Immunotherapy of Extensive stage(ES) Small Cell Lung Cancer(SCLC)

순천향대학교 서울병원
호흡기 내과 김 기업
2021년 10월 23일

Introduction of Small Cell Lung Cancer(SCLC)

SCLC is characterized

1) rapid doubling time, high grow fraction, and early development of widespread metastasis.
2) highly sensitive to initial chemotherapy and radiotherapy; however, most patients eventually die to recurrent disease.
3) a deadly disease that represents about 15% of all lung cancer.
4) strongly associated with heavy tobacco exposure
5) incidence has been decreasing, male-to-female incidence ratio is now 1:1.
6) high mutation rates, universal *TP53* and *RB1* gene inactivation
7) 70% of cases present with extensive-stage disease at diagnosis (ED-SCLC)
8) The overall prognosis for patients with SCLC is poor, with a median overall survival (OS) of 15–20 months for LD-SCLC and 8–13 months for ED-SCLC.

Transl Lung Cancer. Res. 2016;5(1):26–38. Nature. 2015;524(7563):47–53. J Clin Oncol. 2015;33(34):4106–11.

Introduction of Small Cell Lung Cancer(SCLC)

SEER Cancer Statistics Review (CSR) 1975-2016

Table 15.7
Small Cell Cancer of the Lung and Bronchus (Invasive)

Age-adjusted SEER Incidence[a] Rates by Year, Race and Sex

	All Races			Whites			Blacks		
	Total	Males	Females	Total	Males	Females	Total	Males	Females
Year of Diagnosis:									
1975-2016	8.45	10.53	6.89	8.97	10.97	7.46	7.98	10.82	5.98
1975-1979	7.77	12.14	4.47	7.97	12.49	4.61	7.57	11.77	4.35
1980	9.11	14.20	5.25	9.34	14.40	5.56	9.99	17.53	4.38
1981	9.74	14.59	6.13	10.03	14.87	6.48	9.28	15.87	4.34
1982	10.44	15.00	7.17	10.81	15.36	7.62	9.69	16.08	4.92
1983	10.39	14.92	7.10	10.78	15.09	7.66	9.23	15.20	4.95
1984	10.71	15.24	7.41	11.07	15.71	7.76	10.41	14.99	6.86
1985	10.47	14.98	7.10	10.80	15.26	7.52	11.12	17.90	6.27
1986	11.22	15.57	7.98	11.57	16.05	8.27	12.26	17.70	8.35
1987	10.67	14.15	8.22	11.18	14.57	8.86	9.68	14.61	6.20
1988	11.38	15.28	8.53	11.91	15.62	9.23	10.49	17.86	5.30
2006	7.69	8.53	7.08	8.25	8.84	7.86	6.83	8.19	5.89
2007	7.68	8.60	7.02	8.33	8.96	7.92	7.10	9.40	5.44
2008	7.09	7.96	6.46	7.58	8.11	7.20	6.38	8.85	4.87
2009	7.13	7.78	6.69	7.60	8.10	7.27	7.51	8.36	6.94
2010	6.81	7.49	6.34	7.46	7.98	7.13	5.89	6.88	5.15
2011	6.27	6.85	5.86	6.77	7.09	6.57	5.28	6.44	4.49
2012	6.46	7.19	5.89	6.94	7.55	6.46	6.64	8.31	5.62
2013	6.35	7.13	5.79	6.89	7.49	6.48	5.45	6.77	4.66
2014	6.02	6.36	5.80	6.55	6.63	6.56	5.84	6.57	5.29
2015	5.92	6.25	5.70	6.41	6.54	6.38	5.77	6.28	5.38
2016	5.48	6.05	5.06	5.78	6.12	5.56	5.67	6.32	5.11

Introduction of Small Cell Lung Cancer(SCLC)

Continued Cigarette Smoking by Patients Receiving Concurrent Chemo-RT for LS-SCLC Is Associated With Decreased Survival

J Clin Oncol . 2003 Apr 15;21(8):1544-9. doi: 10.1200/JCO.2003.10.089.

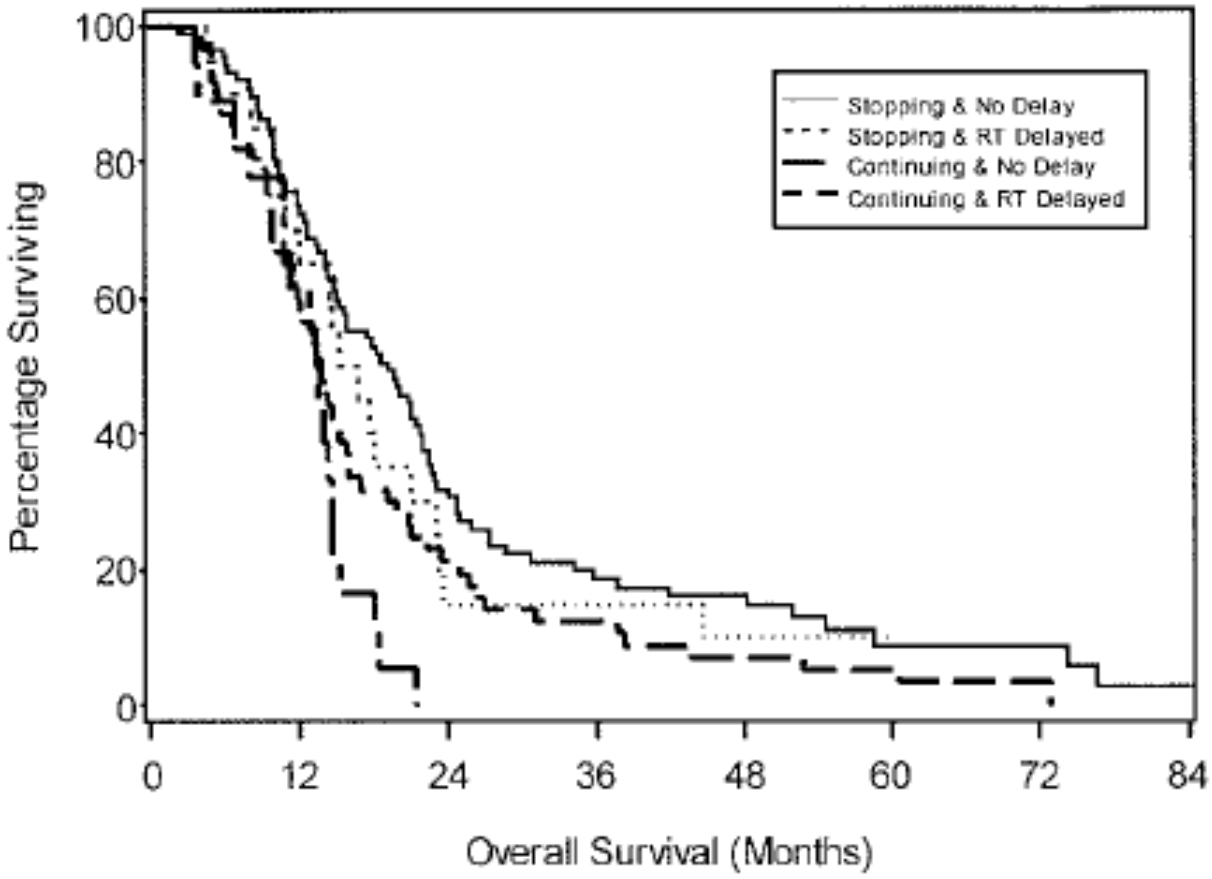


Fig 3. Actuarial overall survival according to smoking status and requirement for toxicity-related treatment breaks (delay) during chemoradiotherapy ($P = .0014$). RT, radiation therapy.

Introduction of Small Cell Lung Cancer(SCLC)

Characteristics and outcomes of SCLC patients diagnosed during two lung cancer CT screening programs in heavy smokers

J Thorac Oncol . 2011 Apr;6(4):818-22. doi: 10.1097/JTO.0b013e31820c2f2e.

TABLE 4. Summary of SCLC Cases Detected During CT Screening Studies With >500 Patients in CT Screening Arm

Study	Study Period	Screening Reported	Number Screened	Age (yr)	Pack-Year History	SCLC Cases Detected
Nawa et al.[9]	1998–2000	Baseline and first annual	7956	≥50	No limitation	0
Sobue et al.[10]	1993–1998	5 yr	1611	40–79	No limitation	1 incidence
Pastorino et al.[11]	2000–2001	Baseline and first annual	1035	≥50	≥20	0
Diederich et al.[7]	1995–1999	5 yr	817	≥40	≥20	1 prevalence, 2 interim
Bastarrika et al.[12]	2000 onward	Baseline and first annual	911	≥40	≥10	1 prevalence
Chong et al.[13]	1999–2003	5 yr	6406	≥45	≥20 high risk, <20 low risk	2 prevalence
Gohagan et al.[14]	2000 onward	Baseline and first annual	1660[a]	55–74	≥30	4 NOS (CT arm)
Swensen et al.[2]	1999–2003	5 yr	1520	≥50	≥20	2 prevalence, 6 incidence/interim
Henschke et al.[15]	1993–2005	Baseline and unspecified annual	31,567	≥40	No limitation	9 prevalence, 7 incidence
Sone et al.[4]	1996–1998	2 yr	5480	40–74	No limitation	1 interim, 4 incidence
Infante et al.[16]	2001–2006	Baseline	1276[a]	60–74	≥20	2 prevalence
Veronesi et al.[17]	2004–2006	Baseline and first annual	5202	≥50	≥20	4 prevalence, 2 incidence
Menezes et al.[1]	2003–2010	5 yr[b]	4782[b]	≥50	≥10	4 prevalence, 2 incidence, 1 interim[b]

[a] Number of patients randomised to CT arm of study and undergoing baseline screening CT thorax.
[b] Updated figures from principal investigator.
SCLC, small cell lung cancer; CT, computed tomography; NOS, not otherwise specified.

Computed tomography screening is ineffective for SCLC. Efforts to reduce mortality of SCLC should instead focus on prevention through **tobacco reduction programs, as well as the development of improved treatment options.**

Pathology of Small Cell Lung Cancer(SCLC)

NCCN Guidelines Version 1.2022 Small Cell Lung Cancer

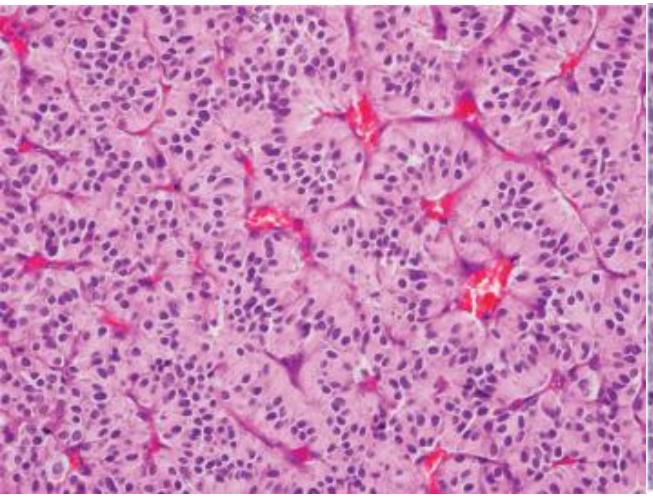


Figure. 1. Typical carcinoid. This tumor shows an organoid nesting pattern with a prominent vascular stroma. The tumor cells are uniform with a moderate amount of eosinophilic cytoplasm and finely granular nuclear chromatin. No necrosis or mitoses are seen.

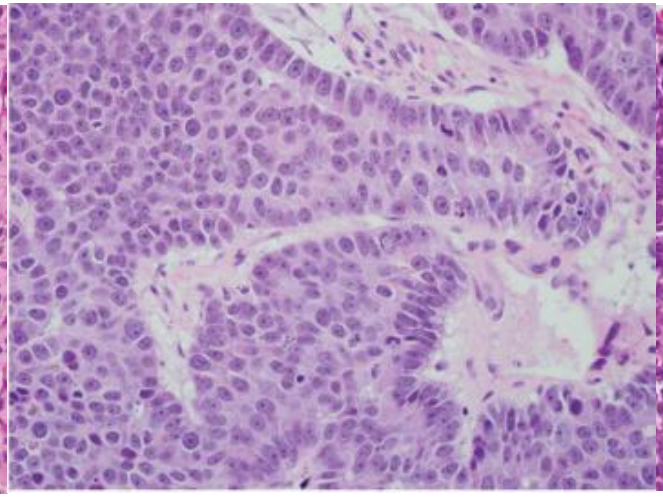


Figure. 3. Large-cell neuroendocrine carcinoma. (A) The tumor grows in sheets with prominent peripheral palisading and vague rosette-like structures. Several mitoses are seen. The tumor cells have abundant cytoplasm, prominent nucleoli.

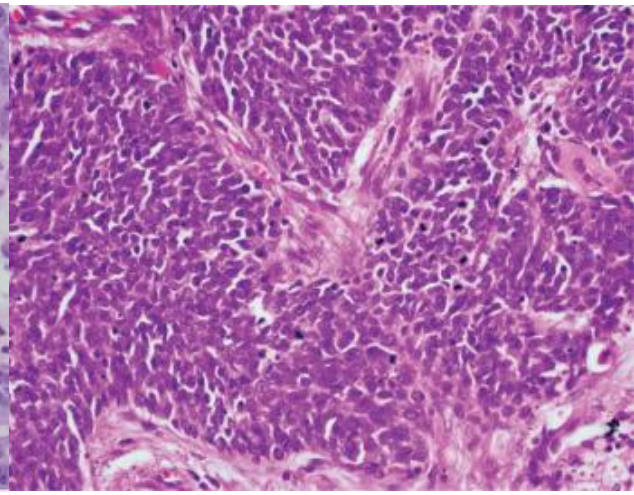


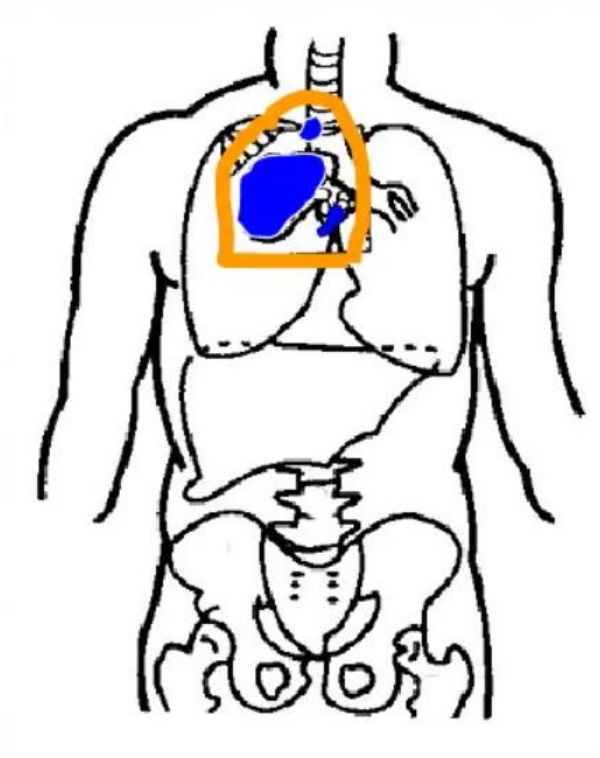
Figure. 4. Small-cell carcinoma. This tumor consists of dense sheets of small cells with scant cytoplasm, finely granular nuclear chromatin, frequent mitoses; nucleoli are inconspicuous or absent.

The role of Ki-67 is mainly to separate the high-grade SCLC and LCNEC from the carcinoid tumors, especially in small biopsies with crushed and/or necrotic tumor cells

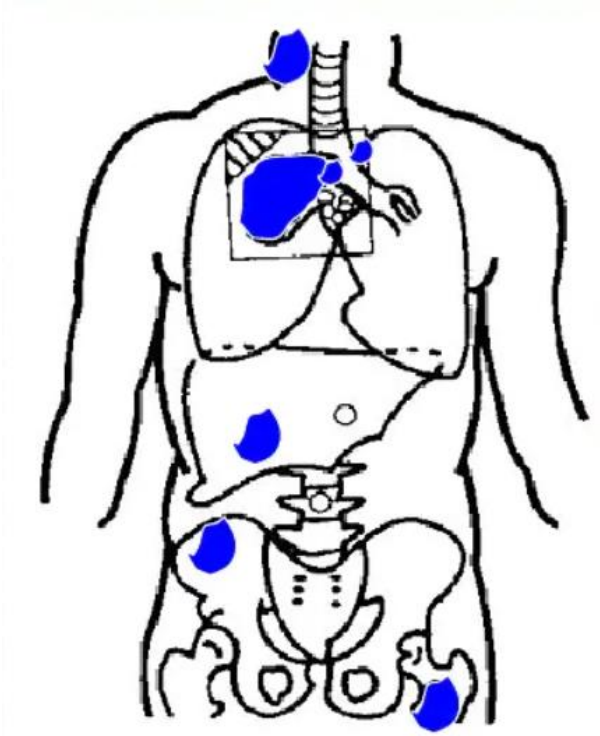
Staging of Small Cell Lung Cancer

NCCN Guidelines Version 1.2022 Small Cell Lung Cancer

The Veterans Administration Lung Study Group (VALSG) 2-stage classification
Keynote address on biostatistics and data retrieval. Cancer Chemother Rep (Part 3) 1973;4:31–42.



Limited-stage



Extensive-stage

Staging of Small Cell Lung Cancer

Modern staging of small cell lung cancer

J Natl Compr Canc Netw. 2013 Jan 1;11(1):99-104. doi: 10.6004/jnccn.2013.0012.

PET in SCLC

Table 1 PET for Initial Staging of Small Cell Lung Cancer

Trial	N	Stage Concordance	LS n	LS Upstaged (LS→ES)	ES n	ES Downstaged (ES→LS)
Prospective						
Chin et al.[18]	18	83%	9	22%	9	11%
Bradley et al.[20]	24	88%	24	8%	_	_
Brink et al.[21]	120	88%	51	20%	69	4%
Kut et al.[23]	18	100%	6	0	12	0
Fischer et al.[24]	29	83%	9	33%	20	5%
Subtotal	**209**	**89%**	**99**	**17%**	**110**	**5%**
Retrospective						
Hauber et al.[15]	7	100%	6	0	1	0
Schumacher et al.[16]	26	73%	13	54%	13	0
Shen et al.[17]	25	92%	10	10%	15	7%
Kamel et al.[19]	24	83%	17	18%	7	14%
Blum et al.[22]	15	67%	15	33%	–	–
Niho et al.[25]	63	92%	63	8%	–	–
Vinjamuri et al.[26]	51	82%	18	6%	33	18%
Azad et al.[27]	46	74%	26	15%	20	40%
Arslan et al.[28]	12	50%	7	71%	5	20%
Subtotal	**269**	**81%**	**175**	**18%**	**94**	**18%**
Total	**478**	**84%**	**274**	**18%**	**204**	**11%**

Abbreviations: ES, extensive stage; LS, limited stage.

Table 2 Change in Initial Management Based on PET Findings

Trial	N	Change in Management	Change in RT Field (n=190)	Change in Treatment (n=130)
Prospective				
Bradley et al.[20]	24	33%	29%	4%
Kut et al.[23]	21	0	NR	0
von Loon et al.[30]	60	30%	30%	NR
Retrospective				
Kamel et al.[19]	24	37%	21%	17%
Blum et al.[22]	15	47%	13%	33%
Azad et al.[27]	46	26%	7%	20%
von Loon et al.[29]	21	24%	24%	NR
Total	**211**	**28%**	**21%**	**15%**

Abbreviations: NR, not reported; RT, radiotherapy.

As therapy improves over time, the finer parsing of disease extent provided by **TNM** staging will hopefully allow practitioners to better define more specific and appropriate individualized treatments for patients with SCLC.

Staging of Small Cell Lung Cancer

NCCN Guidelines Version 1.2022 Small Cell Lung Cancer

Table 2 **- American Joint Committee on Cancer (AJCC) Eighth ed., 2017 Definitions of TNM**

Table 3. **AJCC Prognostic Groups**

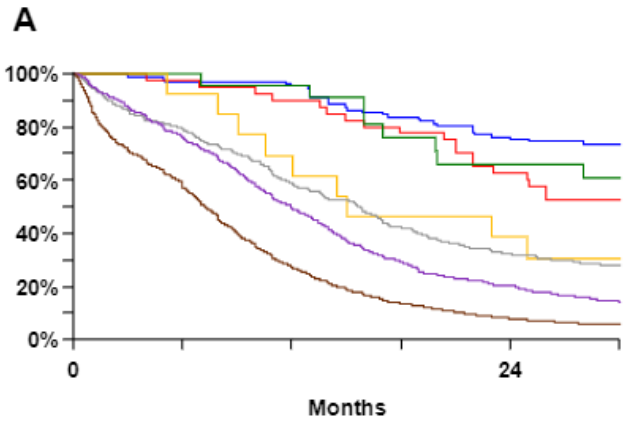
	T	N	M
Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA1	T1mi	N0	M0
	T1a	N0	M0
Stage IA2	T1b	N0	M0
Stage IA3	T1c	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	T1a	N1	M0
	T1b	N1	M0
	T1c	N1	M0
	T2a	N1	M0
	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T1c	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0

Prognostic Stage Groups

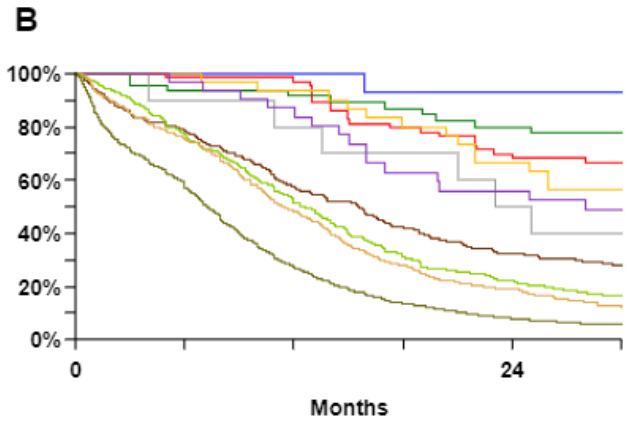
	T	N	M
Stage IIIB	T1a	N3	M0
	T1b	N3	M0
	T1c	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N2	M0
	T4	N2	M0
Stage IIIC	T3	N3	M0
	T4	N3	M0
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a
	Any T	Any N	M1b
Stage IVB	Any T	Any N	M1c

Staging of Small Cell Lung Cancer

The IASLC Lung Cancer Staging Project: Proposals for the Revision of the Clinical and Pathologic Staging of Small Cell Lung Cancer in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer J Thorac Oncol. 2016 Mar;11(3):300-11. doi: 10.1016/j.jtho.2015.10.008. Epub 2015 Dec 24.



cTNM 7th Ed.	Events / N	MST	12 Month	24 Month
IA	45 / 129	NR	95%	75%
IB	22 / 42	32.4	90%	63%
IIA	10 / 28	41.0	96%	66%
IIB	10 / 14	15.0	69%	38%
IIIA	203 / 270	15.7	59%	32%
IIIB	641 / 782	12.0	49%	20%
IV	2620 / 2926	7.3	27%	8%



cTNM Proposed	Events / N	MST	12 Month	24 Month
IA1	3 / 14	NR	100%	93%
IA2	27 / 67	NR	97%	68%
IA3	15 / 48	NR	91%	80%
IB	16 / 32	33.0	93%	67%
IIA	6 / 10	24.1	80%	50%
IIB	17 / 38	28.0	87%	56%
IIIA	191 / 254	15.6	58%	32%
IIIB	326 / 402	12.6	52%	22%
IIIC	330 / 400	11.4	48%	19%
IV	2620 / 2926	7.3	27%	8%

Figure 5. Survival according to (*A*) seventh edition clinical TNM stages and (*B*) proposed eighth edition clinical TNM stages in cases where tumor descriptor data were sufficient to classify according to the proposed eighth edition. ed., edition; N, number of cases; MST, median survival time.

TNM staging allow for more precise assessments of prognosis and specific therapy in the future.

Response assessment of Small Cell Lung Cancer

Primary or Adjuvant Systemic Therapy

Limited stage:

1) Adjuvant chemotherapy or chemotherapy with concurrent RT
   chest and abdomen CT with contrast should occur only after completion of therapy
2) Systemic therapy alone or sequential systemic therapy followed RT
   using CT should occur after every 2 cycles of systemic therapy and again at completion of therapy

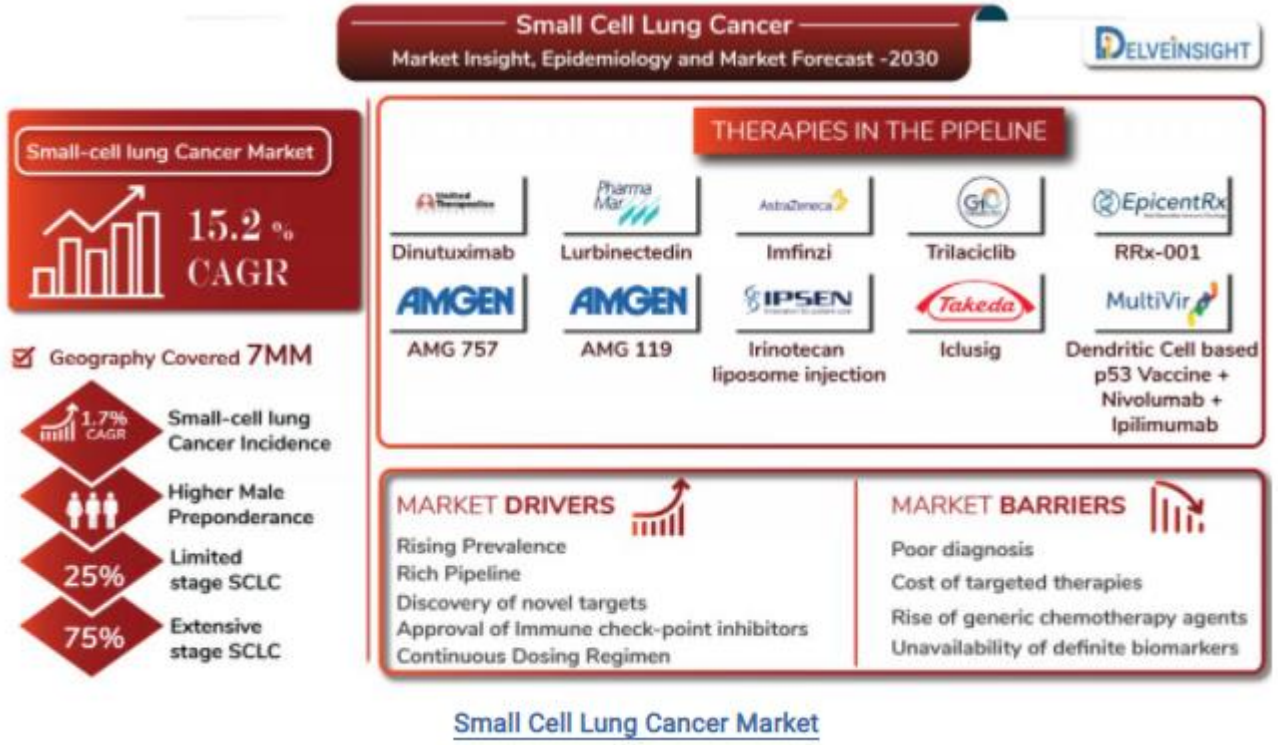
Extensive stage:

Response assessment using CT with contrast should occur after every 2-3 cycles of systemic therapy and again at the completion of therapy.

