Terapie adiuvanti: target therapy e immunoterapia

Giulia Pasello
DiSCOG, Università di Padova
IOV, IRCCS

Disclosures

Advisory Boards / Honoraria / Speakers' fee / Consultant for:

Amgen, AstraZeneca, BMS, Eli Lilly, Jansenn, MSD, Novartis, Roche

Unconditioned research support by:

AstraZeneca, Roche

MDT facing early and locally advanced resectable NSCLC

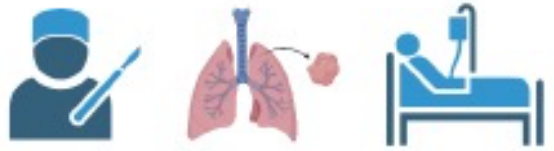
Past

ADJUVANT

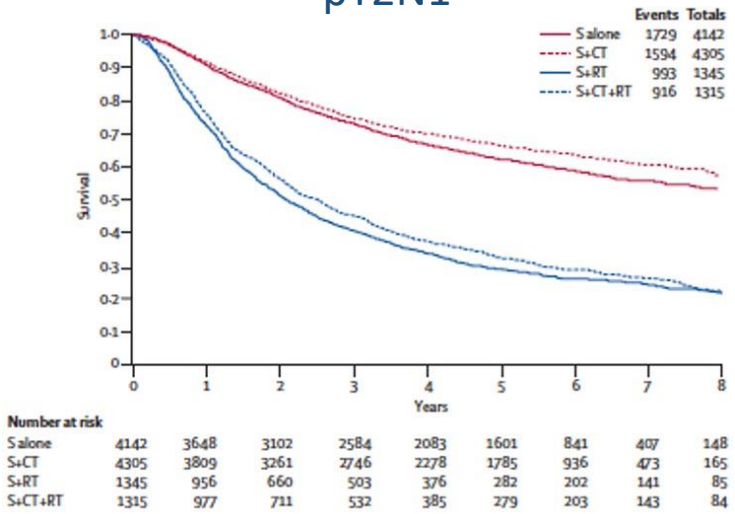
NEO-ADJUVANT

Stage II-III upfront resection

cT2N0

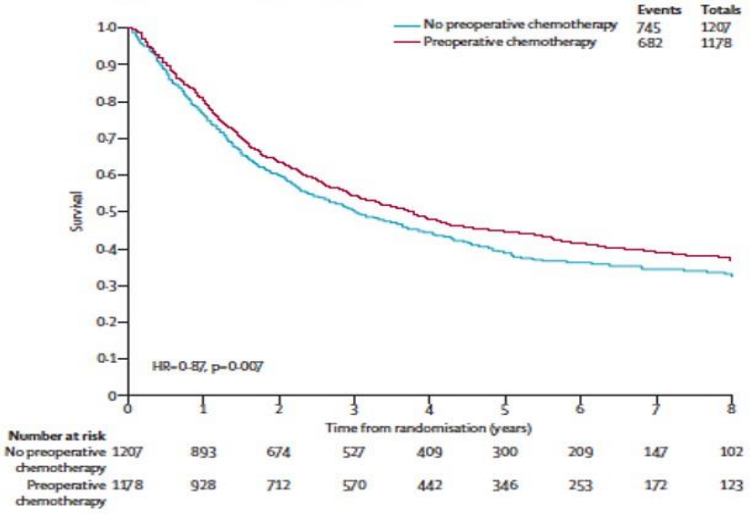


pT2N1



Stage II-III resectable after induction

cT4N1



Five-year survival absolute benefit of 4% with neo/adjuvant chemotherapy

NSCLC Meta-analysis Collaborative Group Lancet 2010; 2014

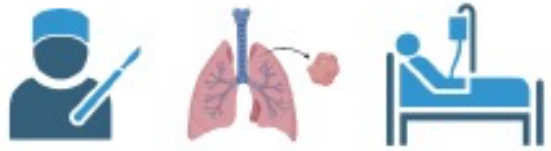
MDT facing early and locally advanced resectable NSCLC

Present

ADJUVANT

Stage II-III upfront resection

cT2N0



pT2N1

Oncogene-addicted

Non oncogene-addicted

Adjuvant chemo or not +
3y osimertinib in EGFRm+

NEO-ADJUVANT

Stage II-III resectable after induction

cT4N1

Non oncogene-addicted

Oncogene-addicted

ADAURA study

Phase III EGFR-TKI studies in resected EGFRm NSCLC

Date	Adjuvant treatment	Phase III study	Key results	Conclusion
2015	Erlotinib vs placebo	RADIANT[1] (stage IB–IIIA)	EGFRm subgroup: DFS HR 0.75 (95% CI: 0.48, 1.16); p=0.1906	**Non-significant DFS improvement**
2020	Gefitinib vs chemotherapy	ADJUVANT / CTONG1104[2,3] (stage II–IIIA)	Updated DFS HR 0.56 (95% CI: 0.40, 0.79); p=0.001; OS HR, 0.92 (95% CI: 0.62, 1.36); p=0.674	**Significant DFS benefit, but no OS benefit**
2020	Osimertinib vs placebo	ADAURA[4,5] (stage IB–IIIA)	DFS HR, 0.20 (99.12% CI: 0.14, 0.30); p<0.0001	**Highly significant DFS benefit**
2021	Gefitinib vs chemotherapy	IMPACT[6] (stage II–III)	DFS HR, 0.92 (95% CI: 0.67, 1.28); p=0.63 OS HR, 1.03 (95% CI: 0.65, 1.65); p=0.89	**No significant DFS or OS benefit**

DFS 65.8 vs 28.1 months
(HR 0.27 – 95% CI 0.21-0.34)

PHASE III ADAURA STUDY DESIGN

Patients with completely resected stage* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:
- ≥18 years (Japan / Taiwan: ≥20)
- WHO performance status 0 / 1
- Confirmed primary non-squamous NSCLC
- Ex19del / L858R‡
- Brain imaging, if not completed pre-operatively
- Complete resection with negative margins§
- Max. interval between surgery and randomisation:
  - 10 weeks without adjuvant chemotherapy
  - 26 weeks with adjuvant chemotherapy

Stratification by:
stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
race (Asian vs non-Asian)

Osimertinib 80 mg, once daily

Randomisation 1:1 (N=682)

Placebo, once daily

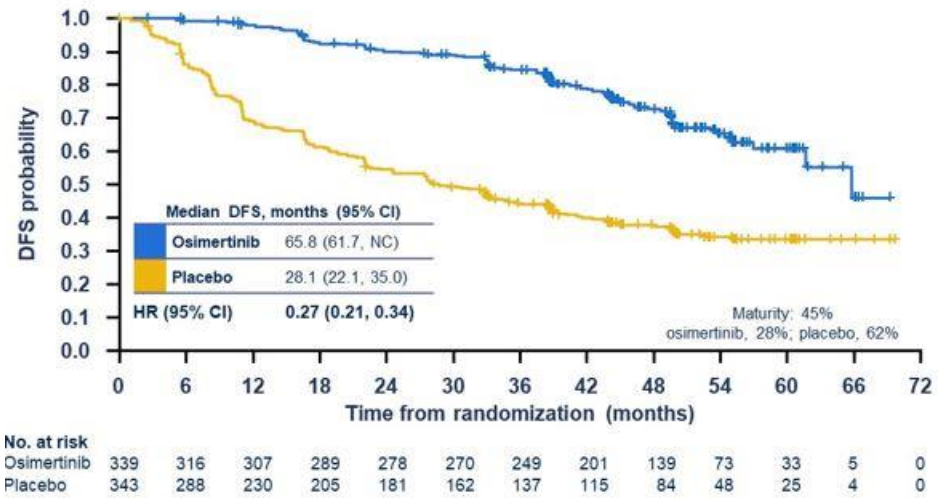
Planned treatment duration: 3 years

Treatment continues until:
- Disease recurrence
- Treatment completed
- Discontinuation criterion met

Follow up:
- Until recurrence: Week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly

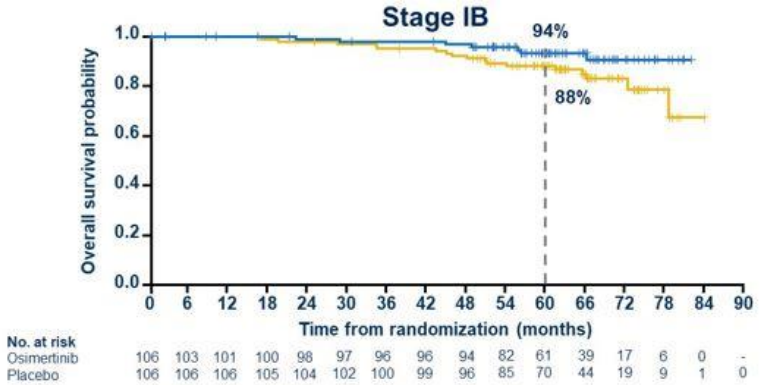
Endpoints
- **Primary endpoint:** DFS by investigator assessment in stage II / IIIA patients, designed for superiority under the assumed DFS HR of 0.70
- **Key secondary endpoints:** DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life
- **Pre-specified exploratory endpoints:** Patterns of recurrence, time to CNS disease recurrence or death (CNS DFS)

