Evidence and practice changing treatments in thoracic tumors

Paolo Borghetti

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Agenda

- SCLC → Paolo Borghetti
- Resectable stage III NSCLC → Paolo Borghetti
- Unresectable stage III NSCLC → Cesare Guida
- SBRT early stage/oligomet → Cesare Guida

SCLC – Limited stage

High-Dose Once-Daily Thoracic Radiotherapy in Limited-Stage Small-Cell Lung Cancer: CALGB 30610 (Alliance)/RTOG 0538

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Accepted on November 22, 2022 and published at ascopubs.org/journal/jco on January 9, 2023: DOI https://doi.org/10.1200/JCO.22.01359

Journal of Clinical Oncology®

2023 ASCO ANNUAL MEETING

#8512 Final survival data form a randomized phase II trial comparing high-dose with standard-dose twice-daily (BID) thoracic radiotherapy (TRT) in limited stage small-cell lung cancer (LS SCLC)

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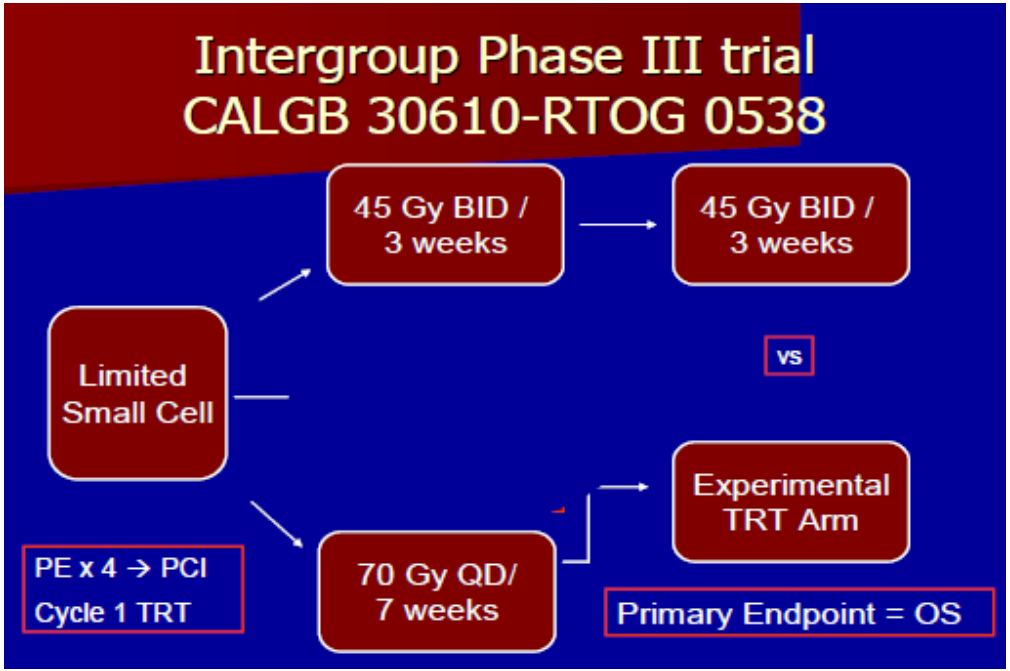
SCLC-LS

CALGB 30610- RTOG 0538: Design



SCLC-LS

CALGB 30610- RTOG 0538: Design

TABLE 1. Baseline Patient Characteristics

Characteristic	45 Gy Group (N = 313)	70 Gy Group (N = 325)	Total (N = 638)
Age, years			
Mean (SD)	63.3 (8.0)	62.4 (8.1)	62.8 (8.1)
Median	64.0	63.0	63.0
Q1-Q3	58.0-69.0	57.0-68.0	57.0-69.0
Range	42.0-81.0	37.0-80.0	37.0-81.0
Race, No. (%)			
White	271 (86.6)	281 (86.5)	552 (86.5)
Black or African American	27 (8.6)	27 (8.3)	54 (8.5)
Asian	4 (1.3)	4 (1.2)	8 (1.3)
American Indian or Alaska Native	2 (0.6)	2 (0.6)	4 (0.6)
More than one race	0 (0.0)	1 (0.3)	1 (0.2)
Not reported	5 (1.6)	4 (1.2)	9 (1.4)
Unknown: patient unsure	4 (1.3)	6 (1.8)	10 (1.6)
Sex, No. (%)			
Male	154 (49.2)	155 (47.7)	309 (48.4)
Female	159 (50.8)	170 (52.3)	329 (51.6)
Ethnicity, No. (%)			
Not Hispanic or Latino	292 (93.3)	302 (92.9)	594 (93.1)
Hispanic or Latino	11 (3.5)	9 (2.8)	20 (3.1)
Not reported	4 (1.3)	4 (1.2)	8 (1.3)
Unknown	6 (1.9)	10 (3.1)	16 (2.5)
Weight loss 6 months before study, No. (%)			
≤ 5.00%/6 months	260 (83.1)	277 (85.2)	537 (84.2)
> 5.00%/6 months	53 (16.9)	48 (14.8)	101 (15.8)
Eastern Cooperative Oncology Group performance score, No. (%)			
0	140 (44.7)	157 (48.3)	297 (46.6)
1	160 (51.1)	149 (45.8)	309 (48.4)
2	13 (4.2)	19 (5.8)	32 (5.0)

