Updates in the management of SCLC

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Contents

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01

Treatment in ES-SCLC

First-line treatment

Second-line treatment

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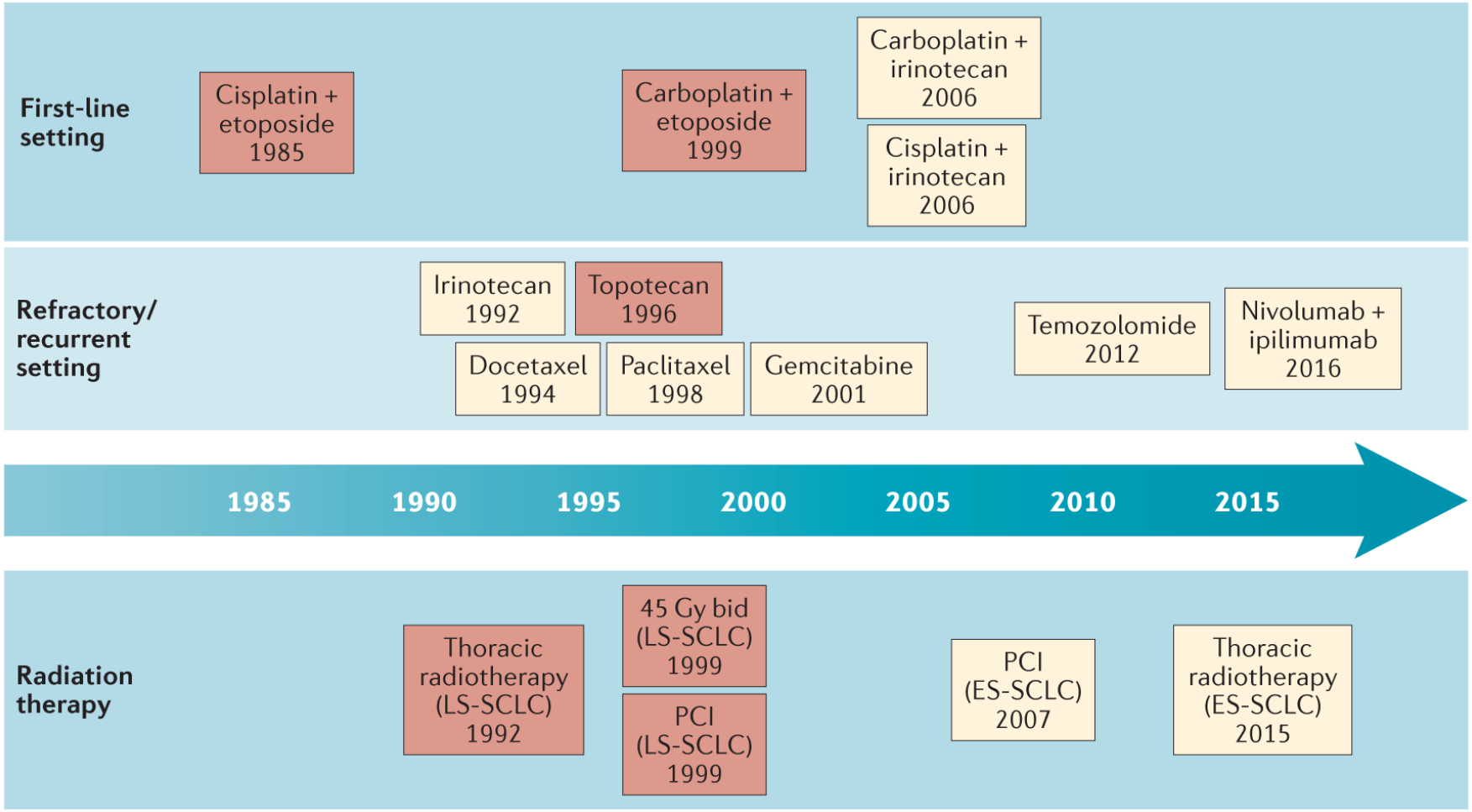
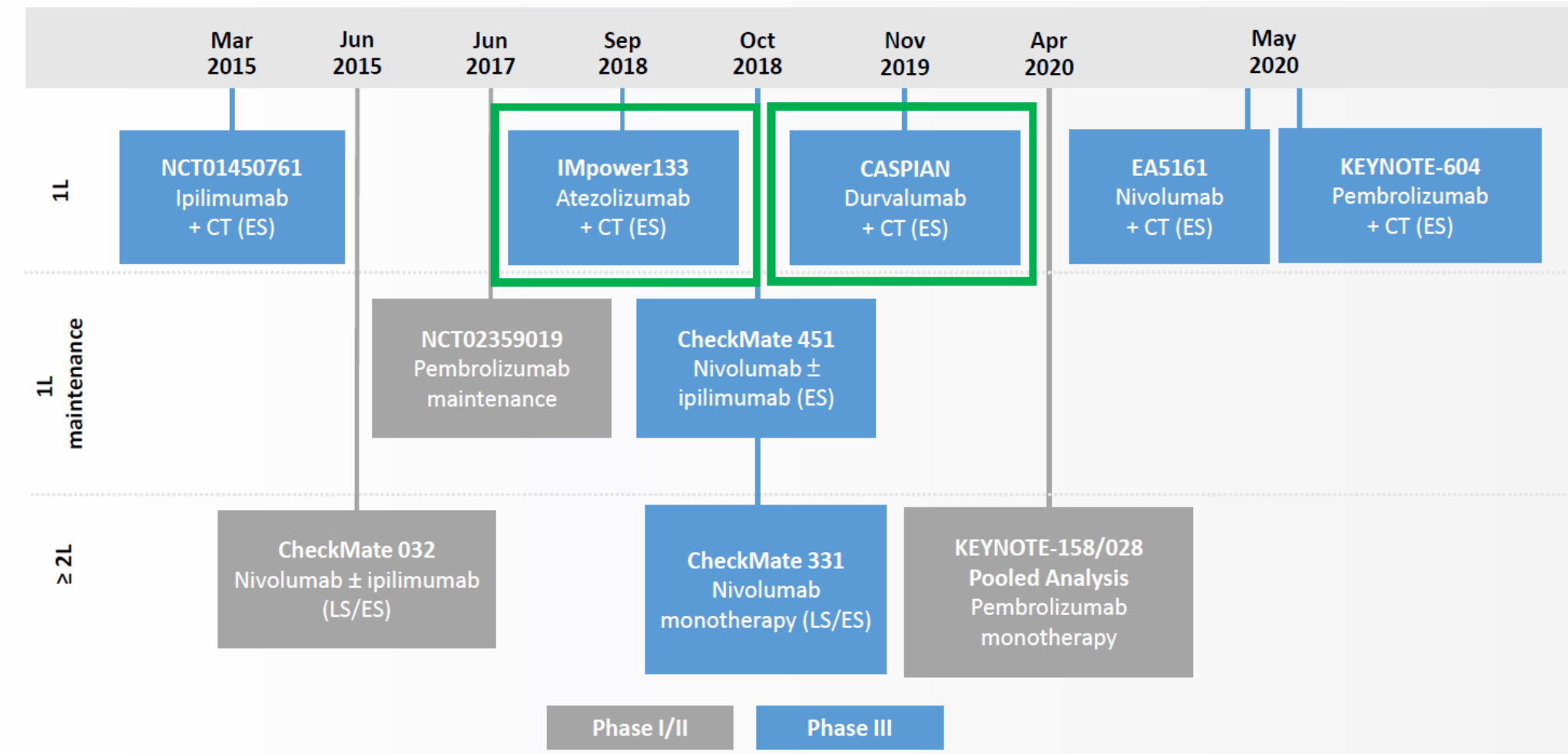
Timeline of therapeutic advances for SCLC



Nat Rev Clin Oncol 2017

Overview of Key studies of immune checkpoint inhibitors in SCLC



Immunotherapy 2019, Modified from 2020 WCLC

1L chemotherapy-IO trials in ES-SCLC

Trial	Treatment	PFS/OS (median, months)	OS HR (95% CI)	PFS HR (95% CI)
IMPower 133	Atezolizumab + carboplatin + etoposide	5.2/12.3	0.76 (0.60-0.95)	0.77 (0.63-0.95)
	Placebo + carboplatin + etoposide	4.3/10.3	✓	✓
CASPIAN	Durvalumab + platinum + etoposide	5.1/12.9	0.75 (0.62-0.91)	0.80 (0.66-0.96)
	Platinum + etoposide	5.4/10.5	✓	✓
KEYNOTE 604	Pembrolizumab + platinum + etoposide	4.5/10.8	0.80 (0.64-0.98)	0.75 (0.61-0.91)
	Placebo + platinum + etoposide	4.3/9.7	✗	✓

NEJM 2018, Lancet Oncol 2021, J Clin Oncol 2020

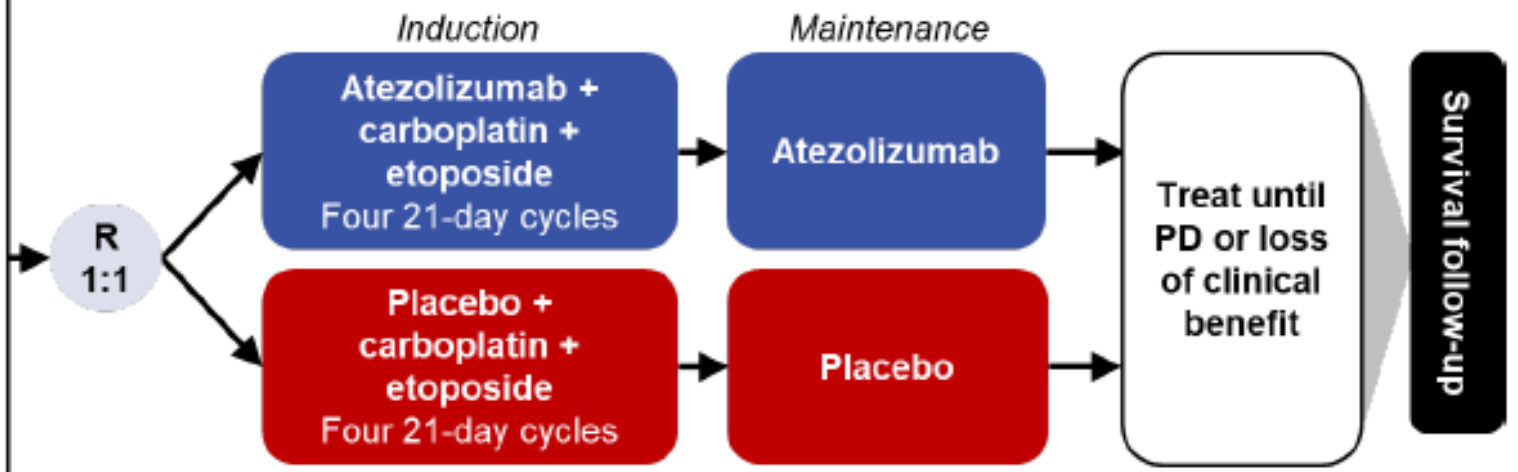
IMpower133 : Atezolizumab plus carboplatin/etoposide

- Measurable ES-SCLC (per RECIST version 1.1)
- ECOG PS 0 or 1
- No prior systemic treatment for ES-SCLC
- Patients with treated asymptomatic brain metastases were eligible

Stratification

- Sex (male vs female)
- ECOG PS (0 vs 1)
- Brain metastases (yes vs no)

