City of Hope®

Advances in Small Cell Lung Cancer and Mesothelioma

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Professor and Chair

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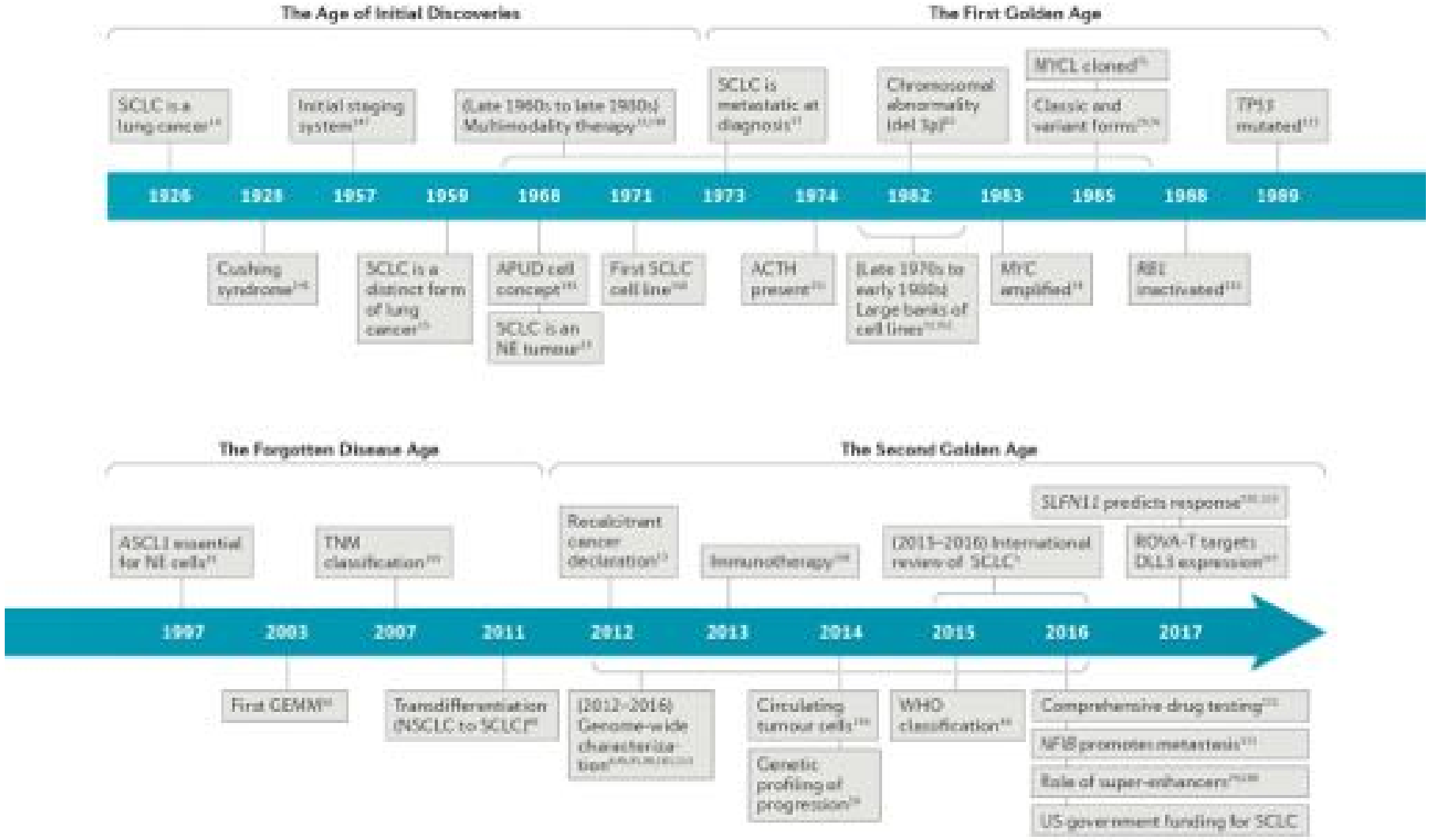
Objectives

- Small Cell Lung Cancer
    - Introduction
    - Recent FDA approvals for first-line ES-SCLC
    - Molecular and subtyping
    - Recently presented clinical trials
    - Ongoing clinical trials
- Mesothelioma
    - Introduction
    - FDA approvals for mesothelioma
    - Molecular
    - Recently presented clinical trials
    - Ongoing clinical trials

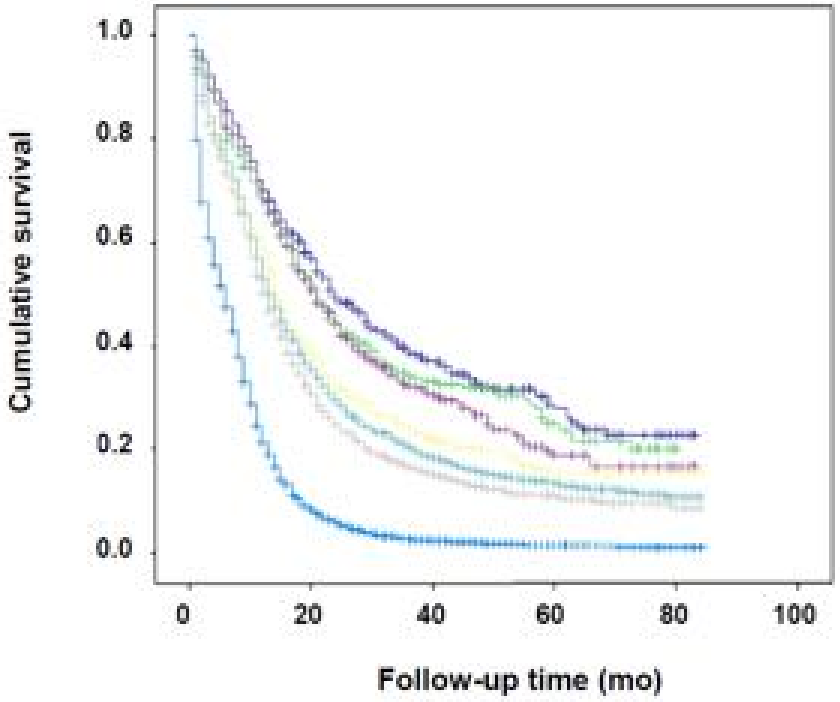
Small Cell Lung Cancer

Timeline of SCLC



Gazdar, Bunn, Minna, Nat Rev Cancer, 2017

SCLC Survival By TNM Stage



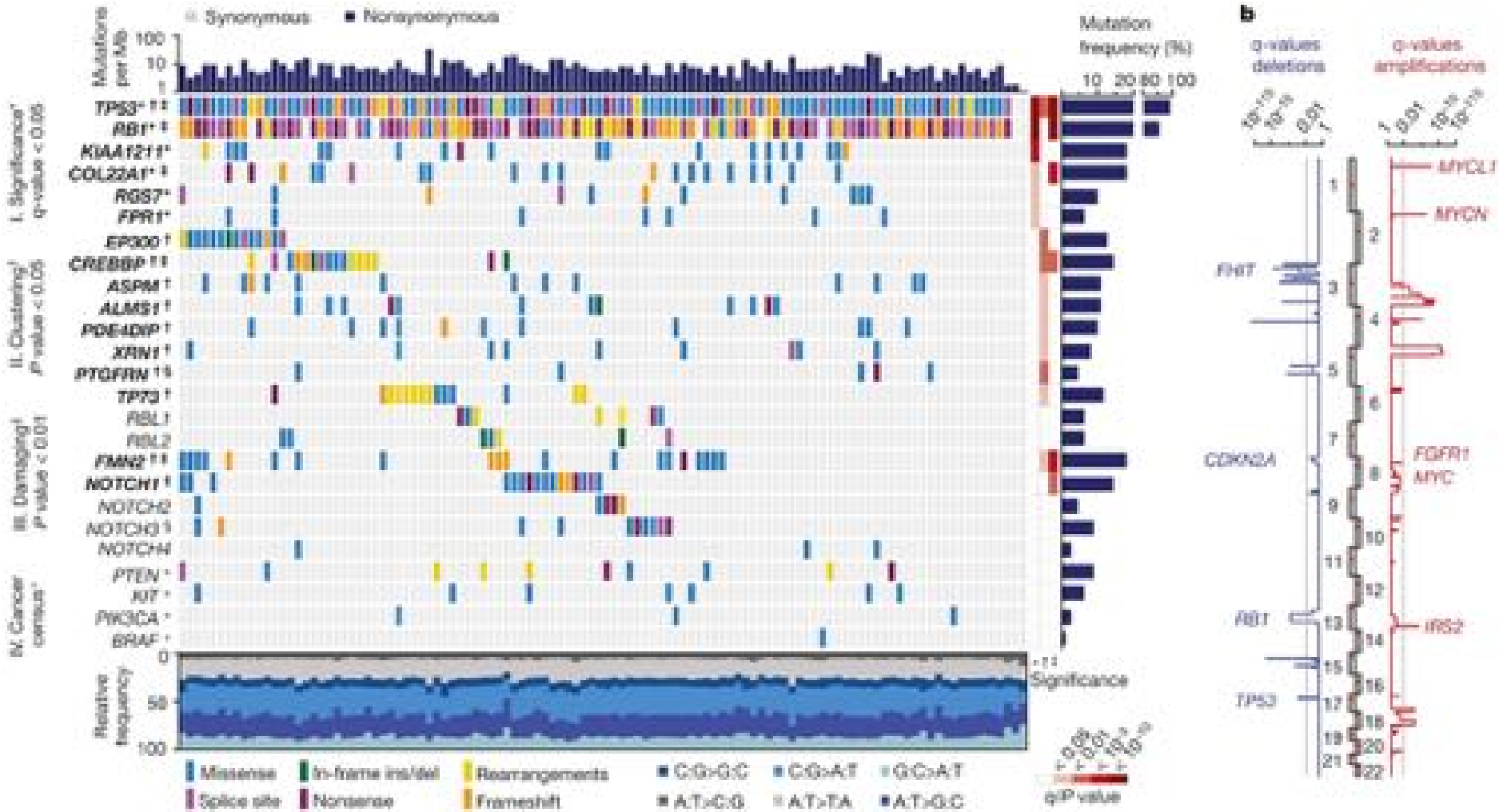
TNM stage	mOS (mo)	95% CI
Stage IA	24.00	20.50–27.50
Stage IB	21.00	17.84–24.16
Stage IIA	21.00	17.96–24.04
Stage IIB	14.00	12.41–15.60
Stage IIIA	14.00	13.37–14.63
Stage IIIB	13.00	12.41–13.59
Stage IV	6.00	5.83–6.17

Table 2. Long-term Survival According to TNM Staging

Survival rates	Stage IA, %	Stage IB, %	Stage IIA, %	Stage IIB, %	Stage IIIA, %	Stage IIIB, %	Stage IV, %
6 mo	85.4	79.6	82.1	74.3	75.6	73.7	47.7
1 y	70.5	67.5	68.4	58.6	53.4	50.4	21.6
2 y	49.7	44.4	44.8	32.3	29.6	25.0	5.9
5 y	28.1	25.1	19.0	15.6	13.6	11.0	1.6

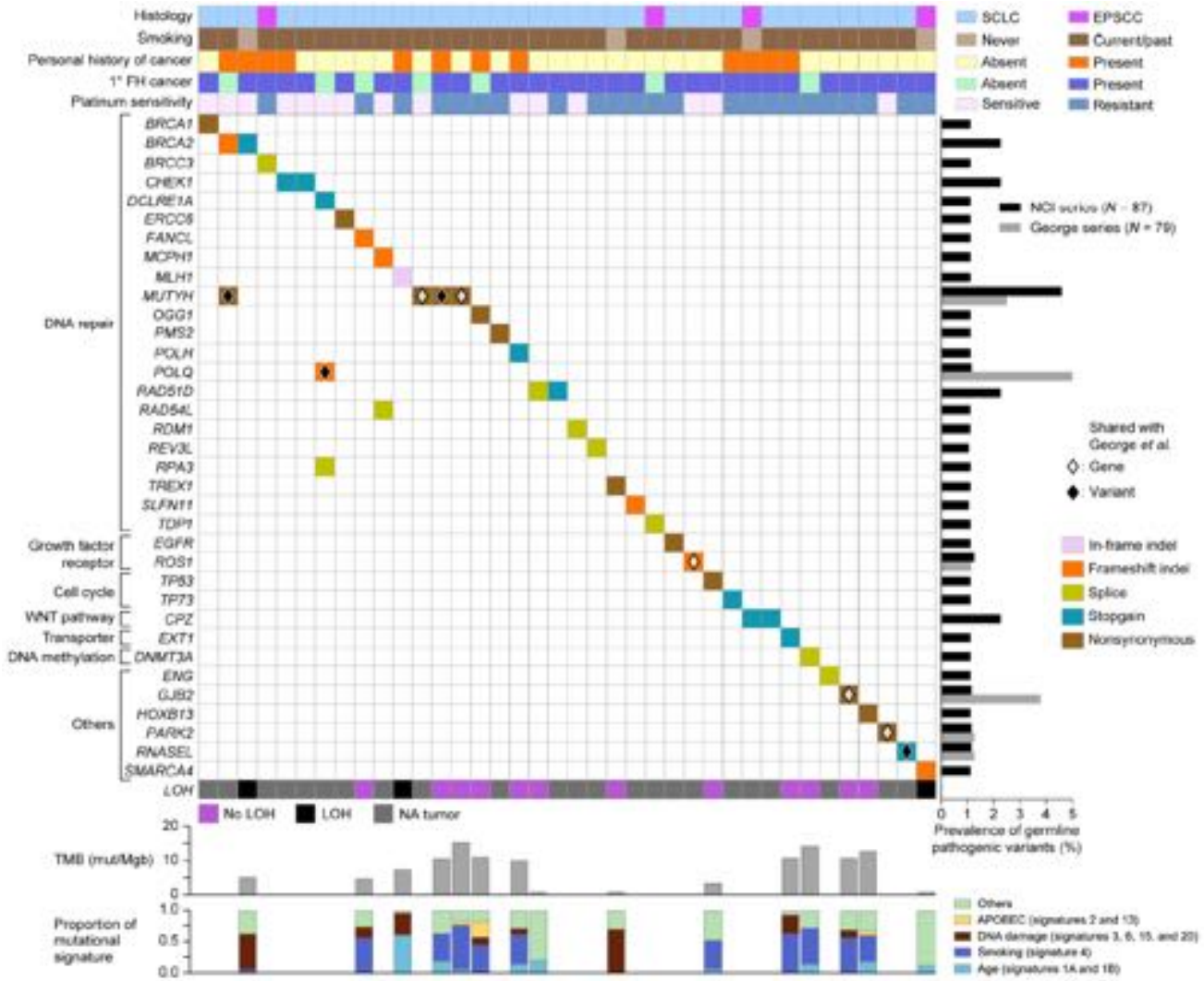
Arriola et al., JTO Clinical and Research Reports, 2022

