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Reshaping Our Approach in SCLC
Latest Therapeutic Options

Stephen V. Liu, MD
Director of Thoracic Oncology
Head of Developmental Therapeutics
Georgetown University

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

http://lombardi.georgetown.edu
Lombardi CancerLine: 202.444.4000

Disclosures

- Advisory Board / Consultant:

  Abbvie, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Candel Therapeutics (DSMB), Catalyst, Daiichi Sankyo, Elevation Oncology, Genentech/Roche, Gilead, Guardant Health, Janssen, Jazz Pharmaceuticals, Merck, Merus, Mirati, Novartis, OSE Immunotherapeutics, Pfizer, RAPT, Regeneron, Revolution Medicines, Sanofi, Takeda, Yuhan

- Research grant (to institution):

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Where will BiTEs be used for ES-SCLC 5 years from now?

- As part of first-line therapy
- As maintenance therapy
- Second-line therapy
- Third-line therapy
- Only for biomarker selected patients

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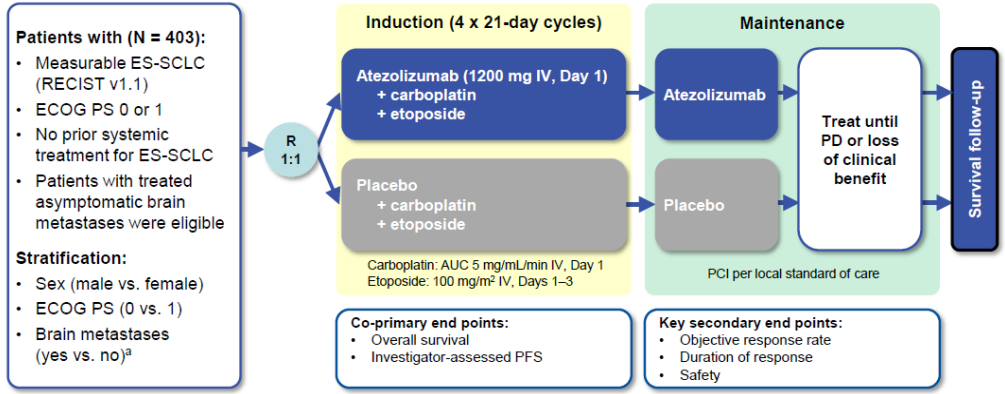
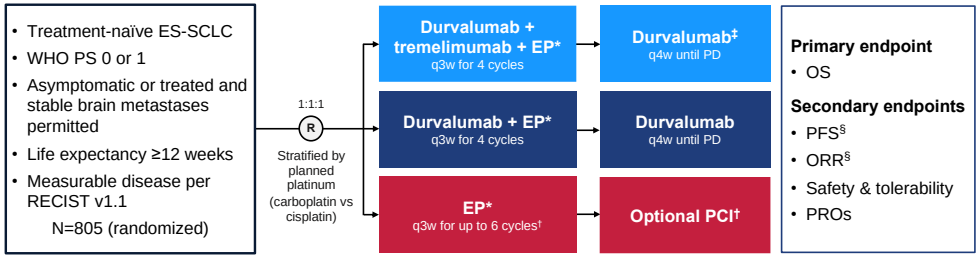
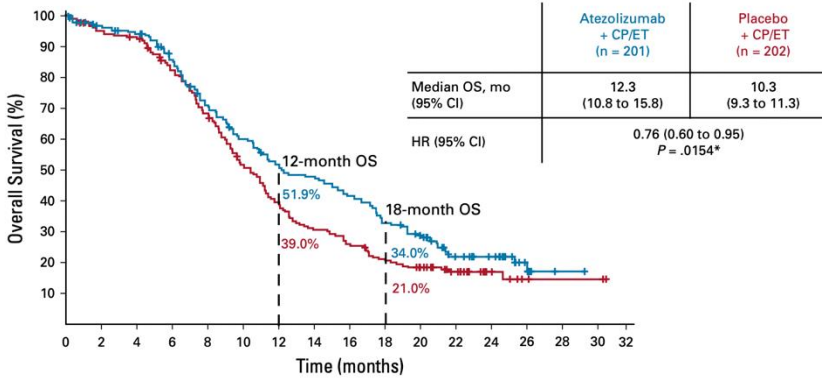
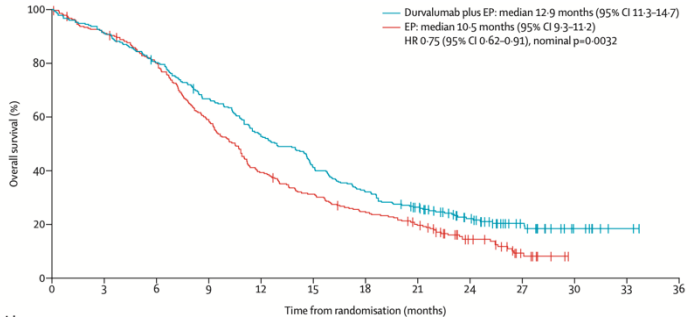
IMpower 133 & CASPIAN









Liu, WCLC 2018; Liu, JTO 2021; Paz-Ares, ASCO 2020; Goldman, Lancet Oncol 2021

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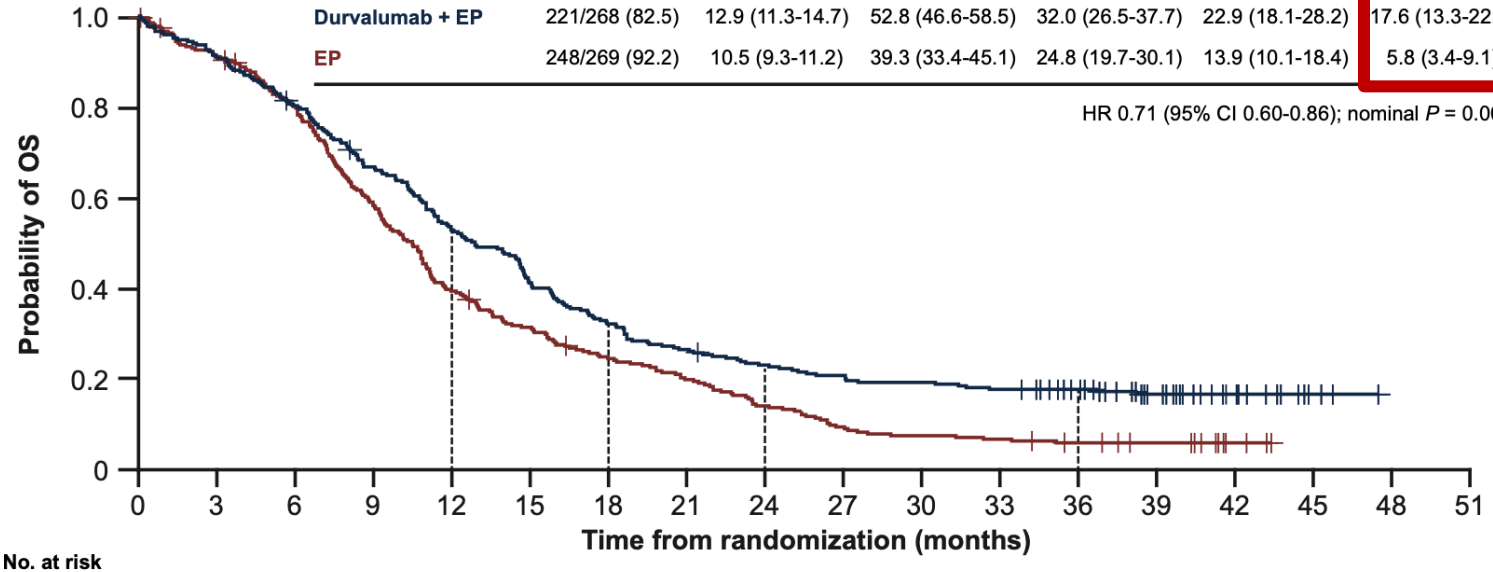
First-Line Treatment of ES-SCLC

Study	Agent	Sample Size	mPFS / HR	mOS / HR	1y OS Rate
IMpower 133 *Liu, JCO 2021*	Atezolizumab	403 pts	5.2m HR 0.77	12.3m HR 0.76	52%
CASPIAN *Paz-Ares, ESMO Open 2022*	Durvalumab	805 pts	5.1m HR 0.80	12.9m HR 0.71	53%
EA5161 (phase II) *Leal, ASCO 2020*	Nivolumab	160 pts	5.5m HR 0.68	11.3m HR 0.73	50%
KEYNOTE 604 *Rudin, WCLC 2022*	Pembrolizumab	453 pts	4.8m HR 0.70	10.8m HR 0.76	45%
ASTRUM 005 *Cheng, JAMA 2022*	Serplulimab	585 pts	5.7m HR 0.48	15.4m HR 0.63	61%
CAPSTONE-1 *Wang, Lancet Oncol 2022*	Adebrelimab	462 pts	5.8m HR 0.67	15.3m HR 0.72	63%
RATIONALE-312 *Cheng, JTO 2024*	Tislelizumab	457 pts	4.7m HR 0.64	15.5m HR 0.75	63%

CASPIAN: 3y Survival

	Events/ patients, *n* (%)	Median OS (95% CI), months	12-month OS rate (95% CI), %	18-month OS rate (95% CI), %	24-month OS rate (95% CI), %	36-month OS rate (95% CI), %
Durvalumab + EP	221/268 (82.5)	12.9 (11.3-14.7)	52.8 (46.6-58.5)	32.0 (26.5-37.7)	22.9 (18.1-28.2)	17.6 (13.3-22.4)
EP	248/269 (92.2)	10.5 (9.3-11.2)	39.3 (33.4-45.1)	24.8 (19.7-30.1)	13.9 (10.1-18.4)	5.8 (3.4-9.1)

HR 0.71 (95% CI 0.60-0.86); nominal *P* = 0.0003



No. at risk																	
Durvalumab + EP	268	244	214	177	140	109	85	70	60	54	50	46	39	25	13	3	0	0
EP	269	243	212	156	104	82	64	51	36	24	19	17	13	10	3	0	0	0

