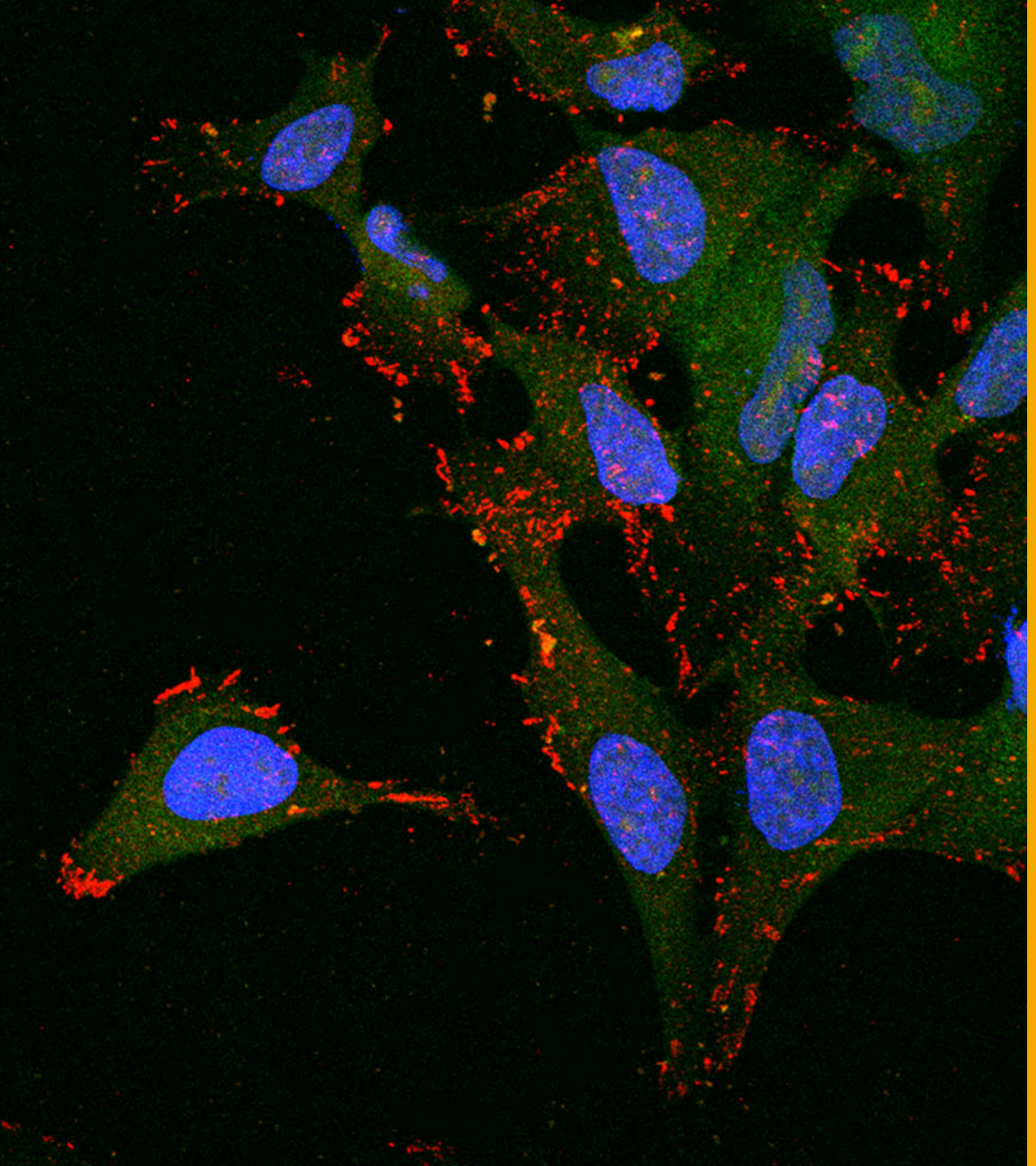


YEAR IN REVIEW 2020:
SMALL CELL LUNG CANCER AND MESOTHELIOMA

Suresh S. Ramalingam, MD, FACP, FASCO.

Roberto C. Goizueta Chair for Cancer Research

Deputy Director, Winship Cancer Institute

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

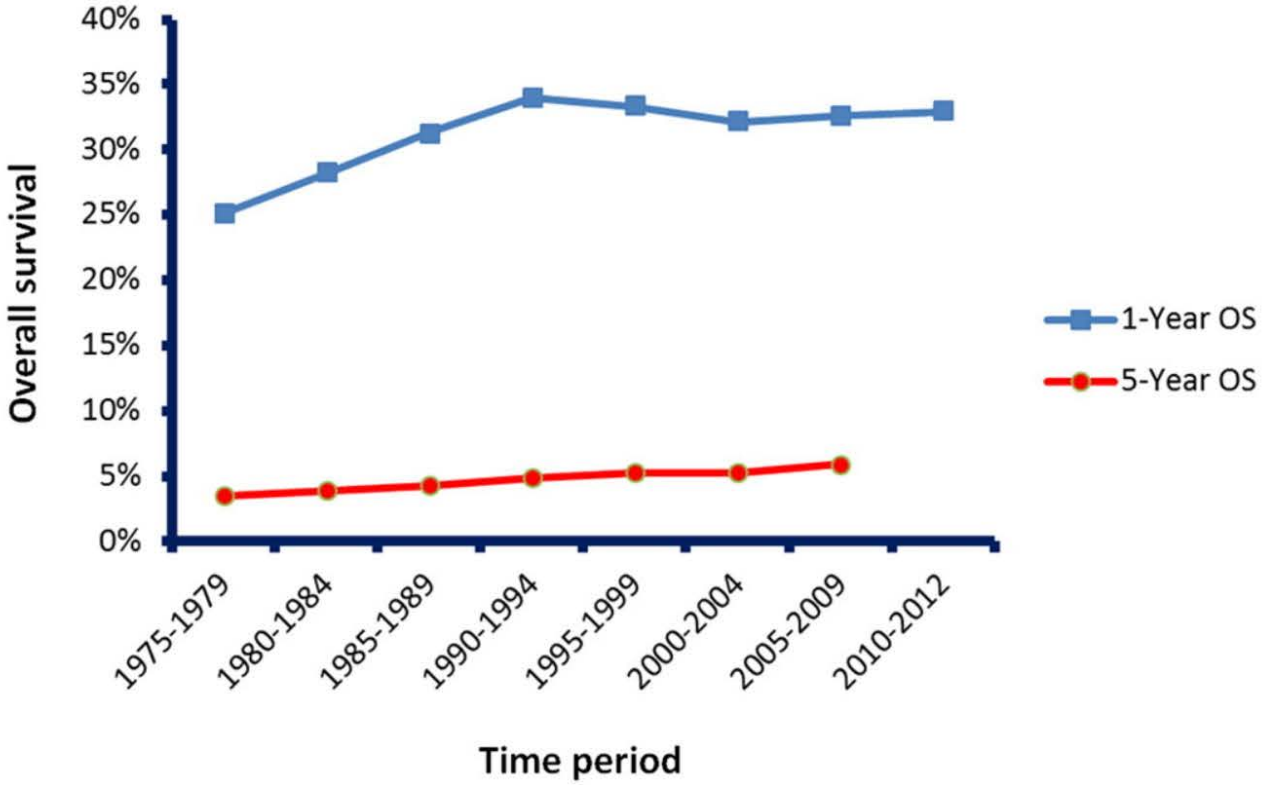
NCI Designated Comprehensive Cancer Center