Somatic Genomic Alterations in SCLC



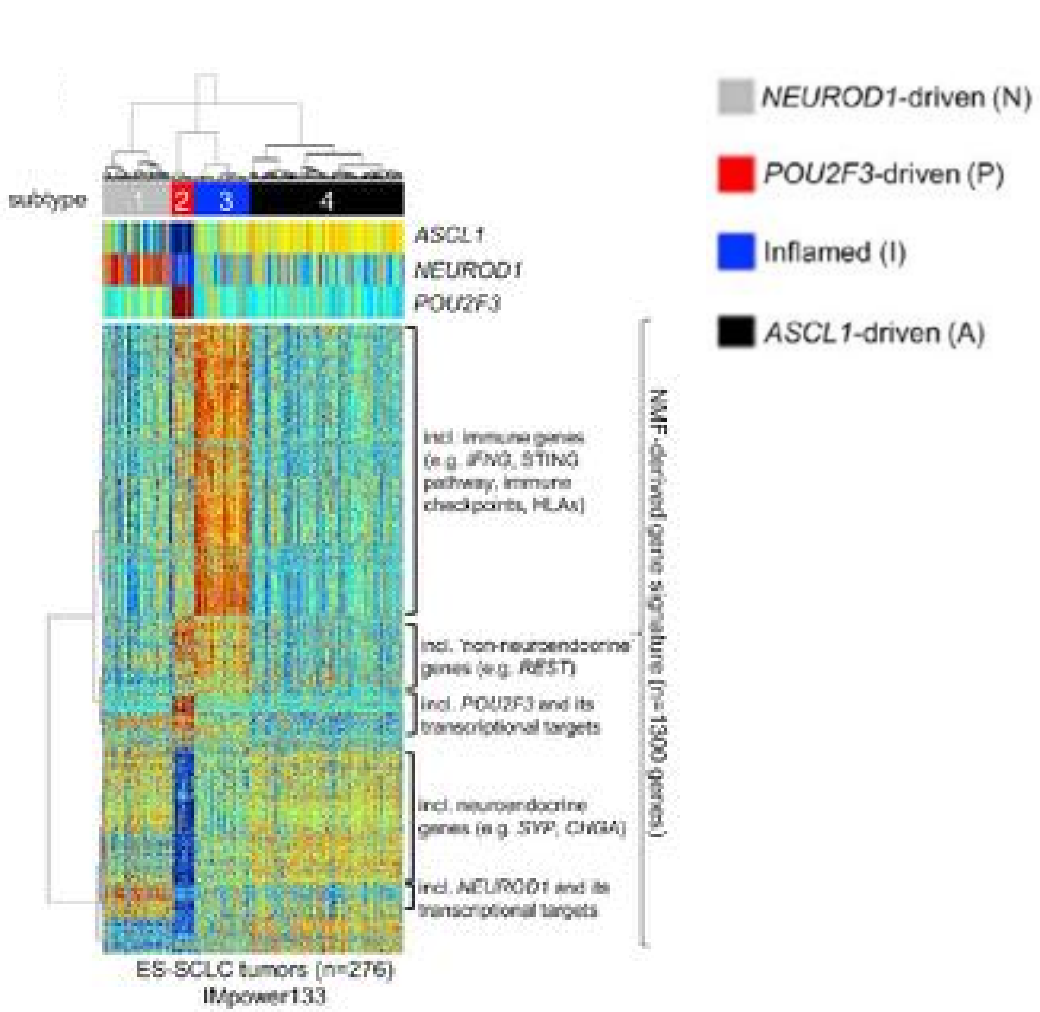
George et al., Nature, 2015

Germline Genomic Alterations in SCLC



Tlemsani et al., Sci. Transcl. Med., 2021

SCLC Subtypes Predicting Survival and Treatment Resistance

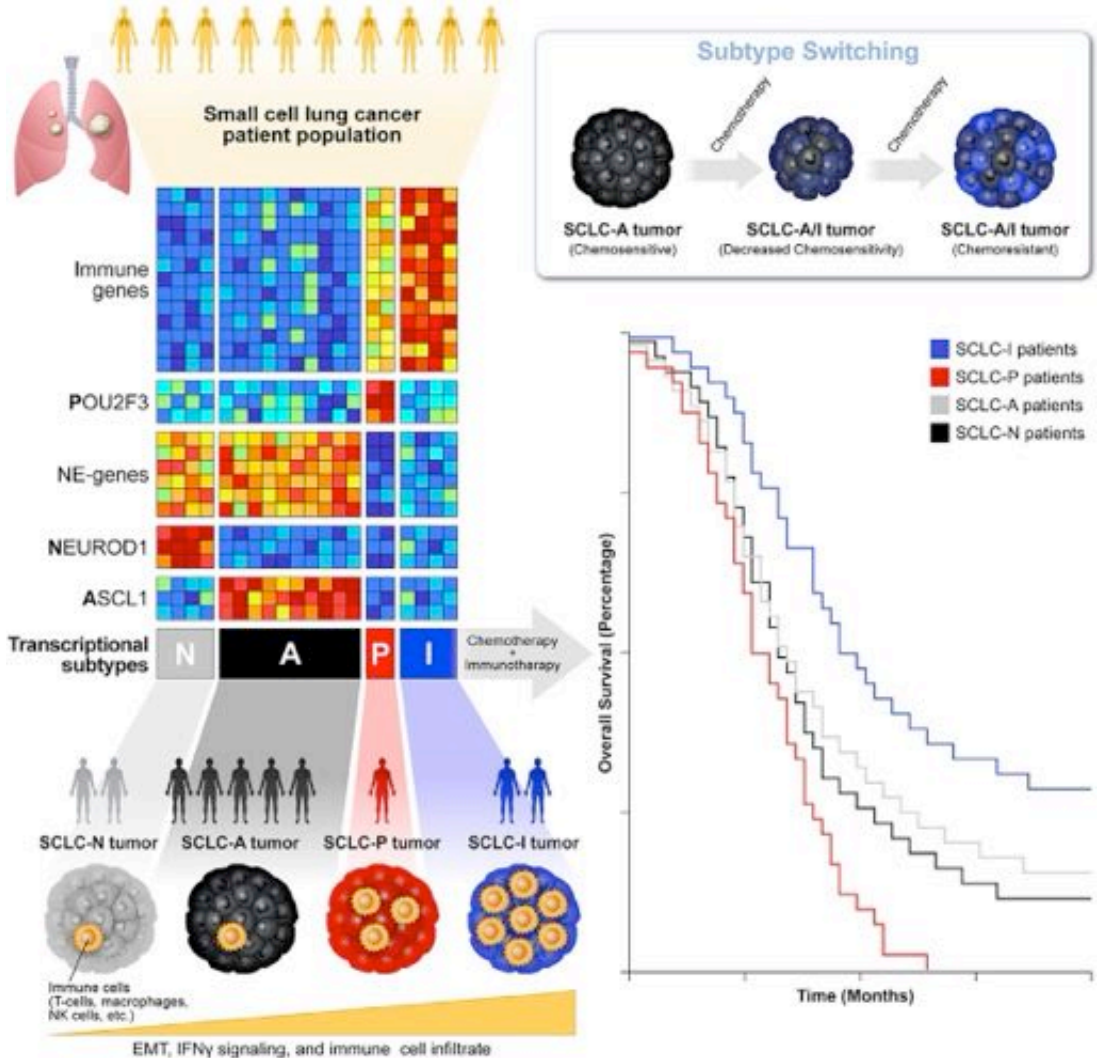


NEUROD1-driven (N)

POU2F3-driven (P)

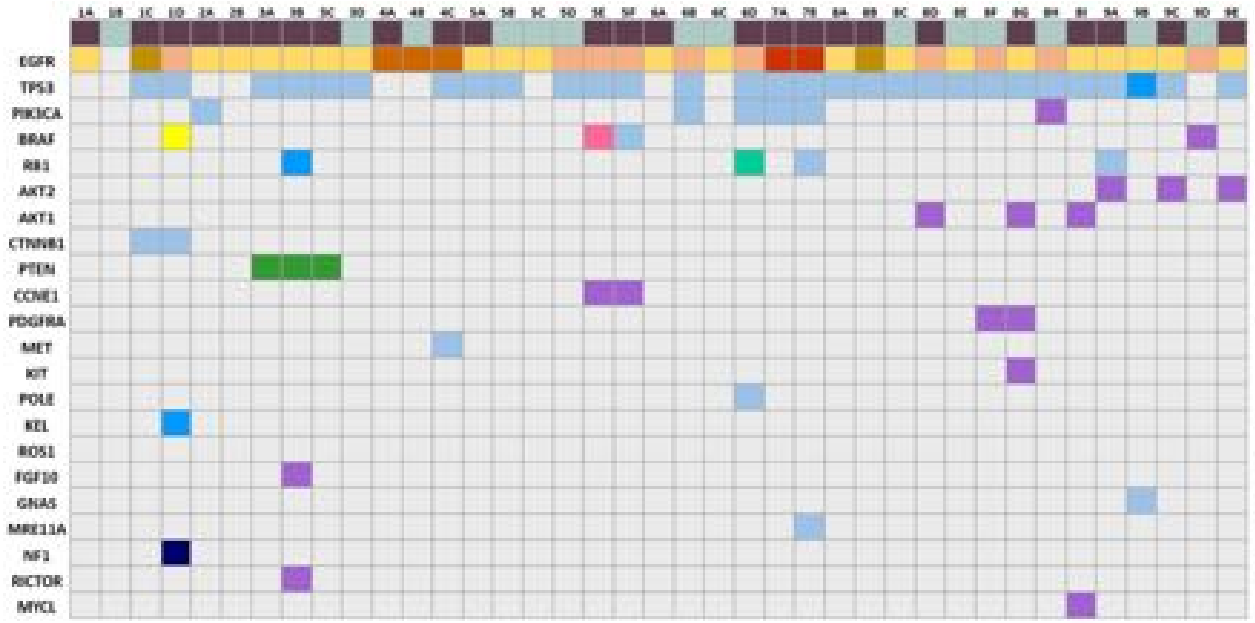
Inflamed (I)

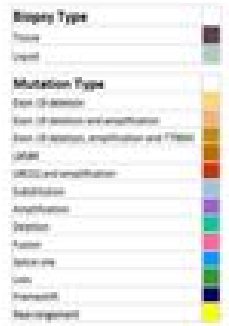
ASCL1-driven (A)

