Long-term Survival and Competing Risks of Death in the ESPATUE Randomized Phase-III Trial in Stage III NSCLC

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ESPATUE Phase III: Overcoming challenges

Based on previous phase II pilot trial (induction protocol with three cycles of cisplatin and paclitaxel and concurrent chemoradiotherapy with 45 Gy, hyperfractionated-accelerated radiotherapy followed by surgery) that demonstrated encouraging long-term survival in patients with IIIA(N2)disease and also in selected patients with stage IIIB disease.

In ESPATUE Phase III , Surgery was compared with Definitive Chemoradiotherapy in resectable stage III disease after induction

ESPATUE Phase III : Study Design

- Induction chemotherapy consisted of 3 cycles of 50 mg/m2 cisplatin D1 and D8 and Paclitaxel 175mg/m2 on D1 in a 21-day cycle
- Neoadjuvant radiotherapy was delivered to a total cumulative dose of 45 Gy, as two 1.5-Gy fractions per day, given 5 days a week
- Concurrent chemotherapy consisted of one cycle of cisplatin and vinorelbine: cisplatin 50 mg/m2 on days 2 and 9 and vinorelbine 20 mg/m2 on days 2 and 9 of neoadjuvant RT
- Definitive boost RT was given at 2 Gy per fraction, 5 fractions/ week, to a cumulative dose of 20 to 26 Gy without a treatment break from neoadjuvant RT
- Patients were reassessed during the last week of concurrent CTRT

Those patients whose tumors were reevaluated and deemed resectable in the last week of radiotherapy were randomly assigned to receive a chemoradiotherapy boost that was risk adapted to between 65 and

71 Gy in arm A or to undergo surgery (arm B). The primary end point was overall survival (OS).

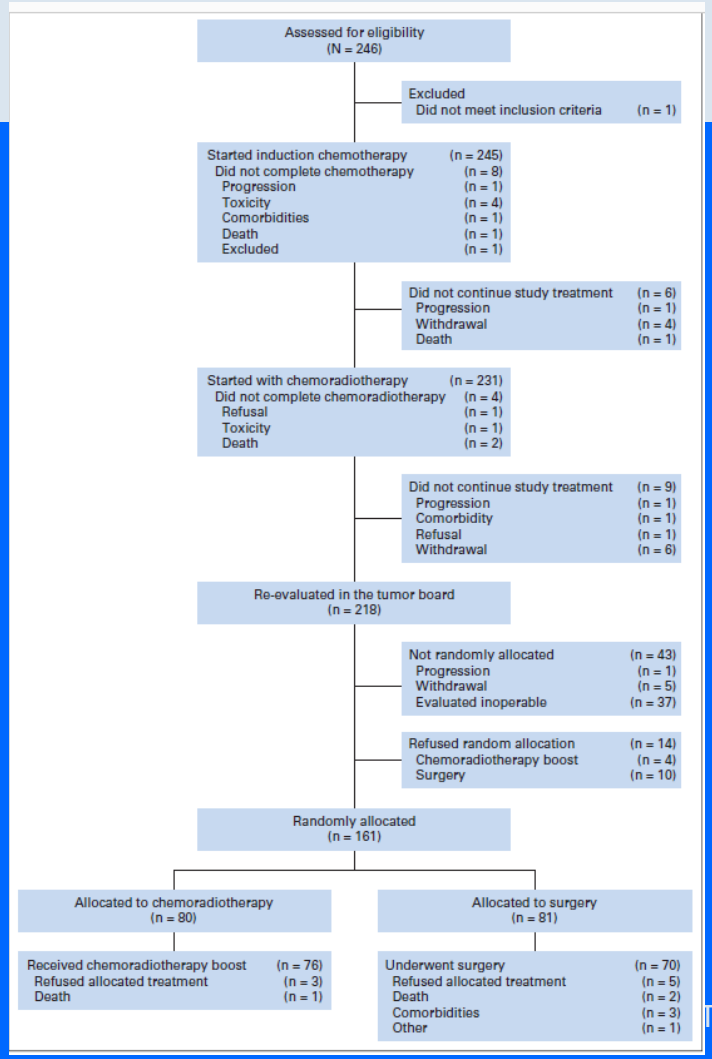
After 246 of 500 planned patients were enrolled, the trial was closed after the second scheduled interim analysis because of slow accrual and the end of funding, which left the study underpowered relative to its primary study end point.