SMALL CELL LUNG CANCER

- Accounts for 10-15% of all cases of lung cancer
- Platinum-based chemotherapy has been the standard of care for decades
- Concomitant use of radiotherapy extends survival in limited stage SCLC
- Prophylactic cranial irradiation improves survival in limited stage SCLC
- No effective salvage therapy options for relapsed/recurrent disease

Courtesy of Suresh S Ramalingam, MD

COURSE OF PROGRESS IN SCLC



% Survival	Subgroups		
	LD and ED SCLC	LD-SCLC	**ED-SCLC**
6 months	68.09%	88.70%	65.36%
12 months	30.92%	57.98%	**29.37%**
24 months	8.08%	21.09%	**6.93%**

Saiama N. Waqar, Daniel Morgensztern; Pharmacology & Therapeutics December 2017, 180:16-23; Amarasena IU, Chatterjee S, Walters JAF. Wood-Baker R. Fong KM. Cochrane Database of Systematic Reviews 2015. 8. Art. No.: CD006849.

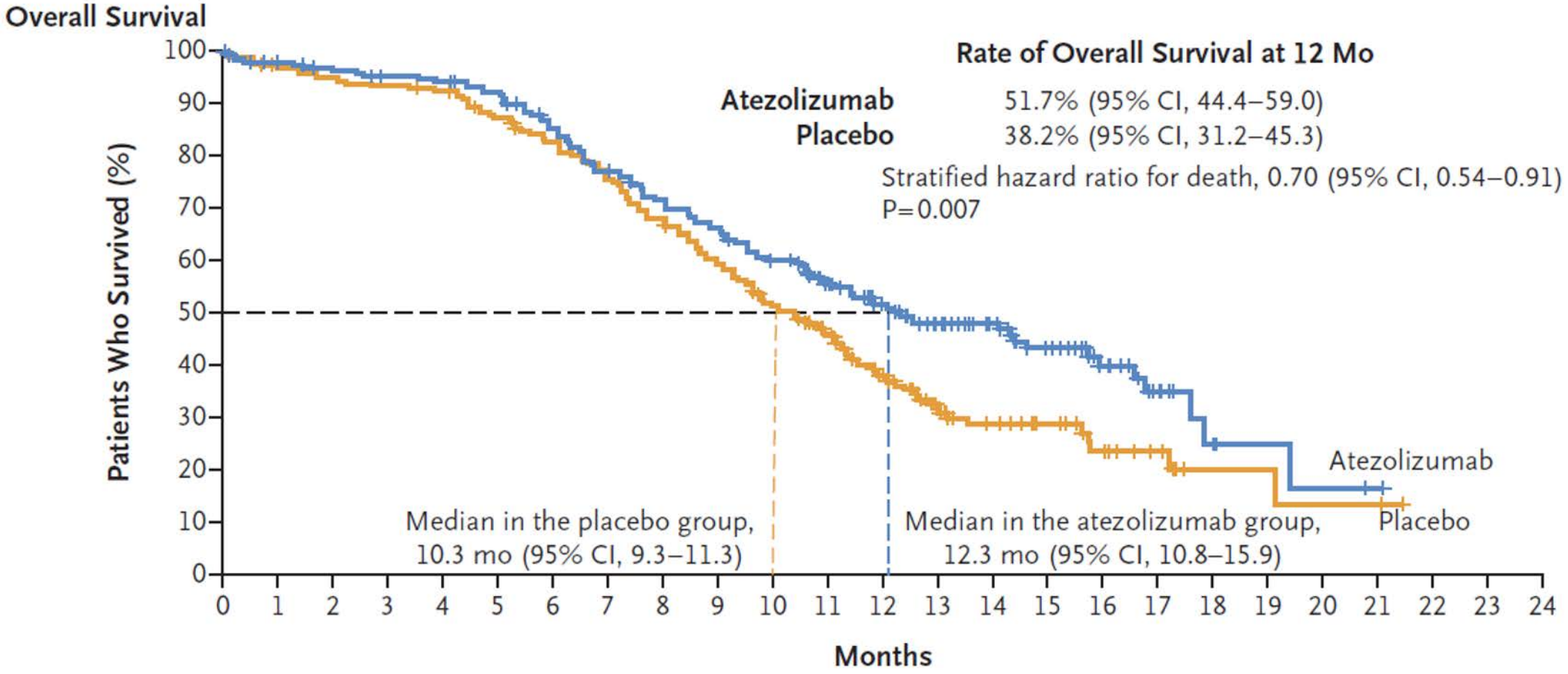
Courtesy of Suresh S Ramalingam, MD

IMMUNOTHERAPY IN FIRST-LINE THERAPY OF SCLC

EMORY
WINSHIP
CANCER
INSTITUTE
National Cancer Institute-Designated
Comprehensive Cancer Center

NCI
Designated
Comprehensive
Cancer Center

CARBOPLATIN-ETOPOSIDE +/- ATEZOLIZUMAB (IMPOWER 133 STUDY)
OVERALL SURVIVAL



Horn et al, N Engl J Med, 2018.