Serial brain imaging who have asymptomatic brain metastasis and are receiving systemic therapy before whole brain RT

Brain MRI or CT with contrast is recommended after every 2 cycles of systemic therapy and again at completion of therapy.

Treatment of Small Cell Lung Cancer



Small Cell Lung Cancer Market

Treatment of Small Cell Lung Cancer

VP-16 and cisplatin as first-line therapy for SCLC

J Clin Oncol. 1985 Nov;3(11):1471-7. doi: 10.1200/JCO.1985.3.11.1471.

Table 1. Clinical Features of 31 Patients Treated with VP-16/Cisplatin as First-Line Therapy

	Extent of Disease		
Features	LD	ED	Total
Number of patients	11	20	31
Median age (yr)	64	59	61
range	(53–75)	(29–77)	(29–77)
M:F ratio	8:3	16:4	24:7
Performance status (ECOG)			
0	0	2	2
1	6	7	13
2	5	9	14
3	0	2	2

Table 3. Response to VP-16/Cisplatin by Disease Extent

	No. of Patients	Response		
Extent	Evaluable	CR	PR	NR/PD
Limited	11	7	2	2
Extensive	17	5	10	2
Total	28	12	12	4

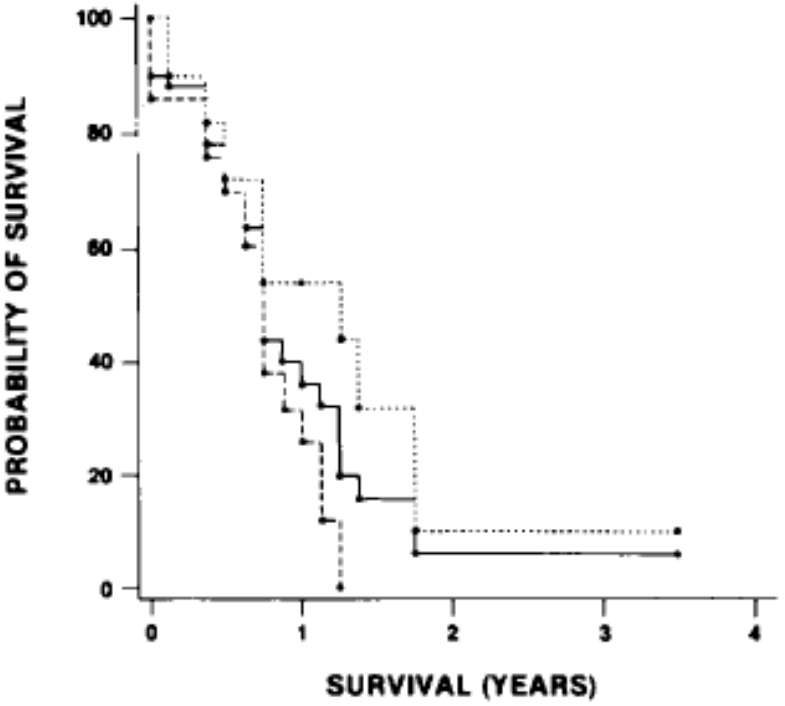


Fig 1. Survival curves for patients treated with VP-16 and cisplatin from date of first treatment. Limited disease, ------; extensive disease, ——; whole group, ——.

Treatment of Small Cell Lung Cancer

A meta-analysis of thoracic radiotherapy for SCLC

N Engl J Med. 1992 Dec 3;327(23):1618-24. doi: 10.1056/NEJM199212033272302.

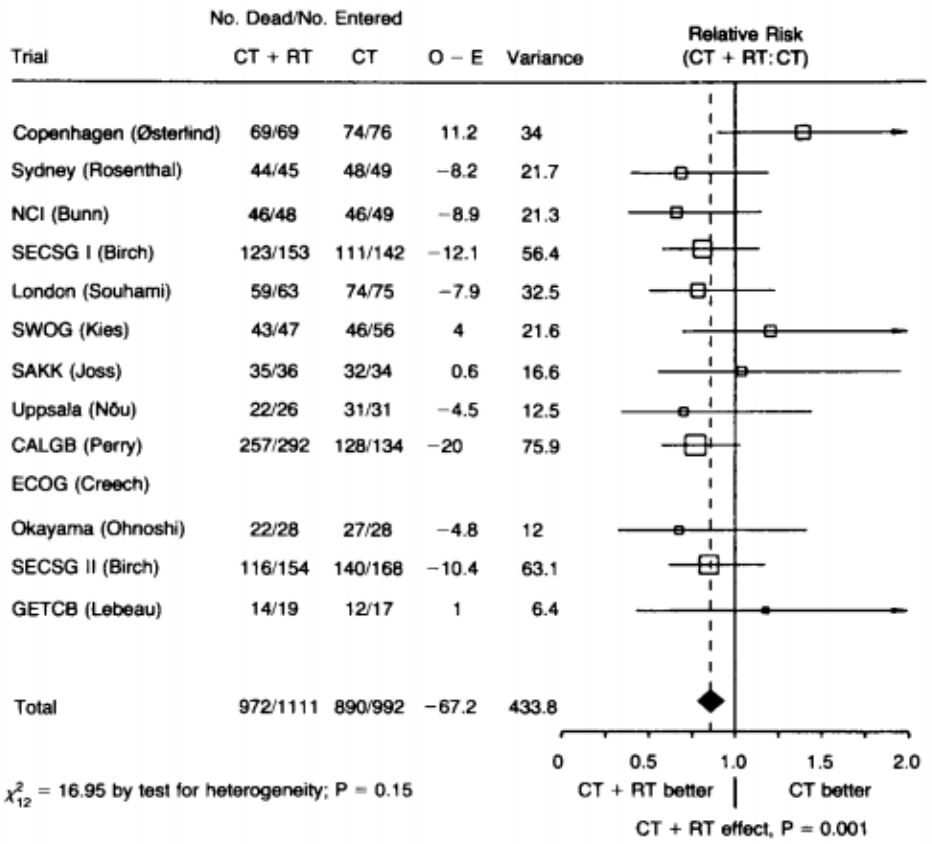


Figure 1. Relative Risk of Death among Patients Receiving Both Chemotherapy and Radiotherapy (CT + RT) as Compared with Patients Receiving Chemotherapy Alone (CT).

Only confined to limited stage

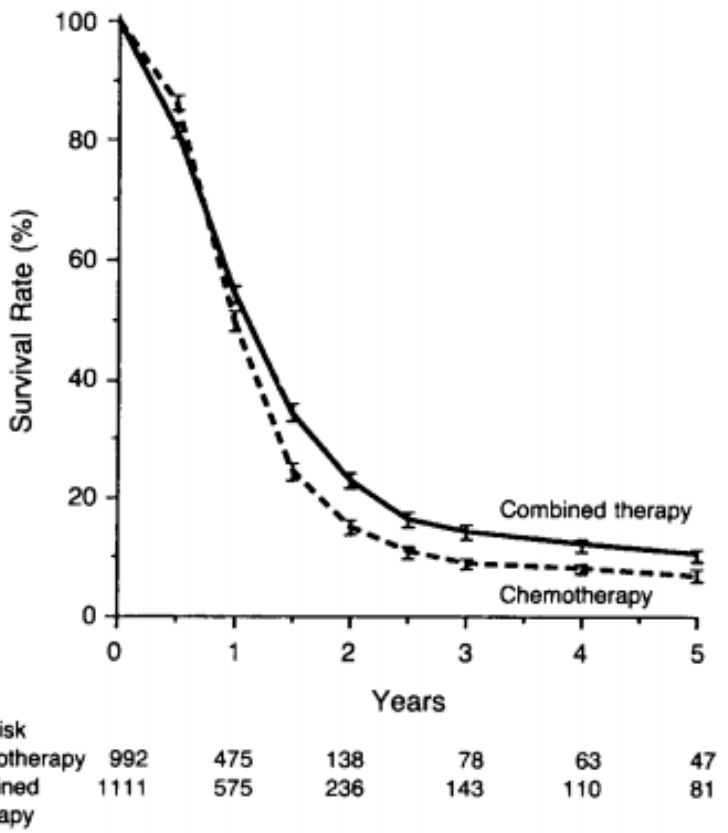


Figure 2. Survival Curves for the Combined-Therapy Group and the Chemotherapy Group.

The three-year survival rates were 14.3±1.1 percent in the combined-therapy group and 8.9±0.9 percent in the chemotherapy group (for a difference of 5.4±1.4 percent; P = 0.001 by stratified log-rank test). Each I bar denotes the standard deviation.

Treatment of Small Cell Lung Cancer

Randomized study of CAV versus EP versus alternation of these two regimens in ES-SCLC: a phase III trial of the Southeastern Cancer Study Group

J Clin Oncol. 1992 Feb;10(2):282-91. doi: 10.1200/JCO.1992.10.2.282.

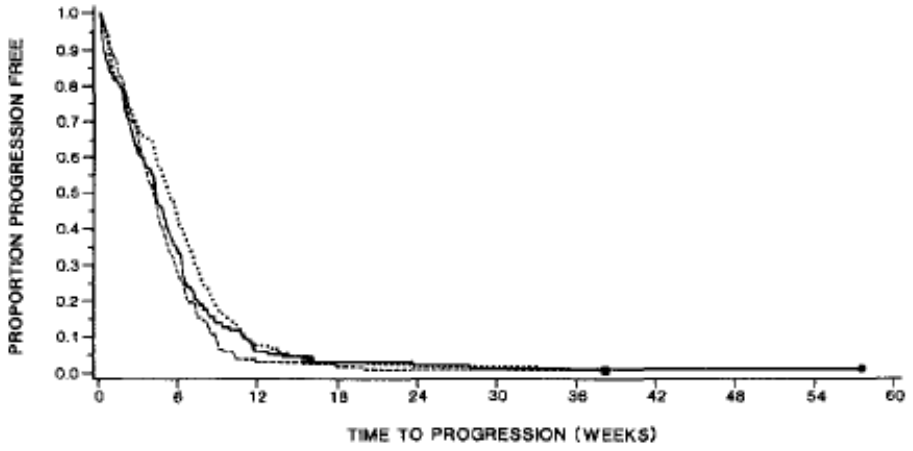


Fig 1. Progression-free survival in 418 assessable patients treated with EP (—), CAV (---), or CAV/EP (·····). The median TTP for EP-treated patients was 4.3 months (95% CI, 3.4 to 5.1); for CAV-treated patients, 4.0 months (95% CI, 3.4 to 4.6); and for alternating therapy-treated patients, 5.2 months (95% CI, 4.4 to 6.0). Log-rank $P = .052$, Wilcoxon $P = .059$.

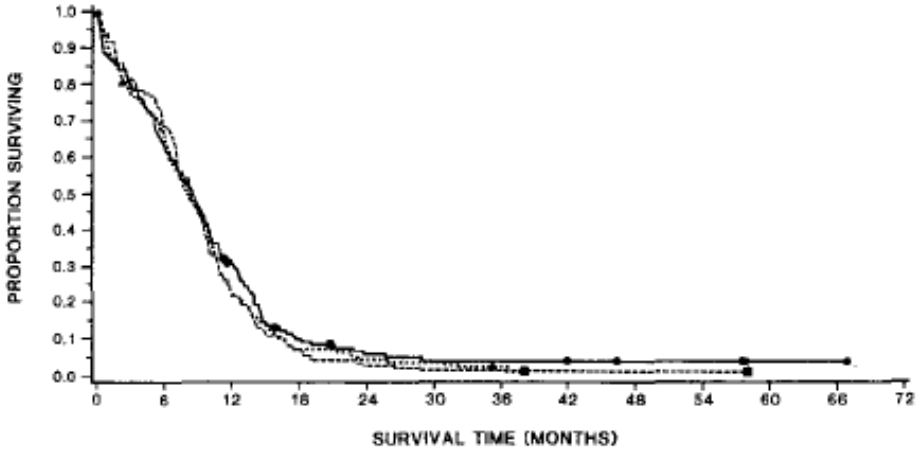


Fig 2. Overall survival in 437 eligible patients treated with EP (—), CAV (---), or CAV/EP (·····). The median survival for EP-treated patients was 8.6 months (95% CI, 7.0 to 9.7; range, 0.1 to 66.9+ months); for CAV-treated patients, 8.3 months (95% CI, 0.3 to 9.4; range, 0.1 to 58+ months); and for alternating therapy-treated patients, 8.1 months (95% CI, 6.8 to 9.4; range, 0.1 to 38+ months). These differences did not achieve statistical significance, with $P = .425$ (log-rank, stratified), or $P = .727$ (Wilcoxon, stratified).

Treatment of Small Cell Lung Cancer

Randomized phase III trial comparing irinotecan/cisplatin with EP in patients with previously untreated ES-SCLC

J Clin Oncol. 2006 May 1;24(13):2038-43. doi: 10.1200/JCO.2005.04.8595.

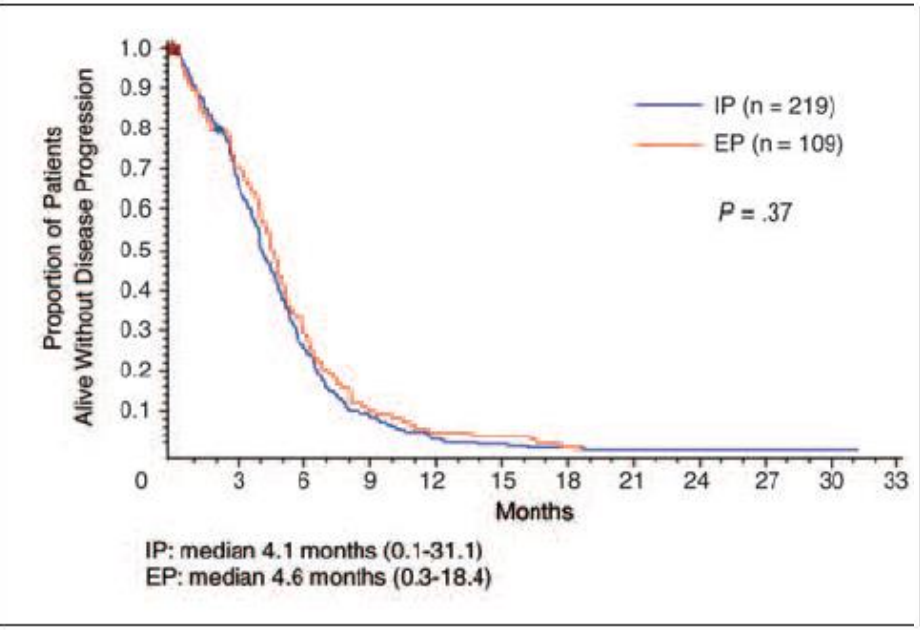


Fig 1. Time to disease progression. IP, irinotecan/cisplatin; EP, etoposide/cispl

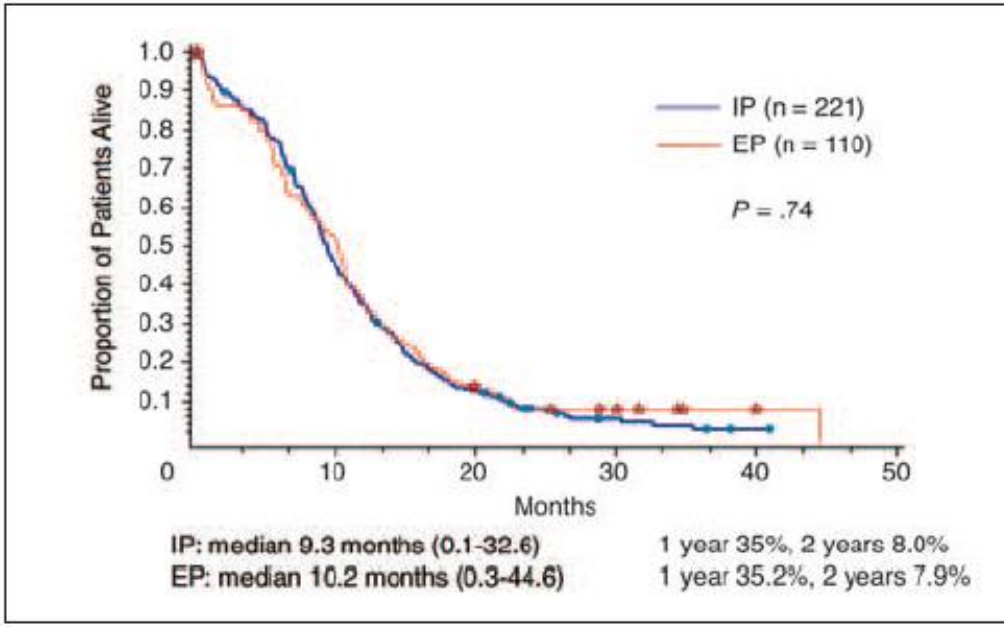


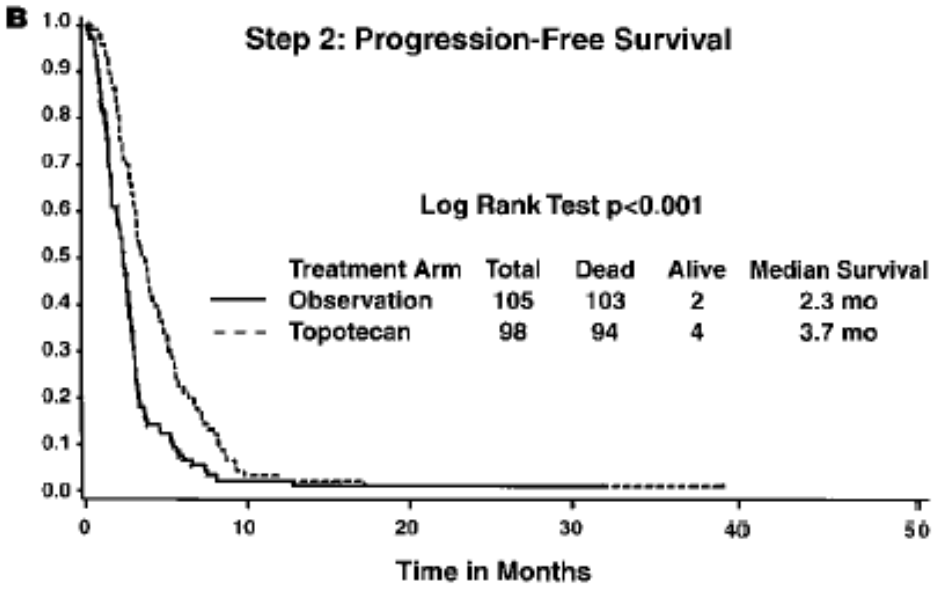
Fig 2. Overall survival. IP, irinotecan/cisplatin; EP, etoposide/cisplatin.

Treatment with this dose and schedule of IP did not result in improved survival when compared with EP.

Treatment of Small Cell Lung Cancer

Topotecan versus observation after EP in ES-SCLC: E7593--a phase III trial of the ECOG
J Clin Oncol. 2001 Apr 15;19(8):2114-22. doi: 10.1200/JCO.2001.19.8.2114.

The use of maintenance or consolidation chemotherapy



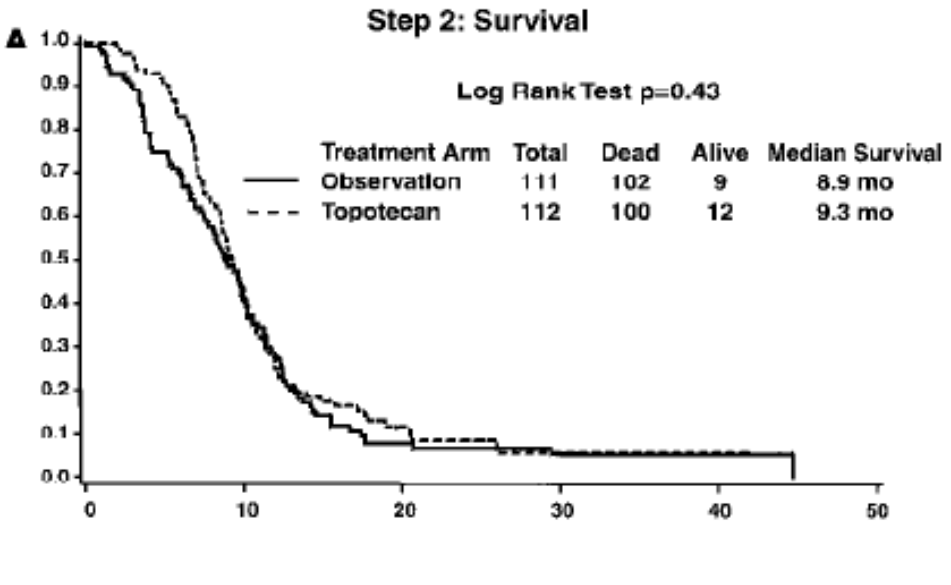


Fig 3. Overall survival (A) and PFS (B) of eligible patients randomized on step 2 (observation vs topotecan). Data were calculated from date of randomization of step

Treatment of Small Cell Lung Cancer

Duration of Chemotherapy for Small Cell Lung Cancer: A Meta-Analysis

PLoS One. 2013 Aug 30;8(8):e73805. doi: 10.1371/journal.pone.0073805.

The use of maintenance or consolidation chemotherapy

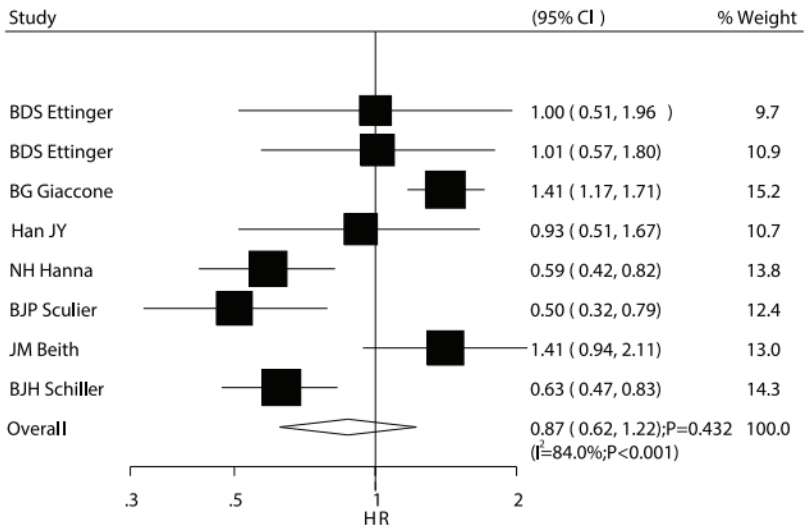


Figure 5. Comparison of progression-free survival (PFS) between maintenance chemotherapy and observation.
doi:10.1371/journal.pone.0073805.g005

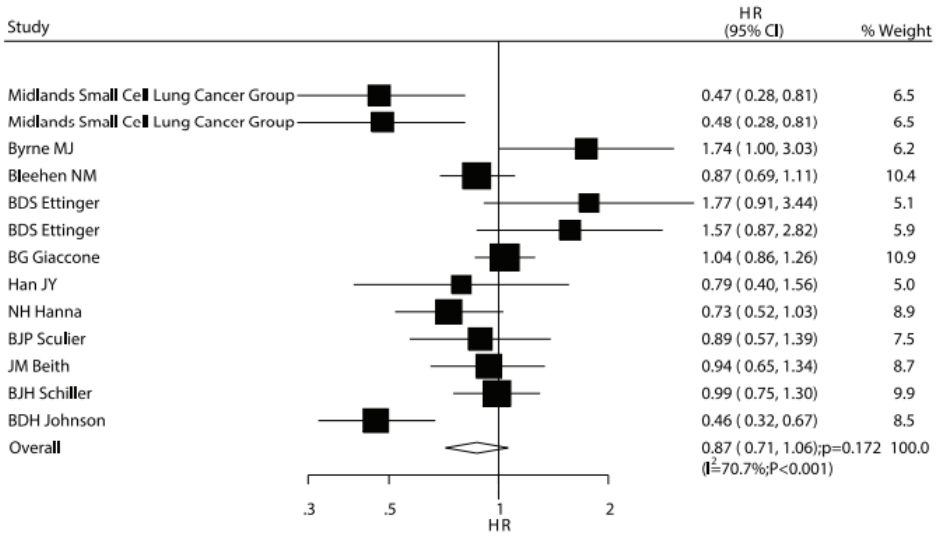


Figure 4. Comparison of overall survival (OS) between maintenance chemotherapy and observation.
doi:10.1371/journal.pone.0073805.g004

Maintenance chemotherapy failed to improve survival outcomes in patients with SCLC. However, a significant advantage in terms of PFS was observed for maintenance chemotherapy in patients with extensive disease.

