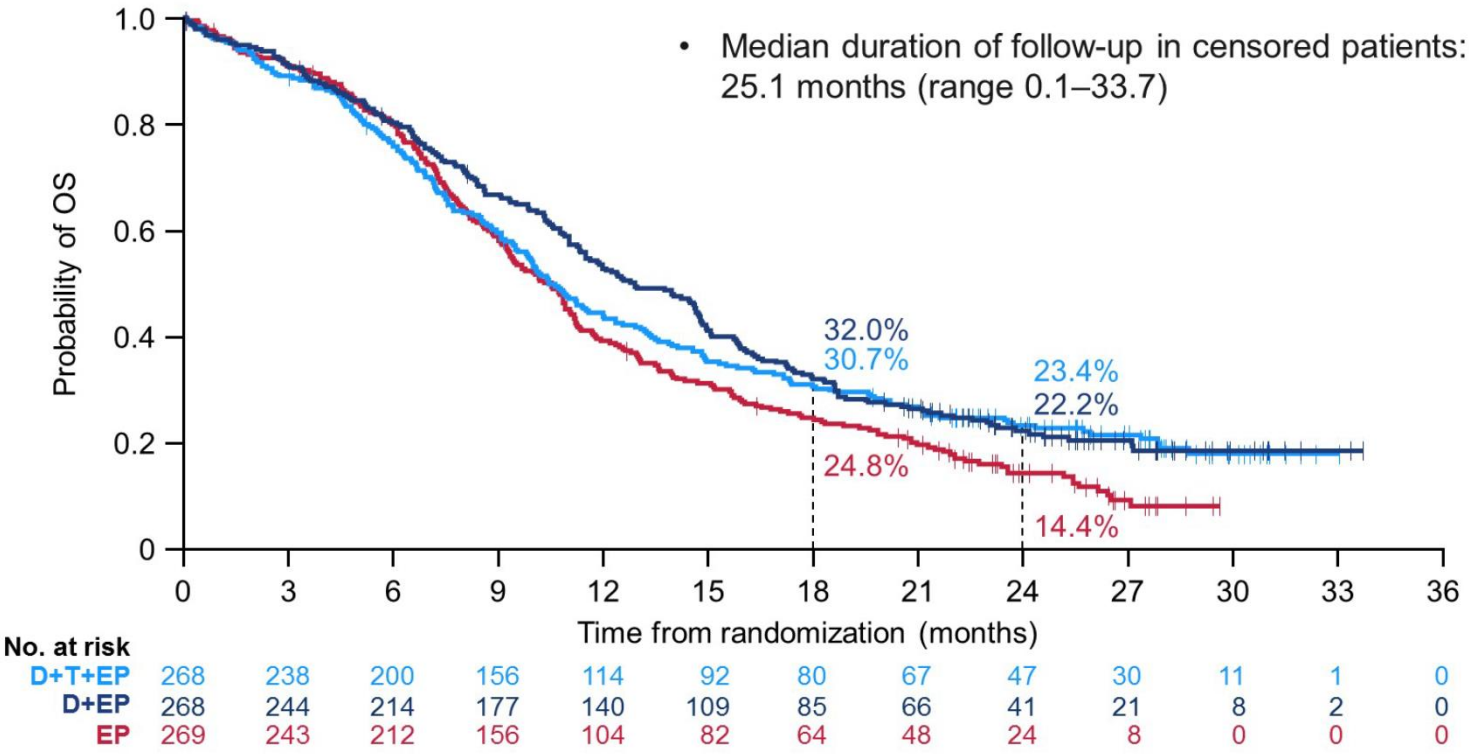
Overall Survival: All Arms



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Updated CASPIAN From ASCO 2020

Safety Summary

	D+T+EP (n=266)	D+EP (n=265)	EP (n=266)
Any-grade all-cause AEs, n (%)	264 (99.2)	260 (98.1)	258 (97.0)
Grade 3/4 AEs	187 (70.3)	165 (62.3)	167 (62.8)
Serious AEs	121 (45.5)	85 (32.1)	97 (36.5)
AEs leading to treatment discontinuation*	57 (21.4)	27 (10.2)	25 (9.4)
Immune-mediated AEs†	96 (36.1)	53 (20.0)	7 (2.6)
AEs leading to death	27 (10.2)	13 (4.9)	15 (5.6)
Treatment-related AEs leading to death‡	12 (4.5)	6 (2.3)	2 (0.8)

*Includes patients who permanently discontinued at least one study drug

†An event that is associated with drug exposure and consistent with an immune-mediated mechanism of action, where there is no clear alternate etiology and the event required treatment with systemic corticosteroids or other immunosuppressants and/or, for specific endocrine events, endocrine therapy; majority of immune-mediated AEs were low grade and thyroid related

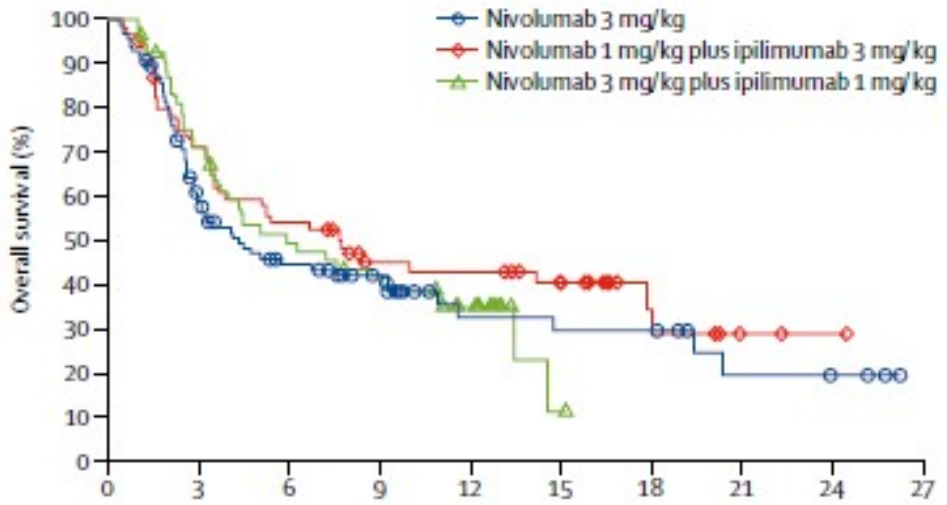
‡AEs assessed by the investigator as possibly related to any study treatment. Causes of death were death, febrile neutropenia, and pulmonary embolism (two patients each), and enterocolitis, general physical health deterioration/multiple organ dysfunction syndrome, pneumonia, pneumonitis/hepatitis, respiratory failure, and sudden death (one patient each) in the durvalumab + tremelimumab + EP arm; cardiac arrest, dehydration, hepatotoxicity, interstitial lung disease, pancytopenia, and sepsis (one patient each) in the durvalumab + EP arm; pancytopenia and thrombocytopenia/haemorrhage (one patient each) in the EP arm

