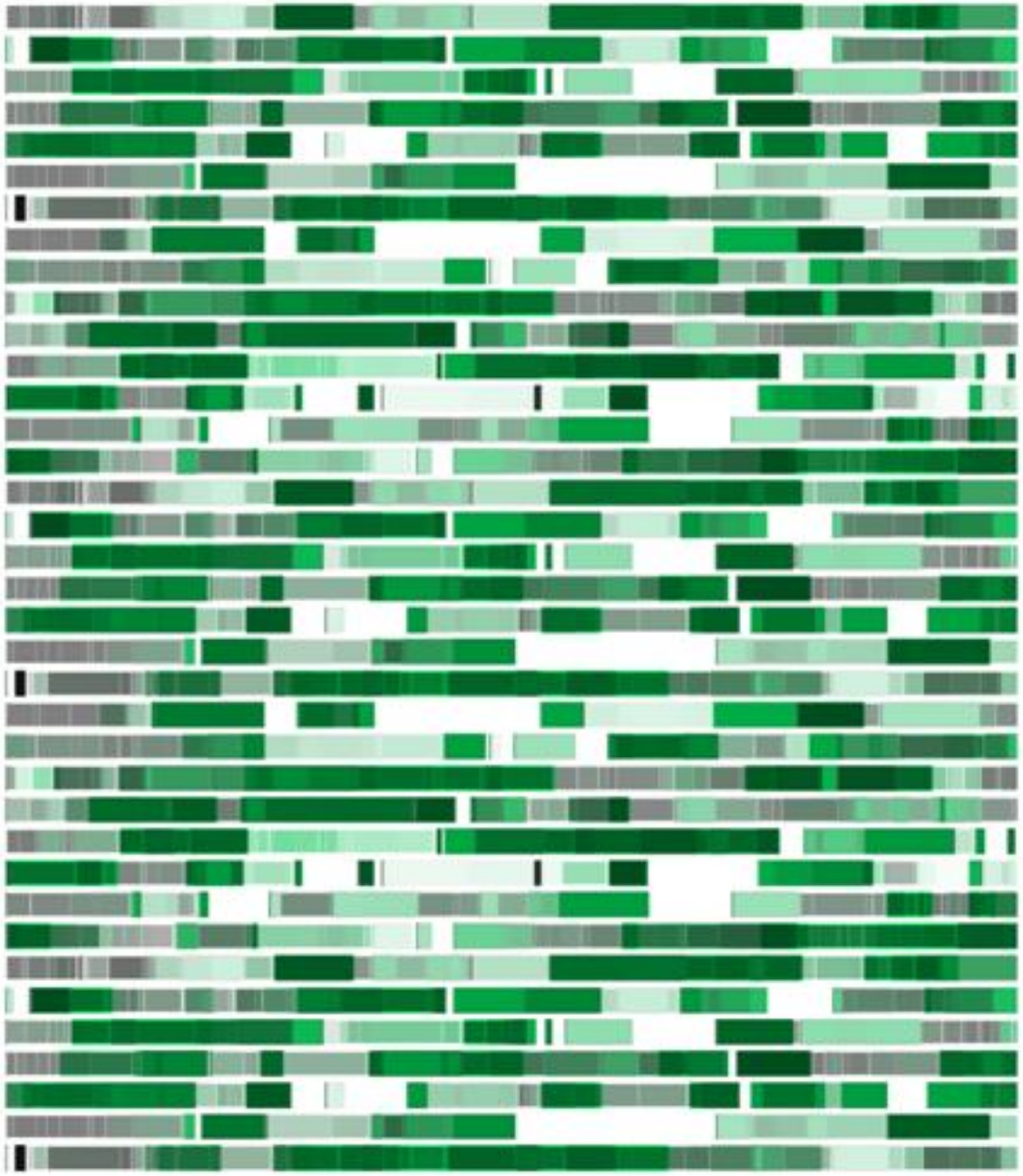
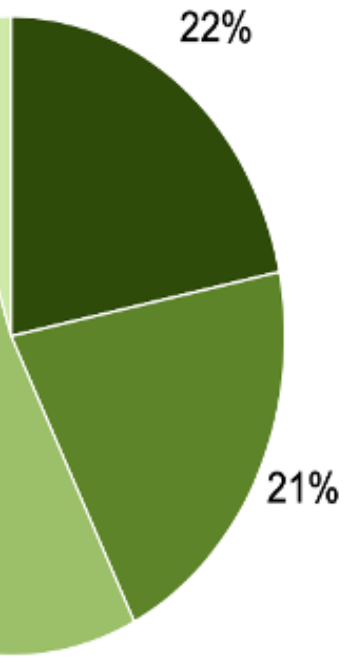
II JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:
A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN
SEVILLA, 6 Y 7 DE FEBRERO DE 2025

NSCLC. Estrategias con la inmunoterapia en estadios precoces: ¿qué aporta cada una de ellas?