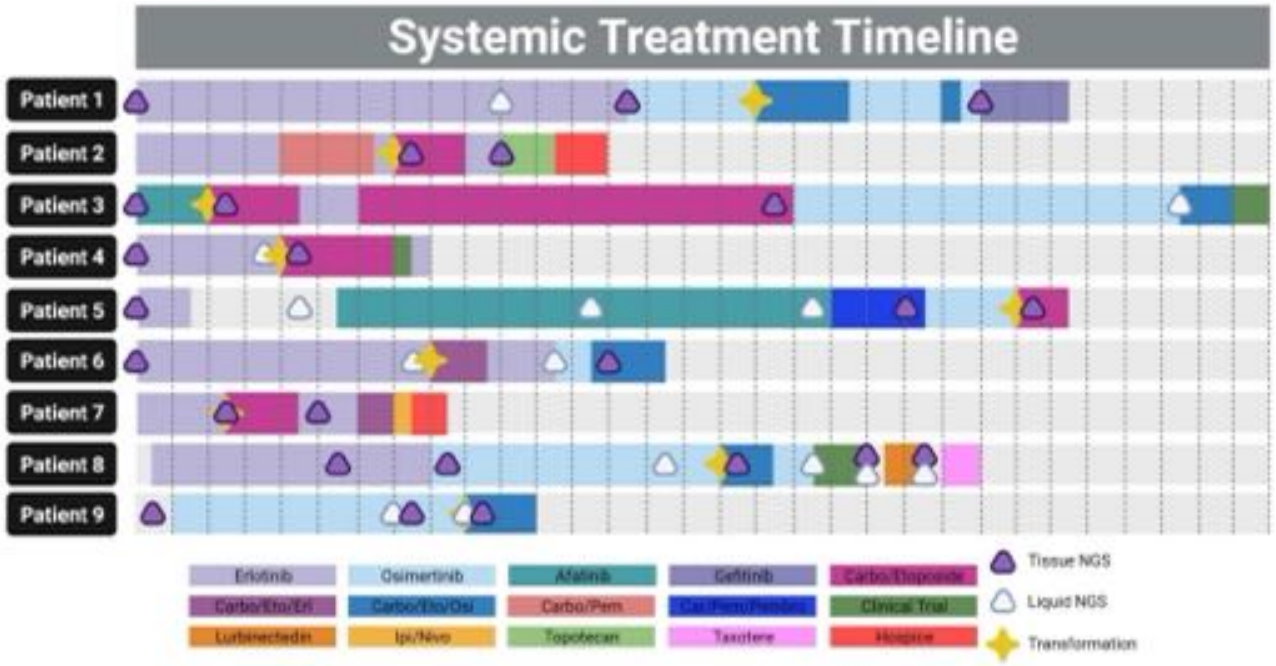


Gay et al., Cancer Cell, 2021

EGFR Transformation to SCLC

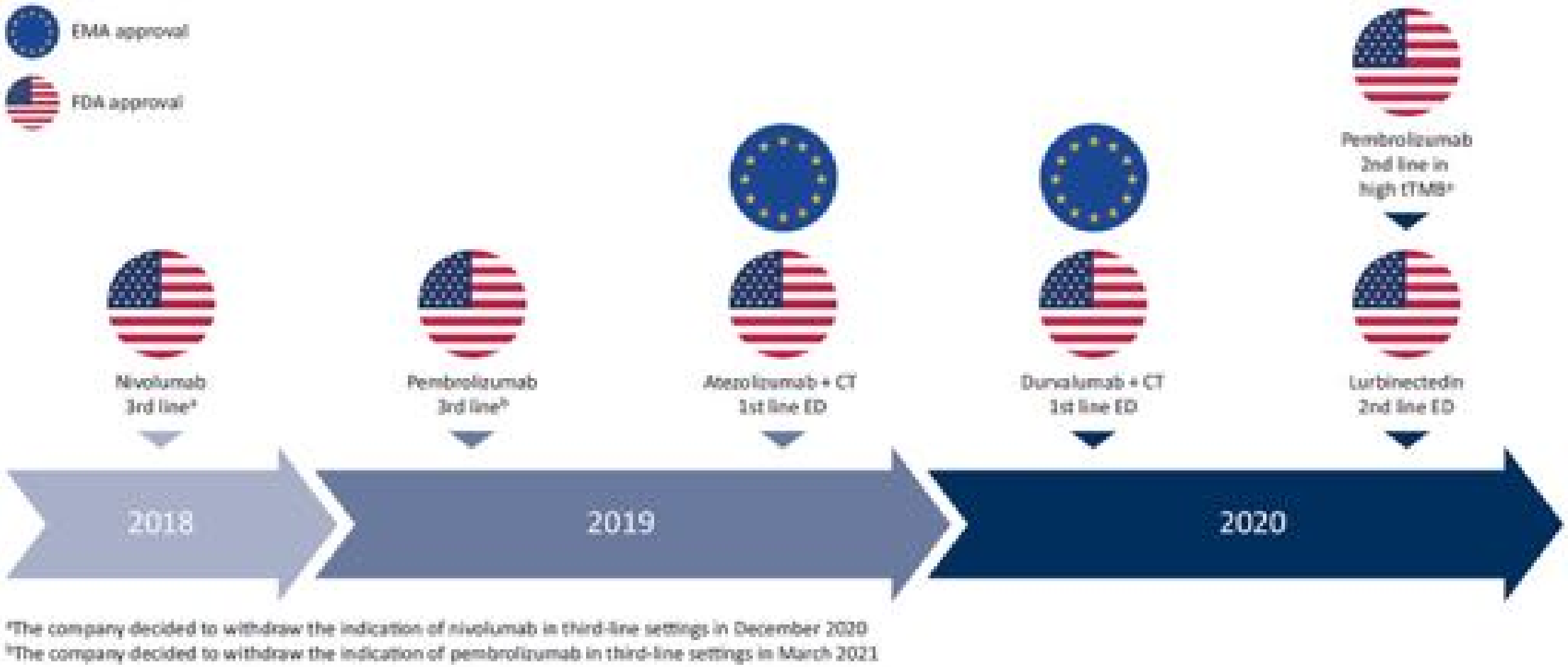






Mambetsariev et int. Salgia, JCM, 2022

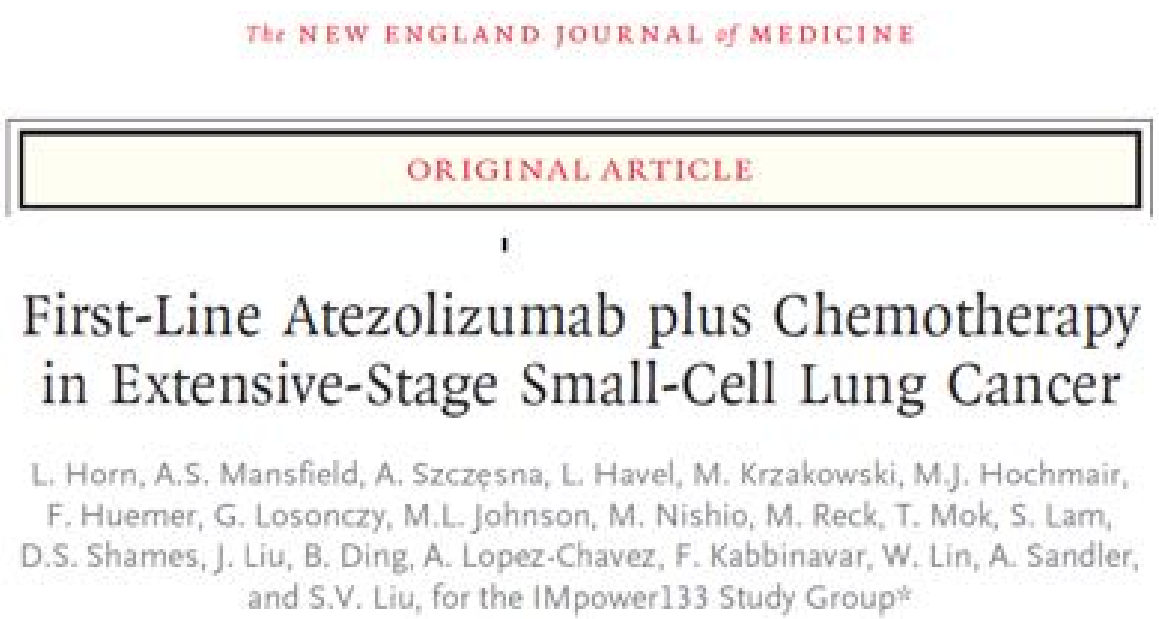
Recent Timeline of Approvals for SCLC

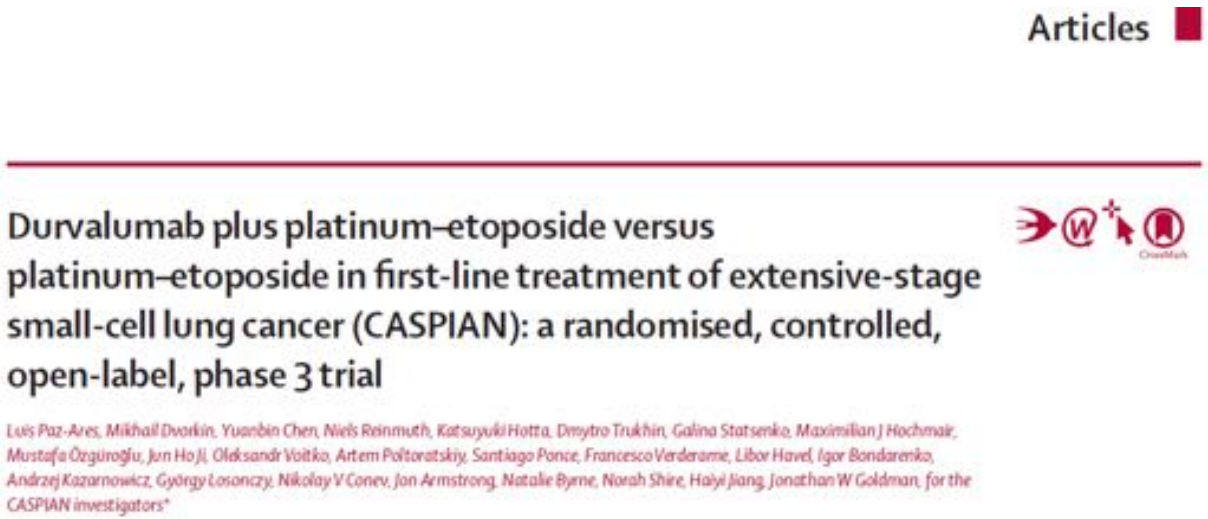


[a]The company decided to withdraw the indication of nivolumab in third-line settings in December 2020
[b]The company decided to withdraw the indication of pembrolizumab in third-line settings in March 2021

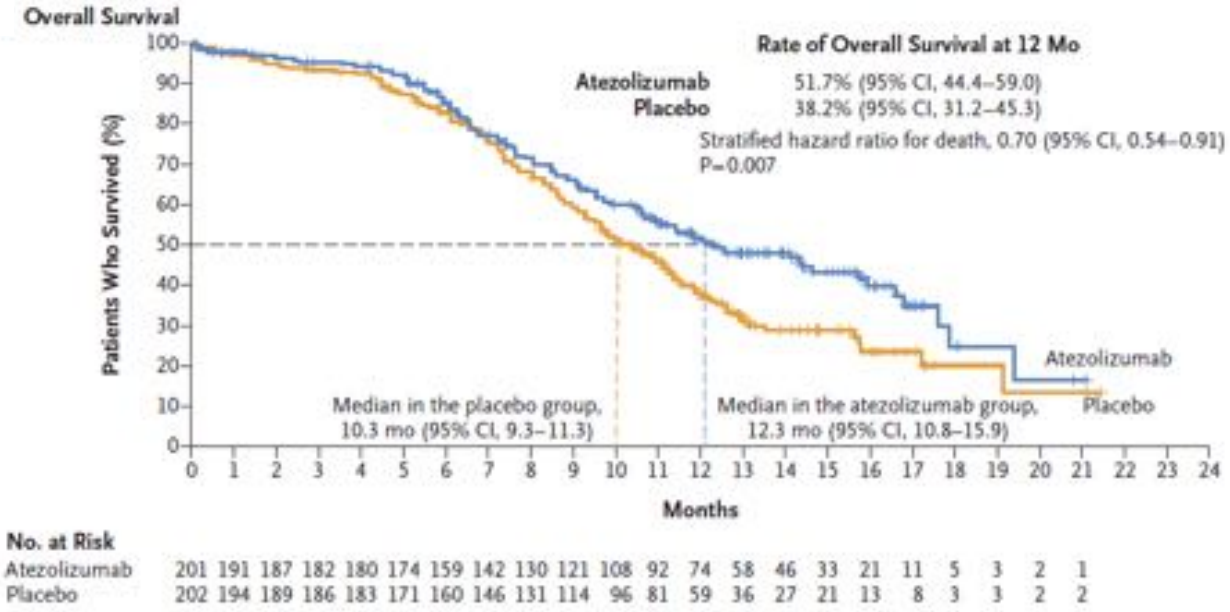
Remon et al., Annals of Oncology, 2021

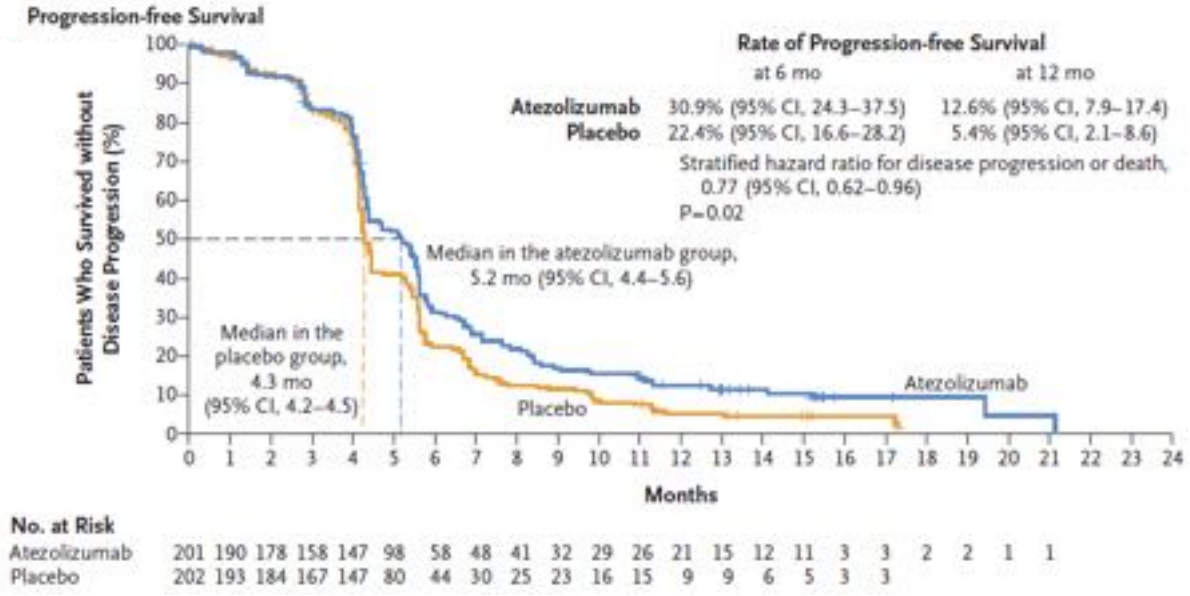
First-Line Treatments for ES-SCLC



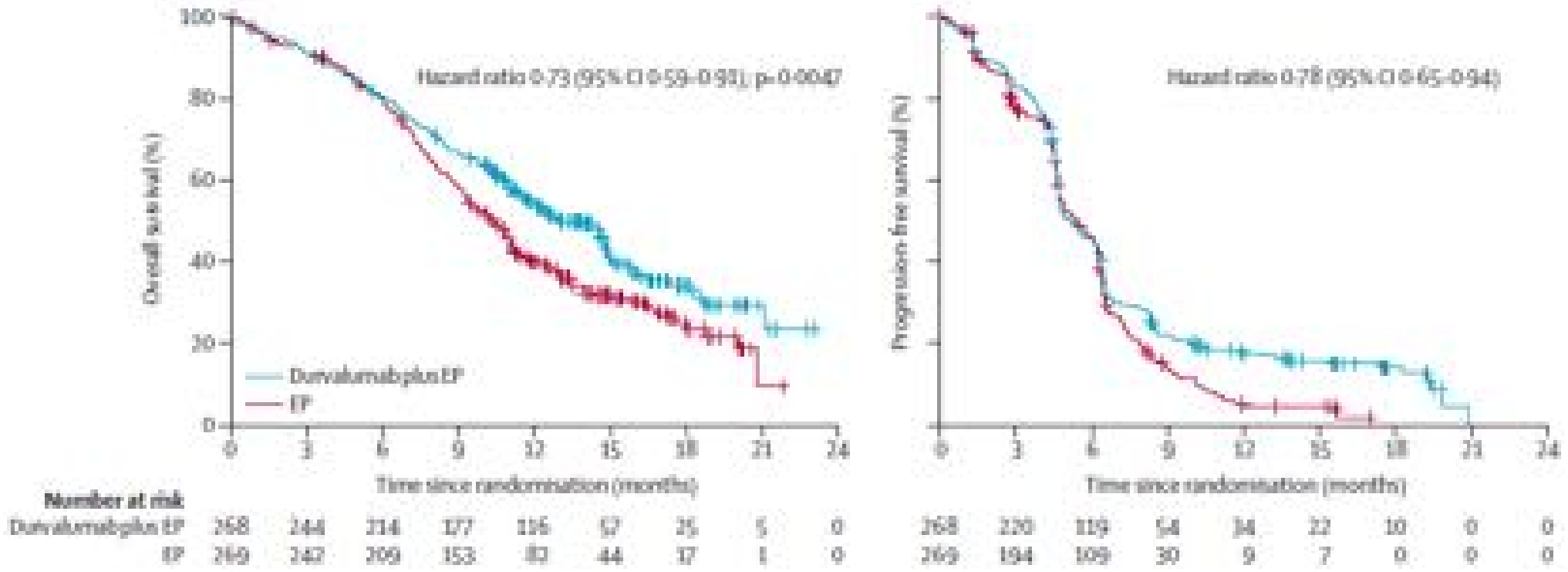


OS and PFS Atezolizumab + Chemotherapy





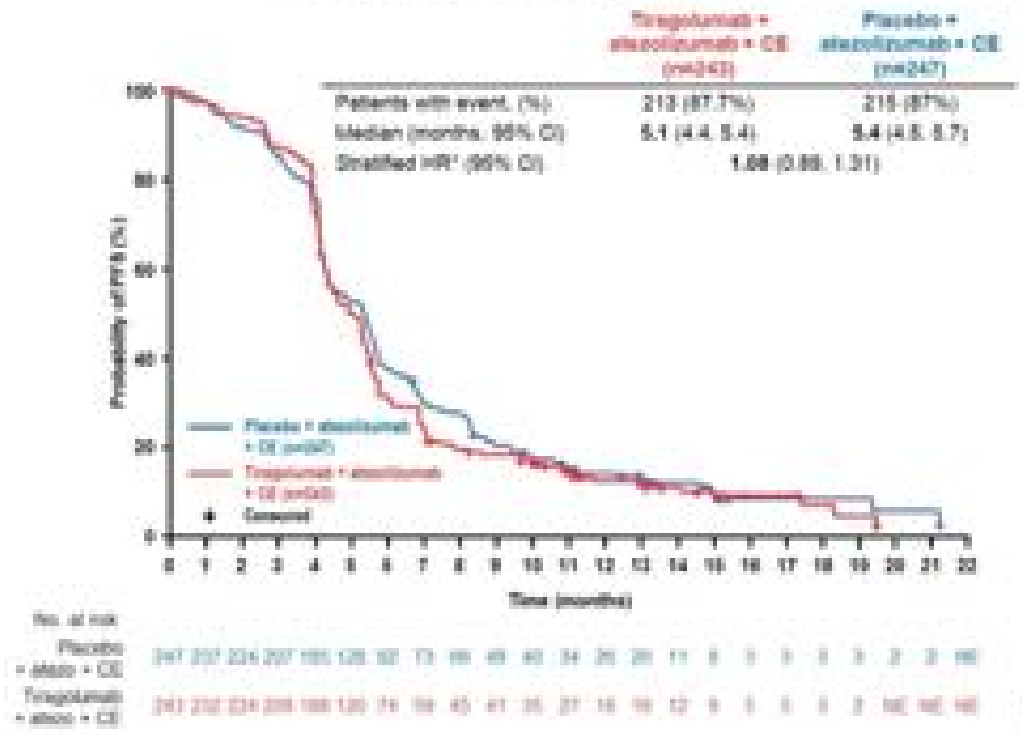
OS and PFS Durvalumab + Chemotherapy



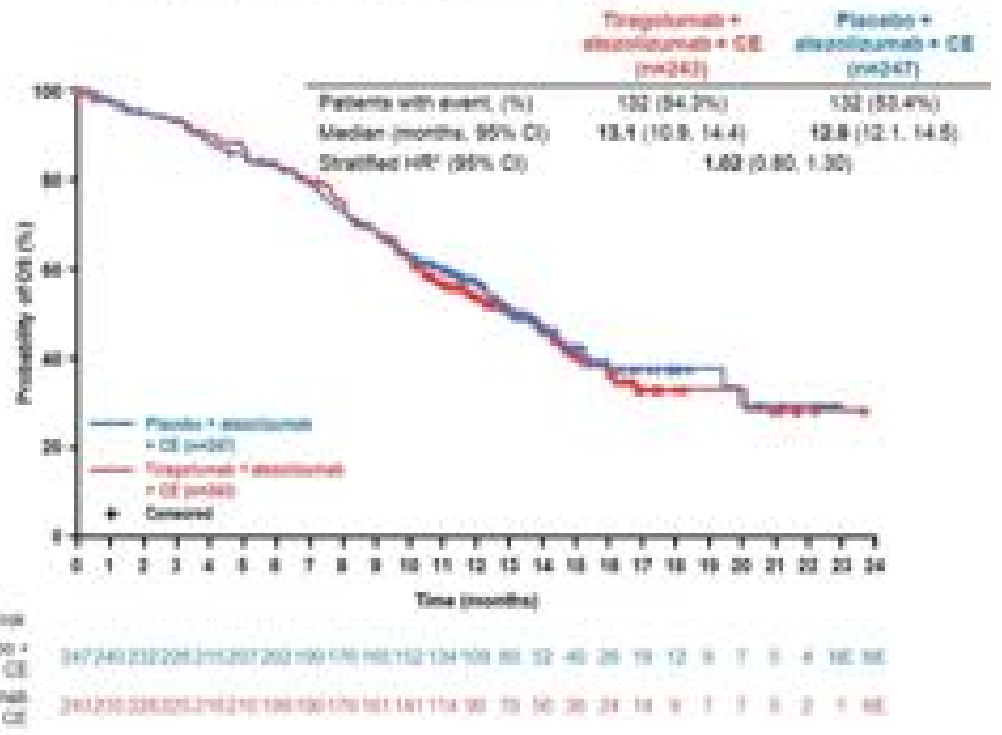
SKYSCRAPER-02: Randomized, double-blind, placebo-controlled study of tiragolumab + atezolizumab + chemotherapy in patients with untreated ES-SCLC