N=403



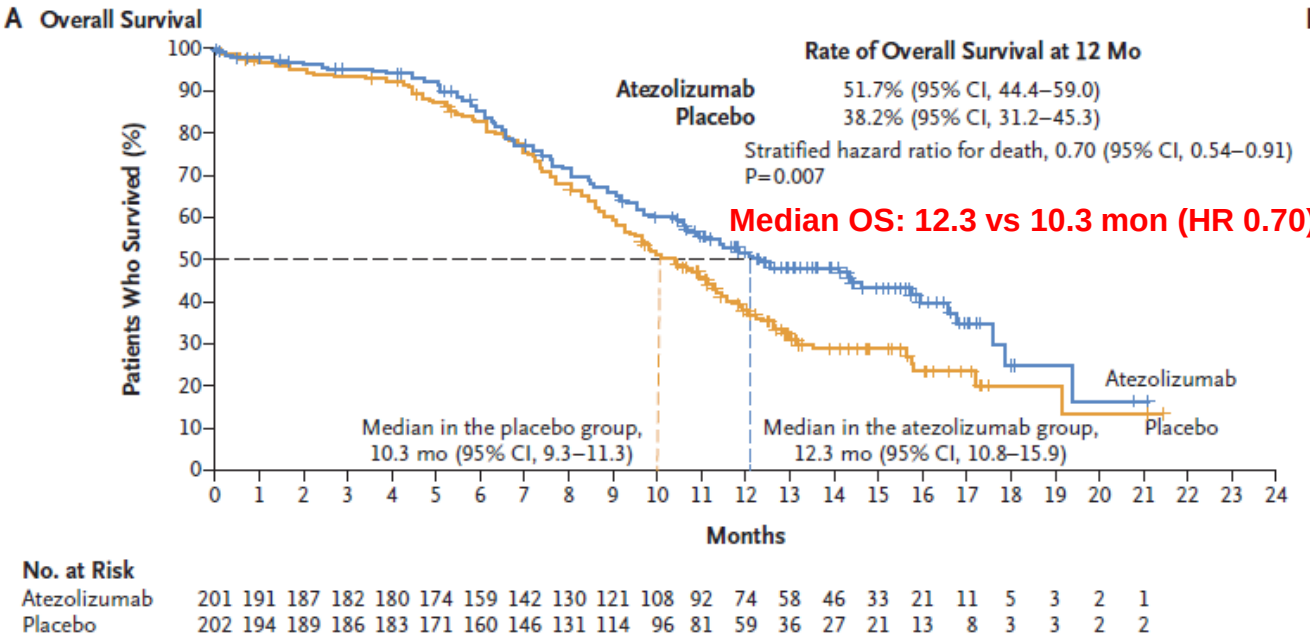
Primary endpoints

- ✓ OS
- ✓ Investigator-assessed PFS

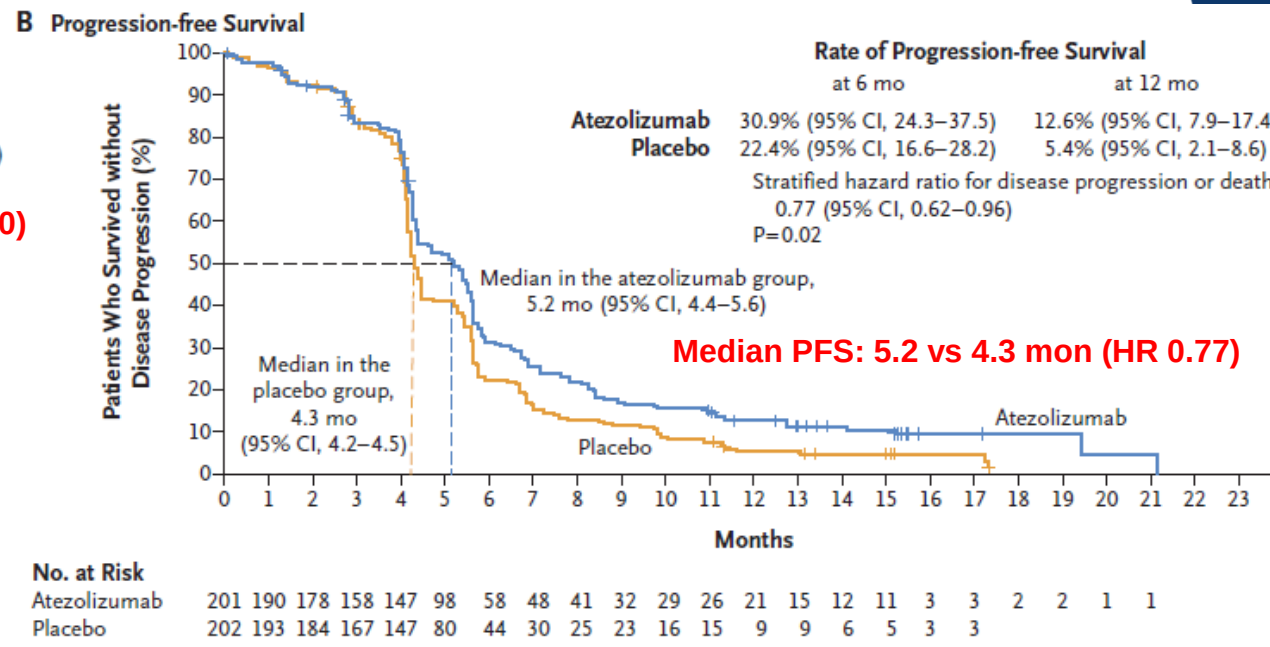
NEJM 2018

IMpower133 : Atezolizumab plus carboplatin/etoposide

[OS]



[PFS]



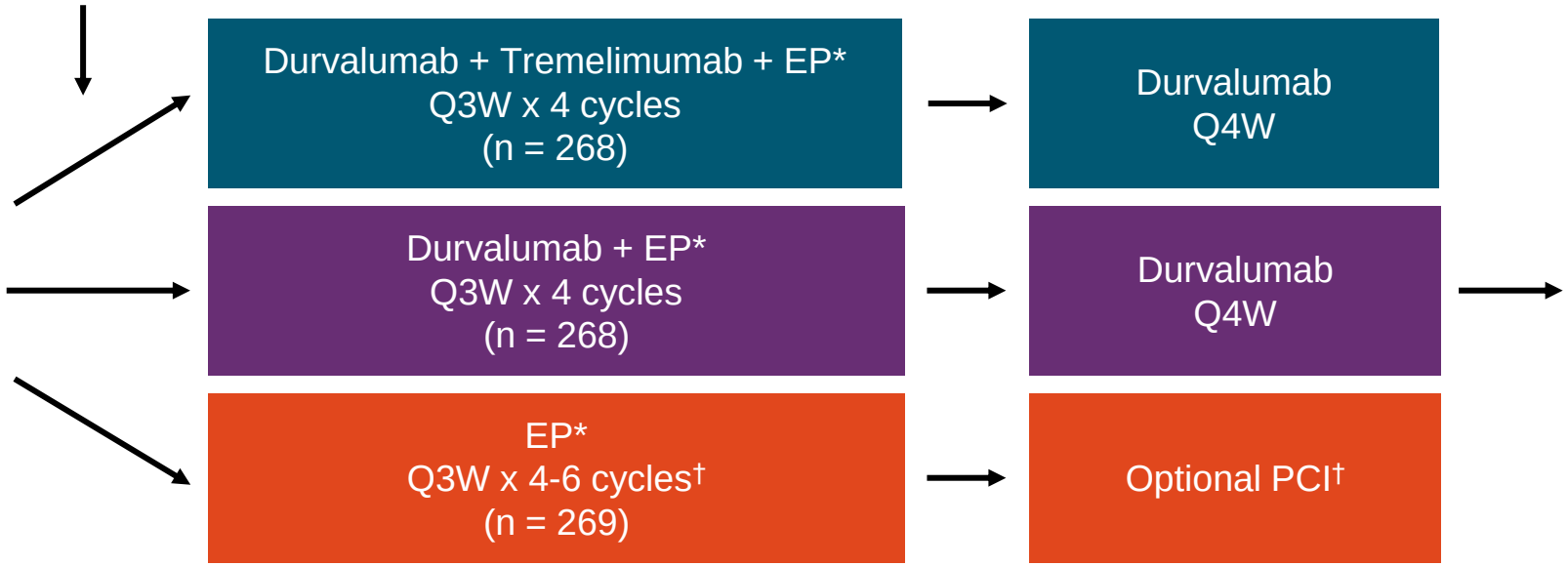
NEJM 2018

CASPIAN: Durvalumab with/out tremelimumab plus PE

Randomized, open-label, multicenter phase III study

Stratified by planned carboplatin vs cisplatin

- Treatment-naive, extensive-stage SCLC
- WHO PS 0/1
- Measurable disease per RECIST v1.1
- Life expectancy ≥ 12 wks
- Asymptomatic or treated and stable brain metastases
  (N = 805)



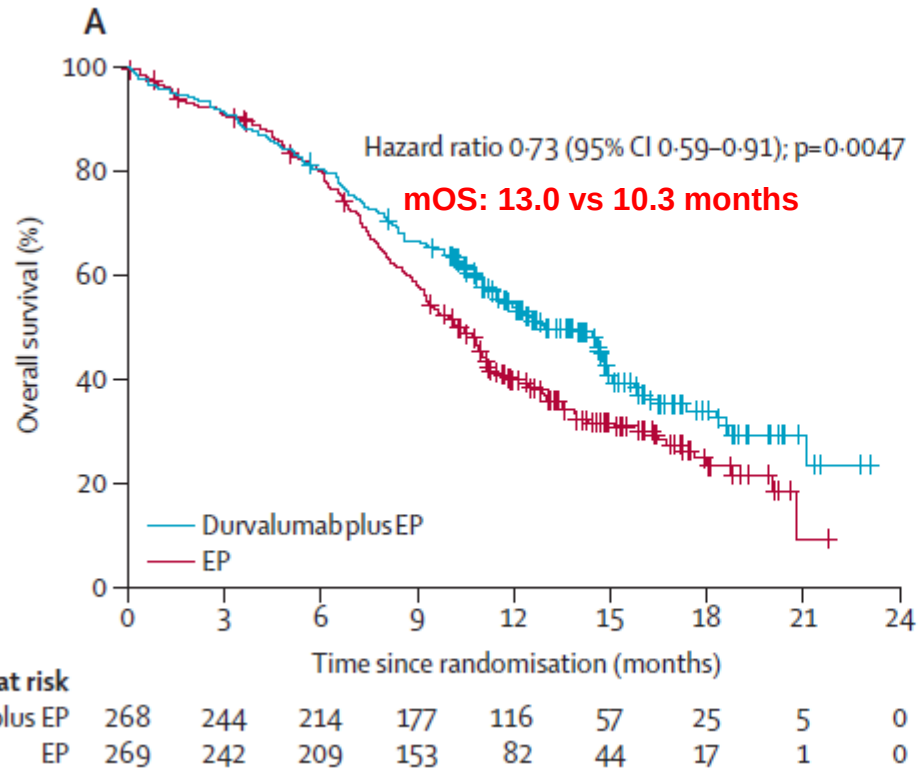
*Etoposide 80-100 mg/m^2 with either carboplatin AUC 5-6 or cisplatin 75-80 mg/m^2, durvalumab 1500 mg, tremelimumab 75 mg.
†Per investigator discretion, additional 2 cycles of EP (6 cycles total) and PCI

*Primary endpoint: OS

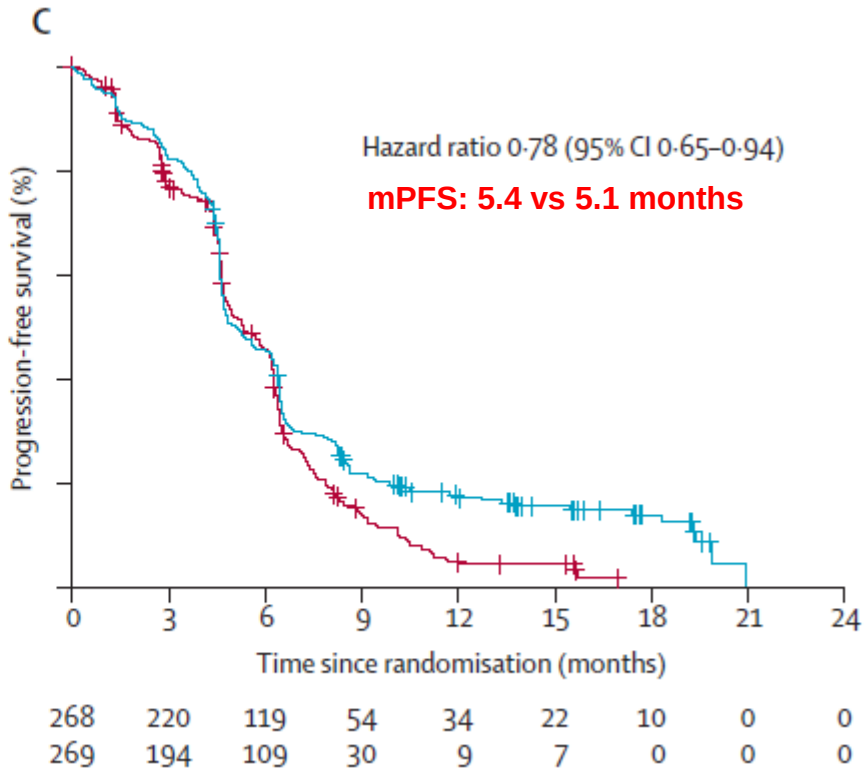
Lancet Oncol 2019

CASPIAN: Durvalumab plus PE vs. PE

[OS]