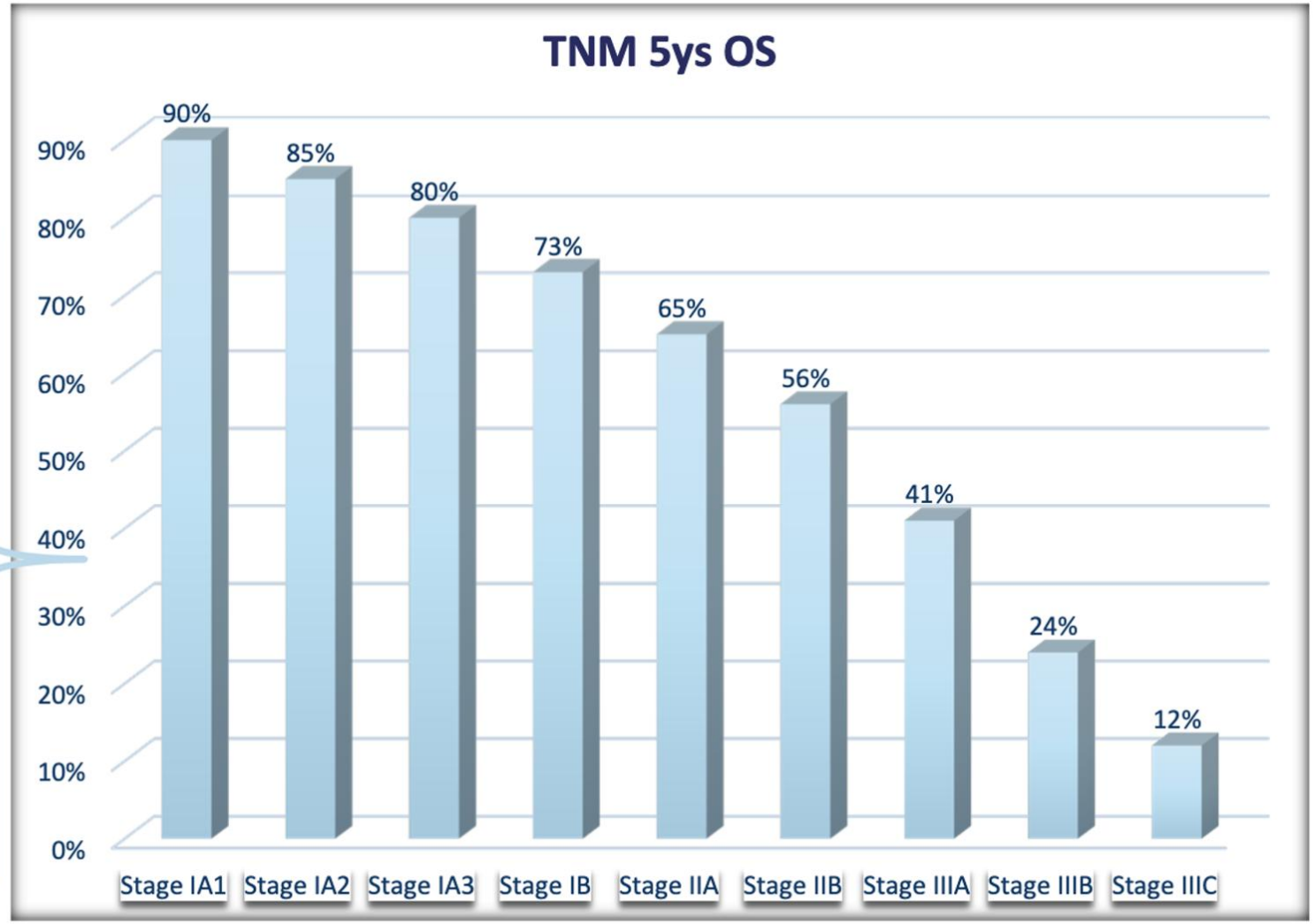
Manuel Cobo Dols
HRU Málaga
7-2-2025



Percent of Cases by Stage



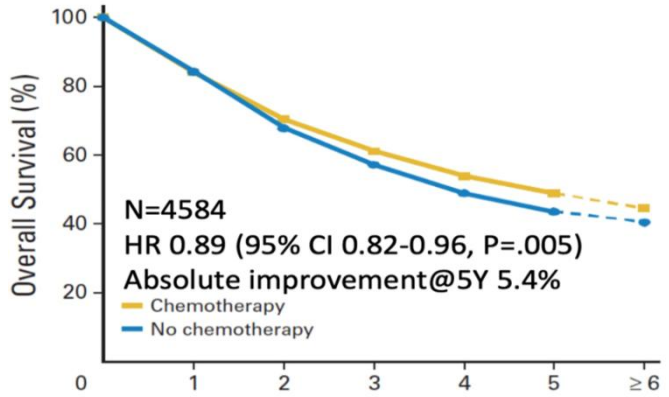
- **Localized (22%)**
  Confined to Primary Site
- **Regional (21%)**
  Spread to Regional Lymph Nodes
- **Distant (53%)**
  Cancer Has Metastasized
- **Unknown (5%)**
  Unstaged