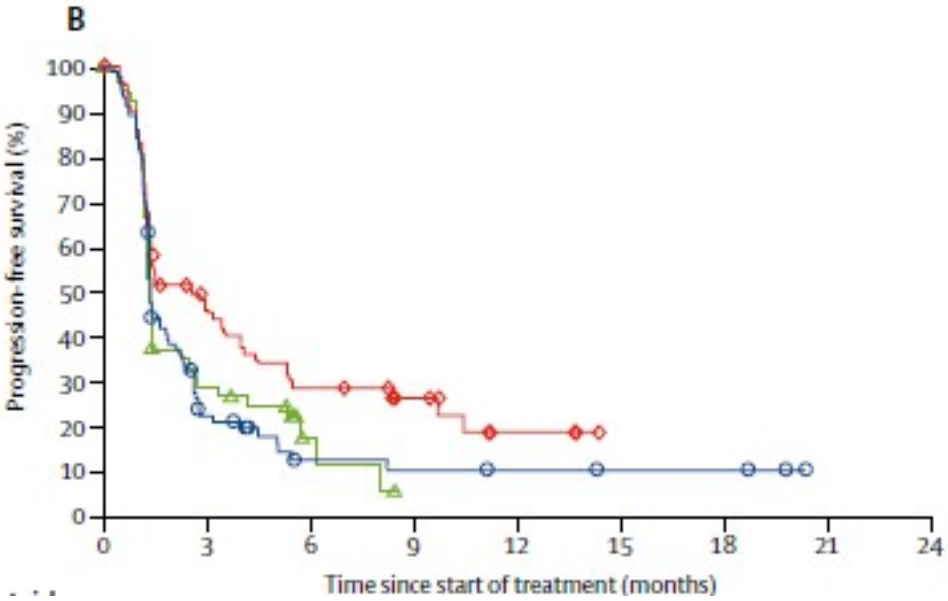
Updated CASPIAN From ASCO 2020

Conclusions

- First-line durvalumab + EP continued to demonstrate sustained improvement in OS compared with a robust control arm that allowed up to 6 cycles of EP and the use of PCI
  - OS HR 0.75 (95% CI 0.62–0.91; nominal p=0.0032)
  - Sustained separation of OS curves with 22.2% vs 14.4% of patients alive at 24 months
  - Benefit was observed across all pre-specified subgroups and key secondary efficacy outcomes
- Addition of tremelimumab to durvalumab + EP did not significantly improve outcomes in CASPIAN
- Safety findings in all arms remained consistent with the known safety profiles of all agents
- **These results further support durvalumab + EP as a new standard-of-care treatment for first-line ES-SCLC offering the flexibility of platinum choice**

Nivolumab +/- Ipilimumab in Recurrent SCLC: CheckMate 032





	Nivolumab 3 mg/kg (n=98)	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (n=61)	Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n=54)
Objective response; 95% CI	10 (10%; 5–18)	14 (23%; 13–36)	10 (19%; 9–31)
Best overall response			
Complete response	0	1 (2%)	0
Partial response	10 (10%)	13 (21%)	10 (19%)
Stable disease	22 (22%)	13 (21%)	9 (17%)
Progressive disease	52 (53%)	23 (38%)	29 (54%)
Unable to determine	12 (12%)	8 (13%)	6 (11%)
Not reported	2 (2%)	3 (5%)	0
Time to objective response (IQR), months	2·0 (1·3–2·8)	2·1 (1·4–2·8)	1·4 (1·3–2·7)

Data are n (%) unless otherwise stated. All patients were enrolled at least 90 days prior to database lock.

Table 2: Tumour response

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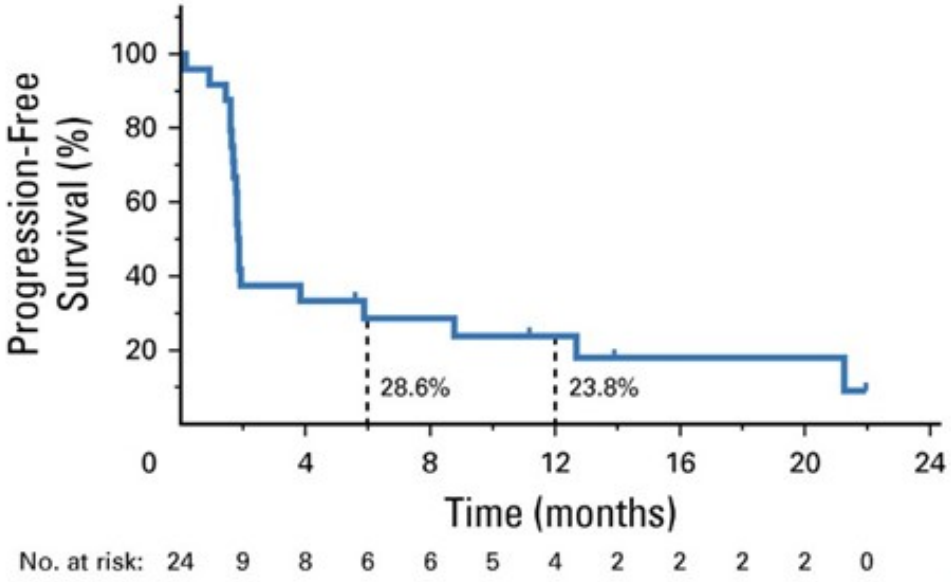
Pembrolizumab for Recurrent SCLC: KEYNOTE-028