Treatment of Small Cell Lung Cancer

NCCN Clinical Practice Guidelines in Oncology

Version 1.2022-August 9, 2021

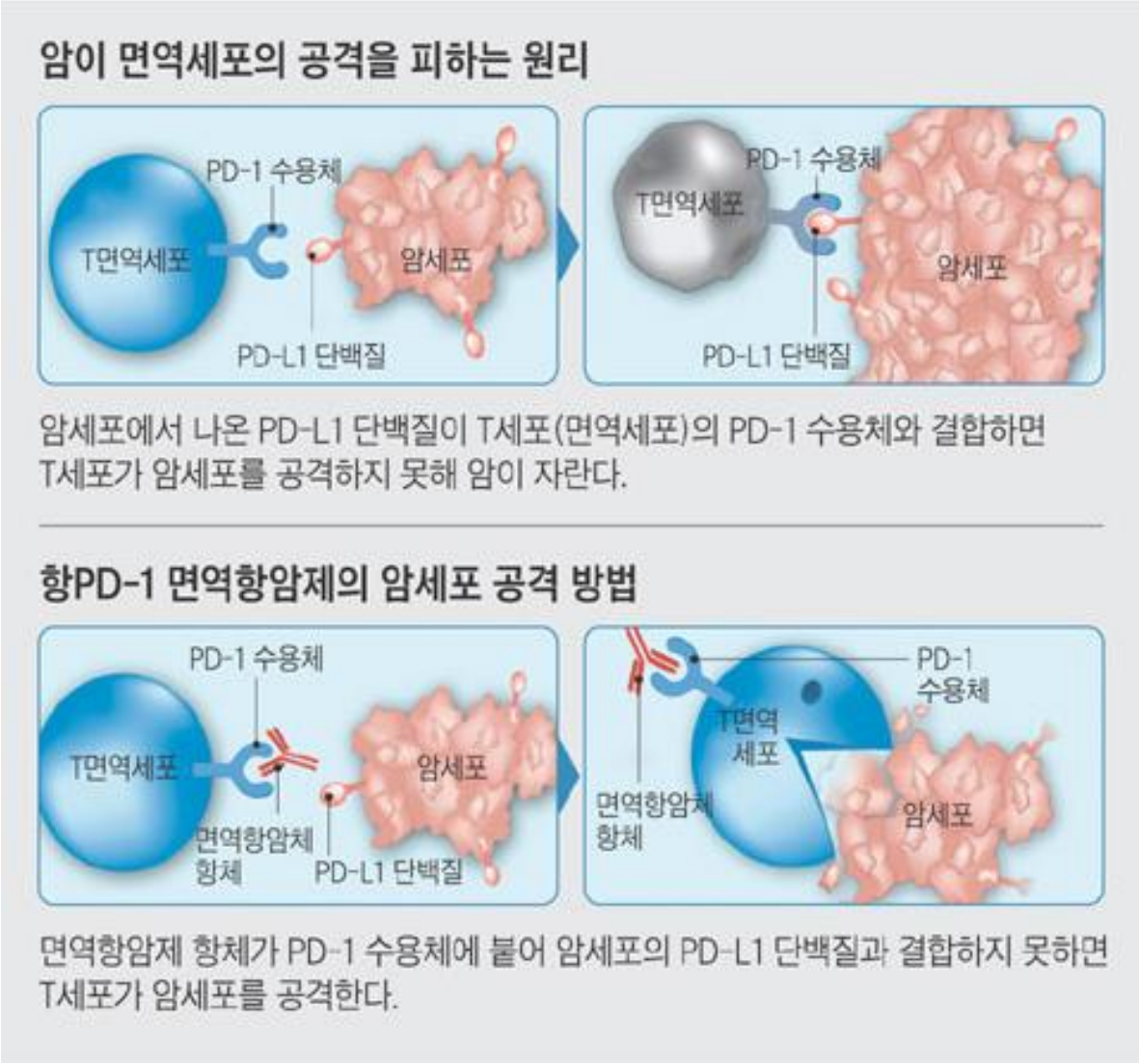
PRIMARY OR ADJUVANT THERAPY FOR LIMITED-STAGE SCLC:
Four cycles of systemic therapy are recommended. Planned cycle length should be every 21–28 days during concurrent RT. During systemic therapy + RT, cisplatin/etoposide is recommended (category 1). The use of myeloid growth factors is not recommended during concurrent systemic therapy plus RT (category 1 for not using GM-CSF).[1]
Preferred Regimens • Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[2] • Cisplatin 60 mg/m² day 1 and etoposide 120 mg/m² days 1, 2, 3[3]
Other Recommended Regimens • Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[2] • Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[a,4]

Treatment of Small Cell Lung Cancer

The 2019 update(Version 1), the NCCN SCLC Panel added a chemo-immunotherapy regimen as a preferred option for patients with extensive-stage SCLC.

Treatment of Small Cell Lung Cancer

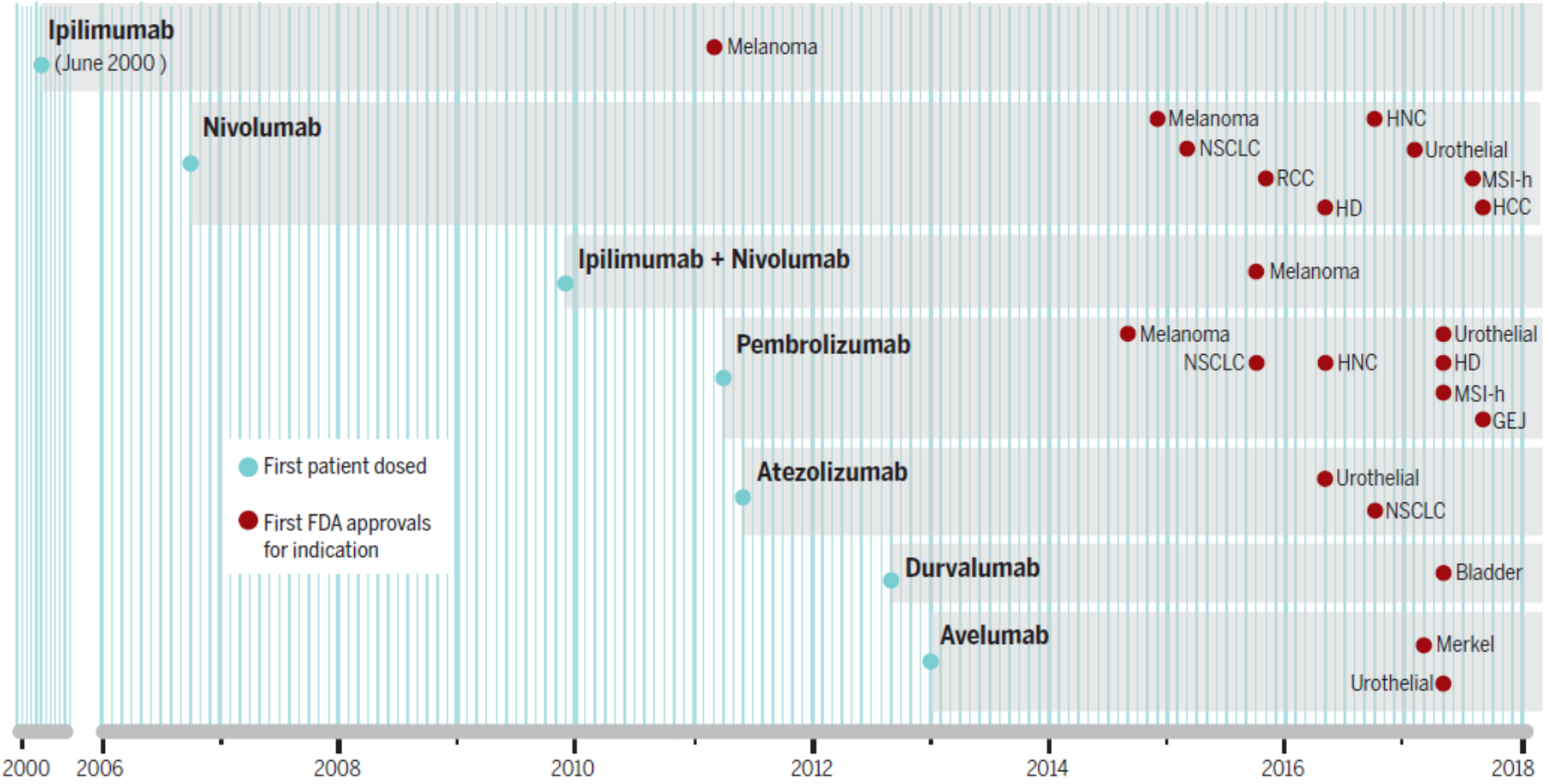
Over view of Immunotherapy



Treatment of Small Cell Lung Cancer

Cancer immunotherapy using checkpoint blockade

Science. 2018 Mar 23;359(6382):1350-1355. doi: 10.1126/science.aar4060. Epub 2018 Mar 22.



CREDITS (GRAPHIC) V. ALTOUNIAN/SCIENCE

Fig. 2. Timing of clinical development of anti–CTLA-4, anti–PD-1, and anti–PD-L1 antibodies, from first administration to humans to FDA approval. Thus far, there has been drug regulatory approval for six antibodies that block immune checkpoints and a combination of two immune checkpoint-blocking antibodies. The gray shading represents the period of clinical development for each of these antibodies, from the dosing of the first patient until regulatory approval (red circles) in different indications. HNC, head and neck cancer; RCC, renal cell carcinoma; MSI-h, high microsatellite instability; HD, Hodgkin's disease; HCC, hepatocellular carcinoma; GEJ, gastroesophageal junction.

Treatment of Small Cell Lung Cancer

Remarkable Publications

1st line

- Horn, L; et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N. Engl. J. Med. **2018**, 379, 2220–2229.
- Paz-Ares, L.; et al. Durvalumab plus EP versus EP in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): A randomised, controlled, open-label, phase 3 trial. Lancet **2019**, 394, 1929–1939.
- Rudin, C.M.; et al. Pembrolizumab or Placebo Plus EP as First-Line Therapy for Extensive-Stage Small-Cell Lung Cancer: Randomized, Double-Blind, Phase III KEYNOTE-604 Study. J. Clin. Oncol. **2020**, 38, JCO2000793.
- Reck, M.; et al. Phase III randomized trial of ipilimumab plus EP versus placebo plus EP in extensive-stage small-cell lung cancer. J. Clin. Oncol. **2016**, 34, 3740–3748.

2nd line

- Reck, M.; et al. LBA5—Ecacy and safety of nivolumab (nivo) monotherapy versus chemotherapy (chemo) in recurrent small cell lung cancer (SCLC): Results from CheckMate 331. Ann. Oncol. **2018**, 29 (Suppl. 10), x43.
- Goldman, J.W.; et al. Safety and antitumor activity of durvalumab monotherapy in patients with pretreated extensive disease small-cell lung cancer (ED-SCLC). J. Clin. Oncol. **2018**, 36, 8518.
- Bondarenko, I.; et al. Preliminary ecacy of durvalumab plus tremelimumab in platinum-refractory/resistant ED-SCLC from arm A of the phase II BALTIC study. Ann. Oncol. **2018**, 29, viii596.
- Pujol, J.-L.; et al. A Randomized Non-Comparative Phase II Study of Anti-Programmed Cell Death-Ligand 1 Atezolizumab or Chemotherapy as Second-Line Therapy in Patients with Small Cell Lung Cancer: Results From the IFCT-1603 Trial. J. Thorac. Oncol. **2019**, 14, 903–913.

3rd line

- Chung, H.C.; et al. Pembrolizumab After Two or More Lines of Previous Therapy in Patients With Recurrent or Metastatic SCLC: Results From the KEYNOTE-028 and KEYNOTE-158 Studies. J. Thorac. Oncol. **2020**, 15, 618–627.
- Ready, N.; et al. Third-Line Nivolumab Monotherapy in Recurrent SCLC: CheckMate 032. J. Thorac. Oncol. **2019**, 14, 237–244.

Treatment of Small Cell Lung Cancer

1st line chemo-immunotherapy

Cancers **2020**, 12, 2522; doi:10.3390/cancers12092522

Table 1. First line immunotherapy in ES-SCLC.

Author	Phase	No. Pts	Treatment	Response Rate (%)	Progression-Free Survival (Months)	Overall Survival (Months)
Horn L et al. [12] IMpower 133	III	403	Atezolizumab + carboplatinum-etoposide vs. placebo + carboplatinum + etoposide	60.2 vs. 64.4	5.2 vs. 4.3, HR: 0.77; 95% CI: 0.62–0.96, $p = 0.02$	12.3 vs. 10.3, HR: 0.70; 95%CI: 0.54–0.91, $p = 0.007$
Paz-Ares L et al. [14] CASPIAN	III	805	Durvalumab + platinum-etoposide vs. platinum-etoposide	79 vs. 70	5.1 vs. 5.4 HR: 0.78; 95%CI: 0.65–0.94	13.0 vs. 10.3, HR: 0.73; 95%CI: 0.59–0.91, $p = 0.0047$
Rudin CM et al. [16] KEYNOTE-604	III	453	Pembrolizumab + platinum-etoposide vs. placebo + platinum + etoposide	70.6 vs. 61.8	4.5 vs. 4.3, HR: 0.75; 95%CI: 0.61–0.91; $p = 0.0023$	10.8 vs. 9.7, HR: 0.80; 95%CI: 0.64–0.98; $p = 0.0164$
Reck M et al. [17] CA184–156 study	III	1132	Ipilimumab + platinum-etoposide vs. platinum-etoposide	62 vs. 62	4.6 vs. 4.4 HR: 0.85; 95%CI: 0.75–0.97	11.0 vs. 10.9 HR: 0.94; 95%CI: 0.81–1.09, $p = 0.3775$

Pts: patients; HR: hazard ratio.

Treatment of Small Cell Lung Cancer

Phase III Randomized Trial of Ipilimumab Plus EP Versus Placebo Plus EP in ES-SCLC

CA184-156 study [clinical trial information: NCT01450761]

J Clin Oncol. 2016 Nov 1;34(31):3740-3748. doi:10.1200/JCO.2016.67.6601.

	chemo plus ipilimumab	chemo plus placebo	
Study population	**478**	**476**	
Median OS	**11.0 months**	**10.9 months**	**HR, 0.94; P = .3775**
Median PFS	**4.6 months**	**4.4 months**	**HR, 0.85;**

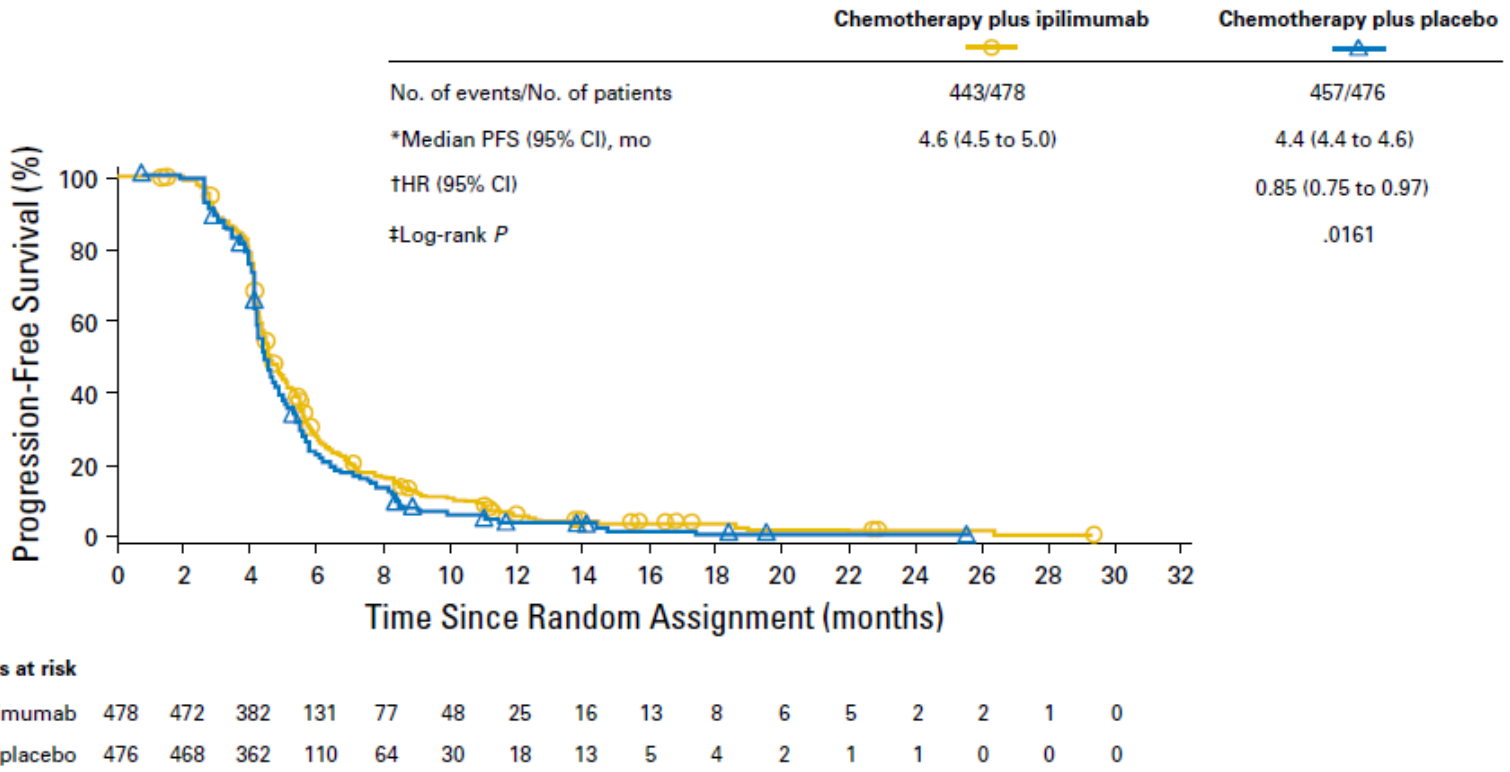


Fig 3. Kaplan-Meier plot of PFS. HR, hazard ratio. (*) Medians and associated two-sided CIs calculated via log-log transformation. (†) Hazard of ipilimumab over hazard of placebo with two-sided 95% CI based on unstratified Cox proportional hazards model with treatment as the single covariate. (‡) Unstratified two-sided log-rank test.

Treatment of Small Cell Lung Cancer

Phase III Randomized Trial of Ipilimumab Plus EP Versus Placebo Plus EP in ES-SCLC

CA184-156 study [clinical trial information: NCT01450761]

J Clin Oncol. 2016 Nov 1;34(31):3740-3748. doi:10.1200/JCO.2016.67.6601.

	chemo plus ipilimumab	chemo plus placebo	
Study population	**478**	**476**	
Median OS	**11.0 months**	**10.9 months**	**HR, 0.94; P = .3775**
Median PFS	**4.6 months**	**4.4 months**	**HR, 0.85;**

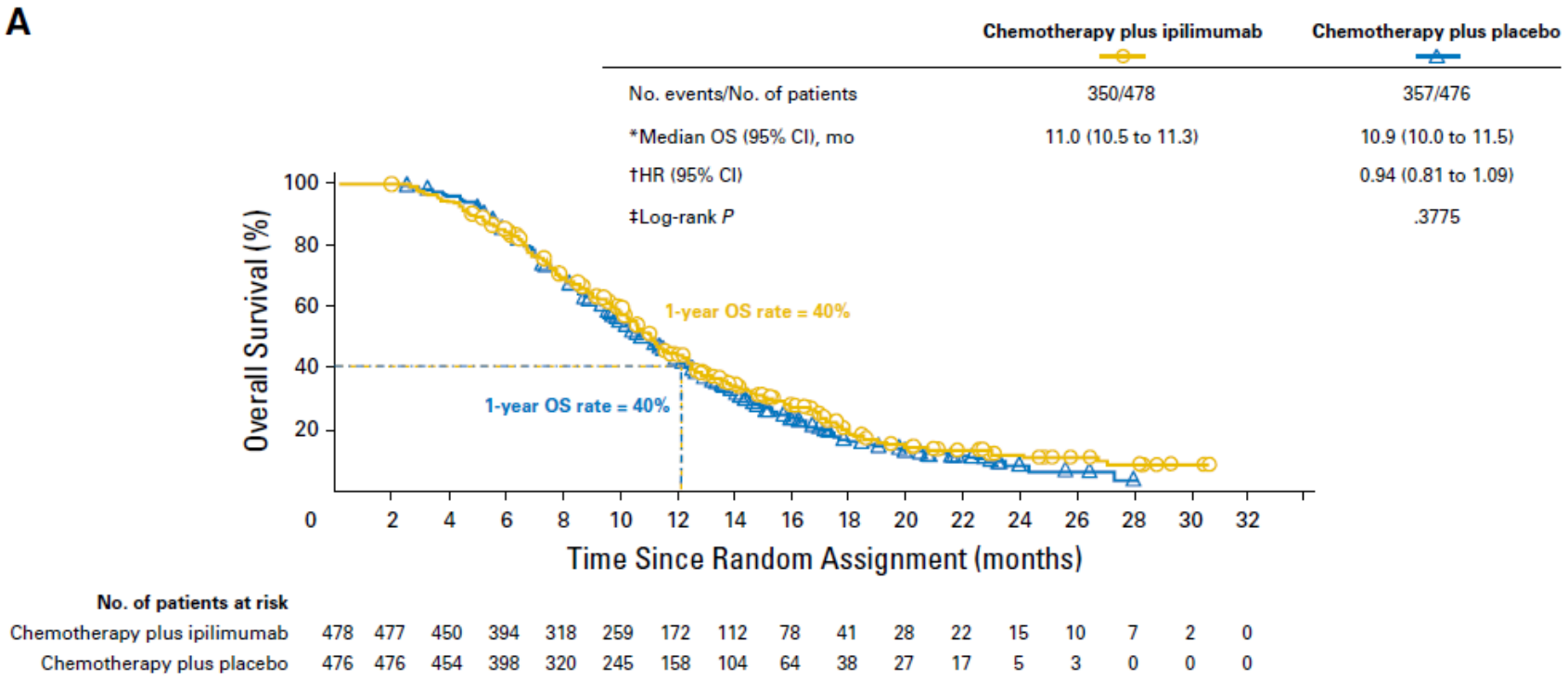


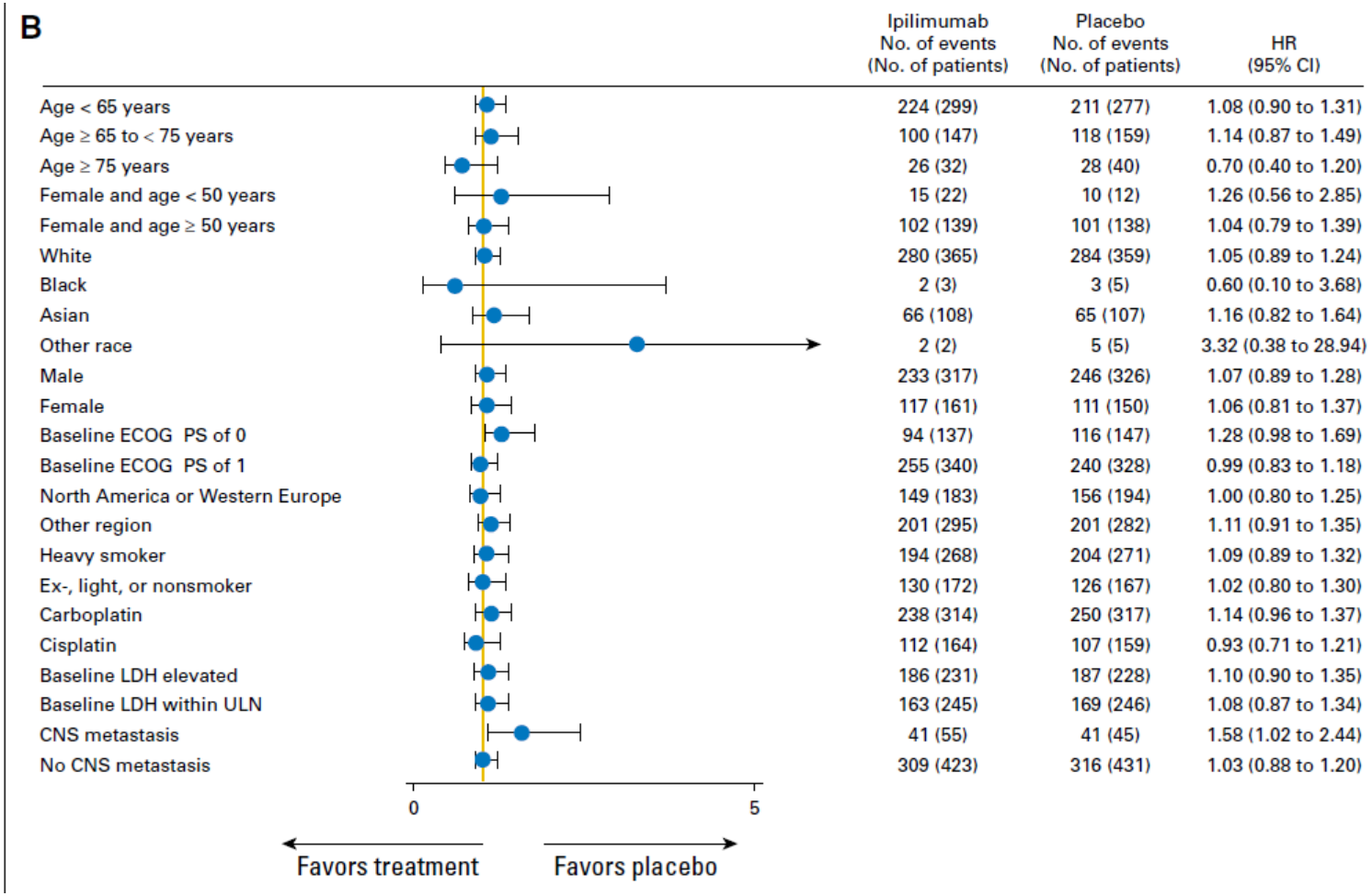
Fig 2. (A) Overall survival (OS) and (B) treatment effect on OS in predefined subsets. (A) Kaplan-Meier plot of OS (chemotherapy plus ipilimumab, [n = 478]; chemotherapy plus placebo, [n = 476]). OS was defined as time from date of random assignment until date of death. As indicated by symbols, patients who had not died or were lost to follow-up were censored on the last date they were known to be alive. Horizontal lines indicate rates of OS at 1 year.

Treatment of Small Cell Lung Cancer

Phase III Randomized Trial of Ipilimumab Plus EP Versus Placebo Plus EP in ES-SCLC

CA184-156 study [clinical trial information: NCT01450761]

J Clin Oncol. 2016 Nov 1;34(31):3740-3748. doi:10.1200/JCO.2016.67.6601.