Paz-Ares, ESMO Open 2022

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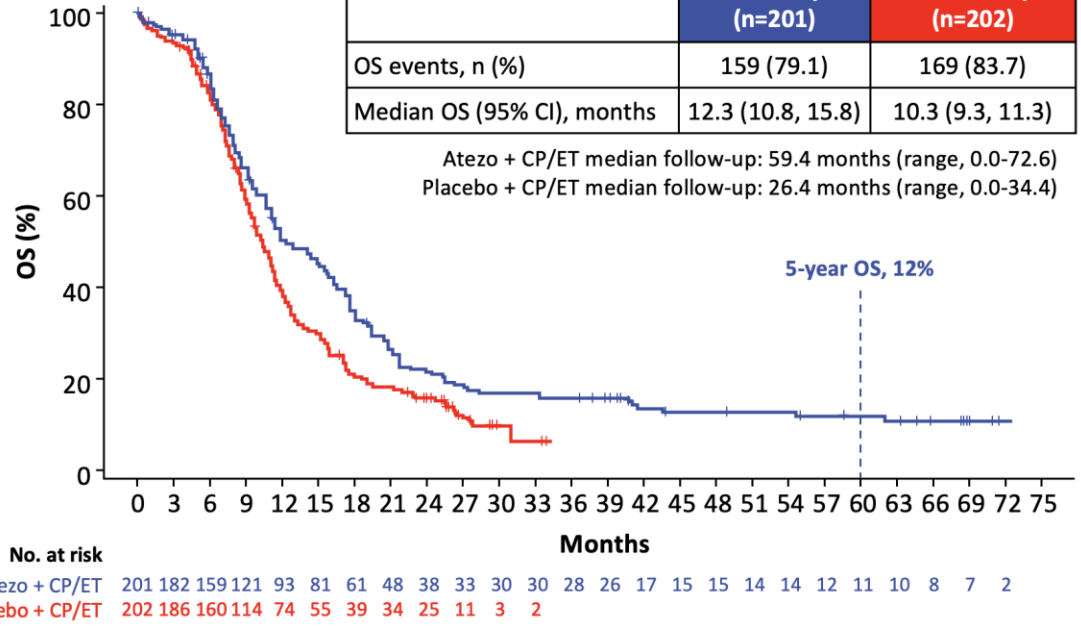
IMbrellaA: 5y OS Atezolizumab in SCLC



	Atezo + CP/ET (n=201)	Placebo + CP/ET (n=202)
OS events, n (%)	159 (79.1)	169 (83.7)
Median OS (95% CI), months	12.3 (10.8, 15.8)	10.3 (9.3, 11.3)

Atezo + CP/ET median follow-up: 59.4 months (range, 0.0-72.6)
Placebo + CP/ET median follow-up: 26.4 months (range, 0.0-34.4)

OS rate (95% CI), %	IMpower133 and IMbrella A Atezo + CP/ET (n=201)	IMpower133 only Placebo + CP/ET (n=202)
1-year	52% (45-59)	39% (32-46)
2-year	22% (16-28)	16% (11-21)
3-year	16% (11-21)	NE[a]
4-year	13% (8-18)	NE[a]
5-year	12% (7-17)	NE[a]

Liu, WCLC 2023

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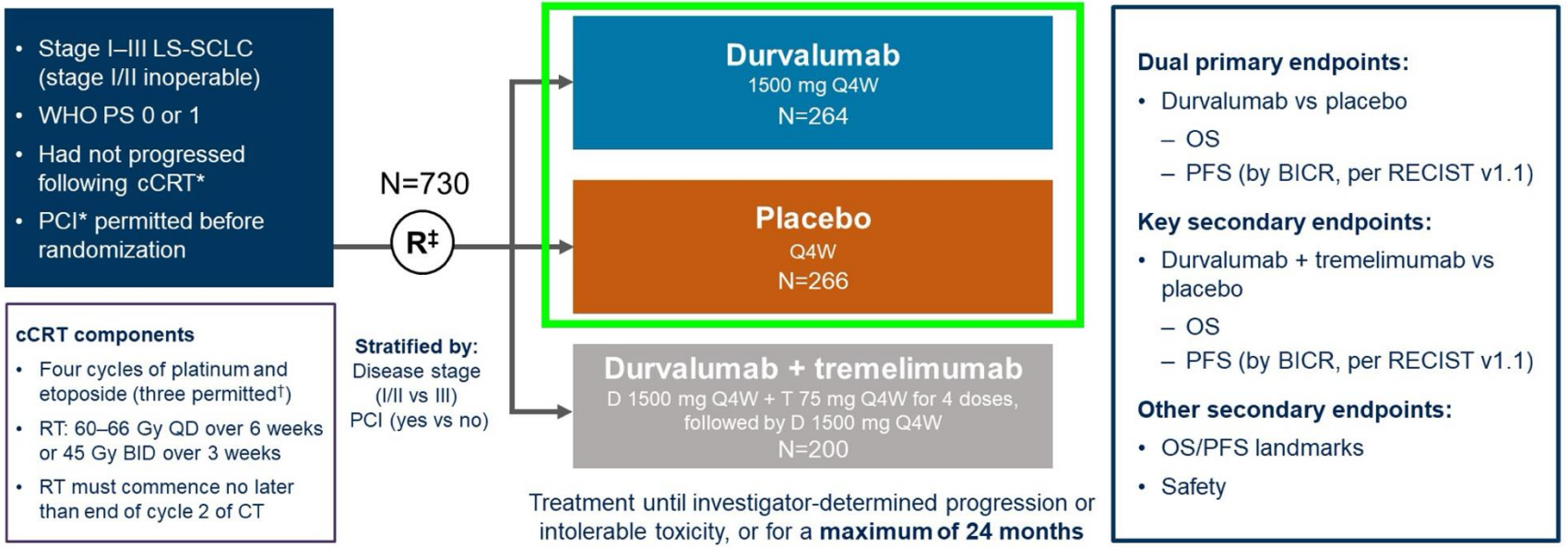
ADRIATIC

- Durvalumab for LS-SCLC after chemoradiation



Spigel, ASCO 2024

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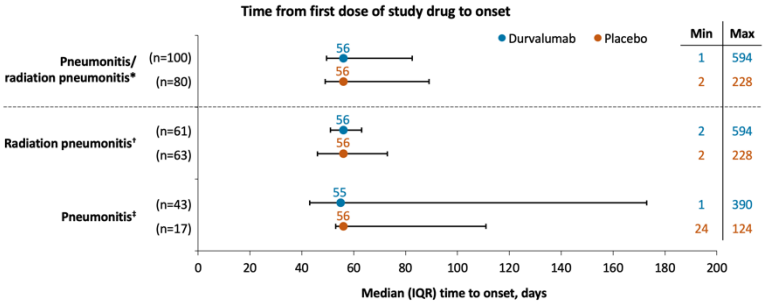
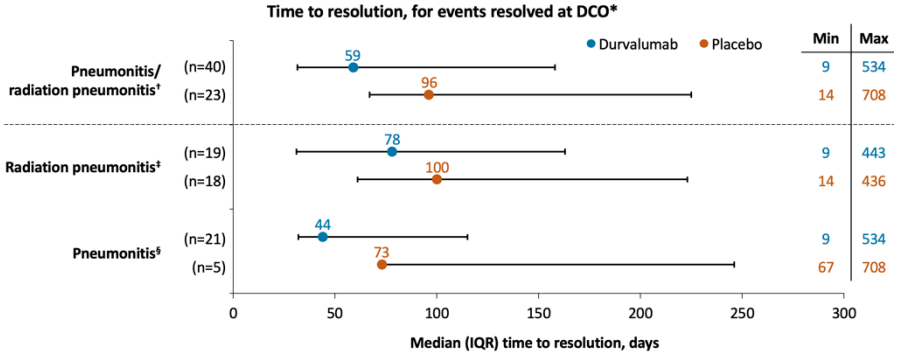
ADRIATIC: Pneumonitis

- Durvalumab increased pneumonitis over placebo
  - Grouped terms: 38.2% vs 30.2%





Iyengar, ASTRO 2024

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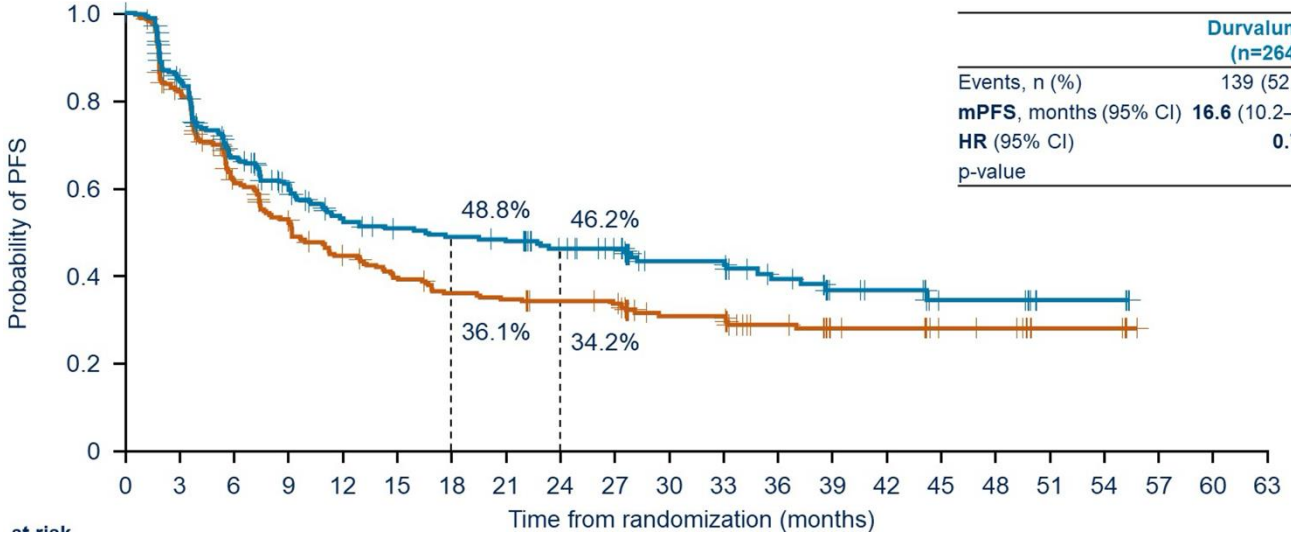
ADRIATIC