ESTADIO I, II → **CIRUGÍA** → **QT**

ESTADIO III → **COMITÉ** → **QT** → **CIRUGÍA**

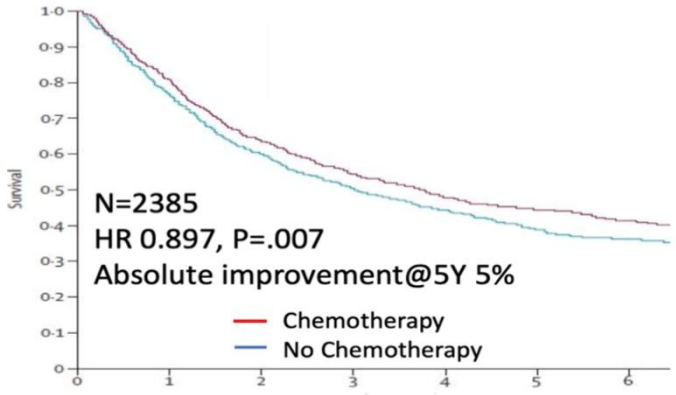
LACE adjuvant meta-analysis



Pignon, JCO 2008

≈ SG

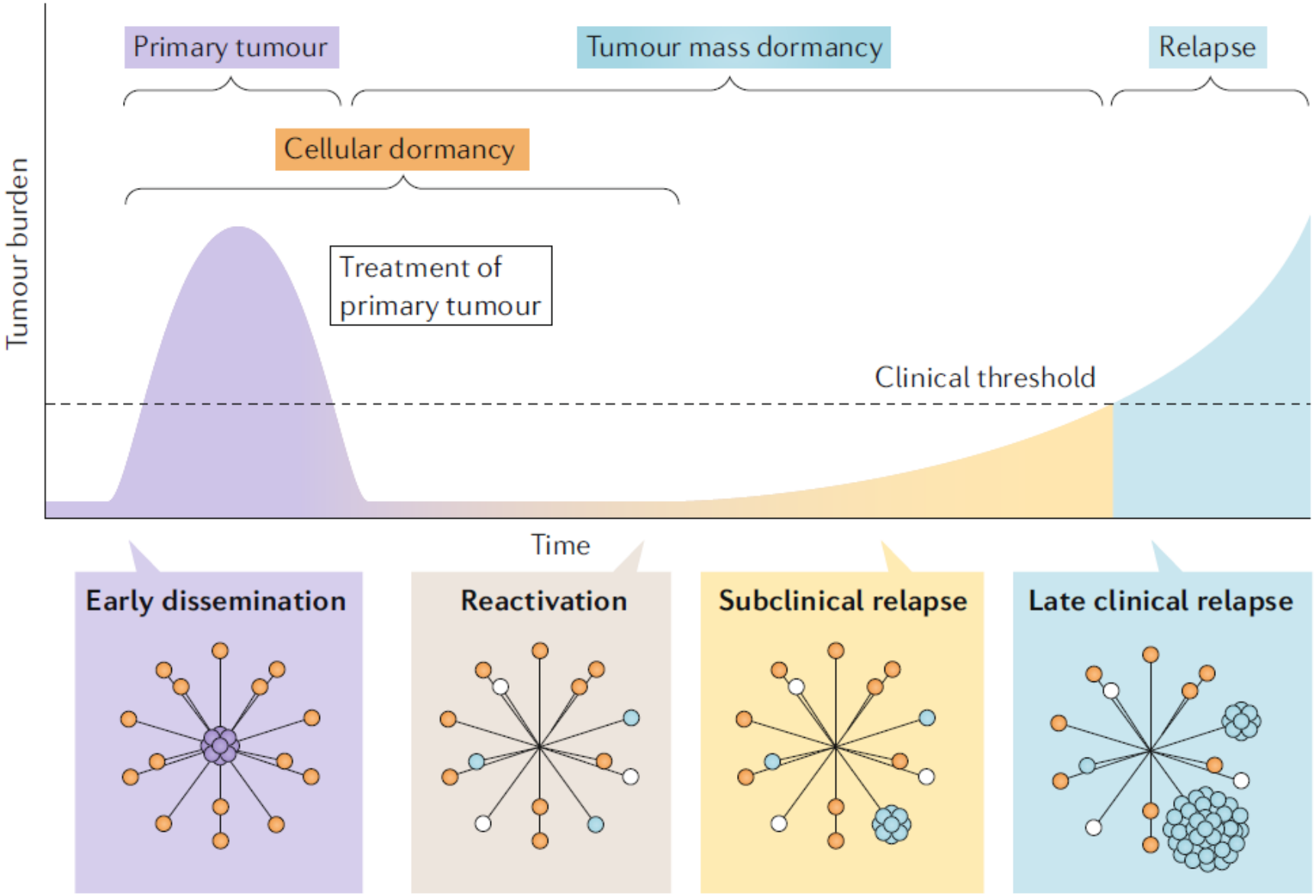
Neoadjuvant meta-analysis



Burdett, Lancet 2014

Control del micronicho metastasico

The time factor is key



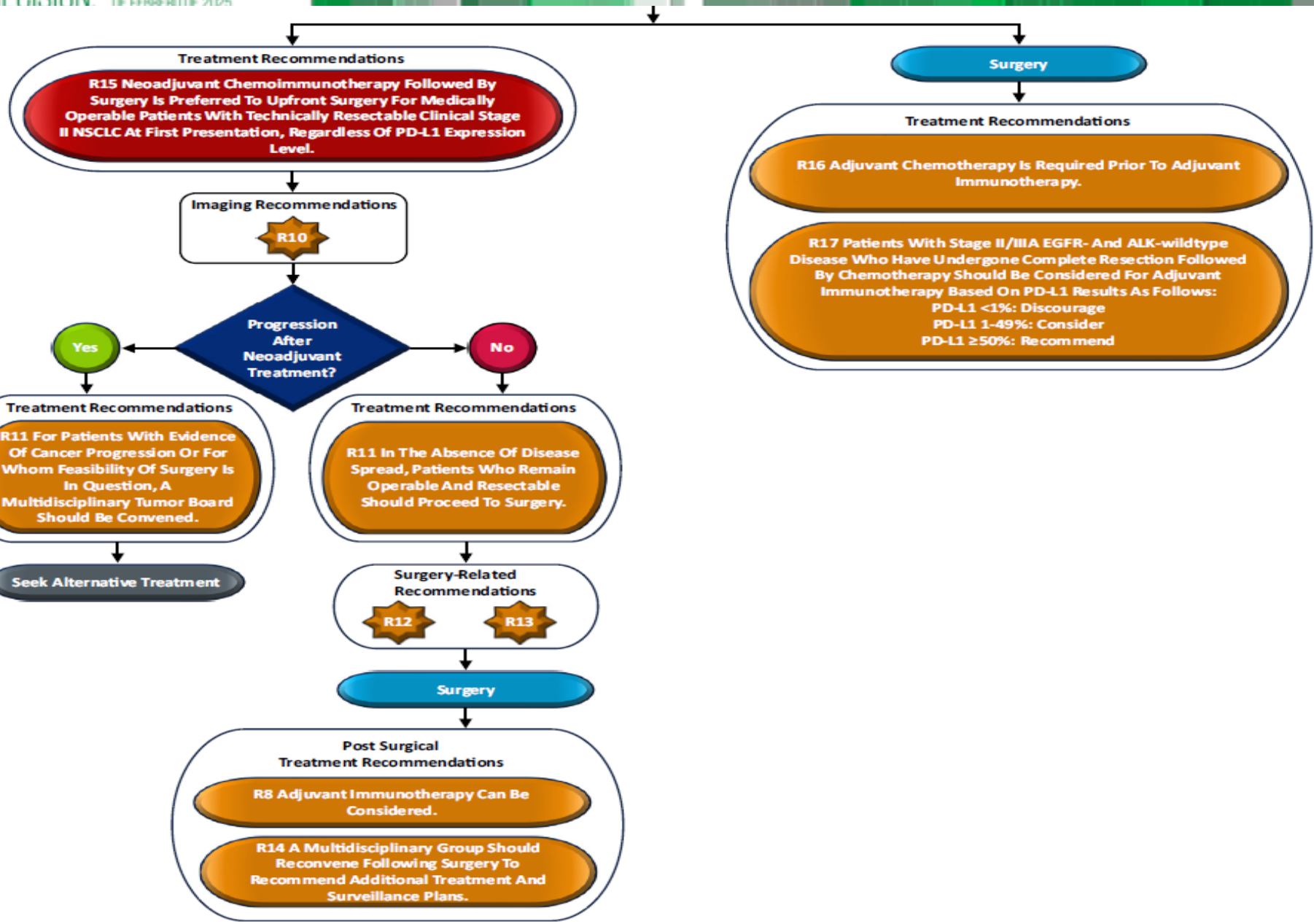
.- cancer cell dissemination (orange circles corresponding to cells), contrary to dogma, can occur early well before the primary tumour (purple circles) is clinically detectable.

.- Cellular dormancy at distant sites begins even before treatment of the primary tumour commences.

.- Some disseminated cancer cells may not survive (white circles) whereas others remain dormant for prolonged periods. At some seemingly random time point, a small number of dormant cancer cells are reactivated (blue circles) and enter a period of subclinical growth before they pass a clinical threshold and become detectable as a late metastatic relapse.

.- During the subclinical phase, both cellular dormancy and tumour mass dormancy may coexist.

Phan TG, Croucher PI. The dormant cancer cell life cycle. *Nat Rev Cancer*. 2020;20(7):398-411. doi:10.1038/s41568-020-0263-0

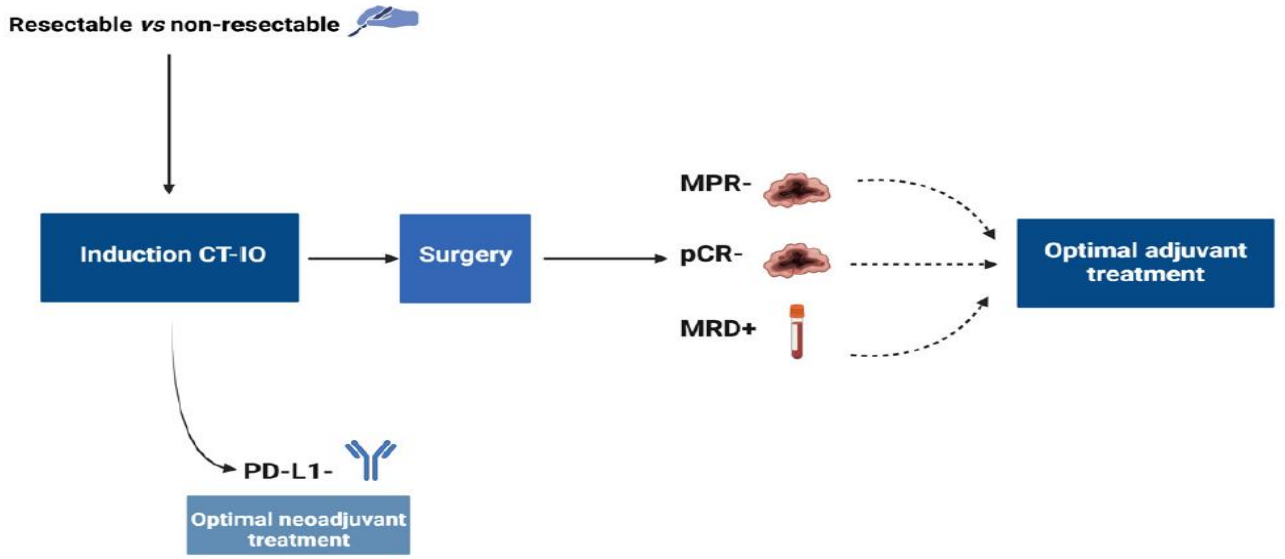

Treatment Recommendations
R15 Neoadjuvant Chemoimmunotherapy Followed By Surgery Is Preferred To Upfront Surgery For Medically Operable Patients With Technically Resectable Clinical Stage II NSCLC At First Presentation, Regardless Of PD-L1 Expression Level.
Imaging Recommendations
R10
Progression After Neoadjuvant Treatment?
Yes
No
Treatment Recommendations
R11 For Patients With Evidence Of Cancer Progression Or For Whom Feasibility Of Surgery Is In Question, A Multidisciplinary Tumor Board Should Be Convened.
Seek Alternative Treatment
Treatment Recommendations
R11 In The Absence Of Disease Spread, Patients Who Remain Operable And Resectable Should Proceed To Surgery.
Surgery-Related Recommendations
R12
R13
Surgery
Post Surgical Treatment Recommendations
R8 Adjuvant Immunotherapy Can Be Considered.
R14 A Multidisciplinary Group Should Reconvene Following Surgery To Recommend Additional Treatment And Surveillance Plans.
Surgery
Treatment Recommendations
R16 Adjuvant Chemotherapy Is Required Prior To Adjuvant Immunotherapy.
R17 Patients With Stage II/IIIA EGFR- And ALK-wildtype Disease Who Have Undergone Complete Resection Followed By Chemotherapy Should Be Considered For Adjuvant Immunotherapy Based On PD-L1 Results As Follows:
PD-L1 <1%: Discourage
PD-L1 1-49%: Consider
PD-L1 ≥50%: Recommend