Courtesy of Suresh S Ramalingam, MD

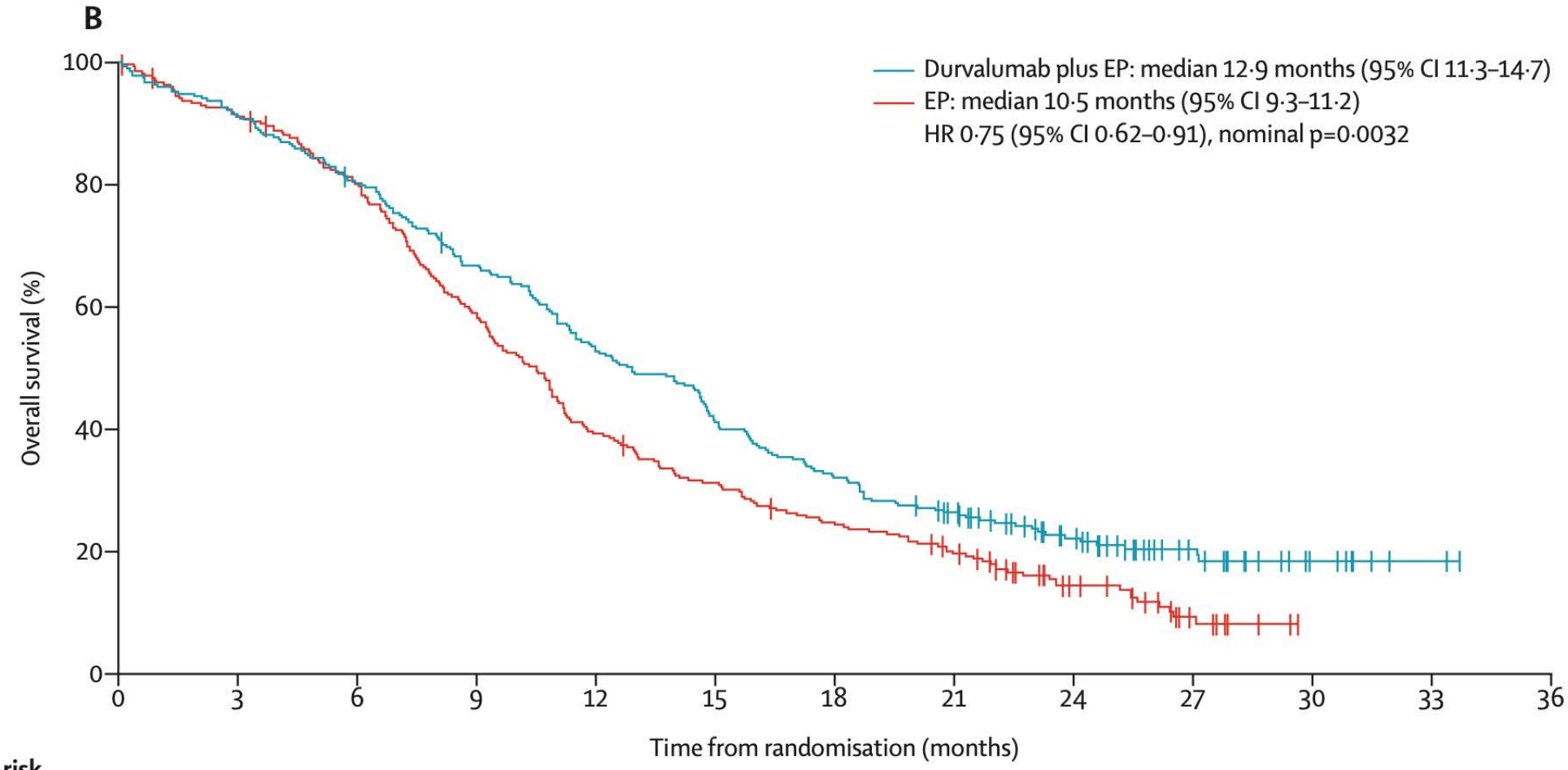
IMPOWER 133: UPDATED EFFICACY

Parameter	Chemo + Atezo	Chemo
Median OS	12.3 m (HR 0.76)	10. 3 m
18m- OS Rate	34%	21%
PD-L1 Expression		
<1% (n=72 pts)	10.2 m	8.3 m
< 5% (n=108 pts)	9.2 m	8.9 m
> 5% (n=29 pts)	21.6 m	9.2 m

Horn et al, AACR 2020.

Courtesy of Suresh S Ramalingam, MD

PLATINUM-ETOPOSIDE +/- DURVALUMAB (CASPIAN STUDY)
OVERALL SURVIVAL



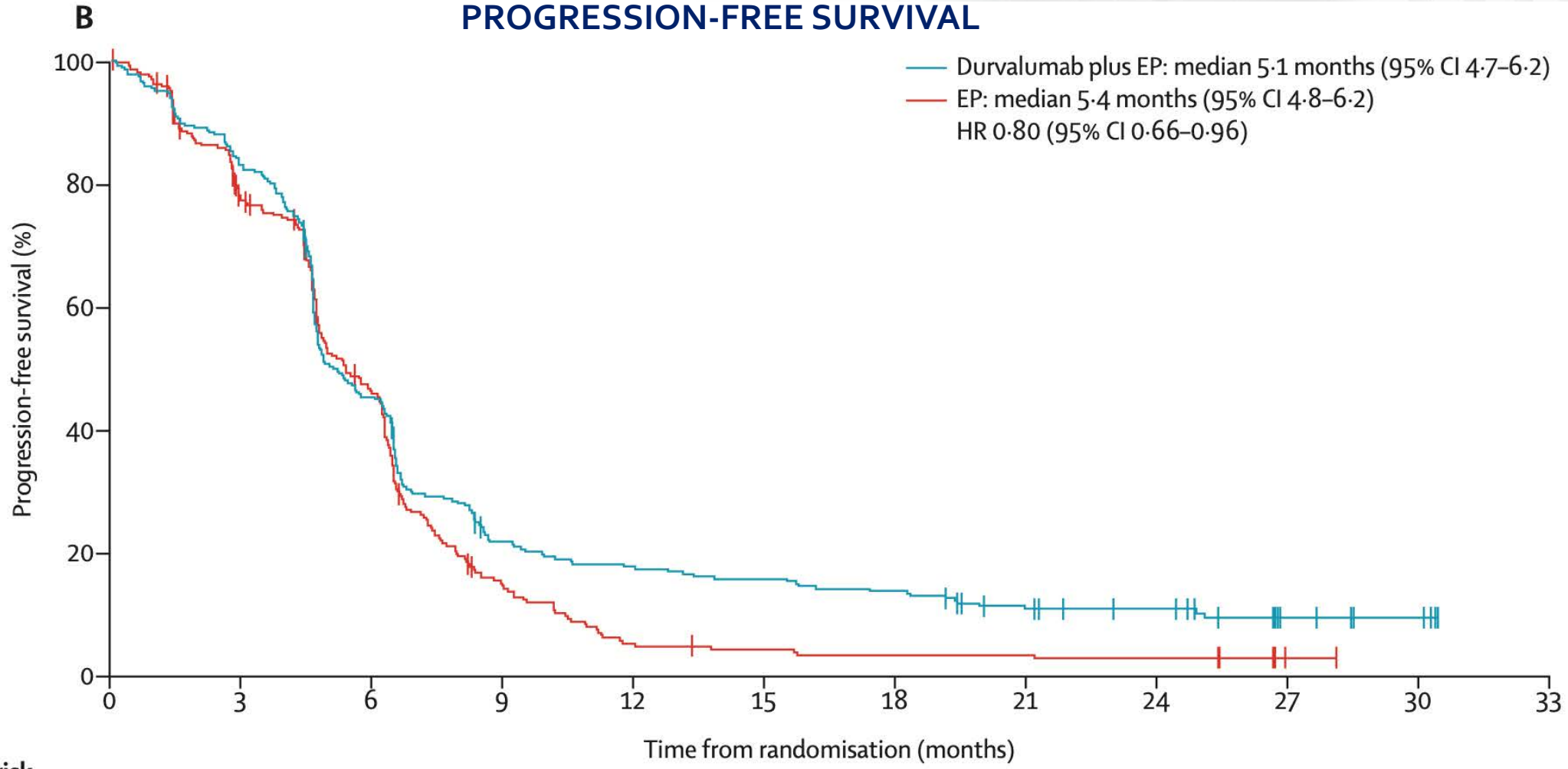
Number at risk (number censored)													
Durvalumab plus EP	268 (0)	244 (0)	214 (1)	177 (2)	140 (2)	109 (2)	85 (2)	66 (6)	41 (22)	21 (39)	8 (50)	2 (56)	0 (58)
EP	269 (0)	243 (2)	212 (4)	156 (4)	104 (4)	82 (5)	64 (6)	48 (9)	24 (22)	8 (31)	0 (38)	0 (38)	0 (38)