Variable	45 Gy (N = 313), No. (%)	70 Gy (N = 325), No. (%)	Total (N = 638), No. (%)	P
Radiotherapy technique				.9499
Intensity modulated	188 (60.1)	196 (60.3)	384 (60.2)	
Three-dimensional conformal	125 (39.9)	129 (39.7)	254 (39.8)	
Radiotherapy start time				.7618
First cycle of chemotherapy	141 (45.0)	137 (42.2)	278 (43.6)	
Second cycle of chemotherapy	172 (54.9)	188 (57.8)	360 (56.5)	
Chemotherapy backbone				.5944
Cisplatin	252 (80.5)	267 (82.2)	519 (81.3)	
Carboplatin	61 (19.5)	58 (17.8)	119 (18.7)	

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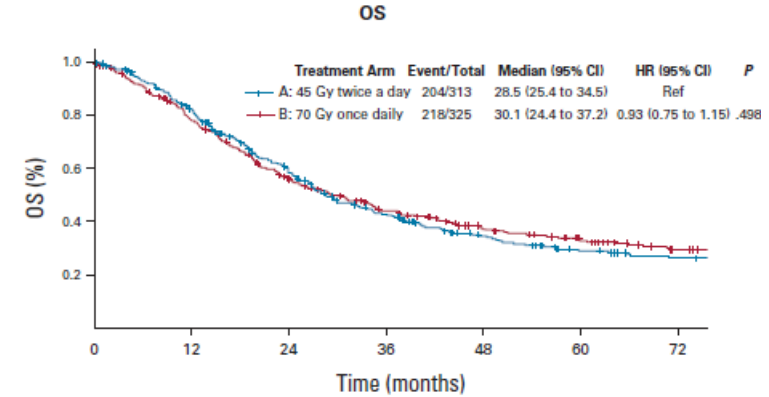
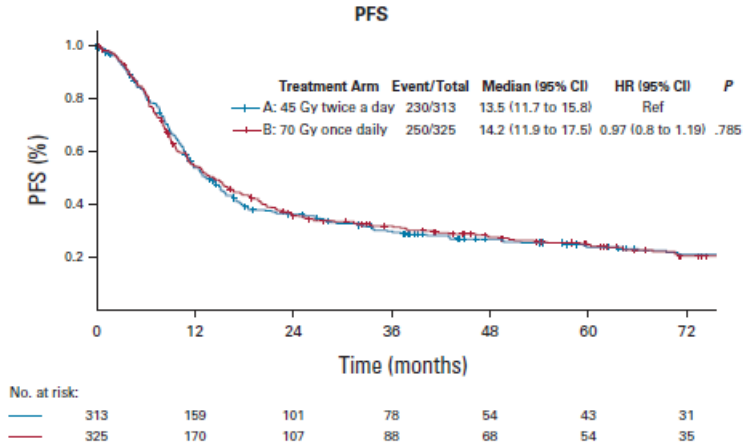
CALGB 30610- RTOG 0538: OS and PFS



	2-Year	3-Year	4-Year	5-Year	6-Year
Arm A	0.58 (0.53 to 0.64)	0.43 (0.38 to 0.49)	0.35 (0.29 to 0.41)	0.29 (0.23 to 0.35)	0.26 (0.21 to 0.32)
Arm B	0.56 (0.51 to 0.62)	0.44 (0.39 to 0.50)	0.37 (0.32 to 0.43)	0.32 (0.27 to 0.39)	0.29 (0.24 to 0.35)



	2-Year	3-Year	4-Year	5-Year	6-Year
Arm A	0.36 (0.31 to 0.42)	0.3 (0.25 to 0.36)	0.27 (0.22 to 0.32)	0.24 (0.19 to 0.29)	0.21 (0.16 to 0.27)
Arm B	0.36 (0.31 to 0.41)	0.32 (0.27 to 0.37)	0.28 (0.23 to 0.33)	0.25 (0.2 to 0.3)	0.21 (0.16 to 0.26)

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CALGB 30610- RTOG 0538: AEs

AE Category	45 Gy (n = 295), No. (%)	70 Gy (n = 301), No. (%)	*P*
Overall grade 3 AE (max)	93 (29.7)	77 (23.7)	.0855
Overall grade 4 AE (max)	149 (47.6)	161 (49.5)	.6250
Overall grade 5 AE	4 (1.3)	11 (3.4)	.0792
Hematologic grade 3 AE	66 (21.1)	70 (21.5)	.8891
Hematologic grade 4 AE	140 (44.7)	157 (48.3)	.3649
Hematologic grade 5 AE	0 (0.0)	0 (0.0)	NA
Nonhematologic grade 3 AE	131 (41.9)	127 (39.1)	.4751
Nonhematologic grade 4 AE	36 (11.5)	49 (15.1)	.1840
Nonhematologic grade 5 AE	4 (1.3)	11 (3.4)	.0792
Neutrophil count decreased	186 (63.1)	198 (65.8)	.4864
Leukocyte count decreased	148 (50.2)	177 (58.8)	.0343
Hemoglobin decreased	60 (20.3)	79 (26.2)	.0882
Platelet count decreased	43 (14.6)	57 (18.9)	.1543
Dehydration	42 (14.2)	39 (13.0)	.6483
Febrile neutropenia	40 (13.6)	38 (12.6)	.7351
Lymphocyte count decreased	28 (9.5)	49 (16.3)	.0135
Esophageal pain	32 (10.8)	36 (12.0)	.6692
Dysphagia	28 (9.5)	34 (11.3)	.4707