Areas de controversia

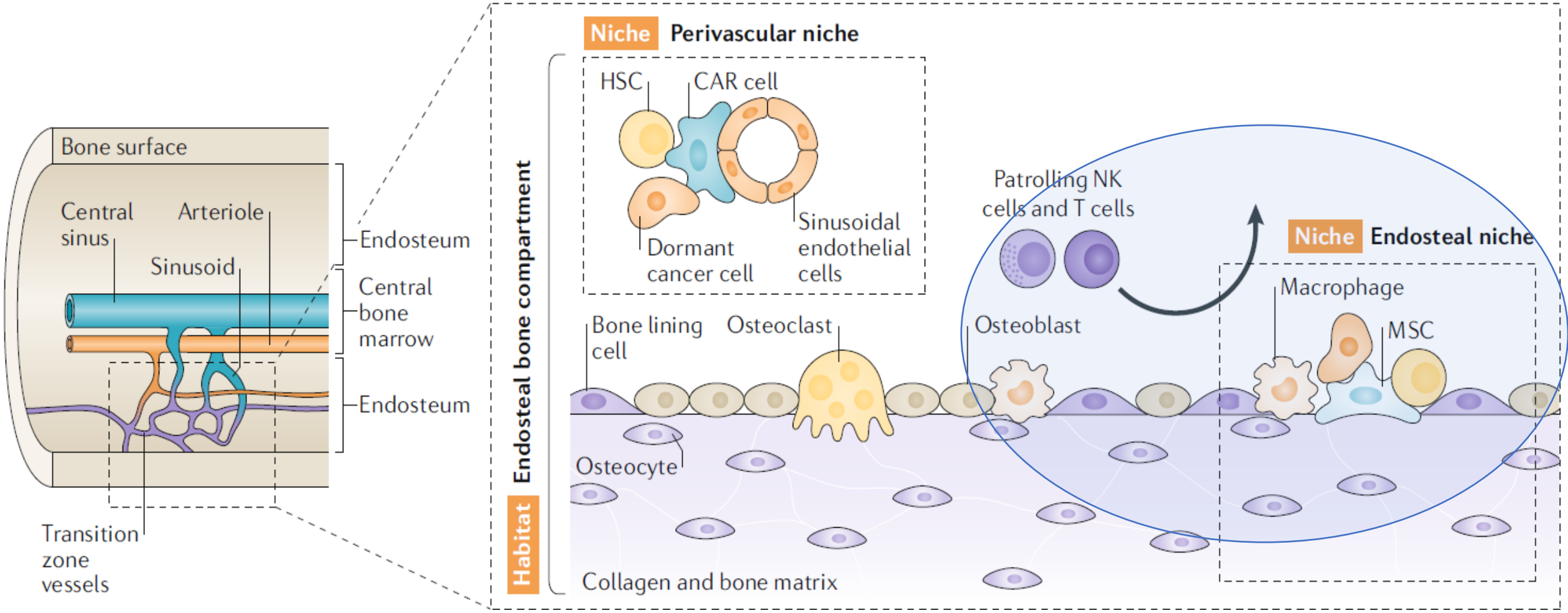
.- Estadio II y IIIa resecables y operables: QT –inmuno Neoadyuvante vs QT-inmuno adyuvante

.- Estadio II y IIIa resecables y operables: QT –inmuno Neoadyuvante vs QT –inmuno Perioperatoria

.- Estadio IIIa/b potencialmente operables: QT –inmuno Neoadyuvante vs QT+RT radical y durvalumab



Immune control in niches of dormant cells



Habitats and niches for dormant cancer cells. In bone, the endosteal bone surface is an anatomical location or habitat that contains multiple niches for different cell types, such as different types of haematopoietic stem cells (HSCs), which can be hijacked by dormant cancer cells. These niches are small nests of cells with precise functions. The endosteal niche consists of primitive osteoblast- lineage cells, such as mesenchymal stem cells (MSCs), bone- lining cells, which are osteoblasts that have completed their bone forming activity, and macrophages. The perivascular niche consists of CXCchemokine ligand 12 (CXCL12)- abundant reticular (CAR) cells, another mesenchymal progenitor cell and endothelial cells. Immune cells such as natural killer (NK) cells and T cells patrol these niches and surveil for ectopic ‘intruders’. Osteoclasts may remodel the endosteal niche to reactivate dormant cancer cells but, unlike mature osteoblasts, are not part of the niche.

Phan TG, Croucher PI. The dormant cancer cell life cycle. *Nat Rev Cancer*. 2020;20(7):398-411. doi:10.1038/s41568-020-0263-0

PERIOPERATIVE STRATEGY

NEOADJUVANT STRATEGY		ADJUVANT STRATEGY	
	SURGERY	IMpower 010: CT → Atezolizumab 1 year	PD-L1 ≥50%
		KEYNOTE 091: CT (Optional) → Pembrolizumab 1 year	After CT
CheckMate 816 : Nivolumab + CT x 3 cycles	SURGERY		PD-L1 ≥1%
CheckMate 77T : Nivolumab + CT x 4 cycles	SURGERY	Nivolumab 1 year	
KEYNOTE 671: Pembrolizumab + CT x 4 cycles		Pembrolizumab 1 year	CHMP
AEGEAN: Durvalumab + CT x 4 cycles		Durvalumab 1 year	
NEOTORCH: Toripalimab + CT x 3 cycles		Toripalimab + CT x 1 → Toripalimab 1 year	
RATIONALE 315: Tislelizumab + CT x 3-4 cycles		Tislelizumab 1 year	

Pernelle Lavaud. Cancers 2024

Areas de controversia

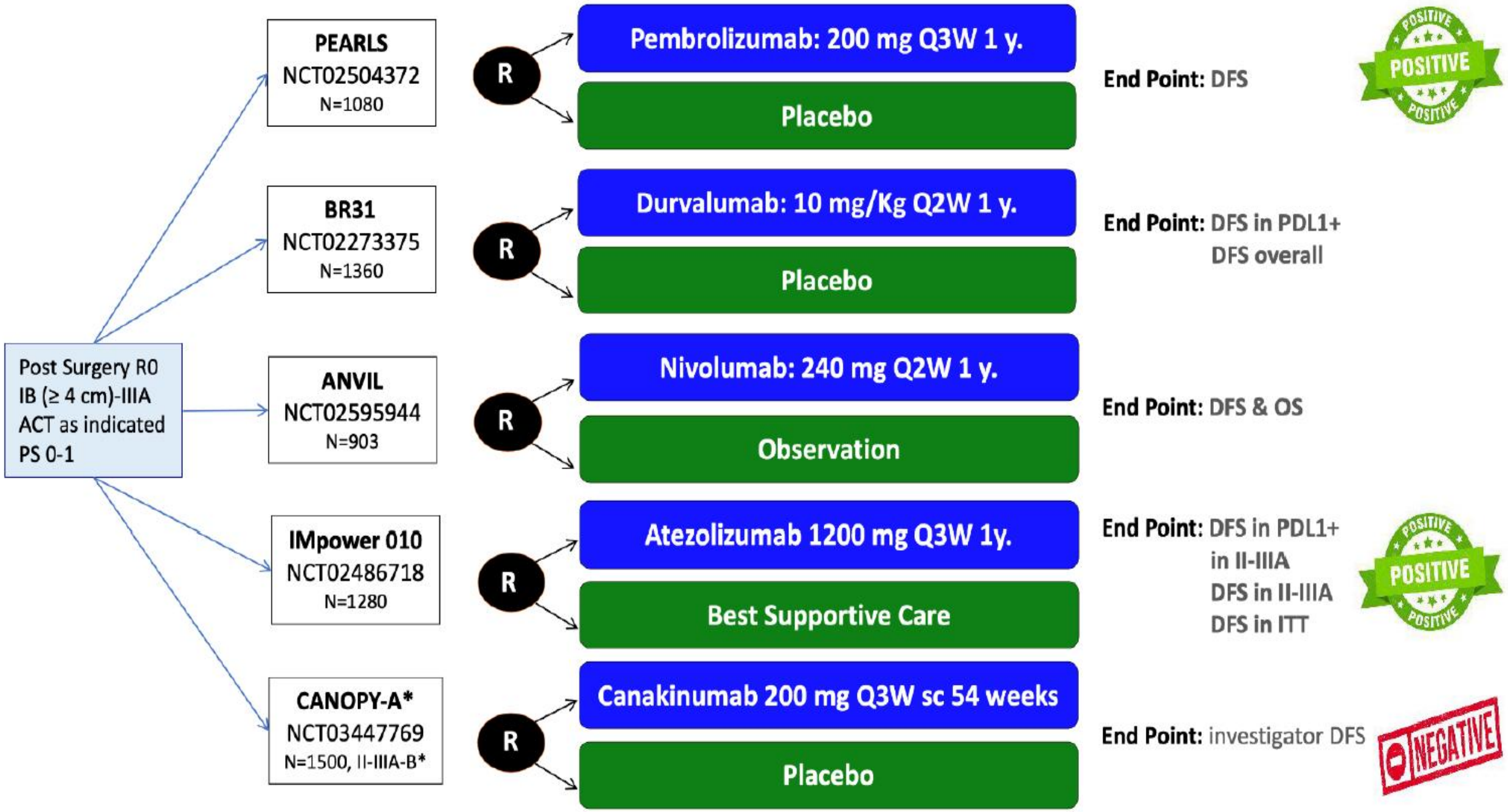
.- **Estadio II y IIIa resecables y operables: QT –inmuno Neoadyuvante vs QT-inmuno adyuvante**

