Lung Cancer UPDATES
ESMO HIGHLIGTHS
17-21 SEPTIEMBRE 2021

Iniciativa científica de:
GECP lung cancer research

Estadios iniciales resecables
Carcinoma no microcítico

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De la investigación a la calidad asistencial

#3563 # Clinical characteristics and survival in stage I-IIIA lung cancer resected patients in Spain, analyzed in the Thoracic Tumor Registry (RTT)

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	Total: 1.314 (100%)
Age at the diagnosis (median)	65 years (range 15-87)
< 55 years	211 (16,1%)
55-64 years	440 (33,5%)
65-74 years	504 (38,4%)
>= 75 years	159 (12,1%)
Tobacco habit	
Unknown	22 (1,7%)
Never smoker	148 (11,3%)
Former smoker	753 (57,3%)
Current smoker	391 (29,8%)
ECOG	
ECOG 0	704 (54%)
ECOG 1	549 (42%)
ECOG >=2	59 (4%)
Histology	
Adenocarcinoma	823 (62,6%)
Squamous	394 (30%)
Large cell carcinoma	44 (3,3%)
Adenosquamous	24 (1,8%)
NOS carcinoma	10 (0,8%)
Sarcomatoid	5 (0,4%)
Other	14 (1,1%)

733 deaths (55.8%) 577 of which due to lung cancer.

Median Survival:

- St I 81.7 months
- St II 45.1 months
- St IIIA 44.7 months

IMpower010 study design

Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial

Enriqueta Felip, Nasser Altorki, Caicun Zhou, Tibor Csőszi, Ihor Vynnychenko, Oleksandr Goloborodko, Alexander Luft, Andrey Akopov, Alex Martinez-Marti, Hirotsugu Kenmotsu, Yuh-Min Chen, Antonio Chella, Shunichi Sugawara, David Voong, Fan Wu, Jing Yi, Yu Deng, Mark McCleland, Elizabeth Bennett, Barbara Gitlitz, Heather Wakelee, for the IMpower010 Investigators*

Completely resected stage IB-IIIA NSCLC per UICC/AJCC v7

- Stage IB tumours ≥4 cm
- ECOG PS 0-1
- Lobectomy/pneumonectomy
- Tumour tissue for PD-L1 analysis

1-4 cycles cisplatin + pemetrexed, gemcitabine, docetaxel or vinorelbine

N=1280

R 1:1

No crossover

Atezolizumab *1200 mg q21d 16 cycles*

N=1005

BSC

Survival follow-up

Stratification factors

- Sex
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumour expression status (TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1)[a]

Primary endpoints

- Investigator-assessed DFS tested hierarchically:
  1. PD-L1 TC ≥1% (**SP263**) stage II-IIIA population
  2. All-randomised stage II-IIIA population
  3. ITT (all-randomised stage IB-IIIA) population

Key secondary endpoints

- OS in ITT (all-randomised stage IB-IIIA) population
- DFS in PD-L1 TC ≥50% (SP263) stage II-IIIA population
- 3-y and 5-y DFS in all 3 populations

N= 1280 → N= 1269 → N= 1005 (79%)

DFS in PD-L1 TC ≥1% stage II-IIIA population[b] N= 476

If positive:

DFS in all-randomized stage II-IIIA population[b]

If positive:

DFS in ITT population[b] (all-randomised stage IB-IIIA)

If positive:

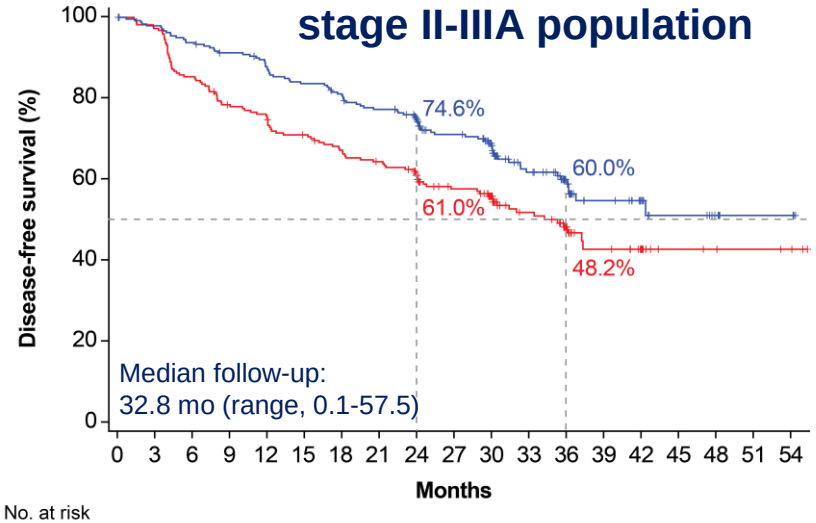
OS in ITT population[b] (all-randomised stage IB-IIIA)

- Endpoint was met at DFS IA
- Endpoint was not met at DFS IA, and follow-up is ongoing
- OS data were immature, and endpoint was not formally tested

Both arms included observation and regular scans for disease recurrence on the same schedule.
IC, tumour-infiltrating immune cells. [a] Per SP142 assay. [b] Two-sided α=0.05.

DFS in the PD-L1 TC ≥1%[a] stage II-IIIA, all-randomised stage II-IIIA and ITT populations (primary endpoint)[1]

PD-L1 TC ≥1% stage II-IIIA population

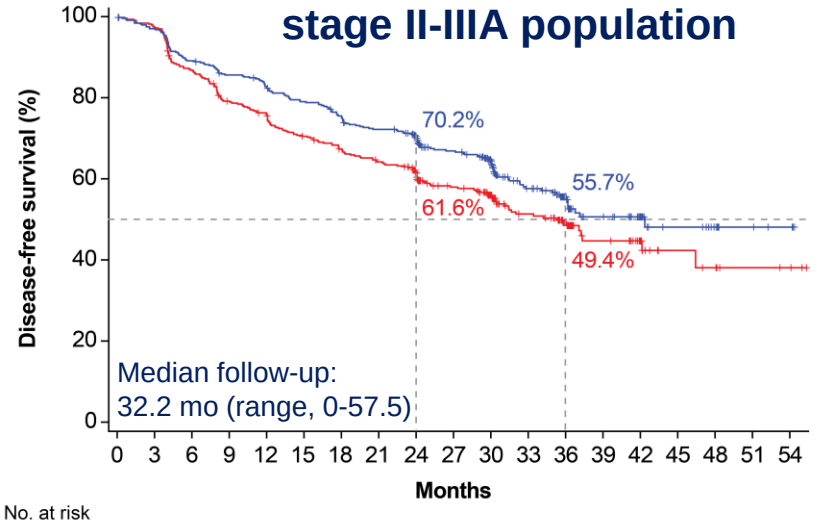


No. at risk

Atezolizumab	248	235	225	217	206	198	190	181	159	134	111	76	54	31	22	12	8	3	3
BSC	228	212	186	169	160	151	142	135	117	97	80	59	38	21	14	7	6	4	3