Goldman J et al, Lancet Oncol, 2020.

Courtesy of Suresh S Ramalingam, MD

PLATINUM-ETOPOSIDE +/- DURVALUMAB (CASPIAN STUDY)

PROGRESSION-FREE SURVIVAL



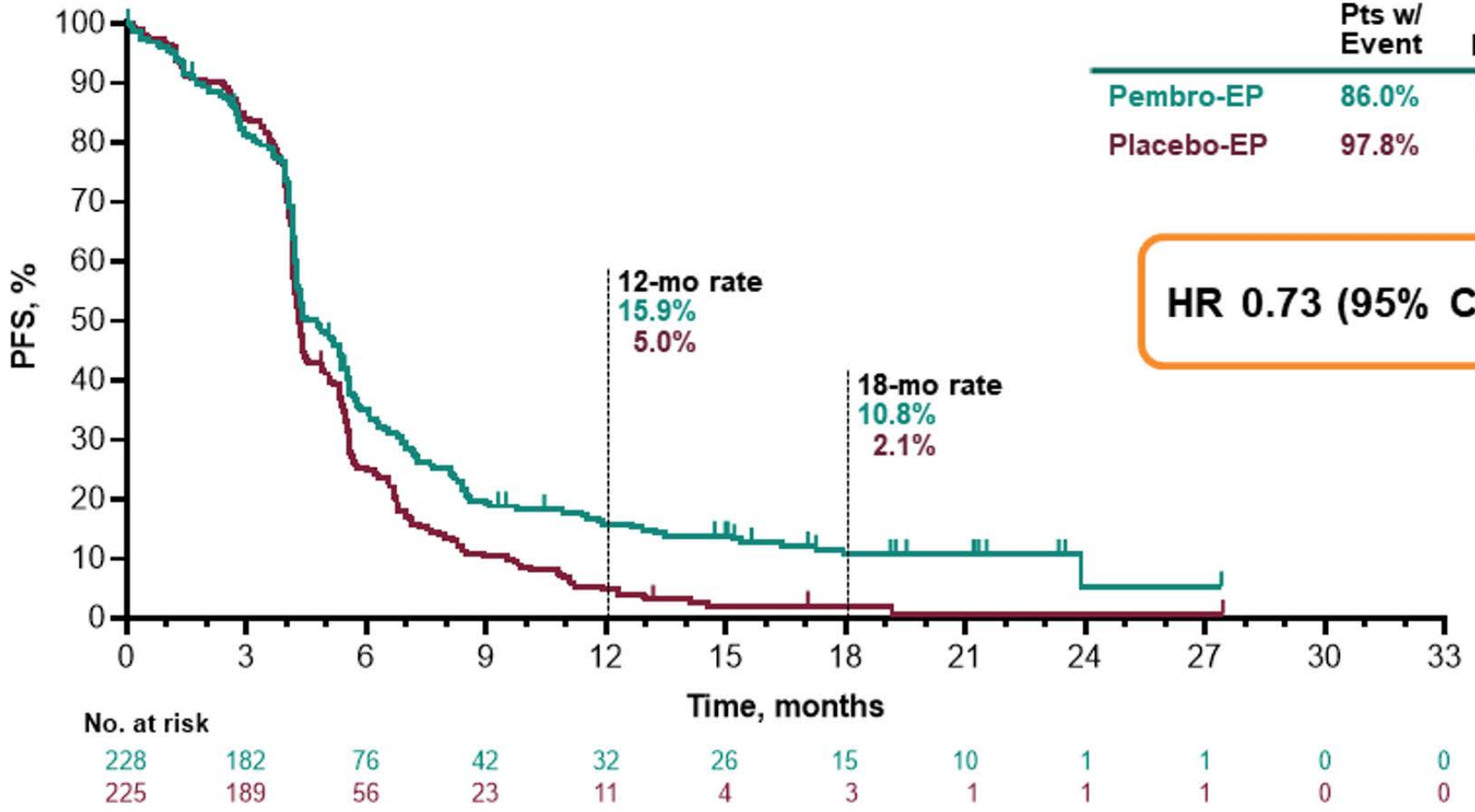
Number at risk (number censored)												
Durvalumab plus EP	268 (0)	220 (3)	119 (5)	55 (8)	45 (8)	40 (8)	35 (8)	24 (12)	18 (18)	8 (26)	5 (29)	0 (34)
EP	269 (0)	195 (15)	110 (23)	33 (26)	12 (26)	9 (27)	7 (27)	7 (27)	6 (27)	1 (32)	0 (33)	0 (33)

Goldman J et al, Lancet Oncol, 2020.