.- Estadio II y IIIa resecables y operables: QT –inmuno Neoadyuvante vs QT –inmuno Perioperatoria

.- Estadio IIIa/b potencialmente operables: QT –inmuno Neoadyuvante vs QT+RT radical y durvalumab

Cuestiones a resolver

.- Conocimiento biología micronicho metastásico
.- Adyuvancia /neoadyuvancia
.- Beneficio compensa toxicidad?
.- DFS se correlaciona con OS en el seno de inmunoterapia?
.- Cómo seleccionar pts:
    .- Expresión de PD-L1
    .- Eficacia en pts con mutaciones oncogénicas
    .- Papel de la quimioterapia adyuvante
    .- Biomarcadores adicionales
    .- PS, comordilidades, polifarmacia, fragilidad



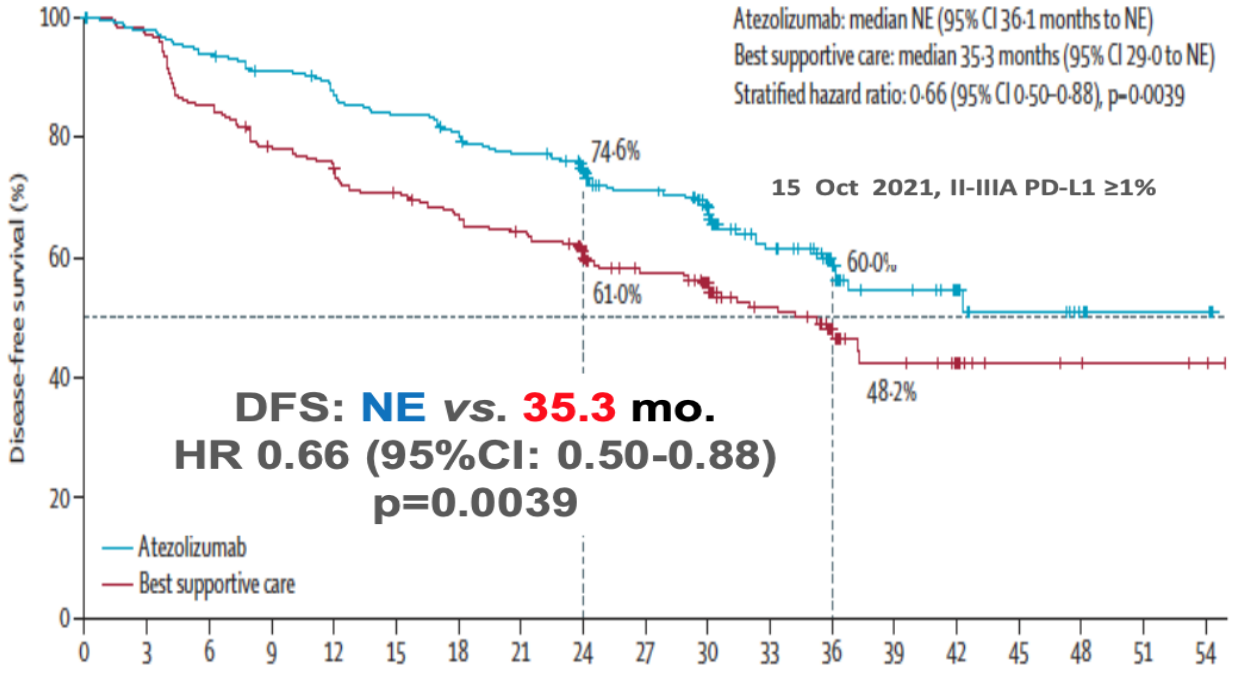
Jordi Remon–JTO 2019-courtesy slide * Garon–ESMO 2022

ESTADIO I, II
ESTADIO III

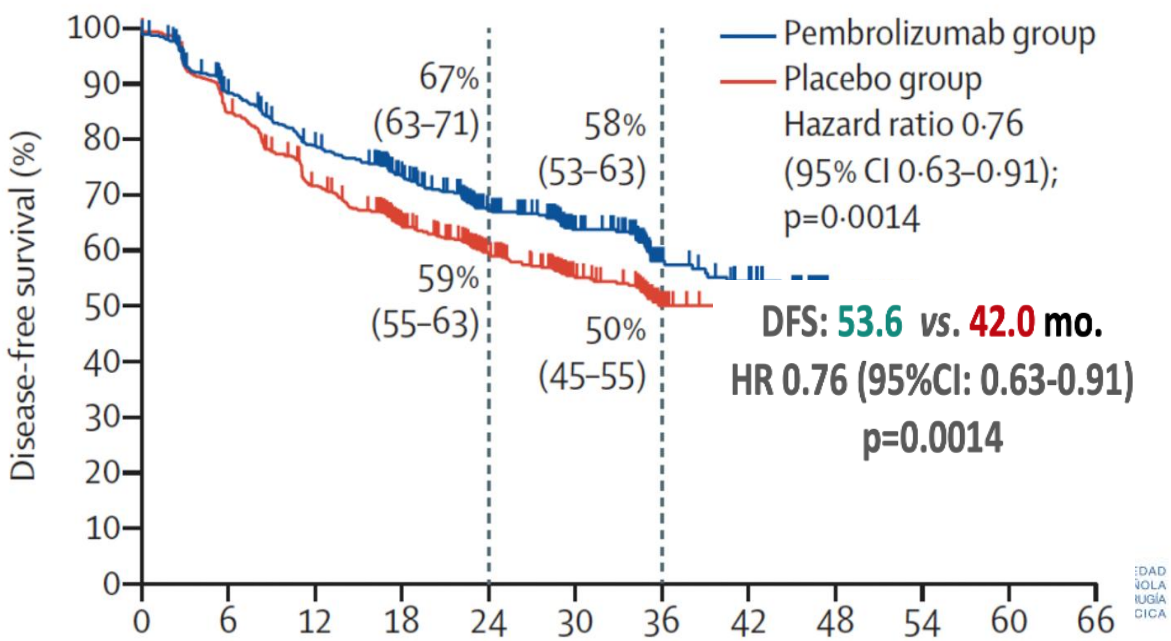
CIRUGÍA → QT

- PDL1>50 → Atezolizumab x 1ª
- ALL commers: Pembrolizumabx1a

IMPOWER010



PEARLS



	Impower 010	PEARLS
Design	Open label	Triple blind
Control arm	BSC	Placebo
Primary EP	DFS II-IIIa, PDL-1 =/> 1% Hierarchical testing DFS II-IIIa all comers	DFS Ib-IIIa all comers DFS Ib-IIIa PD-L1 =/> 50%
Stratification factors	• Sex • Stage (IB vs. II vs. IIIA) • Histology • PD-L1 status	• Stage (IB-II-IIIA) • Adjuvant CT (yes-no) • PD-L1 (neg-weak+-strong+) • Region (WE-EE-ROW-Asia)
Randomized patients	1280	1177
Stage IB/II/IIIa	11.8%, 46.7%, 41.1%	14.3%, 56.7%, 28.8%
PD-L1	44% <1%, 53.5% > 1% (SP263)	39.5% < 1%, 32.3% 1-49%, 28.3% =/> 50% (22C3 Dako)
Adjuvant chemotherapy	100%	85.8% vs 85.9%
Follow up	32.8 m	35.6 m

Wakelee H et al, Lancet 2021 * Felip E et al, ESMO 2021 * Paz-Ares L et al, ESMO Plenary 2022 * O'Brien M et al, Lancet Oncol 2022 * Peters S et al, ESMO 2022

Beneficio de inmunoterapia independientemente del tipo de cirugía

Surgery in adjuvant trials

The light

- Surgeries were performed as per standard
- The benefit is seen regardless of the type of surgery

cancers

Perspective

The Evolving Concept of Complete Resection in Lung Cancer Surgery

Ramón Rami-Porta [1,2]