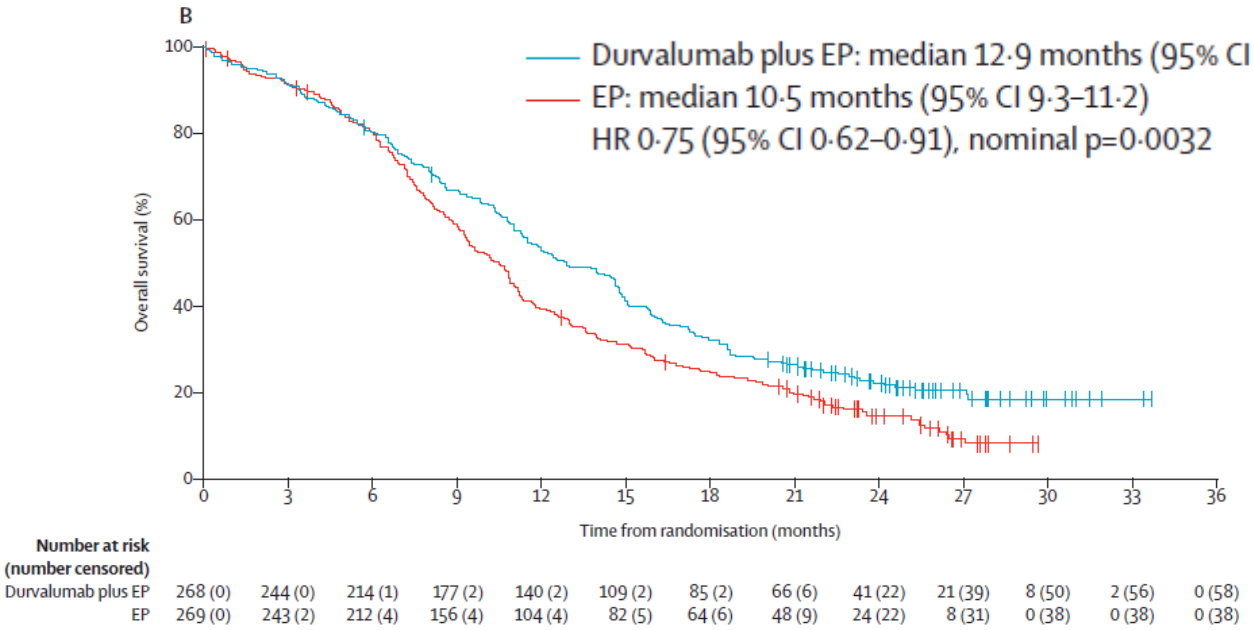
[PFS]



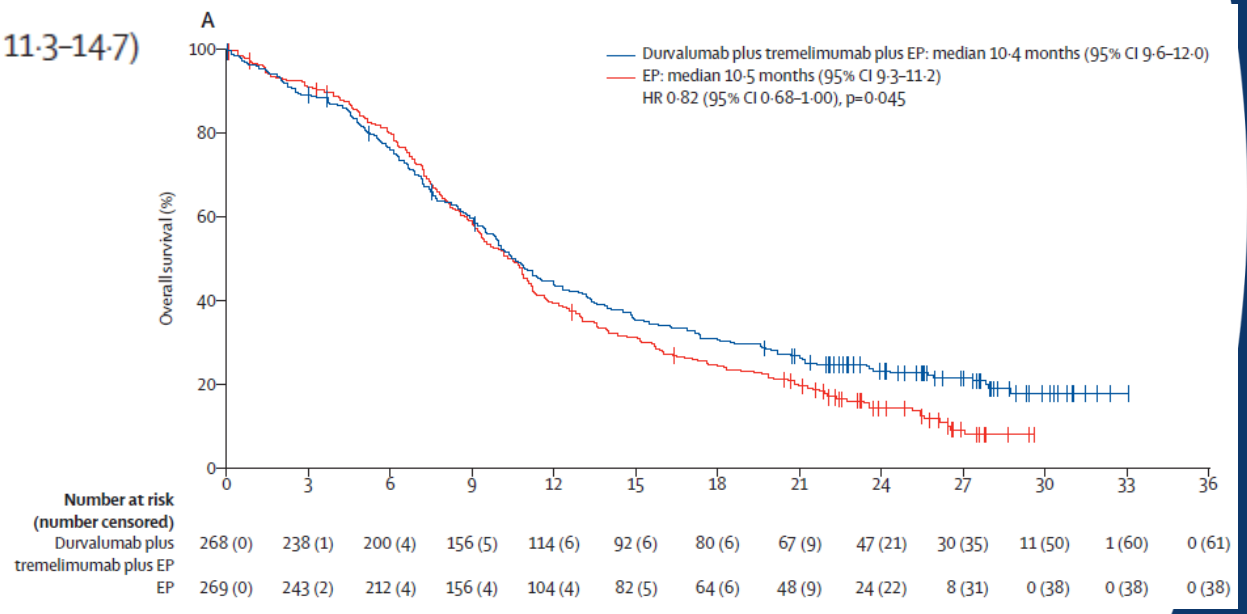
Lancet Oncol 2019

CASPIAN: Durvalumab with/out tremelimumab plus PE

[Durvalumab+EP]



[Durvalumab+tremelimumab+EP]



Lancet Oncol 2021

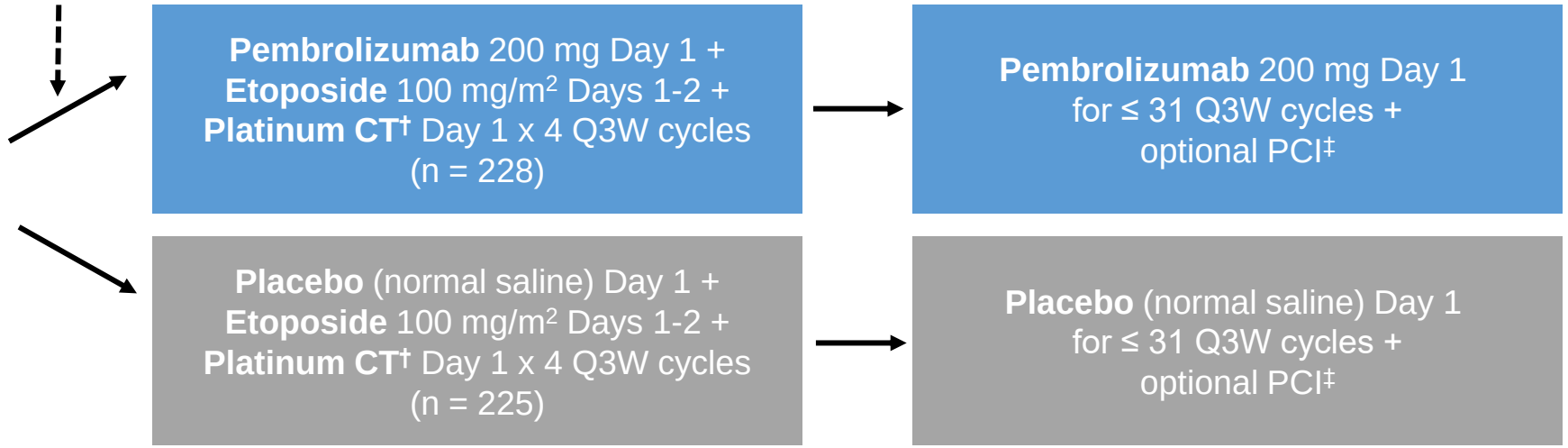
KEYNOTE-604: Pembrolizumab plus PE

Multicenter, double-blind, randomized phase III trial

- Patients with stage IV SCLC
- no previous systemic therapy
- ECOG PS 0/1 with adequate organ function
- life expectancy ≥ 3 mos
- no unstable brain metastases*

(N = 453)

Stratified by platinum (cisplatin vs carboplatin), ECOG PS (0 vs 1), LDH (≤ ULN vs > ULN)



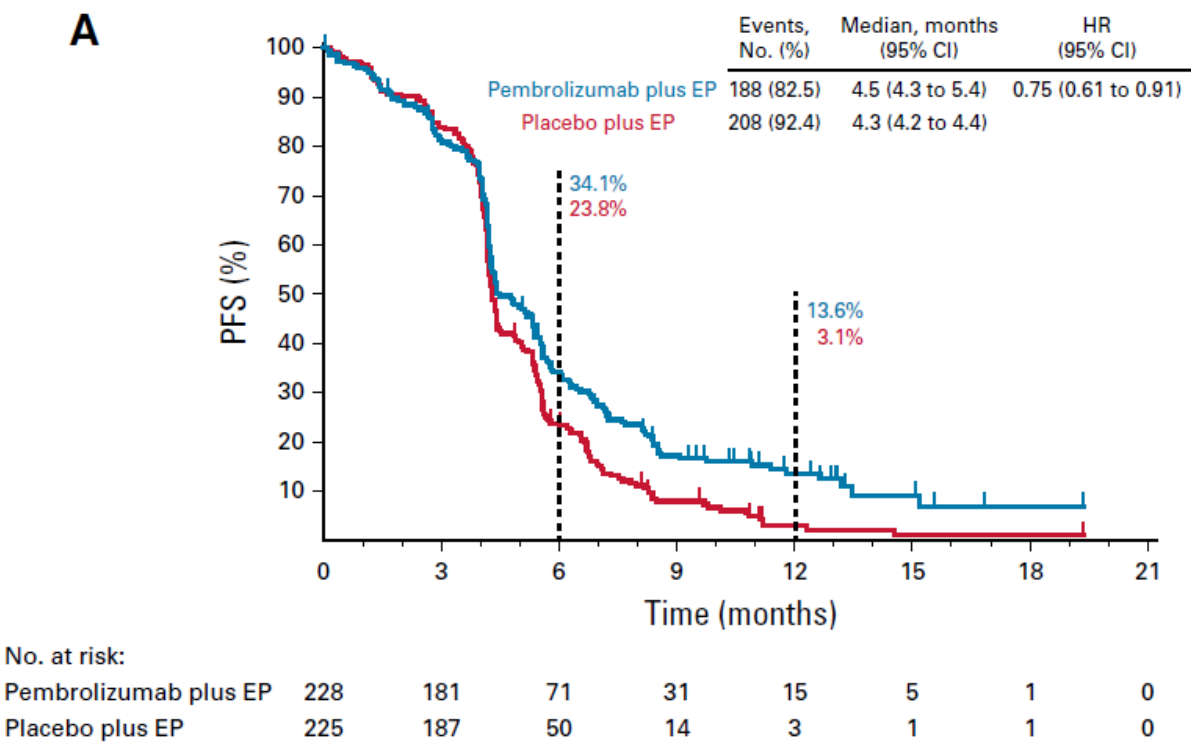
*Pts required to have sample available for biomarker assessment. †Carboplatin AUC 5 or cisplatin 75 mg/m² on Day 1. ‡Pts with CR or PR after Cycle 4 were eligible for ≤ 25 Gy of PCI in 10 fractions at investigator's discretion.

Primary endpoints: PFS per RECIST v1.1 by BICR, OS

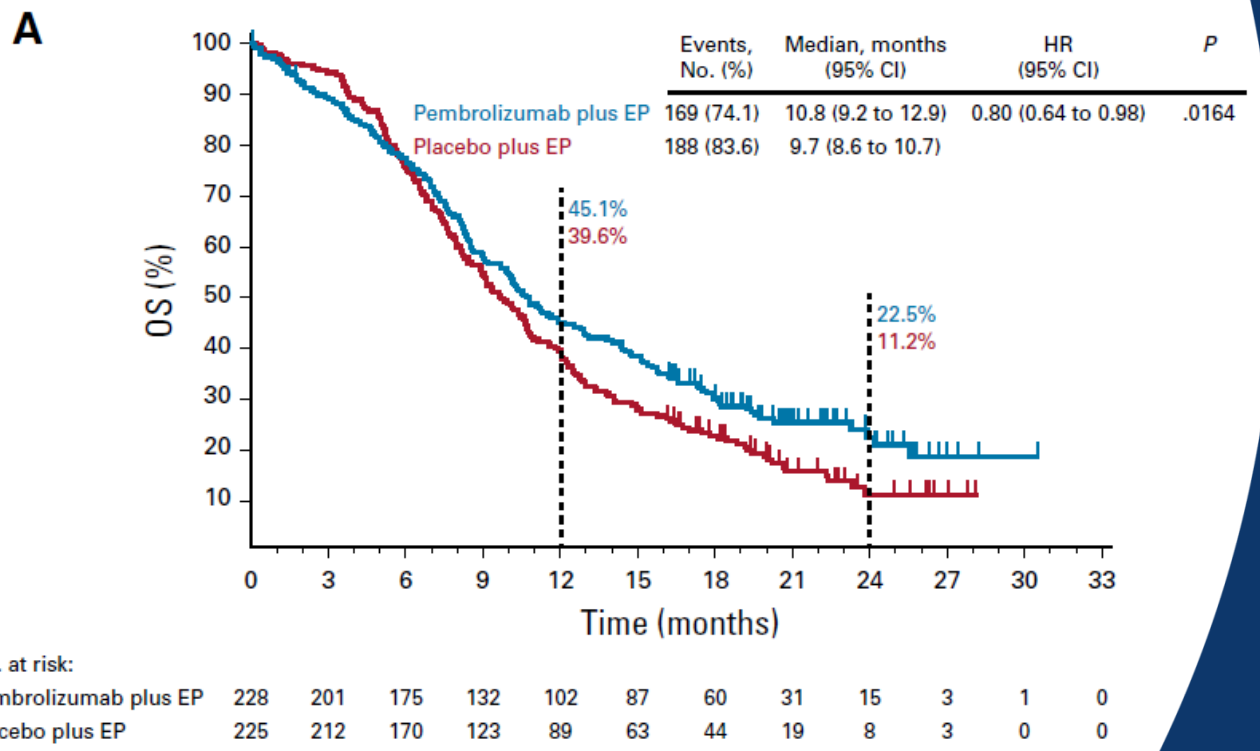
J Clin Oncol 2020

KEYNOTE-604: Pembrolizumab plus PE

[PFS]