ESPATUE: Patient demographics

Characteristic	Arm A: Definitive CT/RT (n = 80) No.	%	Arm B: Surgery (n = 81) No.	%	Patients Not Randomly Assigned (n = 85) No.	%	All Patients (N = 246) No.	%
Age, years								
Median (range)	59 (42-74)		58 (33-72)		59 (41-73)		59 (33-74)	
< 60	41	51	46	57	43	51	130	53
≥ 60	39	49	35	43	42	49	116	47
Sex								
Male	53	66	56	69	67	79	176	72
Female	27	34	25	31	18	21	70	28
ECOG performance status								
0	60	75	60	74	50	59	170	69
1	20	25	21	26	34	40	75	30.5
2	0	0	0	0	1	1	1	0.5
Histology								
Adenocarcinoma	40	50	36	44.5	31	36	107	43.5
Squamous cell carcinoma	28	35	35	43	32	38	95	38.5
Large cell	7	9	4	5	11	13	22	9
Mixed or other	5	6	6	7.5	11	13	22	9
Tumor-node group								
T4, N0 or N1	28	35	24	30	28	33	80	32.4
T1-3, N2	26	32.5	29	36	20	23.5	75	30.5
T1-4, N3 or T4, N2	26	32.5	28	34	37	43.5	91	37
Stage								
IIIA	26	32.5	29	36	20	23.5	75	30.5
IIIB	54	67.5	52	64	65	76.5	171	69.5
PCI policy								
Planned or already performed	21	26	21	26	NA		NA	
Not planned or not proposed	59	74	60	74	NA		NA	
Region								
Germany	79	99	80	99	NA		NA	
Other countries	1	1	1	1	NA		NA	

Abbreviations: CT/RT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; NA, not available; PCI, prophylactic cranial irradiation.

ESPATUE Phase III : Study Design



ESPATUE Phase III : Maximum toxicity

Table 2. Maximum Toxicities Observed in All Patient Groups

	Arm A: Definitive CT/RT (n = 80)						Arm B: Surgery (n = 81)						Patients Not Randomly Assigned (n = 85)						All Patients (N = 246)					
	Grade 3		Grade 4		Grade 5		Grade 3		Grade 4		Grade 5		Grade 3		Grade 4		Grade 5		Grade 3		Grade 4		Grade 5	
Toxicity	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Leukopenia	35	44	13	16	0	0	40	49	9	11	0	0	26	31	6	7	0	0	101	41	28	11	0	0
Anemia	7	9	0	0	0	0	10	12	0	0	0	0	2	2	0	0	0	0	19	8	0	0	0	0
Thrombocytopenia	6	8	2	3	0	0	8	10	1	1	0	0	3	4	1	1	0	0	17	7	4	2	0	0
Nausea/vomiting	7	9	0	0	0	0	10	12	1	1	0	0	3	4	0	0	0	0	20	8	1	< 1	0	0
Neuropathy	5	6	0	0	0	0	5	6	0	0	0	0	4	5	2	2	0	0	14	6	2	1	0	0
Esophagitis	21	26	0	0	0	0	11	14	0	0	0	0	9	11	1	1	0	0	41	17	1	< 1	0	0
Mucositis/stomatitis	2	3	0	0	0	0	3	4	0	0	0	0	2	2	0	0	0	0	7	3	0	0	0	0
Pulmonary	3	4	1	1	1	1	3	4	1	1	5	6	7	8	3	4	2	2	13	5	5	2	8	3
Other GI or renal	5	6	0	0	0	0	7	9	1	1	0	0	9	11	1	1	0	0	21	9	2	1	0	0
Cardiac	2	3	0	0	0	0	4	5	0	0	0	0	3	4	1	1	2	2	9	4	1	< 1	2	1
Miscellaneous infection	1	1	1	1	1	1	7	9	0	0	0	0	3	4	2	2	2	2	11	4	3	1	3	1
Fatigue	8	10	0	0	0	0	5	6	0	0	0	0	4	5	0	0	0	0	17	7	0	0	0	0
Pain	16	20	0	0	0	0	19	23	0	0	0	0	13	15	0	0	0	0	48	20	0	0	0	0