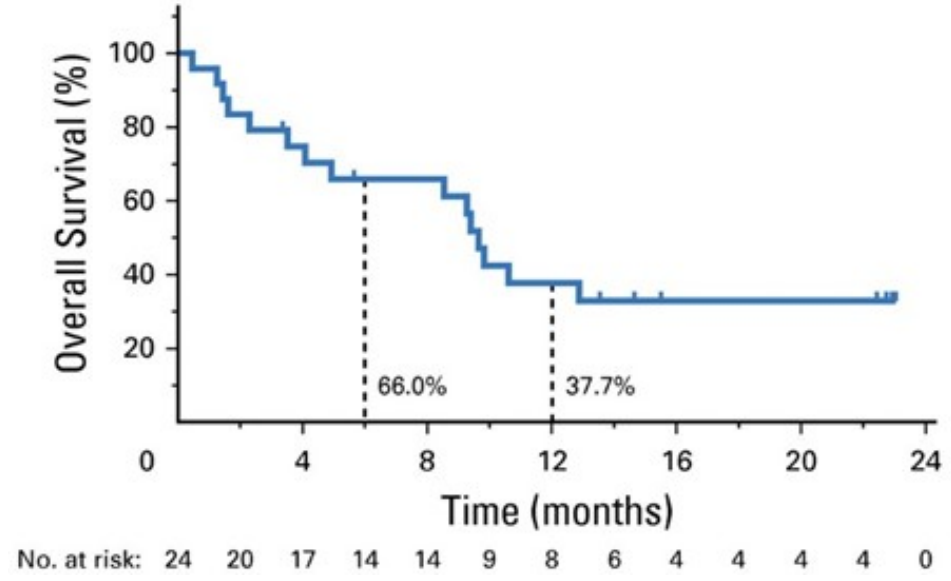


Table 3. Confirmed Efficacy Results (investigator-assessed) in the Total Population

Efficacy	Value of Patient Population (n = 24)
ORR*, No. (% [95% CI])	8 (33.3 [15.6-55.3])
CR, No. (%)	1 (4.2)
PR, No. (%)	7 (29.2)
SD, No. (%)	1 (4.2)
Median DOR, months† (range)	19.4 (≥ 3.6 to ≥ 20.0)
Median TTR, months (95% CI)	2.0 (1.7–3.7)
DCR‡, No. (% [95% CI])	8 (33.3 [15.6-55.3])
Progressive disease, No. (%)	13 (54.2)
Not evaluable, No. (%)	2 (8.3)
PFS	
Events, No. (%)	20 (83.3)
Median, months (95% CI)	1.9 (1.7-5.9)
Six-month rate, % (95% CI)	28.6 (12.4-47.2)
Twelve-month rate, % (95% CI)	23.8 (9.1-42.3)
OS	
Events, No. (%)	15 (62.5)
Median, months (95% CI)	9.7 (4.1-NR)
Six-month rate, % (95% CI)	66.0 (43.3-81.3)
Twelve-month rate, % (95% CI)	37.7 (18.4-57.0)

Abbreviations: CR, complete response; DCR, disease control rate; DOR, duration of response; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; TTR, time to response.
*ORR is CR + PR.
†Calculated with the Kaplan-Meier method for censored data.
‡DCR is CR + PR + SD ≥ 6 months.

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Lubinectedin Phase 2 Trial for 2L SCLC

Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial

José Trigo, Vivek Subbiah*, Benjamin Besse, Victor Moreno, Rafael López, María Angeles Sala, Solange Peters, Santiago Ponce, Cristian Fernández, Vicente Alfaro, Javier Gómez, Carmen Kahatt, Ali Zeaiter, Khalil Zaman, Valentina Boni, Jennifer Arrondeau, Maite Martínez, Jean-Pierre Delord, Ahmad Awada, Rebecca Kristeleit, Maria Eugenia Olmedo, Luciano Wannesson, Javier Valdivia, María Jesús Rubio, Antonio Anton, John Sarantopoulos, Sant P Chawla, Joaquín Mosquera-Martinez, Manolo D'Arcangelo, Armando Santoro, Victor M Villalobos, Jacob Sands, Luis Paz-Ares*

Summary

Background Few options exist for treatment of patients with small-cell lung cancer (SCLC) after failure of first-line therapy. Lurbinectedin is a selective inhibitor of oncogenic transcription. In this phase 2 study, we evaluated the activity and safety of lurbinectedin in patients with SCLC after failure of platinum-based chemotherapy.

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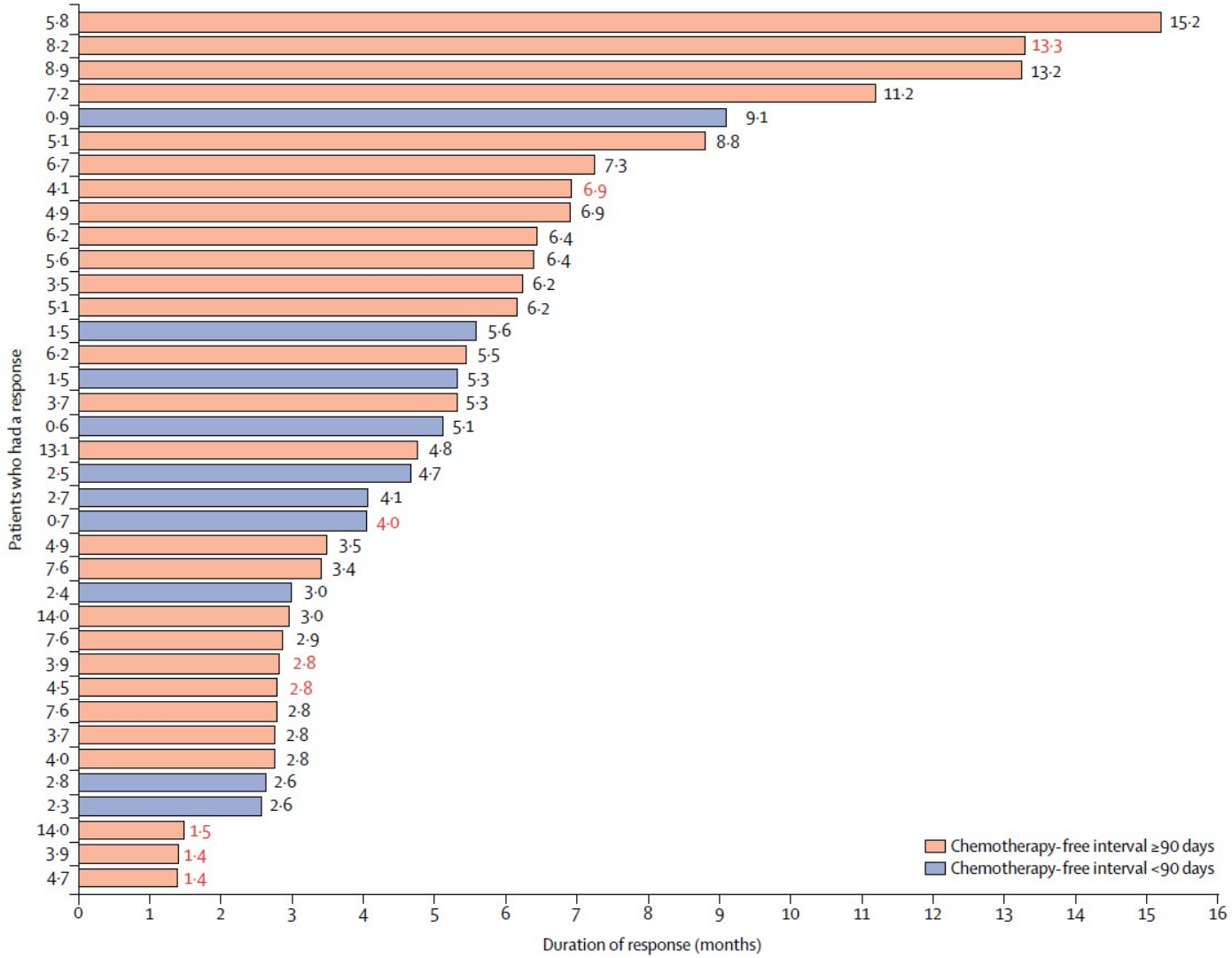
Patients With Lubinectedin Response