Courtesy of Suresh S Ramalingam, MD

PLATINUM-ETOPOSIDE +/- PEMBROLIZUMAB (KN 604 STUDY)

PROGRESSION-FREE SURVIVAL



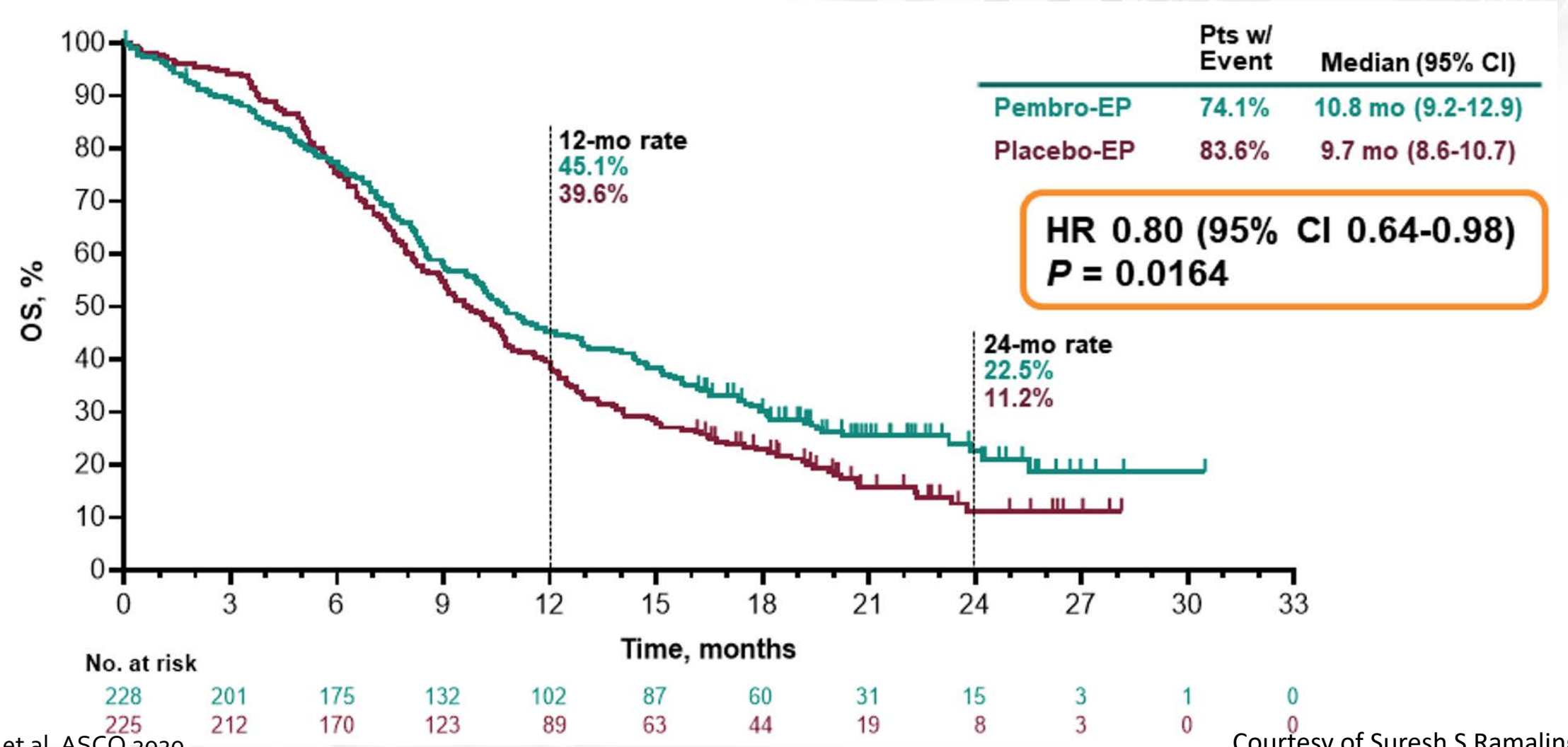
	Pts w/ Event	Median (95% CI)
Pembro-EP	86.0%	4.8 mo (4.3-5.4)
Placebo-EP	97.8%	4.3 mo (4.2-4.5)

HR 0.73 (95% CI 0.60-0.88)

Rudin C et al, ASCO 2020.

Courtesy of Suresh S Ramalingam, MD

PLATINUM-ETOPOSIDE +/- PEMBROLIZUMAB (KN 604 STUDY)
OVERALL SURVIVAL



Rudin C et al, ASCO 2020.

Courtesy of Suresh S Ramalingam, MD

Clinical Implications

- Immune checkpoint inhibition plus atezolizumab/durvalumab is the preferred first-line therapy for SCLC-ED
- Efficacy improvement is relatively modest, yet clinically meaningful
- Immunotherapy is continued as maintenance treatment after 4-6 cycles of chemotherapy
- No predictive value for PD-L1 expression
- No suggestion of higher risk of autoimmune adverse events in SCLC

Future directions

- Biomarkers to select patients remains an important priority
- Novel combination approaches based on chemo+IO strategy are being studied
- Role of IO agents in SCLC-LD is under investigation

Courtesy of Suresh S Ramalingam, MD

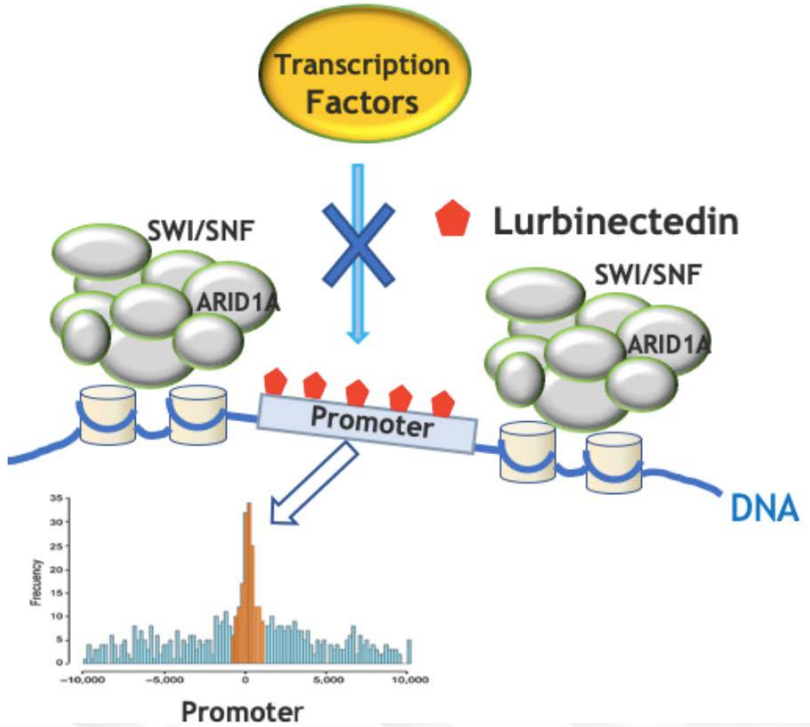
SALVAGE THERAPY FOR SMALL CELL LUNG CANCER

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

LURBINECTEDIN

- Synthetic derivative from a sea sponge
  - Inhibits gene expression
  - ? Other effects??



SCLC-ED

ECOG PS=0-2

No brain metastasis

Prior Chemotherapy

Lurbinectedin3.2 mg/m^2 Q 3 weeks

N=105 Pts

Primary endpoint: Response Rate

Courtesy of Suresh S Ramalingam, MD

LURBINECTEDIN: EFFICACY

	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)
mPFS	3.5 m	2.6 m	4.6 m
mOS:	9.3 m	5 m	11.9 m

Adverse events of interest:
Hematological: Anemia, neutropenia, thrombocytopenia
Non-hematological: Fatigue, nausea, vomiting, diarrhea, transaminitis

Trigo J et al, Lancet Oncol, 2020.