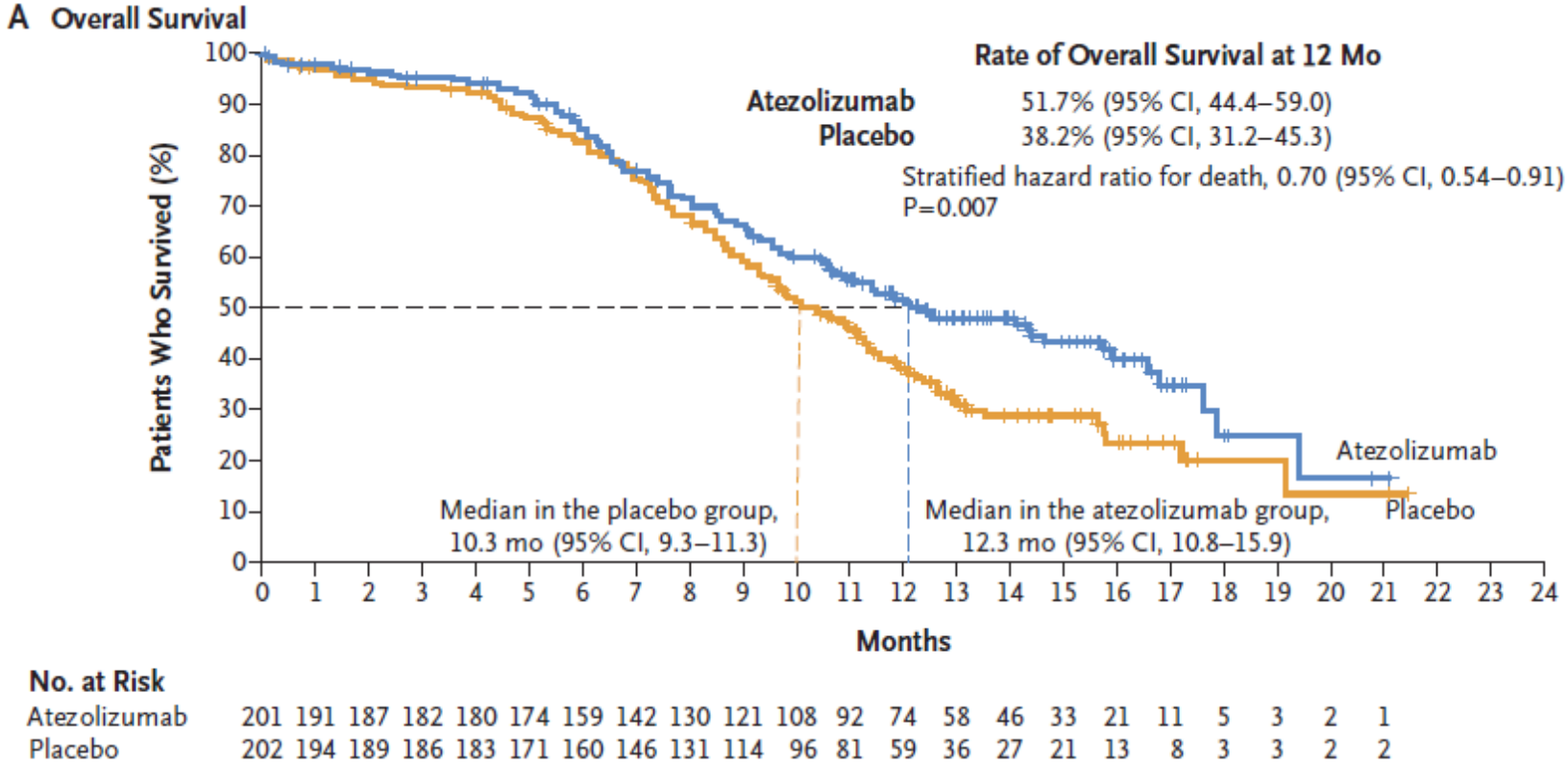


(B) Forest plot of treatment effect on OS in predefined subsets based on unstratified Cox proportional hazards model for patients in indicated subset.

Treatment of Small Cell Lung Cancer

First-Line Atezolizumab plus Chemotherapy in ES-SCLC

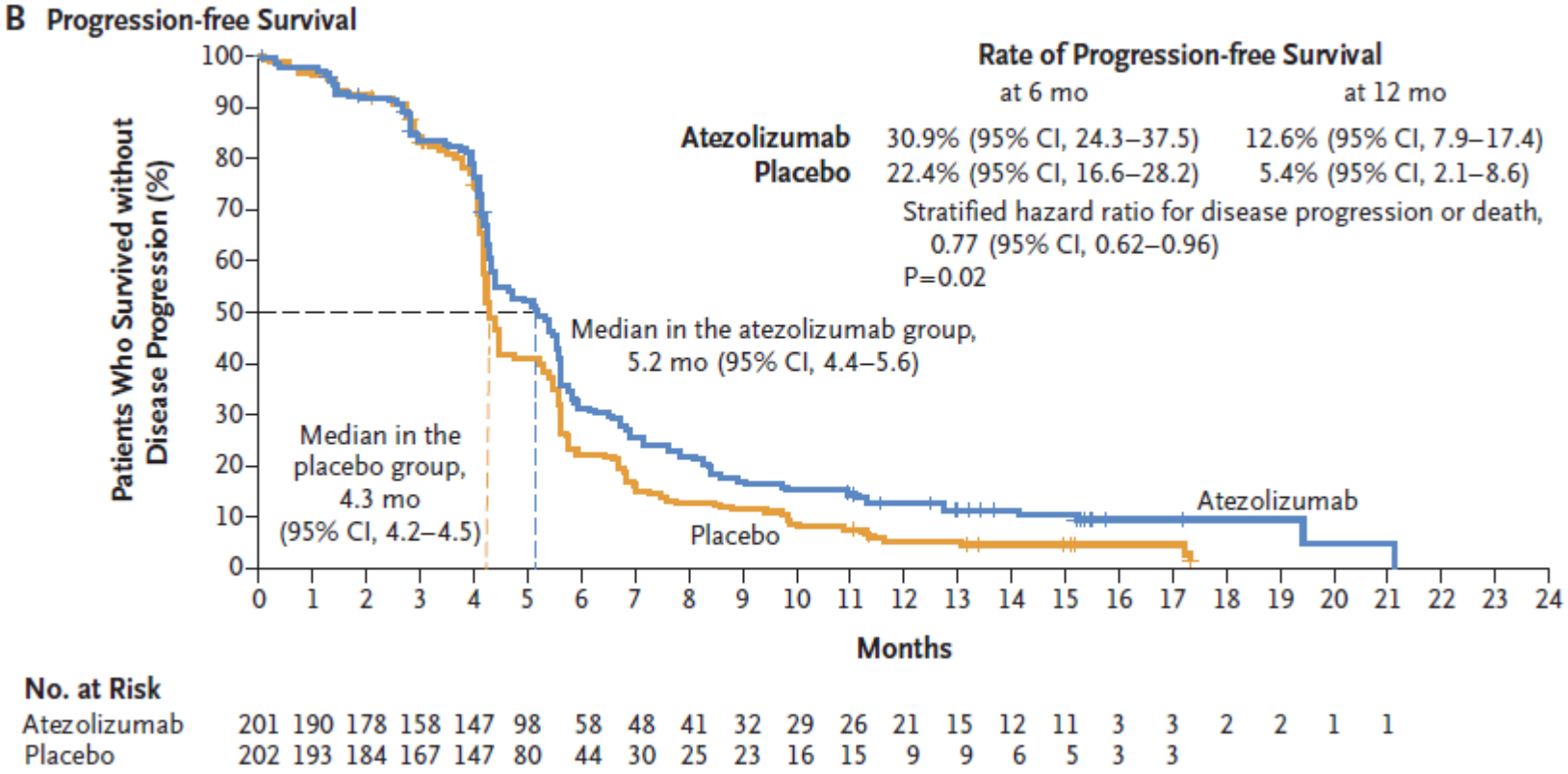
N Engl J Med. 2018 Dec 6;379(23):2220-2229. doi: 10.1056/NEJMoa1809064.



Treatment of Small Cell Lung Cancer

First-Line Atezolizumab plus Chemotherapy in ES-SCLC

N Engl J Med. 2018 Dec 6;379(23):2220-2229. doi: 10.1056/NEJMoa1809064.



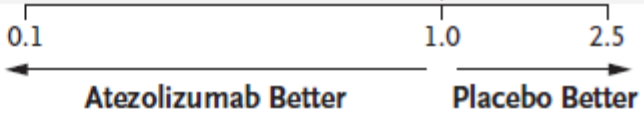
Treatment of Small Cell Lung Cancer

First-Line Atezolizumab plus Chemotherapy in ES-SCLC

N Engl J Med. 2018 Dec 6;379(23):2220-2229. doi: 10.1056/NEJMoa1809064.

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)



Treatment of Small Cell Lung Cancer

First-Line Atezolizumab plus Chemotherapy in ES-SCLC

N Engl J Med. 2018 Dec 6;379(23):2220-2229. doi: 10.1056/NEJMoa1809064.

Table 2. Response Rate, Duration of Response, and Disease Progression.*

Variable	Atezolizumab Group (N=201)	Placebo Group (N=202)
Objective confirmed response†	121 (60.2 [53.1–67.0])	130 (64.4 [57.3–71.0])
Complete response — no. (% [95% CI])	5 (2.5 [0.8–5.7])	2 (1.0 [0.1–3.5])
Partial response — no. (% [95% CI])	116 (57.7 [50.6–64.6])	128 (63.4 [56.3–70.0])
Median duration of response (range) — mo‡	4.2 (1.4§–19.5)	3.9 (2.0–16.1§)
Ongoing response at data cutoff — no./total no. (%)	18/121 (14.9)	7/130 (5.4)
Stable disease — no. (% [95% CI])	42 (20.9 [15.5–27.2])	43 (21.3 [15.9–27.6])
Progressive disease — no. (% [95% CI])	22 (10.9 [7.0–16.1])	14 (6.9 [3.8–11.4])

* The date of data cutoff was April 24, 2018.

† The objective confirmed response rate was assessed in patients in the intention-to-treat population who had measurable disease at baseline. Objective response was defined as confirmed complete response or partial response as determined by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.

‡ Duration of response was assessed in patients who had an objective confirmed response and was defined as the time from the first occurrence of a documented objective response to the time of disease progression as determined by the investigator (according to RECIST) or death from any cause, whichever occurred first.

§ Data for the lower range of the response in the atezolizumab group and the upper range of the response in the placebo group are censored.

Treatment of Small Cell Lung Cancer

Durvalumab plus EP versus EP in 1st-line treatment of ES-SCLC(CASPIAN): a randomised, controlled, open-label, phase 3 trial

Lancet. 2019 Nov 23;394(10212):1929-1939. doi: 10.1016/S0140-6736(19)32222-6.

Table 2: Treatment exposure (safety population)

	Durvalumab plus platinum–etoposide (n=265)	Platinum–etoposide (n=266)
Median number of durvalumab doses	7 (6–11)	..
Patients receiving 12 or more durvalumab doses	64 (24%)	..
Median total duration of durvalumab, weeks	28·0 (20·0–43·1)	..
Platinum received*		
Carboplatin	208 (78%)	208 (78%)
Cisplatin	65 (25%)	67 (25%)
Median number of cycles of platinum–etoposide†	4 (4–4)	6 (4–6)
Patients receiving four or more cycles of platinum–etoposide†	230 (87%)	225 (85%)
Patients receiving five or more cycles of platinum–etoposide†	3 (1%)	167 (63%)
Patients receiving six cycles of platinum–etoposide†	1 (<1%)	151 (57%)
Median total duration of platinum–etoposide, weeks†	11·9 (11·7–12·9)	18·7 (12·3–20·0)

Treatment of Small Cell Lung Cancer

Durvalumab plus EP versus EP in 1st-line treatment of ES-SCLC(CASPIAN): a randomised, controlled, open-label, phase 3 trial

Lancet. 2019 Nov 23;394(10212):1929-1939. doi: 10.1016/S0140-6736(19)32222-6.

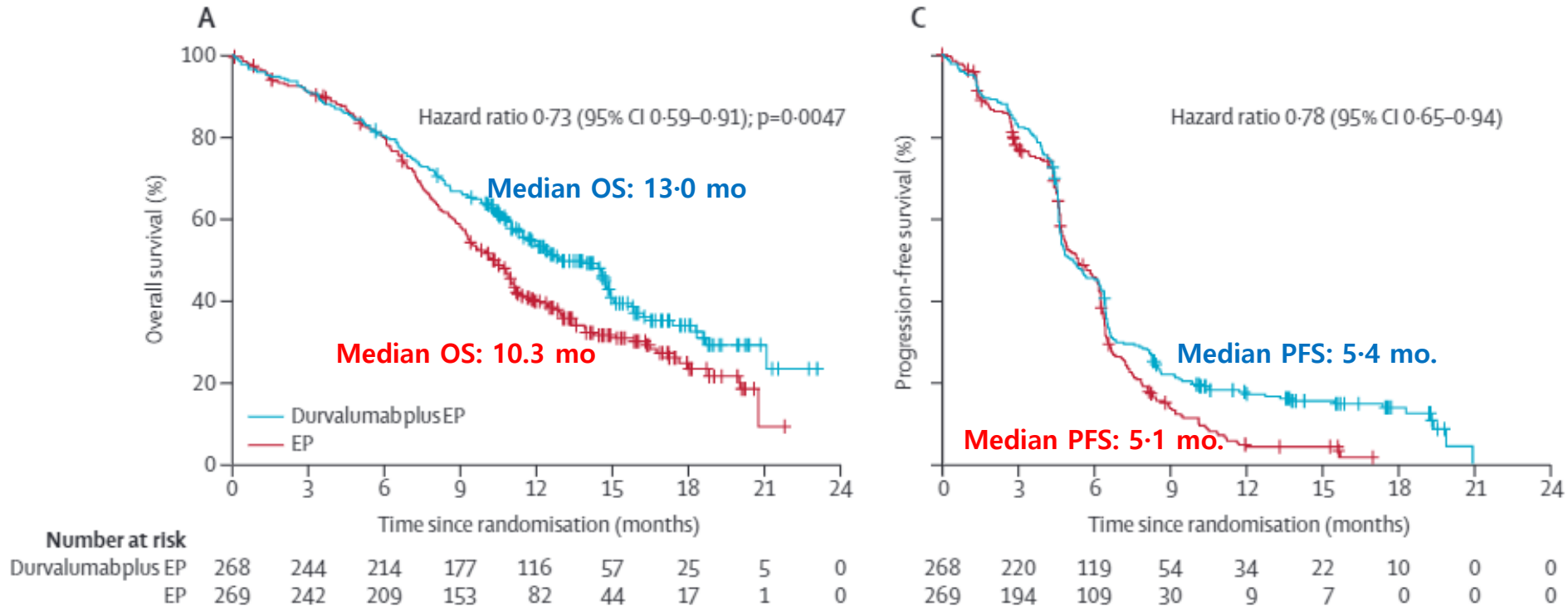


Figure 2: **Overall survival and investigator-assessed progression-free survival in the intention-to-treat population**
(A) Kaplan-Meier graph of overall survival in the intention-to-treat population. (B) Forest plot of subgroup analysis of overall survival. (C) Kaplan-Meier graph of progression-free survival in the intention-to-treat population. Data cutoff was March 11, 2019. AJCC=American Joint Committee on Cancer. EP=etoposide plus either cisplatin or carboplatin.

Treatment of Small Cell Lung Cancer

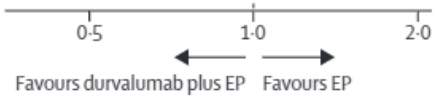
Durvalumab plus EP versus EP in 1st-line treatment of ES-SCLC(CASPIAN): a randomised, controlled, open-label, phase 3 trial

Lancet. 2019 Nov 23;394(10212):1929-1939. doi: 10.1016/S0140-6736(19)32222-6.

Forest plot of subgroup analysis of overall survival.

B

	Durvalumab plus EP events/patients (n)	EP events/patients (n)	Hazard ratio (95% CI)
All patients	**155/268**	**181/269**	**0·73 (0·59–0·91)**
Planned platinum			
Carboplatin	121/201	145/201	0·70 (0·55–0·89)
Cisplatin	34/67	36/68	0·88 (0·55–1·41)
Age (years)			
<65	95/167	105/157	0·74 (0·56–0·98)
≥65	60/101	76/112	0·75 (0·54–1·06)
Sex			
Men	123/190	131/184	0·76 (0·59–0·97)
Women	32/78	50/85	0·63 (0·40–0·98)
WHO performance status score			
0	51/99	55/90	0·71 (0·48–1·04)
1	104/169	126/179	0·76 (0·59–0·99)
Smoking status			
Smoker	141/246	171/254	0·72 (0·58–0·91)
Non-smoker	14/22	10/15	0·90 (0·40–2·11)
Brain or CNS metastases			
Yes	17/28	20/27	0·69 (0·35–1·31)
No	138/240	161/242	0·74 (0·59–0·93)
AJCC disease stage at diagnosis			
Stage III	15/28	13/24	0·92 (0·44–1·98)
Stage IV	140/240	168/245	0·73 (0·58–0·91)
Race			
Asian	18/36	24/42	0·81 (0·43–1·49)
Non-Asian	137/232	156/226	0·73 (0·58–0·92)
Region			
Asia	17/35	23/41	0·82 (0·43–1·54)
Europe	120/200	142/205	0·72 (0·56–0·92)
North America and South America	18/33	16/23	0·72 (0·37–1·44)



Treatment of Small Cell Lung Cancer

Durvalumab, with or without tremelimumab, plus EP versus EP alone in 1st-line treatment of ES-SCLC (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial

Lancet Oncol. 2021 Jan;22(1):51-65. doi: 10.1016/S1470-2045(20)30539-8.

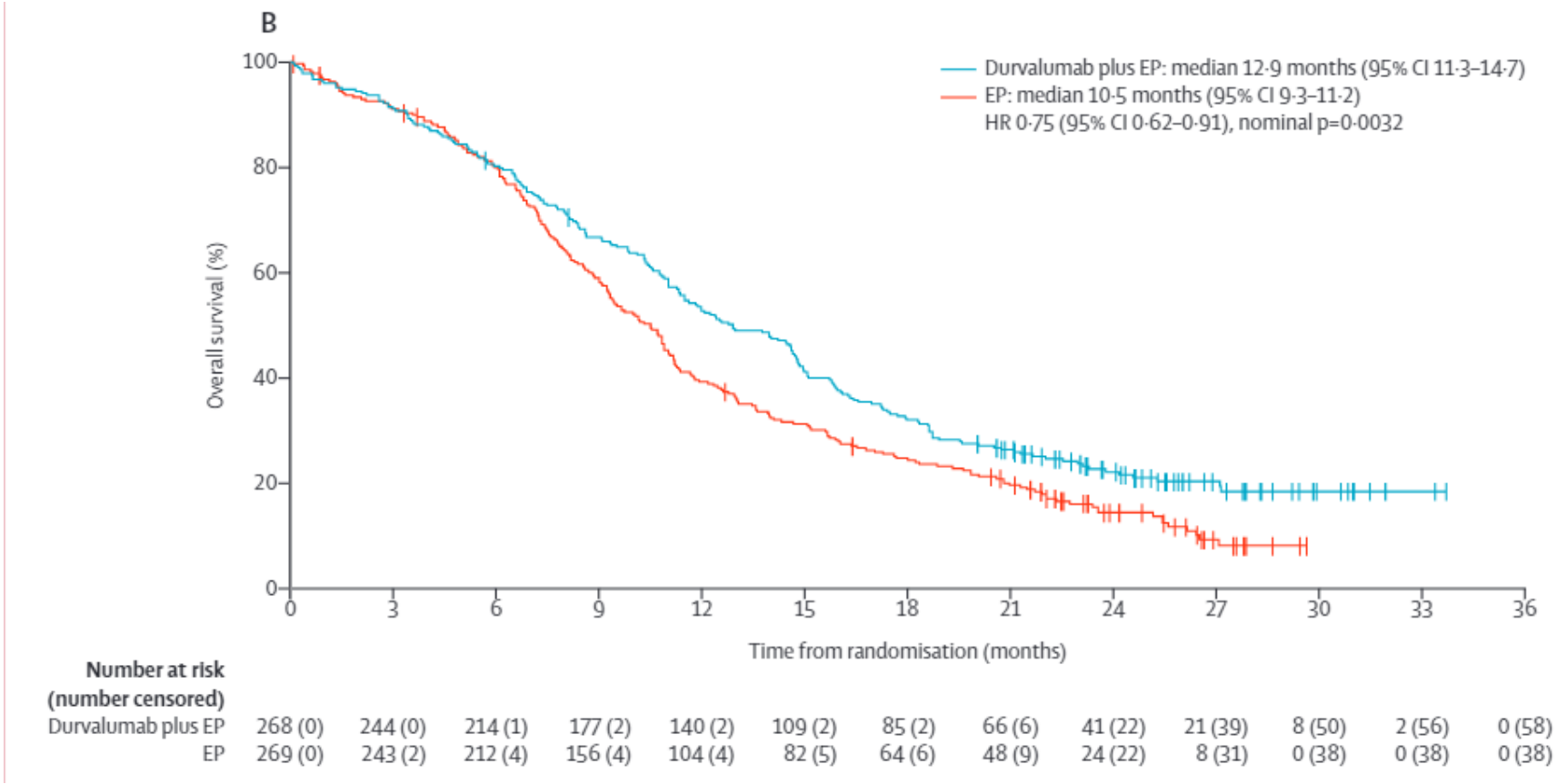


Figure 2: **Overall survival in the intention-to-treat population**

(A) Kaplan-Meier graph of overall survival for durvalumab plus tremelimumab plus EP versus EP. (B) Kaplan-Meier graph of overall survival for durvalumab plus EP versus EP. EP=etoposide plus either cisplatin or carboplatin. HR=hazard ratio.

Treatment of Small Cell Lung Cancer

Durvalumab plus EP versus EP in 1st-line treatment of ES-SCLC(CASPIAN): a randomised, controlled, open-label, phase 3 trial

Lancet. 2019 Nov 23;394(10212):1929-1939. doi: 10.1016/S0140-6736(19)32222-6.

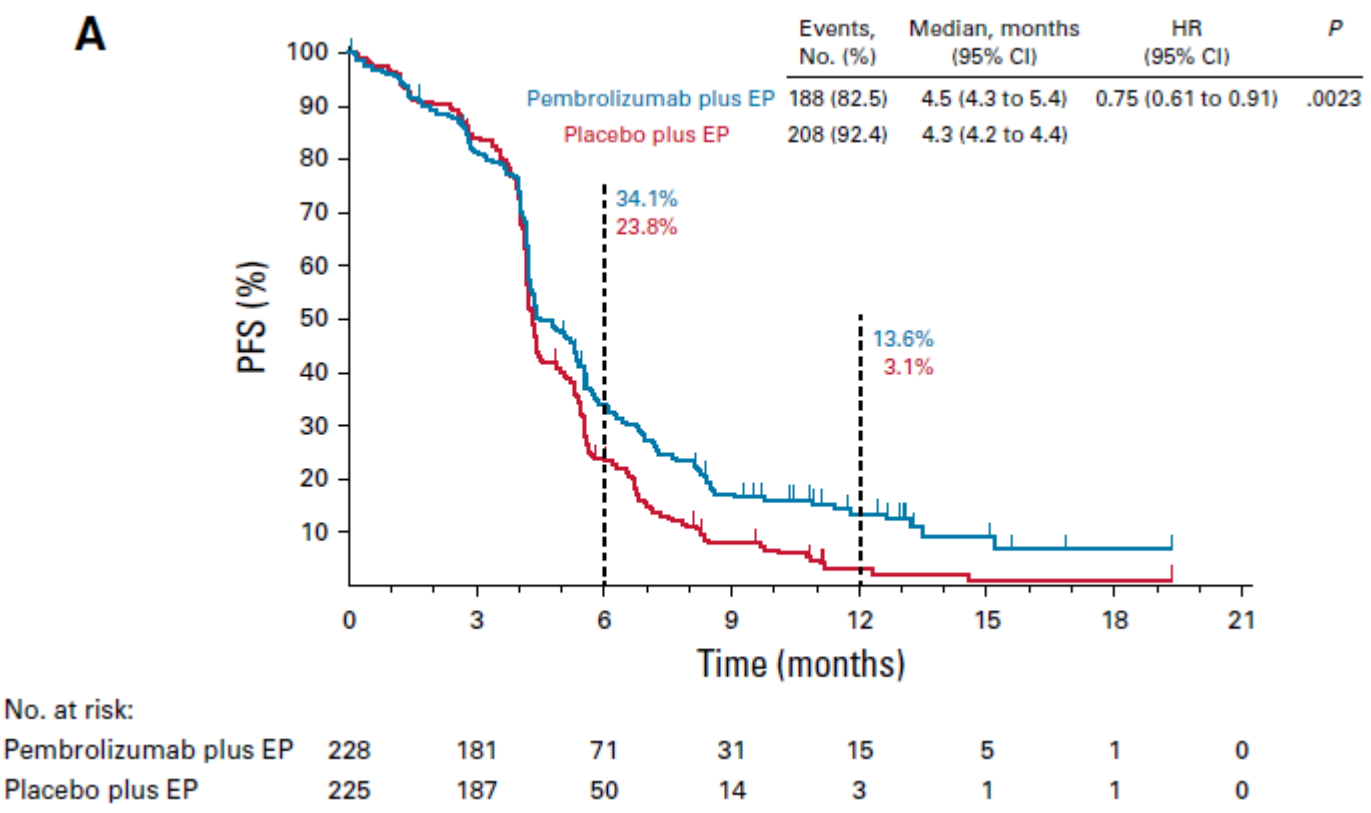
Table 3: Summary of tumour response

	Durvalumab plus platinum–etoposide (n=268)	Platinum–etoposide (n=269)
Unconfirmed objective response*	213 (79%)	189 (70%)
Odds ratio (95% CI)†	1·64 (1·11–2·44)	..
Confirmed objective response*	182 (68%)	155 (58%)
Odds ratio (95% CI)†	1·56 (1·10–2·22)	..
Best objective response		
Complete response	6 (2%)	2 (1%)
Partial response	176 (66%)	153 (57%)
Stable disease for at least 6 weeks	20 (7%)	42 (16%)
Progressive disease	32 (12%)	31 (12%)
Not evaluable	3 (1%)	8 (3%)
Median (IQR) duration of response, months‡	5·1 (3·4–10·4)	5·1 (3·7–6·8)
Remaining in response‡		
6 months	39% (32–46)	34% (26–42)
12 months	23% (17–29)	6% (3–11)

Treatment of Small Cell Lung Cancer

Pembrolizumab or Placebo Plus EP as 1st-line Therapy for ES-SCLC: Randomized, Double-Blind, Phase III KEYNOTE-604 Study

J Clin Oncol. 2020 Jul 20;38(21):2369-2379. doi: 10.1200/JCO.20.00793.