ADAURA updated DFS analysis[3,4] (stage IB–IIIA)†
JCO January 2023

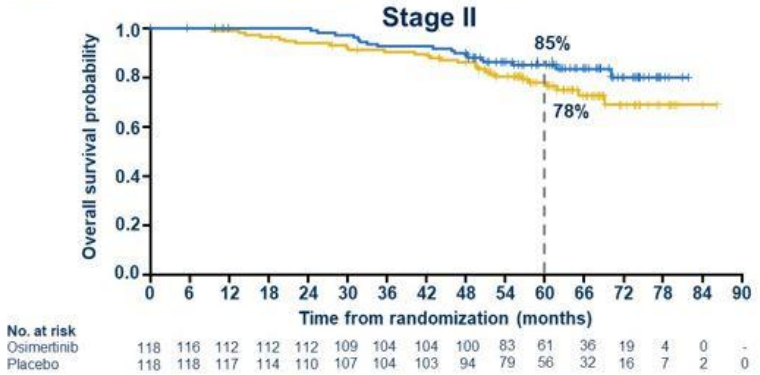


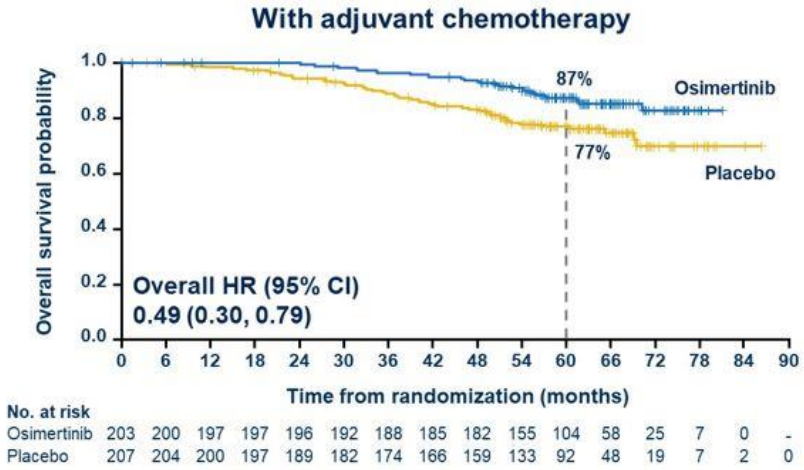
Herbst, ASCO 2023

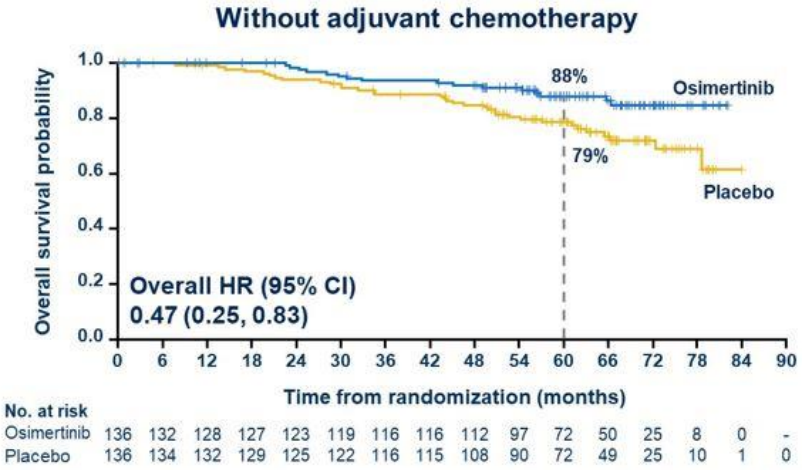
ADAURA – OS data



	Stage IB	Stage II	Stage IIIA
5 year OS rate, % (95% CI)			
Osimertinib	94 (86, 97)	85 (77, 91)	85 (76, 91)
Placebo	88 (80, 93)	78 (69, 85)	67 (57, 75)
Overall HR (95% CI)	0.44 (0.17, 1.02)	0.63 (0.34, 1.12)	0.37 (0.20, 0.64)



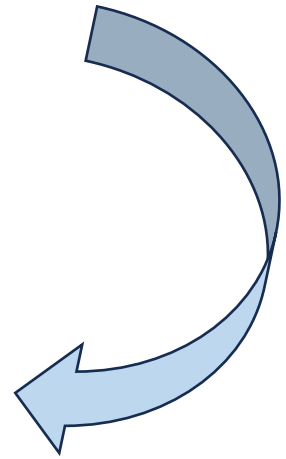




OS still immature

Significant improvement
OS overall population (stage IB-IIIA)
(HR 0.49 – 95.03% CI 0.34-0.70)

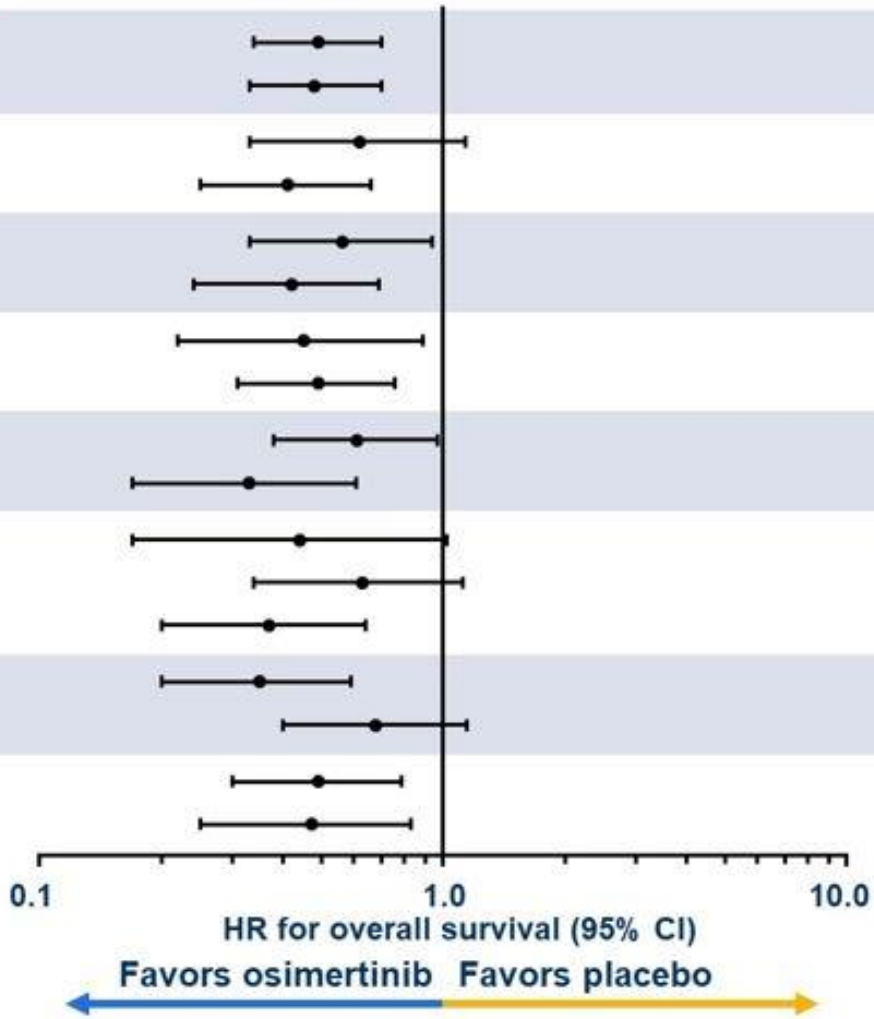
WITH or WITHOUT Chemotherapy??



Herbst, ASCO 2023

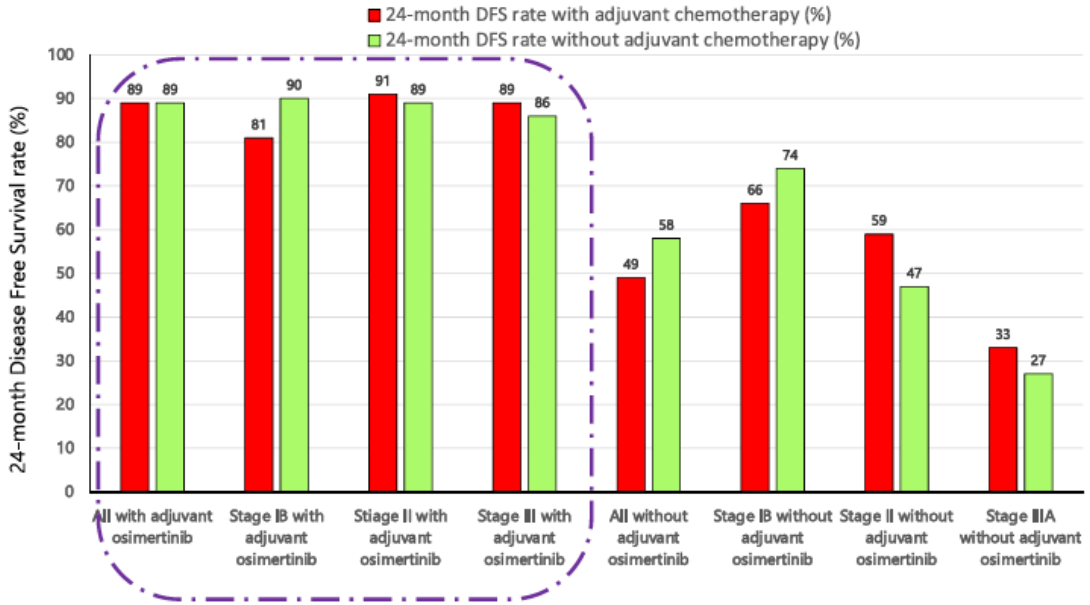
ADAURA – OS data

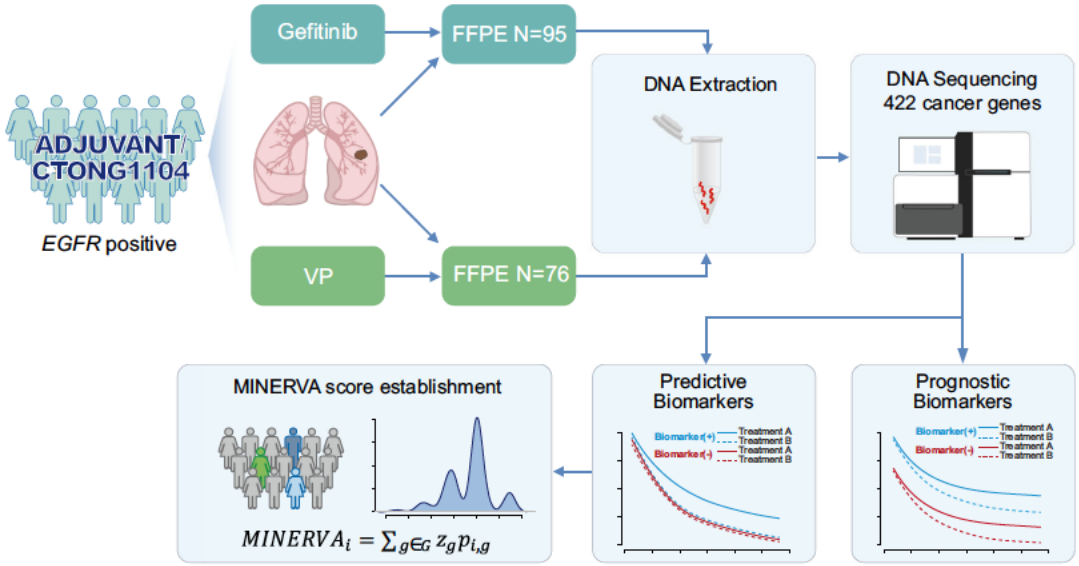
Subgroup		No. of events / patients	HR	95% CI
Overall (N=682)	Stratified log-rank	124 / 682	0.49	0.34, 0.70
	Unadjusted Cox PH	124 / 682	0.48	0.33, 0.70
Sex	Male	42 / 204	0.62	0.33, 1.13
	Female	82 / 478	0.41	0.25, 0.66
Age	<65 years	60 / 380	0.56	0.33, 0.94
	≥65 years	64 / 302	0.42	0.24, 0.69
Smoking history	Yes	34 / 194	0.45	0.22, 0.89
	No	90 / 488	0.49	0.31, 0.76
Race	Asian	73 / 434	0.61	0.38, 0.97
	Non-Asian	51 / 248	0.33	0.17, 0.61
Stage*	IB	24 / 212	0.44	0.17, 1.02
	II	46 / 236	0.63	0.34, 1.12
	IIIA	54 / 234	0.37	0.20, 0.64
EGFR mutation	Ex19del	65 / 378	0.35	0.20, 0.59
	L858R	59 / 304	0.68	0.40, 1.14
Adjuvant chemotherapy	Yes	74 / 410	0.49	0.30, 0.79
	No	50 / 272	0.47	0.25, 0.83