Courtesy of Suresh S Ramalingam, MD

Clinical implications

- Lurbinectedin is available for routine use in salvage therapy setting
- Efficacy is more favorable for patients with chemo-sensitive SCLC
- Adverse event profile includes marrow and GI toxicity

Future directions

- Confirmatory phase 3 trial (ATLANTIS) reported negative for OS- compared Lurbinectedin + Adriamycin to CAV
- Confirmation of efficacy of single agent lurbinectedin is warranted (comparison versus topotecan)

Courtesy of Suresh S Ramalingam, MD

MALIGNANT PLEURAL MESOTHELIOMA

EMORY
WINSHIP
CANCER
INSTITUTE
National Cancer Institute-Designated
Comprehensive Cancer Center

NCI
Designated
Comprehensive
Cancer Center

MALIGNANT PLEURAL MESOTHELIOMA

- Presents at an advanced stage in majority of the patients
- Multi-modality therapy is appropriate for selected subset of patients with early stage disease
- Cisplatin-pemetrexed is the standard systemic therapy
- No approved salvage therapy options
- Initial results with chemo + IO have yielded promising results

Courtesy of Suresh S Ramalingam, MD

IPILIMUMAB + NIVOLUMAB FOR PLEURAL MESOTHELIOMA (CM 743 STUDY)

Key Eligibility Criteria
- Unresectable pleural mesothelioma
- No prior systemic therapy
- ECOG performance status 0-1

Stratified by:
histology (epithelioid vs non-epithelioid) and gender

N = 605
R
1:1

n = 303
NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W (for up to 2 years)

n = 302
Cisplatin or carboplatin + pemetrexed Q3W[b] (6 cycles)

Until disease progression, unacceptable toxicity *or* for 2 years for immunotherapy arm

Primary Endpoint
- OS

Secondary Endpoints
- ORR, DCR, and PFS by BICR
- PD-L1[c] expression as a predictive biomarker

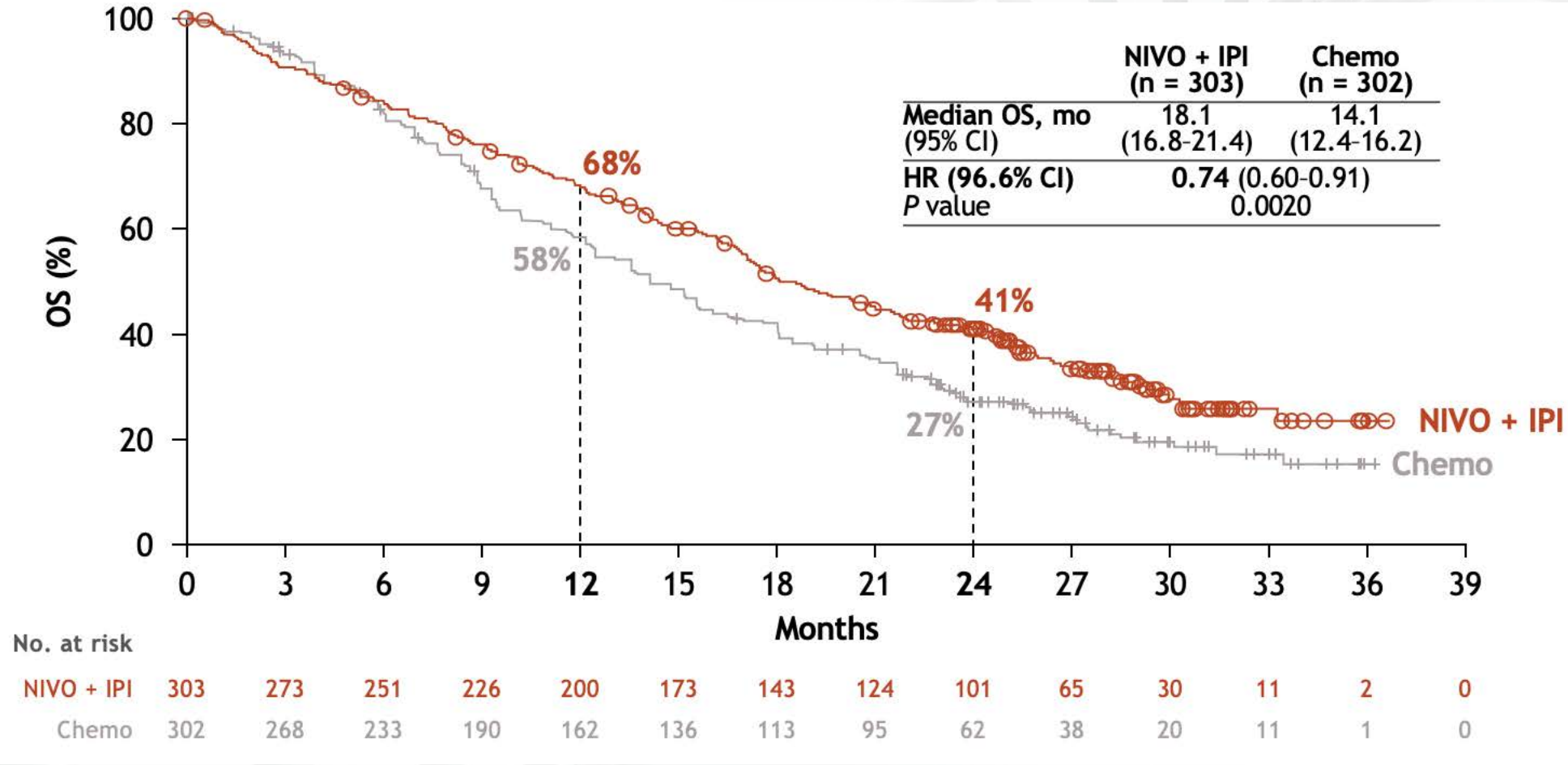
Database lock: April 3, 2020; minimum follow-up for OS: 22.1 months; median follow-up: 29.7 months.

[a]NCT02899299; [b]Cisplatin (75 mg/m^2) or carboplatin (AUC 5) + pemetrexed (500 mg/m^2), Q3W for 6 cycles; [c]Determined by PD-L1 IHC 28-8 pharmDx assay from Dako.

Baas P et al, IASLC 2020.