- Durvalumab significantly improved PFS
  - Median PFS 16.6m vs 9.2m (HR 0.76)
  - 2y PFS rate 46.2% vs 34.2%



	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	139 (52.7)	169 (63.5)
mPFS, months (95% CI)	**16.6** (10.2–28.2)	**9.2** (7.4–12.9)
HR (95% CI)	**0.76** (0.61–0.95)	
p-value	0.0161	

Spigel, ASCO 2024

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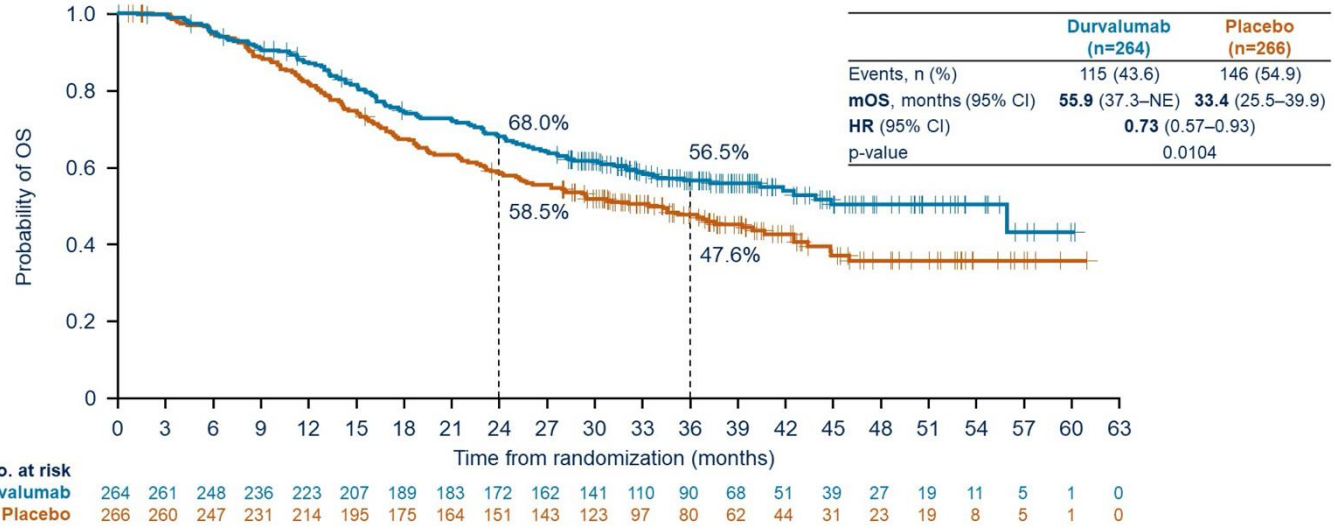
ADRIATIC: Survival

- Durvalumab significantly improved overall survival
  - Median OS 55.9m vs 33.4m (+22.5m), OS HR 0.73



	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	115 (43.6)	146 (54.9)
mOS, months (95% CI)	**55.9** (37.3–NE)	**33.4** (25.5–39.9)
HR (95% CI)	**0.73** (0.57–0.93)	
p-value	0.0104	

Spigel, ASCO 2024

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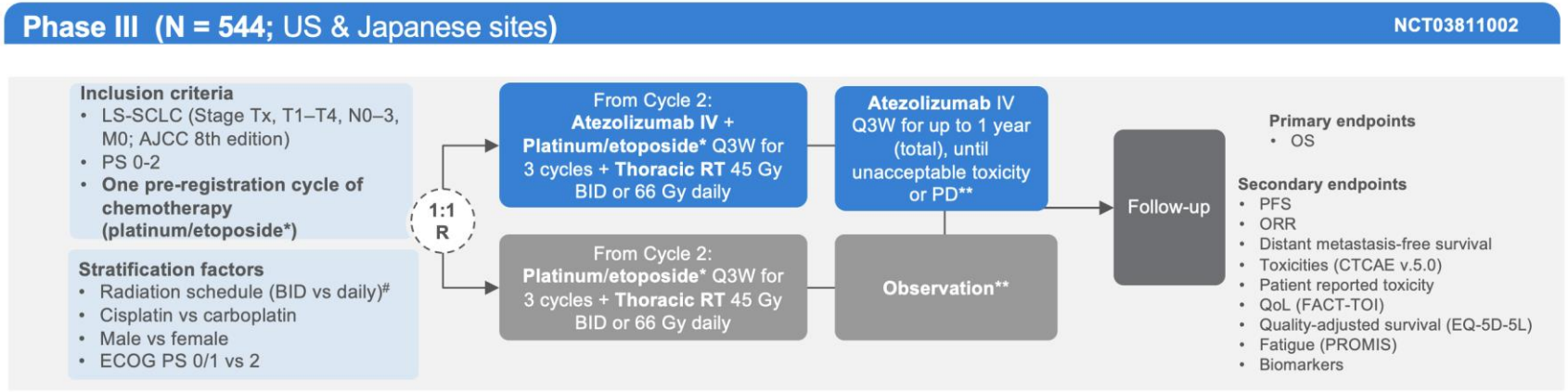
NRG LU005: Concurrent Atezolizumab

- Atezolizumab with and after concurrent chemoradiation for limited-stage SCLC



Higgins, ASTRO 2024

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NRG LU005: Safety

	CRT Only (n = 254)	CRT + Atezo (n = 267)
Any grade AEs	251 (99)	266 (99.6)
Grade 3/4 AEs	235 (92.5)	231 (86.5)
AEs leading to death	4 (1.6)	24 (9)*
Treatment-related AEs leading to death	2 (1)	9 (3)
Grade 3/4 Immune related AEs	16 (6.2)	42 (15.7)
Grade 5 Immune related AEs	0 (0)	4 (1.5)

*Reporting window of 30 days post CRT for control arm and 90 days post end of atezo for experimental arm (11 weeks vs. 15 months)

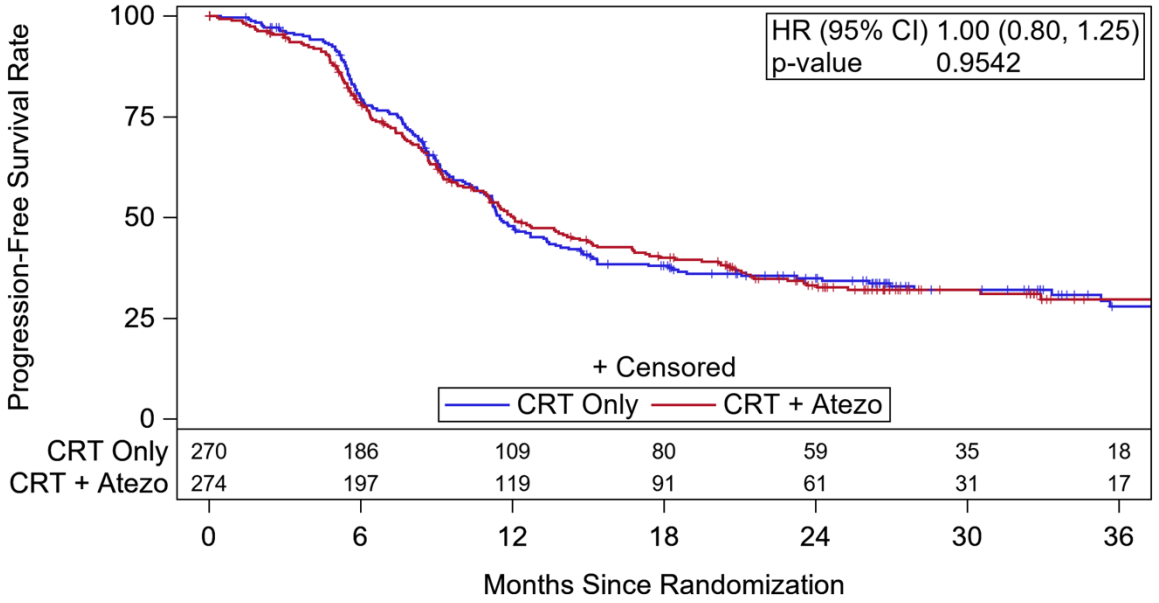
Pneumonitis

	CRT Only (n = 254)	CRT + Atezo (n = 267)
Any grade	30 (11.8)	70 (26.2)
Grade 3/4	8 (3.2)	13 (4.9)
Grade 5	0 (0)	2 (0.7)

Higgins, ASTRO 2024

NRG LU005: Concurrent Atezolizumab

- Atezolizumab with and after concurrent chemoradiation for LS-SCLC did not improve PFS