	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

All-randomised stage II-IIIA population

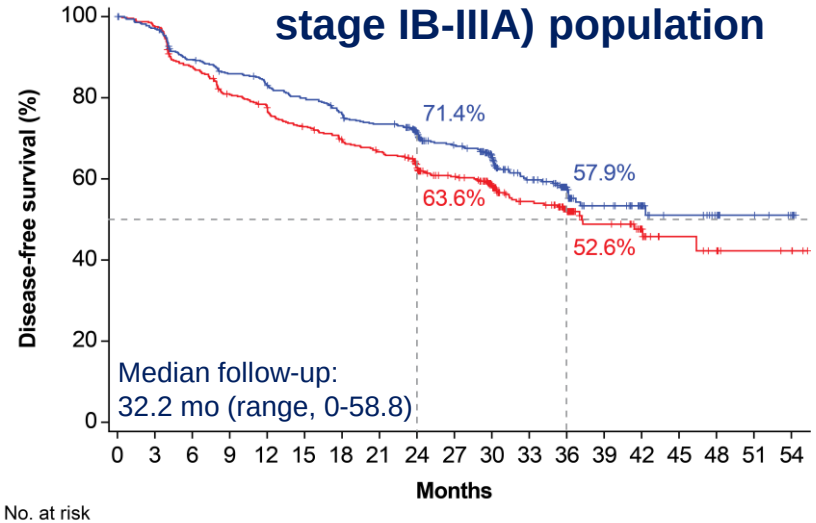


No. at risk

Atezolizumab	442	418	384	367	352	337	319	305	269	225	185	120	84	48	34	16	11	5	3
BSC	440	412	366	331	314	292	277	263	230	182	146	102	71	35	22	10	8	4	3

	Atezolizumab (n=442)	BSC (n=440)
Median DFS (95% CI), mo	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.79 (0.64, 0.96)	
P value[b]	0.02[c]	

ITT (randomised stage IB-IIIA) population



No. at risk

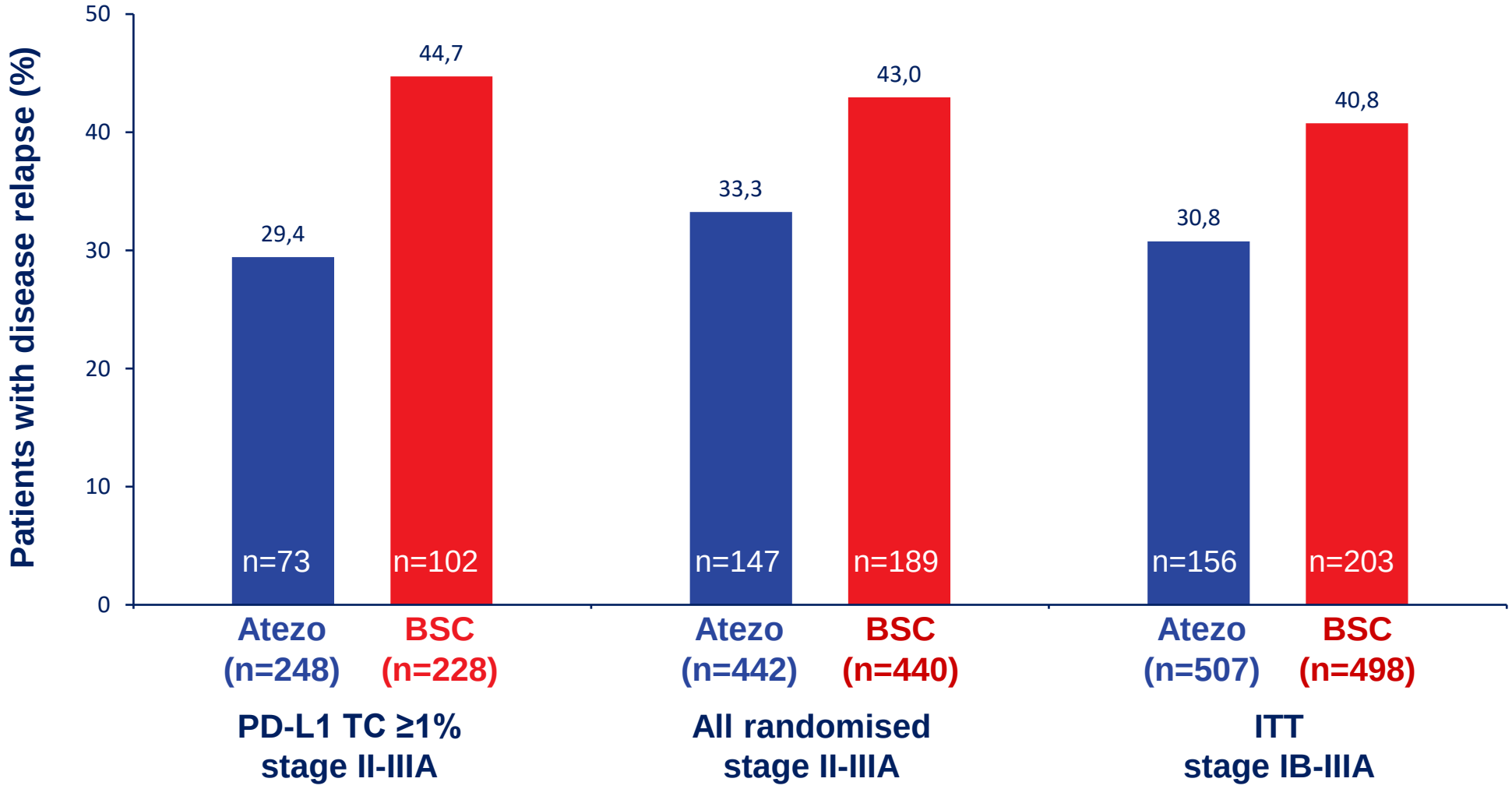
Atezolizumab	507	478	437	418	403	387	367	353	306	257	212	139	97	53	38	19	14	8	4
BSC	498	467	418	383	365	342	324	309	269	219	173	122	90	46	30	13	10	5	4

	Atezolizumab (n=507)	BSC (n=498)
Median DFS (95% CI), mo	NE (36.1, NE)	37.2 (31.6, NE)
Stratified HR (95% CI)	0.81 (0.67, 0.99)	
P value[b]	0.04[d]	

Clinical cutoff: 21 January 2021. [a] Per SP263 assay. [b] Stratified log-rank. [c] Crossed the significance boundary for DFS.
[d] The statistical significance boundary for DFS was not crossed. 1. Wakelee H, et al. J Clin Oncol. 2021;39(suppl 15):8500.