Courtesy of Suresh S Ramalingam, MD

CM743: OVERALL SURVIVAL

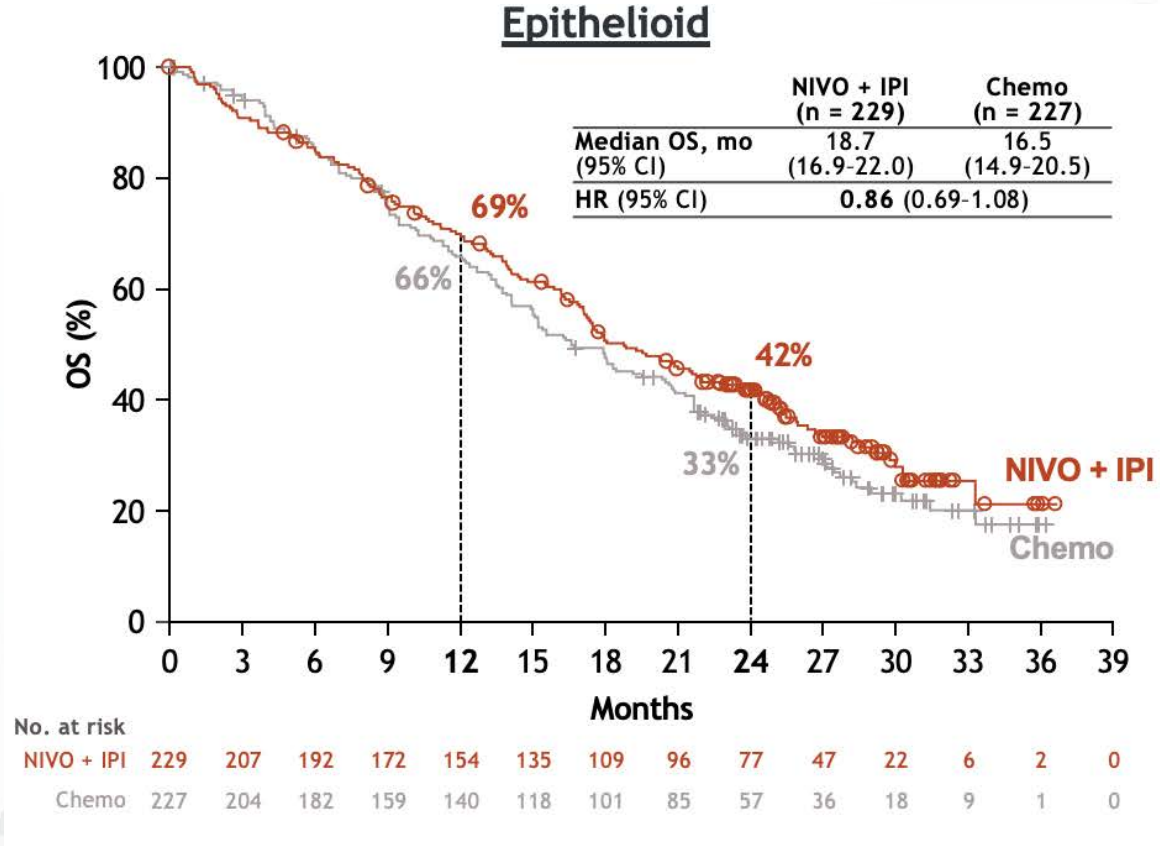


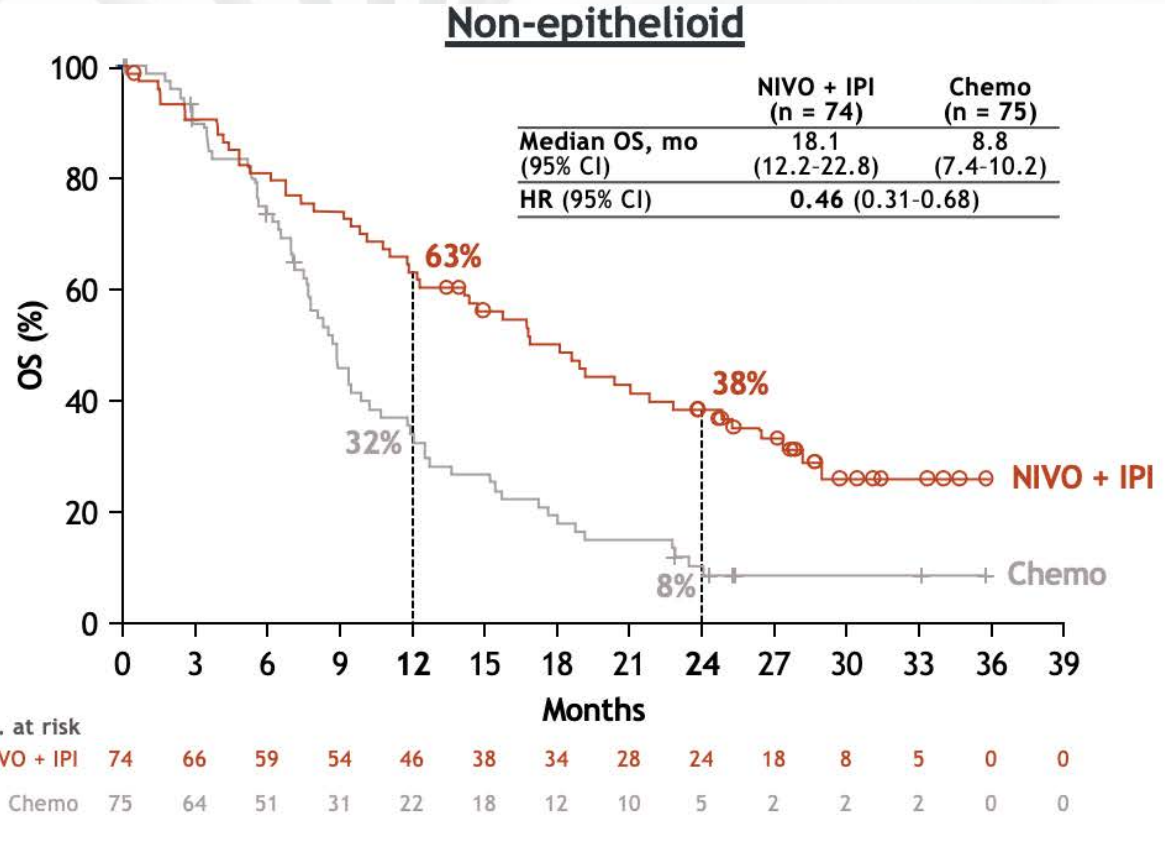
	NIVO + IPI (n = 303)	Chemo (n = 302)
Median OS, mo (95% CI)	18.1 (16.8-21.4)	14.1 (12.4-16.2)
HR (96.6% CI)	0.74 (0.60-0.91)	
P value	0.0020	

Baas P et al, IASLC 2020.