Higgins, ASTRO 2024

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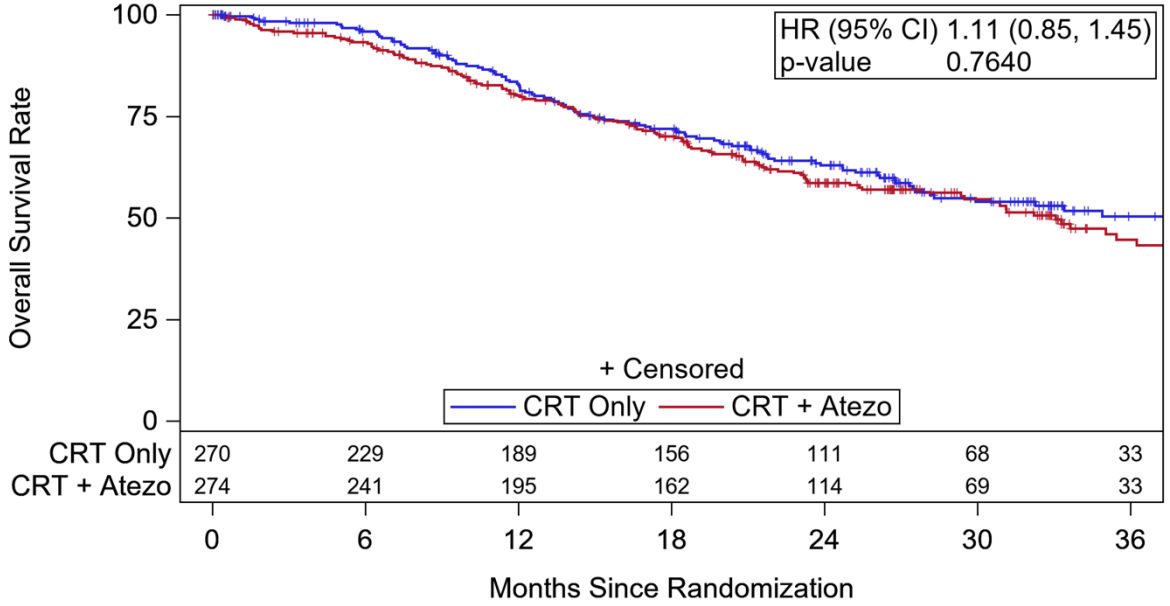
NRG LU005: Concurrent Atezolizumab

- Atezolizumab with and after concurrent chemoradiation for LS-SCLC did not improve OS



Higgins, ASTRO 2024

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ADRIATIC vs LU005

- Why did ADRIATIC have such a profound impact on outcomes and LU005 did not?
  - Durvalumab vs atezolizumab?
    - Unlikely – very similar performance in ES-SCLC
  - Different patient population
    - LU005 included patients who would not have qualified for ADRIATIC after chemoradiation – but control arm did very well
  - Concurrent vs consolidation
    - Does giving PD(L)1 therapy with large field, definitive chemoradiation prevent an immune response?

Immunotherapy and Radiation

- Radiation increases PD-L1 expression in vitro
  - Appealing to partner these modalities
- Positive sequential trials
  - PACIFIC, ADRIATIC
- Positive SBRT trials
- Negative concurrent trials
  - Radiation field (lymph nodes, blood pool)
  - Fractionation and cumulative dose
  - Lymphopenic therapy (radiation and chemotherapy)

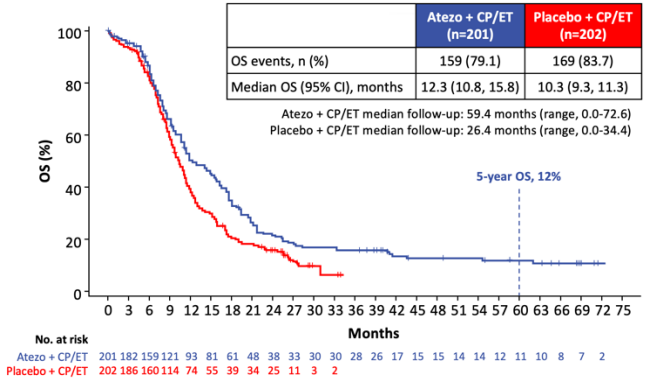
Table. Clinical Trials of Concurrent Immune Checkpoint Inhibitors and Conventionally Fractionated CRT With Negative Outcomes

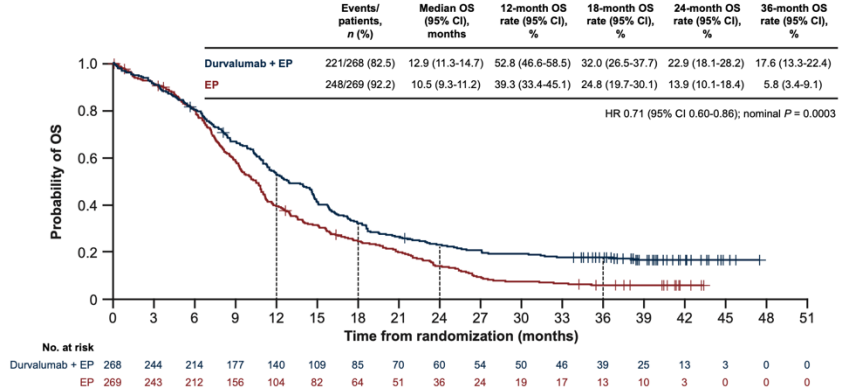
Clinical trial	Phase	Cancer type	Treatment arm
PACIFIC 2	3	NSCLC	Concurrent durvalumab + CRT vs SOC CRT
NRG-HN005	2/3	HNSCC	Concurrent reduced-dose RT + nivolumab vs reduced-dose RT + cisplatin vs SOC CRT
JAVELIN-HNSCC 100	3	HNSCC	Concurrent avelumab + CRT vs SOC CRT
GORTEC-2017-01 (REACH)	3	HNSCC	Concurrent avelumab + cetuximab + RT vs SOC (cisplatin-cetuximab + RT)
KEYNOTE 412	3	HNSCC	Concurrent pembro + CRT vs SOC CRT
CALLA	3	Cervical SCC	Concurrent durvalumab + CRT → adjuvant durvalumab vs SOC CRT
NRG-GI002	2	Rectal cancer	FOLFOX → CRT + pembro preop vs FOLFOX → CRT preop

McGee, JAMA Onc 2024

Immunotherapy is Our Standard

- Adding PD(L)1 inhibitor to 1L chemotherapy improves survival without significant increase in toxicity

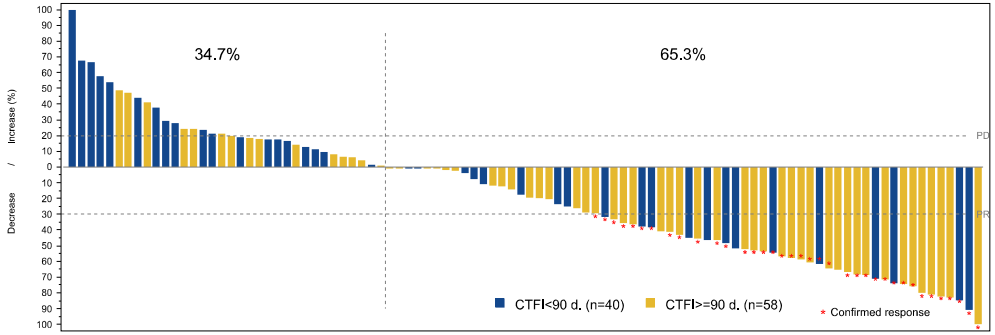




- How do we extend long-term benefit to more patients?

Lurbinectedin

- Marine derived transcription inhibitor
- Single-arm phase II monotherapy study
  - Response rate 35.2%
  - Sensitive RR 45%, resistant RR 22%
  - FDA accelerated approval June 15, 2020

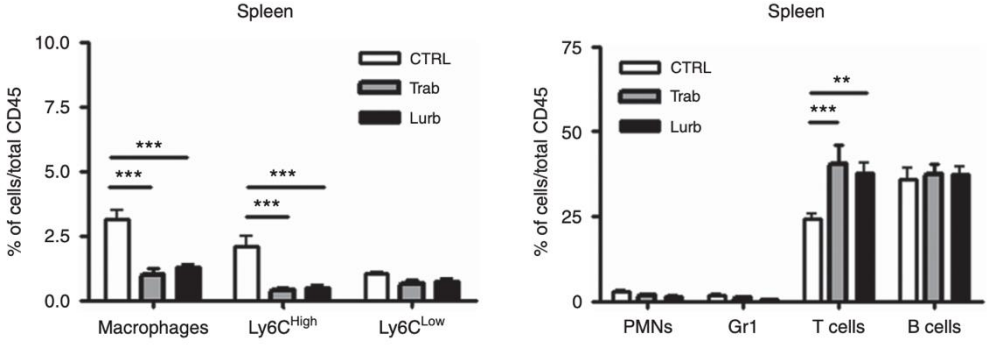


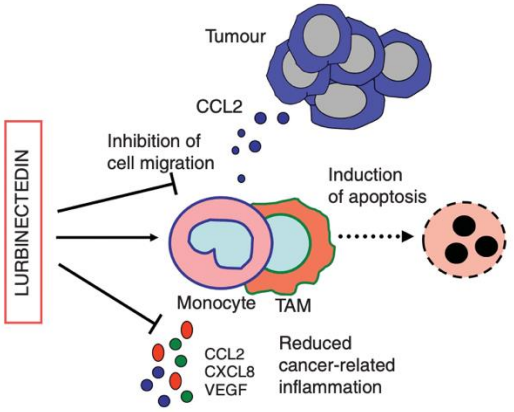
	Grade 1–2	Grade 3	Grade 4
Haematological abnormalities (regardless of relation to study drug)*			
Anaemia	91 (87%)	9 (9%)	0
Leucopenia	53 (50%)	20 (19%)	10 (10%)
Neutropenia	27 (26%)	22 (21%)	26 (25%)
Thrombocytopenia	39 (37%)	3 (3%)	4 (4%)
Biochemical abnormalities (regardless of relation to study drug)*			
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

Trigo, Lancet Oncol 2020

Lurbinectedin

- Lurbinectedin has an effect on the immune TME
- Reduction in tumor associated macrophages



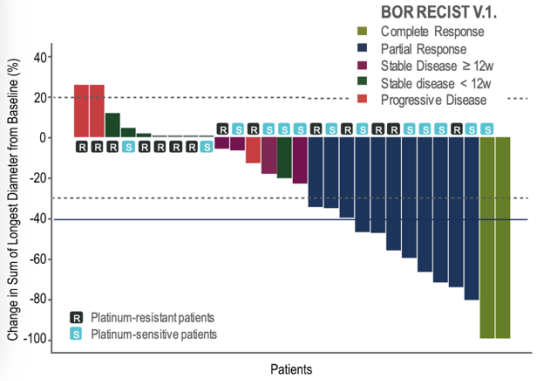


Belgiovini, BJC 2017

Lurbinectedin

- Phase I/II LUPER trial
  - Impact of lurbinectedin on microenvironment
    - Potential synergy with immunotherapy
  - Lurbinectedin + pembrolizumab (in IO naïve SCLC)
    - RR 46.4%, mPFS 5.3m; in platinum sensitive, RR 53.9%, mPFS 10m