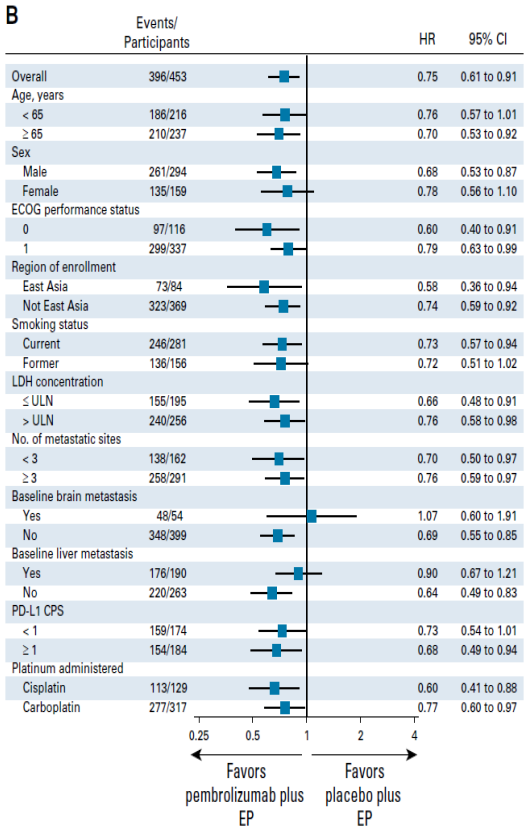
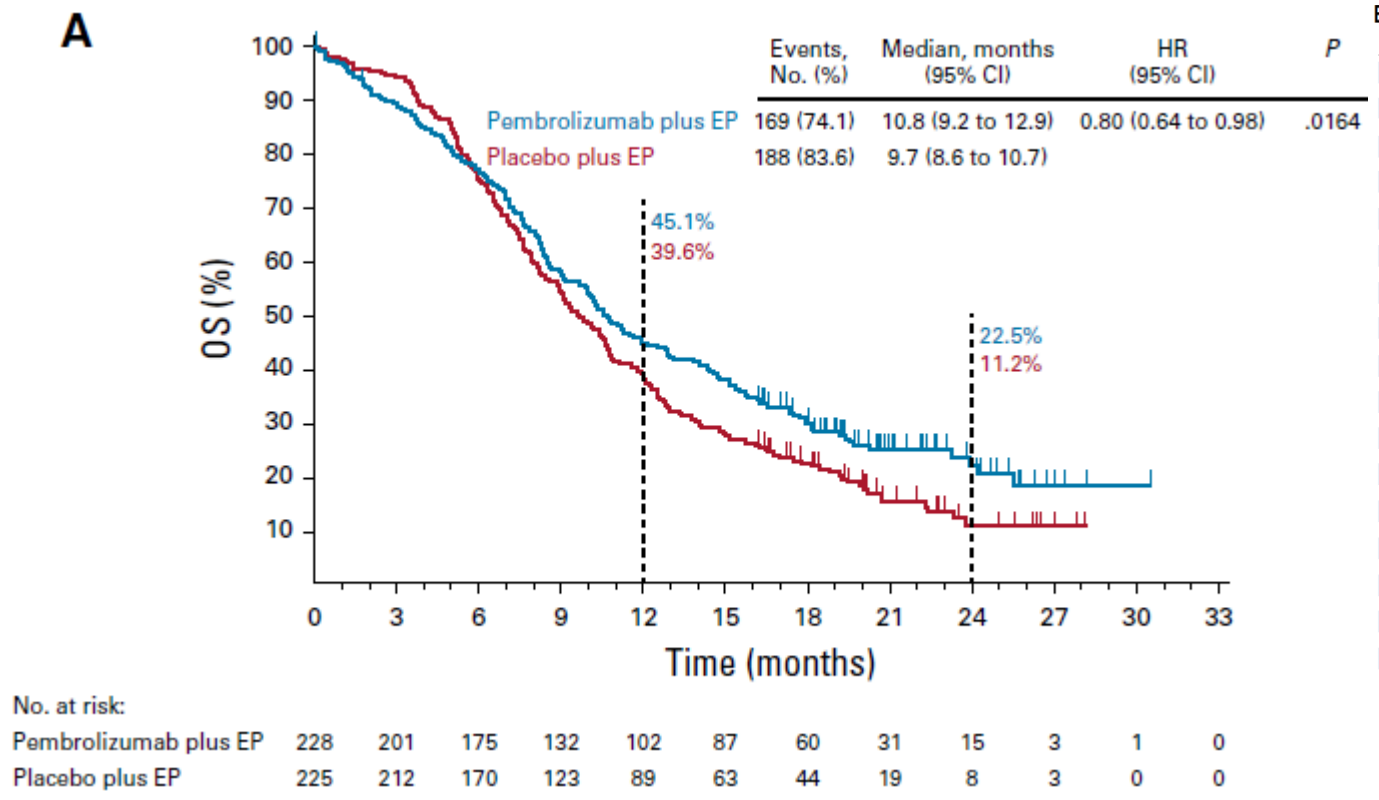


FIG 2. FS assessed per RECIST version 1.1 by blinded, independent central review in the intention-to-treat population at the second interim analysis. (A) Kaplan-Meier estimates of PFS. (B) Forest plot of PFS in subgroups.

Treatment of Small Cell Lung Cancer

Pembrolizumab or Placebo Plus EP as 1st-line Therapy for ES-SCLC: Randomized, Double-Blind, Phase III KEYNOTE-604 Study

J Clin Oncol. 2020 Jul 20;38(21):2369-2379. doi: 10.1200/JCO.20.00793.



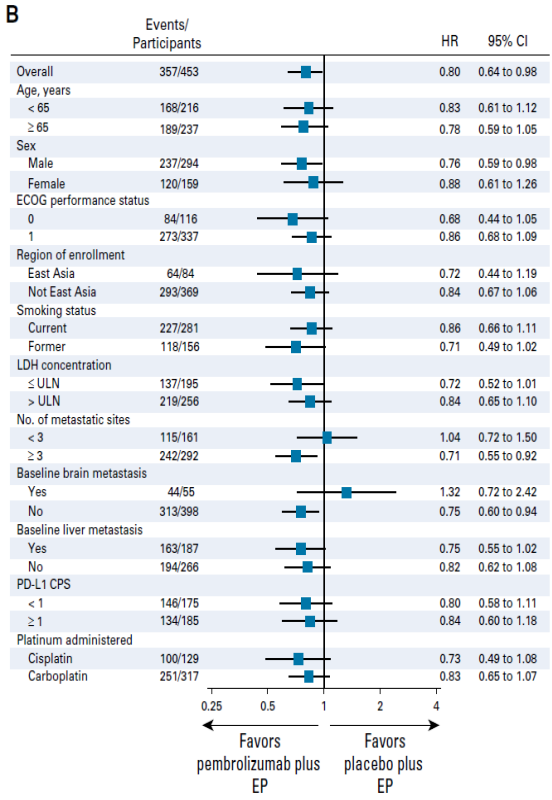


FIG 3. Overall survival (OS) in the intention-to-treat population at final analysis. (A) Kaplan-Meier estimates of OS. (B) Forest plot of OS in subgroups.

Treatment of Small Cell Lung Cancer

Summary of 1st line combined chemo-immunotherapy in ES-SCLC

Cancers **2020**, 12, 2522; doi:10.3390/cancers12092522

Table 1. First line immunotherapy in ES-SCLC.

Author	Phase	No. Pts	Treatment	Response Rate (%)	Progression-Free Survival (Months)	Overall Survival (Months)
Horn L et al. [12] IMpower 133	III	403	Atezolizumab + carboplatinum-etoposide vs. placebo + carboplatinum + etoposide	60.2 vs. 64.4	5.2 vs. 4.3, HR: 0.77; 95% CI: 0.62–0.96, $p = 0.02$	12.3 vs. 10.3, HR: 0.70; 95%CI: 0.54–0.91, $p = 0.007$
Paz-Ares L et al. [14] CASPIAN	III	805	Durvalumab + platinum-etoposide vs. platinum-etoposide	79 vs. 70	5.1 vs. 5.4 HR: 0.78; 95%CI: 0.65–0.94	13.0 vs. 10.3, HR: 0.73; 95%CI: 0.59–0.91, $p = 0.0047$
Rudin CM et al. [16] KEYNOTE-604	III	453	Pembrolizumab + platinum-etoposide vs. placebo + platinum + etoposide	70.6 vs. 61.8	4.5 vs. 4.3, HR: 0.75; 95%CI: 0.61–0.91; $p = 0.0023$	10.8 vs. 9.7, HR: 0.80; 95%CI: 0.64–0.98; $p = 0.0164$
Reck M et al. [17] CA184–156 study	III	1132	Ipilimumab + platinum-etoposide vs. platinum-etoposide	62 vs. 62	4.6 vs. 4.4 HR: 0.85; 95%CI: 0.75–0.97	11.0 vs. 10.9 HR: 0.94; 95%CI: 0.81–1.09, $p = 0.3775$

Pts: patients; HR: hazard ratio.

Treatment of Small Cell Lung Cancer

2nd-line chemo-immunotherapy

Cancers **2020**, 12, 2522; doi:10.3390/cancers12092522

Table 2. Immunotherapy in pretreated SCLC patients.

Author	Phase	Pts	Setting	Treatment	Response Rate (%)	PFS (Months)	OS (Months)
Reck et al. [27] Checkmate 331	Phase 3	569	Second line	Nivolumab (240 mg) vs. topotecan 1.5 mg/m^2 days 1–5 or amrubicin 40 mg/m^2 days 1–3	14 vs. 16	1.4 (CI95%: 1.4–1.5) vs. 3.8 (CI95%: 3.0–4.2)	7.5 vs. 8.4 (HR 0.86 CI95%: 0.72–1.04)
Goldman JW et al. [28]	Phase I/II	21	Second/third line	Durvalumab 10 mg/kg	9.5% (95%CI: 1.2–30.4)	1.5 (95%CI: 0.9–1.8)	4.8 months (95%CI: 1.3–10.4)
Bondarenko I et al. [29] BALTIC, Arm A	Phase II	21	Second line	Durvalumab 1500 mg plus tremelimumab 75 mg	9.5% (95%CI: 1.1–30.3)	n.r.	n.r.
Pujol JL et al. [30]	Phase II	73	Second line	Atezolizumab 1200 mg vs. chemotherapy	2.3% (95%CI: 0.0–6.8)	1.4 (95%CI: 1.2–1.5) vs. 4.3 (95%CI: 1.5–5.9)	9.5 vs. 8.7 (HR: 0.84; 95%CI: 0.45–1.58; $p = 0.60$

Pts: patients; PD: progression disease; PFS: progression-free survival; OS: overall survival, n.r.: not reported.

Treatment of Small Cell Lung Cancer

Phase III Trial Comparing Supportive Care Alone With Supportive Care With Oral Topotecan in Patients With Relapsed SCLC

J Clin Oncol. 2006 Dec 1;24(34):5441-7. doi: 10.1200/JCO.2006.06.5821.

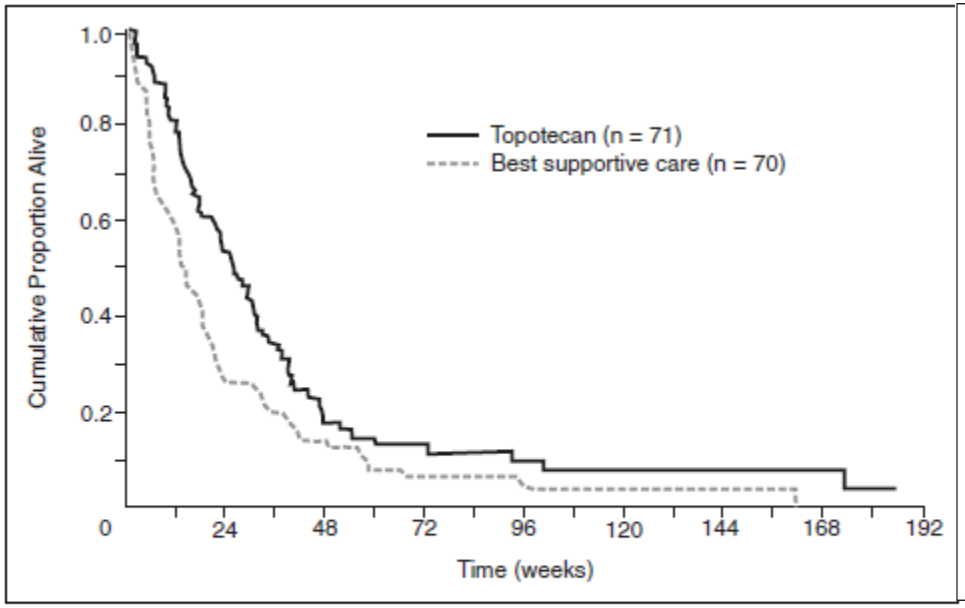


Fig 1. Kaplan-Meier estimates for overall survival in the intent-to-treat population (log-rank $P = .01$). The unadjusted hazard ratio for overall survival was 0.64 (95% CI, 0.45 to 0.90) for topotecan relative to best supportive care alone. Adjusted for stratification factors, the hazard ratio was 0.61 (95% CI, 0.43 to 0.87).

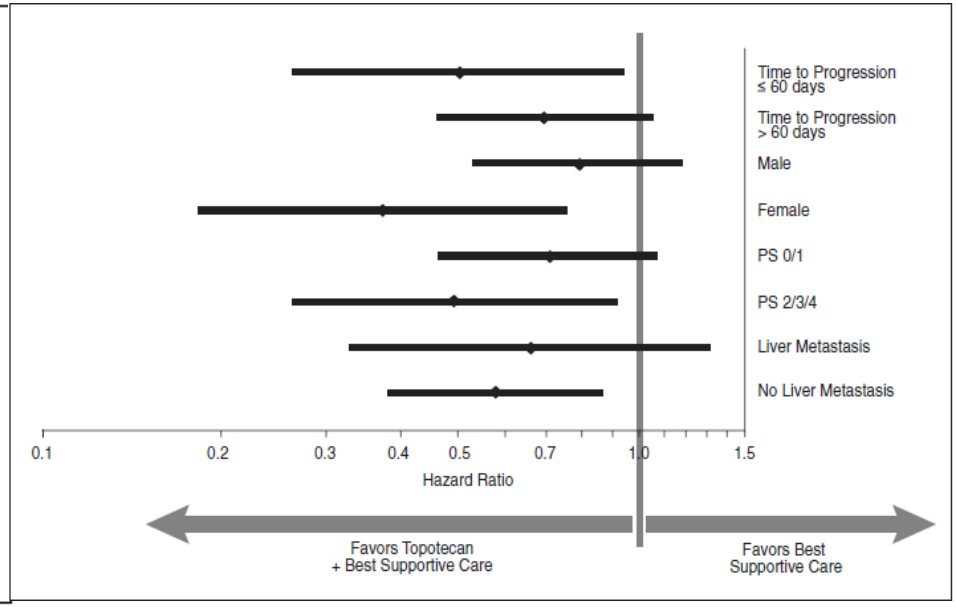


Fig 2. Subgroup analysis of survival according to the stratification factors of sex, performance status (PS), time to progression from prior therapy, and presence of liver metastases.

Chemotherapy with oral topotecan is associated with prolongation of survival and quality of life benefit in patients with relapsed SCLC.

Treatment of Small Cell Lung Cancer

2nd-line nivolumab in relapsed small-cell lung cancer: CheckMate 331

Ann Oncol. 2021 May;32(5):631-641. doi: 10.1016/j.annonc.2021.01.071.

	Nivolumab	Chemo (topotecan)	
Study population	284	285	
Median OS	7.5 months	8.4 months	HR, 0.86; P = .11
Median PFS	1.4 months	3.8 months	HR, 1.41;
Objective RR	13.7%	16.5%	OR, 0.80
Median duration response	8.3 months	4.5 months	

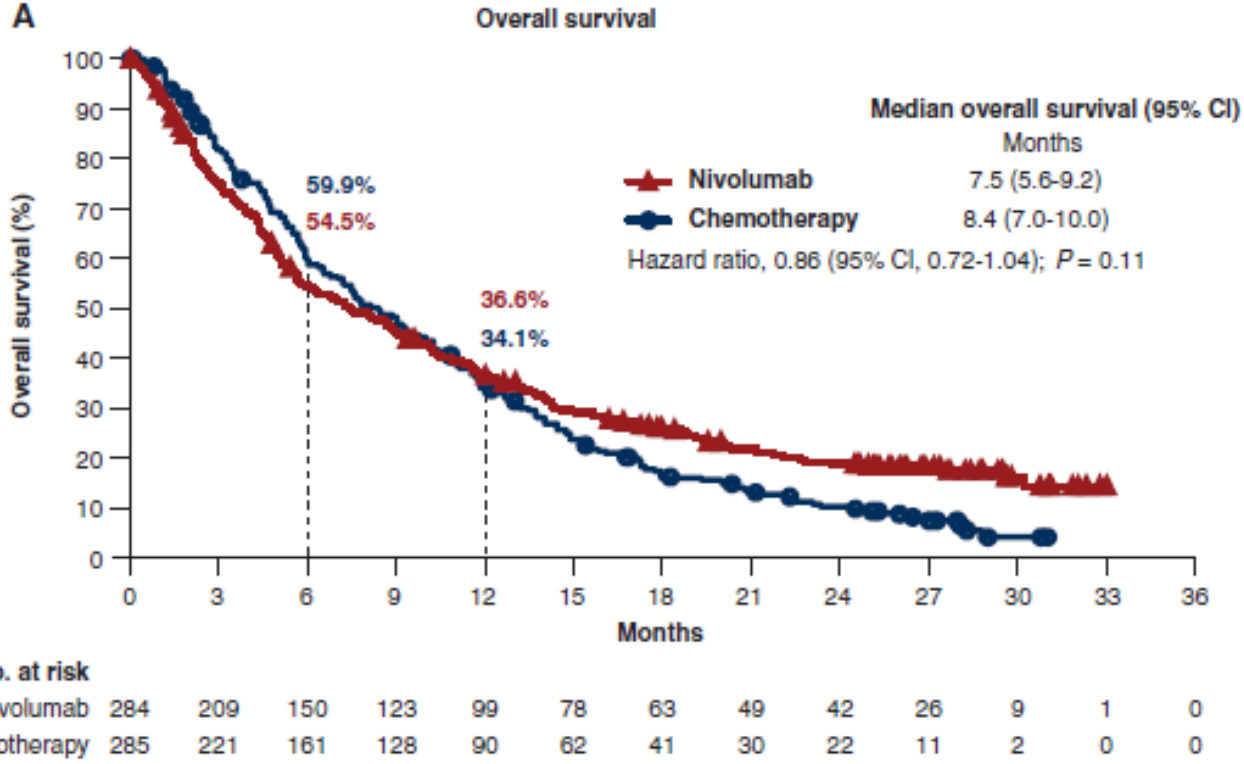


Figure 1. Efficacy of nivolumab versus chemotherapy. (A) Kaplane-Meier estimates of overall survival. (B) Kaplane-Meier estimates of progression-free survival. (C) Kaplane-Meier estimates of duration of response.

Treatment of Small Cell Lung Cancer

2nd-line nivolumab in relapsed small-cell lung cancer: CheckMate 331

Ann Oncol. 2021 May;32(5):631-641. doi: 10.1016/j.annonc.2021.01.071.

	Nivolumab	Chemo (topotecan)	
Study population	284	285	
Median OS	7.5 months	8.4 months	HR, 0.86; P = .11
Median PFS	1.4 months	3.8 months	HR, 1.41;
Objective RR	13.7%	16.5%	OR, 0.80
Median duration response	8.3 months	4.5 months	

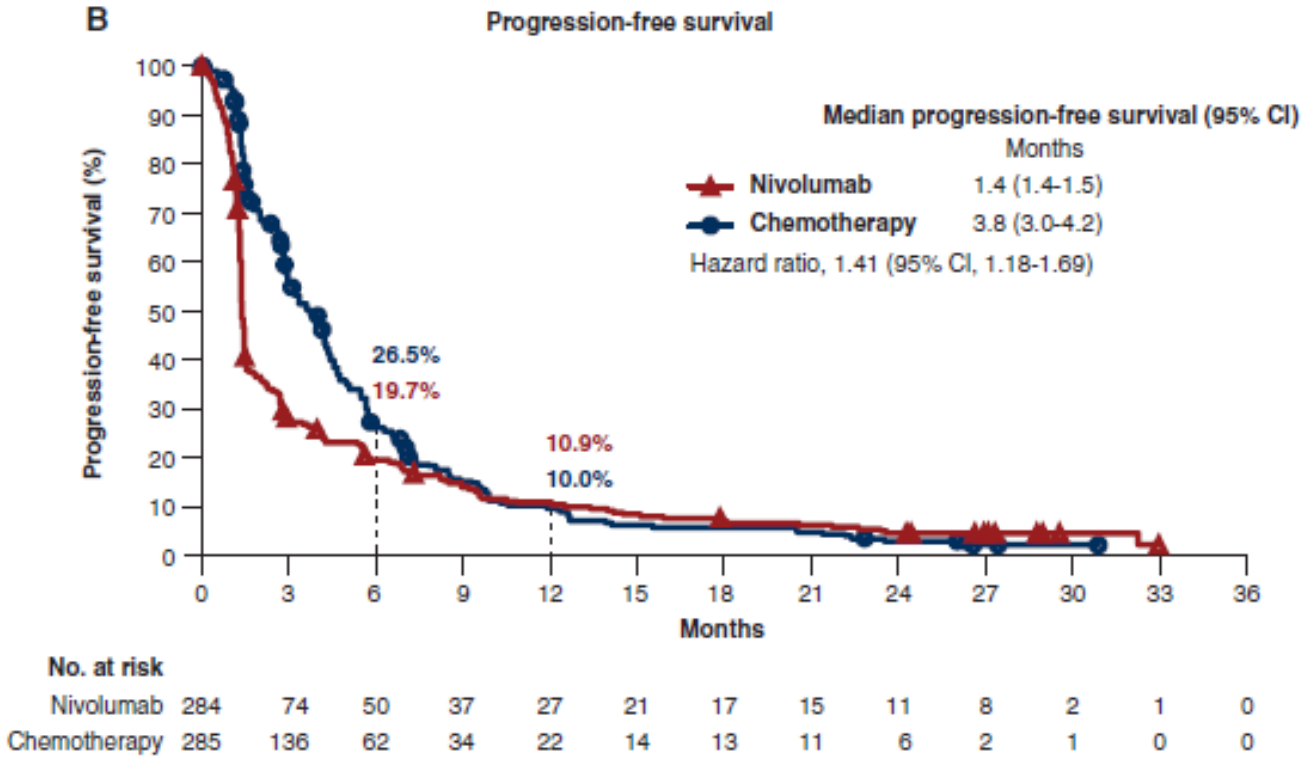


Figure 1. Efficacy of nivolumab versus chemotherapy. (A) Kaplane-Meier estimates of overall survival. (B) Kaplane-Meier estimates of progression-free survival. (C) Kaplane-Meier estimates of duration of response.

Treatment of Small Cell Lung Cancer

2nd-line nivolumab in relapsed small-cell lung cancer: CheckMate 331

Ann Oncol. 2021 May;32(5):631-641. doi: 10.1016/j.annonc.2021.01.071.

	Nivolumab	Chemo (topotecan)	
Study population	284	285	
Median OS	7.5 months	8.4 months	HR, 0.86; P = .11
Median PFS	1.4 months	3.8 months	HR, 1.41;
Objective RR	13.7%	16.5%	OR, 0.80
Median duration response	8.3 months	4.5 months	

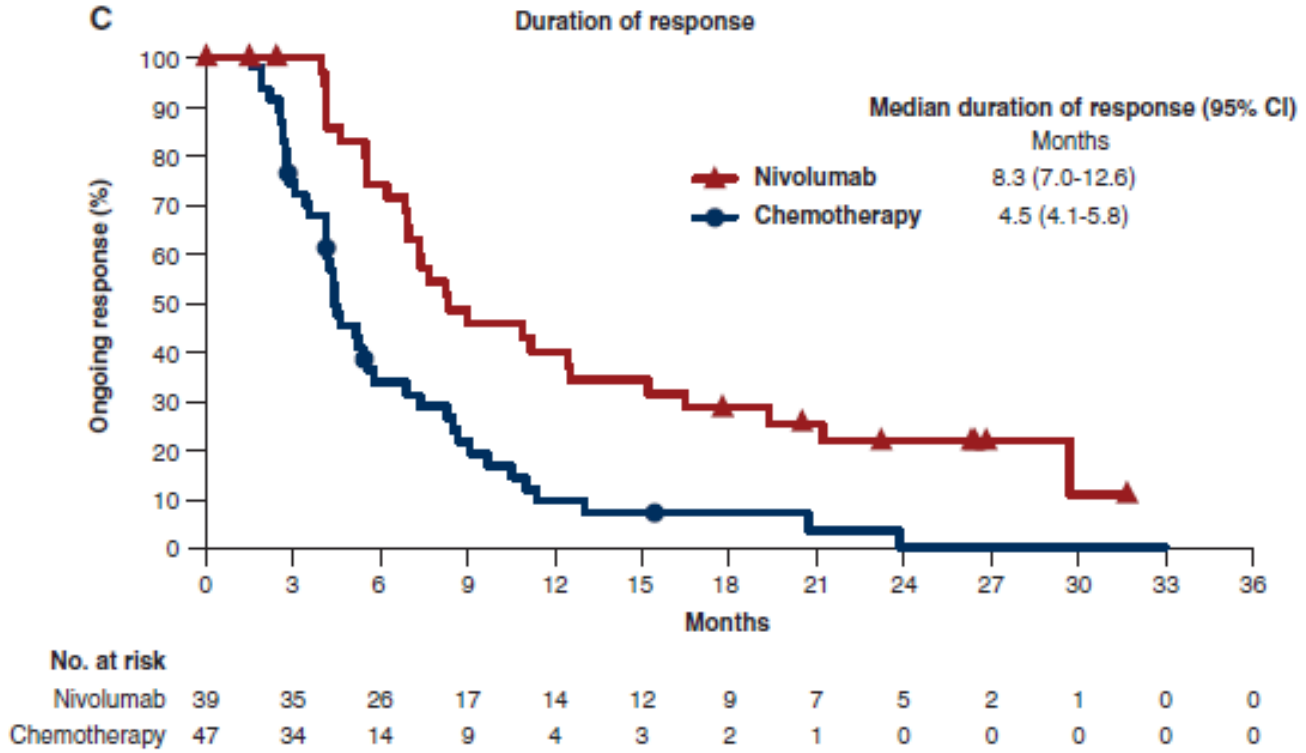


Figure 1. Efficacy of nivolumab versus chemotherapy. (A) Kaplane-Meier estimates of overall survival. (B) Kaplane-Meier estimates of progression-free survival. (C) Kaplane-Meier estimates of duration of response.