PFS and OS: Full Analysis Set

PFS in the Full Analysis Set



Interim OS in the Full Analysis Set

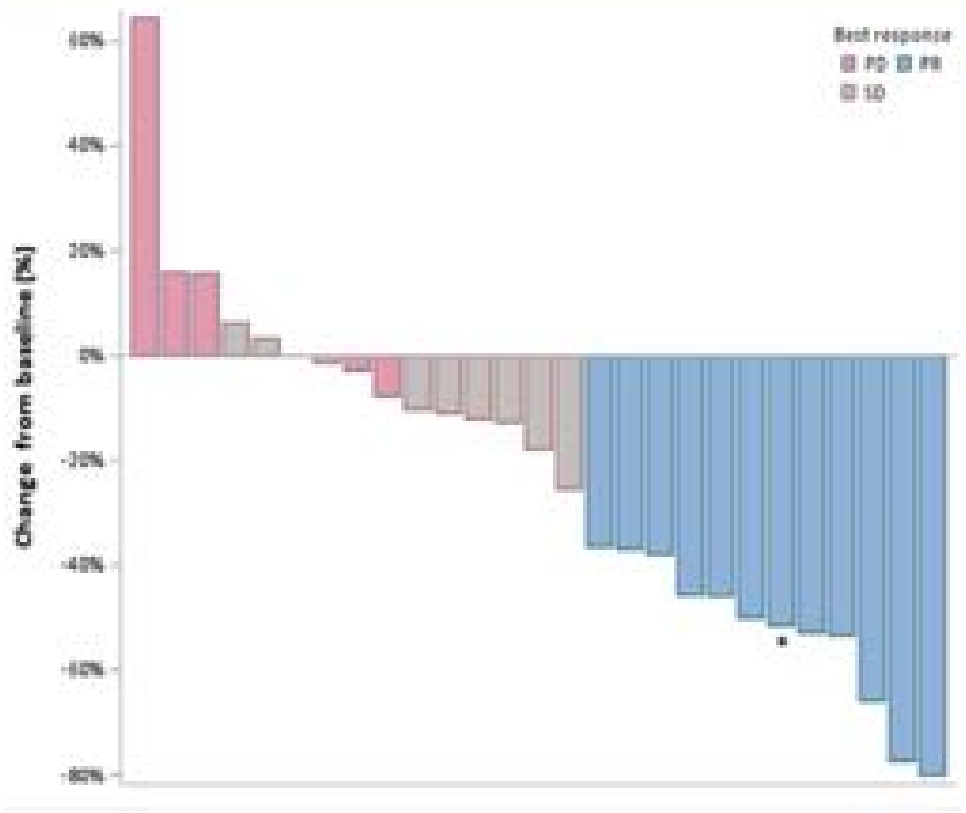


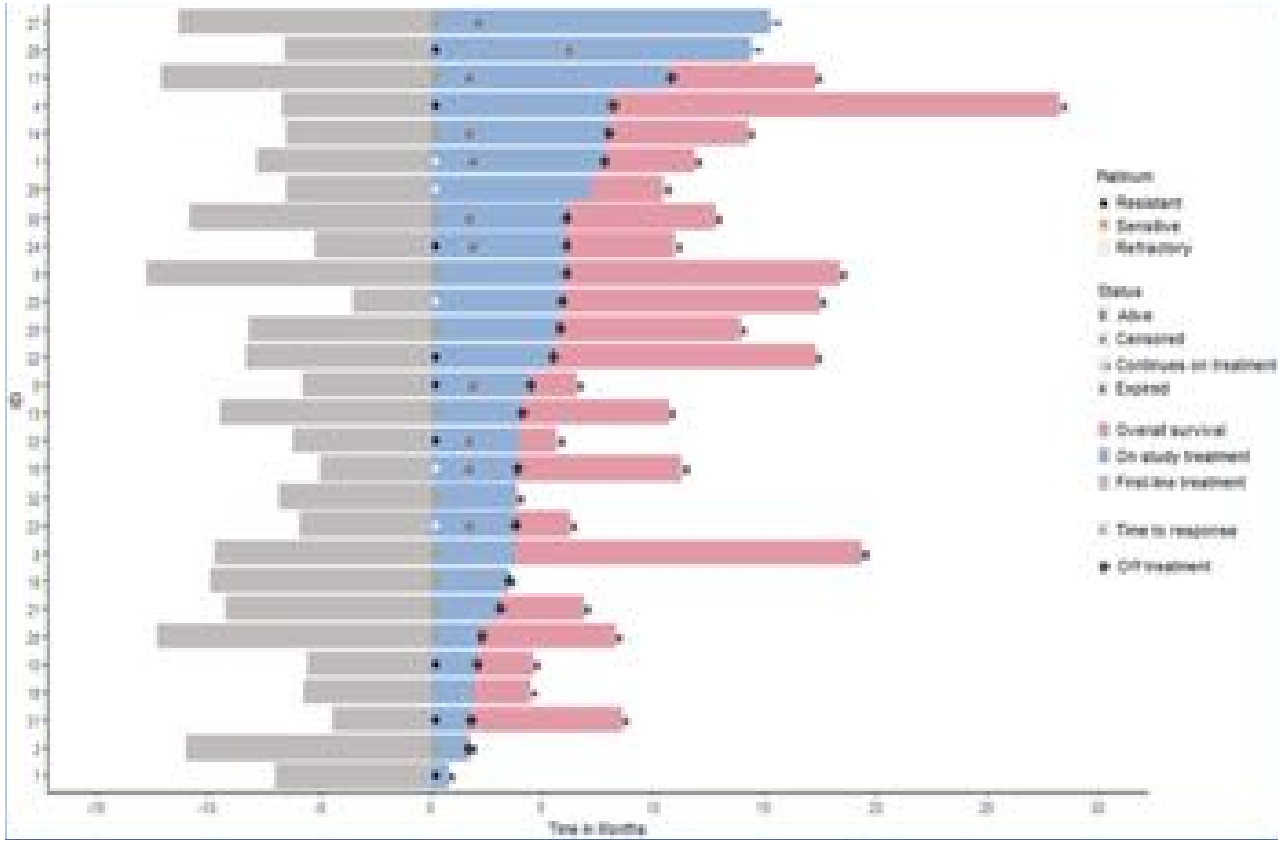
*Stratification factors are ECOG, LDH

Data cut-off: 9 February 2022 (median follow-up 12.9 months)

Rudin et al., Presented at ASCO, 2022

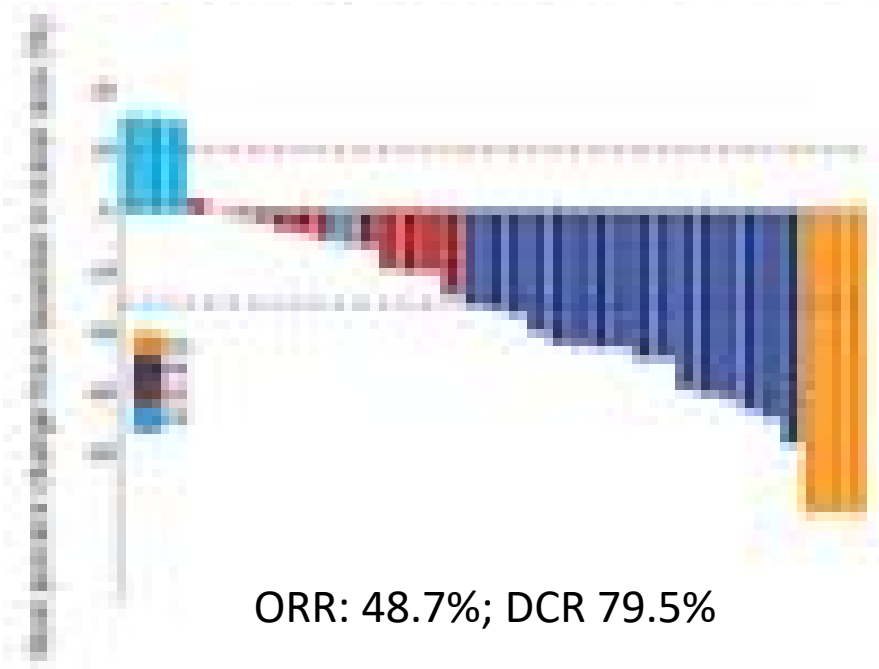
Primary analysis from the phase 2 study of continuous talazoparib (TALA) plus intermittent low-dose temozolomide (TMZ) in patients with relapsed or refractory extensive-stage small cell lung cancer (ES-SCLC)





Goldman et al., Presented at ASCO, 2022

Sintilimab plus anlotinib as second or further-line therapy for small cell lung cancer: An objective performance trial



ORR: 48.7%; DCR 79.5%

mPFS: 6.01 mo

mOS: 16.07 mo

Gentzler et al., Presented at ASCO, 2022

Therapeutic Targets of Interest for SCLC

- Programmed death 1 (PD-1)
- Programmed death ligand 1 (PD-L1)
- Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)
- Polly(ADP-ribose) polymerase (PARP)
- Protein phosphatase 2 (PP2A)
- ATR
- BCL2
- CD80
- CDC25A
- CDK2
- CHK1
- WEE1


LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

Section Editor: Edward S. Kim, MD, MBA

The Next Targets for Small Cell Lung Cancer

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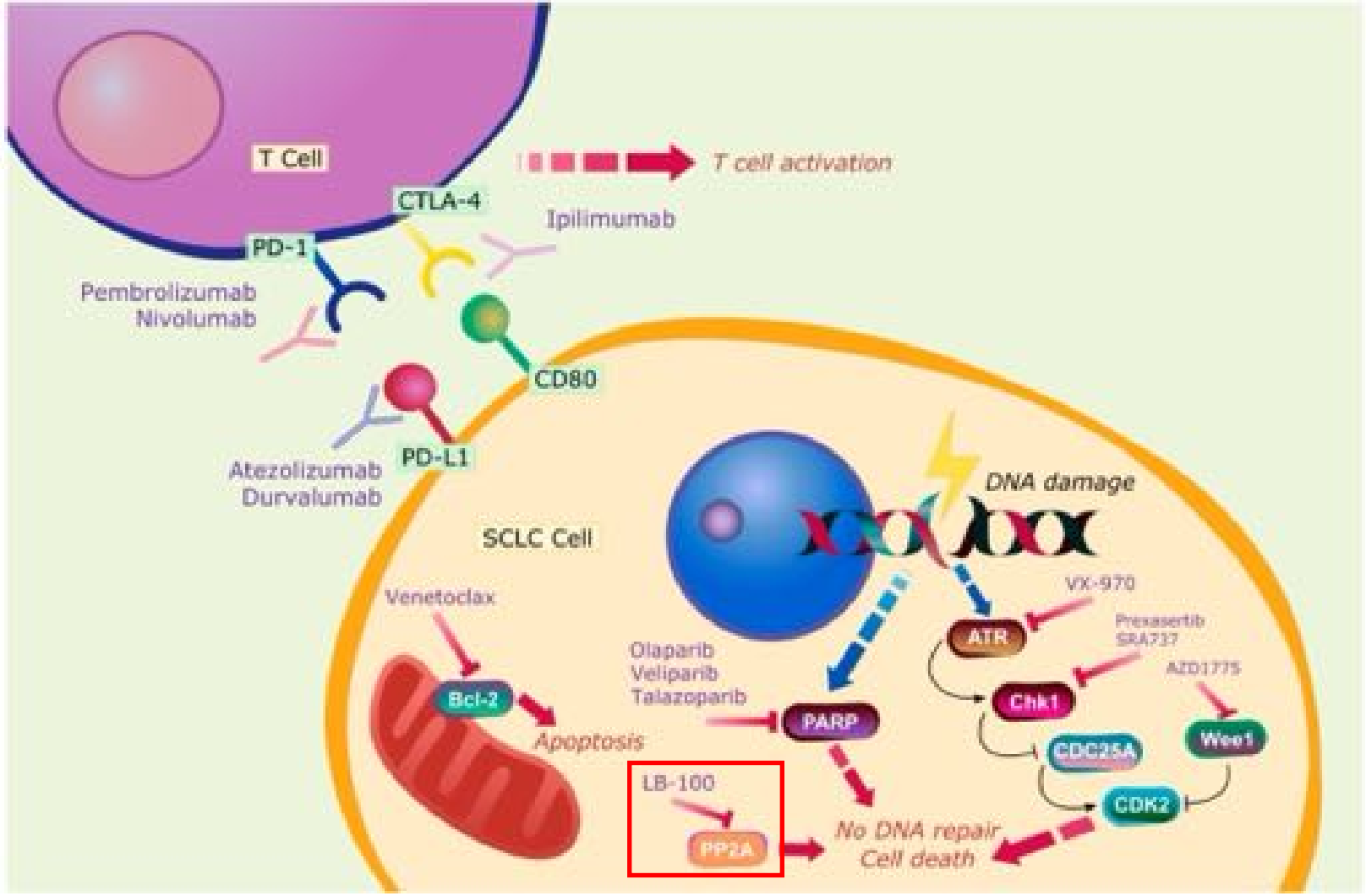
City of Hope Comprehensive Cancer Center
Duarte, California

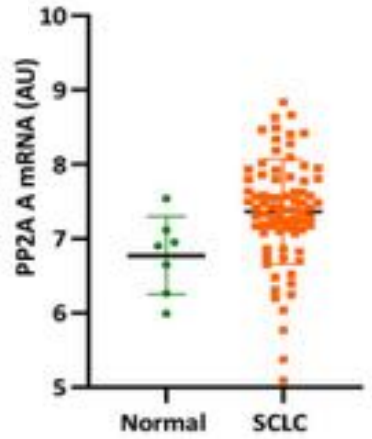
Salgia, Clinical Advances in Hematology & Oncology, 2022

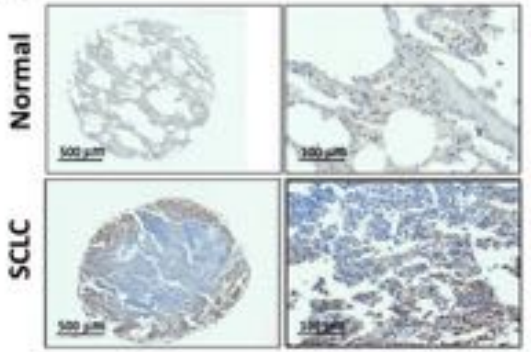
Potential Therapeutic Targets for SCLC

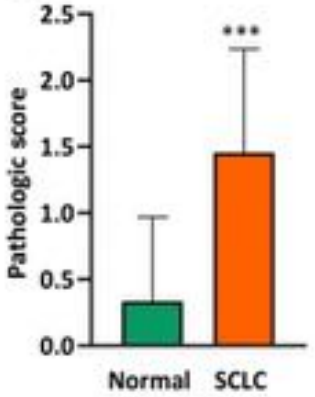


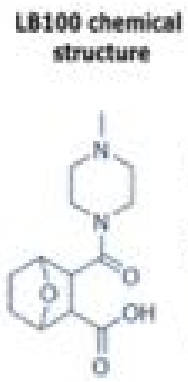
Subbiah, et int. Salgia, J. Clin. Med. 2020