[OS]



J Clin Oncol 2020

01-1

First-line treatment

Table 2. Ongoing trials plus immune checkpoint inhibitors in first-line setting and/or maintenance for extensive stage small-cell lung cancer

Combination	Trial ID	Agent	Phase	N	Study design	Treatment	Endpoint	Status	Completion date
ICI + ChT	NCT02580994 (REACTION)	Pembrolizumab	II	118	Randomised, open-label, crossover of PE with/out pembrolizumab in patients with PR/CR after 2C of PE.	Arm A: PE + pembrolizumab × 4C → pembrolizumab Arm B: PE × 4C	PFS	Recruiting	Aug 2020
	NCT03568097 (PAVE)	Avelumab	II	55	Open-label, single-arm study of phased avelumab plus PE	Arm A: PE + phased avelumab	1 year PFS	Recruiting	Aug 2021
	NCT04063163	HLX10 (PD-1 inhibitor)	III	489	Randomised, double-blind, study of PE with/out HLX10	Arm A: HLX10 + PE Arm B: placebo + PE	PFS	Recruiting	Dec 2021
	NCT03711305	SHR-1316 (PDL-1 inhibitor)	III	396	Randomised, double-blind of PE with/out SHR-1316	Arm A: SHR-1316 + PE × 4-6C → SHR-1316 Arm B: placebo + PE → placebo	PFS and OS	Not yet recruiting	Dec 2022
	NCT04012606	Toripalimab (PDL-1 inhibitor)	III	420	Randomised, Double-blind of toripalimab with/out PE	Arm A: PE + toripalimab → toripalimab Arm B: PE + placebo → placebo	PFS and OS	Recruiting	June 2022
	NCT04005716	Tislelizumab (PD-1 inhibitor)	III	364	Randomised, double-blind of PE with/out tislelizumab	Arm A: tislelizumab + PE × 4C → tislelizumab Control arm: placebo + PE × 4C → placebo	PFS and OS	Recruiting	June 2022
	NCT04221529	Atezolizumab	II	70	Open-label, single-arm study of PE plus atezolizumab in PS 2 patients	Arm A: PE + atezolizumab → atezolizumab	OS	Recruiting	June 2024
ICI doublet + ChT	NCT03963414	Durvalumab + tremelimumab	I	18	Open-label study of PE + durvalumab with/out tremelimumab in PS 2 patients	Arm A: durvalumab + tremelimumab + PE → durvalumab Arm B: durvalumab + PE → durvalumab	Treatment-related adverse event > grade 3	Not yet recruiting	July 2022
ICI + ChT + other agent	NCT03041311	Atezolizumab and Trilaciclib	II	105	Randomised study of PE and atezolizumab with/out trilaciclib	Arm A: PE plus atezolizumab + trilaciclib → atezolizumab Control arm: PE plus atezolizumab + placebo → atezolizumab	Evaluate the potential of trilaciclib to reduce chemotherapy-induced myelosuppression	Active, not recruiting	May 2020
	NCT04256421 (SKYSCRAPER-02)	Atezolizumab and tiragolumab (TIGIT inhibitor)	III	400	Randomised, double-blind study of atezolizumab plus PE with/out tiragolumab	Arm A: PE + atezolizumab plus trilaciclib → atezolizumab Control arm: PE + atezolizumab + placebo → atezolizumab	PFS, OS	Recruiting	August 2023
	NCT04101357	Atezolizumab and BNT411 (TLR7 agonist)	I/II	60	Open-label, single-arm study of BNT411 plus atezolizumab plus PE (part 1B)	Arm A: PE + atezolizumab + BNT411	DLT, AEs, dose reduction and discontinuation due to AEs	Not yet recruiting	Dec 2023
	NCT02934503	Pembrolizumab and RT	II	60	Open-label, single-group. of pembrolizumab and dynamic PD-L1 expression	Arm A: PE + pembrolizumab → pembrolizumab and RT Cohort B: PE + pembrolizumab → pembrolizumab Cohort C: PE → pembrolizumab Cohort D: PE + RT → pembrolizumab	Change in PD-L1 expression status	Recruiting	Oct 2020
Maintenance	NCT03319940	AMG 757 (BiTE targeting DLL3) ± pembrolizumab	I	162	Open-label study of AMG757 monotherapy or in combination with pembrolizumab in first-line/ recurrent SCLC	Part A and C: AMG757 + pembrolizumab in recurrent SCLC Part B: AMG757 in patients with ongoing benefit after 6C of platinum ChT	DLTs	Recruiting	Aug 2023

Continued

Esmoop. 2020

NCCN ver2. 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 Regimen
• Carboplatin AUC 5 day 1 and etoposide 100 mg/m² 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 5–6 day 1 and etoposide 80–100 mg/m² 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/m² day 1 and etoposide 80–100 mg/m² 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/m² days 1, 2, 3[7]
• Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[8]
• Cisplatin 80 mg/m² day 1 and etoposide 80 mg/m² days 1, 2, 3[9]
• Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[10]
Useful In Certain Circumstances
• Carboplatin AUC 5 day 1 and irinotecan 50 mg/m² days 1, 8, 15[11]
• Cisplatin 60 mg/m² day 1 and irinotecan 60 mg/m² days 1, 8, 15[12]
• Cisplatin 30 mg/m² days 1, 8 and irinotecan 65 mg/m² days 1, 8[13]

02-1 Second-line treatment

- 01 / Lurbinectedin
- 02 / Platinum re-exposure
- 03 / Immune checkpoint inhibitors

NCCN ver2. 2021

SCLC SUBSEQUENT SYSTEMIC THERAPY:[c]
Relapse ≤6 months PS 0–2
Preferred Regimens • Topotecan PO or IV[14-16] • Lurbinectedin[37] • Clinical trial Other Recommended Regimens • Pembrolizumab[b,d,19,20,21] • Paclitaxel[22,23] • Docetaxel[24] • Irinotecan[25] • Temozolomide[26,27] • Cyclophosphamide/doxorubicin/vincristine (CAV)[14] • Oral etoposide[28,29] • Vinorelbine[30,31] • Gemcitabine[32,33] • Bendamustine (category 2B)[34] • Nivolumab (category 3)[b,d,17,18]
Relapse >6 months
Preferred Regimens • Original regimen[d,35,36] Other Recommended Regimen • Lurbinectedin[37]

Lurbinectedin

- Synthetic, marine-derived tetrahydroisoquinoline alkaloid
  - Analogue of DNA-damaging agent trabectedin

- Mechanism of action
  - Blocks activated transcription
  - Produces DNA double-strand breaks, generating apoptosis
  - Modulates tumor microenvironment via inhibition of tumor-associated macrophages

J Pharmacol. 2010, Mol Cancer Ther. 2016, ESMO 2017. Abstr 1529PD.

Lurbinectedin – single-arm, open label, phase 2 basket study

PRIMARY OBJECTIVE : ORR by RECIST V.1.1
(Investigator assessed)

SCLC patients
- PS 0-2
- One prior chemotherapy line
- Prior immunotherapy was allowed
- Adequate organ function
- CNS mets excluded

➢ Lurbinectedin 3.2 mg/m², 1h iv, q3wk

≥ 2 responses in first 15 patients* → Enroll up to 100 patients

* 5 confirmed responses observed in the first 15 treated patients

Statistical assumptions for SCLC cohort

Null hypothesis :
≤15% get a response
($p \leq 0.15$)

Alternative hypothesis:
≥30% get a response
($p \geq 0.30$)

Statistical power 95%

≥ 23% of confirmed responses needed to reject the null hypothesis

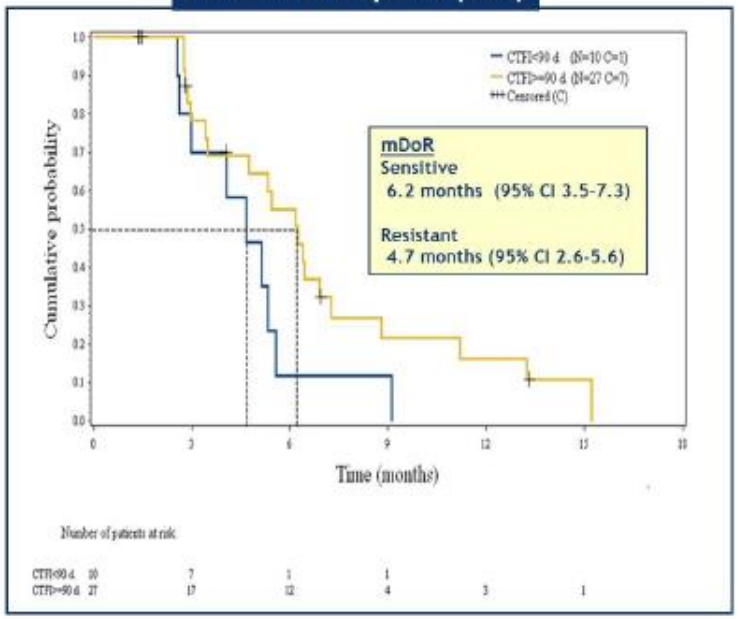
	Overall (n=105)
ORR, % (95% CI)	**35.2 (26.2-45.2)**
Best response	**n (%)**
- PR (confirmed)	37 (35.2) #
- SD	35 (33.3)
- PD	28 (26.7)
- NE* (non- evaluable)	5 (4.8)
Disease Control Rate,% (95% CI)	**68.6 (58.8-77.3)**

	Resistant CTFI< 90 days (n=45)	Sensitive CTFI ≥ 90 days (n=60)
ORR, % (95% CI)	**22.2 (11.2-37.1)**	**45.0 (32.1-58.4)**
Best response (confirmed)	**n (%)**	**n (%)**
- PR	10 (22.2) #	27 (45.0) #
- SD	13 (28.9)	22 (36.7)
- PD	18 (40.0)	10 (16.7)
- NE* (non- evaluable)	4 (8.9)	1 (1.7)
Disease Control Rate), % (95% CI)	**51.1 (35.8-66.3)**	**81.7 (69.6-90.5)**

3 of 5 patients with resistant disease and 2 of 3 patients with sensitive disease who failed prior immunotherapy had confirmed response