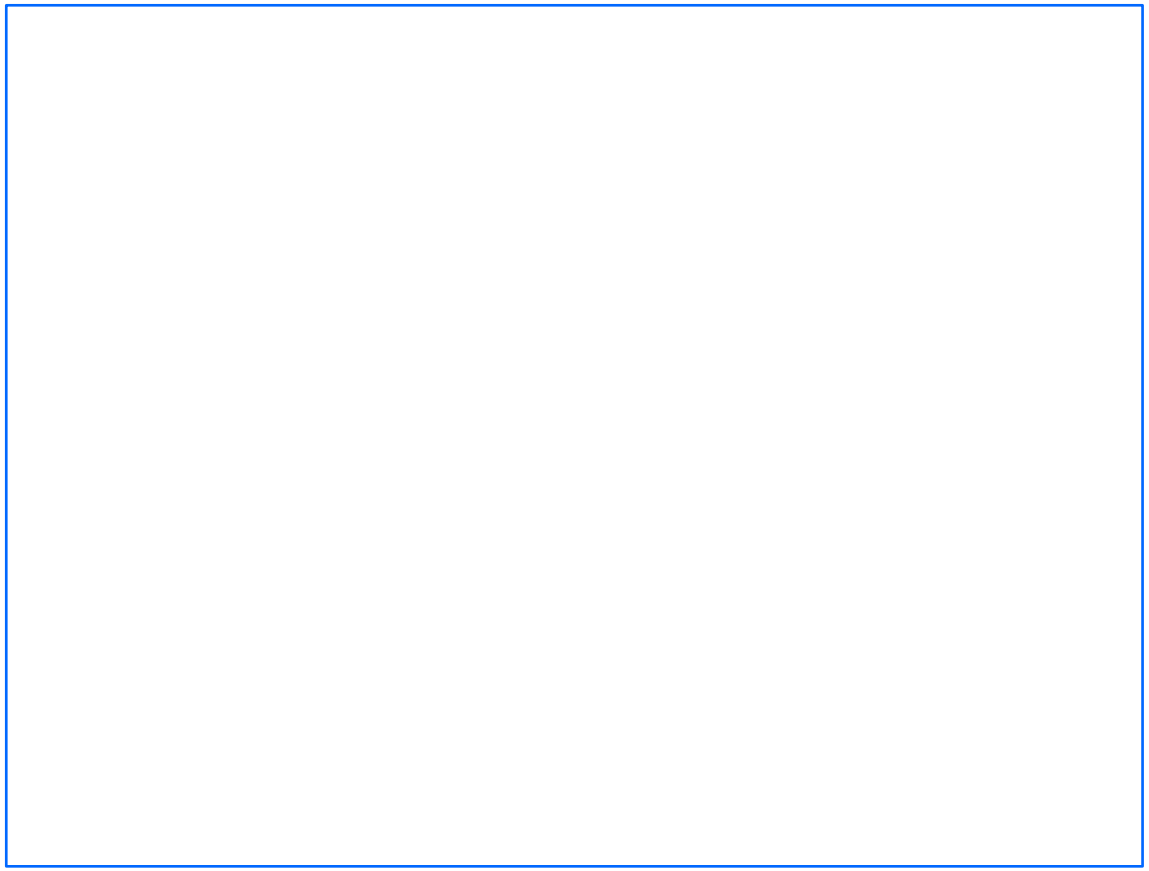
Abbreviation: CT/RT, chemoradiotherapy.