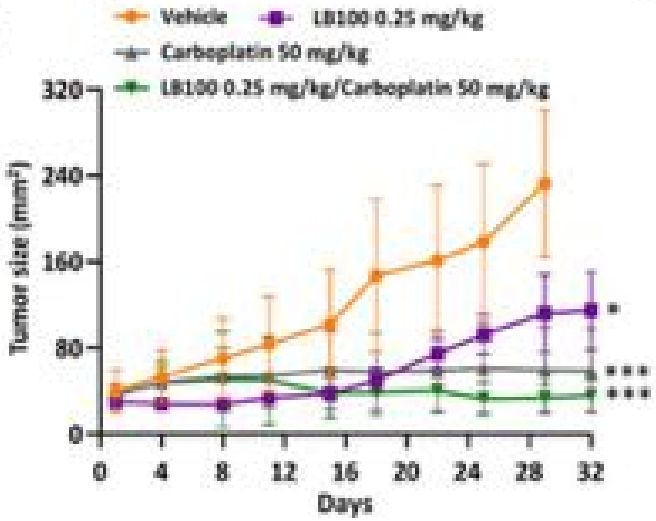
PP2A as a Therapeutic Target in SCLC

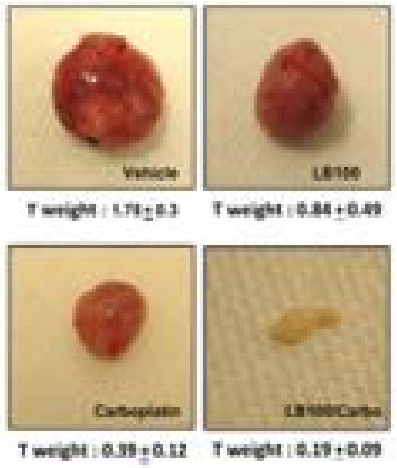


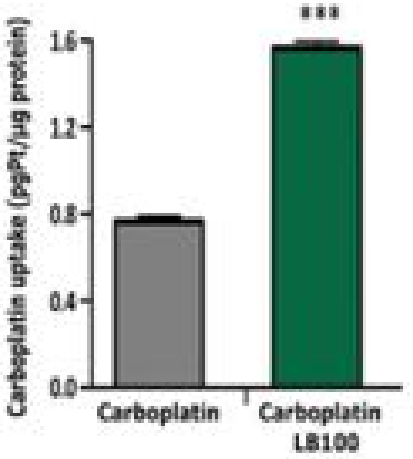












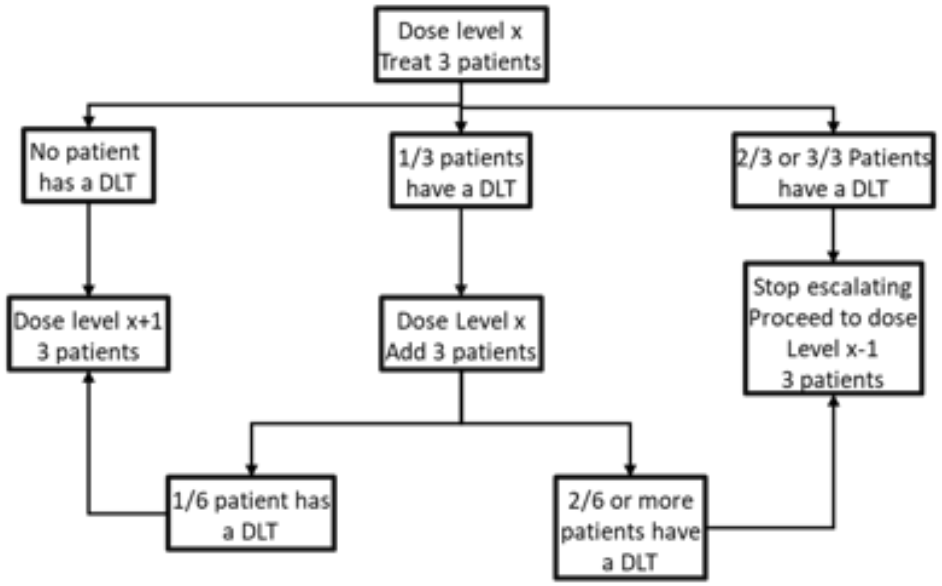
Mirzapoiazova et int. Salgia, Molecular Cancer Therapeutics, 2021

DEPARTMENT OF MEDICAL ONCOLOGY AND THERAPEUTICS RESEARCH

TITLE: A PHASE Ib OPEN-LABEL STUDY OF LB-100 IN COMBINATION WITH CARBOPLATIN/ETOPOSIDE/ATEZOLIZUMAB IN UNTREATED EXTENSIVE-STAGE SMALL CELL LUNG CARCINOMA

Schema and Objectives

Phase I



- Primary Objectives:
  - Determine recommended phase II dose (RP2D) of the combination using DLT during the first cycle as assessed by CTCAE version 5.0
- Secondary Objectives:
  - Objective response rate (ORR) by RECIST v1.1
  - Duration of overall response by RECIST v1.1
  - Safety and Adverse events by assessed by CTCAE version 5.0
  - Progression-free survival (PFS) as defined by RECIST v1.1
  - Overall survival, which is defined as the time from the date of study enrollment to the date of death from any cause. For patients who are still alive as of the data cutoff date, OS time will be censored on the date of the patient's last contact (last contact for patients in post discontinuation is last known alive date in mortality status).

Opening soon at COH

BIG | CANCER RESEARCH CONSORTIUM

Clinical Study Protocol
BTCRC-LUN17-127

A Phase I/II Study of Nivolumab, Ipilimumab and Plinabulin in Patients with Recurrent Small Cell Lung Cancer: Big Ten Cancer Research Consortium BTCRC-LUN17-127

Sponsor Investigator
Salma Jabbour, MD
Rutgers Cancer Institute of New Jersey

Co-Investigator
Jyoti Malhotra, MD, MPH
City of Hope

Outcomes

- Primary Outcome Measures:
  - Phase I: Maximum Tolerated Dose (MTD)
    - Establish MTD of plinabulin in combination with nivolumab and ipilimumab for patients with recurrent SCLC
  - Phase II: Progression-Free Survival (PFS)
    - Determine if the addition of plinabulin (at the 30 mg/m2 dose) to double checkpoint inhibition (PD-1 and CTLA-4) for recurrent SCLC will improve PFS (the time from treatment assignment to the date of the first documented tumor progression, or death due to any cause, whichever occurred first).
- Secondary Outcome Measures:
  - Assess Adverse Events
  - Assess immune-related adverse events (irAEs)
  - Proportion of subjects with a confirmed objective response
  - Clinical Benefit Rate
  - 6-Month Progression-Free Survival
  - 1-year Overall Survival
  - Overall Survival

Ongoing Targeted Therapy Clinical Trials in SCLC

Agent	Target	Trial Phase	Clinical Trial ID(s)
Navitoclax (ABT-263)	BCL-2, BCL-xL, BCL-W	I, II	NCT03366103
APG-1252	BCL-2, BCL-xL, BCL-W	I	NCT03080311, NCT03387332
ABBV-075	BET	I	NCT02391480
Lurbinectedin (PM01183)	CG-rich promoter sequences	III	NCT02566993
Prexasertib (SRA737)	CHK1	II	NCT02735980
Rova-T	DLL3	III	NCT03543358
AMG 757	DLL3	I	NCT03319940
AMG 119	DLL3	I	NCT03392064
BMS-986012	FucGM1	I, II	NCT02247349, NCT02815592
Vistusertib	mTORC1/2	I, II	NCT03366103
Olaparib	PARP	I, II	NCT02446704, NCT03009682, NCT02769962, NCT03532880, NCT03923270, NCT02511795
Talazoparib	PARP	II	NCT03672773
Veliparib	PARP	II	NCT03227016
Rucaparib	PARP	II	NCT03958045
Niraparib	PARP	II	NCT03830918
		II	NCT03516084

BCL-2, B-cell lymphoma 2; BCL-xL, B-cell lymphoma-extra large; BET, Bromodomain and extra-terminal domain; CHK1, checkpoint kinase 1; DLL3, delta-like ligand 3; FucGM1, Ganglioside fucosyl-GM1; mTORC1/2, mTOR Complex 1/2; PARP, Poly (ADP-ribose) polymerase.

Poirier et al., J. of Thor. Onc., 2020

Ongoing Immunotherapy Clinical Trials in SCLC

Study Name	Phase	Stage	Setting	Patients (n)	Intervention
ADRIATIC	III	LS	Maintenance after definitive chemoRT	500	Durvalumab + tremelimumab vs durvalumab + placebo vs placebo alone
ACHILLES	II	LS	Maintenance after definitive chemoRT	212	Atezolizumab vs placebo
NRG-LU005	II/III	LS	Concurrent with chemoRT	506	Atezolizumab + chemoRT vs placebo + chemoRT
NCI-2015–00508	I	LS, ES	LS: concurrent with chemoRT ES: After chemotherapy, maintenance with RT	80	LS: pembrolizumab with chemoRT ES: After chemotherapy, maintenance pembrolizumab with consolidation RT
CLOVER	I	LS	Concurrent with chemoRT	105	Durvalumab ± tremelimumab concurrent with chemoRT
RAPTOR	II/III	ES	Maintenance with RT	138	Maintenance atezolizumab + RT vs atezolizumab alone
SKYSCRAPER-02	III	ES	Upfront first line	490	Carboplatin + etoposide + atezolizumab + tiragolumab vs carboplatin + etoposide + atezolizumab + placebo
PRIO	I/II	ES	Upfront first line	63	Carboplatin + etoposide + durvalumab + olaparib ± RT
NCT04334941	II	ES	Maintenance in SFLN11+ patients	94	Atezolizumab + talazoparib vs atezolizumab alone
NCT04560972	Ib	ES	Upfront first line	18	Carboplatin + etoposide + atezolizumab + LB-100

chemoRT = concurrent chemotherapy + radiation; RT = radiotherapy.

Barrows et al., Seminars in Cancer Biology, 2022

Ongoing Chemotherapy Clinical Trials in SCLC

Drug	Phase	Intervention	ITT			Toxicities (G3-4 AEs)
			mOS	mPFS	ORR	
Nab-paclitaxel	II (NABSTER)	Nab-paclitaxel 100 mg/mq die 1–8 15q28	3.65 refractory 6.64 sensitive	1.84 refractory 1.88 sensitive	11.8%	Fatigue (34%) Anaemia (38%) Neutropenia (29%) Leukopenia (26%) Diarrhea (21%)
Liposomal Irinotecan (Nal-IRI)	Ib/II	Nal-IRI 70 mg/m^2 or 85 mg/m^2 every 2 weeks	N/A	N/A	33.3%	Diarrhea (n = 5) Neutropenia (n = 4) Anemia (n = 2) Thrombocytopenia (n = 2)
Belotecan	II	Belotecan 0.5 mg/m^2 1–5q21	9.9	2.2	28%	Neutropenia (grade 3–4) (88%) Thrombocytopenia (40.0%)
	II	Belotecan 0.5 mg/m^2 1–5q21	6.5 sensitive 4.0 refractory	2.8 sensitive 1.5 refractory	20% sensitive 10% refractory	Neutropenia (58%) Thrombocytopenia (36%) Anemia (32%)
	IIb	Belotecan 0.5 mg/m^2 1–5q21 vs. Topotecan 1.5 mg/m^2 1–5q21	13.2 vs. 8.2 $p = 0.038$	4.8 vs. 3.8 $p = 0.96$	33 vs. 25% $p = 0.09$	Hematological disorders (≥10%) Neutropenia Thrombocytopenia Anaemia
Amrubicin	II	amrubicin (40 mg/m^2 on days 1 through 3) or topotecan (1.0 mg/m^2 on days 1 through 5) every 3 weeks	8.1 vs. 8.4	3.5 vs. 2.2	38% (95% CI, 20 to 56%) vs. 13% (95% CI, 3 to 25%)	Neutropenia (79%) Febrile Neutropenia (14%) Anemia (21%) Thrombocytopenia (26%)
	II	Amrubicin 40 mg/m^2 on days 1 to 3 every 3 weeks	11.2	2.6 refractory 4.2 sensitive	32%	Neutropenia (83%) Thrombocytopenia (20%) Anemia (33%) Febrile neutropenia (5%)
	II	Amrubicin (40 mg/m^2/d for 3 every 21 days) (NB: refractory patients)	6.0 (95% CI, 4.8 to 7.3)	3.2 (95% CI, 2.4 to 4.0)	21.3% (95% CI, 12.7 to 32.3%)	Neutropenia (67%) Thrombocytopenia (41%) Anemia (36%) Febrile neutropenia (12%)
	II	amrubicin (40 mg/m^2 on days 1 through 3) or topotecan (1.0 mg/m^2 on days 1 through 5) every 3 weeks NB: platinum sensitive	9.2 vs. 7.6	4.5 vs. 3.3	44 vs. 15% $p = 0.021$	Neutropenia (61%) Thrombocytopenia (39%) Leukopenia (39%) Anemia (25%) Febrile neutropenia (10%)
	III	amrubicin (40 mg/m^2 on days 1 through 3) or topotecan (1.0 mg/m^2 on days 1 through 5) every 3 weeks	7.5 vs. 7.8 (HR = 0.880; p = 0.370)	4.1 vs. 3.5 (HR, 0.802; p = 0.058)	31.1 vs. 16.9% (odd ratio 2.223; p = 0.001)	Neutropenia (41%) Thrombocytopenia (21%) Anemia (16%) Infections (16%) Febrile neutropenia (10%) Cardiac disorders (5%) Need of transfusion (32%)
	III	cisplatin (60 mg/m^2, day 1) amrubicin (40 mg/m^2, days 1–3) vs. cisplatin and eto-poside (100 mg/m^2, days 1–3) once every 21 days.	11.8 vs. 10.3 (p = 0.08)	6.8 vs. 5.7 months (p = 0.38)	69.8 vs. 57.3%	Neutropenia (54.4 %) Leukopenia (34.9 %) Thrombocytopenia (16.1 %)
Temozolomide (TMZ)	II	TMZ 75 mg/mq/die 1→21q28	NA	NA	22% sensitive 59% refractory	Thrombocytopenia and neutropenia (34%)
	II	TMZ 200 mg/mq/die 1→5 q28	1.8	3.8	12%	Anemia, thrombocytopenia and neutropenia (20%)

Cortinovis et al., Cancers, 2021

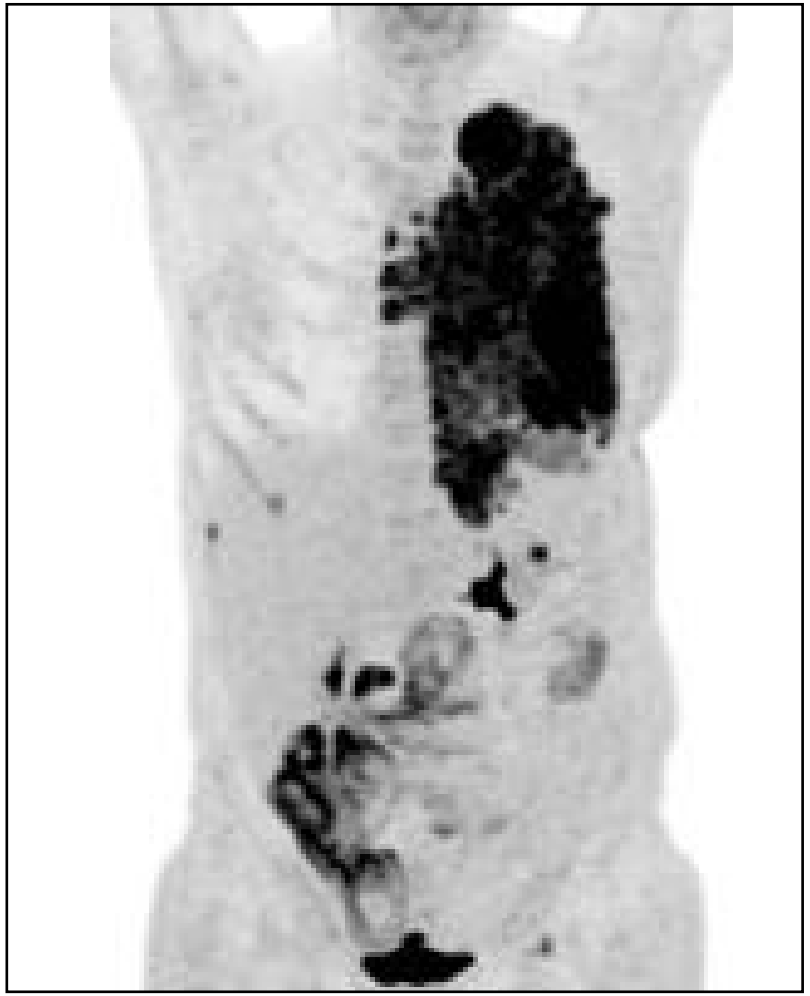
Ongoing Lurbinectedin Clinical Trials in SCLC