IASLC

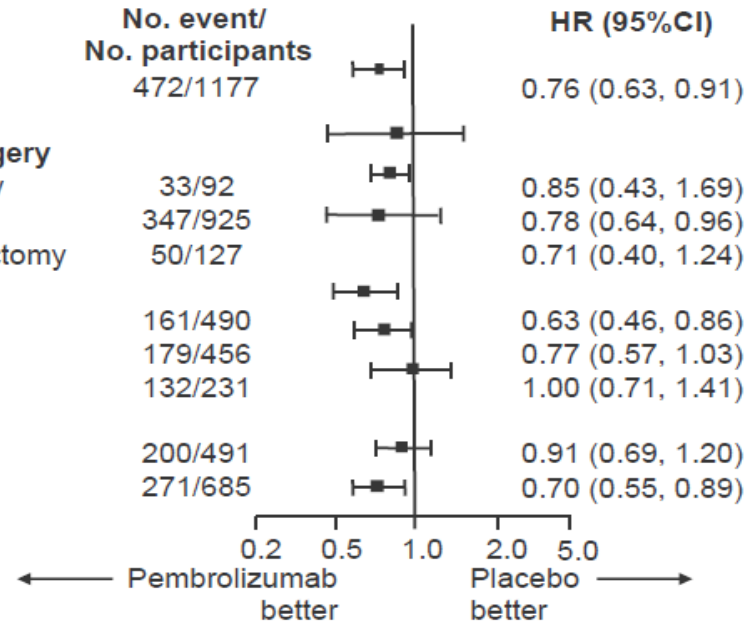
COMMENTARY

Complete Resection in Lung Cancer Surgery: From Definition to Validation and Beyond

Check for updates

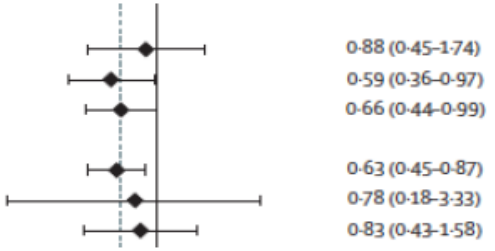
European Lung

PEARLS/KEYNOTE-091



IMPOWER 010

Regional lymph node stage (pN)					
N0	60/106	36·7 (35·5–NE)	46/106	NE (32·0–NE)	0·88 (0·45–1·74)
N1	100/194	NE (NE–NE)	94/194	NE (30·4–NE)	0·59 (0·36–0·97)
N2	88/176	32·3 (24·2–NE)	88/176	21·3 (15·7–31·4)	0·66 (0·44–0·99)
Type of surgery					
Lobectomy	186/359	NE (36·0–NE)	173/359	33·4 (26·7–37·3)	0·63 (0·45–0·87)
Bilobectomy	15/24	36·7 (36·1–NE)	9/24	NE (6·2–NE)	0·78 (0·18–3·33)
Pneumonectomy	43/85	36·1 (30·1–NE)	42/85	NE (19·4–NE)	0·83 (0·43–1·58)



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Beneficio de inmunoterapia en pacientes que recibía quimioterapia adyuvante

CT in adjuvant trials

The light

- CT was given even when the protocol allowed for flexibility

PEARLS/KEYNOTE-091

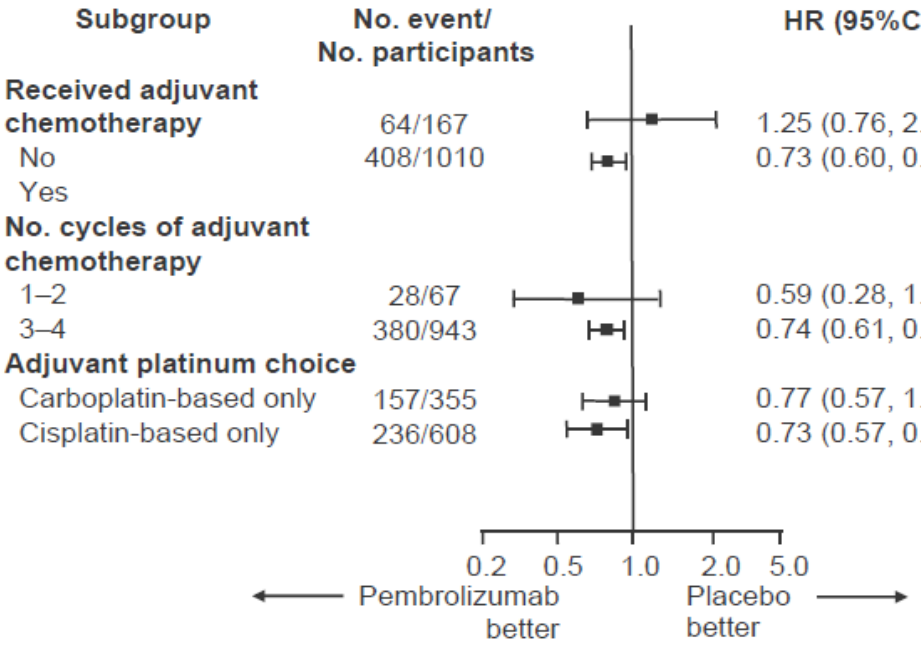
Received adjuvant chemotherapy				
No	84 (14%)	83 (14%)	25 (15%)	24 (15%)
Yes†	506 (86%)	504 (86%)	143 (85%)	141 (85%)
1–2 cycles	35 (6%)	32 (5%)	8 (5%)	8 (5%)
3–4 cycles	471 (80%)	472 (80%)	135 (80%)	133 (81%)

IMPOWER 010

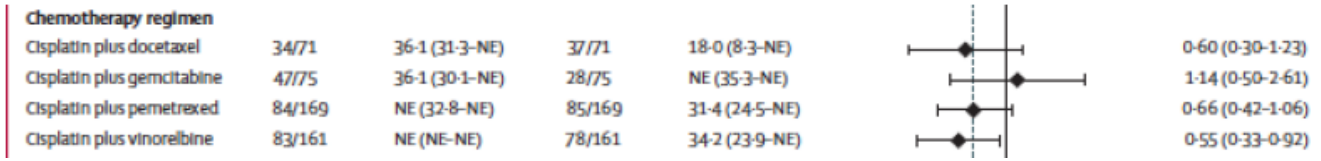
	PD-L1 TC≥1% (SP263) (stage II-IIIA)		All Randomised (stage II-IIIA)		ITT (stage IB-IIIA)	
No. of cycles	Atezolizumab (n = 248)	BSC (n = 228)	Atezolizumab (n = 442)	BSC (n = 440)	Atezolizumab (n = 507)	BSC (n = 498)
1	1 (<1%)	11 (5%)	6 (1%)	14 (3%)	7 (1%)	14 (3%)
2	8 (3%)	11 (5%)	18 (4%)	19 (4%)	22 (4%)	22 (4%)
3	28 (11%)	18 (7.9%)	40 (9%)	35 (8%)	42 (8%)	39 (8%)
4	211 (85%)	188 (83%)	378 (86%)	372(85%)	436 (86%)	423 (85%)

Data are n (%).
BSC, best supportive care; ITT, intent-to-treat.