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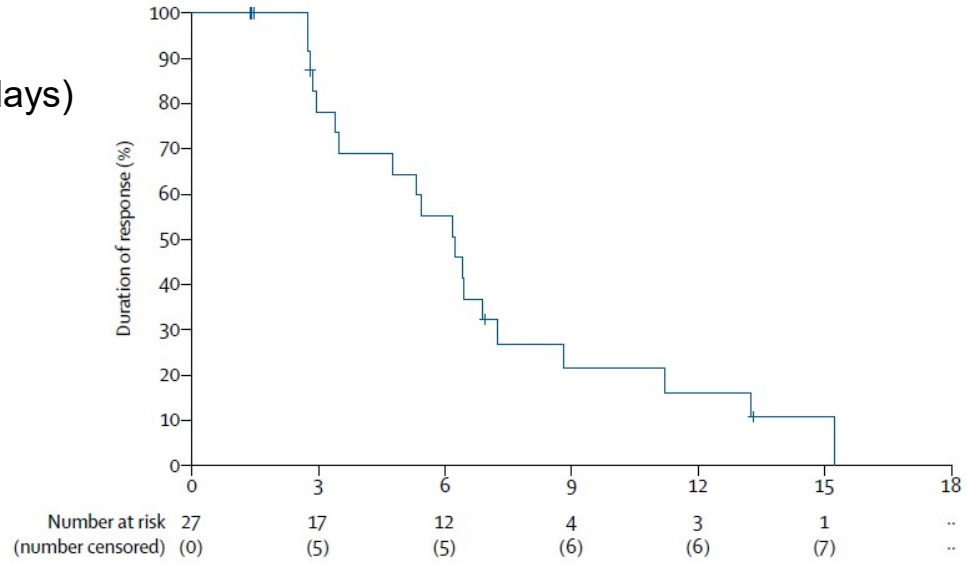
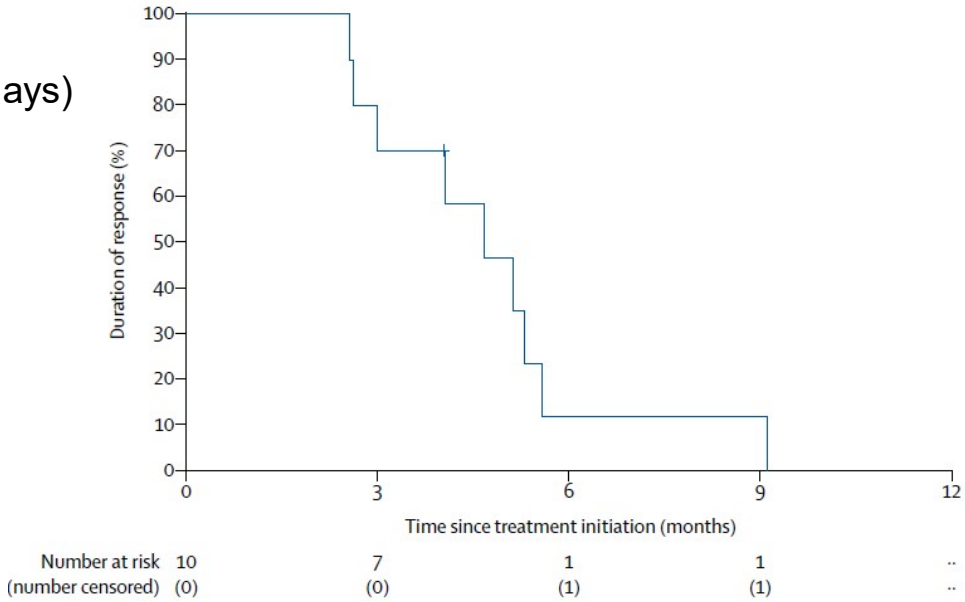
Lubinectedin Duration Response

Sensitive Disease
(Chemo-free interval ≥90 days)



Resistant Disease
(Chemo-free interval <90 days)



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Overall Efficacy of Lurbinectedin