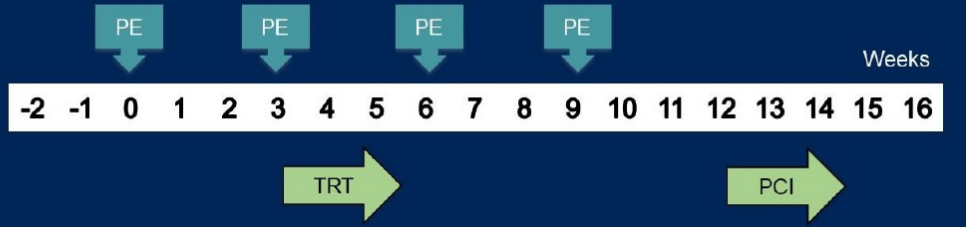
SCLC-LS

Phase II trial: High Dose BID vs Standard Dose BID: Design

LS SCLC according to the IASLC definition; ECOG PS 0-2; measurable disease (RECIST 1.1); and adequate bone marrow/liver/kidney function

Study treatment

PE:
Cisplatin 75 mg/m² BSA *or*
carboplatin AUC 5-6 IV day 1 *and*
etoposide 100 mg/m² BSA IV days 1-3 q3w



TRT:
Commenced 21-28 days after first chemotherapy course, RT fields were limited to PET-CT positive lesions plus margins

Thoracic Radiotherapy:
Arm A: 45 Gy/30 fractions BID
Arm B: 60 Gy/40 fractions BID

Prophylactic Cranial Irradiation:
25 Gy/10 or 30 G/15 fractions QD

SCLC-LS

Phase II trial: High Dose BID vs Standard Dose BID: population

- 170 pts (22 Scandinavian Hospitals) 60Gy: 89 vs 45 Gy:81
- Median age: 65 yrs
- ≥70 yrs: 31.2%
- PS 0-1: 89.4%
- ≥ 5% weight loss: 20.0%

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Phase II trial: High Dose BID vs Standard Dose BID: treatment

Treatment completion

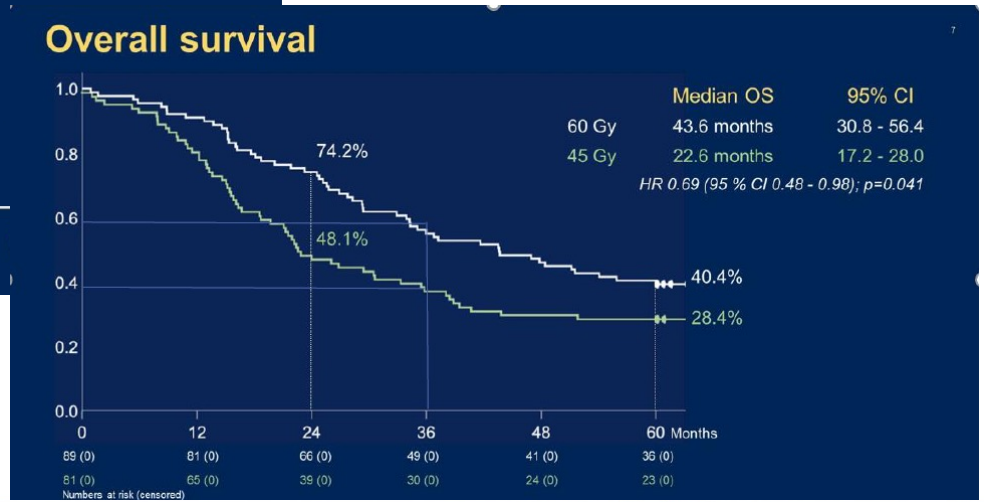
	60 Gy (n=89)		45 Gy (n=81)	
Mean no. chemo-courses	3.87		3.73	
Any dose reduction	58	65%	66	82%
≥1 course of carboplatin	31	35%	34	42%
Completed TRT	86	97%	74	91%
Median PTV (IQR) in cm^3	303 (196-457)		336 (226-541)	
Received PCI	72	85%	68	85%
2nd-line chemotherapy	41	47%	39	48%

Response rates

	60 Gy (n=89)		45 Gy (n=81)		*p*
Overall response	69	78%	62	77%	*0.88*
Complete response	16	18%	17	21%	
Partial response	53	60%	45	56%	
Stable disease	4	5%	6	7%	
Progression	5	6%	5	6%	
Not evaluated	11	12%	8	10%	

SCLC-LS

Phase II trial: High Dose BID vs Standard Dose BID: PFS and OS



SCLC – Oligometastasis

Clinical and Translational Radiation Oncology 41 (2023) 100637

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Stereotactic body radiotherapy for extra-cranial oligoprogressive or oligorecurrent small-cell lung cancer☆

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CLINICAL Lung Cancer

ORIGINAL STUDY | ARTICLES IN PRESS

Sterotactic Ablative radiotherapy in a Multicentric series of Oligometastatic SCLC: the SAMOS cohort

Paolo Borghetti # • Giorgio Facheris # • Patrizia Ciammella • Marco Galaverni • Lorenzo Granello • Vieri Scotti • Davide Franceschini • Andrea Romei • Niccolò Giaj Levra • Manuela Federico • Maria La Vecchia • Anna Merlotti • Matteo Sepulcri • Gaia Piperno • Giulia Marvaso • Nicola Simoni • Emanuele Ali • Antonio Pontoriero • Anna Cappelli • Valeria Dionisi • Jessica Menis • Antonella Martino • Stefano Vagge • Stefania Canova • Giampaolo Montesi • Francesco Cuccia • Luca Boldrini • Ciro Franzese • Salvatore Grisanti • Alessio Bruni • Marta Scorsetti • Show less • Show footnotes