* Treatment discontinuation without any tumor assessment performed

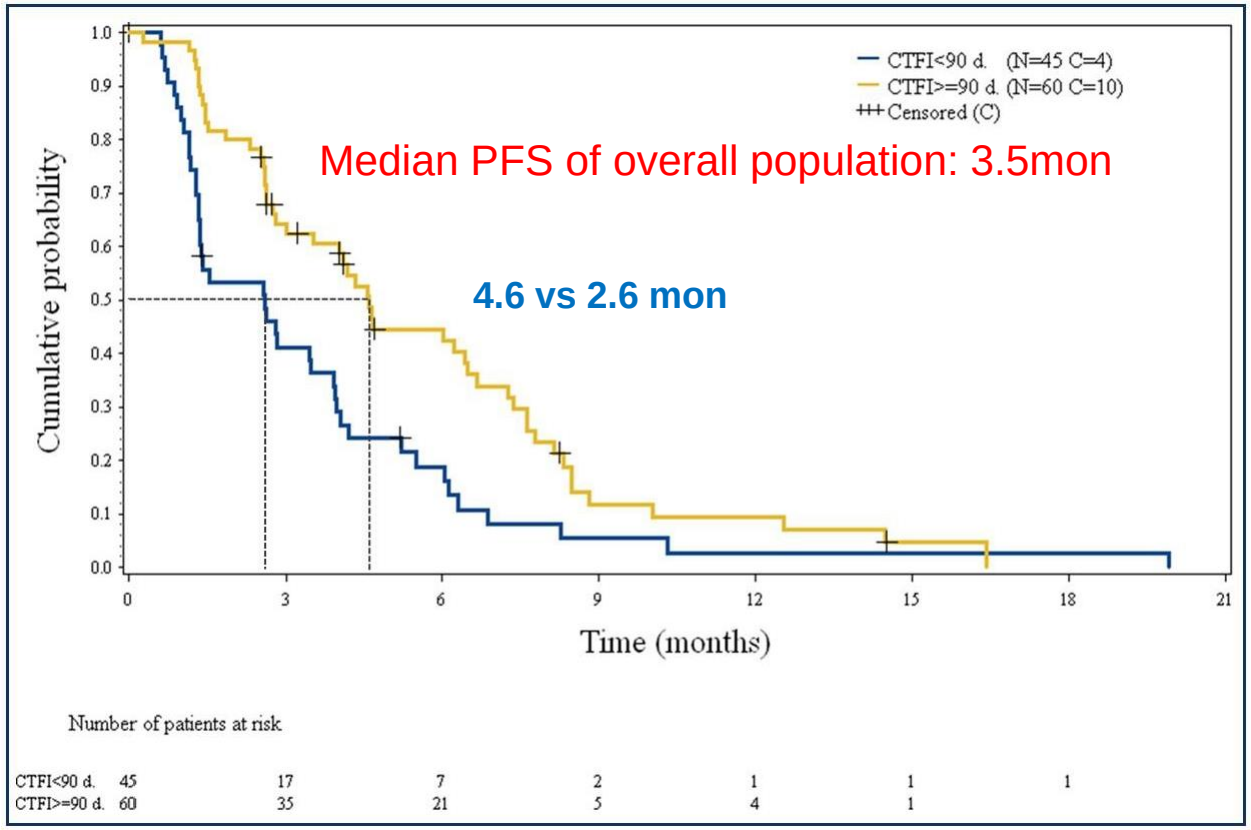
Duration of Response (DoR)



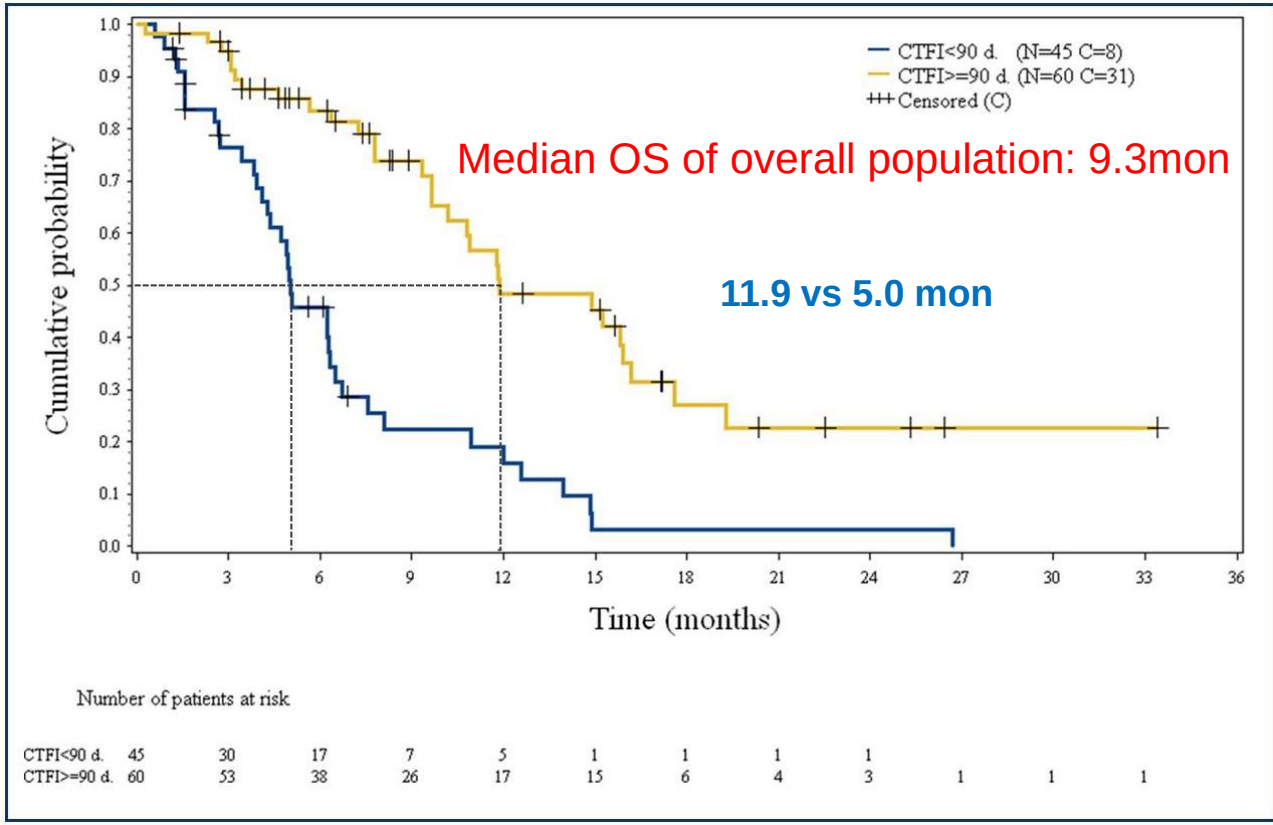
Lancet Oncol 2020

PFS and OS of Lurbinectedin : sensitive and resistant population

[PFS]



[OS]



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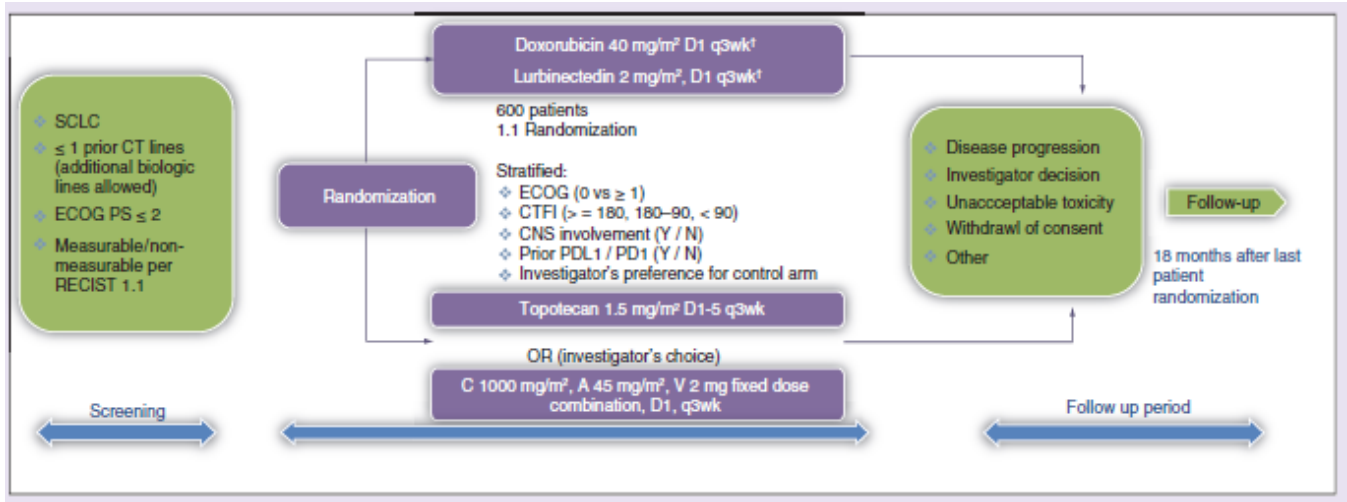
Lurbinectedin

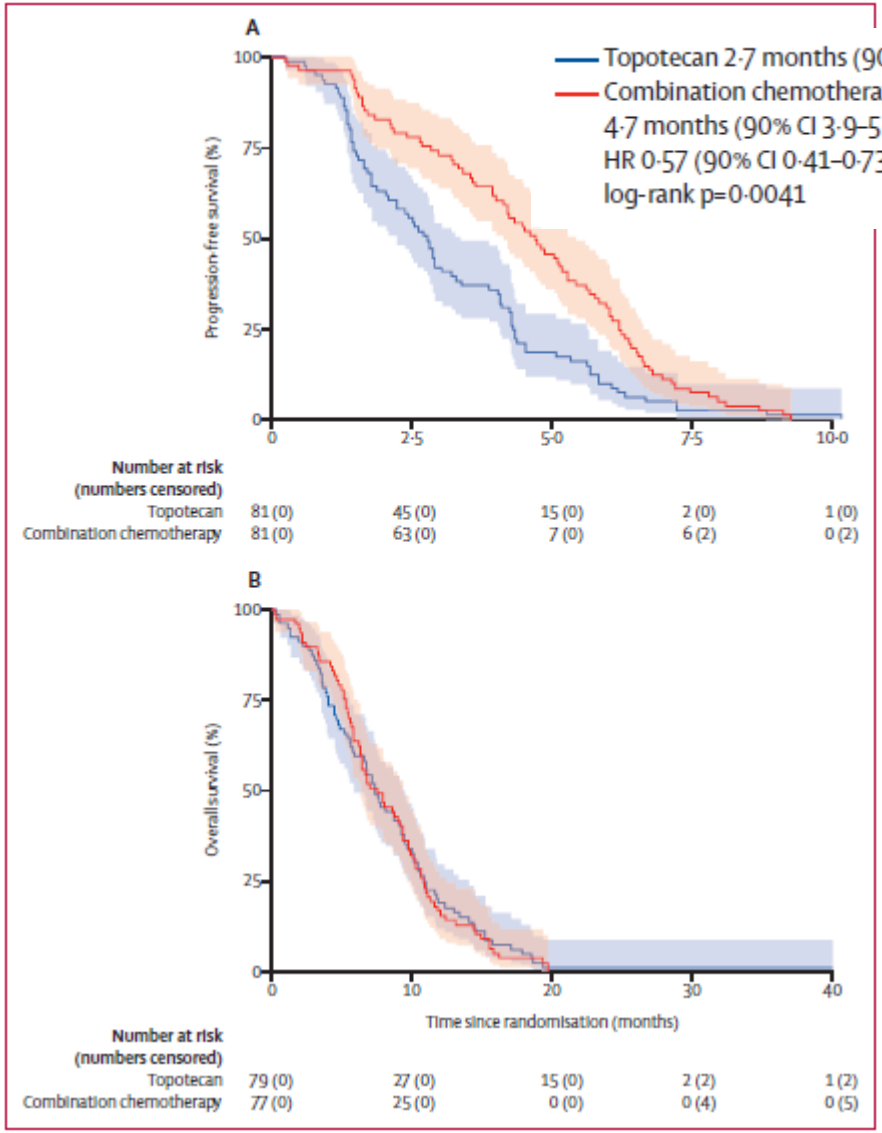
- Active as single-agent in 2L SCLC (ORR: 35.2%, mOS: 9.3 months)
  - Antitumor activity is notable in Sensitive disease (ORR=45.0%), as well as in Resistant disease (ORR: 22.2%) where no drugs are approved
- Outcomes with 2L Lurbinectedin numerically higher than historical outcomes with second-line topotecan (ORR 24%, mPFS 2.8 months, mOS 5.6 months)
- Results from phase III ATLANTIS trial of second-line lurbinectedin+ doxorubicin vs investigator's choice of topotecan or CAV awaited
  – Press release: Fails to Meet Primary End Point of OS for Patients with SCLC