Phase	N	Intervention	ITT			Platinum Sensitive			Platinum Refractory		
			mOS	mPFS	ORR	mOS	mPFS	ORR	mOS	mPFS	ORR
II	105	Lurbinectedin 3.2 mg/m2 1q21	9.3 (6.3–11.8)	3.5 (2.6–4.3)	35.2% (26.2–45.2)	11.9 (9.7–16.2)	4.6 (2.8–6.5)	45.0% (32.1–58.4)	5.0 (4.1–6.3)	2.6 (1.3–3.9)	22.2% (11.2–37.1)
I	27	Doxorubicin 50 mg/m^2 Lurbinectedin 4.0 mg (dose escalation from 3.5 mg) 1q21	7.9 (5.0–12.1)	4.1 (1.4–5.8)	57.7% (36.9–76.6)	11.5 (13.5–8.5)	5.8 (3.6–10.9)	91.7% (61.5–9.8)	4.9 (7.3–2.8)	3.5 (1.1–8.0)	33.3% (7.5–70.1)
Ib/II	13	Irinotecan 75 mg/m^2 1,8q21 lurbinectedin 2.0 mg day 1q21 (dose escalation from 1.0 mg)	N/A	5.4	61.5%	N/A	N/A	N/A	N/A	N/A	N/A
III	613	Lurbinectedin 2.0 + Doxorubicin 40.0 mg1q21 versus cyclophos-phamide + doxorubicin + vincristine (CAV) versus topotecan	N/A	N/A	50%	N/A	N/A	N/A	N/A	N/A	N/A
Ib/II	7	Paclitaxel 80 mg/mq 1,8q21 + lurbinectedin 2.2 mg day 1q21 (dose escalation from 1.0 mg)	N/A	4.8	71%	N/A	N/A	N/A	N/A	N/A	N/A

Cortinovis et al., Cancers, 2021

Mesothelioma

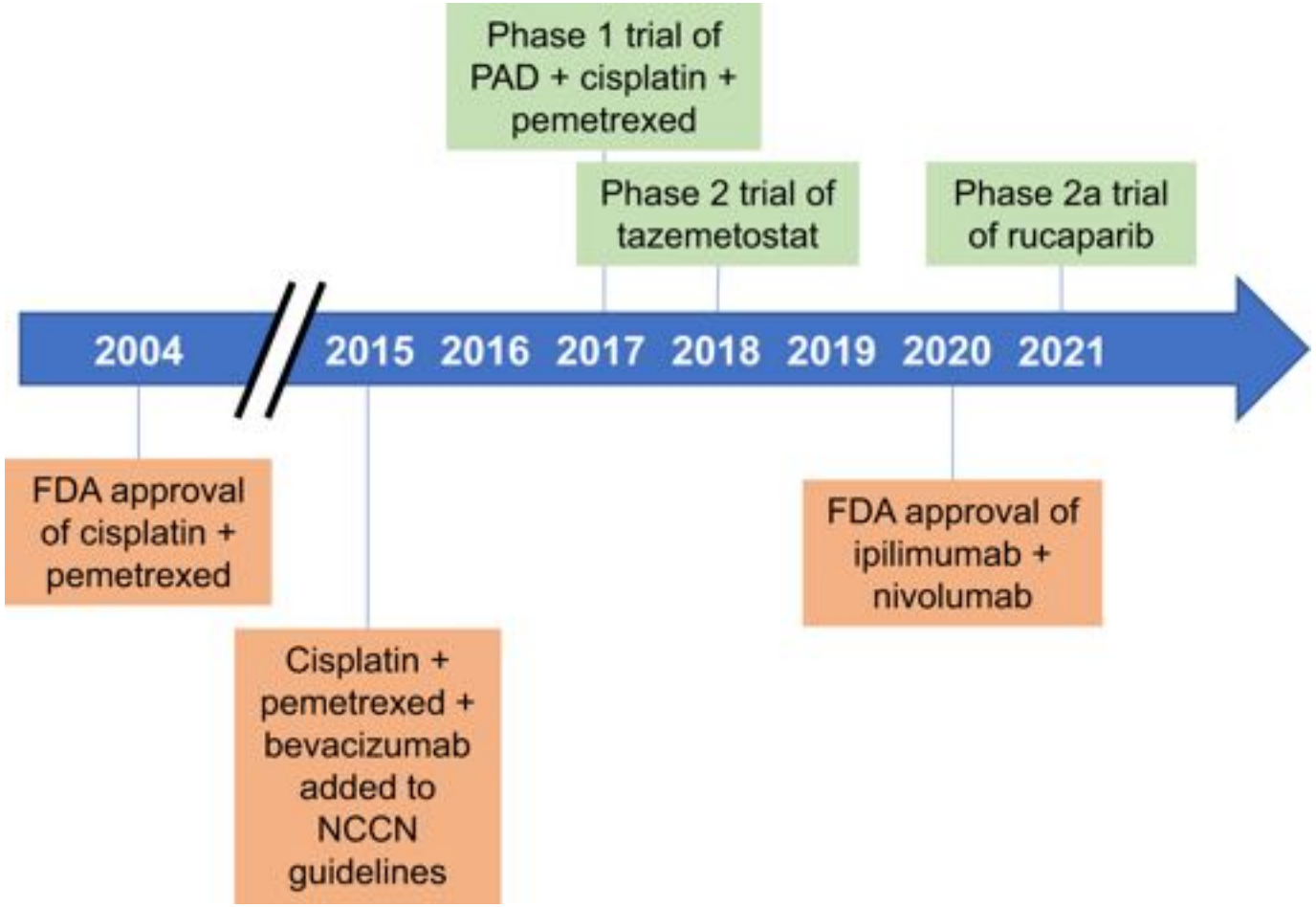
Malignant Mesothelioma is an Aggressive Cancer with Poor Prognosis



- 3,000 new cases in US each year
- Majority of patient not candidates for surgery
- Staging and radiologic assessment difficult
- Pemetrexed plus cisplatin FDA approved, 2004
- Nivolumab plus ipilimumab FDA approved, 2020
- Median overall survival ~18 months

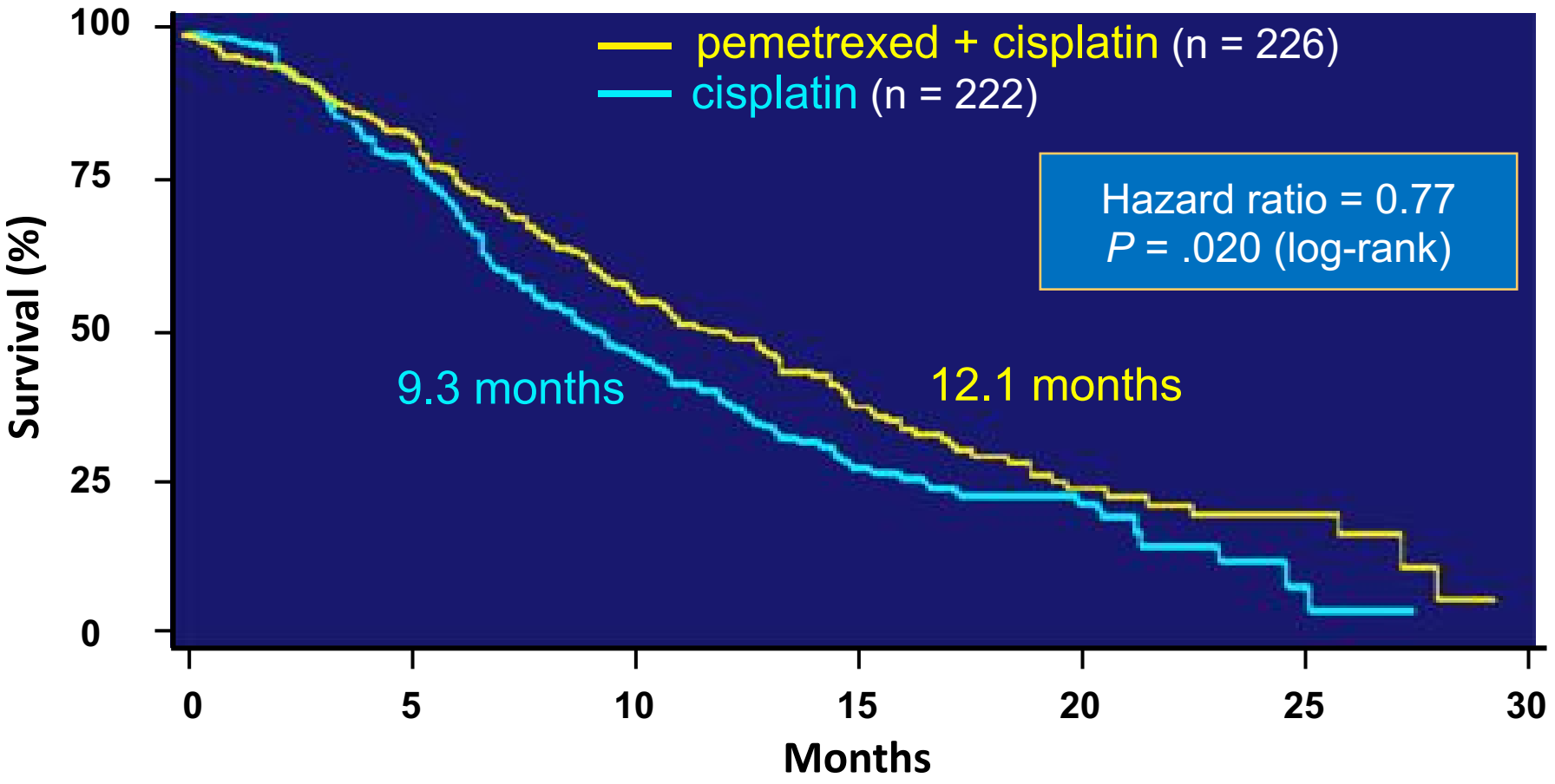
Kinder, Hassan, J Clin Oncol, 2018
Rusch et al., J Thorac Oncol, 2016
Vogelzang et al., J Clin Oncol, 2003
Baas et al., Lancet, 2021

Timeline of Mesothelioma Treatment



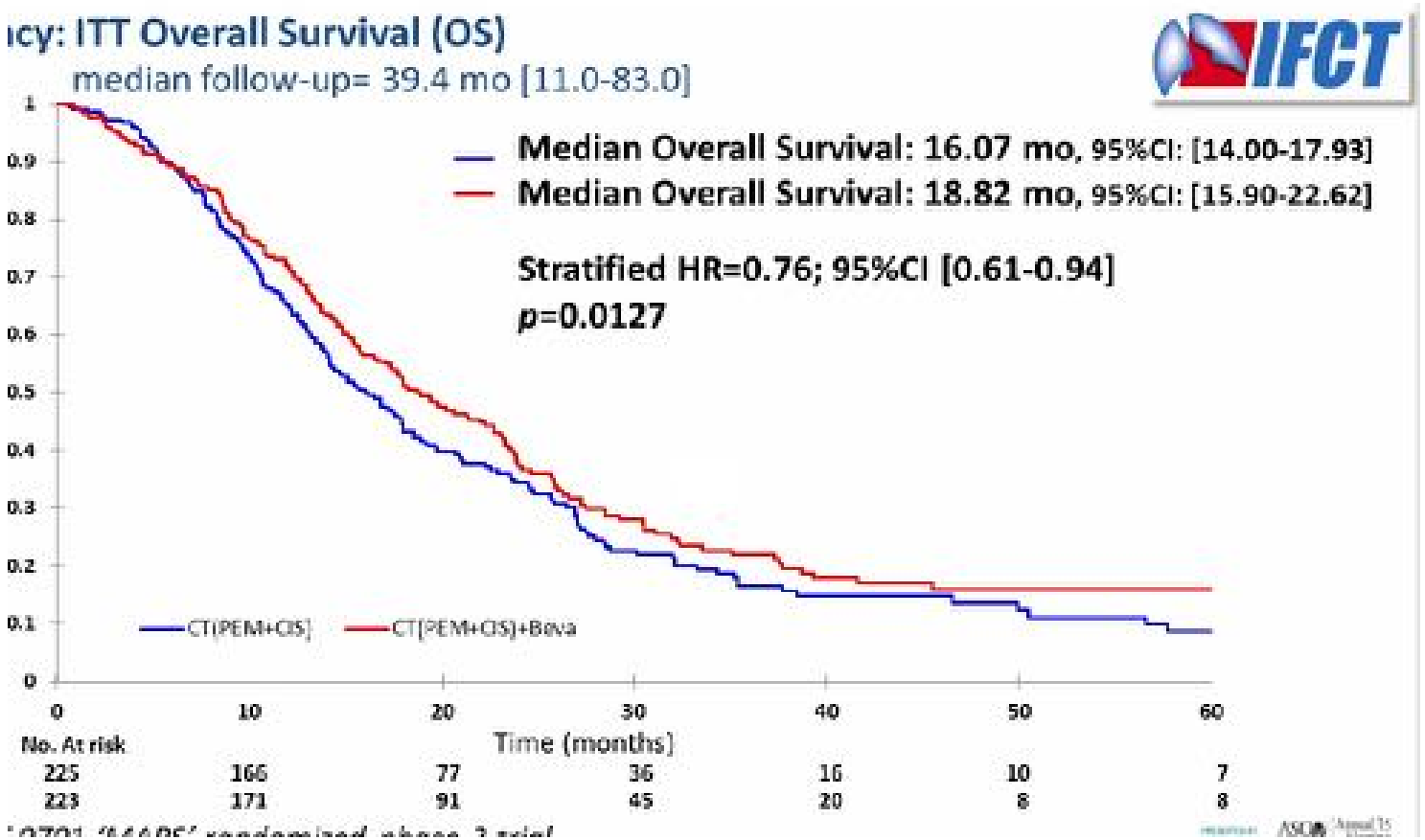
Zauderer, Nature Communications, 2021

Phase III Study of Pemetrexed plus Cisplatin in MPM



Vogelzang NJ et al. J Clin Oncol 2003

Increased overall survival in patients receiving bevacizumab plus pemetrexed and cisplatin



Zalcman G et al. Lancet 2015

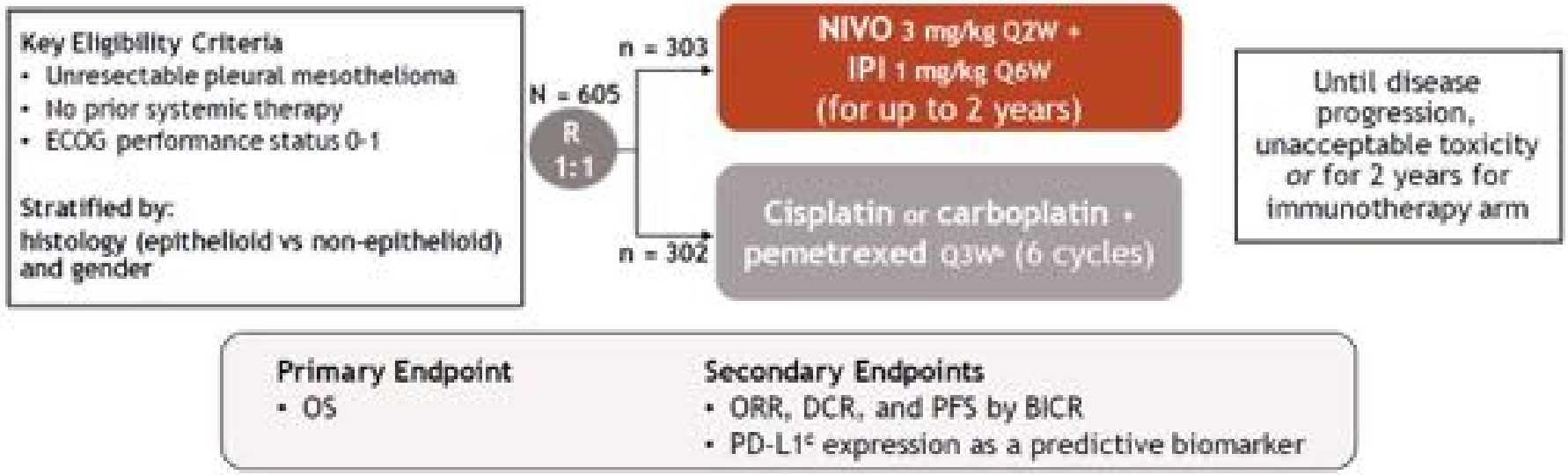
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