	All patients (n=105)	Chemotherapy-free interval <90 days (n=45)	Chemotherapy-free interval ≥90 days (n=60)
RECIST responses			
Complete response	0	0	0
Partial response	37 (35%)	10 (22%)	27 (45%)
Stable disease*	35 (33%)	13 (29%)	22 (37%)
Progressive disease	28 (27%)	18 (40%)	10 (17%)
Not evaluable†	5 (5%)	4 (9%)	1 (2%)
Overall response, % (95% CI)	35·2% (26·2–45·2)	22·2% (11·2–37·1)	45·0% (32·1–58·4)
Disease control, % (95% CI)‡	68·6% (58·8–77·3)	51·1% (35·8–66·3)	81·7% (69·6–90·5)
Duration of response			
Disease progression, relapse, or death events in responding patients, n/N (%)	29/37 (78%)	9/10 (90%)	20/27 (74%)
Median duration of response, months	5·3 (4·1–6·4)	4·7 (2·6–5·6)	6·2 (3·5–7·3)
Patients still responding at 6 months	43·0% (25·6–60·5)	11·7% (0·0–33·1)	55·3% (34·5–76·0)
Progression-free survival			
Progression-free survival events, n (%)	90 (86%)	41 (91%)	49 (82%)
Median progression-free survival, months (95% CI)	3·5 (2·6–4·3)	2·6 (1·3–3·9)	4·6 (2·8–6·5)
4-month progression-free survival (95%CI)	46·6% (36·7–56·5)	29·1% (15·3–42·8)	59·9% (47·1–72·7)
6-month progression-free survival (95% CI)	32·9% (23·3–42·5)	18·8% (6·8–30·9)	43·5% (30·1–56·9)
Overall survival			
Deaths	66 (63%)	37 (82%)	29 (48%)
Median overall survival, months (95% CI)	9·3 (6·3–11·8)	5·0 (4·1–6·3)	11·9 (9·7–16·2)
6-month overall survival (95%CI)	67·1% (57·6–76·7)	45·8% (30·4–61·3)	83·6% (73·7–93·5)
12-month overall survival (95% CI)	34·2% (23·2–45·1)	15·9% (3·6–28·2)	48·3% (32·5–64·1)

RECIST=Response Evaluation Criteria in Solid Tumors. *Includes five patients with partial response not confirmed. †Five patients were not evaluable because they had no radiological assessment during treatment due to early death from malignant disease (n=2), symptomatic deterioration because of disease progression (n=2), and patient refusal (n=1). ‡Partial response or stable disease.

Table 2: **Overall efficacy of lurbinectedin treatment by investigator assessment and subgroup analyses by chemotherapy-free interval**

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Lab Abnormalities and AE's of Lubinectedin

	Grade 1–2	Grade 3	Grade 4
Haematological abnormalities (regardless of relation to study drug)*			
Anaemia	91 (87%)	9 (9%)	0
Leucopenia	53 (50%)	20 (19%)	10 (10%)
Neutropenia	27 (26%)	22 (21%)	26 (25%)
Thrombocytopenia	39 (37%)	3 (3%)	4 (4%)
Biochemical abnormalities (regardless of relation to study drug)*			
Creatinine†	86/104 (83%)	0	0
Alanine aminotransferase	69/103 (67%)	5/103 (5%)	0
γ-glutamyl transferase	52/103 (50%)	13/103 (13%)	2/103 (2%)
Aspartate aminotransferase	44/103 (43%)	2/103 (2%)	0
Alkaline phosphatase	31/103 (30%)	3/103 (3%)	0
Treatment-related adverse events			
Fatigue	54 (51%)	7 (7%)	0
Nausea	34 (32%)	0	0
Decreased appetite	22 (21%)	0	0
Vomiting	19 (18%)	0	0
Diarrhoea	13 (14%)	1 (1%)	0
Febrile neutropenia	0	2 (2%)	3 (3%)
Pneumonia	0	2 (2%)	0
Skin ulcer	0	1 (1%)	0

Data are n (%) of patients. NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. *Based on all patients with laboratory data available. †Version 4.0 of NCI-CTCAE grades any creatinine increases from baseline as abnormalities, even if creatinine values remain within the normal range.

Table 3: **Most common NCI-CTCAE laboratory abnormalities and treatment-related adverse events**

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Lurbinectedin Recently Approved for 2L

FDA grants accelerated approval to lurbinectedin for metastatic small cell lung cancer

On June 15, 2020, the Food and Drug Administration granted accelerated approval to lurbinectedin(ZEPZELCA, Pharma Mar S.A.) for adult patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy.

Efficacy was demonstrated in the PM1183-B-005-14 trial (Study B-005; NCT02454972), a multicenter open-label, multi-cohort study enrolling 105 patients with metastatic SCLC who had disease progression on or after platinum-based chemotherapy. Patients received lurbinectedin 3.2 mg/m^2 by intravenous infusion every 21 days until disease progression or unacceptable toxicity.