Tumor response, n (%)	Platinum-free interval <90 days (n = 14)	Platinum-free interval ≥90 days (n = 13)	Overall (N = 28)
Best Overall Response			
CR*	0 (0%)	1 (7.7%)	2 (7.1%)
PR	5 (35.7%)	6 (46.2%)	11 (39.3%)
SD ≥ 12w	1 (7.1%)	3 (23.1%)	4 (14.3%)
SD < 12w	2 (14.3%)	2 (15.4%)	4 (14.3%)
PD	3 (21.4%)	0 (0%)	3 (10.7%)
NE	3 (21.4%)	1 (7.7%)	4 (14.3%)
Objective Response Rate			
Yes*	5 (35.7%)	7 (53.9%)	13 (46.4%)
No	9 (64.3%)	6 (46.1%)	15 (53.6%)
Clinical Benefit Rate			
Yes*	6 (42.9%)	10 (76.9%)	17 (60.7%)
No	8 (57.1%)	3 (23.1%)	11 (39.3%)



Calles, ESMO 2023

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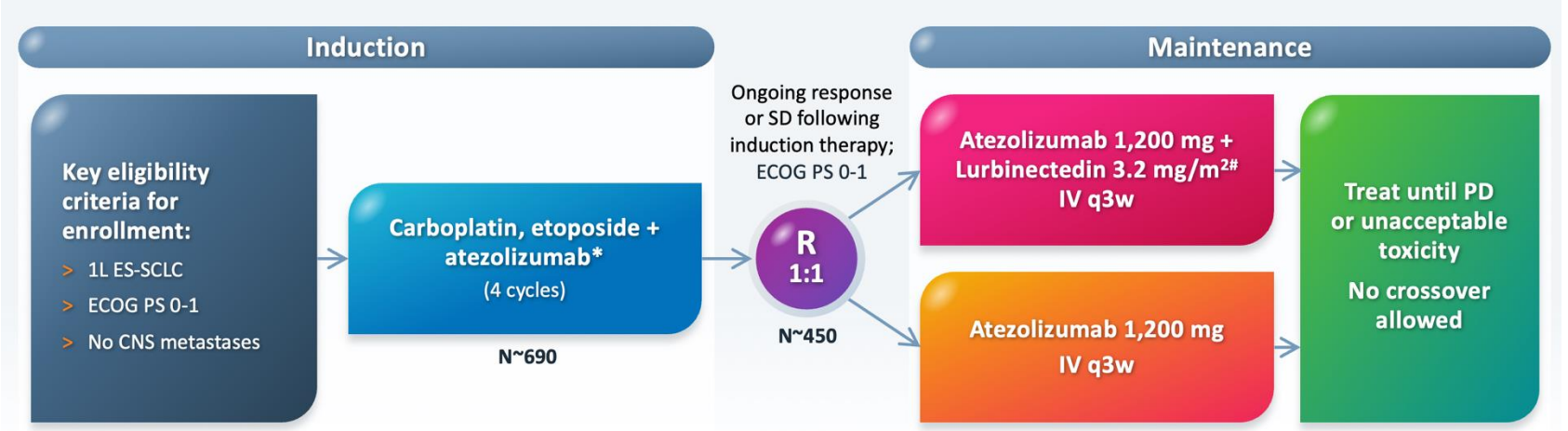
Lurbinectedin



Stratification factors:

> ECOG PS 0 vs 1 *(at maintenance baseline)*
> LDH (≤ULN vs >ULN) *(at maintenance baseline)*
> Presence of liver mets *(at induction baseline)*
> Prior receipt of PCI

Primary endpoints:

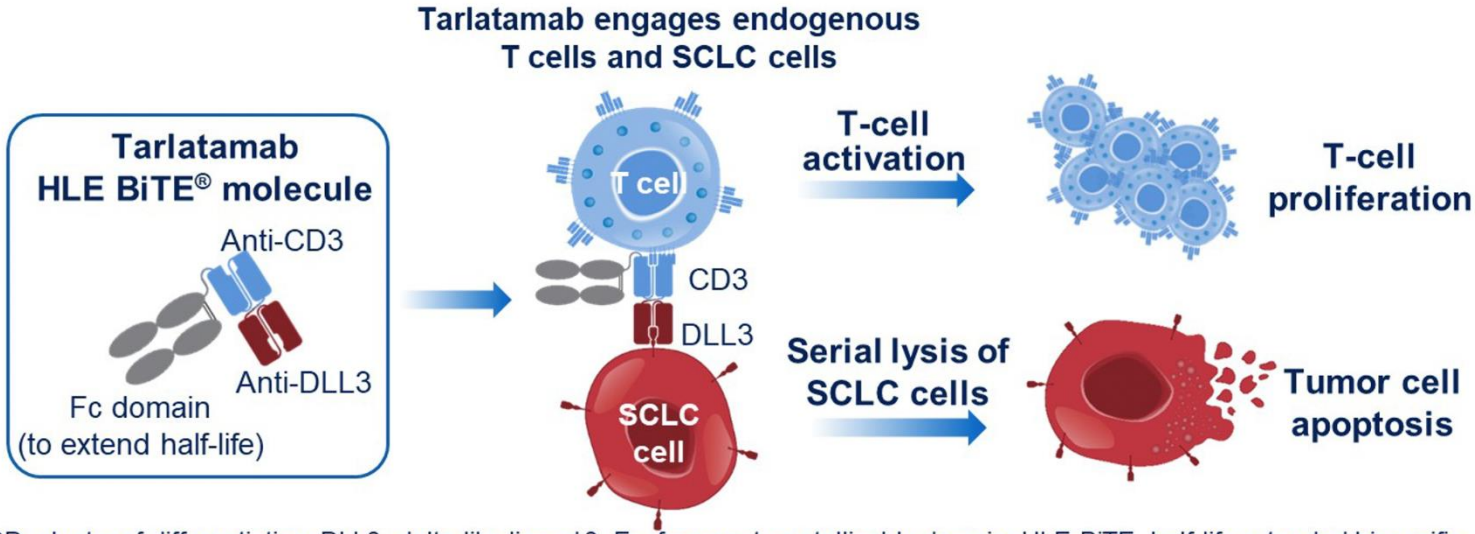
> IRF-assessed PFS and OS

Secondary endpoints:

> Inv-assessed PFS, ORR, DOR, landmark PFS & OS, safety

Tarlatamab (AMG 757)

- Bispecific T-cell Engager (BiTE) targeting DLL3 + CD3

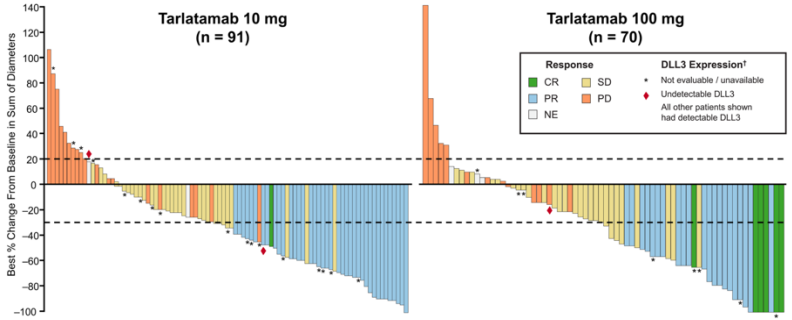


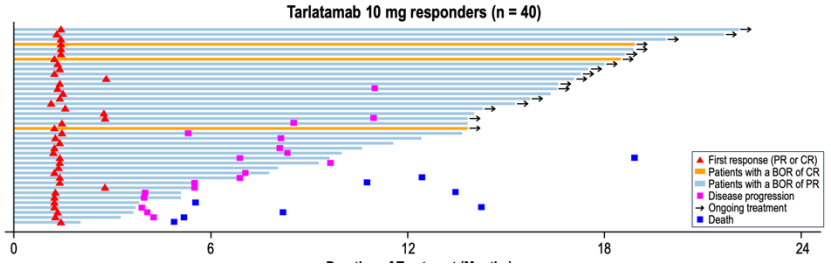
CD, cluster of differentiation; DLL3, delta-like ligand 3; Fc, fragment crystallizable domain; HLE BiTE, half-life extended bispecific T-cell engager; SCLC, small cell lung cancer.