Procedures and Maximum Postoperative Toxicity Observed in Arm B

Table 3. Surgical Procedures and Maximum Postoperative Toxicity Observed in Arm B

Toxicity by Procedure	No. of Toxicities by Grade in Arm B (surgery; n = 70)		
	Grade 3	Grade 4	Grade 5
Lobectomy (n = 39)			
Anemia	2	0	0
Pulmonary	3	0	4
Other GI or renal	1	0	0
Cardiac	3	0	0
Miscellaneous infection	2	0	0
Pain	6	0	0
Pneumonectomy (n = 23)			
Anemia	3	0	0
Cardiac	1	0	0
Miscellaneous infection	1	0	0
Pain	5	0	0
Bilobectomy (n = 7)			
Anemia	1	0	0
Pulmonary	0	0	1
Segmentectomy (n = 1)			
Other GI or renal	1	0	0

ESPATUE Phase III: Overall survival of randomly assigned arms.



P Value:

P:.34 for OS

P:.21 for PFS

The 5-years OS rate in armA was 40% (95% CI, 29% to 52%) and was 44% (95% CI, 32% to 56%) in arm B.

ESPATUE Phase III: Overall survival of randomly assigned arms.

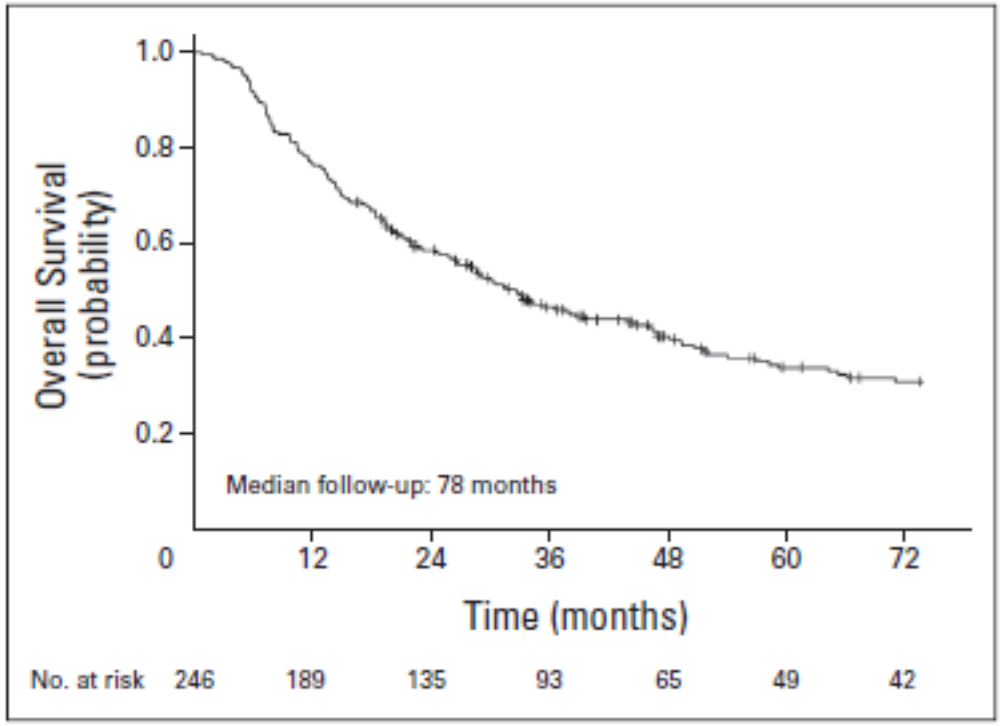
P Value:

P:.34 for OS

P:.21 for PFS

The 5-year PFS rate in arm A was 35% (95% CI, 25% to 46%) and was 32% (95% CI, 22% to 43%) in arm B

ESPATUE Phase III: Overall survival of randomly assigned arms.



The 5-year OS for all 246 initially recruited patients for entry onto this trial was 34.1% (95% CI, 27% to 41%;)

Summary

- The 5-year-OS data in randomly assigned patients with resectable stage III NSCLC were excellent in both treatments. Both are acceptable strategies for this good prognosis group.
- We could not substantiate a benefit in the 5-year OS rate for surgery versus individually dose-escalated chemoradiotherapy after induction chemotherapy and concurrent chemoradiotherapy
- Both interventions showed acceptable toxicities, which was in line with data reported in the literature

ESPATUE III -2022 UPDATE

An increasing number of stage III non-small-cell lung cancer (NSCLC) patients experience long-term survival (LTS).