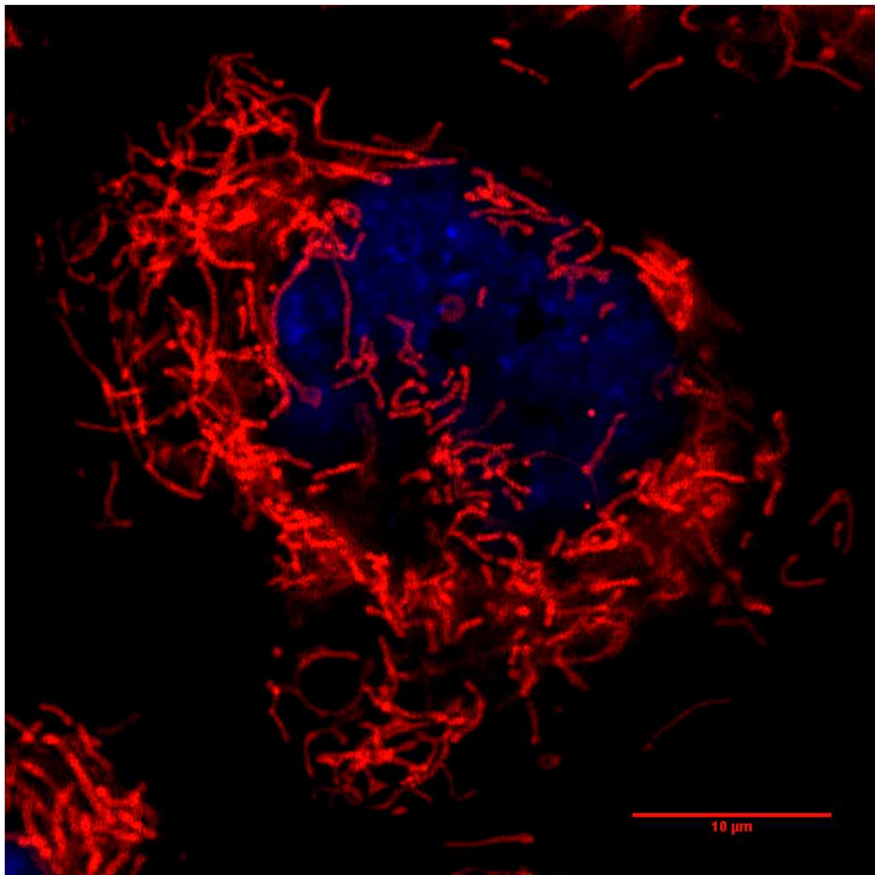
SCLC Clinical Trials

Name & Identifier	Name & Identifier	Name & Identifier
Phase Ib Study of Chiauranib in Patients With Small Cell Lung Cancer (NCT03216343)	Study Evaluating Safety, Tolerability and PK of AMG 757 in Adults With Small Cell Lung Cancer (NCT03319940)	Trial of Topotecan With VX-970 (M6620), an ATR Kinase Inhibitor, in Small Cell Cancers and Extrapulmonary Small Cell Cancers (NCT02487095)
Navitoclax and Vistusertib in Treating Patients With Relapsed Small Cell Lung Cancer and Other Solid Tumors (NCT03366103)	Combination Immunotherapy-Ipilimumab-Nivolumab-Dendritic Cell p53 Vac - Patients With Small Cell Lung Cancer (SCLC) (NCT03406715)	A Phase II, Study to Determine the Preliminary Efficacy of Novel Combinations of Treatment in Patients With Platinum Refractory Extensive-Stage Small-Cell Lung Cancer (NCT02937818)
Clinical Trial of Lurbinectedin (PM01183)/Doxorubicin Versus CAV or Topotecan as Treatment in Patients With Small-Cell Lung Cancer (ATLANTIS) (NCT02566993)	RRx-001 Sequentially With a Platinum Doublet or a Platinum Doublet in Third-Line or Beyond in Patients With Small Cell Lung Cancer (REPLATINUM) (NCT03699956)	A Phase 1 Study Evaluating the Safety, Tolerability and Efficacy of AMG 119 in Subjects With RR SCLC (NCT03392064)
Pembrolizumab in Untreated Extensive SCLC (REACTION) (NCT02580994)	Carboplatin, Etoposide, and Atezolizumab With or Without Trilaciclib (G1T28), a CDK 4/6 Inhibitor, in Extensive Stage Small Cell Lung Cancer (SCLC) (NCT03041311)	A Phase I/II Study of MEDI4736 in Combination With Olaparib in Patients With Advanced Solid Tumors (MEDIOLA) (NCT02734004)
A Dose Escalation Study to Investigate the Safety, Pharmacokinetics (PK), Pharmacodynamics (PD), and Clinical Activity of GSK525762 Plus Trametinib in Subjects With Solid Tumors (NCT03266159)	A Dose Escalation and Expansion Study of RO7121661, a PD-1/TIM-3 Bispecific Antibody, in Participants With Advanced and/or Metastatic Solid Tumors (NCT03708328)	A Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of GSK525761 in Subjects With NUT Midline Carcinoma (NMC) and Other Cancers (NCT01587703)
A Phase I Study of Safety, Tolerability, and PK of AZD2811 in Patients With Advanced Solid Tumors (NCT02579226)	A Study Of Avelumab In Combination With Other Cancer Immunotherapies In Advanced Malignancies (JAVELIN Medley) (NCT02554812)	A Study Evaluating the Safety and Pharmacokinetics of ABBV-075 in Subjects with Cancer (NCT02391480)
AZD1775 Combined With Olaparib in Patients With Refractory Solid Tumors (NCT02511795)	PDR001 Plus LAG525 for Patients With Advanced Solid and Hematologic Malignancies (NCT03365791)	Phase I/II Study of IMMU-132 in Patients With Epithelial Cancers (NCT01631552)