Incidence of disease relapse

Subset of DFS events that includes disease recurrence only



Clinical cutoff: 21 January 2021. Median follow-up in the ITT population was 32.2 mo (range, 0-58.8).

ITT stage IB-IIIA: sites of relapse

Site of relapse, n (%)	Atezolizumab (n=156)	BSC (n=203)
Locoregional only[a]	**59 (37.8)**	**75 (36.9)**
Distant only[b]	**67 (42.9)**	**82 (40.4)**
CNS	16 (10.3)	29 (14.3)
Bone/bone marrow	14 (9.0)	14 (6.9)
Contralateral lung	10 (6.4)	16 (7.9)
Liver	10 (6.4)	8 (3.9)
Lymph node	8 (5.1)	11 (5.4)
Ipsilateral lung	6 (3.8)	8 (3.9)
Subcutaneous tissue	1 (0.6)	2 (1.0)
Other	16 (10.3)	15 (7.4)
Locoregional and distant	**27 (17.3)**	**38 (18.7)**
Bone/bone marrow	11 (7.1)	8 (3.9%)
Contralateral lung	7 (4.5)	10 (4.9)
Liver	6 (3.8)	4 (2.0)
Lymph node	5 (3.2)	9 (4.4)
Ipsilateral lung	5 (3.2)	1 (0.5)
CNS	3 (1.9)	6 (3.0)
Subcutaneous tissue	1 (0.6)	0
Other	6 (3.8)	13 (6.4)

- Overall patterns of the sites of relapses in the PD-L1 TC ≥1% stage II-IIIA and all-randomised stage II-IIIA populations were consistent with that of the ITT stage IB-IIIA population

Clinical cutoff: 21 January 2021.

[a] Includes patients with 'local' and/or 'regional' recurrence only. [b] Includes patients with distant sites only; patients could have >1 distant site.

Time from randomisation to relapse[a]

PD-L1 TC ≥1% stage II-IIIA

Atezo: *Median (range) time to any relapse: 17.6 mo (0.7-42.3)*

BSC: *Median (range) time to any relapse: 10.9 mo (1.3-37.3)*

All randomised stage II-IIIA

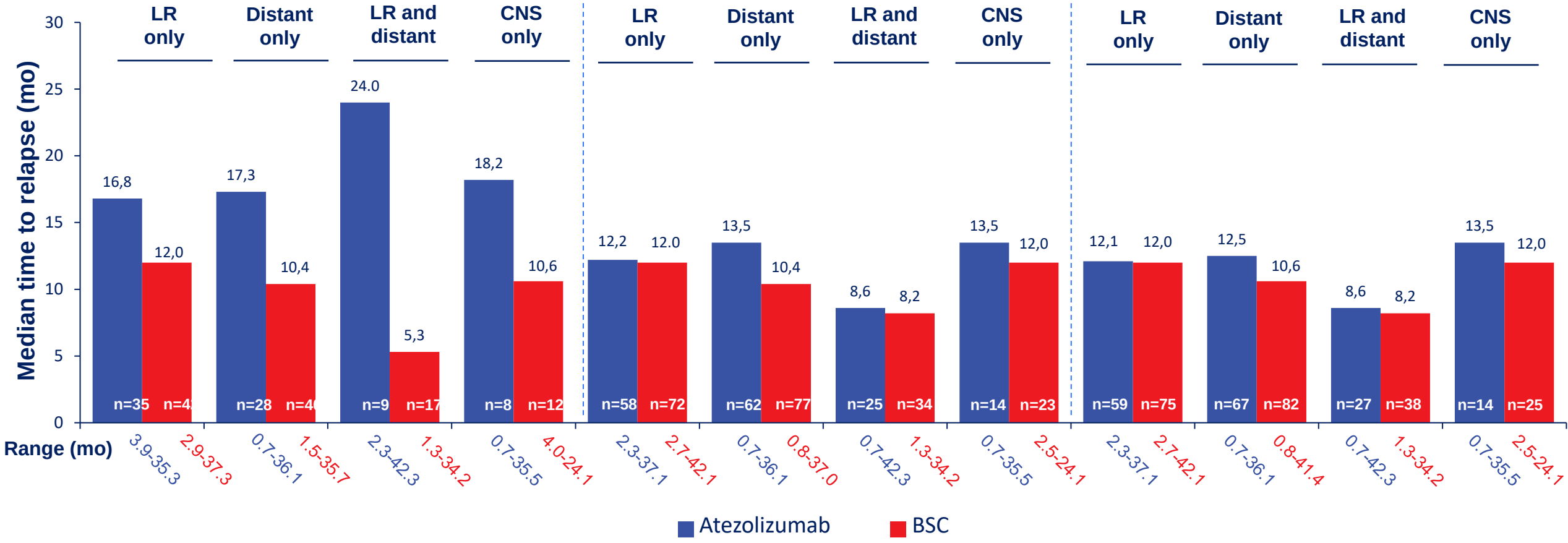
Median (range) time to any relapse: 12.4 mo (0.7-42.3)

Median (range) time to any relapse: 11.1 mo (0.8-42.1)

ITT stage IB-IIIA

Median (range) time to any relapse: 12.3 mo (0.7-42.3)

Median (range) time to any relapse: 12.0 mo (0.8-42.1)

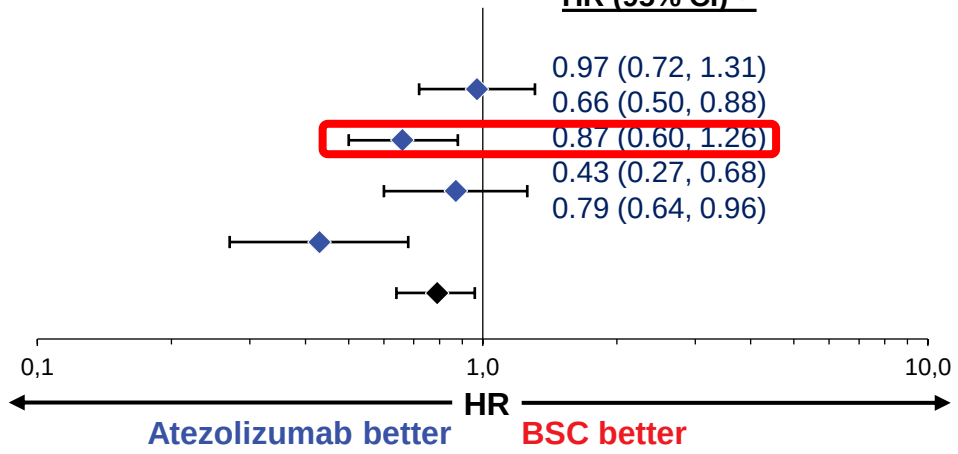


Clinical cutoff: 21 January 2021. LR, locoregional. [a] Post-hoc descriptive analysis.