Owonikoko, ASCO 2021

Tarlatamab (AMG 757)

- Phase II DeLLphi-300 Study
  - 10mg dose comparable to 100mg in efficacy, better safety
  - RR 40% at 10mg, 32% at 100mg, 58-61% lasting ≥ 6m





Paz-Ares, ESMO 2023

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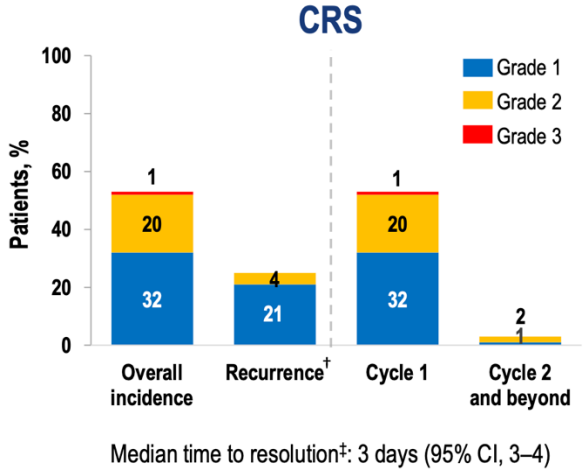
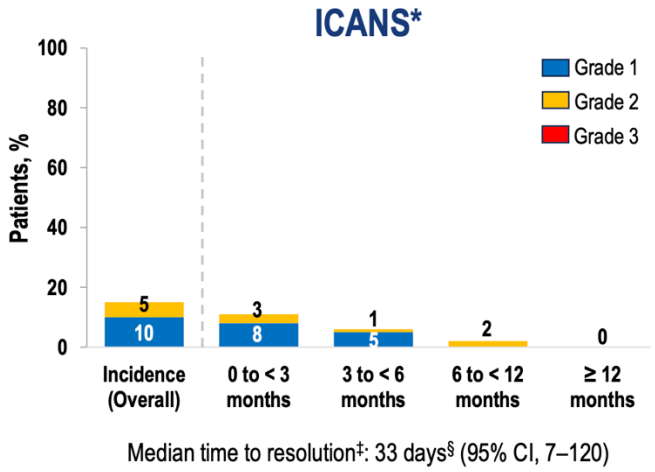
Tarlatamab (AMG 757)

- Phase II DeLLphi-300 Study (pooled 10mg doses)
  - CRS was typically with cycles 1 or 2
  - ICANS was uncommon, early onset, and grade 1 or 2



Median time to resolution‡: 3 days (95% CI, 3–4)



Median time to resolution‡: 33 days§ (95% CI, 7–120)

Sands, WCLC 2024

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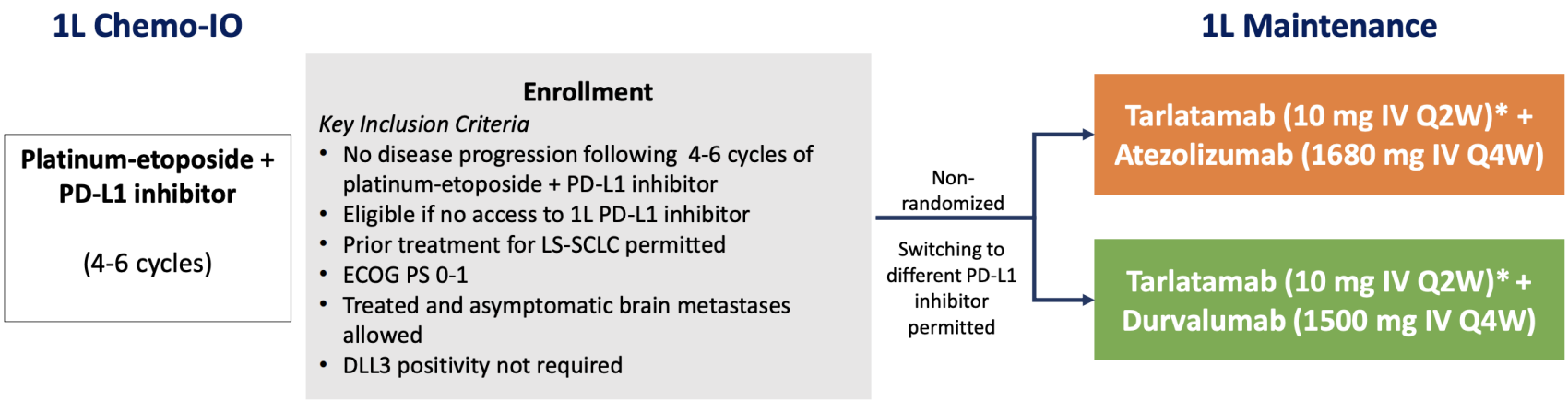
Tarlatamab (AMG 757)

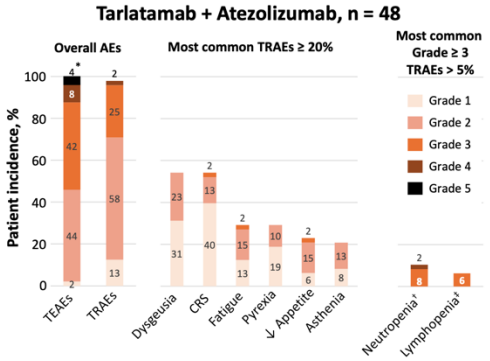
- Phase Ib DeLLphi-303 Study

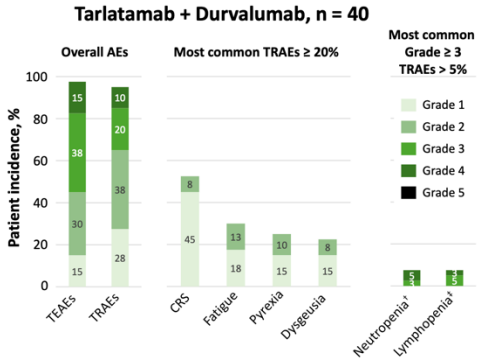


- RR 62.5% in both arms

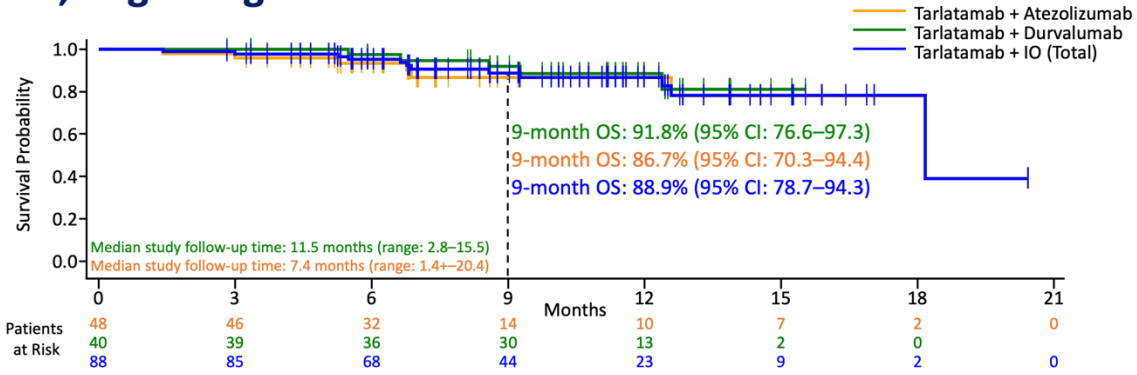
Lau, WCLC 2024

Tarlatamab (AMG 757)





OS, beginning from 1L maintenance



Lau, WCLC 2024

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Tarlatamab (AMG 757)

- Close observation required

Table 1. Recommended Dosage and Schedule of IMDELLTRA

Dosing Schedule	Day	Dose of IMDELLTRA	Administration Instructions	Recommended Monitoring
Step-up Dosing Schedule Cycle 1	Day 1[a]	Step-up dose[a] 1 mg	Administer IMDELLTRA as a 1-hour intravenous infusion in an appropriate healthcare setting.	Monitor patients from the start of the IMDELLTRA infusion for 22 to 24 hours on Cycle 1 Day 1 and Cycle 1 Day 8 in an appropriate healthcare setting. Recommend that patients remain within 1-hour of an appropriate healthcare setting for a total of 48 hours from start of the infusion with IMDELLTRA, accompanied by a caregiver.
	Day 8[a]	10 mg[a]		
	Day 15	10 mg		Observe patients for 6-8 hours post IMDELLTRA infusion[b].
Cycle 2	Day 1 and 15	10 mg		Observe patients for 6-8 hours post IMDELLTRA infusion[b].
Cycles 3 and 4	Day 1 and 15	10 mg		Observe patients for 3-4 hours post IMDELLTRA infusion[b].
Cycle 5 and subsequent infusions	Day 1 and 15	10 mg		Observe patients for 2 hours post IMDELLTRA infusion[b].

FDA.gov

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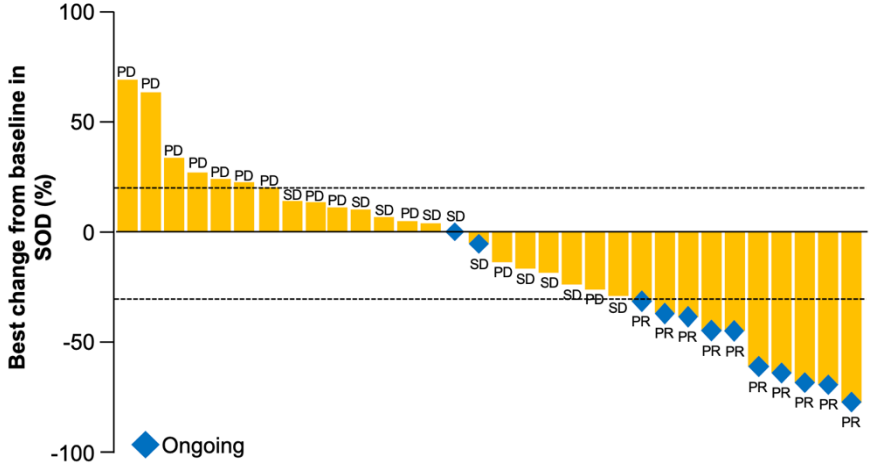
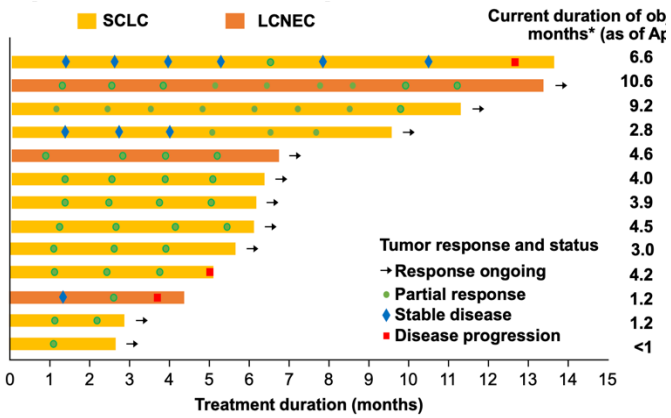
T-Cell Engagers for SCLC

- Tarlatamab – FDA accelerated approval 5/16/24
- BI 764532 (obrixtamig)
  - SCLC at doses ≥ 90mcg/kg