PEARLS/KEYNOTE-091



IMPOWER 010



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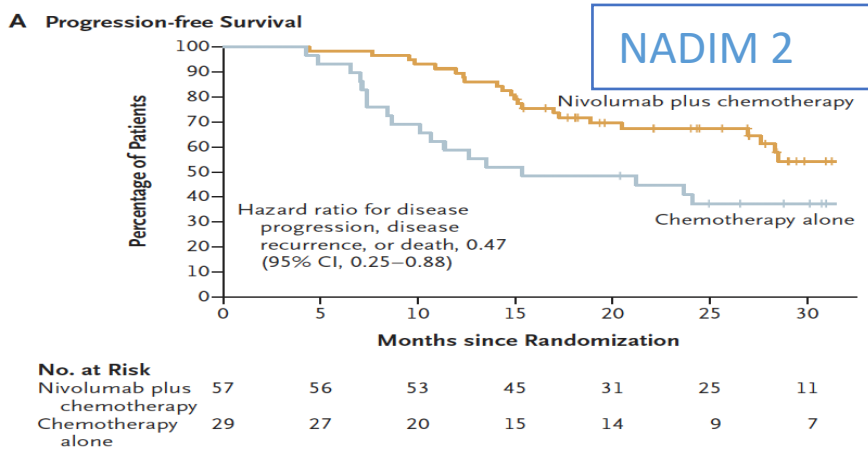
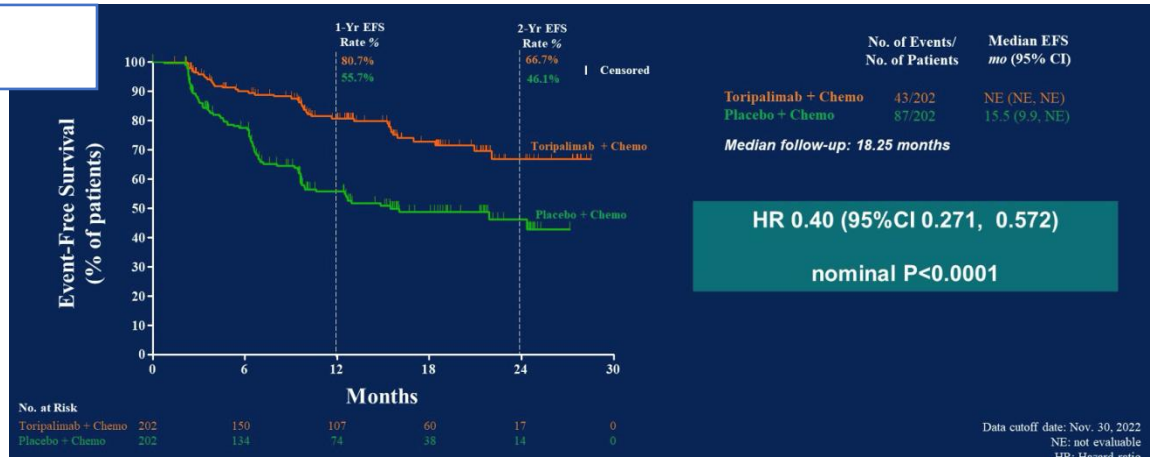
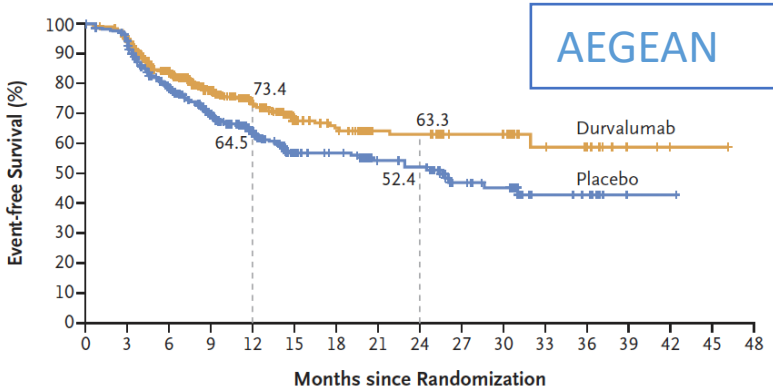
NADIM 2



Neo_TORCH



AEGEAN



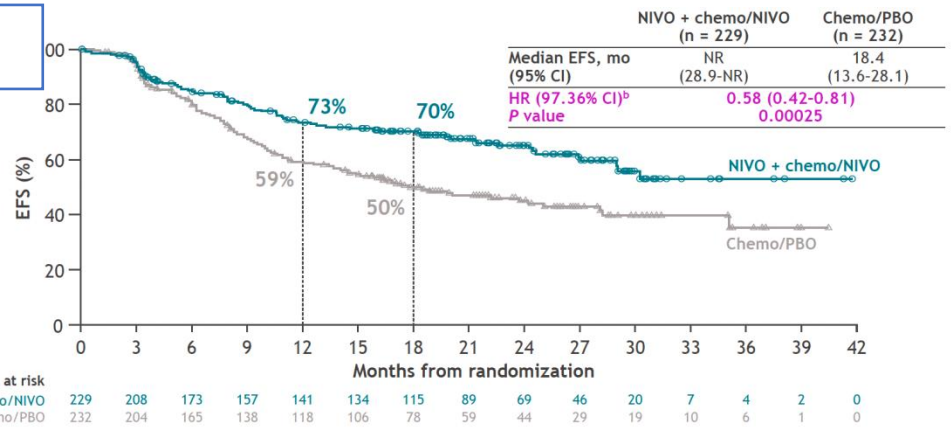
	No. of Events/ No. of Patients	Median Event-free Survival (95%CI) mo
Durvalumab	98/366 (26.8)	NR (31.9–NR)
Placebo	138/374 (36.9)	25.9 (18.9–NR)

Stratified hazard ratio for disease progression, recurrence, or death, 0.68 (95% CI, 0.53–0.88) P=0.004 by stratified log-rank test

No. at Risk

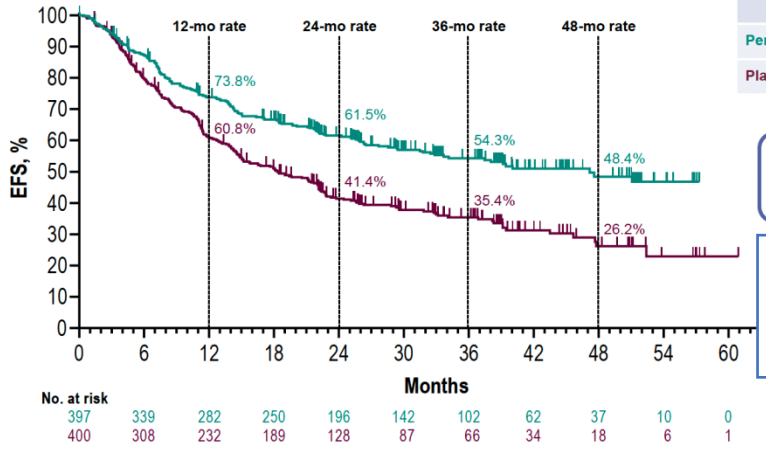
Durvalumab	366	336	271	194	140	90	78	50	49	31	30	14	11	3	1	1	0
Placebo	374	339	257	184	136	82	74	53	50	30	25	16	13	1	1	0	0

CM 77T



- EFS per investigator assessment, NIVO + chemo/NIVO vs chemo/PBO: HR, 0.56; 95% CI, 0.41-0.76

KEYNOTE 671



	Pts w/ Event	Median (95% CI), mo
Pembro arm	43.8%	47.2 (32.9-NR)
Placebo arm	62.0%	18.3 (14.8-22.1)

HR 0.59 (95% CI, 0.48-0.72)

RATIONALE 315

Per BICR (ITT Analysis Set)

	Events (%)	Median (95% CI), months	HR (95% CI)	*P*-value
TIS arm	58 (25.7)	NR (NE, NE)	**0.56 (0.40, 0.79)**	0.0003
PBO arm	83 (36.6)	NR (16.6, NE)		

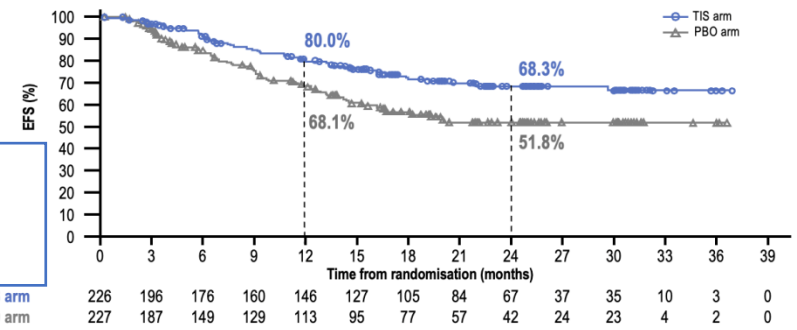


Table. Main Characteristics of Included Neoadjuvant ICI-Chemotherapy Randomized Clinical Trials and Outcomes of Interest