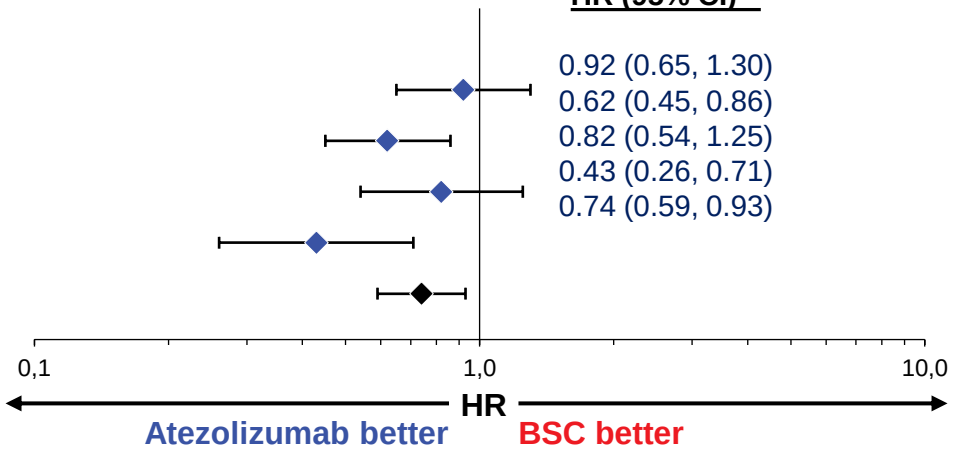
DFS by PD-L1 status[a]

All-randomised stage II-IIIA population (with and without known EGFR/ALK+ disease)

Subgroup *(including EGFR/ALK+)*	n	HR (95% CI)[b,c]
PD-L1 status by SP263		
TC <1%	383	0.97 (0.72, 1.31)
TC ≥1%	476	0.66 (0.50, 0.88)
TC 1-49%	247	0.87 (0.60, 1.26)
TC ≥50%	229	0.43 (0.27, 0.68)
All patients[d]	882	0.79 (0.64, 0.96)

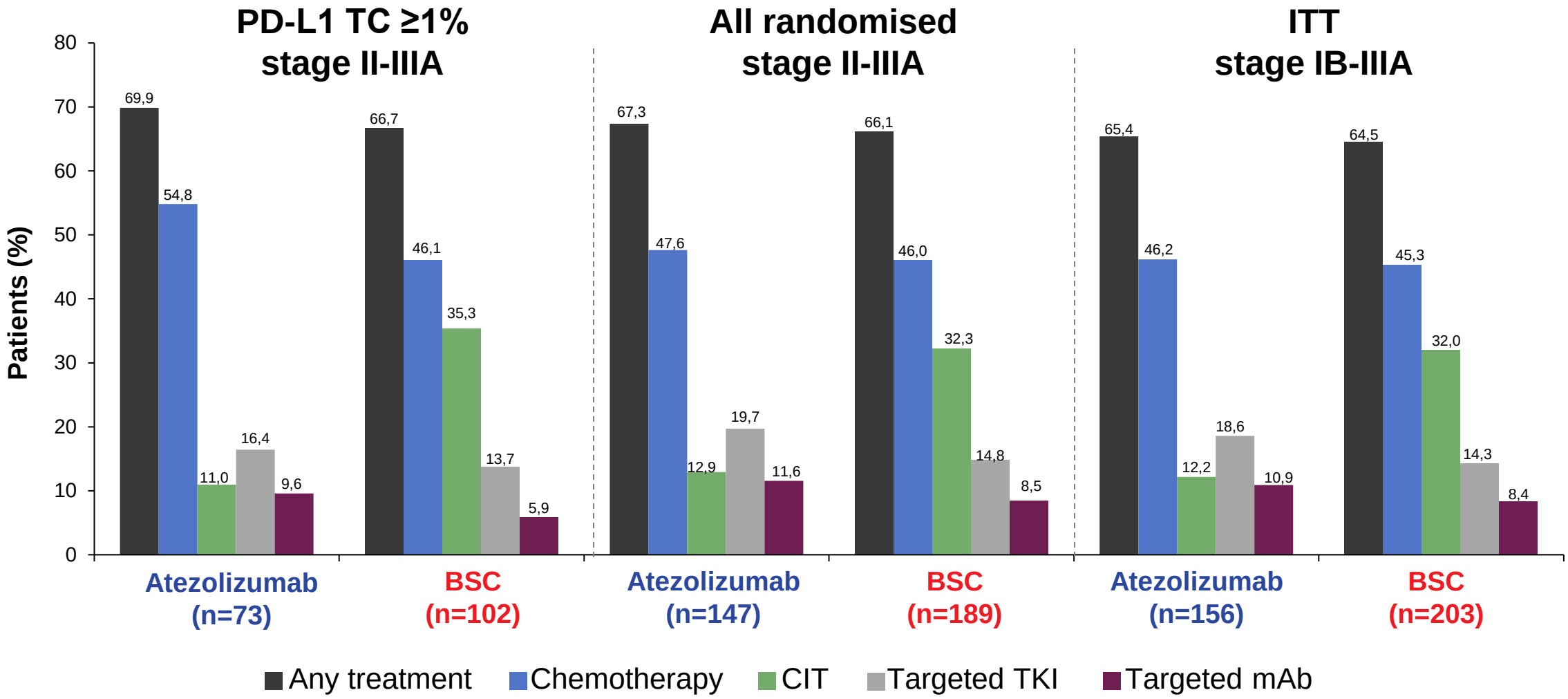


Subgroup *(excluding EGFR/ALK+)*[e]	n	HR (95% CI)[f,g]
PD-L1 status by SP263		
TC <1%	312	0.92 (0.65, 1.30)
TC ≥1%	410	0.62 (0.45, 0.86)
TC 1-49%	201	0.82 (0.54, 1.25)
TC ≥50%	209	0.43 (0.26, 0.71)
All patients[h]	743	0.74 (0.59, 0.93)



Clinical cutoff: 21 January 2021. [a] Per SP263 assay.
[b] Stratified for all patients and PD-L1 TC ≥1%; unstratified for all other subgroups. [c] DFS analyses in the PD-L1 TC <1% and TC 1-49% subgroups were exploratory. [d] 23 patients had unknown PD-L1 status as assessed by SP263. [e] Excluding patients with known *EGFR/ALK*+ NSCLC. [f] Unstratified for all subgroups. [g] EGFR/ALK+ exclusion analyses were post hoc. [h] 21 patients had unknown PD-L1 status as assessed by SP263.

Post-relapse systemic non-protocol anticancer therapy



Clinical cutoff: 21 January 2021. CIT, cancer immunotherapy; mAb, monoclonal antibody; TKI, tyrosine kinase inhibitor.