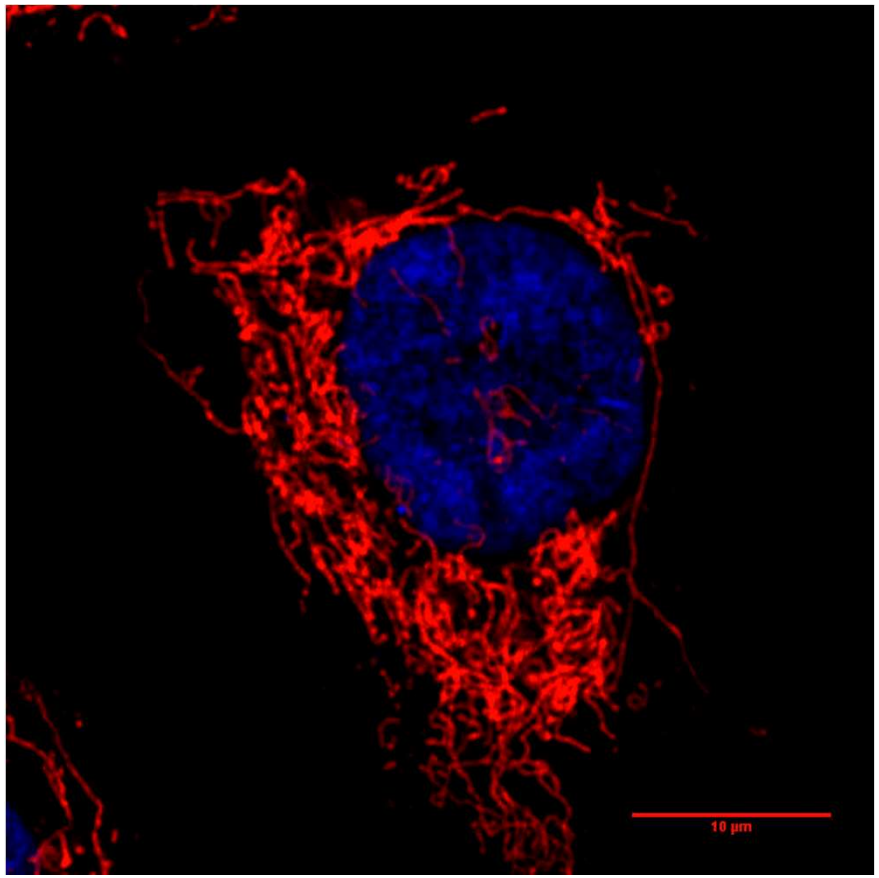
Mitochondria as a Therapeutic Target

SCLC Cell Lines are Densely Packed with Mitochondria in 3D Reconstruction

Untreated



HGF Treated



Mirzapoiazova et int. Salgia, JCM, 2019

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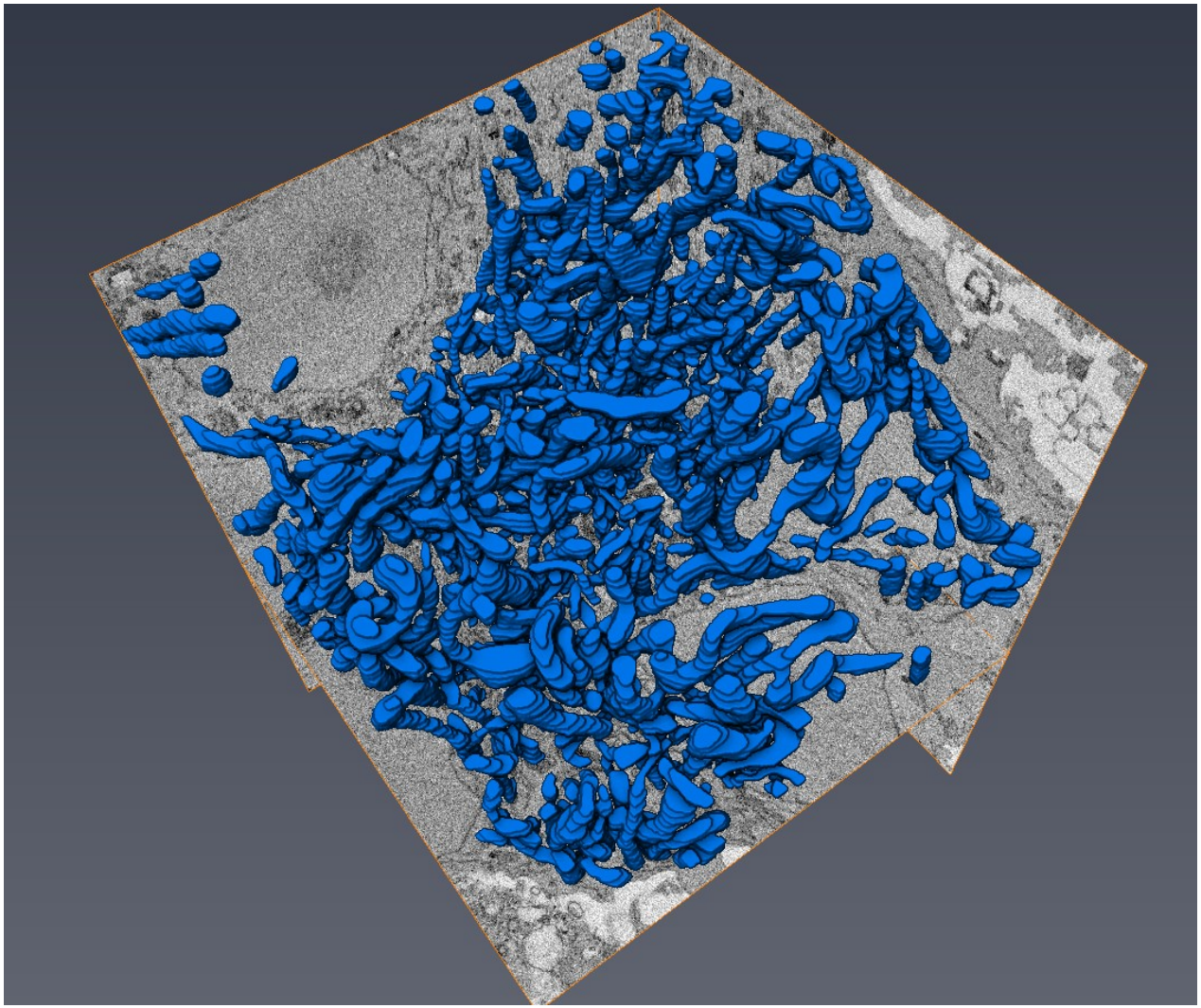
SCLC Cell Lines are Densely Packed with Mitochondria in 3D Reconstruction



Mirzapoiazova et int. Salgia, JCM, 2019

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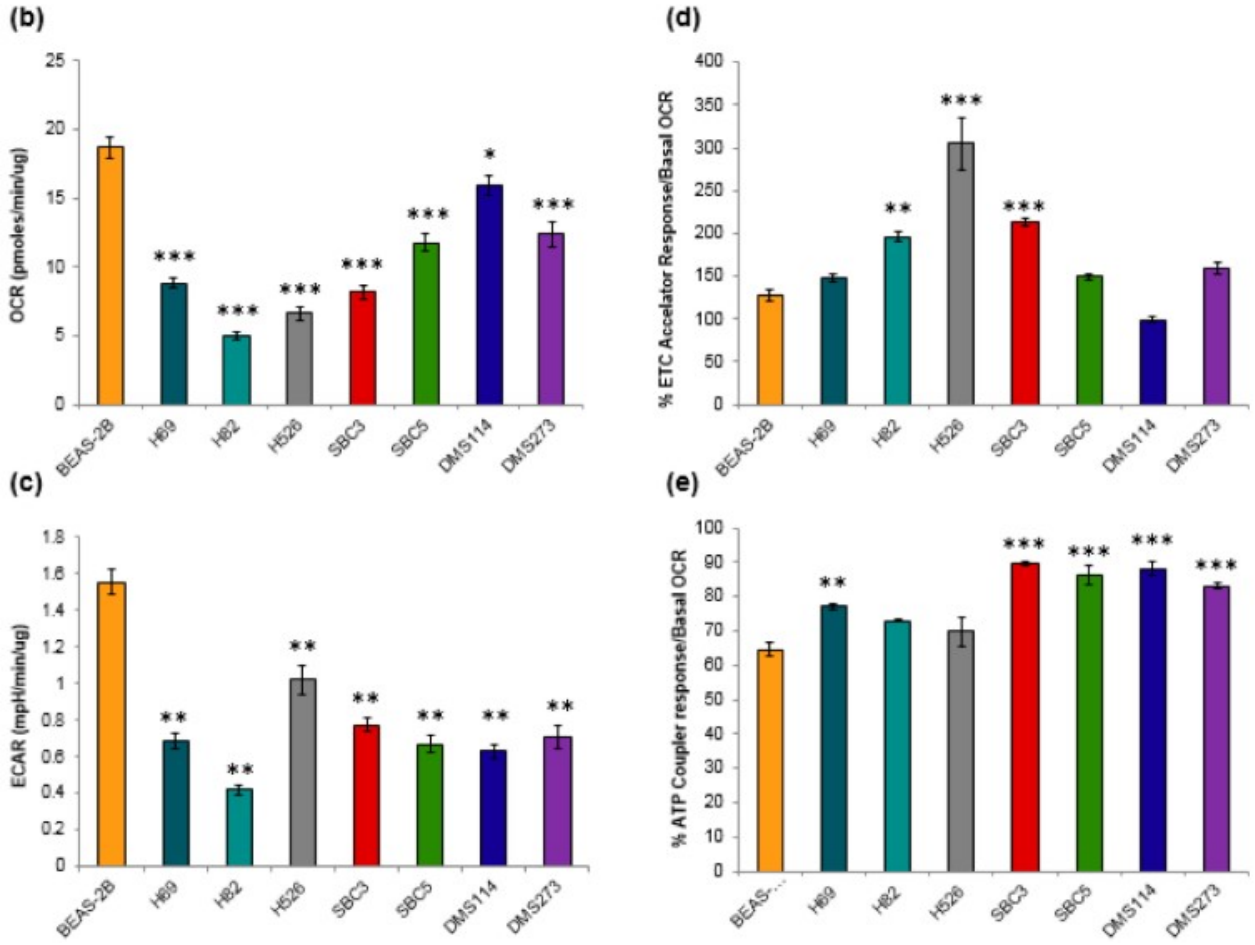
Mitochondrial Metabolic Profiles of SCLC