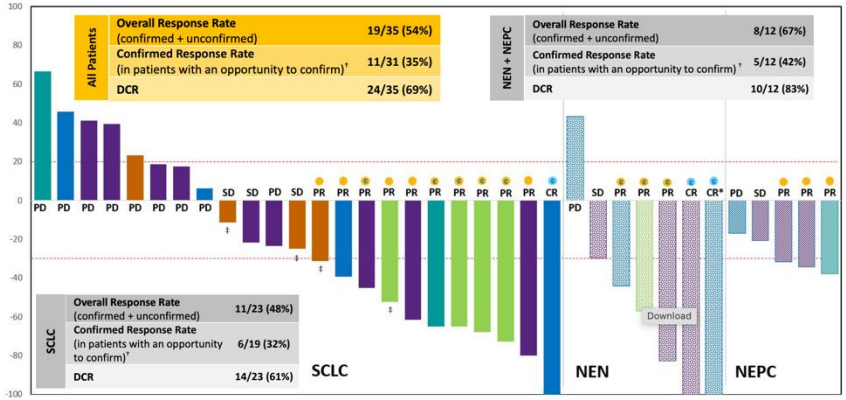


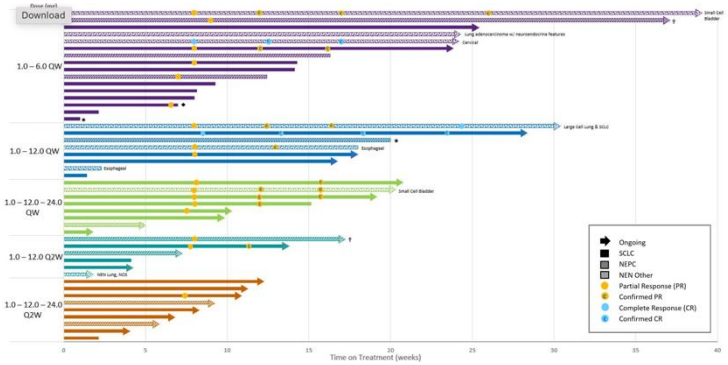


Wermke, WCLC 2023

T-Cell Engagers for SCLC

- Tarlatamab – FDA accelerated approval 5/16/24
- BI 764532 (obrixtamig)
- MK-6070 (HPN328)

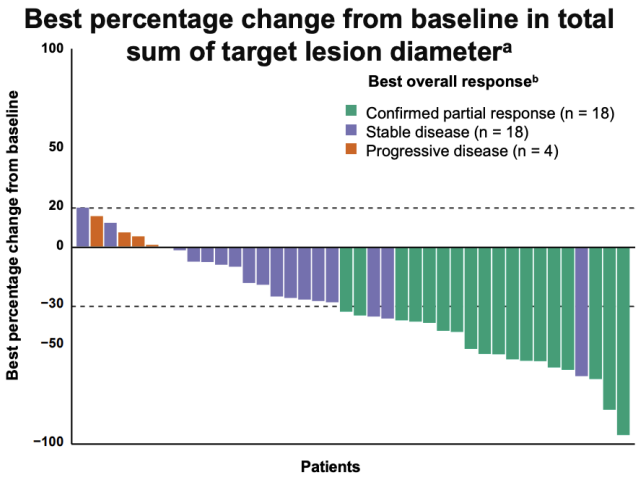


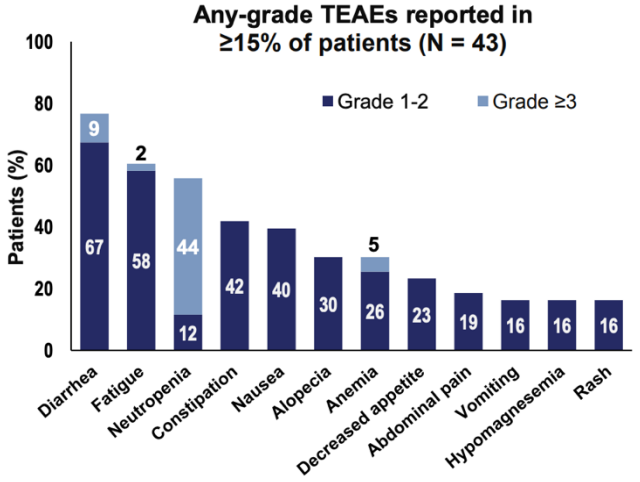


Choudhury, ESMO 2023

Antibody Drug Conjugates

- Sacituzumab govitecan (TROP2-ADC)
  - Phase II TROPiCS-03 Basket Trial
  - RR 41.9%, mDOR 4.7m, PFS 4.4m, OS 13.6m





Dowlati, WCLC 2024

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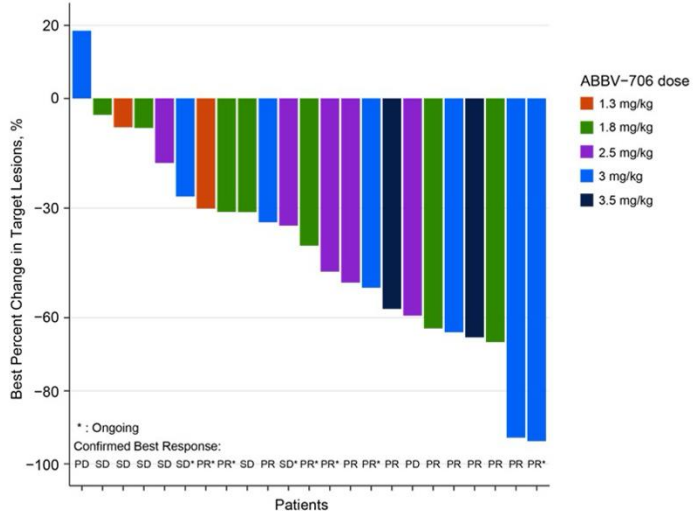
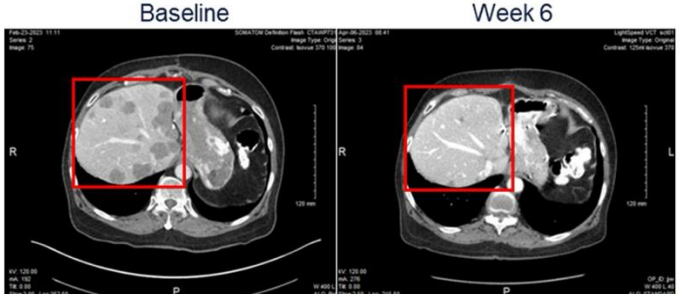
Antibody Drug Conjugates

- ABBV-706 (SEZ6 ADC)
  - First-in-human study
  - RR 60.9%, PFS/OS immature





Chandana, ASCO 2024

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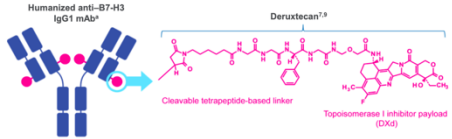
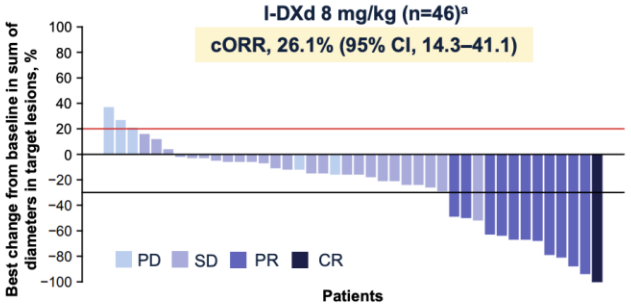
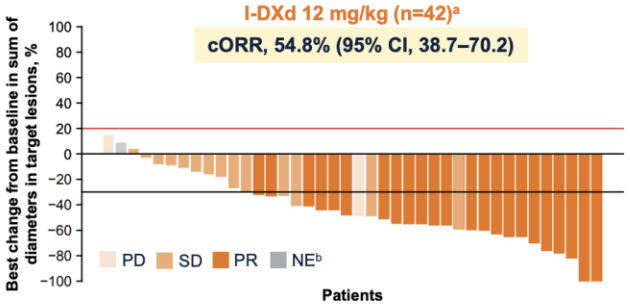
Antibody Drug Conjugates

- Ifinatamab deruxtecan (I-DXd, DS-7300)
  - B7-H3 ADC with topoisomerase I payload
  - IDeate-Lung01 study of two doses





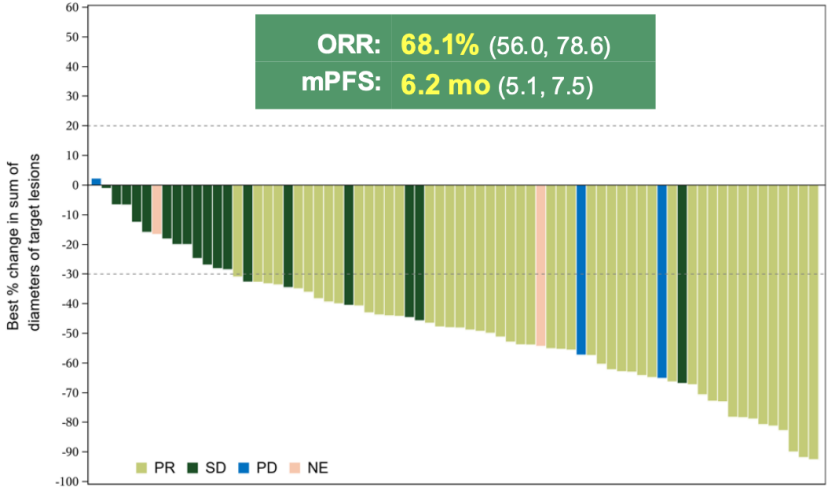


Confirmed response by BICR[c]	I-DXd 8 mg/kg n=46	I-DXd 12 mg/kg n=42
ORR, % (95% CI)	26.1 (14.3–41.1)	54.8 (38.7–70.2)
CR, n (%)	1 (2.2)	0
PR, n (%)	11 (23.9)	23 (54.8)
DCR, % (95% CI)	80.4 (66.1–90.6)	90.5 (77.4–97.3)