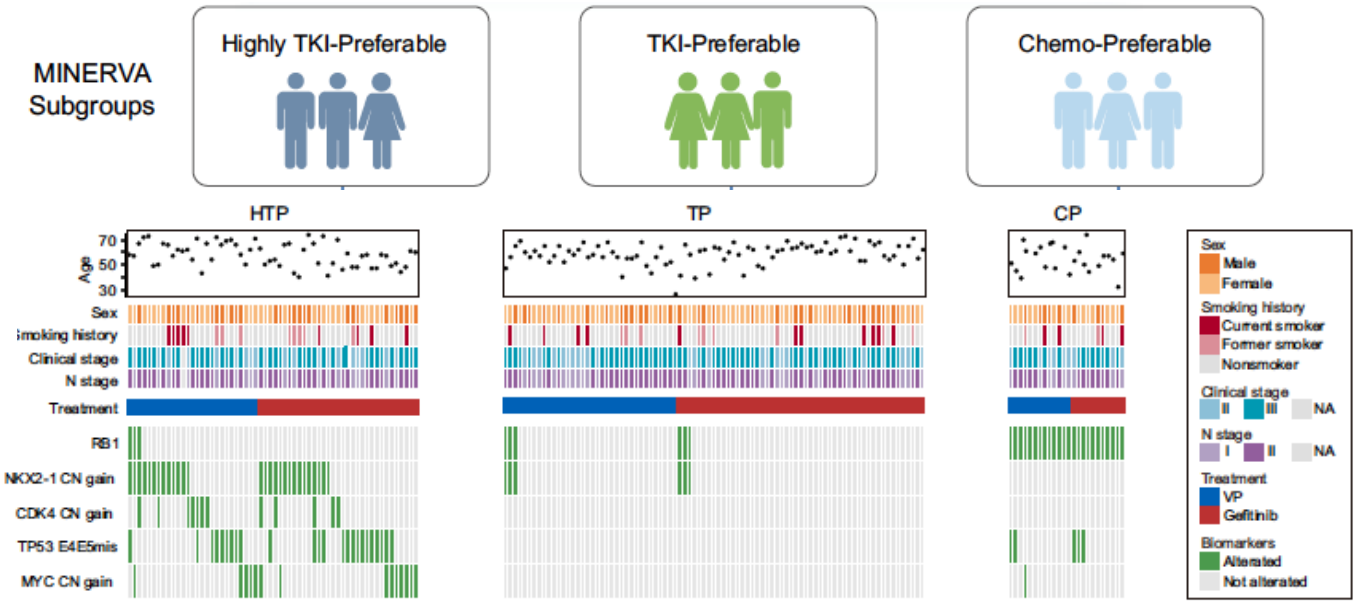


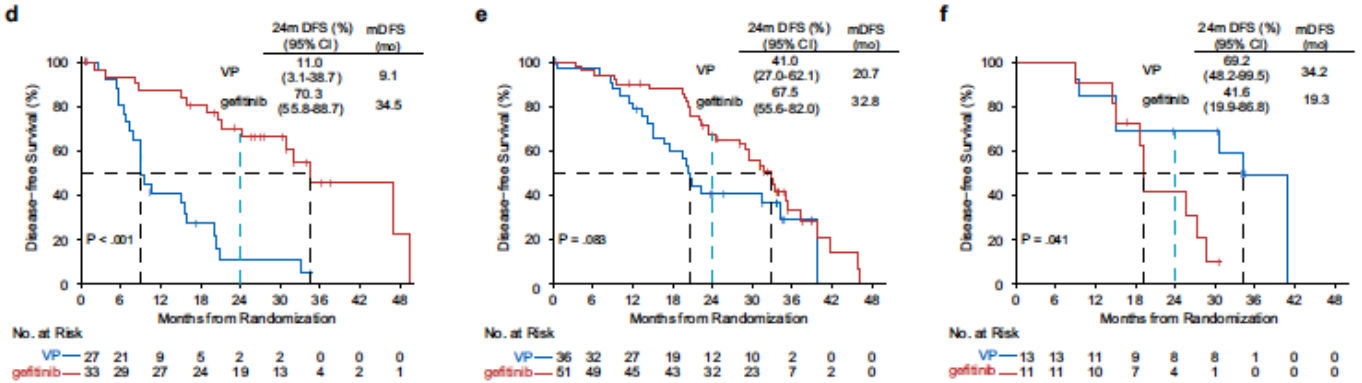
Herbst, ASCO 2023

Osimertinib W/O Chemotherapy – comutations as predictors









Zhang SS; Lung Cancer Targets and Ther 2022; Liu SY, Nat Commun 2021

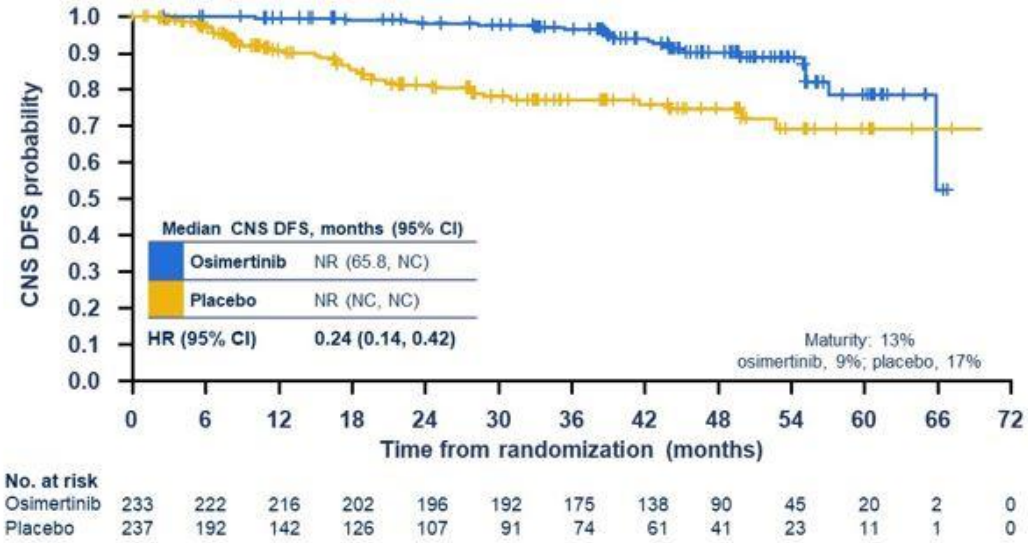
ADAURA – CNS DFS

Improved CNS efficacy with osimertinib treatment

- Osimertinib has shown greater penetration of the blood-brain barrier and higher exposure in the brain compared with other EGFR-TKIs[2–4]
- Adjuvant osimertinib demonstrated CNS DFS* benefit vs placebo in both the stage II–IIIA and IB–IIIA populations[5,6]

ADAURA updated CNS DFS analysis[5,6] (stage II–IIIA)

JCO January 2023



No. at risk													
Osimertinib	233	222	216	202	196	192	175	138	90	45	20	2	0
Placebo	237	192	142	126	107	91	74	61	41	23	11	1	0

AE, any cause*, n (%)	**Osimertinib (n=337)**	**Placebo (n=343)**
Any AE	330 (98)	309 (90)
Any AE Grade ≥3	79 (23)	48 (14)
Any AE leading to death	1 (<1)	2 (1)
Any serious AE	68 (20)	47 (14)
Any AE leading to discontinuation	43 (13)	9 (3)
Any AE leading to dose reduction	42 (12)	3 (1)
Any AE leading to dose interruption	91 (27)	43 (13)
AE, possibly causally related*†, n (%)		
Any AE	308 (91)	199 (58)
Any AE Grade ≥3	36 (11)	7 (2)
Any AE leading to death	0	0
Any serious AE	10 (3)	2 (1)

Herbst, ASCO 2023

Stage IA Adjuvant Phase 3 Design: ADAURA2

Adjuvant Osimertinib vs Placebo in Completely Resected Stage IA EGFRm NSCLC

Study Population

Patients with pStage IA2 or IA3 (8th edition) NSCLC

- ❑ Post complete (R0) resection
- ❑ Exon 19 deletion or L858R EGFR mutation
- ❑ Tumor sample submission for central pathology assessment of:
  - Invasive tumour size
  - Lymphovascular invasion
  - Tumour histology
- ❑ PS 0-1
- ❑ No pre-/post-operative RT or systemic therapy
- ❑ Not eligible for any local SOC treatment

N=380

R

1

1

Adjuvant (3-year treatment duration)

Arm A
Osimertinib 80 mg PO QD

Arm B
Placebo PO QD

Primary: DFS per investigator in high-risk* stratum

Secondary:
DFS in ITT
OS in high-risk stratum
OS in ITT
HRQoL
Safety/tolerability
PK
Exploratory: MRD

Stratification

- High risk* vs low risk
- Exon 19 del vs L858R
- Race (Chinese Asian vs non-Chinese Asian vs non-Asian)

***High risk defined as presence of ≥ 1 of the following factors:**

- Invasive tumour size > 2 cm
- Lymphovascular invasion
- ≥20% micropapillary, solid or complex gland adenocarcinoma histology

Low risk defined as absence of any high-risk factors

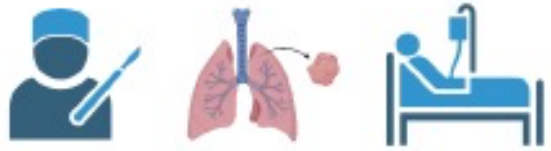
Estimated prevalence of high risk ~60%
Enrich high risk to 67% of ITT population (33% cap on low risk)