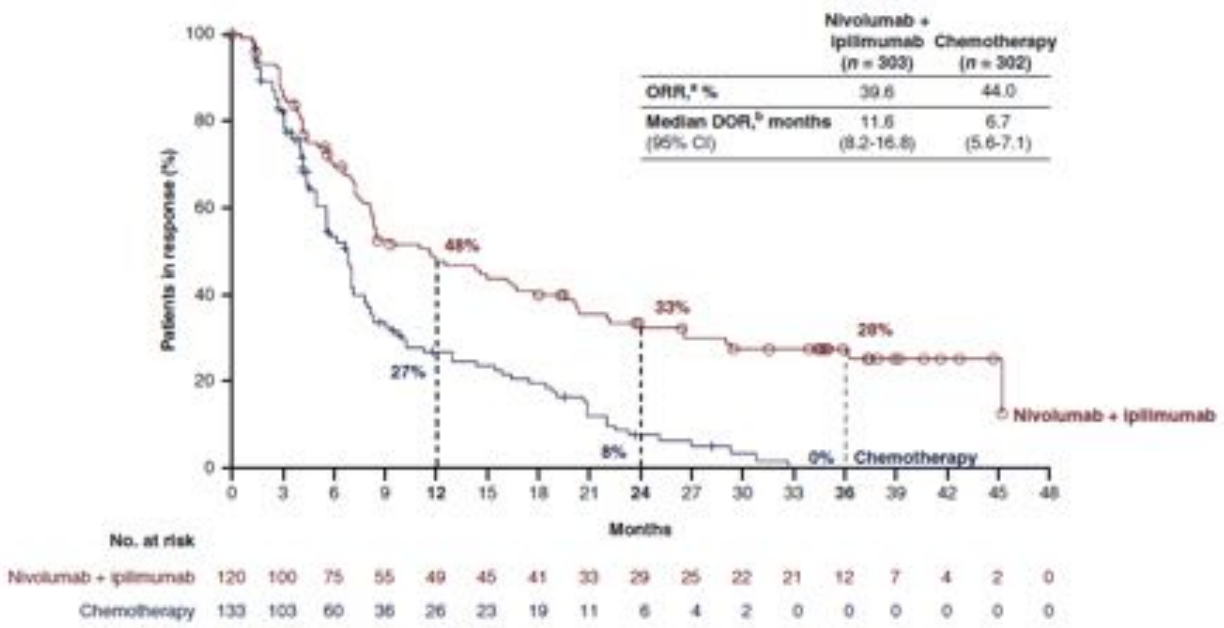
ORIGINAL ARTICLE

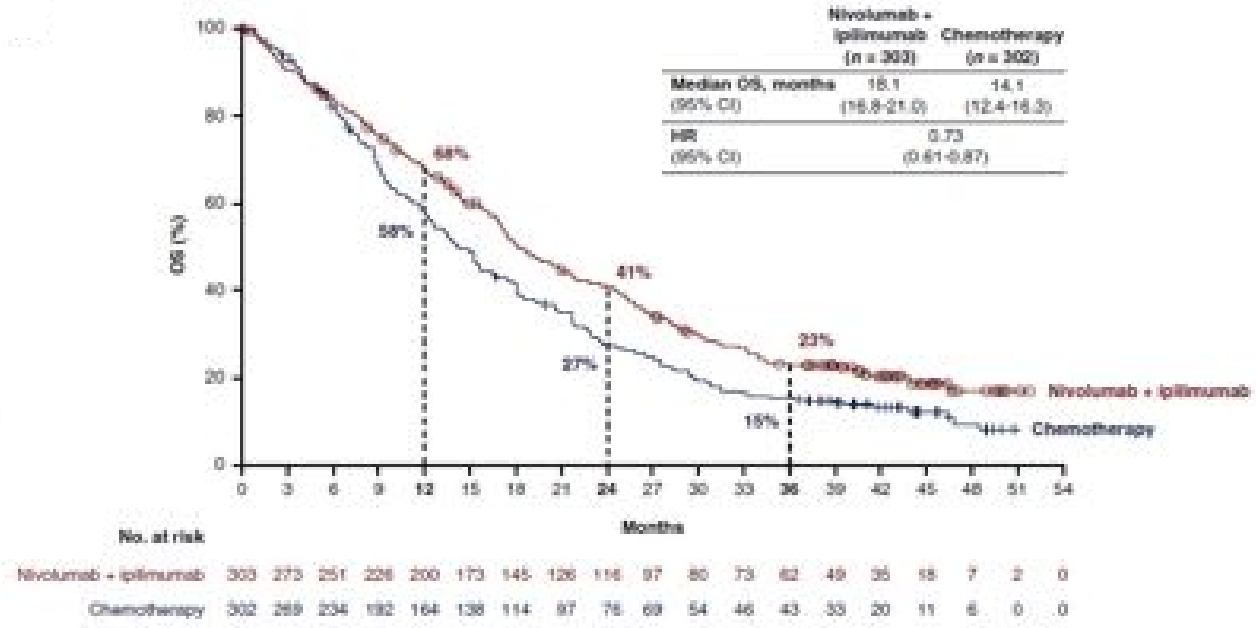
First-line nivolumab plus ipilimumab versus chemotherapy in patients with unresectable malignant pleural mesothelioma: 3-year outcomes from CheckMate 743

S. Peters[1*], A. Scherpereel[2], R. Cornelissen[3], Y. Oulkhouir[4], L. Greillier[5], M. A. Kaplan[6], T. Talbot[7], I. Monnet[8], S. Hiret[9], P. Baas[10], A. K. Nowak[11], N. Fujimoto[12], A. S. Tsao[13], A. S. Mansfield[14], S. Popat[15,16], X. Zhang[17], N. Hu[18], D. Balli[19], T. Spires[20] & G. Zalcman[21]

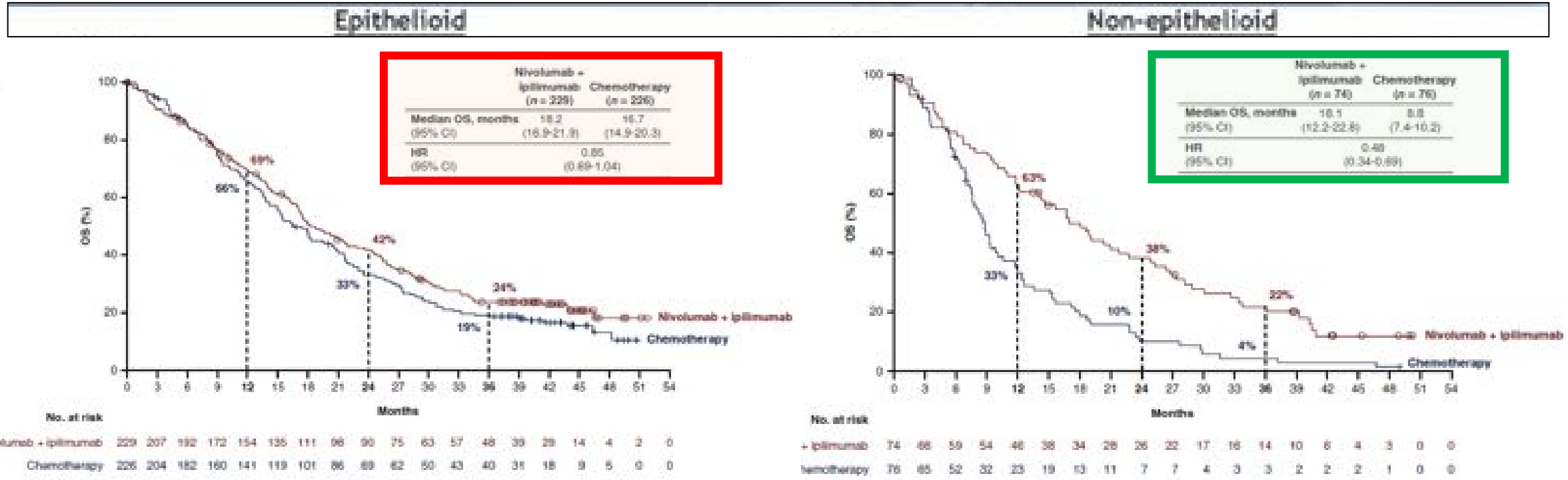


Response Rate and OS

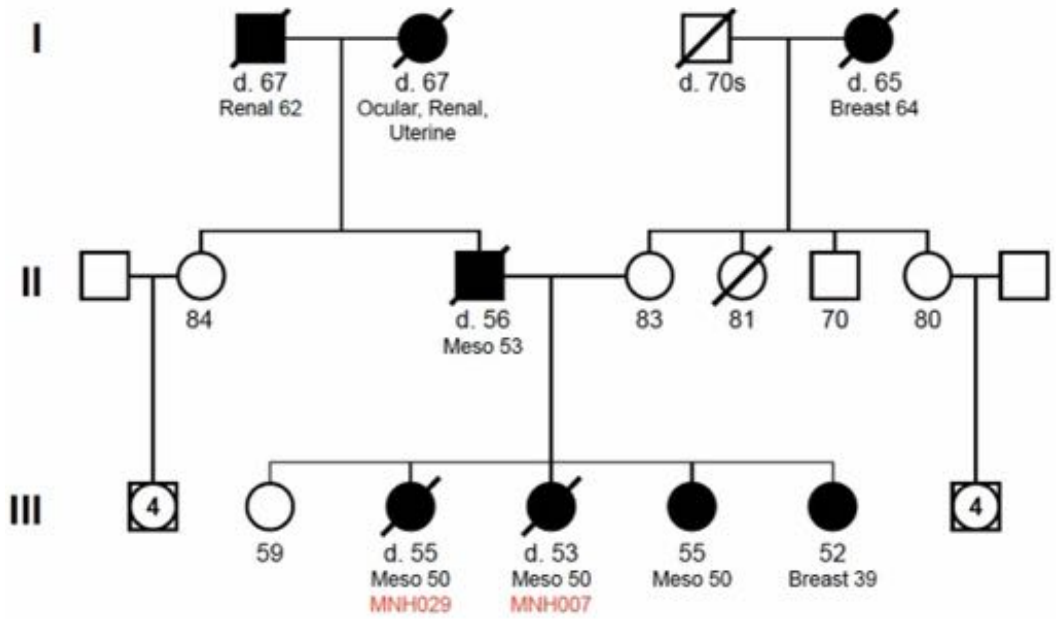


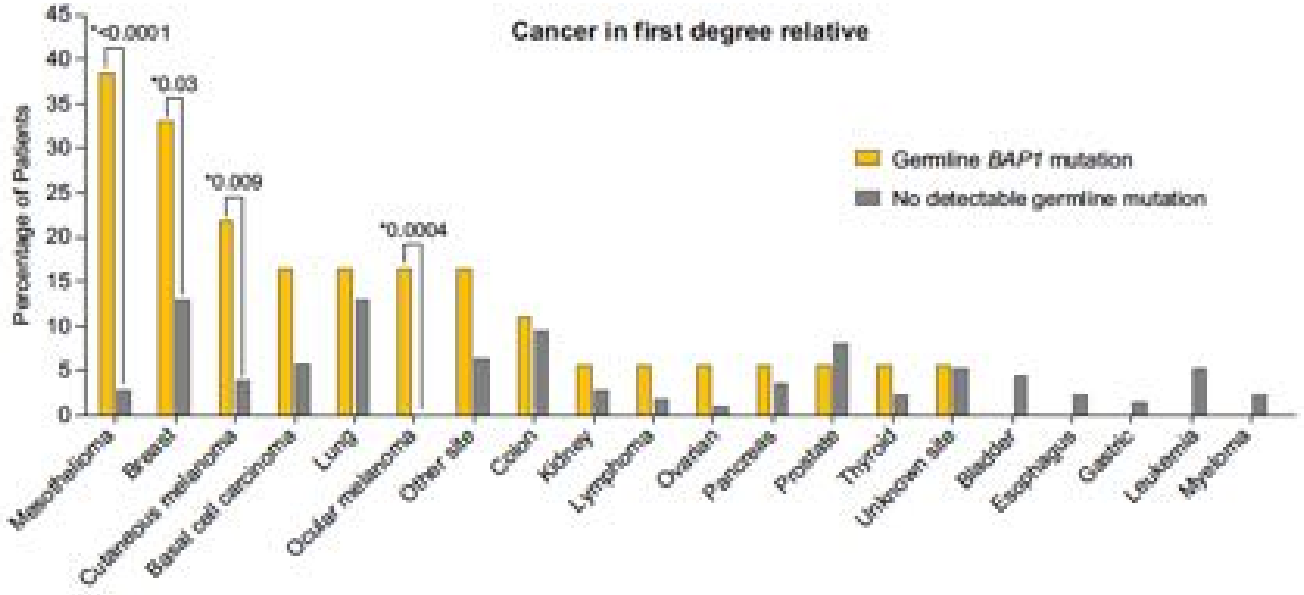


Overall Survival by Histology



Patients and Family Members with Germline BAP1 Mutations with Increased Risk for Mesothelioma and Other Cancers





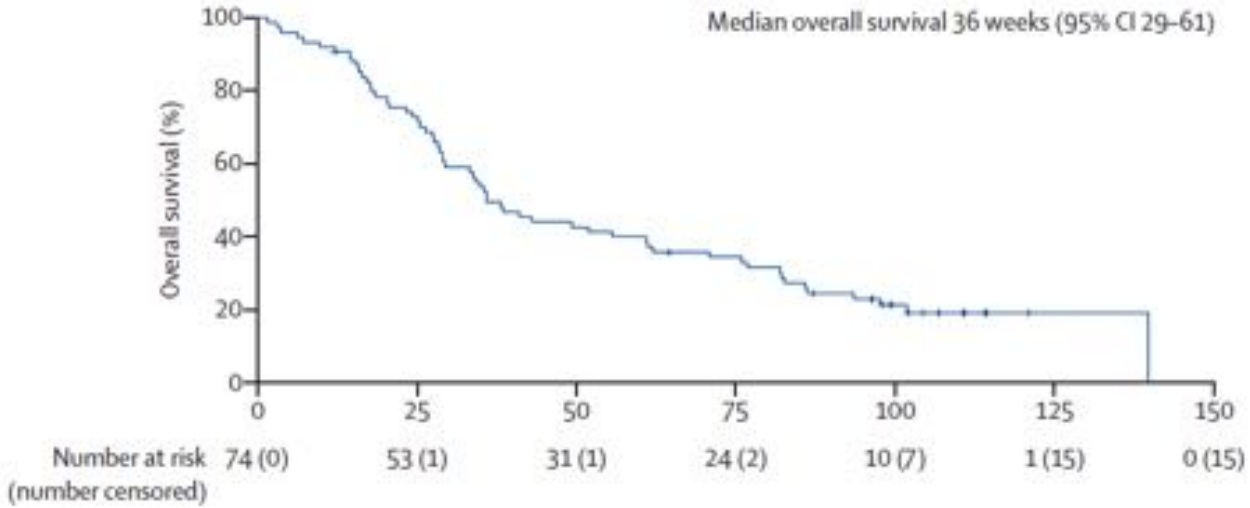
Hassan et al., PNAS, 2019

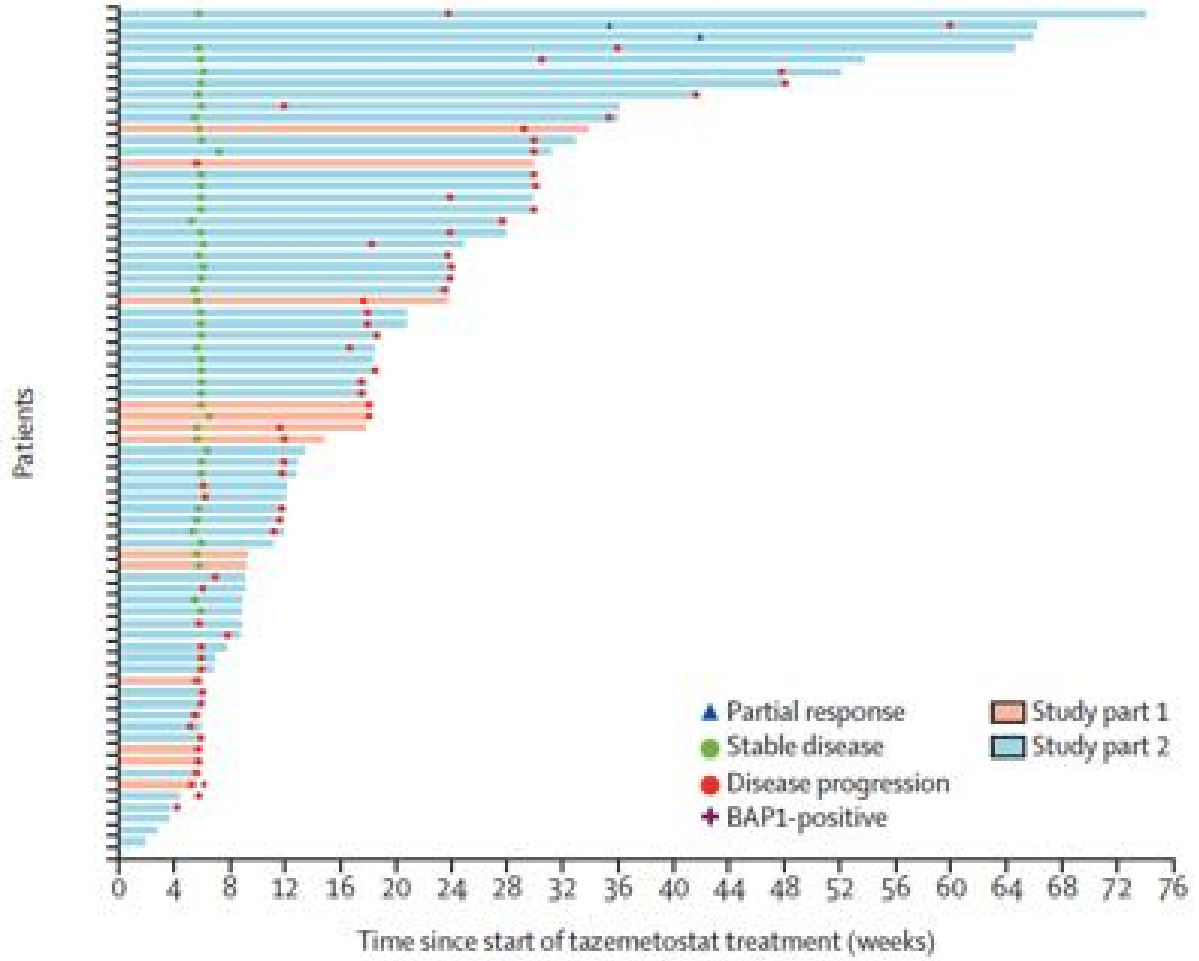
Frequently Mutated Genes in MPM

bold = mutation frequency >5%

Illei, Clin Cancer Res, 2003
Bueno et al., Nat Genet, 2016
Hmeljak et al., Cancer Discov, 2018