Published: November 15, 2023 • DOI: https://doi.org/10.1016/j.cllc.2023.11.005

SCLC-oligometastasis

	n (%)
Median age (years, range)	67.7 (43.1–76.4)
Gender	
Male	12 (60)
Female	8 (40)
Initial stage	
Limited	12 (60)
Extensive	8 (40)
Prior treatments	
Thoracic chemoradiotherapy	12 (60)
PCI	11 (55)
First line doublet-chemotherapy	8 (40)
Chemo-immunotherapy	1 (5)
Palliative thoracic irradiation	2 (10)
WBRT	5 (25)
Subsequent line(s) of chemotherapy	7 (35)
Brain SRS	1 (5)
Local ablative treatments	1 (5)
Type of oligometastatic disease	
Oligoprogression	6 (30)
Oligorecurrence	14 (70)
ECOG PS before SBRT	
0	4 (20)
1	16 (80)
SBRT (n = 24 lesions)	
Median dose (Gy, range)	48 (30–60)
Median EQD2 (Gy, range)	83.3 (40–110)
Median number of fractions (range)	5 (3–10)
Median duration (days, range)	9 (3–17)
Median lesion size (mm, range)	26 (7–57)
Techniques	
Static 3D (4D-CT, free breathing)	10 (42)
Static 3D (DIBH)	2 (8)
VMAT (4D-CT, free breathing)	7 (29)
Tracking CyberKnife®	5 (21)
Locations	
Lung	17 (71)
Adrenal	5 (21)
Spine	1 (4)
Pancreas	1 (4)

Levy A. et al.

- Median DR 4.5 months
- Median OS 17.2 months
- 3-year distant control and OS rates were 25% and 37%

Univariate analyses for overall survival and distant relapse.

	Death from SBRT		Distant relapse from SBRT	
	Univariate		Univariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
LD (vs ED)	0.2 (0–0.7)	0.006	0.3 (0–0.9)	0.03
Oligorecurrent (vs OPD)	0.3 (0–0.8)	0.02	0.5 (0.2–1.3)	0.1
Lungs or prior brain mets (vs systemic mets)	0.3 (0–0.95)	0.04	0.5 (0.2–1.3)	0.1
Diagnosis to OMD delay > 1 year (vs < 1 year)	0.1 (0.1–1.2)	0.1	0.5 (0.2–1.5)	0.2

SCLC-oligometastasis

Borghetti P. et al.

Age at the time of SABR	
Median 64 years	Range 36-86
Gender	
Male	49 (52.7%)
Female	44 (47.3%)
PS - ECOG	
0	54 (58.1%)
1	38 (40.8%)
2	1 (1.1%)
VALSG stage at the diagnosis	
LS-SCLC	41 (44.1%)
ES-SCLC	52 (55.9%)
TNM-AJCC stage at the diagnosis	
Stage I	1 (1.1%)
Stage II	9 (9.7%)
Stage III	38 (40.8%)
Stage IV	45 (48.4%)
Oligometastatic state	
Synchronous Oligometastatic	22 (23.7%)
Metachronous Oligometastatic	33 (35.5%)
Oligoprogressive	38 (40.8%)
Total dose of SABR (Gy)	
Mean 31.6	Range 18-60
Dose/fraction of SABR (Gy/fraction)	
Mean 10.7	Range 5-25
Site of metastasis	
Brain	55 (41.7%)
Lung	27 (20.4%)
Liver	11 (8.3%)
Bone	8 (6 %)
Lymph node	10 (7.5%)
Adrenal gland	20 (15.4%)
Others	1 (0.7%)
Number of treated metastases	
1	43 (46.2%)
>1	50 (53.8%)
PCI	
Yes	37 (39.8%)
No	56 (60.2%)

	Median OS (Months)	1-Year OS	2-Year OS	Mean TtNT (Months)	TtNT Range (Months)
Synchronous Oligomet	16	50.5%	35.4%	10.2	0-58
Metachronous Oligomet	12	58.3%	34%	9	0-37
Oligoprogressive	14	50.6%	14.8%	7.5	0-59
Total population	14	53%	27%	8.8	0-60

		Univariate Analysis		Multivariate Analysis		
		Median OS (Months)	*P*	HR	CI	*P*
Age	<65 years	15	NS	-	-	-
	≥ 65 years	15				
Gender	Female	13	NS	-	-	-
	Male	16				
PS - ECOG	0	18	NS	-	-	-
	1-2	11				
VALS stage	LS	16	NS	-	-	-
	ES	13				
Oligometastatic state	SyO	16	NS	-	-	-
	MeO	12				
	OIP	14				
Site of metastasis	Brain	9	0.009	0.495	0.281-0.845	.011
	No brain	20				
Number of treated metastasis	1	21	0.014	2.031	1.141-3.617	.016
	>1	10				
PCI	Yes	18	NS	-	-	-
	No	10				

Stage III - Resectability

OA06.05
Consensual Definition of Stage III NSCLC Resectab... with Oth...
A.-M. Ding... C. Faivre-... J.C. Trujil... M. Gucke... R. De Ang... E. Ruffine... A. Mariol... M. Brandao, T. Be...

P1.28-08
Definition of Resectable Stage III Non-Small Cell Lung Cancer: Cancer C...
E. Xenopl... G. Grisay, E. Priscia... C. Dickho... D. De Ruy...