MDT facing early and locally advanced resectable NSCLC

Future

Stage II-III upfront resection

cT2N0



pT2N1

Oncogene-addicted

Non oncogene-addicted

Stage II-III resectable after induction

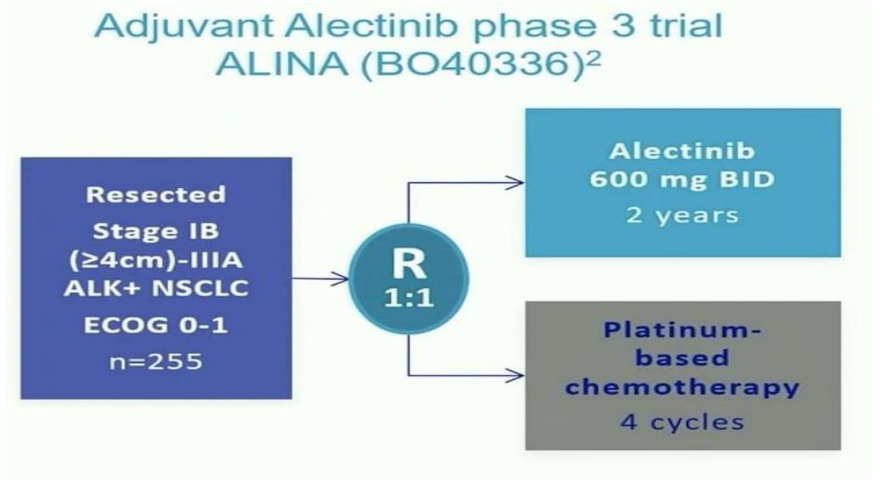
cT4N1

Non oncogene-addicted

Oncogene-addicted

Future adjuvant option in oncogene-addicted

ALINA: ALK+ NSCLC; adjuvant setting

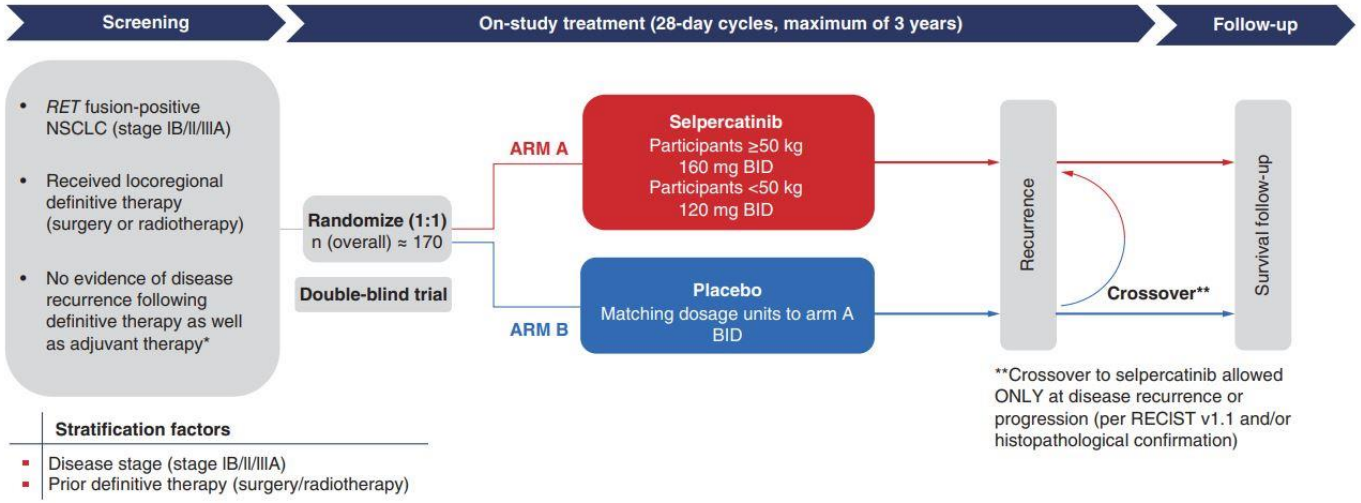


Alectinib Delivers Unprecedented Phase III Results for People With ALK-Positive Early-Stage Lung Cancer

MADRID 2023 ESMO congress

MADRID SPAIN
20-24 OCTOBER 2023

LIBRETTO 432: RET+ NSCLC; adjuvant setting

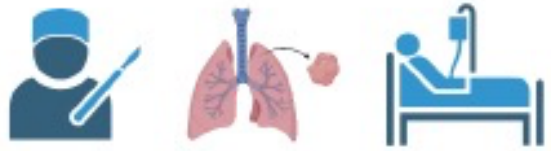


MDT facing early and locally advanced resectable NSCLC

Present

Stage II-III upfront resection

cT2N0



pT2N1

Oncogene-addicted

Adjuvant chemo or not + 3y osimertinib in EGFRm+

Non oncogene-addicted

Adjuvant chemo + 1y atezolizumab in PDL1≥50%

[EGFR and ALK neg]

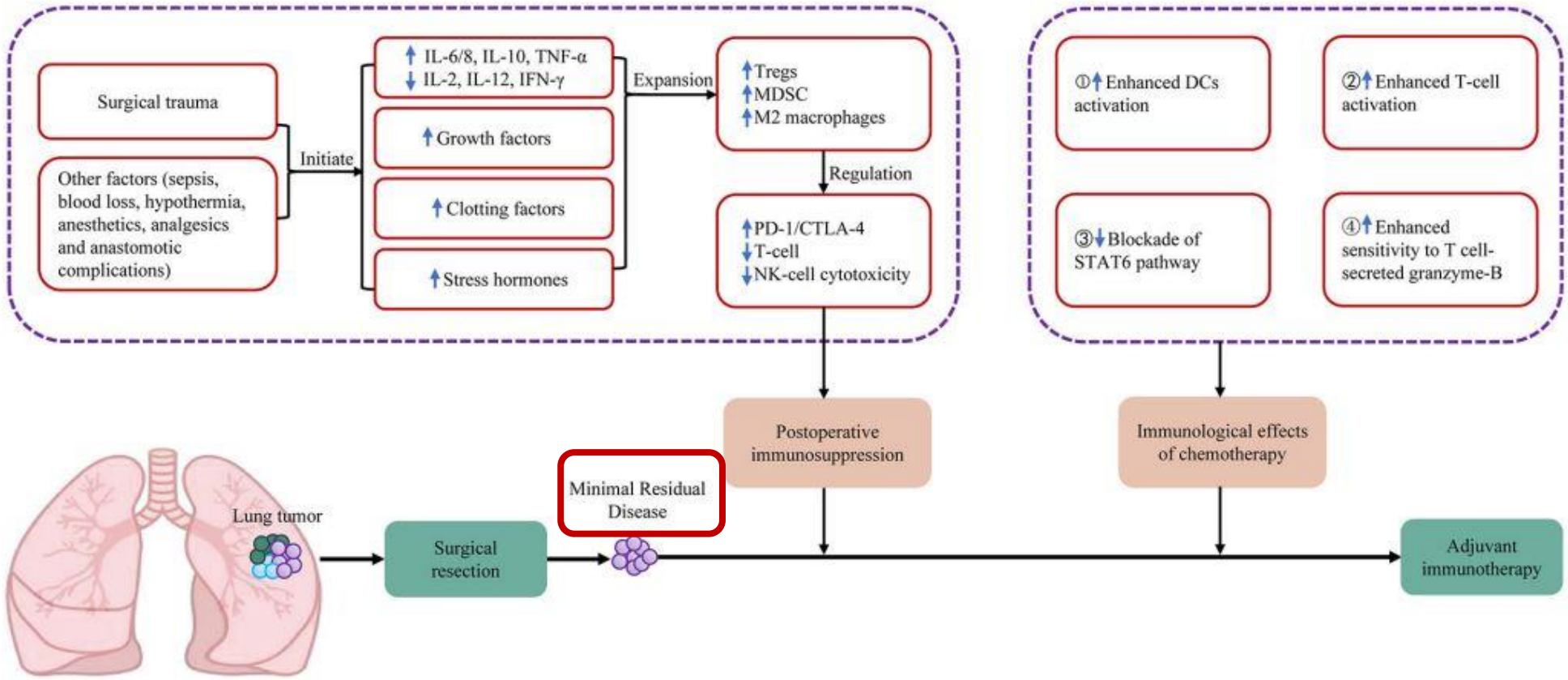
Stage II-III resectable after induction

cT4N1

Non oncogene-addicted

Oncogene-addicted

Rationale for adjuvant chemotherapy + immunotherapy



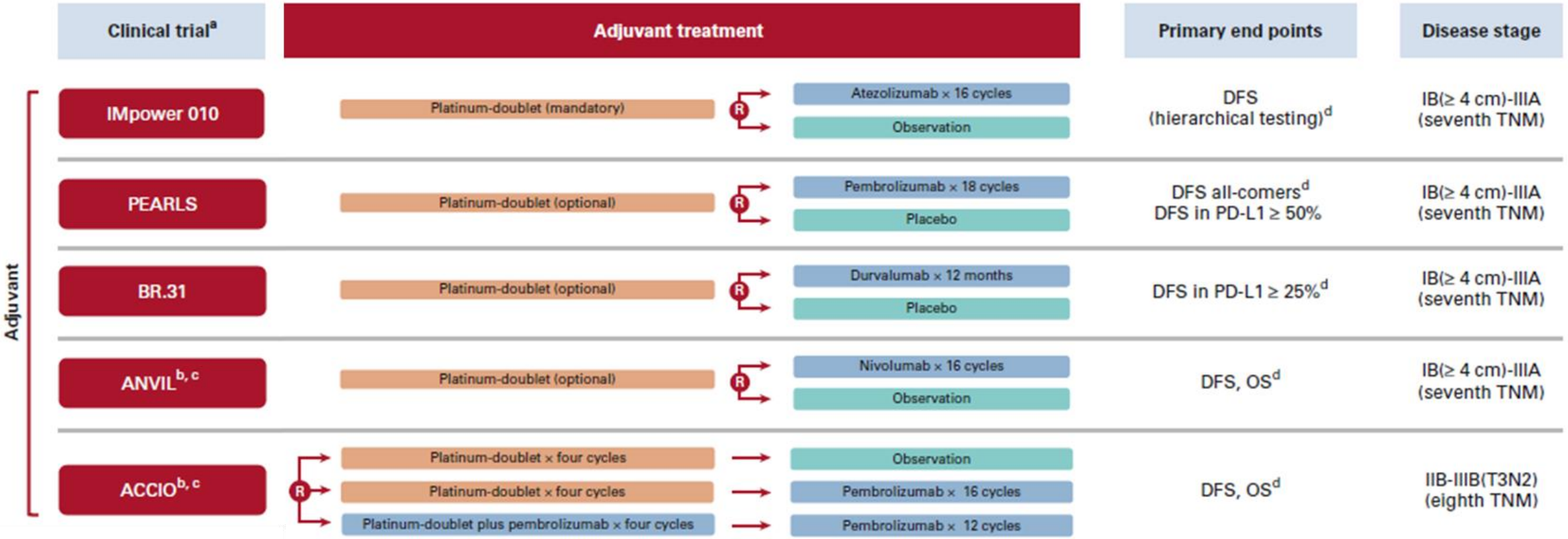
CHEMOTHERAPY + IMMUNOTHERAPY: SINERGISTIC effect on MINIMAL RESIDUAL DISEASE

ANTIGENICITY + ADJUVANTICITY =

1) Activation of the innate immune system
2) Promotion of dendritic cell maturation
3) Activation of effector T cells