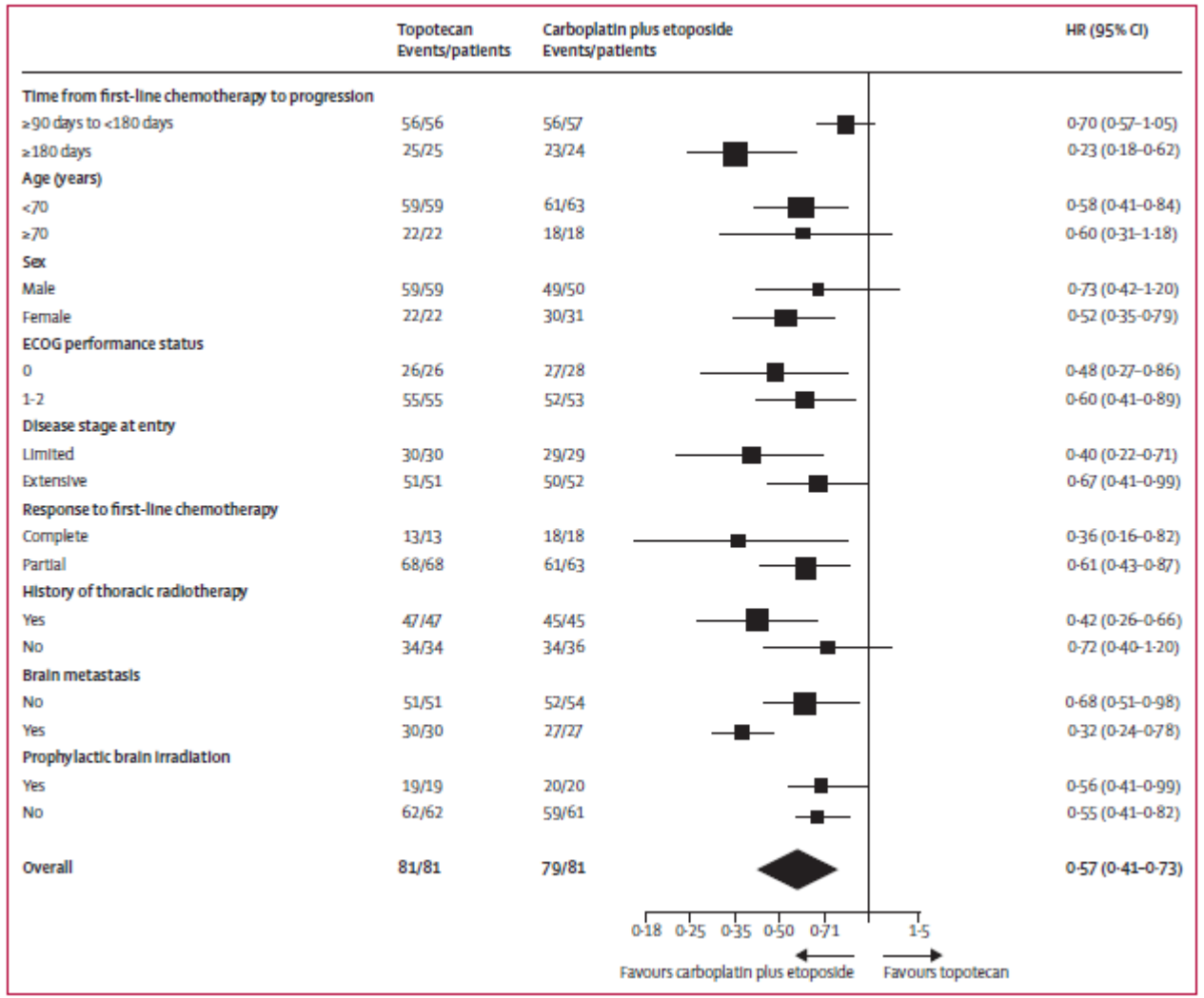
Role of platinum re-exposure

[PFS]

[OS]



Carboplatin plus etoposide versus topotecan as second-line treatment for patients with sensitive relapsed small-cell lung cancer: an open-label, multicentre, randomised, phase 3 trial



Lancet Oncol 2020

NCCN ver2. 2021

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Relapse >6 months
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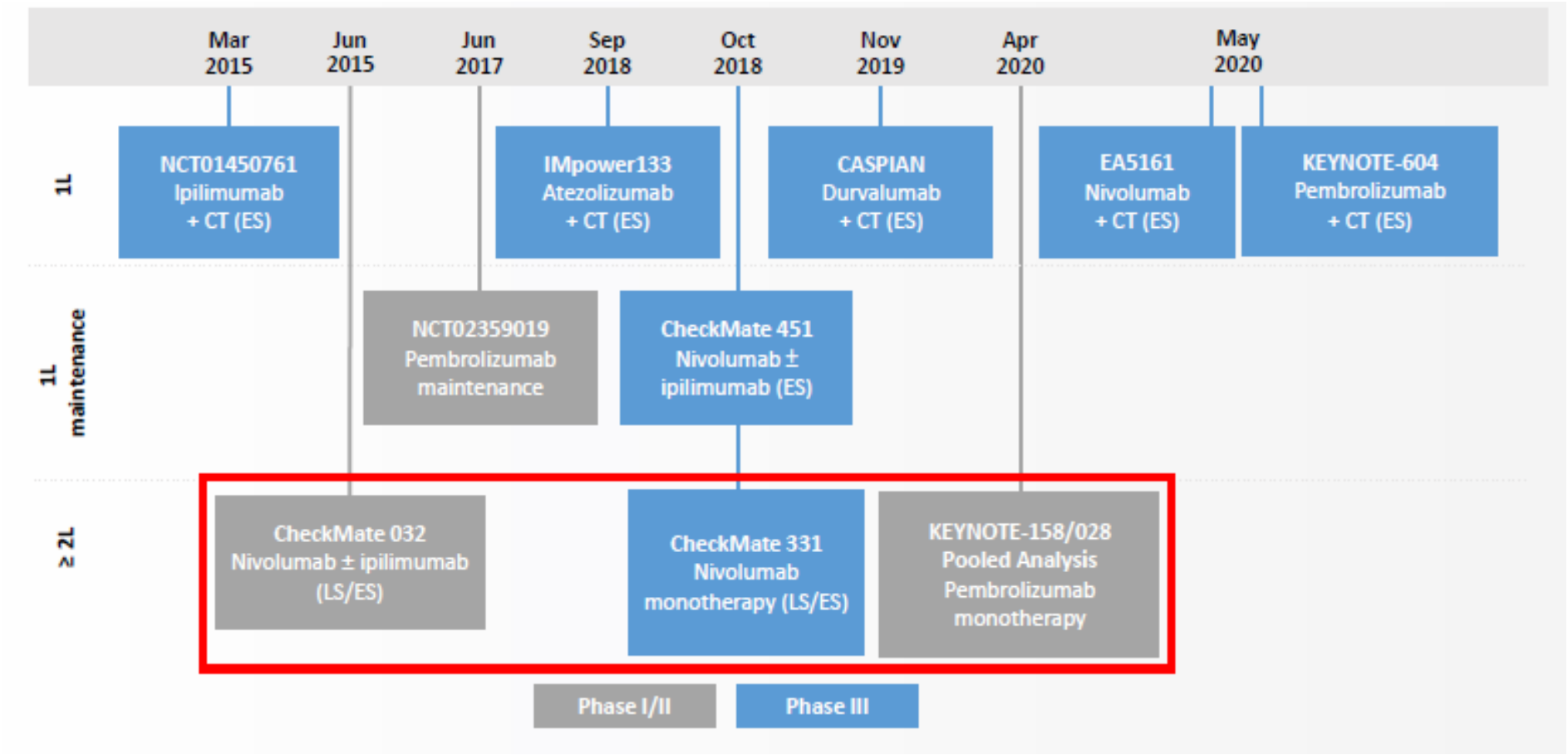
IO as second-line treatment



Immunotherapy 2019, Modified from 2020 WCLC

IO as second-line treatment

- Immunomonotheray shows a relatively low response rate
  - Nivolumab vs. topotecan or amrubicin (CM-331) : median PFS 1.4 months vs. 3.8 months, median OS 7.5 months and 8.4 months
  - Pembrolizumab (KN-158): ORR 18.7%, median PFS 2.0months, median OS 9.1months
  - Atezolizumab vs. topotecan or re-induction of initial chemotherapy (IFCT-1603): median PFS 1.4 months vs. 4.2 months, median OS 9.5 months and 8.7 months

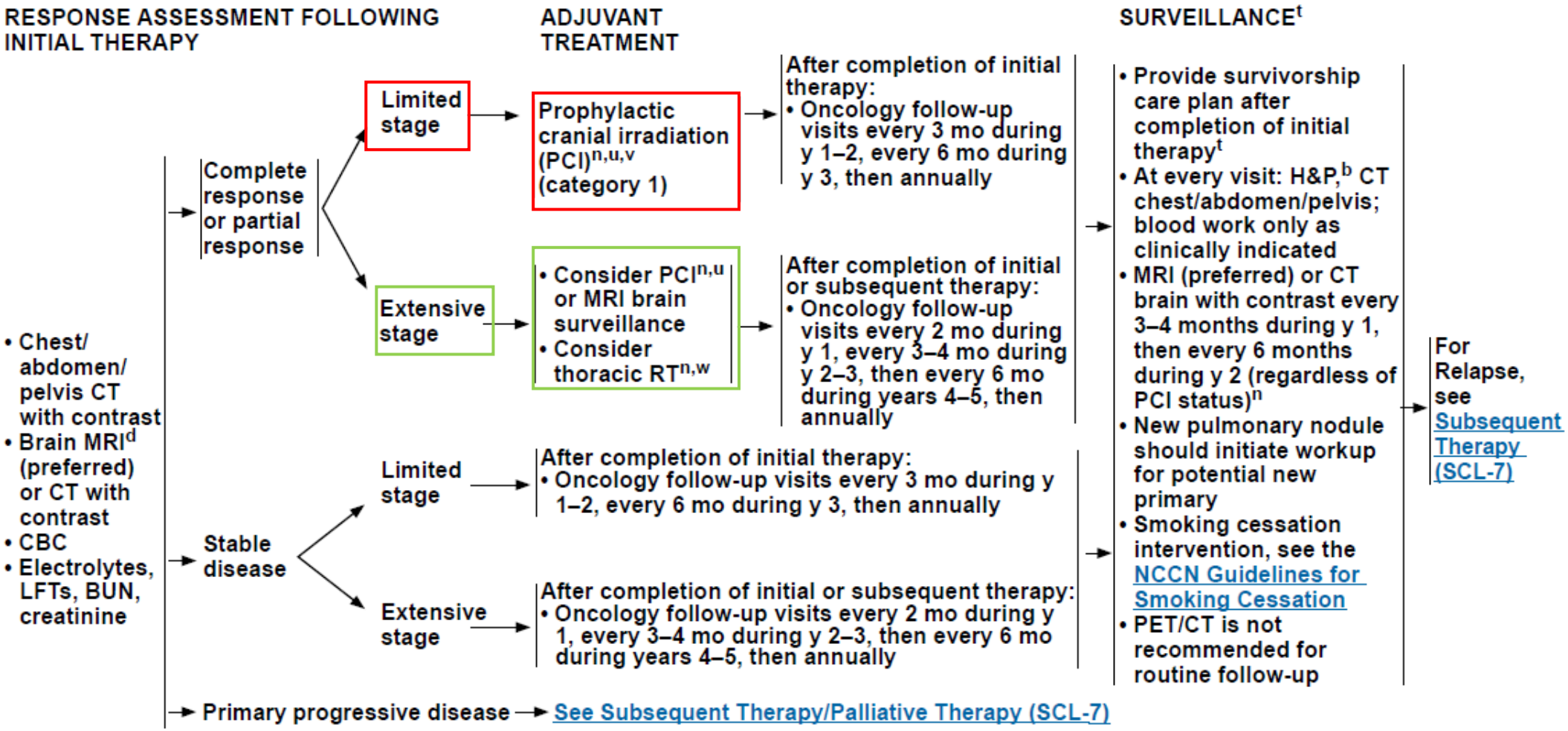
TranslOncol 2021

02

PCI strategy in SCLC

PNU 부산대학교병원
Pusan National University Hospital

NCCN ver2. 2021



PCI in LS-SCLC

The New England Journal of Medicine

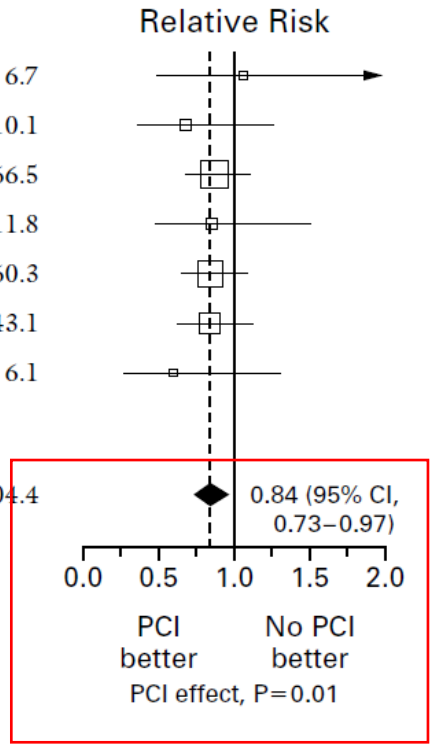
PROPHYLACTIC CRANIAL IRRADIATION FOR PATIENTS WITH SMALL-CELL LUNG CANCER IN COMPLETE REMISSION

A

Death

Study	No. of Events/No. Enrolled		O−E	Variance
	PCI	no PCI		
UMCC	14/15	13/14	0.4	6.7
Okayama	21/23	21/23	−3.8	10.1
PCI-85	133/149	135/151	−8.9	66.5
Danish−NCI	24/28	24/27	−1.8	11.8
UKCCCR−EORTC	154/194	106/120	−10.1	60.3
PCI-88	80/100	94/111	−7.6	43.1
ECOG−RTOG	14/17	13/15	−3.2	6.1
Total	440/526	406/461	−35.0	204.4