P1.28-09
Definition of Resectable Stage III Non-small Cell Lung Cancer (NSCLC): A Clinical Case Review by a Pan-European Expert Panel
M. Brandao,[1] E. Prisciandaro,[2] E. Xenophontos,[3] A. Mariolo,[4]
A.H. Sa... C. Dick... D. Sanc... E. Fade... I. Houc... J.C. Ber... K. Hart... M. Occ... N. Regu... R. Hors... S. Popat,[37] T. Pierret,[38] T. Gerriet Blum,[39] U. Ricardi,[40] V. Dionisi,[41]
T. Berghmans,[1] A.-M. Dingemans[5] [1]*Institut Jules Bordet - Hôpital*

OA06.03
An International EORTC Survey on Resectability of Stage III Non-small Cell Lung Cancer
I. Houda,[1] I. Bahce,[1] C. Dickhoff,[1] T.E. Kroese,[2] S.G.C. Kroeze,[3]
A.V. Mariolo,[4] M. Tagliamento,[5] L. Moliner,[6] M. Brandao,[7]
J. Edwards,[8] I. Opitz,[2] C. Faivre-Finn,[9] D. de Ruysscher,[10]
J. Remon,[11] T. Berghmans,[7] A.-M.C. Dingemans,[12] B. Besse,[5]
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IASLC

2023 World Conference on Lung Cancer

SEPTEMBER 9-12, 2023
SINGAPORE

Stage III - Resectability

Complete Resection: IASLC definition

- ✓ Confirmation of negative surgical margins in the resected specimen
- ✓ Highest mediastinal node negativity at the time of surgery
- ✓ Systematic nodal dissection, with removal of at least 3 mediastinal lymphnode stations, always including subcarinal station 7.

Incomplete resection (R1, R2), uncertain resection

Rami-Porta R, Lung Cancer 2005

Stage III - Resectability

EORTC Survey: area of controversy

	N0	N1	N2 SINGLE	N2 MULTI	N2 BULKY	N2 INVASIVE	N3
T1-2	NOT STAGE III DISEASE	NOT STAGE III DISEASE	POTENTIALLY RESECTABLE	?	UNRESECTABLE[2]	UNRESECTABLE	UNRESECTABLE
T3 size	NOT STAGE III DISEASE	RESECTABLE	POTENTIALLY RESECTABLE	?	UNRESECTABLE	UNRESECTABLE	
T3 satellite	NOT STAGE III DISEASE	POTENTIALLY RESECTABLE	POTENTIALLY RESECTABLE	?	UNRESECTABLE	UNRESECTABLE	
T3 invasion	NOT STAGE III DISEASE	POTENTIALLY RESECTABLE	?[1]	?	UNRESECTABLE	UNRESECTABLE	
T4 size	POTENTIALLY RESECTABLE	POTENTIALLY RESECTABLE	?	UNRESECTABLE[2]	UNRESECTABLE	UNRESECTABLE	
T4 satellite	POTENTIALLY RESECTABLE	?[1]	?	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE	
T4 invasion	?[1]	?[1]	?	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE	

TN-subgroups for stage III NSCLC; Some results may deviate from the results in the final consensus; ?, no consensus achieved;
1, no consensus achieved but considered as potentially resectable by thoracic surgeons; 2, consensus unresectable but no consensus in the group of thoracic surgeons.

Stage III - Resectability

EORTC Consensus: Delphi method

- 13-item online survey with general and resectability questions
- Distribution to members of EORTC, ESTS, ETOP, ESTRO, ERS, and IASLC
- Definition of **consensus**: **75% agreement** among participants

- T-stage and N-stage according to the 8th TNM edition
- N2 (ipsilateral mediastinal and/or subcarinal nodes) working definition:
  - *N2 single*: single station, non-bulky (≤3cm), discrete*
  - *N2 multi*: multi-level, non-bulky (≤3cm), discrete
  - *N2 bulky*: bulky (>3cm) and discrete
  - *N2 invasive*: invasive growth#

** discrete = well defined/with identifiable borders*
 # invasive = infiltration in the surrounding tissues

Stage III - Resectability

EORTC Consensus

	N0	N1	N2 SINGLE (non-bulky, non-invasive)	N2 MULTI (non-bulky, non-invasive)	N2 BULKY¶	N2 INVASIVE	N3
T1-2	NOT STAGE III DISEASE	NOT STAGE III DISEASE	RESECTABLE	POTENTIALLY RESECTABLE*	UNCLEAR	UNRESECTABLE	UNRESECTABLE
T3 size / satellite / invasion	NOT STAGE III DISEASE	RESECTABLE	RESECTABLE	POTENTIALLY RESECTABLE*	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE
T4 size / satellite	RESECTABLE	RESECTABLE	RESECTABLE	POTENTIALLY RESECTABLE*	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE
T4 invasion	POTENTIALLY RESECTABLE§	POTENTIALLY RESECTABLE§	POTENTIALLY RESECTABLE§	POTENTIALLY RESECTABLE*§	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE

***Multiple station N2**: case-by-case discussion; the exact number of nodes/stations cannot be defined
¶**Bulky N2**: lymph nodes with a short-axis diameter >2.5-3 cm; in specific situations of *highly selected patients*, including those patients in multidisciplinary trials with surgery as local therapy can be discussed
§Some **T4 tumours by infiltration of major structures** are potentially resectable – see Table 1

Stage III - Resectability

EORTC Consensus

Stage IIIA – cT1-2 N2 tumors

Single-sta

•Single-stati

Multiple-s

•Absence o
the clinical
answered th

•Case-by-ca
multi- station involvement m
a tumor to be still considered

Stage IIIA – cT1-2 N2 tumors

Bulky N2

•No consen

•Most cases

•During the

•In specifi
multidisci

Stage IIIA – cT4 N0-1 tumors

Table 1	Unre-sectable	Potentially resectable

- **T4** co
- **T4** (T **bo** *di* an re de

Stage IIIB – cT3-4 N2 tumors

- cT3N2 and cT4 (size or satellite) N2 are considered **resectable** if **single-station N2**
- **Case-by-case discussion:** highly and carefully selected patients with ***"limited" discrete N2 multi-station*** *involvement* (non bulky, non invasive), while the exact number of nodes/stations defining "limited" cannot be defined