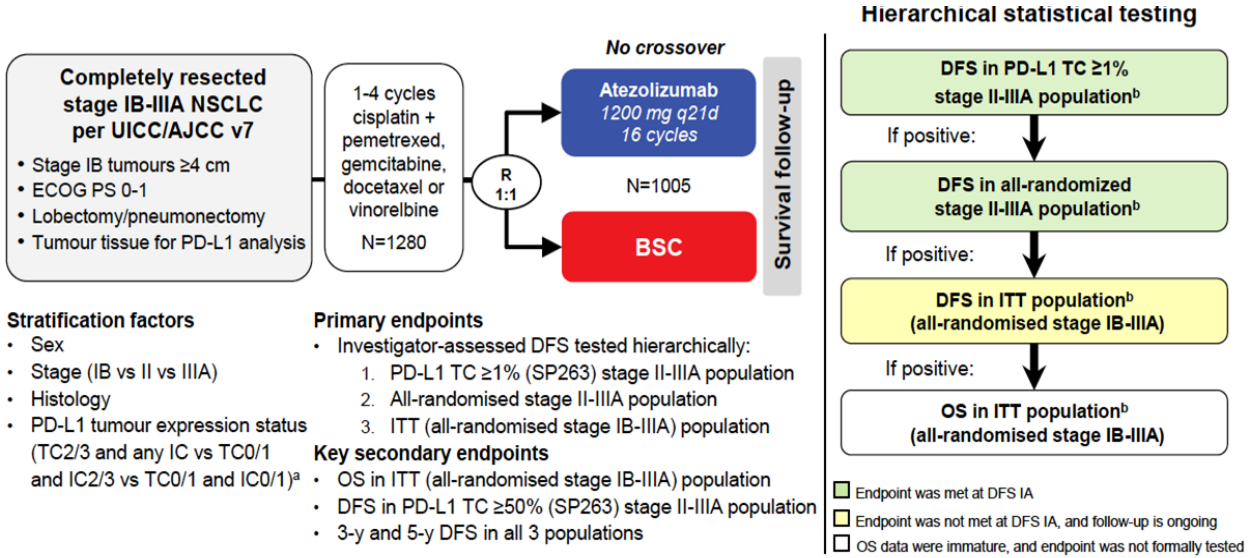
Tang et al, Frontiers, 2023

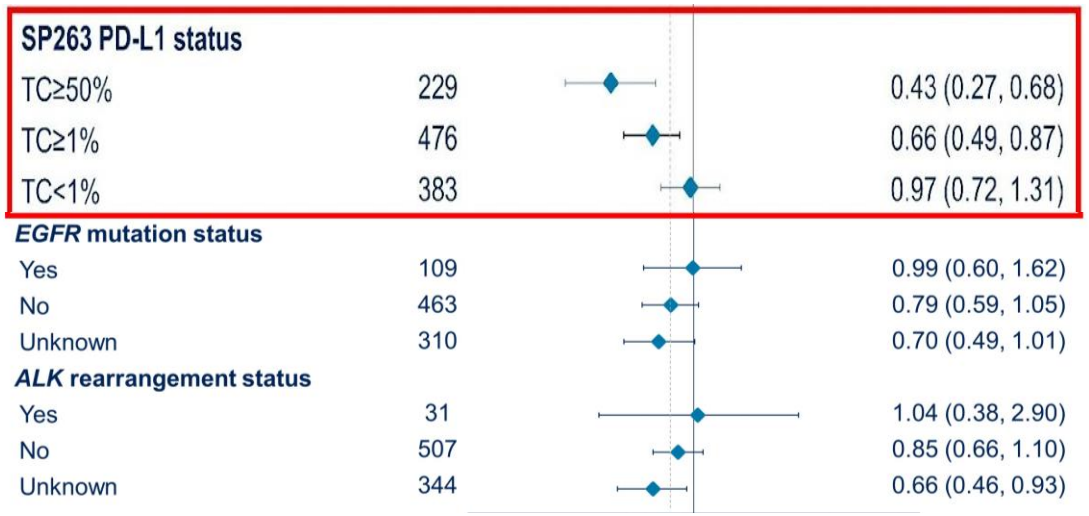
Clinical trials with ICIs in the adjuvant setting



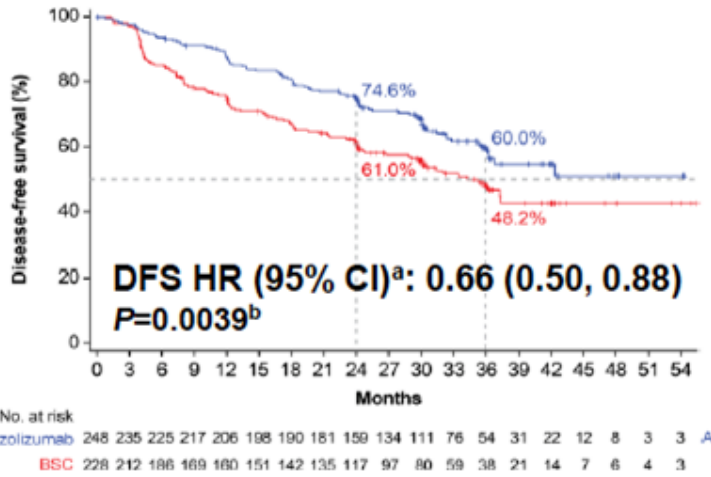
Passaro A, JCO 2022

IMpower 010 study

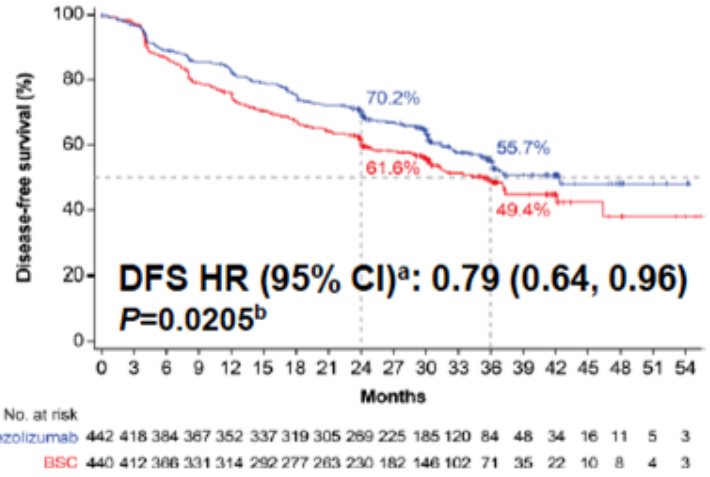




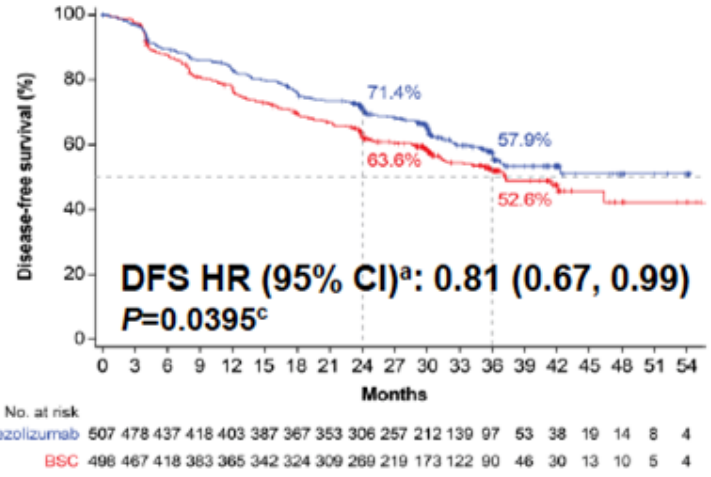
DFS: PD-L1 TC ≥1% stage II-IIIA population



DFS: All-randomised stage II-IIIA population



DFS: ITT (randomised stage IB-IIIA) population

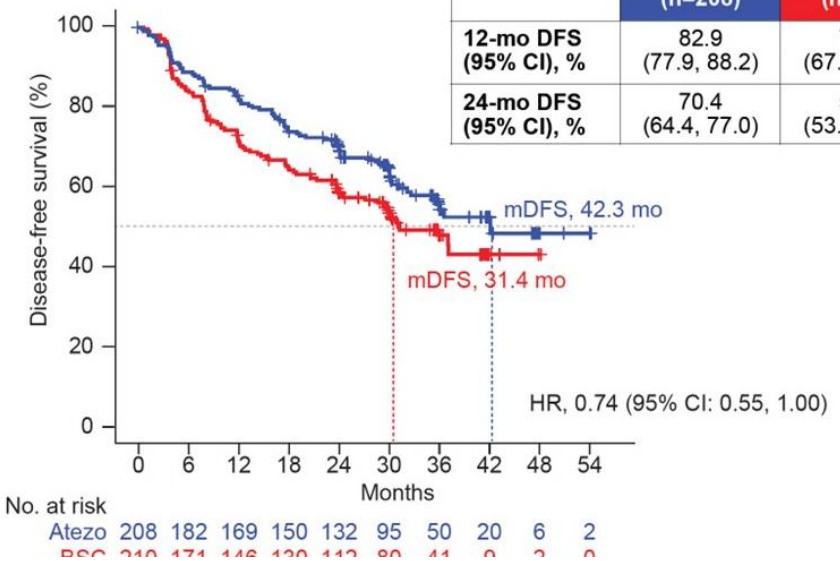


Felip E, WCLC 2022; Wakelee H, ASCO 2021

IMpower 010 study: DFS by KRAS status

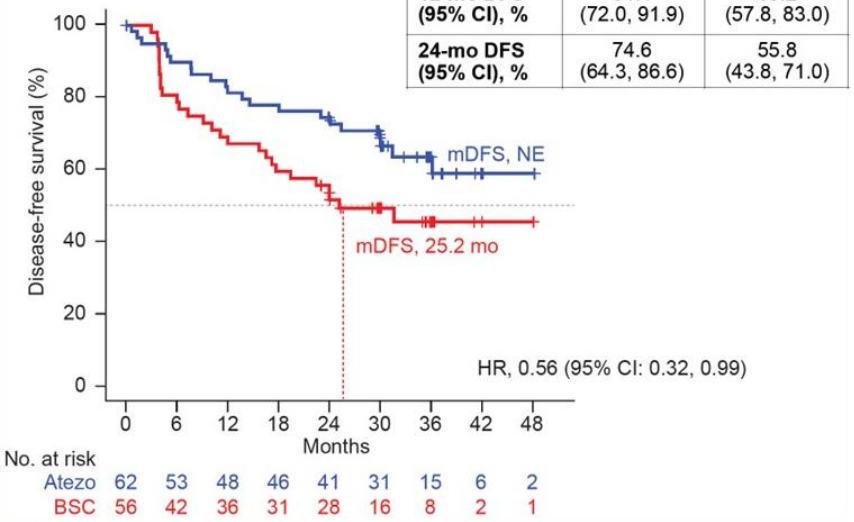
B *KRAS* WT, stage II-IIIA

	Atezo (n=208)	BSC (n=210)
12-mo DFS (95% CI), %	82.9 (77.9, 88.2)	72.9 (67.1, 79.3)
24-mo DFS (95% CI), %	70.4 (64.4, 77.0)	59.8 (53.4, 67.0)



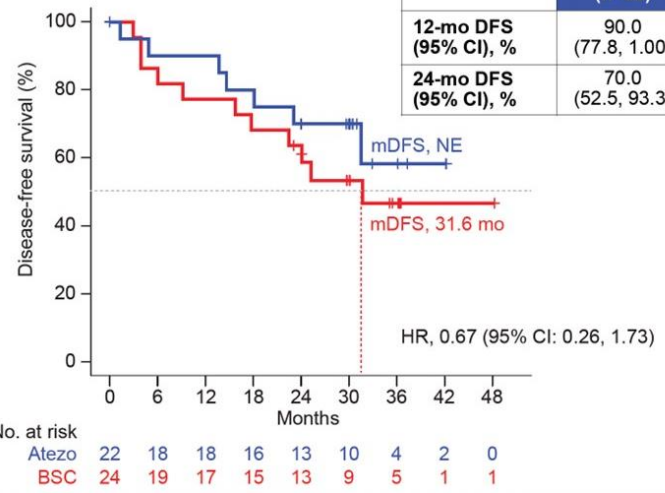
C m*KRAS*, stage II-IIIA

	Atezo (n=62)	BSC (n=56)
12-mo DFS (95% CI), %	81.4 (72.0, 91.9)	69.2 (57.8, 83.0)
24-mo DFS (95% CI), %	74.6 (64.3, 86.6)	55.8 (43.8, 71.0)