Test for heterogeneity: $\chi^2_6 = 1.62$, P=0.95

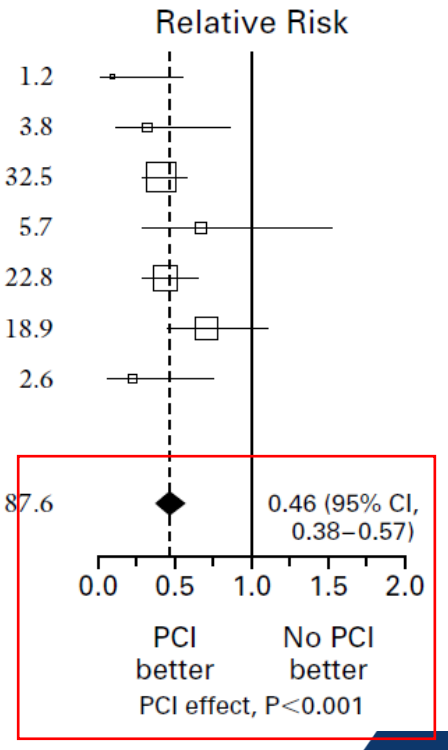


B

Brain Metastasis

Study	No. of Events/No. Enrolled		O−E	Variance
	PCI	no PCI		
UMCC	0/14	5/12	−2.9	1.2
Okayama	5/23	11/23	−4.4	3.8
PCI-85	46/149	87/151	−28.7	32.5
Danish−NCI	10/27	13/25	−2.3	5.7
UKCCCR−EORTC	46/194	54/120	−18.7	22.8
PCI-88	32/100	44/111	−6.4	18.9
ECOG−RTOG	4/17	8/15	−3.9	2.6
Total	143/524	222/457	−67.2	87.6

Test for heterogeneity: $\chi^2_6 = 9.71$, P=0.14



NEJM 1999

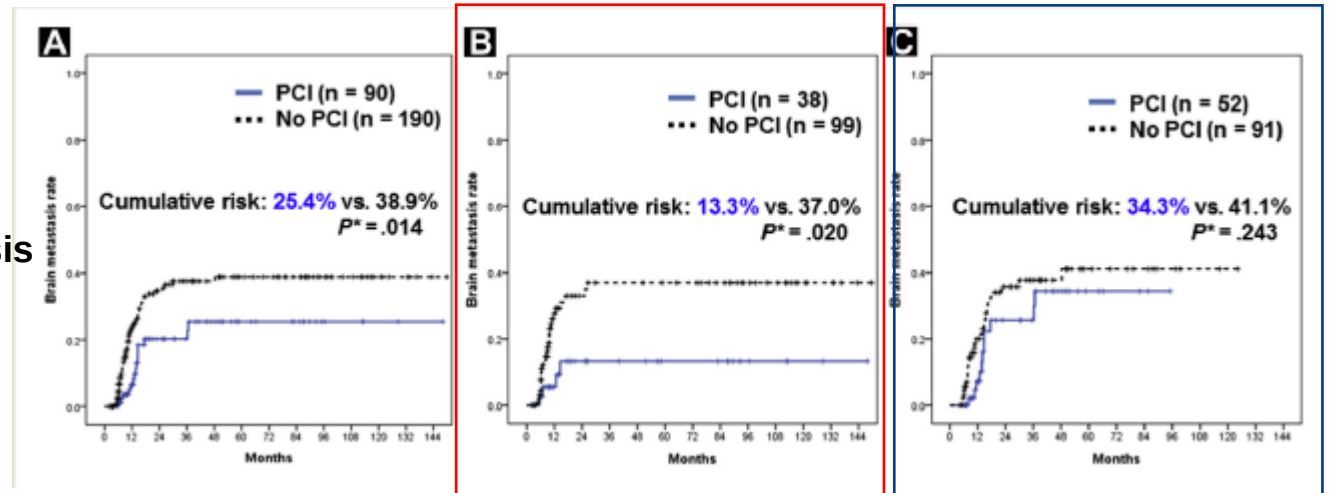
PCI in LS-SCLC

[Effect of PET/CT]

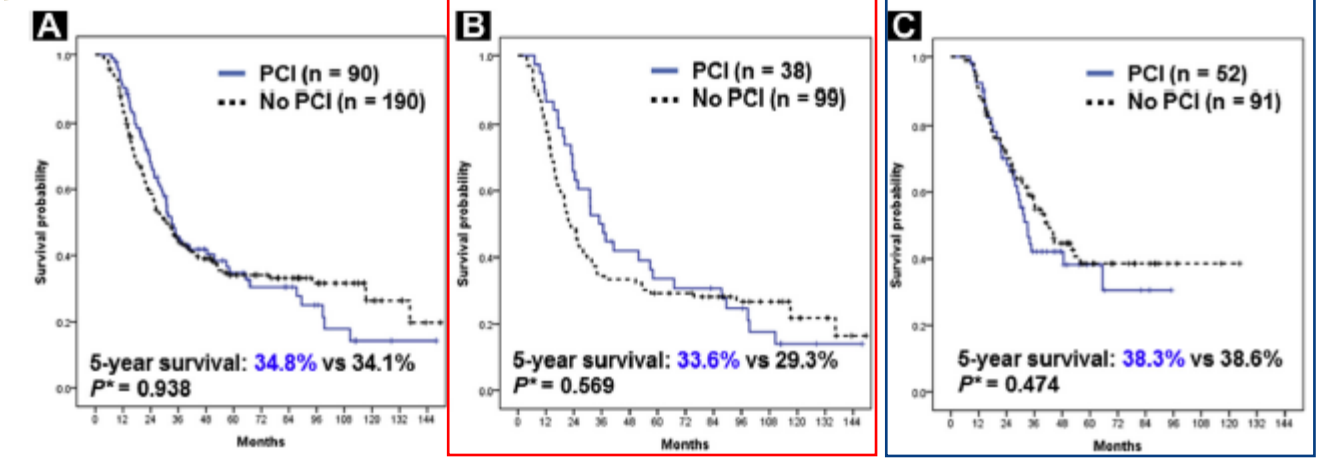
[Effect of Early detection]

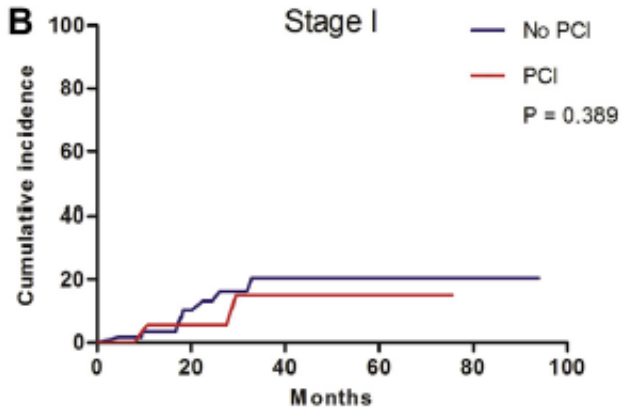
No PET **PET**

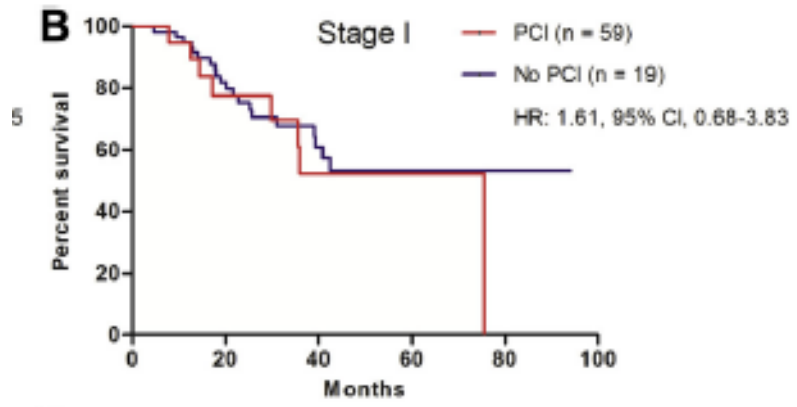
Brain metastasis



OS







Clin Lung Cancer 2017, J Thorc Oncol 2016

PCI in ES-SCLC

Results of PCI use in ES-SCLC clinical trials are conflicting

[EORTC study]

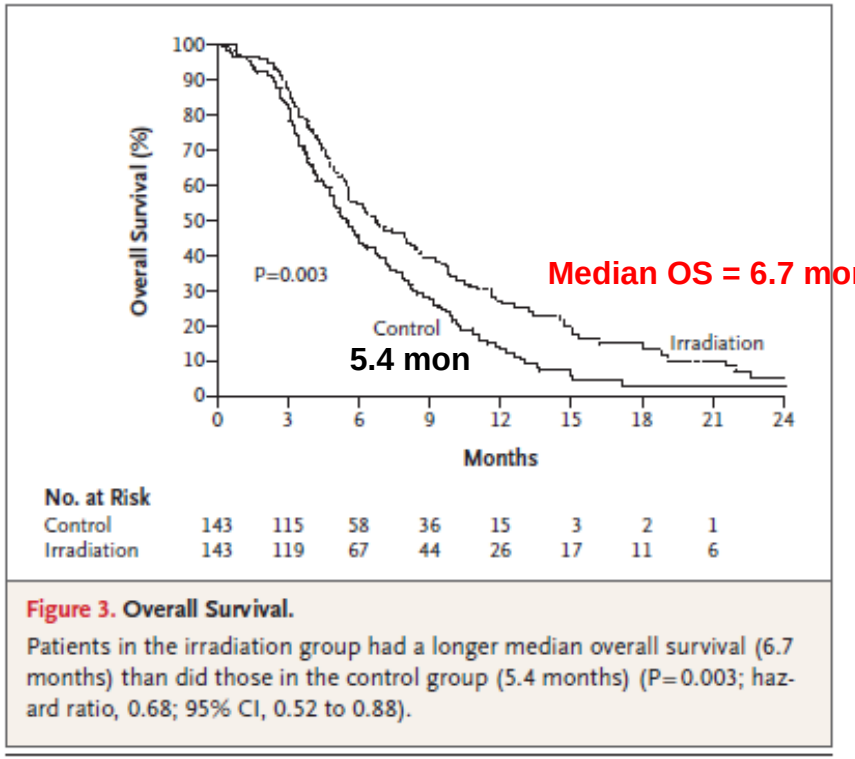
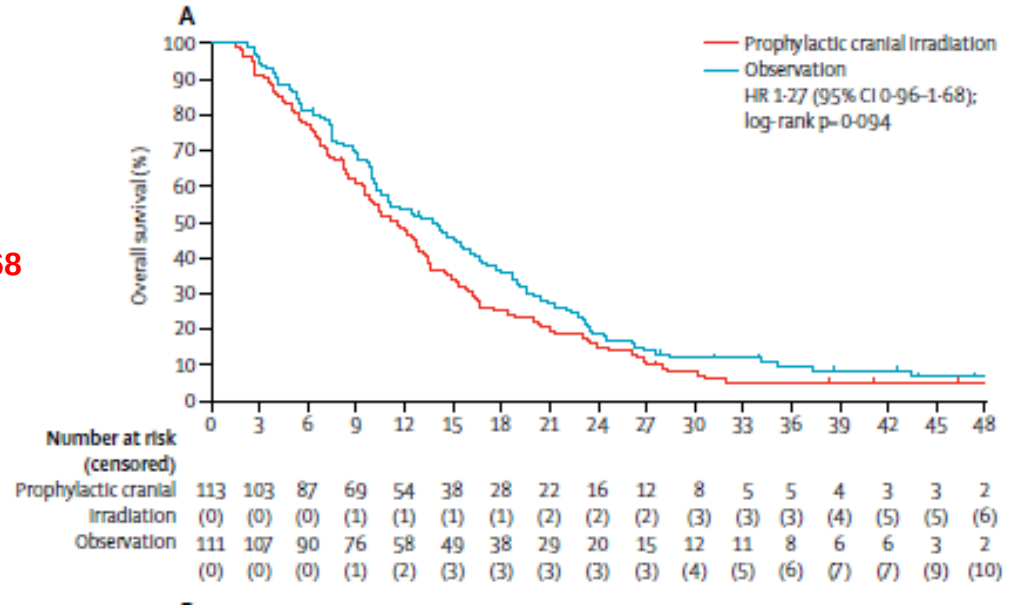


Figure 3. Overall Survival.

Patients in the irradiation group had a longer median overall survival (6.7 months) than did those in the control group (5.4 months) (P=0.003; hazard ratio, 0.68; 95% CI, 0.52 to 0.88).