Stage IIIB – cT1-2 N3 tumors

- cT1-2N3 tumors are considered **unresectable**

Stage IIIC – cT3-4 N3 tumors

- Tumors with major structures infiltration and N3 disease are considered **unresectable**

Stage III - Resectability

AEGEAN: Perioperative immunotherapy

AEGEAN: A Phase 3 Trial of Neoadjuvant Durvalumab + Chemotherapy Followed by Adjuvant Durvalumab in Patients with Resectable NSCLC

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Perioperative Durvalumab for Resectable Non–Small-Cell Lung Cancer

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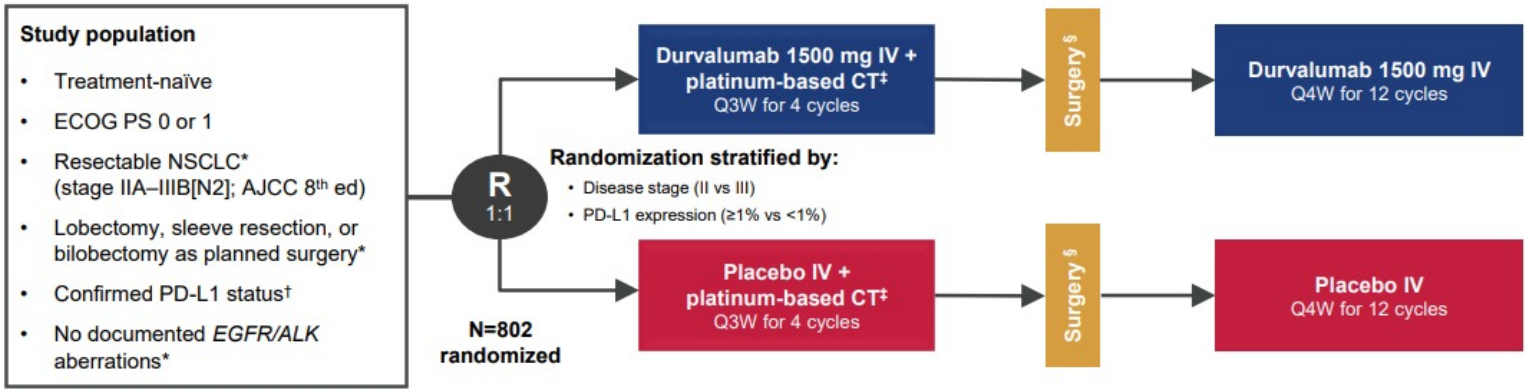
Stage III - Resectability

AEGEAN: Design & EndpointsPerioperative immunotherapy



Endpoints: All efficacy analyses performed on a modified population that excludes patients with documented *EGFR/ALK* aberrations¶

Primary:

- pCR by central lab (per IASLC 2020[1])
- EFS using BICR (per RECIST v1.1)

Key secondary:

- MPR by central lab (per IASLC 2020[1])
- DFS using BICR (per RECIST v1.1)
- OS

Stage III - Resectability

AEGEAN: Baseline characteristics

- Baseline characteristics were largely balanced between the study arms
- The planned neoadjuvant CT doublet regimen was carboplatin-based for >70% of patients

TNM classification†		D arm (N=366)	PBO arm (N=374)
Primary tumor, %	T1	12.0	11.5
	T2	26.5	28.9
	T3	35.0	34.5
	T4	26.5	25.1
Regional lymph nodes, %	N0	30.1	27.3
	N1	20.5	23.3
	N2	49.5	49.5

Characteristics*		D arm (N=366)	PBO arm (N=374)
Age	Median (range), years	65.0 (30–88)	65.0 (39–85)
	≥75 years, %	12.0	9.6
Sex, %	Male	68.9	74.3
	Female	31.1	25.7
ECOG PS, %	0	68.6	68.2
	1	31.4	31.8
Race‡, %	Asian	39.1	43.9
	White	56.3	51.1
	Other	4.6	5.1
Region, %	Asia	38.8	43.6
	Europe	38.5	37.4
	North America	11.7	11.5
	South America	10.9	7.5
Smoking status, %	Current	26.0	25.4
	Former	60.1	59.6
	Never	13.9	15.0
Disease stage (AJCC 8th ed.), %	II	28.4	29.4
	IIIA	47.3	44.1
	IIIB	24.0	26.2
Histology, %	Squamous	46.2	51.1
	Non-squamous	53.6	47.9
PD-L1 expression, %	TC <1%	33.3	33.4
	TC 1–49%	36.9	38.0
	TC ≥50%	29.8	28.6
Planned neoadjuvant platinum agent, %	Cisplatin	27.3	25.7
	Carboplatin	72.7	74.3

DCO = Nov 10, 2022. *Characteristics with missing/other responses are histology (0.3% in the D arm and 1.1% in PBO arm had 'other' histology) and disease stage (0.3% in D arm had stage IV disease, and 0.3% in the PBO arm had stage III [NOS] disease, as reported per the electronic case report form [eCRF]). †All patients were M0 except one patient in the D arm who was classified as M1 (NOS). ‡Race was self-reported per the eCRF. NOS, not otherwise specified; TC, tumor cells.