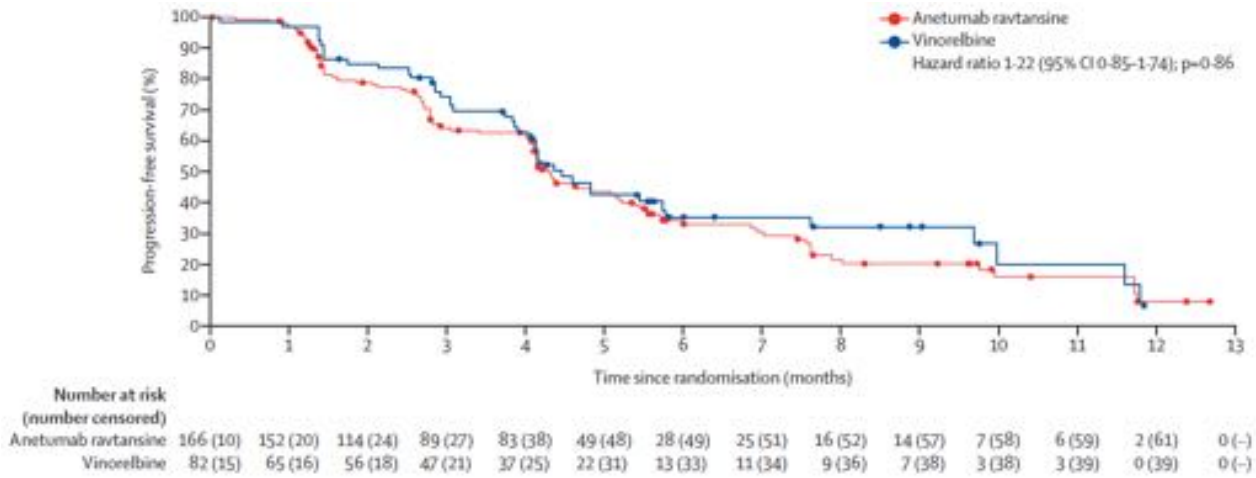
EZH2 inhibitor tazemetostat in patients with relapsed or refractory, BAP1-inactivated malignant pleural mesothelioma: a multicentre, open-label, phase 2 study

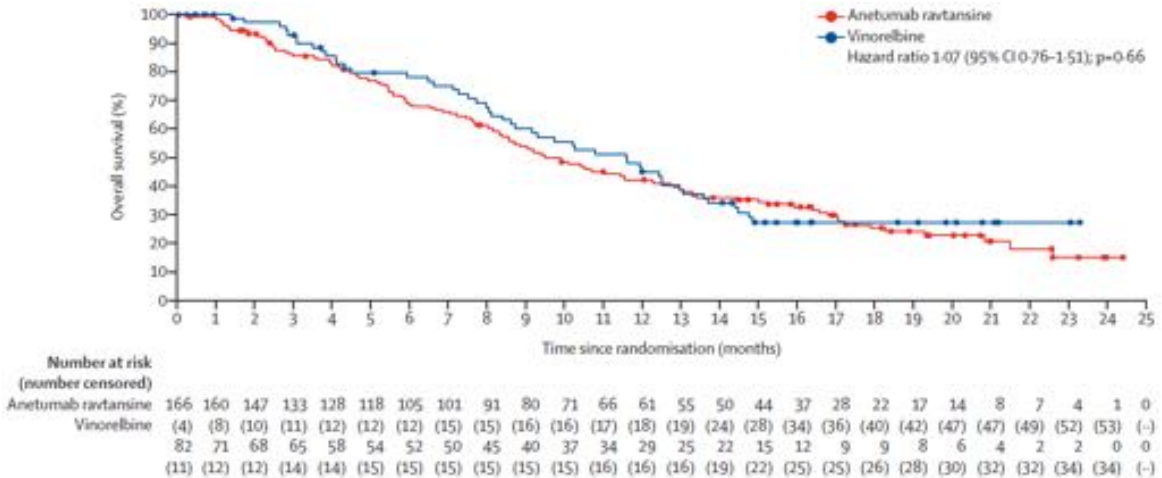




Zauderer et al., Lancet, 2022

Anetumab ravtansine versus vinorelbine in patients with relapsed, mesothelin-positive malignant pleural mesothelioma (ARCS-M): a randomised, open-label phase 2 trial





Kindler et al., Lancet, 2022

PEMbrolizumab plus lenvatinib in second and third line malignant pleural MEsotheLiomA patients; a single arm phase II study (PEMMELA)

ORR

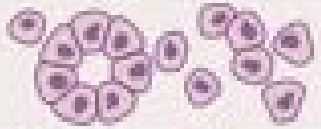
	Local investigator	Independent central reviewer (2nd endpoint)
	PEM+LEN (N=38)	PEM+LEN (N=38)
Objective response (95% CI) -%	58 (41-74)	42 (26-59)
Best overall response – n(%)		
CR	0	0
PR	22 (58)	16 (42)
SD	16 (42)	22 (58)
PD	0	0
Objective response (only confirmed) (95% CI) -%	40 (24-57)	37 (22-54)

At evaluation, 13 patients still on treatment

	All patients (n=38)
Sex (male), n(%)	33 (86.8)
Median age (range), years	70.5 (36-83)
ECOG PS 0, n(%)	19 (50)
Histology, n(%)	
Epithelioid	34 (89.5)
Non-epithelioid	2 (5.3)
Mixed	2 (5.3)
PD-L1 status, n(%)	
Positive (≥1%)	18 (47.4)
Negative (<1%)	17 (44.7)
Not available	3 (7.9)

Douma et al., Presented at the 2022 World Conference on Lung Cancer, 2022

Targets for Current and Future Approaches

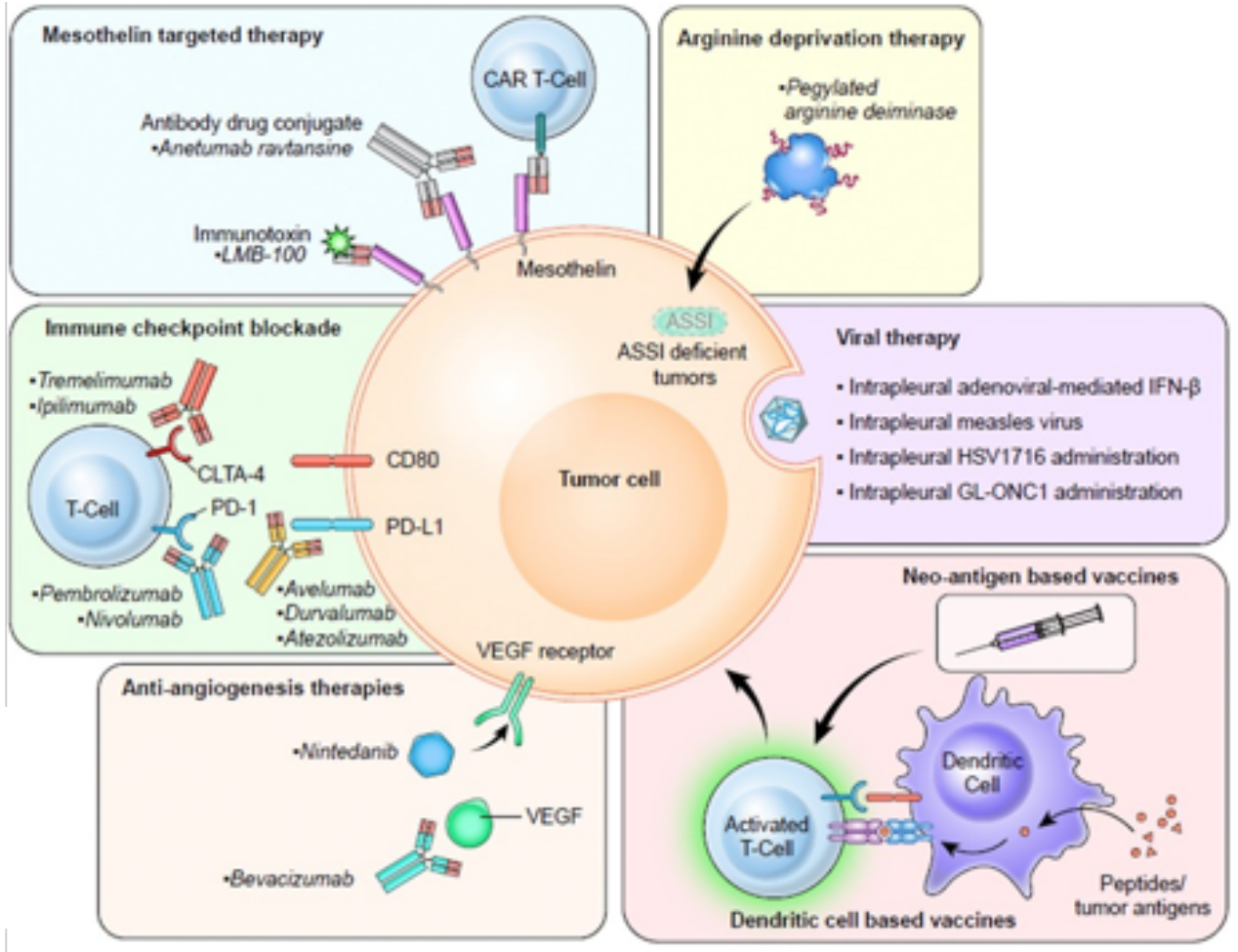
Phenotypic Histologic Subtypes	
Epithelioid (30–60% of cases)	
Biphasic (30–40% of cases)	
Sarcomatoid (10% of cases)	

Current and Future Systemic Approaches
Chemotherapy
Antibody-drug conjugates
Immune checkpoint inhibition (PD-1 or PD-L1 inhibition)
Ferroptosis inducers
Cellular therapy (CAR-T cells targeting mesothelin)
Angiogenesis inhibition

Genomic or Epigenomic Landscape	
Mutation	**Therapeutic Targets**
BAP1	EZH2; PARP
CDKN2A	p16
NF2	FAK; YAP-TEAD; mTOR and PI3K
ASS1	Arginine

Janes et al., NEJM, 2021

Different Strategies Currently in Clinical Trial for Therapy of Malignant Mesothelioma



Luciano M,…Hassan, R. JTO, 2018

Ongoing and Completed Trials for MPM

Intervention	Original indication	Clinical phase	Sponsor
Olaparib	Advanced ovarian cancer	Phase-II	National Cancer Institute (NCI), National Institutes of Health Clinical Center (CC)
Lurbinectedin	Small cell lung cancer	Phase-II	Swiss Group for Clinical Cancer Research
YS110	Anti-CD28 monoclonal antibody	Phase-I, Phase-II	Eisai Pharmaceutical Co., Ltd.
Ipilimumab + nivolumab	Ipilimumab: melanoma; nivolumab: melanoma, lung cancer	USFDA Approved	The Netherlands Cancer Institute, Bristol-Myers Squibb
Atezolizumab	Non-small cell lung cancer, triple negative breast cancer	Phase-II	Health Pharma Professional Research, ILS Clinical Research
Pembrolizumab + defactinib	Pembrolizumab: melanoma, lung cancer; defactinib: solid tumors	Phase-I	Raphael Bueno, MD, Merck Sharp & Dohme Corp., Dana-Farber Cancer Institute
Pembrolizumab + cisplatin/ pemetrexed	Pembrolizumab: melanoma, lung cancer;	Phase-I	Abramson Cancer Center of the University of Pennsylvania
rAD IFN + celecoxib and gemcitabine	rAD IFN: non-muscle invasive bladder cancer; celecoxib: NSAID; gemcitabine: ovarian cancer, lung cancer	Phase-III	Trivedi Lui., University of Pennsylvania
MTG201 + nivolumab	MTG201: gene therapy for various cancer; nivolumab: melanoma, lung cancer	Phase-II	Mosaicco-Gene Inc., Baylor College of Medicine, Synovarc, Inc.
Pembrolizumab + lenvatinib	Pembrolizumab: melanoma, lung cancer; lenvatinib: thyroid cancer	Phase-II	The Netherlands Cancer Institute, Merck Sharp & Dohme Corp.
Carboplatin + pemetrexed + bevacizumab + atezolizumab	Carboplatin: platinum chemotherapy; pemetrexed: antifolate chemotherapy; bevacizumab: various type of cancer; atezolizumab: non-small cell lung cancer, triple negative breast cancer	Phase-III	European Thoracic Oncology Platform, Hoffmann-La Roche
Nivolumab + cisplatin/ pemetrexed	Nivolumab: melanoma, lung cancer	Phase-I	Memorial Sloan Kettering Cancer Center, Bristol-Myers Squibb

Kulkarni, Gupta, Life Sciences, 2022

Molecular Targets and Repurposed Drugs in Development

Intervention	Molecular target	Development phase	Status
Zoledronic Acid	Caspases and cell cycle arrest	Phase-I	NA
Defactinib	Focal adhesion kinases (FAK)	Phase-II	Withdrawn due to funding complications
Cediranib	Vascular endothelial growth factor receptor (VEGF)	Phase-II	Inadequate clinical efficacy
Nintedanib	Tyrosine kinase	Phase-III	Study endpoints unmet with inadequate clinical efficacy
Lurbinectedin	C-C Motif Chemokine Ligand 2 (CCL2)	Phase-II	Promising Phase-II results
Nivolumab + ipilimumab	CTLA-4 and PD-1	USFDA approved	Commercially Available

Repurposed molecule	Molecular target	Comments
Pyrvinium Pamoate	Wnt pathway, PI3K/AKT	Highly effective in shunting MPM progression
Metformin	m-TOR, AMPK pathways	Formulation development helped reducing effective therapeutic dose, in-vitro
Fingolimod (FTY720)	Sphingosine kinase-1, protein phosphatase 2A	Excellent efficacy in pre-clinical testing

Kulkarni, Gupta, Life Sciences, 2022

Summary

- Small Cell Lung Cancer
  - Early diagnosis can lead to cure
  - Extensive disease is still difficult to treat
    - Immunotherapy has now become approved
    - Second-line therapy has also advanced
  - Novel therapies need to be tested more rapidly
- Mesothelioma
  - Prognoses for patients diagnosed with mesothelioma remains poor
  - Targeted approaches that take advantage of the mutational profile in mesothelioma have not come to fruition
  - Frontline IO therapy with ipilimumab plus nivolumab increased overall survival for patients with sarcomatoid mesothelioma
  - There is a need for more biomarker-drive trials in mesothelioma

THANK YOU

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