Median OS = 6.7 mon, HR 0.68

[Japanese consortium]

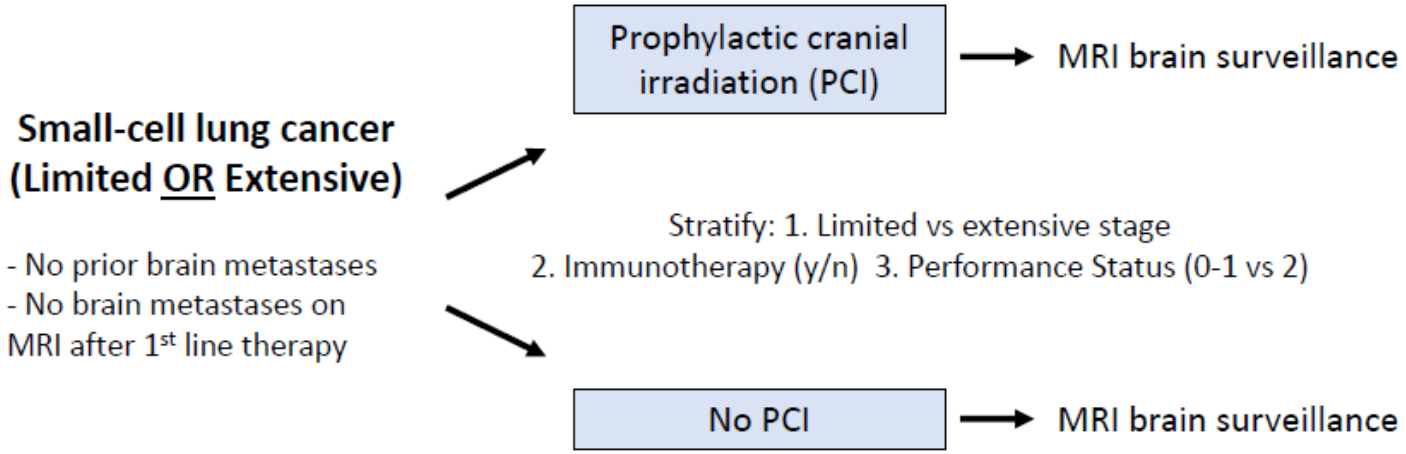


NEJM 2007, Lancet Oncol 2017

Looking Forward

MAVERICK (SWOG1827): MRI Brain Surveillance Alone Versus MRI Surveillance and Prophylactic Cranial Irradiation

—A Randomized Phase III Trial in Small-Cell Lung Cancer



Primary Endpoint
- Overall survival (non-inferiority)

Secondary Endpoints
- Cognitive function
- OS in limited and extensive stage
- Brain metastases free survival

Translational Endpoints
-Longitudinal brain MRI changes
-ctDNA correlation to PFS, OS

Accrual goal: 600 analyzable pts

- MRI brain surveillance scheduled at 3, 6, 9, 12, 18, 24 months
- Hippocampal-avoidance PCI and WBRT are allowed
- Radiation therapy is recommended at the time of brain metastases (WBRT and SRS allowed)
- Patients managed with any/all NCCN-acknowledged first-line treatment strategies are eligible

PIs Chad Rusthoven and Paul Brown

Clinicaltrials.gov

03

Molecular subtypes of SCLC

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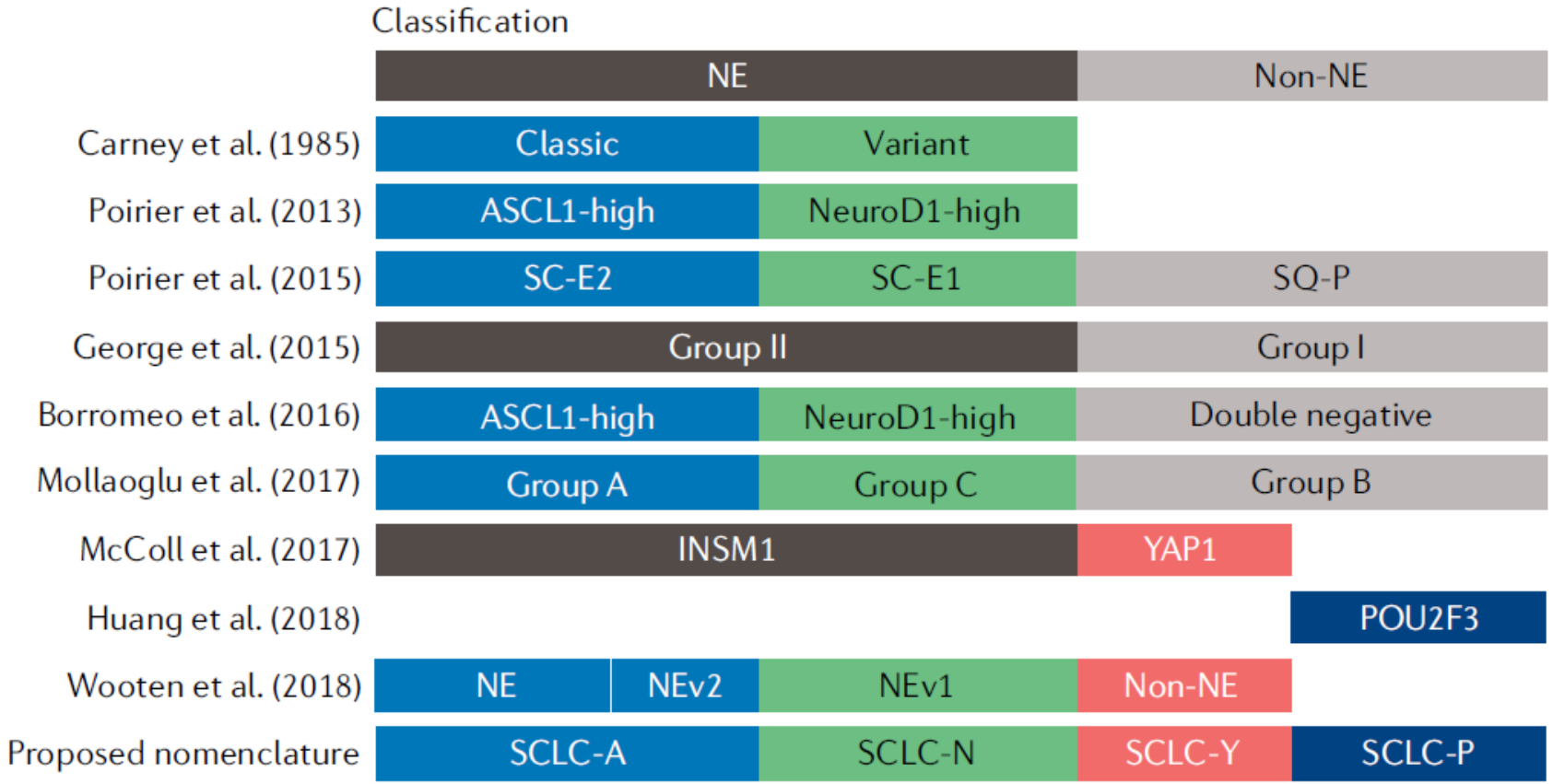
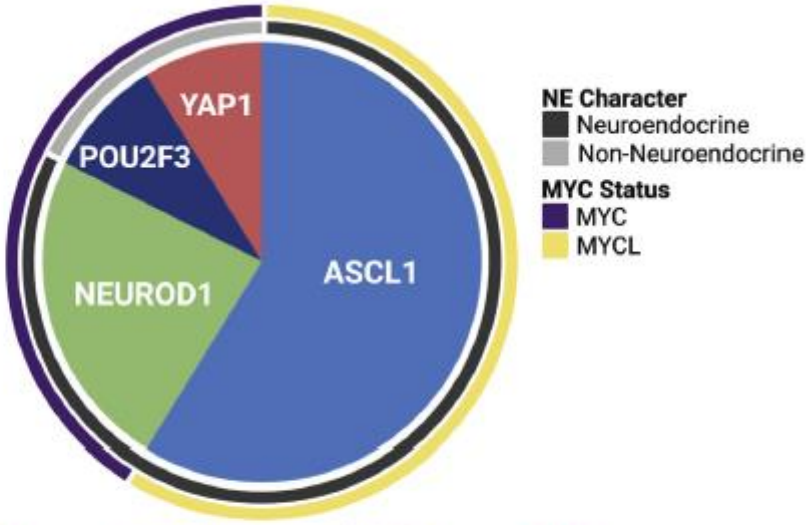
Molecular subtypes of SCLC

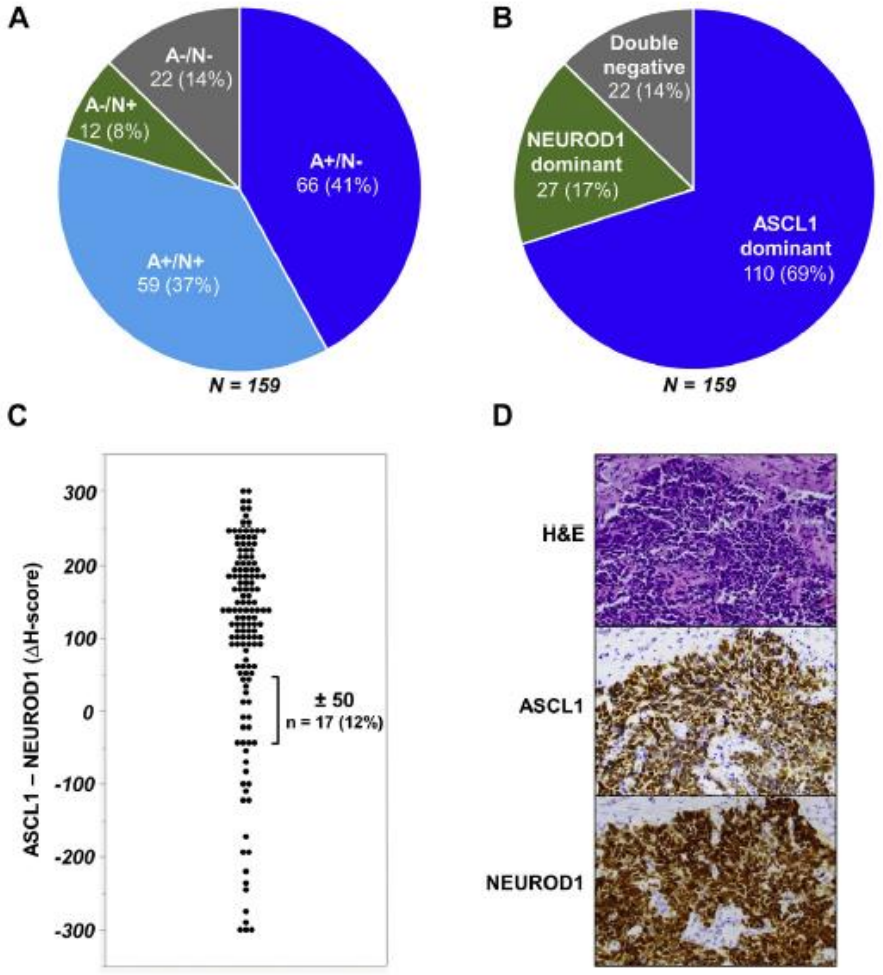


Nat Rev 2019

Four molecular subtypes of SCLC



	ASCL1	NEUROD1	POU2F3	YAP1
Targeted Therapies	BCL2 CREBBP DLL3 LSD1	Arginine Deprivation AURKA/B CHK1 IMPDH LSD1	Arginine Deprivation AURKA/B CHK1 IGF-R1 IMPDH	Arginine Deprivation AURKA/B CHK1 IMPDH IO



J Thorac Oncol 2020

04

Summary

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Summary(1)

- **First-line treatment of ES-SCLC**
  - After more than three decades of limited progress in ES-SCLC, some chemotherapy-IO combination has improved OS in the first-line setting
- **Second-line treatment of ES-SCLC**
  - Many factors should be considered including prior therapy, nature of disease – resistant vs. sensitive disease
  - Lurbinectidin is now approved for subsequent therapy
  - ICI monotherapy is not recommended

Summary(2)

- **PCI**
  - PCI significantly decreased the risk of brain metastases in both limited and extensive disease, but its role in improving survival is less clear
  - The use of PCI should be adapted to risk
- **Molecular subtypes of SCLC**
  - Recent studies have identified subtypes of SCLC defined by the RNA expression of ASCL1, NEUROD1, POU2F3, and YAP1 transcriptional regulators
  - Further studies are warranted to determine whether expression-based subtypes of SCLC are associated with distinct patient outcomes and/or predict distinct therapeutic vulnerabilities.

Thank you!

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