Felip et al. IMpower010 Relapse Patterns. https://bit.ly/3mNMSAi

Conclusion

Impower 010 is the first adjuvant study establishing ICB as a new standard of care

DFS benefit in stage II-IIIA (UICC/AJCC v7)
We need to cure more, not to delay relapse (OS immature)

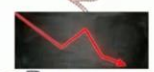
Absence of benefit in PD-L1 <1%
Optimal population to be defined

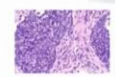
Best peri-operative strategy to be defined

« If approved, I would prescribed adjuvant atezolizumab… until I see the OS curves »

The 2020 decade fight

Neoadjuvant	Adjuvant
Better to treat with primary tumor?	Better if tumor burden is lower?
Rate of drop off?	Less eligible patients?
Surgery procedure : more difficult?	Surgery vs. immune system?
Maybe 4 cycles of IO is enough	1 yr IO too much or not enough?
pCR/MPR surrogate of OS?	More easy to assess biomakers





IoNESCO IFCT-1601 Study design

Immune Neoajuvant therapy in Early Stage Non Small Cell CarcinOma

- Stage IB ≥ 4cm, II, IIIA non-N2 NSCLC
- ECOG 0 or 1
- age ≥ 18 years
- pre-therapeutic tissue required

INCLUSION →

Anti-PD-L1
durvalumab
750 mg IV*
Day1, 15, 29

Surgery
2 to 14 days after last infusion

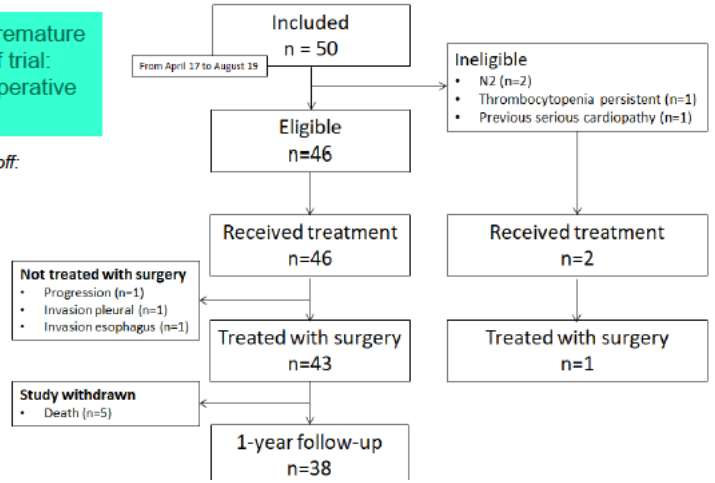
Surgical snap-frozen[1] tissue (tumor + nodes) required

Follow-up
4 weeks,
6 months
one year
after surgery

Patient enrollment and disposition

Reason for premature termination of trial: 90-day postoperative mortality

Data analysis cutoff: 01-MAY-2020



Patient demographics and results

IFCT-1601 IONESCO - NCT03030131

	N = 46
Age (median [range])	61.0 [46.7-80.5]
Male / Female	31 (67.4%) / 15 (32.6 %)
Smokers	45 (97.8%)
ECOG 0 / 1	38 (82.6%) / 8 (17.4%)
Histology : Adenocarcinoma / Squamous / Other	23 (50%) / 19 (41.3%) / 4 (8.7%)
Stage : IB / IIA / IIB / IIIA	5 (10.9%) / 13 (28.3%) / 27 (58.7%) / 1 (2.2%)
Surgical procedures ; Lobectomy / Bilobectomy / Pneumonectomy	31 (72.1%) / 3 (6.8%) / 9 (20.9%)
Number of pts receiving 3 durvalumab doses	43 (93.5%)

	N	
Complete resection (R0)	46	41 (89,1%)
RECIST 1.1 CR / PR / SD / PD	46	0 (0%) / 4 (8.7%) / 36 (78.3%) / 6 (13%)
RVT (median [range])	43	36.1% [0-73.3]
Complete PR	43	3 (7%)
MPR*	46	8 (18.6%)
12m-DFS (% [95% IC])	46	78.3% [63.4-87.7]
12m-OS (% [95% IC])	46	89.1% [75.8-95.3]
18m-DFS (% [95% IC])	46	73.7% [58.4-84.1]
18m-OS (% [95% IC])	46	89.1% [75.8-95.3]

MPR was significantly associated with DFS (N=43, p=0.04) : 100% of patients with MPR* were disease-free at 12 months *vs* 77.1% [95% IC 59.5-87.6] patients with >10% RVT (N=35).

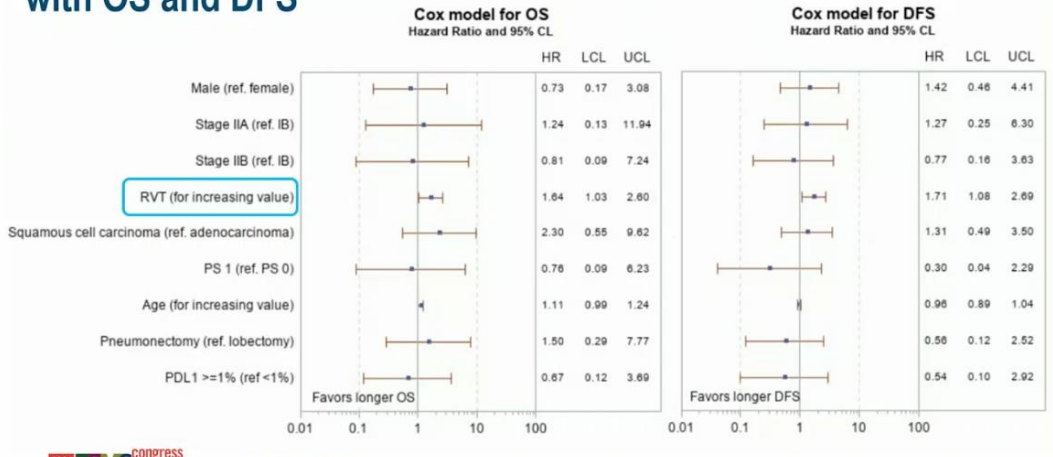
*Major Pathologic Response (MPR) defined as ≤10% of residual viable tumor cells (RVT)

Median follow-up [95% IC] : 28.4 months [26.7-29.7]