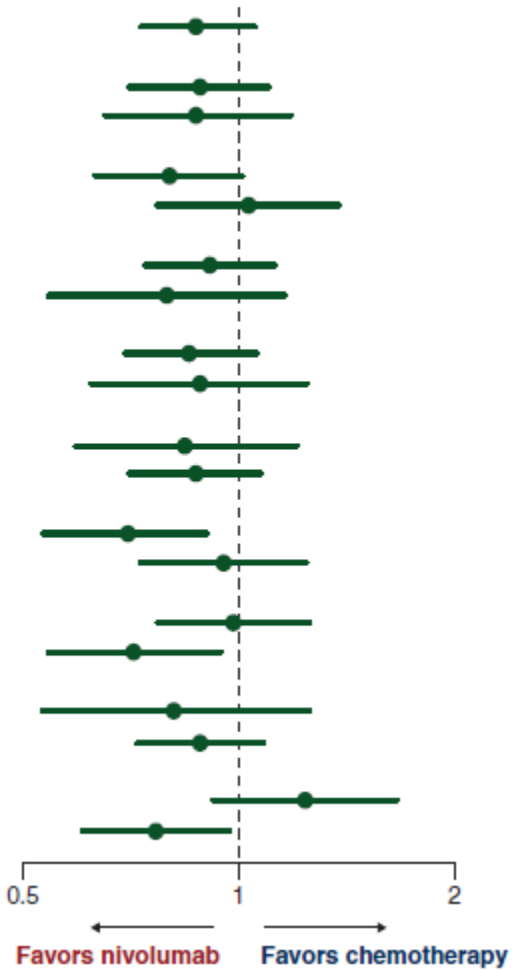
Treatment of Small Cell Lung Cancer

2nd-line nivolumab in relapsed small-cell lung cancer: CheckMate 331

Ann Oncol. 2021 May;32(5):631-641. doi: 10.1016/j.annonc.2021.01.071.

Exploratory subgroup analysis of overall survival.

Subgroup	Nivolumab (No. of patients)	Chemotherapy (No. of patients)	Unstratified hazard ratio (95% CI)
Overall	284	285	0.87 (0.73-1.05)
Age category			
< 65	184	177	0.88 (0.70-1.10)
≥ 65	100	108	0.87 (0.65-1.18)
Sex			
Male	174	177	0.80 (0.63-1.01)
Female	110	108	1.03 (0.77-1.38)
Race			
White	211	211	0.91 (0.74-1.12)
Asian	70	71	0.79 (0.54-1.16)
Disease stage at initial diagnosis			
Extensive	210	191	0.85 (0.69-1.06)
Limited	74	94	0.88 (0.62-1.24)
Baseline ECOG PS			
0	75	81	0.84 (0.59-1.20)
≥ 1	209	204	0.87 (0.70-1.07)
Baseline LDH			
≤ ULN	137	156	0.70 (0.53-0.90)
> ULN	138	108	0.95 (0.73-1.24)
Response to first-line therapy			
Platinum sensitive	163	160	0.98 (0.77-1.25)
Platinum resistant	121	125	0.71 (0.54-0.94)
CNS metastases			
Yes	50	46	0.81 (0.53-1.25)
No	234	239	0.88 (0.72-1.08)
Liver metastases			
Yes	97	108	1.24 (0.92-1.66)
No or not reported	187	177	0.77 (0.61-0.97)

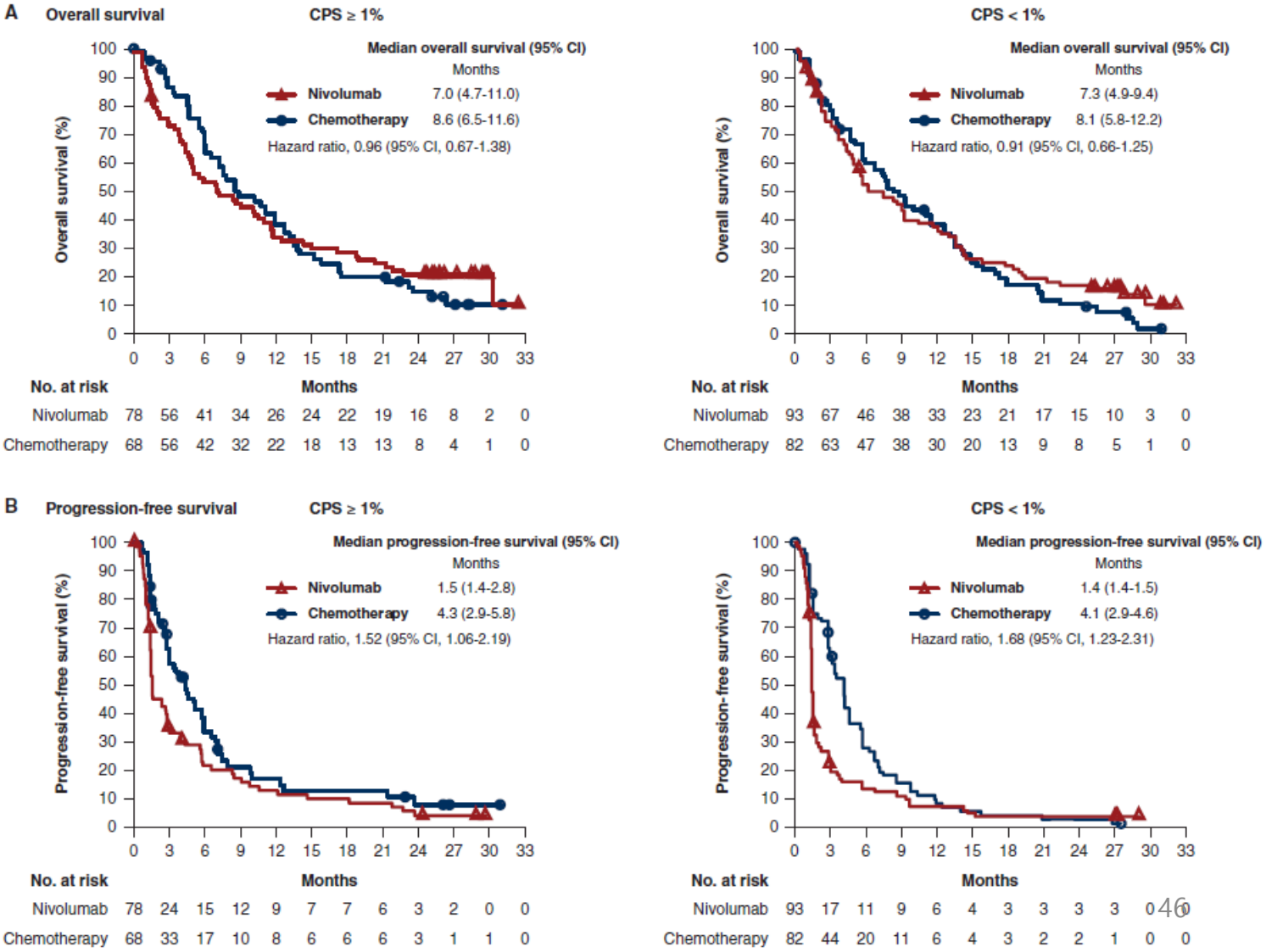


Treatment of Small Cell Lung Cancer

2nd-line nivolumab in relapsed small-cell lung cancer: CheckMate 331

Ann Oncol. 2021 May;32(5):631-641. doi: 10.1016/j.annonc.2021.01.071.

Efficacy by PD-L1 CPS.
(A) Kaplane-Meier estimates of overall survival.
(B) Kaplane-Meier estimates of progression-free survival.
CI, confidence interval; CPS, combined positive score; PD-L1, programed death-ligand 1.



Treatment of Small Cell Lung Cancer

Summary of 2nd line immunotherapy compare to chemotherapy in ES-SCLC

Cancers **2020**, 12, 2522; doi:10.3390/cancers12092522

Table 2. Immunotherapy in pretreated SCLC patients.

Author	Phase	Pts	Setting	Treatment	Response Rate (%)	PFS (Months)	OS (Months)
Reck et al. [27] Checkmate 331	Phase 3	569	Second line	Nivolumab (240 mg) vs. topotecan 1.5 mg/m^2 days 1–5 or amrubicin 40 mg/m^2 days 1–3	14 vs. 16	1.4 (CI95%: 1.4–1.5) vs. 3.8 (CI95%: 3.0–4.2)	7.5 vs. 8.4 (HR 0.86 CI95%: 0.72–1.04)
Goldman JW et al. [28]	Phase I/II	21	Second/third line	Durvalumab 10 mg/kg	9.5% (95%CI: 1.2–30.4)	1.5 (95%CI: 0.9–1.8)	4.8 months (95%CI: 1.3–10.4)
Bondarenko I et al. [29] BALTIC, Arm A	Phase II	21	Second line	Durvalumab 1500 mg plus tremelimumab 75 mg	9.5% (95%CI: 1.1–30.3)	n.r.	n.r.
Pujol JL et al. [30]	Phase II	73	Second line	Atezolizumab 1200 mg vs. chemotherapy	2.3% (95%CI: 0.0–6.8)	1.4 (95%CI: 1.2–1.5) vs. 4.3 (95%CI: 1.5–5.9)	9.5 vs. 8.7 (HR: 0.84; 95%CI: 0.45–1.58; $p = 0.60$

Pts: patients; PD: progression disease; PFS: progression-free survival; OS: overall survival, n.r.: not reported.

Treatment of Small Cell Lung Cancer

More than 2nd line

Table 2. Immunotherapy in pretreated SCLC patients.

Author	Phase	Pts	Setting	Treatment	Response Rate (%)	PFS (Months)	OS (Months)
Ott et al. [21] Keynote 028	Phase Ib	24	standard treatment; PDL 1+	Pembrolizumab (10 mg/kg)	33.3	1.9 (95%CI: 1.7–5.9)	9.7 (95%CI: 4.1–n.r.)
Chung et al. [22] Keynote 158	Phase II	107	PD after standard treatment	Pembrolizumab (200 mg)	18.7 (95%CI: 11.8–27.4)	2 (95%CI: 1.9–2.1)	9.1 (95%CI: 5.7–14.6)
Antonia et al. [24] Checkmate 032	Phase I,II	216	PD after at least one line with platinum based therapy	Nivolumab (3 mg/kg)	10 (CI95%: 5–18)	1.4 (CI95%: 1.4–1.9)	4.4 (CI95%: 3–9.3)
				Nivolumab (1 mg/kg) + Ipilimumab (3 mg/kg)	23 (CI95%: 13–36)	2.6 (CI95%: 1.4–4.1)	7.7 (CI95%: 3.6–18)
				Nivolumab (3 mg/kg) + Ipilimumab (1 mg/kg)	19 (CI95%: 9–31)	1.4 (CI95%: 1.3–2.2)	6 (CI95%: 3.6–11)
Ready et al. [26] Checkmate 032	Expansion cohort of randomized part	147	PD after at least one line with platinum based therapy	Nivolumab (3 mg/kg) vs. nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg)	11.6 (95%CI: 6.9–17.9) vs. 21.9 (95%CI: 14.1–31.5) [odds ratio: 2.12; 95%CI: 1.06–4.26; p0.03]	1.4 (CI95%: 1.3–1.4) vs. 1.5 (95%CI: 1.4–2.2)	5.7 (CI95%: 3.8–7.6) vs. 4.7 (95%CI: 3.1–8.3)

Treatment of Small Cell Lung Cancer

More than 2nd line

Pembrolizumab in Patients With ES-SCLC: Results From the Phase Ib KEYNOTE-028 Study ClinicalTrials.gov identifier: NCT02054806).

J Clin Oncol 35:3823-3829. doi.org/10.1200/JCO.2017. 72.5069

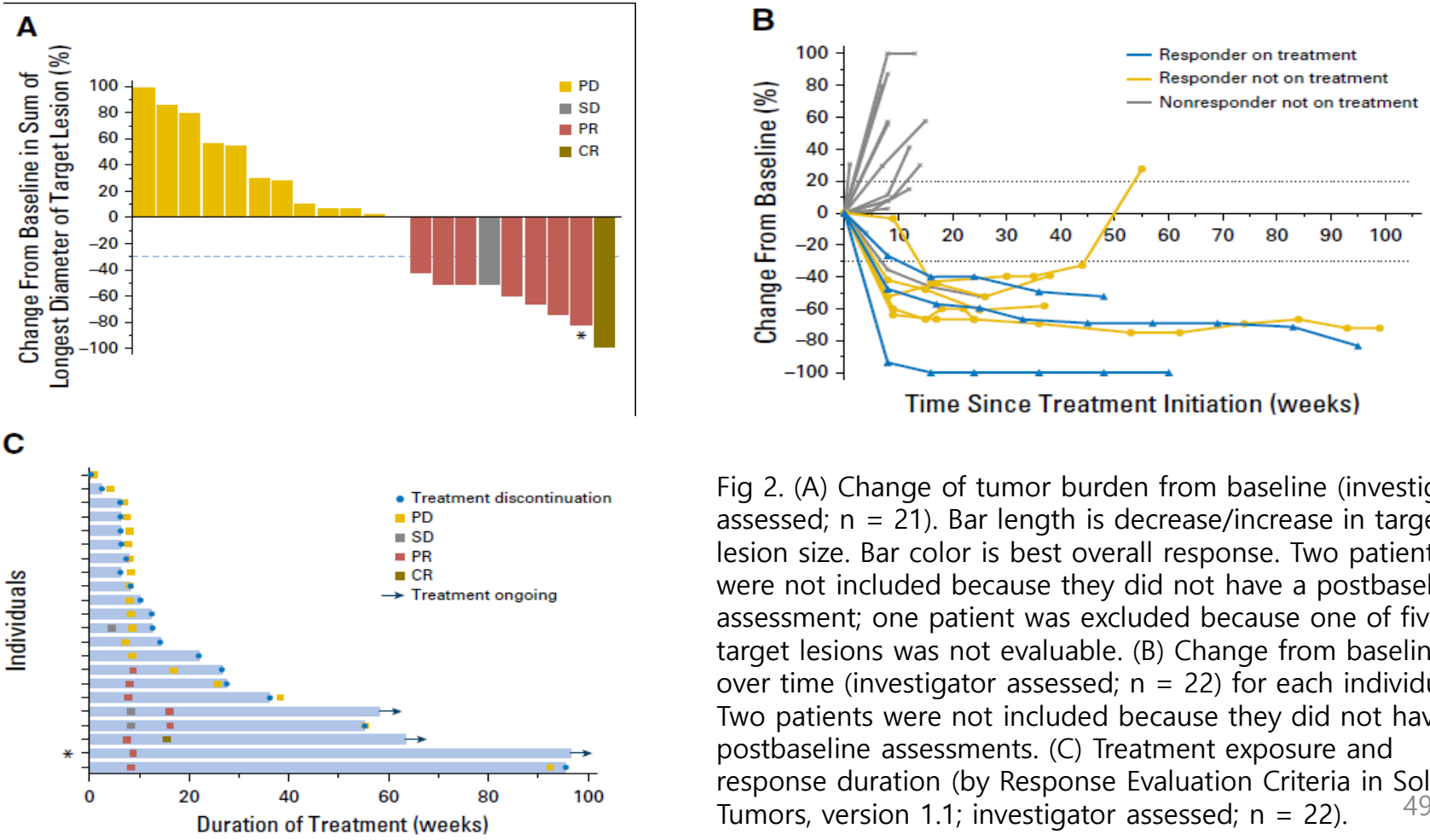


Fig 2. (A) Change of tumor burden from baseline (investigator assessed; n = 21). Bar length is decrease/increase in target lesion size. Bar color is best overall response. Two patients were not included because they did not have a postbaseline assessment; one patient was excluded because one of five target lesions was not evaluable. (B) Change from baseline over time (investigator assessed; n = 22) for each individual. Two patients were not included because they did not have postbaseline assessments. (C) Treatment exposure and response duration (by Response Evaluation Criteria in Solid Tumors, version 1.1; investigator assessed; n = 22).

Treatment of Small Cell Lung Cancer

More than 2nd line

Pembrolizumab in Patients With ES-SCLC: Results From the Phase Ib KEYNOTE-028 Study ClinicalTrials.gov identifier: NCT02054806).

J Clin Oncol 35:3823-3829. doi.org/10.1200/JCO.2017. 72.5069

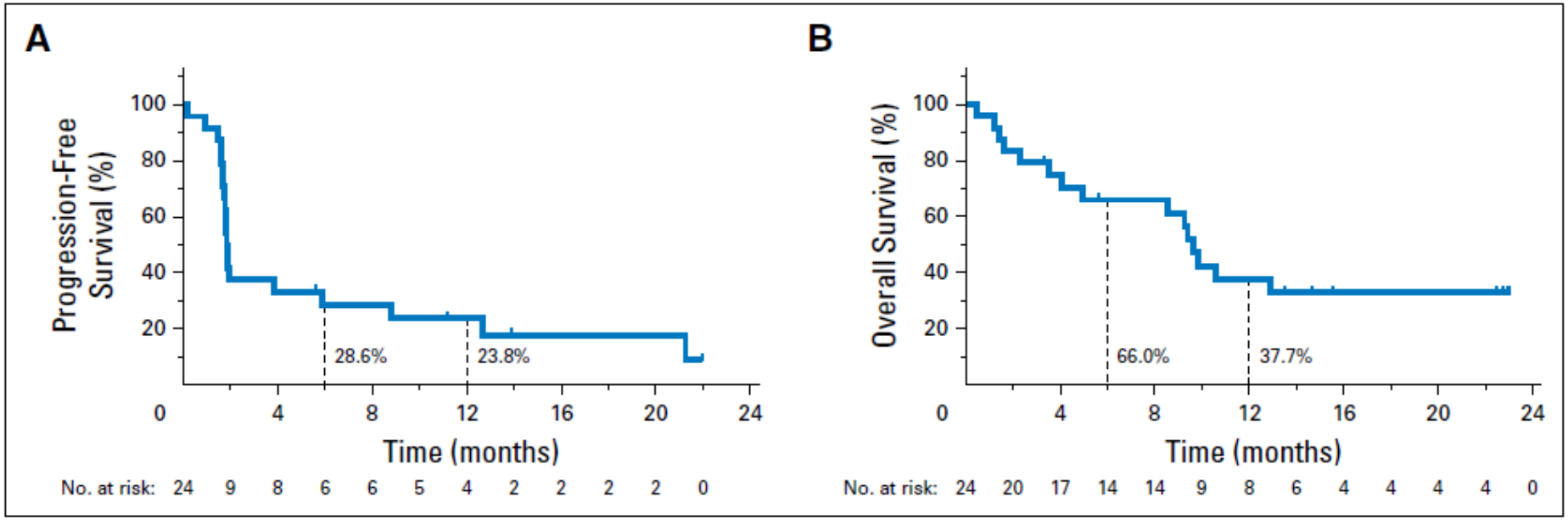


Fig 3. Survival of patients with small-cell lung cancer in KEYNOTE-028: (A) progression-free survival; (B) overall survival. Percentages are the proportion of patients with survival at that time point.

Treatment of Small Cell Lung Cancer

More than 2nd line

Phase 2 study of pembrolizumab in advanced small-cell lung cancer (SCLC): KEYNOTE-158.

J. Clin. Oncol. **2018**, 36, 8506.

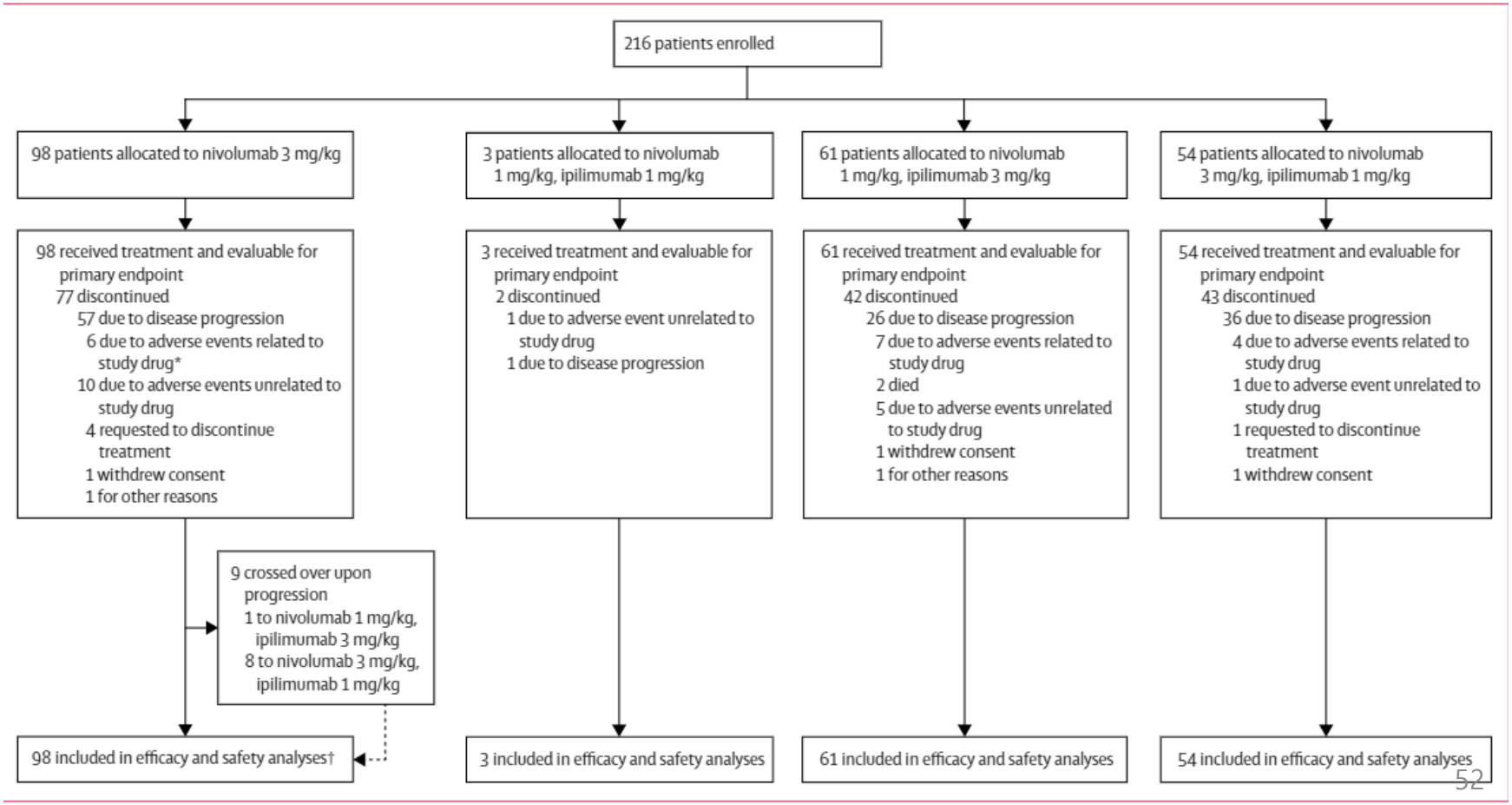
Background: The antitumor activity of pembrolizumab, an IgG4 anti-PD-1 monoclonal antibody, was evaluated in patients (pts) with SCLC in KEYNOTE-158 (NCT02628067), a phase 2 basket study of 11 cancer types. **Methods:** Enrolled pts were aged ≥18 y with advanced SCLC; had measurable disease per RECIST v1.1; ECOG PS ≤1; incurable disease with prior failure of, progression on, or intolerance to standard therapy; and evaluable tumor samples for PD-L1 (PD-L1 IHC 22C3 pharmDx assay [Agilent Technologies]) and other biomarkers. Pembrolizumab 200 mg Q3W was administered for 2 y or until disease progression or intolerable toxicity. The primary endpoint was ORR. DOR, PFS, and OS were secondary endpoints and were estimated by the Kaplan-Meier method. Tumor imaging was performed every 9 wks for the first year, then every 12 wks. Response was assessed per RECIST v1.1 by independent central radiologic review. PD-L1–positive was defined as PD-L1 combined positive score ≥1. **Results:** Among 107 SCLC pts, median age was 63 y (range, 24–84) and 85 (79%) had 1–2 prior therapies. At the data cutoff date (Aug 23, 2017), 36 pts (34%) were continuing on-study; median follow-up was 10.1 mo (range, 0.5–17.5). Tumors were PD-L1–positive in 42 pts (39%) and PD-L1–negative in 50 (47%); 0 had microsatellite instability-high (MSI-H) tumors and 83 (78%) had microsatellite-stable (MSS) tumors. ORR was 18.7% (20/107; 95% CI, 11.8–27.4) overall, 35.7% (15/42; 95% CI, 21.6–52.0) in pts with PD-L1–positive tumors, and 6.0% (3/50; 95% CI, 1.3–16.5) in pts with PD-L1–negative tumors. Overall, median DOR had not been reached (range, 2.1+ to 13.2+ mo); 12 pts (77%) had DOR ≥9 mo. Median PFS was 2.0 mo (95% CI, 1.9–2.1) in all pts, 2.1 mo (95% CI, 2.0–9.9) in pts with PD-L1–positive tumors, and 1.9 mo (95% CI, 1.6–2.0) in pts with PD-L1–negative tumors. Median OS was 9.1 mo (95% CI, 5.7–14.6) overall, 14.6 mo (5.6–not estimable) in pts with PD-L1–positive tumors, and 7.7 mo (95% CI, 3.9–10.4) in pts with PD-L1–negative tumors. Treatment-related AEs occurred in 63 pts (59%) and led to 4 discontinuations and 1 death (pneumonia). **Conclusions:** Pembrolizumab has shown promising antitumor activity and durable responses in advanced SCLC, especially in pts with PD-L1–positive tumors. Clinical trial information: NCT02628067.