Courtesy of Suresh S Ramalingam, MD

CM743: SURVIVAL BASED ON HISTOLOGY

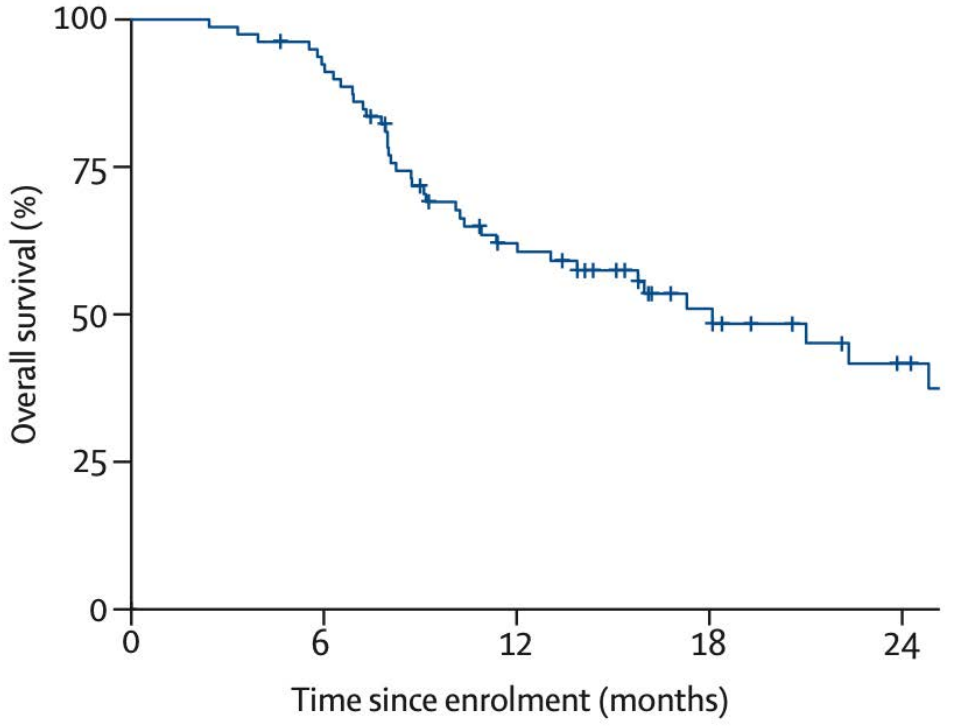


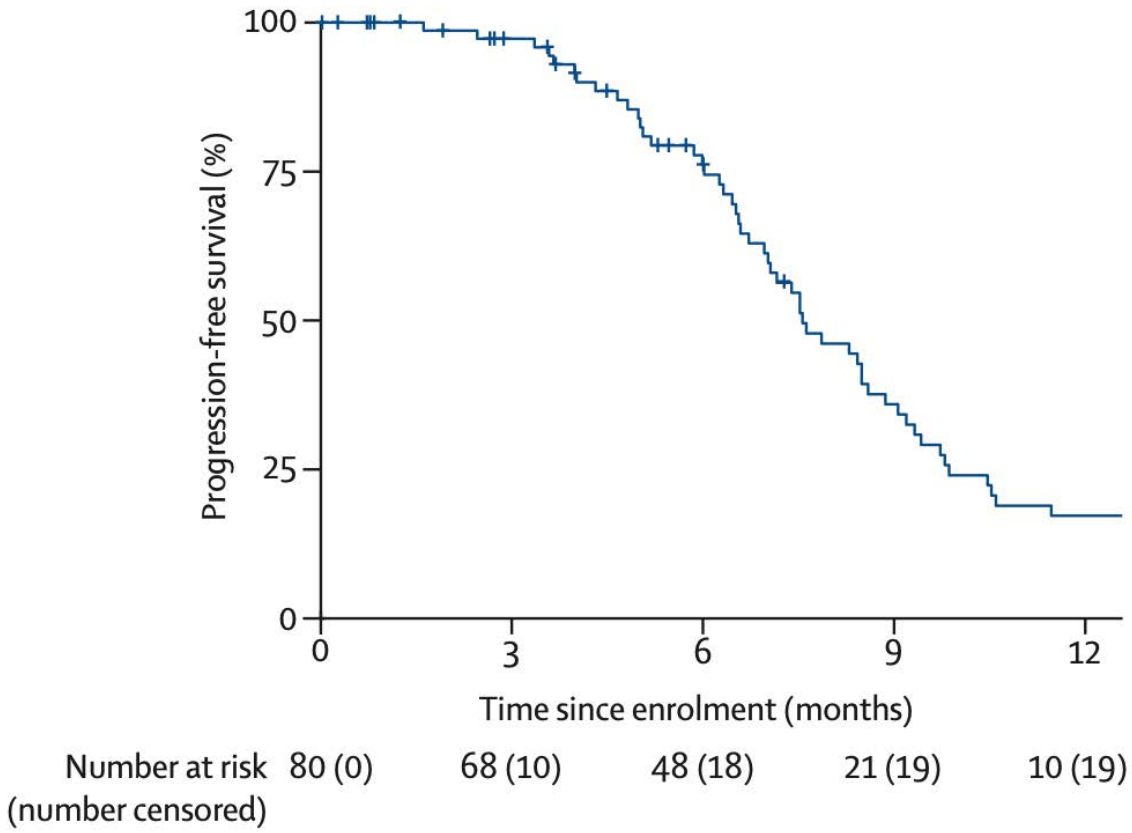


Baas P et al, IASLC 2020.

Courtesy of Suresh S Ramalingam, MD

CHEMOTHERAPY PLUS TUMOR-TREATING FIELDS (TTF) FOR MESOTHELIOMA





Adverse event of interest: skin toxicity grade 1-2: 66%; grade 3: 5%.

Ceresoli et al, Lancet Oncol, 2019.

Courtesy of Suresh S Ramalingam, MD

Clinical implications

- Ipilimumab plus nivolumab is an effective first line therapy option for mesothelioma
- Results are of even greater impact for patients with sarcomatoid histology
- Chemotherapy + TTF is another option for advanced mesothelioma patients

Future directions

- Chemotherapy +/- IO is being studied in randomized trials
- Need for effective salvage therapy options
- Biomarkers to individualize therapy remains an unmet need

Courtesy of Suresh S Ramalingam, MD

CONCLUSIONS

Small cell lung cancer

- Chemotherapy plus IO has emerged as standard first line therapy
- Atezolizumab and durvalumab are both approved by the FDA for 1st line use
- PD-L1 expression level is not a predictive biomarker in SCLC
- Lurbinectedin has promising results as salvage therapy for SCLC

Mesothelioma

- Ipilimumab plus nivolumab is now approved as first line therapy for advanced mesothelioma
- Chemotherapy plus TTF is another approved option based on phase 2 data
- Role of chemo plus IO is currently under investigation

Courtesy of Suresh S Ramalingam, MD