Marie Wislez, MD, PhD

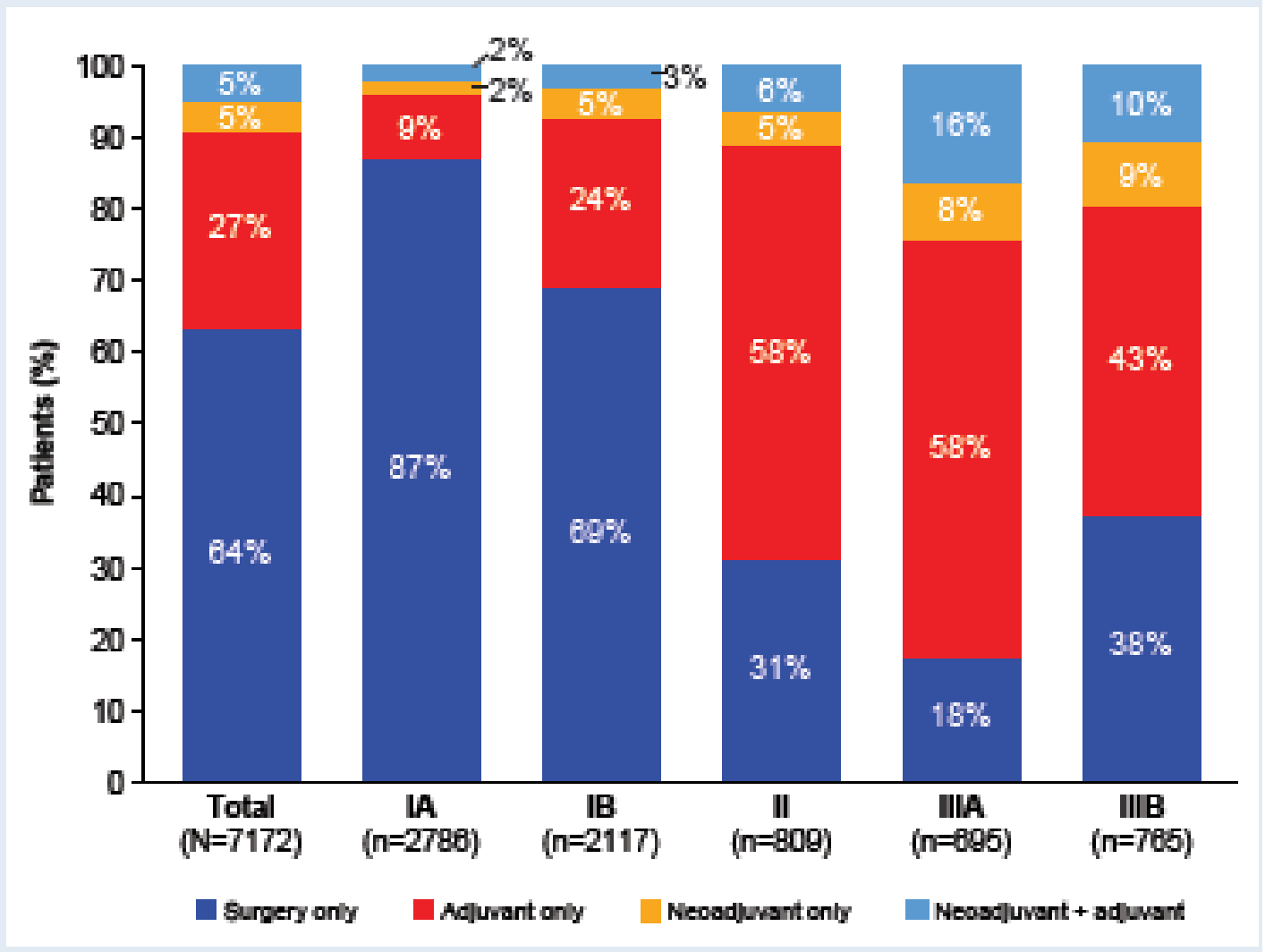
Wislez M, Annals of Oncology (2020) 31(suppl_4):S735-S743.10.1016/annonc/annonc282

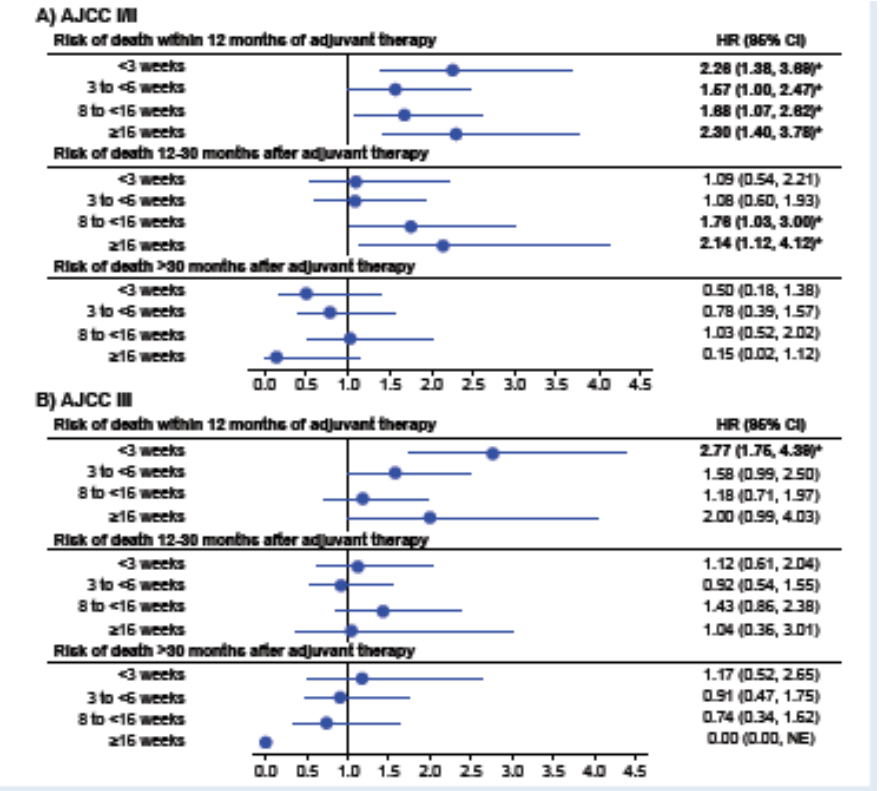
RVT(%) as a continuous variable is associated with OS and DFS