Treatment of Small Cell Lung Cancer

More than 2nd line

Nivolumab alone and nivolumab plus ipilimumab in recurrent SCLC (CheckMate 032): a multicentre, open-label, phase 1/2 trial ClinicalTrials.gov, number NCT01928394

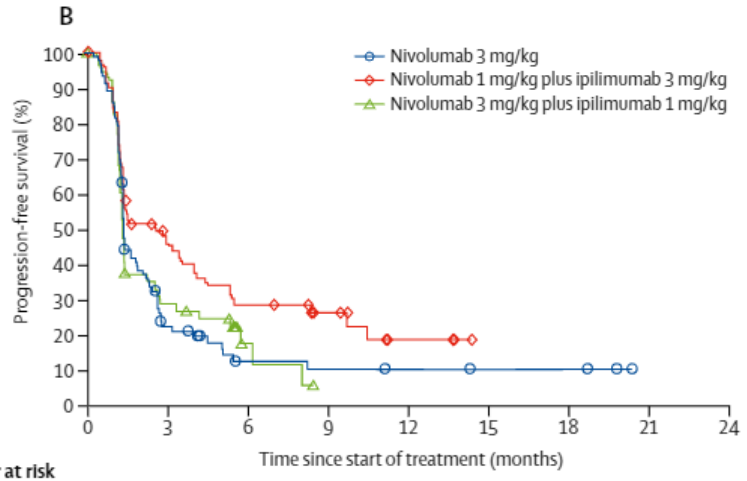
Lancet Oncol. 2016 Jul;17(7):883-895. doi: 10.1016/S1470-2045(16)30098-5.



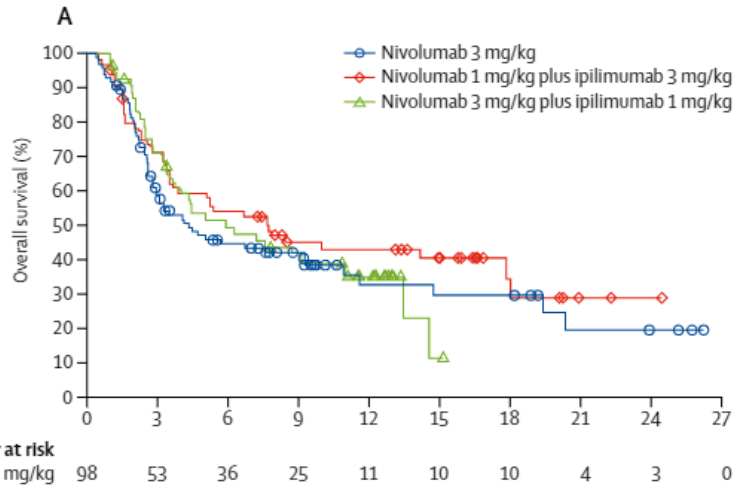
Treatment of Small Cell Lung Cancer

More than 2nd line

Nivolumab alone and nivolumab plus ipilimumab in recurrent SCLC (CheckMate 032): a multicentre, open-label, phase 1/2 trial ClinicalTrials.gov, number NCT01928394
Lancet Oncol. 2016 Jul;17(7):883-895. doi: 10.1016/S1470-2045(16)30098-5.



Number at risk									
Nivolumab 3 mg/kg	98	17	6	5	4	3	3	0	0
Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg	61	24	15	9	3	0	0	0	0
Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg	54	14	3	0	0	0	0	0	0
Number of censored patients									
Nivolumab 3 mg/kg	0	12	17	17	18	19	19	22	22
Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg	0	5	5	10	14	17	17	17	17
Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg	0	4	11	12	12	12	12	12	12



Number at risk										
Nivolumab 3 mg/kg	98	53	36	25	11	10	10	4	3	0
Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg	61	42	32	22	21	15	6	2	1	0
Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg	55	37	25	20	12	1	0	0	0	0
Number of censored patients										
Nivolumab 3 mg/kg	0	6	11	20	30	30	30	34	35	38
Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg	0	2	2	7	7	12	20	23	24	25
Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg	0	3	4	5	10	19	20	20	20	20

Treatment of Small Cell Lung Cancer

More than 2nd line

Nivolumab Monotherapy and Nivolumab Plus Ipilimumab in Recurrent SCLC: Results From the CheckMate 032 Randomized Cohort

J. Thorac. Oncol. 2020, 15, 426–435. doi: 10.1016/j.jtho.2019.10.004.

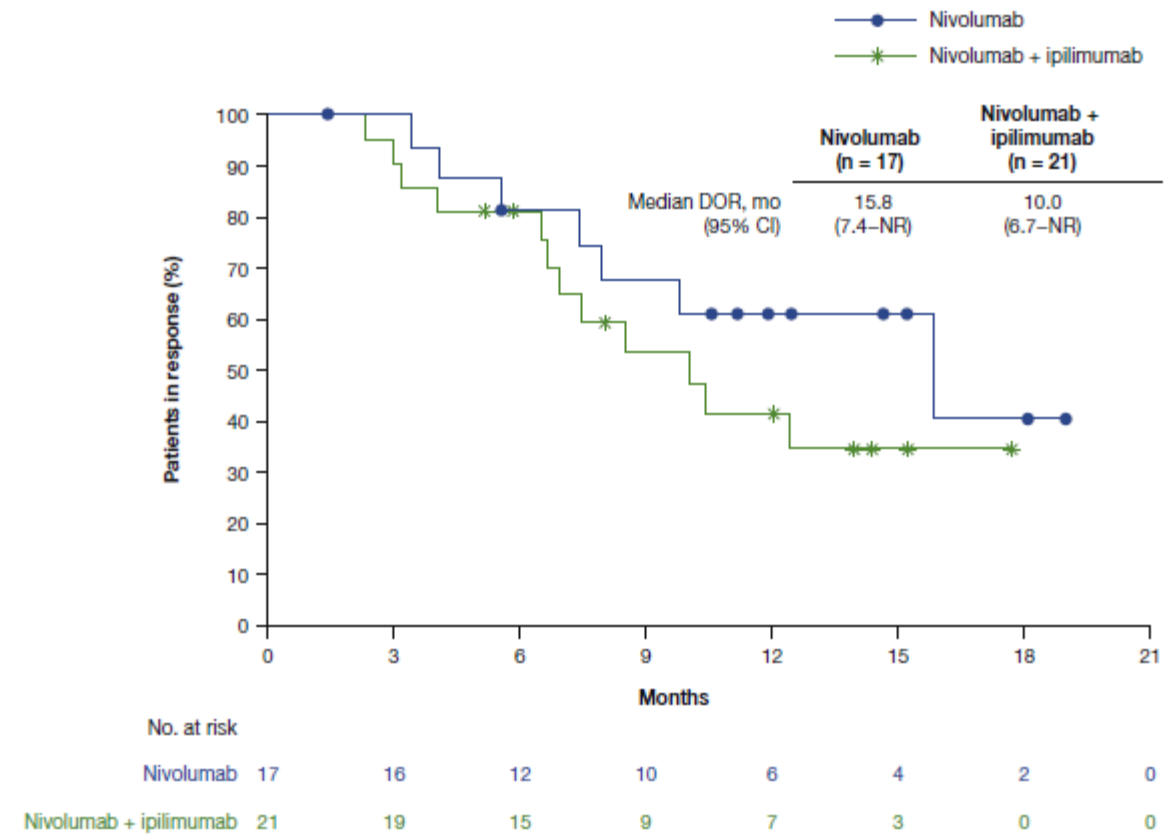


Figure 1. Duration of response. Data are based on a database lock of November 6, 2017. CI, confidence interval; DOR, duration of response; NR, not reached.

Treatment of Small Cell Lung Cancer

More than 2nd line

Nivolumab Monotherapy and Nivolumab Plus Ipilimumab in Recurrent SCLC: Results From the CheckMate 032 Randomized Cohort

J. Thorac. Oncol. 2020, 15, 426–435. doi: 10.1016/j.jtho.2019.10.004.

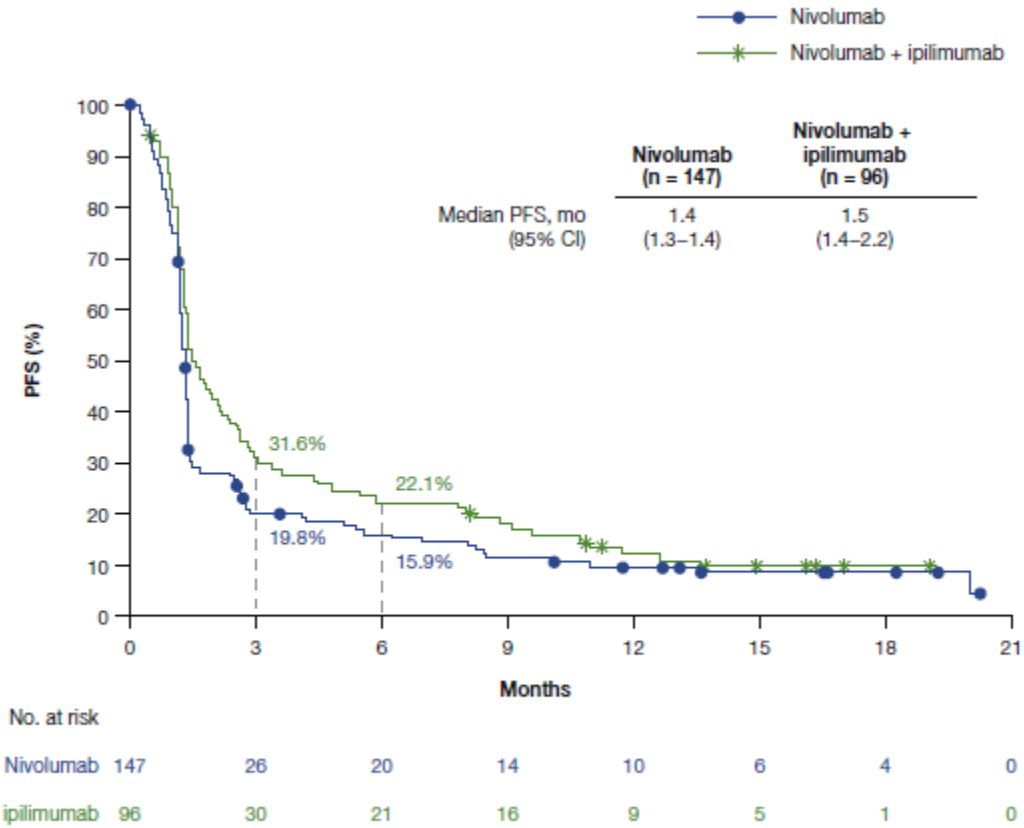


Figure 2. Progression-free survival. Data are based on a database lock of November 6, 2017. CI, confidence interval; mo, months; PFS, progression-free survival.

Treatment of Small Cell Lung Cancer

More than 2nd line

Nivolumab Monotherapy and Nivolumab Plus Ipilimumab in Recurrent SCLC: Results From the CheckMate 032 Randomized Cohort

J. Thorac. Oncol. 2020, 15, 426–435. doi: 10.1016/j.jtho.2019.10.004.

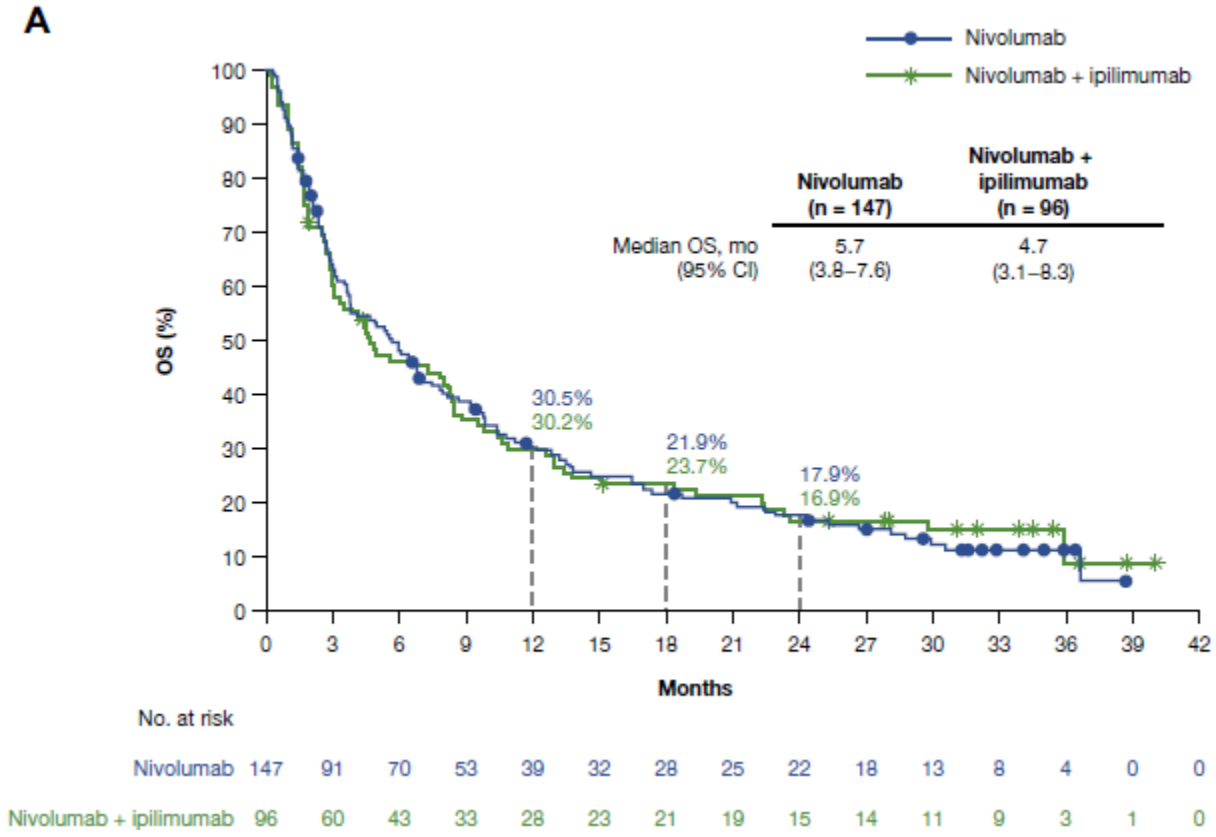


Figure 3. Long-term overall survival in total patient population (A) and in selected subgroups of patients

Treatment of Small Cell Lung Cancer

More than 2nd line

Nivolumab Monotherapy and Nivolumab Plus Ipilimumab in Recurrent SCLC: Results From the CheckMate 032 Randomized Cohort

J. Thorac. Oncol. 2020, 15, 426–435. doi: 10.1016/j.jtho.2019.10.004.

B

Subgroup	N	Nivolumab + ipilimumab mOS (95% CI)	Nivolumab mOS (95% CI)	Unstratified HR (95% CI)
Overall	243	4.7 (3.1–8.3)	5.7 (3.8–7.6)	0.99 (0.75–1.31)
Age				
< 65 y	129	7.8 (3.9–12.6)	6.1 (3.8–9.4)	0.91 (0.61–1.35)
≥ 65 y	114	3.2 (2.1–8.2)	4.8 (3.0–8.0)	1.11 (0.74–1.66)
Sex				
Male	147	4.7 (2.9–8.2)	5.4 (3.7–9.5)	1.17 (0.82–1.67)
Female	96	5.6 (3.0–12.9)	5.7 (3.0–8.7)	0.78 (0.49–1.25)
Baseline ECOG PS				
0	76	12.9 (4.5–23.4)	9.5 (6.0–21.0)	0.79 (0.45–1.37)
1	166	3.2 (2.7–7.3)	3.9 (3.0–6.5)	1.05 (0.75–1.46)
Prior lines of therapy				
1	161	3.4 (2.7–5.6)	6.0 (3.8–9.4)	1.17 (0.83–1.65)
2–3	82	8.4 (3.9–22.4)	5.7 (2.5–8.0)	0.70 (0.43–1.15)
Platinum sensitivity				
Resistant	113	3.1 (2.1–4.7)	3.1 (2.4–6.6)	1.12 (0.75–1.69)
Sensitive	128	8.5 (4.5–12.9)	7.6 (5.5–10.8)	0.92 (0.62–1.37)
Baseline liver metastases				
Yes	112	2.8 (1.8–7.0)	3.6 (2.5–6.0)	1.08 (0.72–1.61)
No	131	8.8 (4.4–13.9)	7.6 (5.0–10.4)	0.87 (0.58–1.30)
Smoking status				
Current/former	227	5.0 (3.2–8.4)	6.0 (3.8–7.9)	0.98 (0.73–1.31)
Never smoked	14	2.9 (1.2–12.6)	4.8 (0.8–11.2)	NA
Baseline TMB				
All evaluable	164	4.5 (3.0–7.8)	5.5 (3.2–8.0)	1.05 (0.74–1.47)
TMB low	53	3.0 (1.9–7.3)	4.2 (2.4–14.6)	1.52 (0.83–2.78)
TMB medium	56	3.9 (1.8–7.0)	3.2 (2.4–6.8)	1.29 (0.73–2.30)
TMB high	55	10.7 (1.8–23.6)	6.6 (3.2–12.0)	0.74 (0.39–1.40)

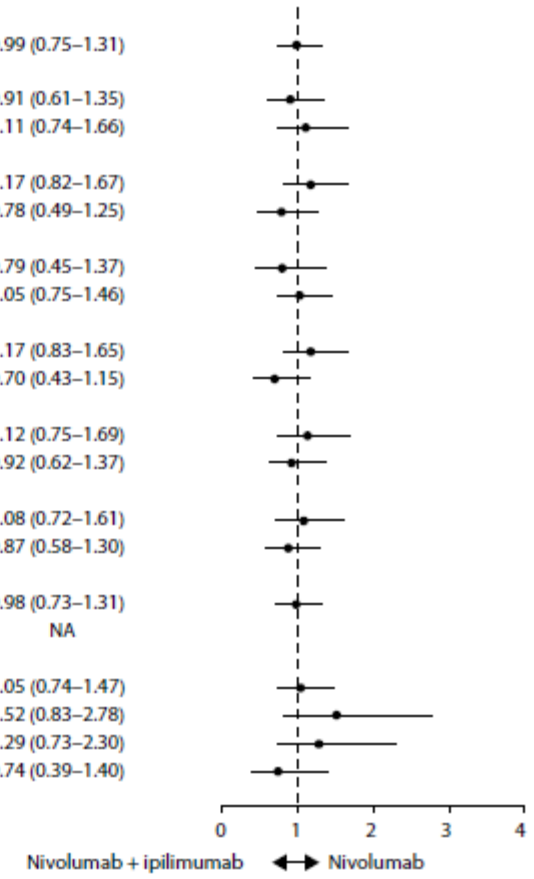


Figure 3. in selected subgroups of patients (B)

Treatment of Small Cell Lung Cancer

3rd-line chemo-immunotherapy

Cancers **2020**, 12, 2522; doi:10.3390/cancers12092522

Table 2. Immunotherapy in pretreated SCLC patients.

Author	Phase	Pts	Setting	Treatment	Response Rate (%)	PFS (Months)	OS (Months)
Chung et al. [23] Keynote 028/158	Pooled analysis	83	III line	Pembrolizumab (10 mg/kg or 200 mg)	19.3 (95%CI: 11.4–29.4)	2.0 (95%CI: 1.9–3.4)	7.7(95%CI: 5.2–10.1)
Ready et al. [25] Checkmate 032	Expansion cohort of phase II	109	III line	Nivolumab (3 mg/kg)	11.9 (CI95% 6.5–19.5)	1.4 (CI95% 1.3–1.6)	5.6 (CI95%: 3.1–6.8)

Treatment of Small Cell Lung Cancer

3rd-Line Chemotherapy in SCLC: An International Analysis

Clin Lung Cancer. 2014 Mar;15(2):110-8. doi: 10.1016/j.cllc.2013.11.003.

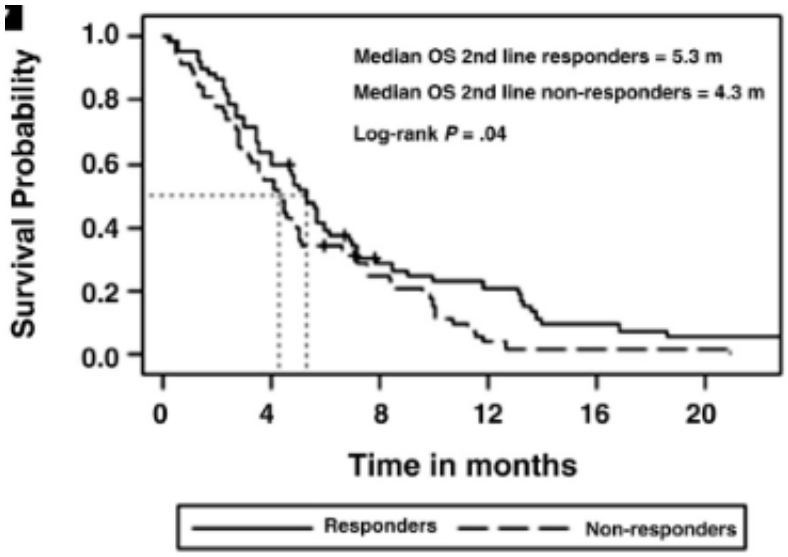
Study population : 120
Duration: from2000 to 2010
Performance: 0-1 (ECOG)

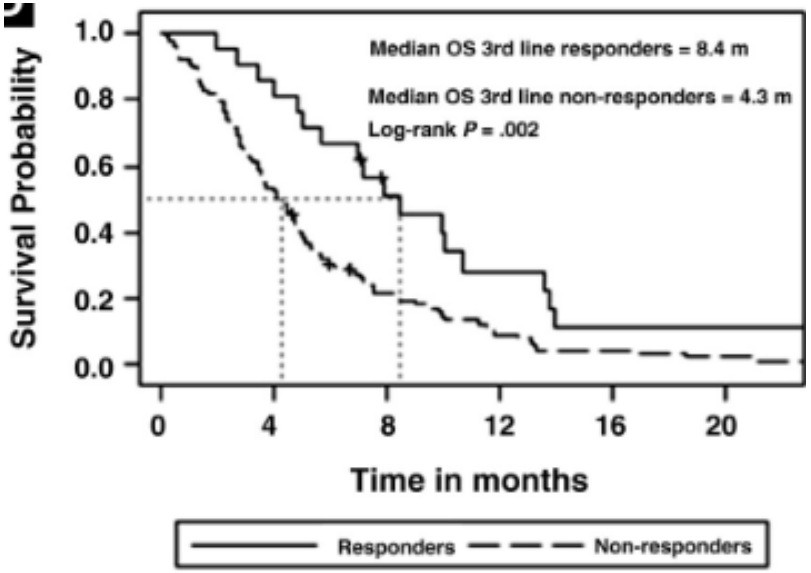
	Regimen (%)	Median Cycles	Response Rate (%)	PFS(Mo.)	OS(Mo.)
1st line	EP (99%)	6	90	9	
2nd line	Platinum based (57%) Clincal Trial (17%) CAV(26%) Topotecan (6%)	4	51	4.6	
3rd line	CAV(43%) Platinum based (24%) Topotecan(17%) Others(16%)	3	18	2.0	4.7

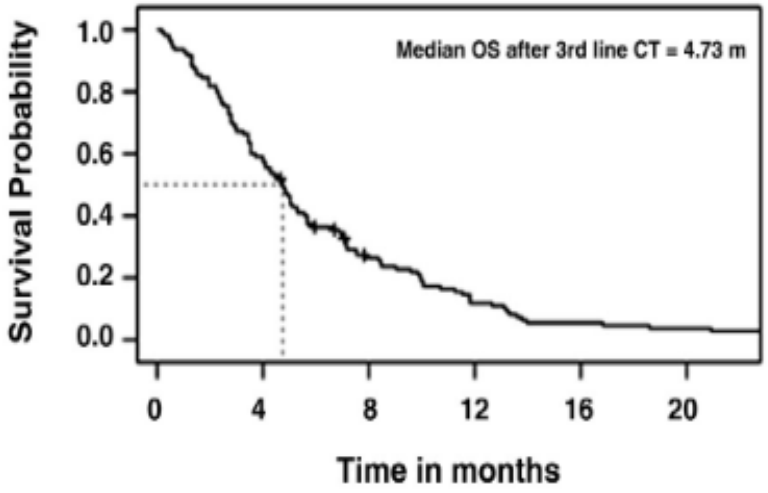
Treatment of Small Cell Lung Cancer

3rd-Line Chemotherapy in SCLC: An International Analysis

Clin Lung Cancer. 2014 Mar;15(2):110-8. doi: 10.1016/j.cllc.2013.11.003.







Response and survival in the third-line setting are modest.

Lack of response to second-line chemotherapy and elevated baseline LDH level might predict lack of benefit from third-line treatment.

Treatment of Small Cell Lung Cancer

3rd-Line Nivolumab Monotherapy in Recurrent SCLC: CheckMate 032 NCT01928394

J Thorac Oncol. 2019 Feb;14(2):237-244. doi: 10.1016/j.jtho.2018.10.003.