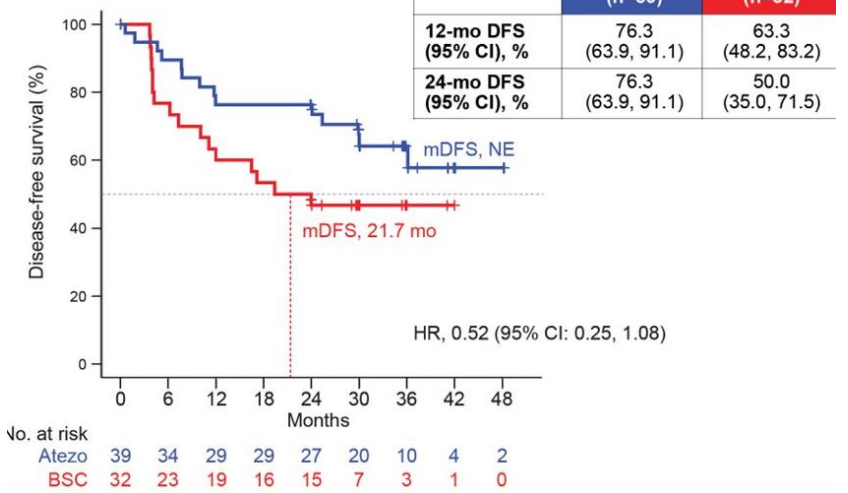
B m*KRAS*, stage II-IIIA: PD-L1 TC <1%

	Atezo (n=22)	BSC (n=24)
12-mo DFS (95% CI), %	90.0 (77.8, 1.00)	77.3 (61.6, 96.9)
24-mo DFS (95% CI), %	70.0 (52.5, 93.3)	63.6 (46.4, 87.3)



C m*KRAS*, stage II-IIIA: PD-L1 TC ≥ 1%

	Atezo (n=39)	BSC (n=32)
12-mo DFS (95% CI), %	76.3 (63.9, 91.1)	63.3 (48.2, 83.2)
24-mo DFS (95% CI), %	76.3 (63.9, 91.1)	50.0 (35.0, 71.5)



Reck M, ASCO 2023

KEYNOTE 091 study

Eligibility for Registration
- Confirmed stage IB (T ≥4 cm), II, or IIIA NSCLC per AJCC v7
- Complete surgical resection with negative margins (R0)
- Provision of tumor tissue for PD-L1 testing

PD-L1 testing done centrally using PD-L1 IHC 22C3 pharmDx

Eligibility for Randomization
- No evidence of disease
- ECOG PS 0 or 1
- Adjuvant chemotherapy
  - Considered for stage IB (T ≥4 cm) disease
  - Strongly recommended for stage II and IIIA disease
  - Limited to ≤4 cycles

R 1:1

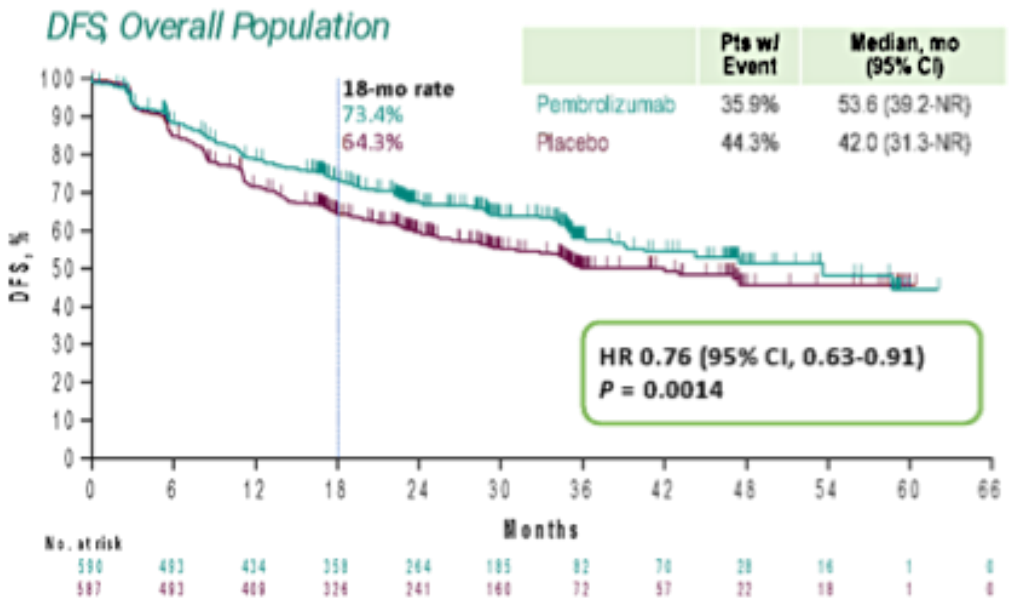
- **Pembrolizumab 200 mg Q3W for ≤18 administrations (~1 yr)**
- **Placebo Q3W for ≤18 administrations (~1 yr)**

Stratification Factors
- Disease stage (IB vs II vs IIIA)
- PD-L1 TPS (<1% vs 1-49% vs ≥50%)
- Receipt of adjuvant chemotherapy (yes vs no)
- Geographic region (Asia vs Eastern Europe vs Western Europe vs rest of world)

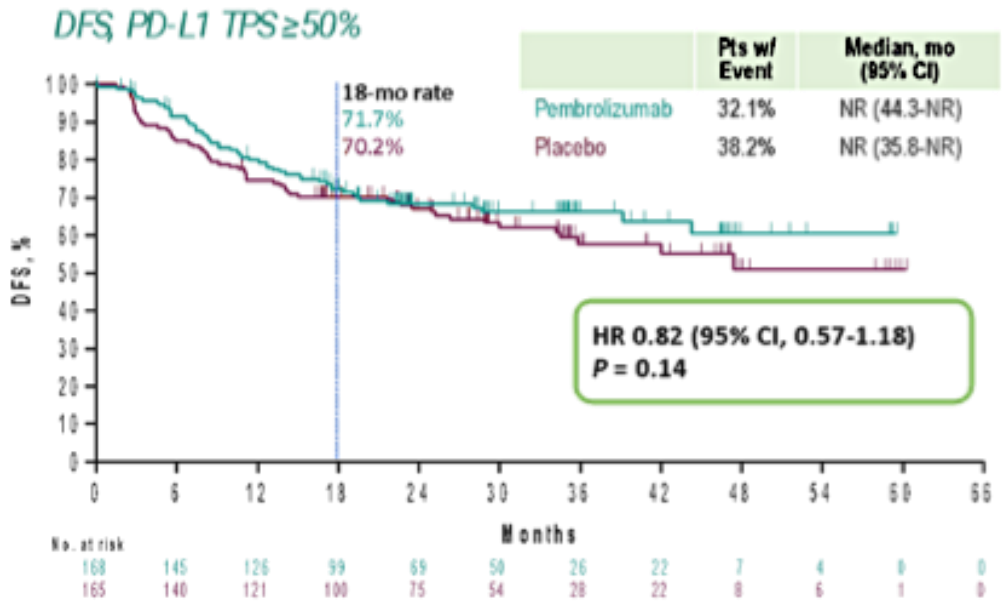
Dual Primary End Points
- DFS in the overall population
- DFS in the PD-L1 TPS ≥50% population

Secondary End Points
- DFS in the PD-L1 TPS ≥1% population
- OS in the overall, PD-L1 TPS ≥50%, and PD-L1 TPS ≥1% populations
- Lung cancer-specific survival in the overall population
- Safety

No significant DFS benefit
Placebo overperformance?



Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021



Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

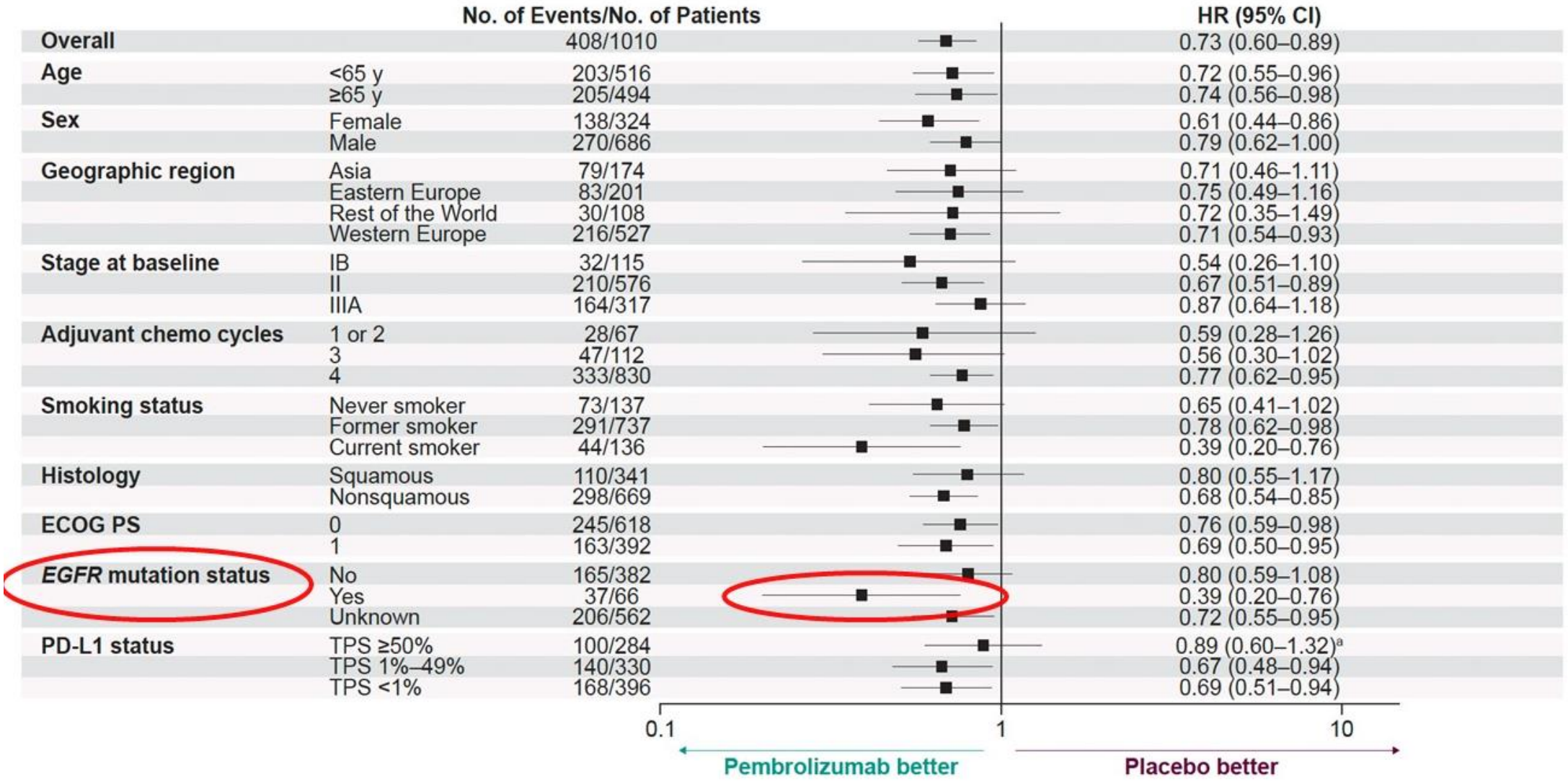
Paz-Ares L, ESMO Virtual Plenary 2022

KEYNOTE091 and IMpower-010

	IMpower010	PEARLS/Keynote 091
Control Arm	Observation (open-label)	Placebo ★
Description	Global, open label	ETOP/EORTC placebo controlled
Primary endpoint	Hierarchical testing **DFS** pII-IIIA PD-L1≥1% DFS pII-IIIA; all comers DFS pIB-IIIA; all comers OS	Co-primary endpoints (dual-testing) **DFS** pIB-IIIA; all comers DFS pIB-IIIA; PD-L1≥50%
Randomized patients	1280	1177
Stratification Factors	Sex / Tumor histology / Stage / PD-L1 expression	Stage / CT adjuvant / PD-L1 expression
Stage pIB / II / IIIA (7th)	11.8% / 46.7% / 41.1%	14.3% / 56.7% / 28.8%
PD-L1 distribution	**<1% / ≥1%:** 44% / 53.5%	**<1% / 1-49% / ≥50%:** 39.5% / 32.3% / 28.3%
Adjuvant CT	1-4 Cisplatin-based cycles	Recommended for stage pII/IIIA, (Carboplatin allowed)
Design / Compliance	Atezolizumab post-CT / 65% ★	Pembrolizumab post-CT / 48%
Follow up, months	46	35.6
Primary endpoint: DFS	•**pII-IIIA, PD-L1≥1%:** HR 0.66 (0.50, 0.88) •**pII-IIIA:** HR 0.79 (0.64, 0.96) •**ITT pIB-IIIA**: 0.81 (0.67, 0.99) ★	•**pIB-IIIA:** HR 0.76 (0.63, 0.91) •**pIB-IIIA, PD-L1≥50%**: HR 0.82 (0.57, 1.18)
Approval	•**FDA**: PD-L1+ (TC ≥1%) Stage II–IIIA •**EMA**: PD-L1+ (TC ≥50%) with EGFR / ALK - ★	•**FDA**: Stage IB (T ≥4 cm), II or IIIA •**EMA**: not approved yet