Marie Wislez, MD, PhD

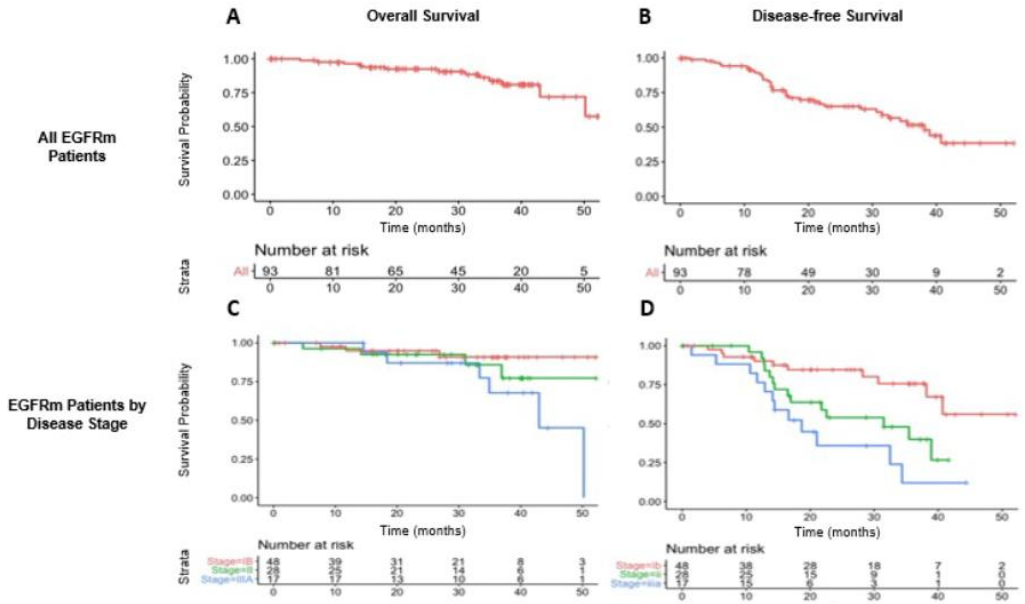
RWD adjuvant/neoadjuvant 2010-2015





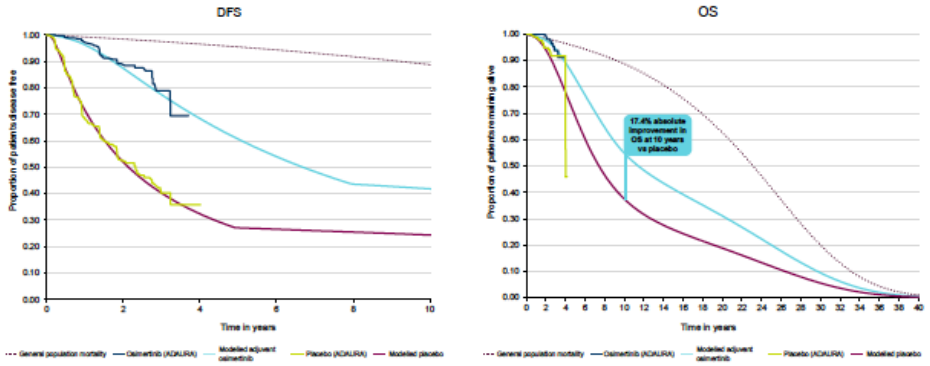
Poster 1158P

Osimertinib adjuvant



Poster 1152P

Figure 2. Modelled DFS and OS



DFS, disease-free survival; OS, overall survival.

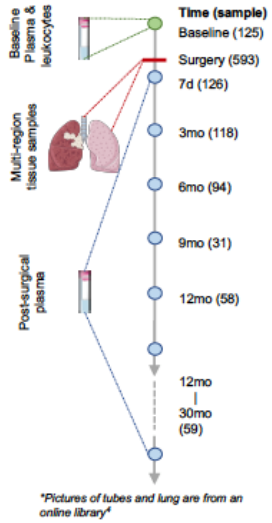
Table 2. Modelled disease free/alive at 5-, 10- and 20-year landmarks

	Median DF life-years (95% CI)	Patients DF at 5 years (95% CI)	Patients DF at 10 years (95% CI)	Patients DF at 20 years (95% CI)	Median life-years OS (95% CI)	Patients alive at 5 years (95% CI)	Patients alive at 10 years (95% CI)	Patients alive at 20 years (95% CI)
Osimertinib	6.67 (4.44, 8.59)	60.6% (57.6, 63.5)	41.8% (38.9, 44.6)	28.6% (26.6, 30.6)	11.42 (9.09, 14.66)	83.2% (80.0, 84.4)	54.9% (52.0, 57.6)	31.0% (28.7, 32.9)
Placebo	2.08 (1.73, 2.26)	27.0% (24.6, 29.4)	24.3% (22.1, 26.5)	16.4% (14.9, 18.0)	7.33 (6.76, 7.97)	68.9% (65.4, 72.1)	37.5% (34.0, 40.9)	18.8% (17.2, 20.5)
Incremental life-years osimertinib vs placebo	4.59 (2.87, 6.32)	-	-	-	4.08 (1.53, 7.09)	-	-	-

Poster 1165P

Monitoring MRD in adjuvant setting

Figure 1. Overview of sample collection and patient demography



Pictures of tubes and lung are from an online library

Characteristics	Patients (n = 127)
Age (years)	
Mean ± SD	62.2 ± 8.3
Median (min - max)	63 (39 - 79)
Sex	
Female	55 (43.3%)
Male	72 (56.7%)
Smoking history	
Ever	33 (26.0%)
Never	94 (74.0%)
Histology	
LUAD	100 (78.7%)
LUSC	21 (16.5%)
Other	6 (4.8%)
Focality	
Multifocal	44 (34.6%)
Unifocal	83 (65.4%)
Stage	
I	55 (43.3%)
II	24 (18.9%)
III	47 (37.0%)
IV	1 (0.8%)
Lymph node metastasis	
Positive	57 (44.9%)
Negative	70 (55.1%)

Figure 2. Detection of ctDNA at different pathological stages

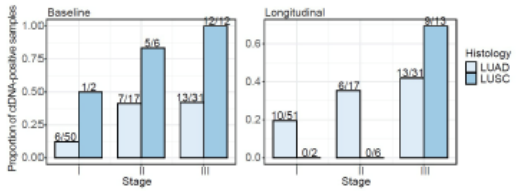
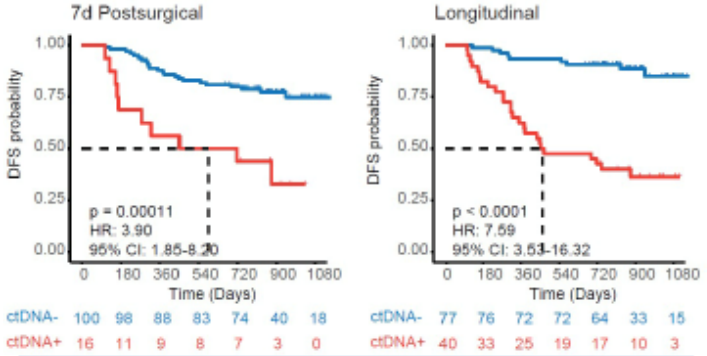


Figure 2: ctDNA was more frequently detected in patients with more advanced diseases both pre- and post-surgically.