Nivolumab monotherapy 3 mg/kg/ every 2 wks
Primary end point: objective response rate (ORR), Secondary end points: DOR PFS, OS and safety

Table 2. ORRs with Third-or Later-Line Nivolumab Monotherapy

Endpoint	Third-or Later-Line Nivolumab (n = 109)
ORR by BICR[a]	
No. of patients	13
% of patients (95% CI)	11.9 (6.5-19.5)
Best overall response, n (%)	
Complete response	1 (0.9)
Partial response	12 (11.0)
Stable disease	25 (22.9)
Progressive disease	56 (51.4)
Unable to determine	14 (12.8)
Not reported	1 (0.9)
Median time to response, mo	1.6
Duration of response	
≥6 mo, n (%)	10 (76.9)
≥12 mo, n (%)	8 (61.5)
Median (95% CI), mo[b]	17.9 (7.9-42.0)
Range, mo	3.0-42.1

[a]Per the Response Evaluation Criteria in Solid Tumors version 1.1.
[b]Computed by using the Kaplan-Meier method.
BICR, blinded independent central review; CI, confidence interval; ORR, objective response rate.

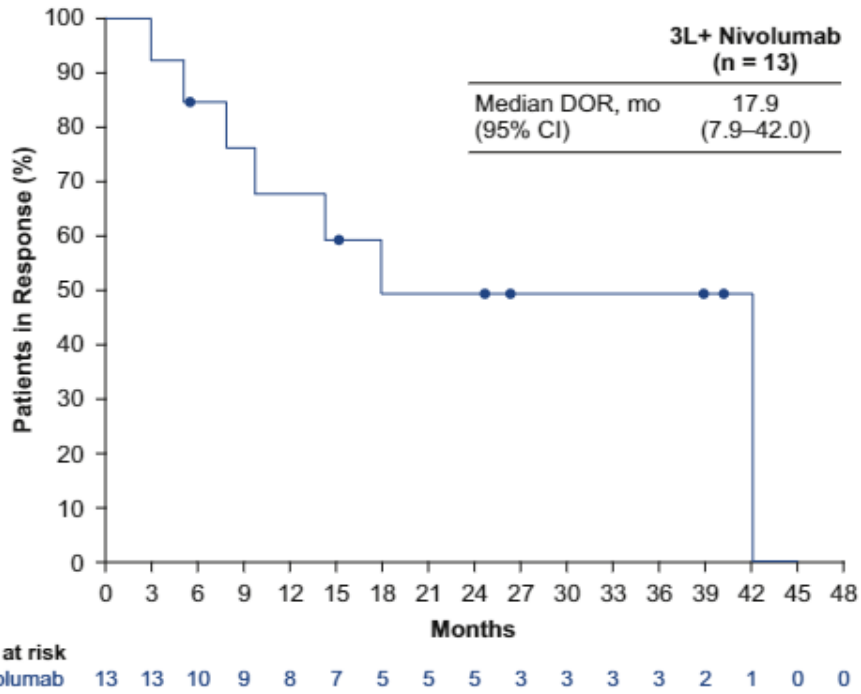


Figure 1. Duration of response (DOR) by blinded independent central review with third- or later-line (3L+) nivolumab monotherapy. CI, confidence interval.

Treatment of Small Cell Lung Cancer

3rd-Line Nivolumab Monotherapy in Recurrent SCLC: CheckMate 032 NCT01928394

J Thorac Oncol. 2019 Feb;14(2):237-244. doi: 10.1016/j.jtho.2018.10.003.

Nivolumab monotherapy 3 mg/kg/ every 2 wks
Primary end point: objective response rate (ORR), Secondary end points: DOR PFS, OS and safety

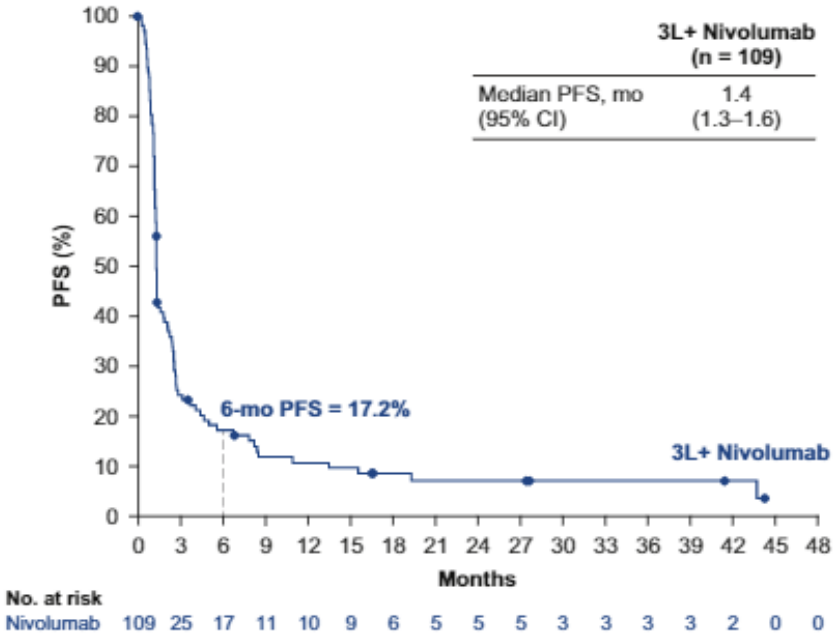


Figure 2. Progression-free survival (PFS) by blinded independent central review with third- or later-line (3L+) nivolumab monotherapy. CI, confidence interval.

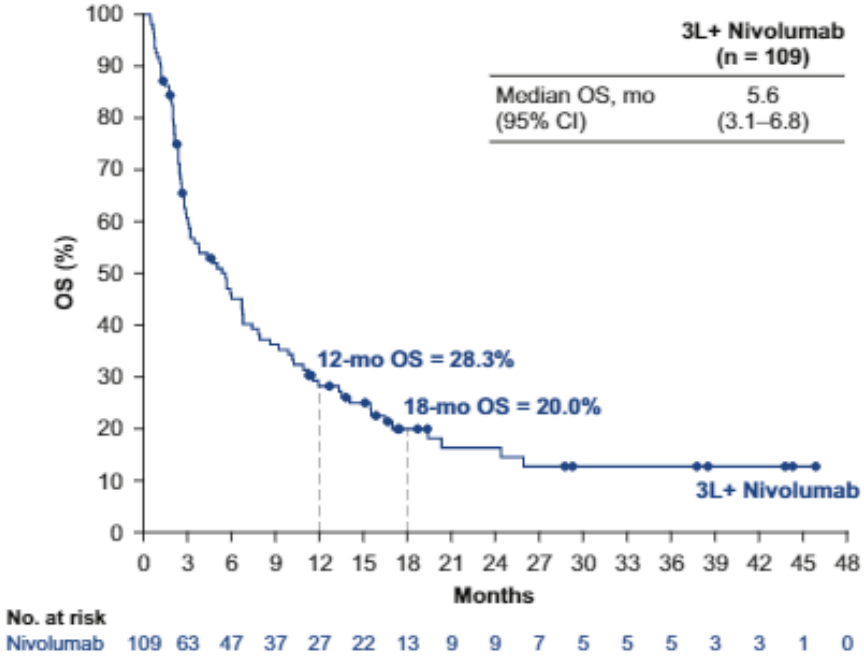
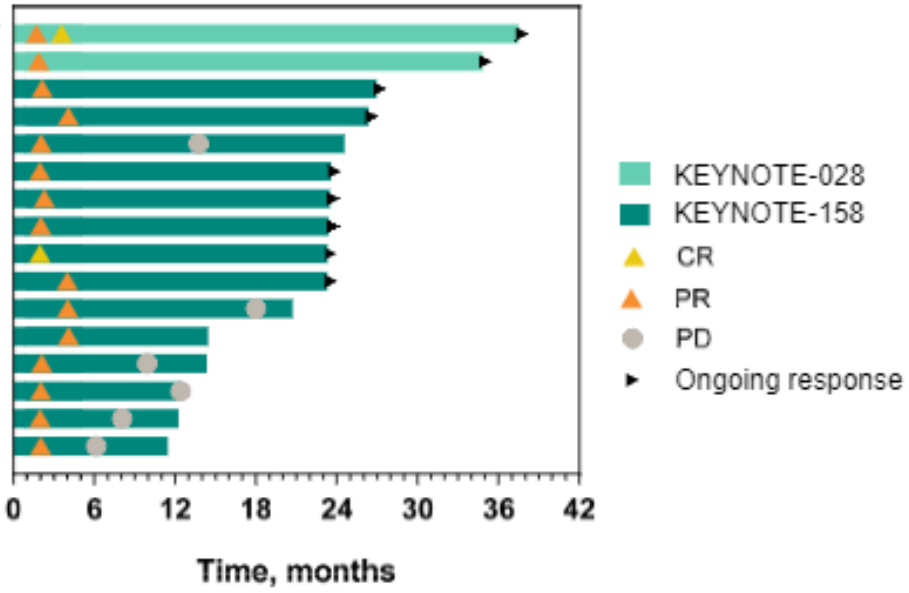


Figure 3. Overall survival (OS) with third- or later-line (3L+) nivolumab monotherapy. CI, confidence interval.

Treatment of Small Cell Lung Cancer

Pembrolizumab After Two or More Lines of Previous Therapy in Patients With Recurrent or Metastatic SCLC: Results From the KEYNOTE-028 and KEYNOTE-158 Studies

J Thorac Oncol. 2020 Apr;15(4):618-627. doi: 10.1016/j.jtho.2019.12.109. Epub 2019 Dec 20.



Time to response in individual patients with (A) a confirmed objective response on the basisof Response Evaluation Criteria in Solid Tumors version 1.1 by central radiology assessment

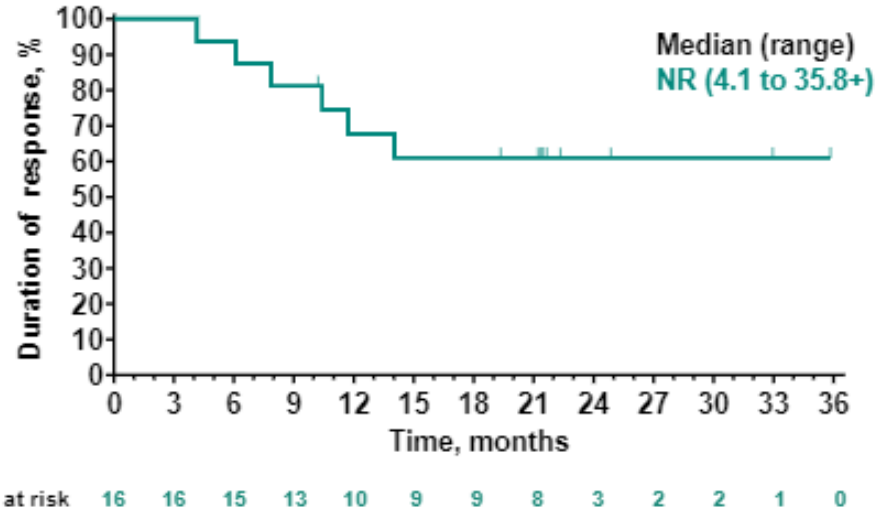


Figure 1. Duration of response by Response Evaluation Criteria in Solid Tumors version 1.1 by independent review. Analysis included patients who achieved a confirmed complete or partial response with pembrolizumab therapy after at least two lines of previous therapy. Patients with an ongoing response were defined as those who were alive without disease progression, had not initiated a new cancer treatment, were not lost to follow-up, and whose last disease assessment was within 5 months of the data cutoff date. NR, not reached.

Treatment of Small Cell Lung Cancer

Pembrolizumab After Two or More Lines of Previous Therapy in Patients With Recurrent or Metastatic SCLC: Results From the KEYNOTE-028 and KEYNOTE-158 Studies

J Thorac Oncol. 2020 Apr;15(4):618-627. doi: 10.1016/j.jtho.2019.12.109. Epub 2019 Dec 20.

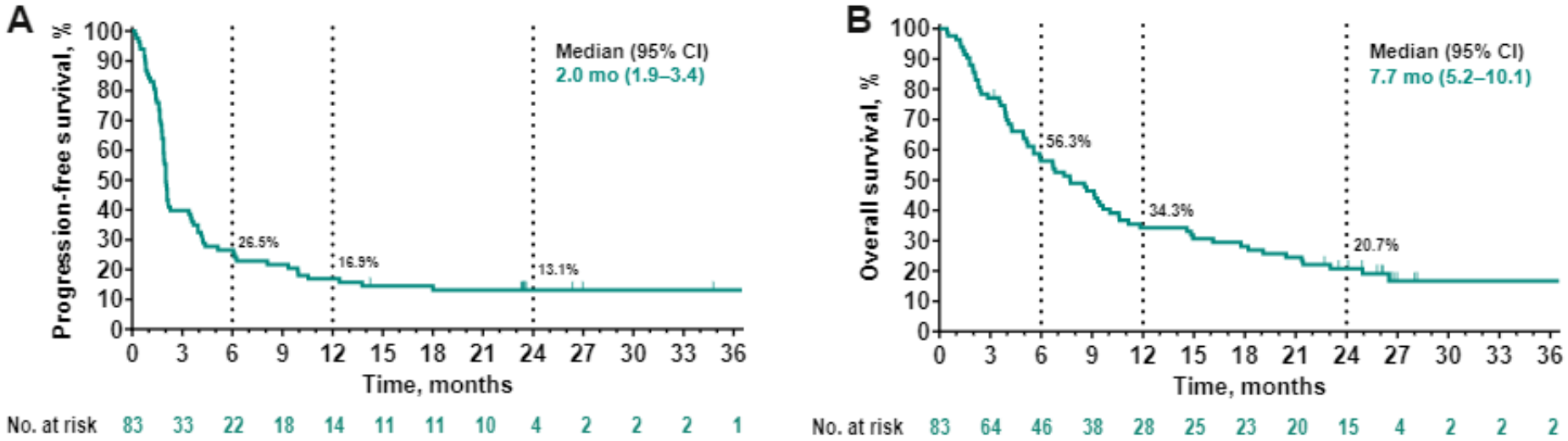


Figure 3. Kaplan-Meier analysis of (*A*) progression-free survival on the basis of Response Evaluation Criteria in Solid Tumors version 1.1 by independent review and (*B*) overall survival. Tick marks represent censored patients. All patients received at least one dose of pembrolizumab therapy after at least two lines of previous therapy. Vertical dotted lines indicate 6- and 12-month overall and progression-free survival rates. CI, confidence interval.

Treatment of Small Cell Lung Cancer

Summary of 3rd-line combined chemo-immunotherapy in ES-SCLC

Cancers **2020**, 12, 2522; doi:10.3390/cancers12092522

Table 2. Immunotherapy in pretreated SCLC patients.

Author	Phase	Pts	Setting	Treatment	Response Rate (%)	PFS (Months)	OS (Months)
Chung et al. [23] Keynote 028/158	Pooled analysis	83	III line	Pembrolizumab (10 mg/kg or 200 mg)	19.3 (95%CI: 11.4–29.4)	2.0 (95%CI: 1.9–3.4)	7.7(95%CI: 5.2–10.1)
Ready et al. [25] Checkmate 032	Expansion cohort of phase II	109	III line	Nivolumab (3 mg/kg)	11.9 (CI95% 6.5–19.5)	1.4 (CI95% 1.3–1.6)	5.6 (CI95%: 3.1–6.8)

Side effects of immunotherapy

TABLE 3. All-Cause Adverse Events With Incidence ≥ 10% in Either Group in the As-Treated Population at Final Analysis

	Pembrolizumab Plus EP (n = 223), No. (%)		Placebo plus EP (n = 223), No. (%)	
Adverse Event	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Neutropenia	127 (57.0)	97 (43.5)	119 (53.4)	91 (40.8)
Anemia	108 (48.4)	35 (15.7)	104 (46.6)	34 (15.2)
Nausea	86 (38.6)	2 (0.9)	96 (43.0)	3 (1.3)
Alopecia	75 (33.6)	0 (0.0)	84 (37.7)	1 (0.4)
Decreased appetite	69 (30.9)	1 (0.4)	55 (24.7)	4 (1.8)
Constipation	66 (29.6)	1 (0.4)	59 (26.5)	2 (0.9)
Fatigue	61 (27.4)	6 (2.7)	61 (27.4)	4 (1.8)
Thrombocytopenia	59 (26.5)	31 (13.9)	49 (22.0)	25 (11.2)
Leukopenia	50 (22.4)	26 (11.7)	46 (20.6)	21 (9.4)
Diarrhea	47 (21.1)	6 (2.7)	42 (18.8)	6 (2.7)
Cough	44 (19.7)	1 (0.4)	45 (20.2)	2 (0.9)
Asthenia	41 (18.4)	8 (3.6)	43 (19.3)	11 (4.9)
Dyspnea	40 (17.9)	3 (1.3)	38 (17.0)	4 (1.8)
Vomiting	36 (16.1)	2 (0.9)	40 (17.9)	4 (1.8)
Pyrexia	34 (15.2)	1 (0.4)	15 (6.7)	1 (0.4)
Dizziness	32 (14.3)	0 (0.0)	15 (6.7)	0 (0.0)
Headache	30 (13.5)	0 (0.0)	34 (15.2)	1 (0.4)
Rash	30 (13.5)	3 (1.3)	13 (5.8)	0 (0.0)
Back pain	26 (11.7)	1 (0.4)	26 (11.7)	0 (0.0)
Pneumonia	26 (11.7)	15 (6.7)	25 (11.2)	10 (4.5)
Hyponatremia	25 (11.2)	0 (0.0)	20 (9.0)	0 (0.0)
Insomnia	25 (11.2)	0 (0.0)	28 (12.6)	0 (0.0)
Pruritus	25 (11.2)	0 (0.0)	18 (8.1)	0 (0.0)
Hypothyroidism	23 (10.3)	0 (0.0)	5 (2.2)	0 (0.0)
Peripheral edema	17 (7.6)	0 (0.0)	27 (12.1)	0 (0.0)

Data are presented in order of descending incidence in the pembrolizumab plus etoposide and platinum (EP) group.

Treatment of Small Cell Lung Cancer

Clinical Trials SCLC

Table 2 Clinical trials of immune-checkpoint inhibitors in SCLC

Immunotherapy	Study name	Study phase	Clinicaltrials.gov study identifier	Status
ES-SCLC: first line				
Ipilimumab + carboplatin/placitaxel vs. carboplatin/paclitaxel	CA184-041	II	NCT00527735	Complete
Ipilimumab + carboplatin/etoposide	ICE	II	NCT01331525	Complete
Ipilimumab + platinum/etoposide vs. platinum/etoposide	CA184-156	III	NCT01450761	Complete
Nivolumab + platinum/etoposide vs. platinum/etoposide	EA5161	II	NCT03382561	Ongoing
Pembrolizumab + platinum/etoposide vs. platinum/etoposide	KEYNOTE-604	III	NCT03066778	Ongoing
Pembrolizumab + platinum/etoposide vs. platinum/etoposide	REACTION	II	NCT02580994	Ongoing
Pembrolizumab + cisplatin/etoposide	KEYNOTE-011	I	NCT01840579	Ongoing
Pembrolizumab + chemotherapy ± radiotherapy	16-01031	II	NCT02934503	Ongoing
Atezolizumab + carboplatin/etoposide vs. carboplatin/etoposide	IMpower133	I/III	NCT02763579	Complete
Atezolizumab + carboplatin/etoposide ± trilaciclib	G1T28-05	II	NCT03041311	Ongoing
Durvalumab ± tremelimumab + chemotherapy vs. chemotherapy	CASPIAN	III	NCT03043872	Ongoing
ES-SCLC: maintenance				
Nivolumab ± ipilimumab vs. placebo	CheckMate 451	III	NCT02538666	Complete
Pembrolizumab	NCI-2015-00107	II	NCT02359019	Complete

Treatment of Small Cell Lung Cancer

Table 2 Clinical trials of immune-checkpoint inhibitors in SCLC

Immunotherapy	Study name	Study phase	Clinicaltrials.gov study identifier	Status
ES-SCLC: second line and beyond				
Nivolumab ± ipilimumab	CheckMate 032	I/II	NCT03527251	Complete
Nivolumab vs. topotecan	CheckMate 331	III	NCT02481830	Complete
Nivolumab ± ipilimumab + Rova-T	M16-300	I/II	NCT03026166	Closed
BMS-986012 ± nivolumab	CA001-030	I/II	NCT02247349	Complete
INCAGN01876 + nivolumab, ipilimumab, or nivolumab + ipilimumab	INCAGN 1876-201	I/II	NCT03126110	Ongoing
INCAGN01949 + nivolumab, ipilimumab, or nivolumab + ipilimumab	INCAGN 1949-201	I/II	NCT03241173	Ongoing
Nivolumab + RGX-104	RGX-104-001	I	NCT02922764	Ongoing
Nivolumab + ipilimumab + Ad.p53-DC	CA209-9KN	II	NCT03406715	Ongoing
Nivolumab + 177Lu-DOTA0-Tyr3-Octreotate	2017-1081	I/II	NCT03325816	Ongoing
Pembrolizumab	KEYNOTE-028	Ib	NCT02054806	Complete
Pembrolizumab	KEYNOTE-158	II	NCT02628067	Complete
Pembrolizumab + paclitaxel	MISP-MK3475	II	NCT02551432	Ongoing
Pembrolizumab + irinotecan	PembroPlus	Ib/II	NCT02331251	Ongoing
Pembrolizumab + amrubicin	MK-3475-IIT-55441	II	NCT03253068	Ongoing
Pembrolizumab vs. topotecan	AFT-17	II	NCT02963090	Ongoing
Pembrolizumab + pegzilarginase	KEYNOTE PN758	I/II	NCT03371979	Ongoin
Pembrolizumab + epacadostat	ALCMI-005	II	NCT03402880	Closed
Pembrolizumab + INCB050465	39110-107	Ib	NCT02646748	Ongoin
Atezolizumab	GO27831	Ia	NCT01375842	Comple
Atezolizumab vs. topotecan	IFCT-1603	II	NCT03059667	Comple
Atezolizumab + hypofractionated radiotherapy	ML39728	II	NCT03262454	Ongoin
Durvalumab + tremelimumab	BALTIC	II	NCT02937818	Ongoin
Durvalumab + olaparib	MEDIOLA	I/II	NCT02734004	Comple
Durvalumab + tremelimumab ± radiotherapy	NCI-2016-00026	II	NCT02701400	Ongoin

SCLC small cell lung cancer, *LS-SCLC* limited-stage disease SCLC, *ES-SCLC* extensive-stage disease SCLC

Treatment of Small Cell Lung Cancer

NCCN Clinical Practice Guidelines in Oncology

Version 1.2022-August 9, 2021

PRIMARY THERAPY FOR EXTENSIVE-STAGE SCLC:

Four cycles of therapy are recommended, but some patients may receive up to 6 cycles based on response and tolerability after 4 cycles.

Preferred Regimens

- Carboplatin AUC 5 day 1 and etoposide 100 mg/m^2 days 1, 2, 3 and atezolizumab 1,200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1,200 mg day 1, every 21 days (category 1 for all)[b,5]
- Carboplatin AUC 5 day 1 and etoposide 100 mg/m^2 days 1, 2, 3 and atezolizumab 1,200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1,680 mg day 1, every 28 days[b]
- Carboplatin AUC 5–6 day 1 and etoposide 80–100 mg/m^2 days 1, 2, 3 and durvalumab 1,500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1,500 mg day 1 every 28 days (category 1 for all)[b,6]
- Cisplatin 75–80 mg/m^2 day 1 and etoposide 80–100 mg/m^2 days 1, 2, 3 and durvalumab 1,500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1,500 mg day 1 every 28 days (category 1 for all)[b,6]

Other Recommended Regimens

- Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m^2 days 1, 2, 3[7]
- Cisplatin 75 mg/m^2 day 1 and etoposide 100 mg/m^2 days 1, 2, 3[8]
- Cisplatin 80 mg/m^2 day 1 and etoposide 80 mg/m^2 days 1, 2, 3[9]
- Cisplatin 25 mg/m^2 days 1, 2, 3 and etoposide 100 mg/m^2 days 1, 2, 3[10]

Useful In Certain Circumstances

- Carboplatin AUC 5 day 1 and irinotecan 50 mg/m^2 days 1, 8, 15[11]
- Cisplatin 60 mg/m^2 day 1 and irinotecan 60 mg/m^2 days 1, 8, 15[12]
- Cisplatin 30 mg/m^2 days 1, 8 and irinotecan 65 mg/m^2 days 1, 8[13]

Subsequent Systemic Therapy (SCL-E 2 of 5)
Response Assessment (SCL-E 3 of 5)
References (SCL-E 4 of 5)

Treatment of Small Cell Lung Cancer

주요 암종별 항암요법

1 소세포폐암(Small Cell Lung Cancer)

가. 투여단계: 1차(first-line)

연번	항암요법	투여대상
1	etoposide + platinum (개정 제2021-46호: 2021.3.1)	LD, ED
2	irinotecan + platinum	
3	atezolizumab[주1] + etoposide + carboplatin (개정 제2020-216호: 2020.8.1)	ED

주1. 면역관문억제제(nivolumab, pembrolizumab 등)는 예상치 못한 부작
의료기관에서 항암치료요법에 대한 지식과 경험이 충분한 의사에
현황 등에 관한 자료를 건강보험심사평가원장에게 제출하여야 한다.

나. 투여단계: 2차 이상

연번	항암요법	투여대상
1	cyclophosphamide + doxorubicin + vincristine (개정 제2021-46호: 2021.3.1)	LD, ED
2	etoposide + platinum (개정 제2021-46호: 2021.3.1)	
3	irinotecan + platinum	
4	irinotecan	
5	belotecan	
6	topotecan(IV, PO) ※ 'PO 제제'는 식약처 허가사항에 따라 소세포폐암 성인 환자에게 사용 시 요양급여를 인정함 (개정 제2009-6호: 2009.10.1)	
7	paclitaxel (개정 제2017-21호: 2017.2.1)	

Treatment of Small Cell Lung Cancer

Summary of ED-SCLC

1. incidence has been decreasing, male-to-female incidence ratio is now 1:1.

2. Stop smoking and good compliance increased survival

3. CT screening is ineffective for SCLC. Efforts to reduce mortality of SCLC should instead focus on prevention through tobacco reduction programs, as well as the development of improved treatment options.

4. TNM staging allow for more precise assessments of prognosis and specific therapy in the future.

5. 1st line combined immuno-chemotherapy increase PFS and OS compared chemotherapy.

6. 3rd line single immunotherapy increase OS compare to best supportive care.