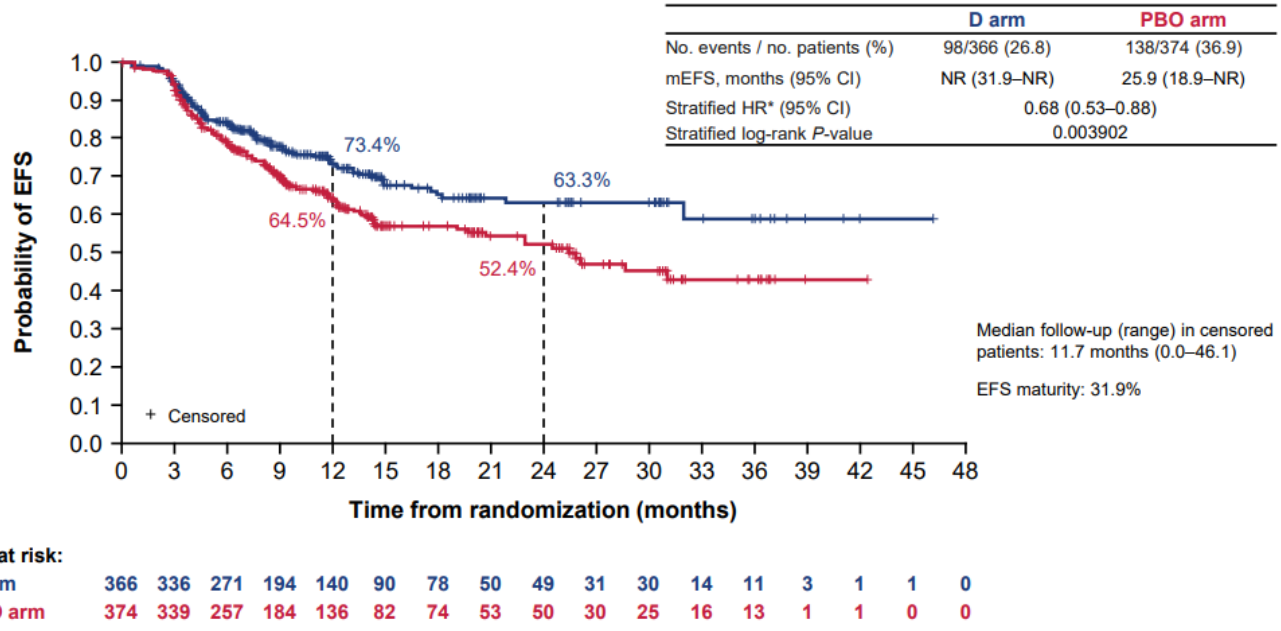
Stage III - Resectability

AEGEAN: Treatment Summary

Study phase*		D arm (N=366)	PBO arm (N=374)
Neoadjuvant phase	Randomized, n (%)	366 (100)	374 (100)
	Received Tx, n (%)	366 (100)	371 (99.2)
	Completed 4 cycles of both CT agents, n (%)	310 (84.7)	326 (87.2)
	Completed 4 cycles of D / PBO, n (%)	318 (86.9)	331 (88.5)
Surgery	Underwent surgery†, n (%)	295 (80.6)	302 (80.7)
	Did not undergo surgery†‡, n (%)	71 (19.4)	72 (19.3)
	Completed surgery†, n (%)	284 (77.6)	287 (76.7)
	– R0 resection, n (% of completed surgery)	269 (94.7)	262 (91.3)
	Did not complete surgery†, n (%)	11 (3.0)	15 (4.0)
Adjuvant phase (*ongoing*)	Started D / PBO§, n (%)	241 (65.8)	237 (63.4)
	Completed D / PBO, n (%)	88 (24.0)	79 (21.1)
	Discontinued D / PBO, n (%)	68 (18.6)	70 (18.7)
	Ongoing D / PBO, n (%)	85 (23.2)	88 (23.5)

Stage III - Resectability

AEGEAN: Event Free Survival (EFS)



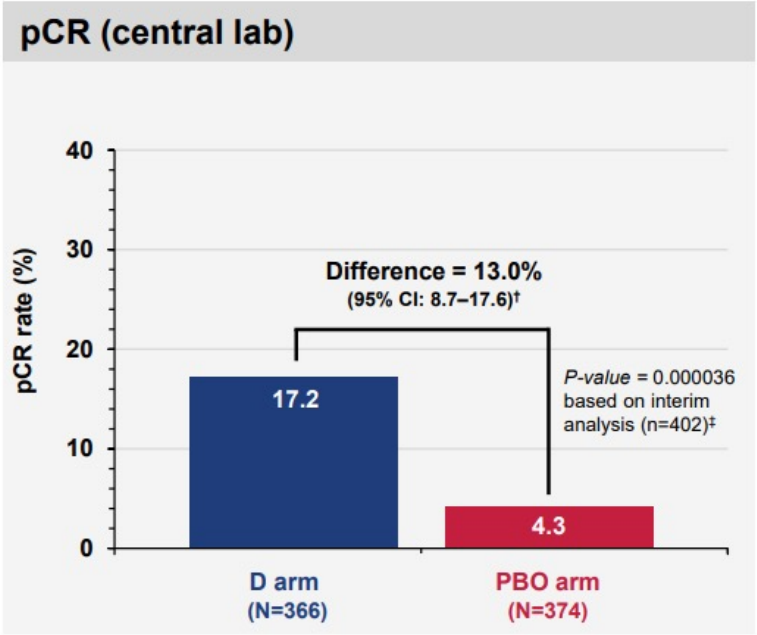
	D arm	PBO arm
No. events / no. patients (%)	98/366 (26.8)	138/374 (36.9)
mEFS, months (95% CI)	NR (31.9–NR)	25.9 (18.9–NR)
Stratified HR* (95% CI)	0.68 (0.53–0.88)	
Stratified log-rank *P*-value	0.003902	