Rudin, WCLC 2024

Antibody Drug Conjugates

- YL201
  - B7-H3 ADC, cleavable linker, potent Topo1 inhibitor
  - In previously treated SCLC, RR 68.1%, mPFS 6.2m



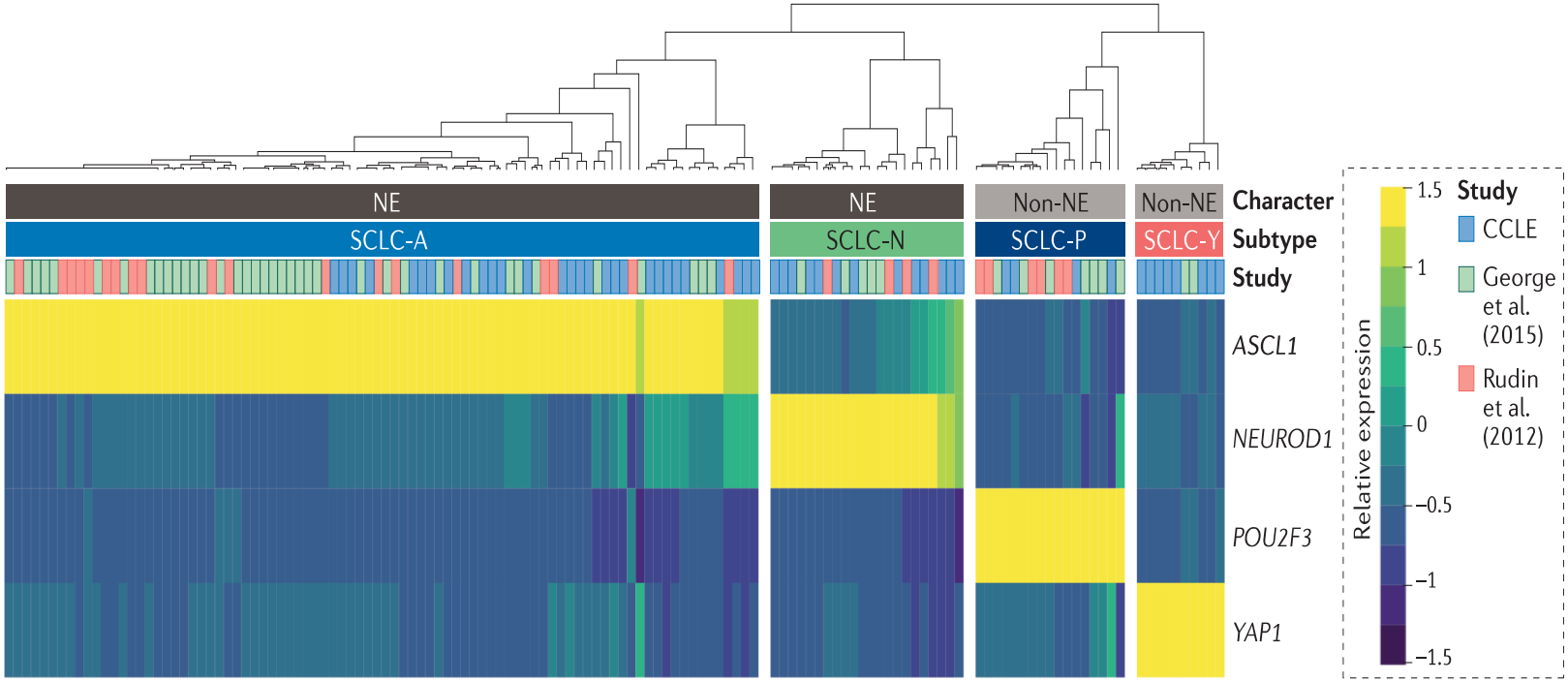
TRAE in ≥10% patients	Total * (N=312)	
	All grades	Grade ≥3
Hematological, n (%)		
Leukopenia	63%	29%
Anemia	63%	22%
Neutropenia	60%	30%
Lymphopenia	35%	19%
Thrombocytopenia	31%	13%
Non-hematological, n (%)		
Decreased appetite	34%	1%
Nausea	24%	1%
Hypoalbuminemia	20%	0%
Alanine aminotransferase increased	17%	0.6%
Alopecia	17%	0%
Hyponatremia	17%	1%
Fatigue	17%	0.6%
Diarrhea	17%	0.6%
Vomiting	17%	1%

Zhao, ESMO 2024

Novel Agents for SCLC

- High response rates and durable responses are very encouraging in previously treated SCLC
  - Very often do not translate to improvements in earlier lines
- Different populations being explored
  - Later line patients have a unique biology that seems to be enriched in highly selective phase I studies and underrepresented in pragmatic phase III studies
- Key to transformative change will be understanding *why* a certain drug works, not just noting that it does

Predictive Biomarkers for Chemo-IO



Rudin, Nat Rev Cancer 2019

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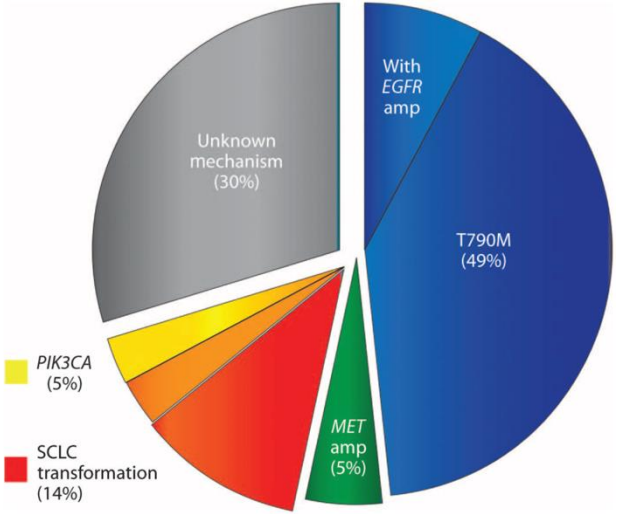
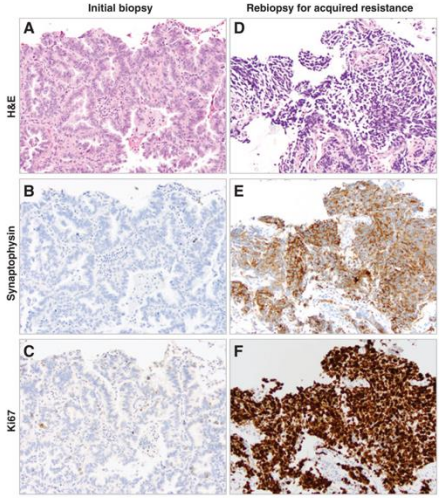
SCLC Transformation

- Lineage plasticity is an increasingly seen mechanism of resistance to targeted therapy
  - Underdiagnosed – only seen with tissue biopsy





Sequist, STM 2011; Yu, CCR 2013

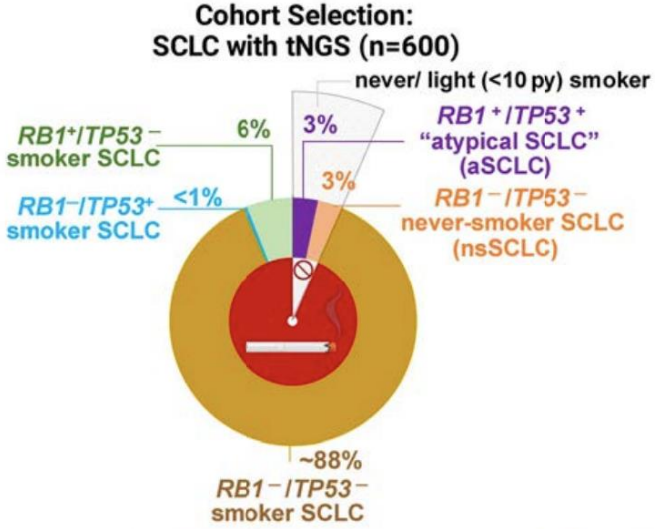
SCLC Transformation

- In EGFR mutant NSCLC transformed to SCLC
  - Median time to transformation 17.8m
  - Median OS from transformation 10.9m
  - TP53, Rb1, PIK3CA commonly co-mutated
  - EGFR mutation retained, protein expression decreases
  - Highly responsive to chemotherapy but not immunotherapy
- Baseline TP53 + Rb1 increased risk of transformation
  - Initial chemotherapy does not prevent transformation

Marcoux, JCO 2019; Yu, ASCO 2024

SCLC without Smoking History

- Analysis of *de novo* SCLC in light/never smokers
  - Two distinct populations observed
  - "Typical" TP53/Rb1 loss
    - Mirrors transformed SCLC
  - "Atypical" TP53/Rb1 intact
    - Chromothripsis of ch11/12
    - Extrachromosomal amplification
      - CCND1
      - CCND2/CDK4/MDM2



Rekhtman, Cancer Disc 2024

SCLC without Smoking History

Study	Agent	Sample Size
IMpower 133 *Horn, NEJM 2018*	Atezolizumab	403 pts
CASPIAN *Paz-Ares, Lancet 2019*	Durvalumab	805 pts
KEYNOTE 604 *Rudin, JCO 2020*	Pembrolizumab	453 pts
ASTRUM 005 *Cheng, JAMA 2022*	Serplulimab	585 pts
CAPSTONE-1 *Wang, Lancet Oncol 2022*	Adebrelimab	462 pts
RATIONALE-312 *Cheng, JTO 2024*	Tislelizumab	457 pts

SCLC: Room for Hope

- New standard now established for ES and LS SCLC
  - Incorporation of atezolizumab or durvalumab improves survival and gives the potential for long-term survival
  - Long-term benefit only delivered to a subset of patients
- Next steps to advance the care of SCLC
  - Identify who derives long-term benefit and who does not
    - Biomarkers that reflect the heterogeneity in biology and response
  - Develop new agents to control relapsed disease
    - Novel strategies to get long-term benefit for more patients
  - Early detection, risk modification, and prevention when possible

Thank You International Lung Cancer Summit!

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