Figure 3. Post-surgical ctDNA detection indicated higher risk of relapse

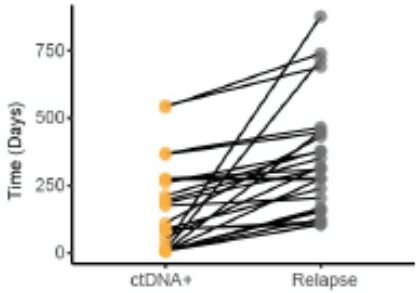


Group	7d Postsurgical		Longitudinal	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
LUAD	26.1 (6/23)	94.4 (68/72)	73.9 (17/23)	81.9 (59/72)
LUSC	37.5 (3/8)	88.9 (8/9)	77.8 (7/9)	88.9 (8/9)
Overall*	30.3 (10/33)	92.8 (77/83)	73.5 (25/34)	81.9 (68/83)

including other types of pathological histology

Figure 3: ctDNA detection at 7 days post surgeries and during longitudinal monitoring indicated higher risk of relapse (HR = 3.90 & 7.59, respectively). Longitudinal ctDNA monitoring achieved 73.5% sensitivity for predicting relapse occurrence while maintaining 81.9% specificity.

Figure 5. ctDNA detection led radiological relapse



Histology	Lead day median (min - max)
LUAD	144 (0-847)
LUSC	150 (33-264)
Overall*	145 (0-847)

including other types of pathological histology

Figure 5: ctDNA detection during longitudinal monitoring led radiological relapse by a median of 144 days in LUAD cases and 150 days in LUSC cases.

Poster 1154P

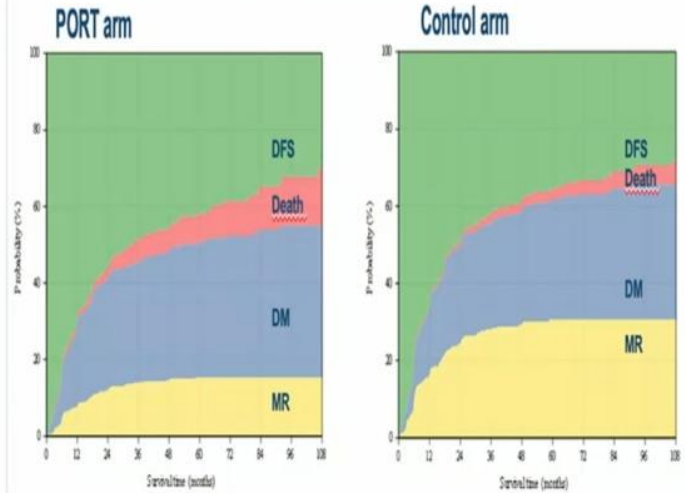
ESMO 2021: PATTERNS OF RELAPSE

Components of DFS

Event (n(%))	PORT (n=144)	Control (n=152)	Total (n = 296)	HR (95%CI)*
Mediastinal relapse (MR)	36 (25%)	70 (46%)	106 (36%)	0,45 [0,30-0,69]
All Distant Metastases (DM)	87 (60%)	74 (49%)	161 (54%)	1,17 [0,86-1,60]
including Brain Metastases (BM)	34 (24%)	27 (18%)	61 (21%)	1,33 [0,78-2,26]
Death	21 (15%)	8 (5%)	29 (10%)	2,63 [1,18-5,84]

- Patients can have more than one event at the same time
- Causes of death: Control arm: 2 2nd Primary,1 vascular,4 unknown, 1 non cancer related
  PORT arm: 11 cardio-pulmonary; 2 PORT toxicity; 4 2nd Primary; 1 progression, 3 unknown.

Cumulative incidence functions (competing risks analysis)



MEDIASTINAL RELAPSE AND PROGNOSTIC FACTORS FOR DFS

- **Administration of PORT reduces the risk of Mediastinal Relapse (MR) in resected stage IIIAN2 NSCLC patients but has no significant impact on DFS.**
- MR:
  - Total 106 (36%), **PORT arm 36 (25%),** Control arm 70 (46%); (unadjusted HR= 0.46)
  - It occurs mainly within initially involved nodes (66% in control arm, 47% in PORT arm)
- There is no robust evidence of predictive factors for PORT on DFS components:
  - Clinical factors:
    - Age ≥ 70 years old. HR for death 3.97; p: 0.004
    - PS ECOG 1, 2 vs 0
  - Treatment related factors:
    - Quality of resection
    - RT treatment: HR for death 2.73 (p 0.002)
      - Toxicity driven?
  - Nodal involvement

Variable	HR for MR	p-value (MR)	HR for DM	p-value (DM)	HR for death	p-value (death)
Treatment arm radiotherapy (vs control)	0.38*	<.0001	1.25	0.18	2.73*	0.02
Age >= 70 (vs < 70 years old)	0.62	0.13	1.12	0.64	3.97*	0.004
Performance status (WHO) 1 (vs 0)	1.57*	<.0001	0.93	0.82	1.24*	<.0001
Performance status (WHO) 2 (vs 0)	0*	<.0001	1.32	0.82	0*	<.0001
pT 0, 1 (vs 2)	0.94	0.08	0.63	0.08	1.33	0.79
pT 3, 4 (vs 2)	1.77	0.08	0.96	0.08	0.94	0.79
Surgery type = pneumonectomy (vs other)	1.13	0.75	1.49	0.11	0.58	0.52
No adjuvant CT (vs post-operatory CT alone)	2.08	0.27	1.34	0.25	0.34	0.3
Pre-operative CT (vs post-operatory CT alone)	1.37	0.27	1.5	0.25	0.45	0.3
Time from surgery to randomisation <130 days (median time, as = 130 days)	1.35	0.23	0.72	0.09	1.09	0.85
Histology Squamous cell carcinoma (vs other)	1.58	0.1	0.35*	0.0002	1.81	0.2
ECE unspecified	0.84	0.73	1.17	0.73	0.76	0.22
ECE+ (vs no)	0.75	0.73	1.03	0.73	1.85	0.22
No involved station (vs 1)	1.13	0.93	0.94	0.28	0*	<.0001
>=2 involved stations involved (vs 1)	0.93	0.93	1.33	0.28	0.93*	<.0001
LNR >= 25% (vs < 25%)	1.62*	0.03	0.89	0.52	2.76*	0.04
N2 involvement with N1 involvement (vs without)	1.17	0.53	1.38	0.1015	1.04	0.92
Quality of resection R1uni (vs R0)	1.06*	<.0001	1.29*	<.0001	0.49*	<.0001
Quality of resection R1(ECN) (vs R0)	1.94*	<.0001	1.08*	<.0001	0.23*	<.0001
Quality of resection R2 (vs R0)	13.07*	<.0001	0*	<.0001	0*	<.0001

[1]Liu T. J Cancer 2019; [2]Gao F et al. JNCCN 2020; [3] Lei T et al. Frontiers in Oncol 2021; [4] Sura K et al, Clin Lung Cancer 2018

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GRACIAS

GECP lung cancer research

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