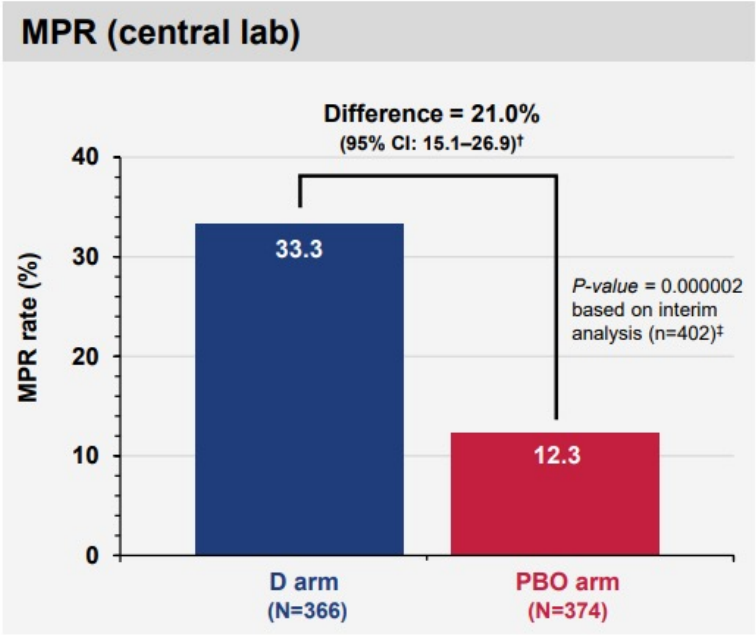
Median follow-up (range) in censored patients: 11.7 months (0.0–46.1)

EFS maturity: 31.9%

Stage III - Resectability

AEGEAN: Pathological Response





Stage III - Resectability

AEGEAN: Adverse Effects AEs

Overall study period (inclusive of the neoadjuvant, surgical, and adjuvant Tx phases)†	D arm (N=400)	PBO arm (N=399)
Any-grade all-causality AEs, n (%)	386 (96.5)	378 (94.7)
Max. grade 3 or 4	169 (42.3)	173 (43.4)
SAE	150 (37.5)	126 (31.6)
Outcome of death	23 (5.8)	15 (3.8)
Leading to discontinuation of D / PBO	48 (12.0)	24 (6.0)
Leading to cancellation of surgery	7 (1.8)	4 (1.0)
Any-grade AEs possibly related to D / PBO / CT, n (%)	346 (86.5)	322 (80.7)
Max. grade 3 or 4	129 (32.3)	132 (33.1)
Outcome of death‡	7 (1.8)	2 (0.5)
Any-grade immune-mediated AEs §, n (%)	94 (23.5)	39 (9.8)
Grade 3 or 4	16 (4.0)	10 (2.5)
Pneumonitis (any grade)¶	15 (3.8)	7 (1.8)

Stage III - Resectability

Candadian Consensus Reccomendations

Current Oncology

MDPI

Guidelines

Canadian Consensus Recommendations for the Management of Operable Stage II/III Non-Small-Cell Lung Cancer: Results of a Modified Delphi Process

James Tankel [1], Jonathan Spicer [1], Quincy Chu [2], Pierre Olivier Fiset [3], Biniam Kidane [4], Natasha B. Leighl [5], Philippe Joubert [6], Donna Maziak [7], David Palma [8], Anna McGuire [9], Barbara Melosky [10], Stephanie Snow [11], Houda Bahig [12] and Normand Blais [13,*]

Stage III - Resectability

Candadian Consensus Recommendations

The suitability for resection should be assessed prior to the initiation of neoadjuvant treatment and depends on a clinical assessment of the patient's physiological reserve; medical comorbidities; anatomical feasibility of achieving an R0 resection based on pre-treatment imaging; and consent of the patient to undergo pulmonary resection after a balanced discussion regarding treatment alternatives.	Class I (strong)	Level B-NR
For patients deemed physiologically unsuitable, who decline surgical resection or for whom an R0 resection may not be possible due to borderline resectability or N2 disease, timely consultation with a radiation oncologist ensures consideration of chemoradiotherapy with consolidation immunotherapy as an alternative treatment with curative intent.	Class I	Level B-R
If during neoadjuvant therapy physiological decline renders a patient unsuitable for surgical resection, definitive chemoradiotherapy and consolidation immunotherapy should be considered according to patient tolerance.	Class I (strong)	Level C-LD
Postoperative radiotherapy should be considered if a positive resection margin is found in the final pathological analysis on a case-by-case basis and discussed by the multidisciplinary team	Class IIa (moderate)	Level B-R

Stage III - Resectability

Perioperative CHT-IO

	CM816 (Chemo-Nivolumab)	AEGEAN (Chemo-Durvalumab)	Neotorch (Chemo-Toripalimab)	Keynote 671 (Chemo-Pembro)
Randomized	358	802	404	797
Endpoints	PCR, EFS	PCR, EFS	MPR, EFS (by stage groups)	EFS, OS
Stages	IB-IIIA (AJCC7) or II-IIIB (AJCC8)	II-IIIB (Possible pneumonectomy excluded)	III (stage II results not yet presented)	II-IIIB
Systemic plan	Neoadj (3 cycles)	Periadj (4+12 cycles)	Periadj (3-4+13 cycles)	Periadj (4+13 cycles)
Surgery	83%	81%	82%	82%
Impact on surgical outcomes	Grade 3/4 AE = 11.4% 3.4% 90-day mortality	N/A	N/A	Grade 3-4 AE = 18.2% 4% 90-day mortality
R0 rate	83%	95%	96%	92%
EFS @ 2 years	65%	63.3%	67%	62.4%
OS @ 2 years	82.7% (HR 0.57, 95% CI 0.38-0.87)	N/A	81.2%	80.9% (HR 0.73, 95% CI 0.54-0.99)

Courtesy of dr. L. Voltolini