PAX5 and PP2A may be involved in SCLC's dysregulated active metabolism

Mambetsariev et int. Salgia, JCM, 2019

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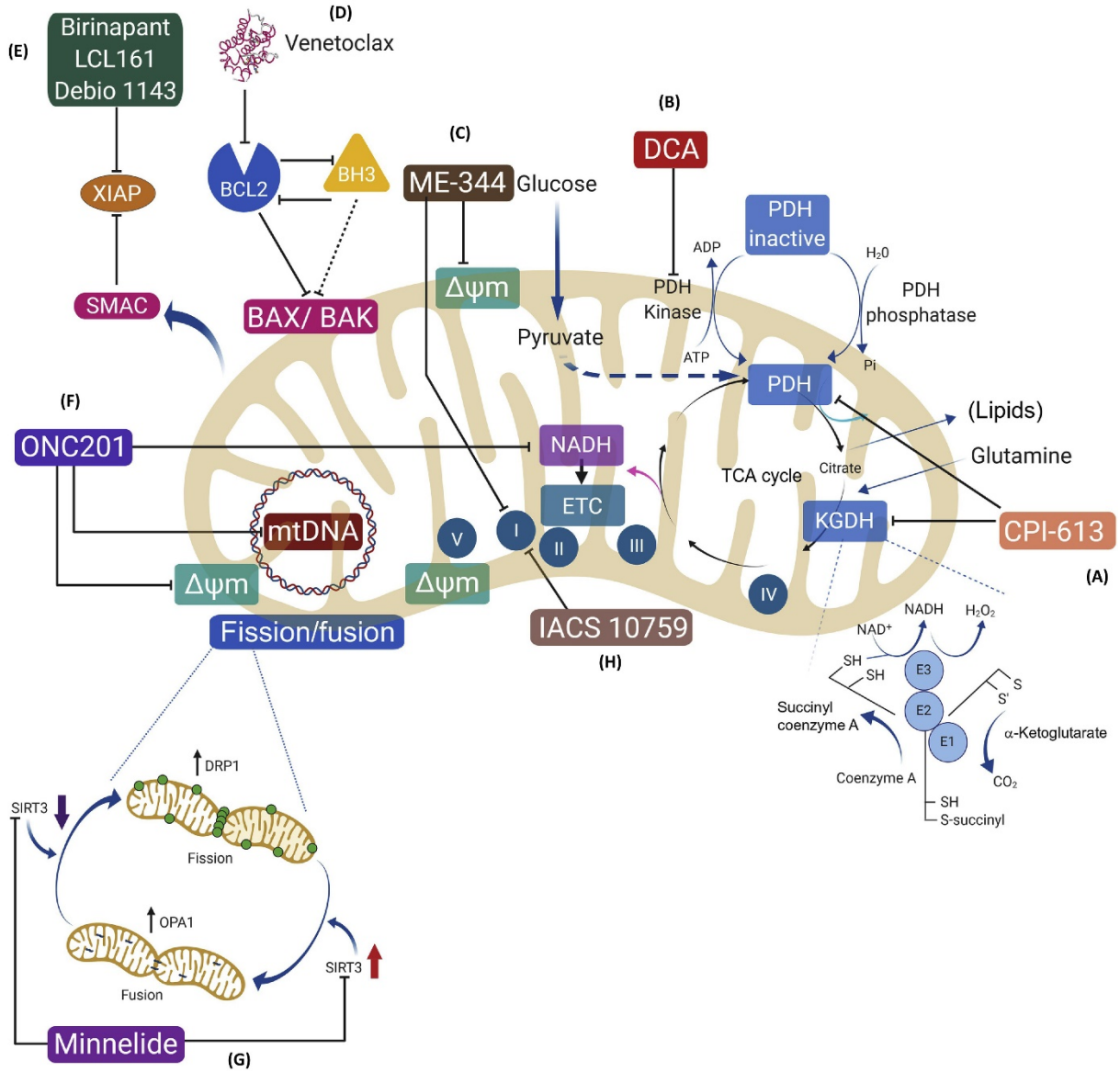
Mitochondrial Therapeutic Targets Undergoing Evaluation in Trials



Roth et int. Salgia, Trends in Molecular Medicine, 2020

Trends in Molecular Medicine

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Conclusions--SCLC

- Novel Therapies need to be tested more rapidly
- Immunotherapy has now become approved
- Second line therapy has also advanced
- For the future, biomarker driven studies need to be considered