Isla, WCLC 2023

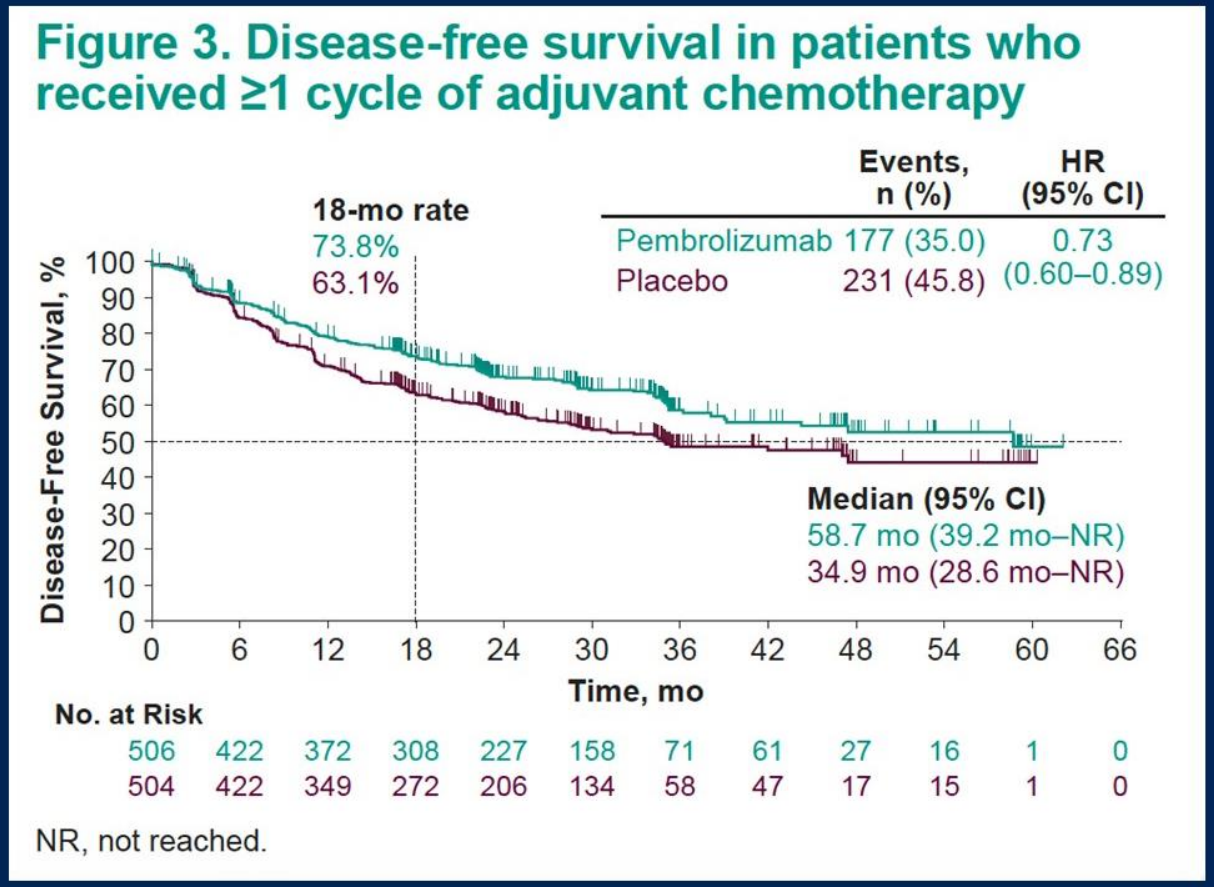
KN091 study: subset analysis in pts receiving adjuvant chemotherapy



[a]For the PD-L1 TPS ≥50% subgroup, HR for DFS by multivariate Cox regression model with treatment adjusted by stratification factors, histology (squamous vs nonsquamous), and smoking status (never vs former/current) was 0.80 (95% CI, 0.54–1.20).

Oselin K; Ramalingam SS, ASCO 2023

KN091 study: subset analysis in pts receiving adjuvant chemotherapy



- 1010 out of 1178 (86%) randomized patients received > 1 cycle of adjuvant chemotherapy
- No major differences in baseline characteristics between Pembro and placebo groups for this patient subset

Oselin K et al, Abstract # 8520

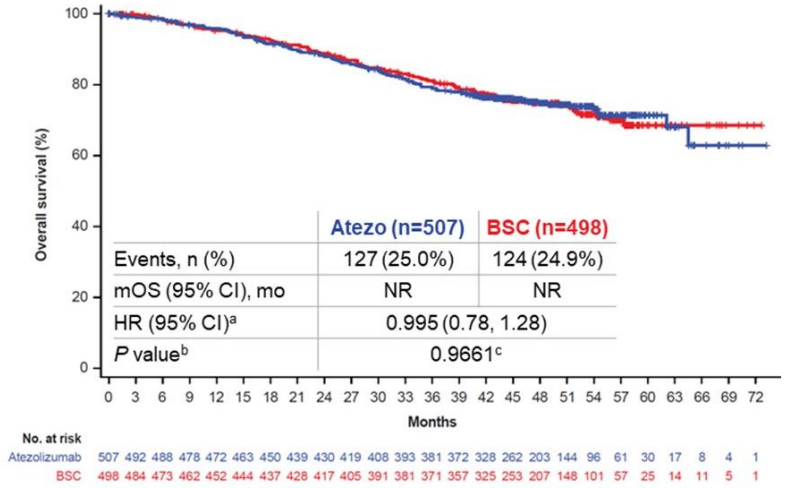
Oselin K; Ramalingam SS, ASCO 2023

Adjuvant immunotherapy: open questions

- *Number of chemo cycles?*
- *Type of chemo regimen?*
- *Patients selection and treatment duration*
- *Survival benefit*

	IMpower010 Atezolizumab *vs.* BSC	KN091 Pembrolizumab *vs.* placebo
All G AEs	92.5% *vs.* 70.9%	95.9 *vs.* 91%
AEs G ≥ 3	23.8% *vs.* 0.6%	34.1% *vs.* 25.8%

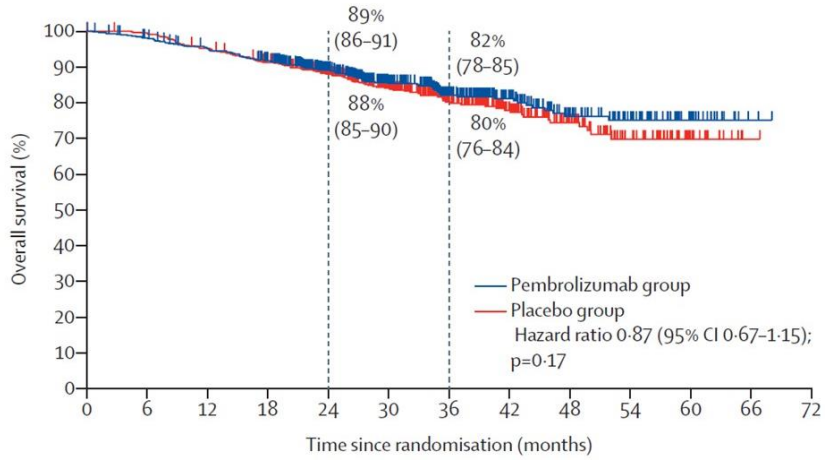
IMpower 010
ITT population stage IB-IIIA



	Atezo (n=507)	BSC (n=498)
Events, n (%)	127 (25.0%)	124 (24.9%)
mOS (95% CI), mo	NR	NR
HR (95% CI)[a]	0.995 (0.78, 1.28)	
P value[b]	0.9661[c]	

Median Follow Up: 45 months (interim analysis)

KEYNOTE-091/PEARLS



Median Follow Up: 35.6 months (interim analysis)

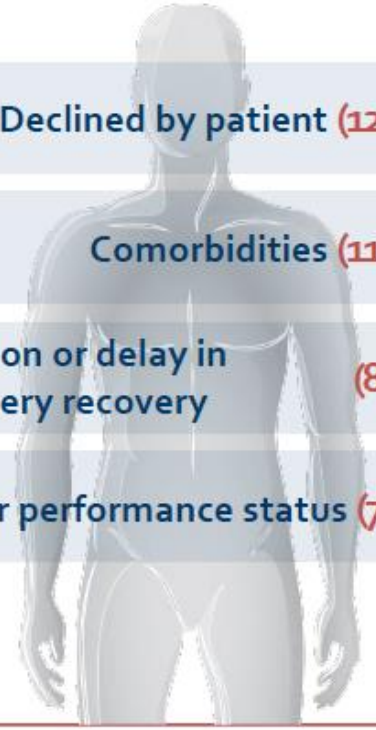
Awad MM, ASCO 2023

Patient’s selection for adjuvant NSCLC

Relapse risk prevention
Survival improvement
CURE

Stage
Histological features
Age
Comorbidities
Performance Status
Recovery from surgery
Quality of life
Risk of toxicity
Compliance
Patient's preference

Reasons for not receiving adjuvant chemotherapy[1]



- Declined by patient (12.6%)
- Comorbidities (11.9%)
- Complication or delay in surgery recovery (8.4%)
- Poor performance status (7.0%)