New treatment principles of checkpoint inhibitor (CPI)-immunotherapy have specific impact on LTS in all LC stages.

ESPATUE Phase III: Sep 2022

Therefore, randomized phase-III trial datasets looking at optimum local treatment needs to be reassessed.

Randomized phase-III ESPATUE-trial results looking at definitive surgery versus definitive boost-radiochemotherapy following complex induction (Eberhardt et al, J Clin Oncol 2015) has already been reported..

ESPATUE Phase III: Sep 2022

Now , 5-and 10 yrs LTS data and report competing risk of deaths for the different treatment strategies has been reported.

Here, LTS based on follow-up until 1/2022 for all pts still alive including recent surveillance/follow-up visits is updated. JMP 15.2 was used for survival functions.

For survival comparison between both arms log-rank-test was used.

SAS 9.4 was used for a competing risk of deaths analysis over the whole period of follow-up until 1/2022.

LTS data of both arms were presented with percentages(%) and confidence intervals(CI). Comparison between arms was performed with the Gray test.

RESULTS

From 1/2004 until 1/2013 246 patients enrolled to the trial in selected centers in Germany and the Netherlands.

Following induction 161 pts potentially resectable were randomized to definitive RTx/CTx-boost(arm A;n1⁄480) or surgery(arm B;n1⁄481).

RESULTS

At last follow-up(1/2022) 37 of 246 pts were still alive, median follow-up of patients still alive was 129 months(range 76-204), pts alive 15/80 arm A, 16/81 arm B.

Overall survival(OS,%,CI) following randomization: 5-y-OS: A (43.8(32.7-54.2)) B (43.2(32.3-53.6)); 10-y-OS: A (28.3(18.8-38.5)) B (29.9(20.2-40.3));p1⁄40.70 log-rank.

Progression-free survival(PFS,%,CI) following randomization: 5-y-PFS: A

(30.0(20.4-40.2) B (29.2(19.7-39.4)); 10-y-PFS: A (23.3(14.6-33.1)) B

(19.8(11.8-29.4));p1⁄40.94 log-rank.

ESPATUE Phase III: Sep 2022

Table 1. Competing Risks of Deaths

	A:10-yrs	A:15-yrs	B:10-yrs	B:15-yrs	p Gray-test
DfFLC%,CI	50.1 (38.6 - 60.5)	50.1 (38.6 - 60.5)	44.4 (33.3 - 55.0)	44.4 (33.3 - 55.0)	0.3733
TRD%,CI	2.5 (0.5 - 7.9)	2.5 (0.5 - 7.9)	6.2 (2.3 - 12.9)	6.2 (2.3 - 12.9)	0.2568
DfCMB%,CI	10.2 (4.7 -18.3)	20.8 (10.7 - 33.2)	10.0 (4.6-17.8)	16.3 (8.3 - 26.8)	0.9068
DfSCwLC%,CI	1.3 (0.1 - 6.1)	1.3 (0.1 - 6.1)	1.2 (0.1- 6.0)	3.6 (0.5 - 11.9)	0.9609
DfSLC%,CI	7.7 (3.1 - 15.1)	13.0 (5.4 - 24.0)	8.3 (3.3 - 16.2)	13.0 (5.8 - 23.2)	0.8631

- LTS-rates in stage III show encouraging 5-y-OS and 10-y-OS and -PFS results and no significant differences between surgery and radiochemotherapy as definitive Local-Tx(B vs A).
- No clear signals for relevant differences between both arms in DfFLC, TRD, DfCMB, DfSCwLC, and DfSLC.

DfCMB and DfSLC turn out to be major long-term-risks of patients in these stages.

These important phase-III data may serve as baseline information to compare with those in future protocols including CPI-immunotherapy.

DfSLC may potentially be decreased by prospective LC-screening.

DfCMB is mainly related to cardiovascular/vascular events,pulmonary events and infections/septicemia.

Thank you