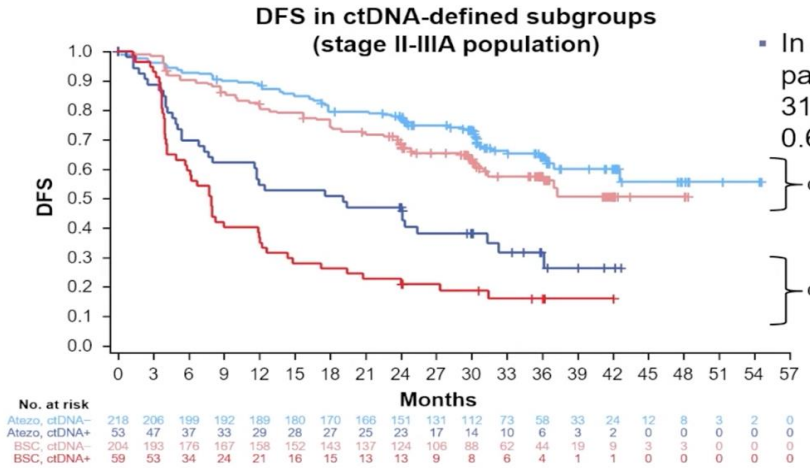
52% did not receive adjuvant chemotherapy

Retrospective analysis of 831 French, German, and UK patients with complete resection of stage IB-IIIA[a] NSCLC

Patient's selection for adjuvant chemotherapy is the key point: a cumulative dose intensity of 300 mg/sm should be administered. Early interruption of adjuvant chemo translate into a worse prognosis and a delay of subsequent adjuvant strategies

Adjuvant immunotherapy: the role of MRD

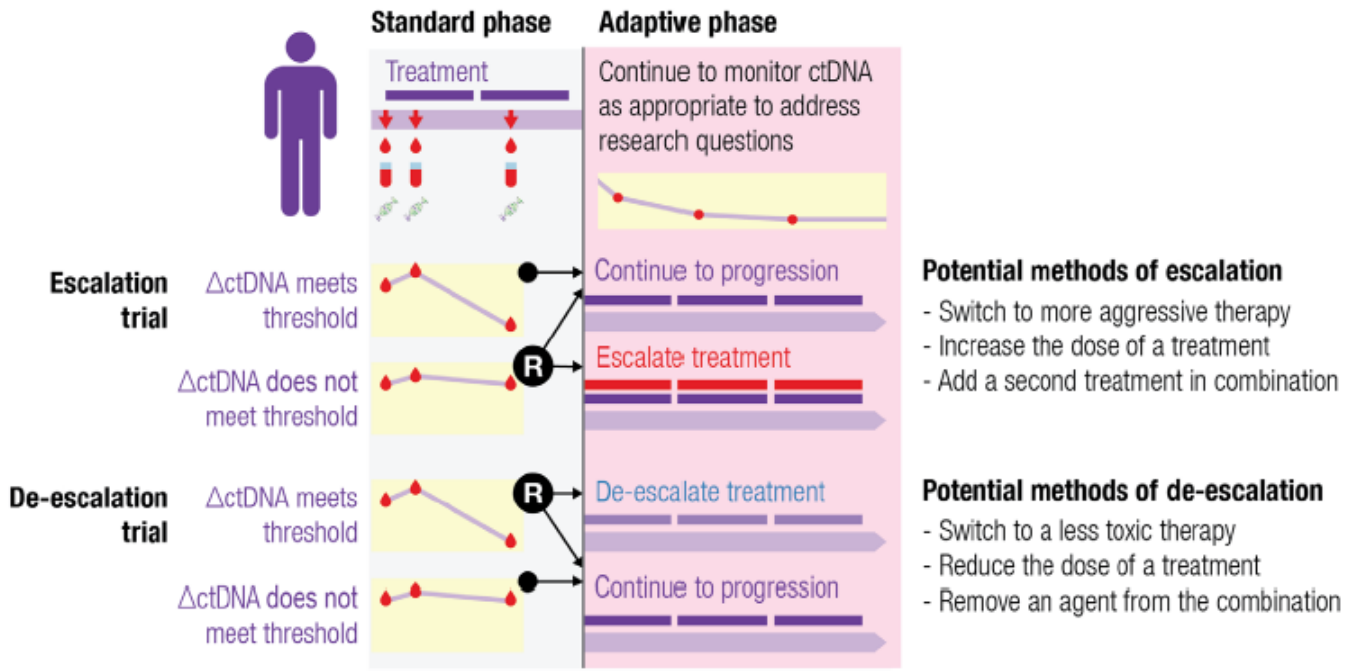
Impower 010 – Exploratory results for ctDNA



- In all ctDNA-evaluable stage II-IIIA patients, mDFS was NR (atezo) vs 31.4 months (BSC), with an HR of 0.69 (95% CI: 0.53, 0.89)

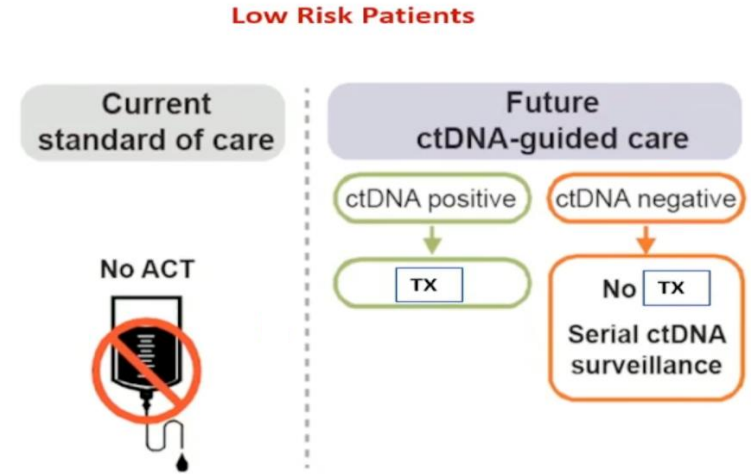
ctDNA–	Atezo (n=218)	BSC (n=204)
mDFS, mo	NR	NR
HR (95% CI)	0.72 (0.52, 1.00)	

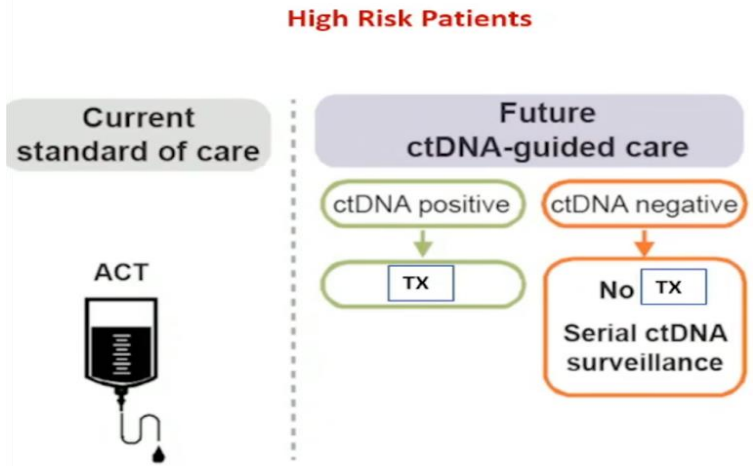
ctDNA+	Atezo (n=53)	BSC (n=59)
mDFS, mo	19.1	7.9
HR (95% CI)	0.61 (0.39, 0.94)	



Potential methods of escalation
- Switch to more aggressive therapy
- Increase the dose of a treatment
- Add a second treatment in combination

Potential methods of de-escalation
- Switch to a less toxic therapy
- Reduce the dose of a treatment
- Remove an agent from the combination





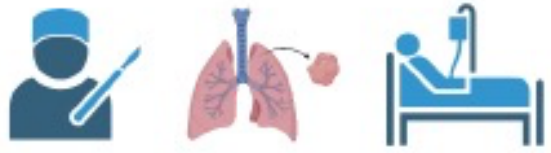
Sanz-Garcia E, Sci Adv 2022

MDT facing early and locally advanced resectable NSCLC

Future

Stage II-III upfront resection

cT2N0



pT2N1

Oncogene-addicted

Non oncogene-addicted

Stage II-III resectable after induction

cT4N1

Non oncogene-addicted

- ***NEOADAURA***
- ***ALNEO***

Oncogene-addicted

- ***CM816***
- ***KN671***
- ***AEGEAN***
- ***NEOTORCH***
- ***CM77T***
- ***RATIONALE315***
- ***NCT05157776***

9th edition TNM proposal

T → *No changes*

N → *Split in N2a and N2b*

Proposed 9th Edition N-categories			9th Edition
NX		Regional lymph nodes cannot be assessed	No changes
N0		No regional lymph node metastasis	No changes
N1		Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension	No changes
N2		Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)	
	N2a	Single N2 station involvement	Subdivided
	N2b	Multiple N2 station involvement	Subdivided
N3		Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)	No changes

M → *Split in M1c1 and M1c2*

Proposed 9th Edition M-categories			9th Edition
M0		No distant metastasis	No changes
M1		Distant metastasis	No changes
	M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion. Most pleural (pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.	No changes
	M1b	**Single** extrathoracic metastasis in a **single** organ and involvement of a single distant (non-regional) node	No changes
	M1c1	**Multiple** extrathoracic metastases in a **single** organ system	Subdivided
	M1c2	**Multiple** extrathoracic metastases in **multiple** organ systems	Subdivided

8th Ed TNM Categories

T/M	Label	N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2a >3-4	IB	IIB	IIIA	IIIB
	T2b >4-5	IIA	IIB	IIIA	IIIB
T3	T3 >5-7	IIB	IIIA	IIIB	IIIC
	T3 Inv	IIB	IIIA	IIIB	IIIC
	T3 Sat	IIB	IIIA	IIIB	IIIC
T4	T4 > 7	IIIA	IIIA	IIIB	IIIC
	T4 Inv	IIIA	IIIA	IIIB	IIIC
	T4 Ipsi Nod	IIIA	IIIA	IIIB	IIIC
M1	M1a Contr Nod	IVA	IVA	IVA	IVA
	M1a Pleur	IVA	IVA	IVA	IVA
	M1b Single Lesion	IVA	IVA	IVA	IVA
	M1c Multiple Lesions	IVB	IVB	IVB	IVB

Proposed 9th Ed TNM Categories

T/M	Label	N0	N1	N2		N3
9th				N2a	N2b	
T1	T1a ≤1 cm	IA1	IIA	IIB	IIIA	IIIB
	T1b >1 to ≤2 cm	IA2	IIA	IIB	IIIA	IIIB
		IA3	IIA	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB	IIIB
	T2a >3 to ≤4 cm	IB	IIB	IIIA	IIIB	IIIB
	T2b >4 to ≤5 cm	IIA	IIB	IIIA	IIIB	IIIB
T3		IIB	IIIA	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Satellite nodules	IIB	IIIA	IIIA	IIIB	IIIC
T4	T4 > 7 cm	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Ipsilateral nodules	IIIA	IIIA	IIIB	IIIB	IIIC
M1	M1a Contralateral nodules	IVA	IVA	IVA	IVA	IVA
	M1a Pleural, pericardial effusion	IVA	IVA	IVA	IVA	IVA
	M1b Single Extrathoracic Lesion	IVA	IVA	IVA	IVA	IVA
	M1c1 Mult. Lesions, Single Organ system	IVB	IVB	IVB	IVB	IVB
	M1c2 Mult. Lesions, Mult. Organ systems	IVB	IVB	IVB	IVB	IVB

Today

T1N1 → Stage IIB

T1N2 → Stage IIIA

Future

T1N1 → Stage IIA

T1N2a → Stage IIB

T1N2b → Stage IIIA

Asamura, WCLC 2023

giulia.pasello@iov.veneto.it
giulia.pasello@unipd.it