Source (phase)	Treatment (No. of cycles)		Primary end point	Patients, No.		2-y EFS (95% CI)		P value	pCR rate (95% CI)		P value	Surgery, exp vs control, %
	Control	Exp		Control	Exp	Control	Exp		Control	Exp		
Forde et al,[13] 2022; CheckMate 816 (3)	PBC (3), surgery	Nivolumab, 360 mg, plus PBC (3), surgery	EFS and pCR	179	179	45.3 (NR)	63.8 (NR)	<.001	2.2 (0.6-5.6)	24.0 (18.0-31.0)	<.001	83.2 vs 75.4
Heymach et al,[21] 2023; AEGEAN (3)	Placebo plus PBC (4), surgery, and placebo (12)	Durvalumab, 1500 mg, plus PBC (4), surgery, and durvalumab (12)	EFS by BICR; pCR	374	366	52.4 (45.4-59.0)	63.3 (56.1-69.6)	<.001	4.3 (2.5-6.9)	17.2 (13.5-21.5)	<.001	77.6 vs 76.7
Lei et al,[22] 2023; TD-FOREKNOW (2)	Platinum based chemotherapy with nab-paclitaxel (3), surgery	Camrelizumab, 200 mg, every 3 wk for 3 cycles plus PBC plus nab-paclitaxel (3), surgery	pCR	45	43	67.6 (48.0-81.2)	76.9 (56.3-88.7)	NA	8.9 (2.5-21.2)	32.6 (19.1-48. 5)	<.001	93.0 vs 93.3
Zhang et al,[15] 2021; Neotorch (3)	Placebo plus PBC (3), surgery, placebo plus PBC (1), and then placebo (13)	Toripalimab, 240 mg, every 3 wk plus PBC (3), surgery, toripalimab, 240 mg, every 3 wk plus PBC (1), and toripalimab, 240 mg (13)	EFS in stage III by investigators; mPR evaluated by BIPR in stage III	202	202	38.7 (NR)	64.7 (NR)	<.001	1 (0.1-3.5)	28.2 (22.1-35.0)	<.001	82.2 vs 73.3
Provencio et al,[23] 2023; NADIM II (2)	PBC (3), surgery, and observation	Nivolumab, 360 mg, plus PBC (3), surgery, and nivolumab, 480 mg (6)	pCR	29	57	40.9 (26.2-63.6)	67.2 (55.8-81.0)	NA	7 (1-23)	37 (24-51)	.02	93.0 vs 69.0
Wakelee et al,[14] 2023; KEYNOTE-671 (3)	Placebo plus PBC (4), surgery, and placebo (13)	Pembrolizumab, 200 mg, plus PBC (4), surgery, and pembrolizumab, 200 mg (13)	EFS and OS	400	397	40.6 (34.8-46.3)	62.4 (56.8-67.5)	<.001	4 (2.3-6.4)	18.1 (14.5-22.3)	<.001	82.1 vs 79.4
Cascone et al,[16] 2023; CheckMate 77T (3)	Placebo plus PBC (4), surgery, and placebo (12)	Nivolumab, 360 mg, plus PBC (4), surgery, and nivolumab, 480 mg (12)	EFS by BICR	232	229	50.0 (NR)	70.0 (NR)	<.001	4.7 (2.4-8.3)	25.3 (19.8-31.5)	NR	78.0 vs 77.0
Yue et al,[24] 2023; RATIONALE-315 (3)	Placebo plus PBC (4), surgery, and placebo (8)	Tislelizumab, 200 mg, plus PBC (3), surgery, and tislelizumab, 400 mg (8)	mPR by BIPR and EFS by BICR	227	226	NR	NR	NA	5.7 (NR)	40.7 (NR)	<.001	84.1 vs 76.2

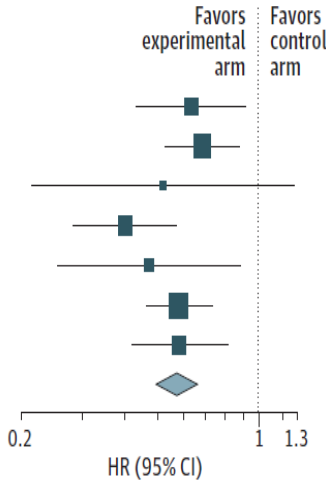
Giuseppe Luigi Banna,. *JAMA Network Open. 2024;7(4):e246837. doi:10.1001/jamanetworkopen.2024.6837*

2. Subgroup Meta-Analysis of 2-Year Event-Free Survival

A Two-year EFS

Study	HR (95% CI)	Weight, %
Forde et al,[13] 2022	0.63 (0.43-0.91)	12.44
Heymach et al,[21] 2023	0.68 (0.53-0.88)	23.35
Lei et al,[22] 2023	0.52 (0.21-1.29)	2.40
Zhang et al,[15] 2021	0.40 (0.28-0.57)	13.56
Provencio et al,[23] 2023	0.47 (0.25-0.88)	4.85
Wakelee et al,[14] 2023	0.58 (0.46-0.72)	27.86
Cascone et al,[16] 2023	0.58 (0.42-0.81)	15.55
Overall	0.57 (0.50-0.66)	

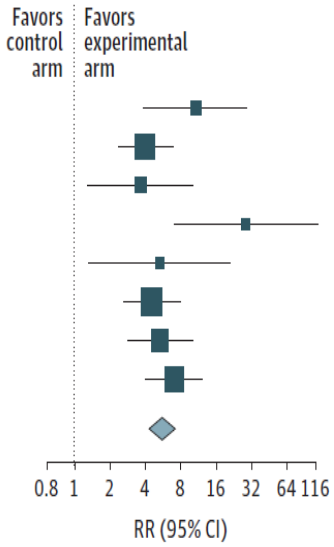
Heterogeneity: $I^2 = 15.92\%$
Test of heterogeneity: $Q_6 = 6.34$; $P = .39$
Test of overall effect: $z = -7.71$; $P < .001$



B Pathologic complete response

Study	Pathologic complete response, No.				RR (95% CI)
	Treatment		Control		
	Yes	No	Yes	No	
Forde et al,[13] 2022	43	136	4	175	10.75 (3.94-29.32)
Heymach et al,[21] 2023	63	303	16	358	4.02 (2.37-6.83)
Lei et al,[22] 2023	14	29	4	41	3.66 (1.31-10.26)
Zhang et al,[15] 2021	57	145	2	200	28.50 (7.05-115.16)
Provencio et al,[23] 2023	21	36	2	27	5.34 (1.34-21.23)
Wakelee et al,[14] 2023	72	325	16	384	4.53 (2.69-7.65)
Cascone et al,[16] 2023	58	171	11	221	5.34 (2.88-9.91)
Yue et al,[24] 2023	92	134	13	214	7.11 (4.10-12.33)
Overall					5.58 (4.27-7.29)

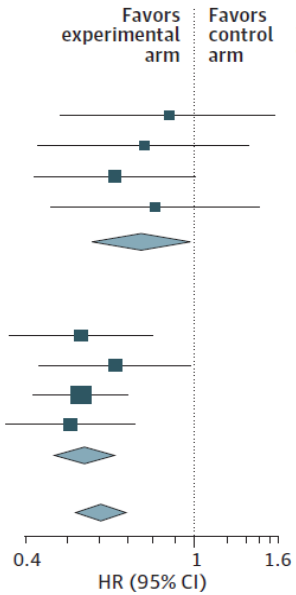
Heterogeneity: $I^2 = 9.19\%$
Test of heterogeneity: $Q_7 = 10.35$; $P = .17$
Test of overall effect: $z = 12.60$; $P < .001$



A Stages IB-II and III

Study	HR (95% CI)	Weight, %
Stage IB-II		
Forde et al,[13] 2022	0.87 (0.48-1.56)	5.69
Heymach et al,[21] 2023	0.76 (0.43-1.34)	6.11
Wakelee et al,[14] 2023	0.65 (0.42-1.01)	10.26
Cascone et al,[16] 2023	0.81 (0.46-1.43)	6.14
Heterogeneity: $I^2 = 0.00\%$	0.75 (0.57-0.97)	
Test of heterogeneity: $Q_3 = 0.72$; $P = .87$		
Stage III		
Forde et al,[13] 2022	0.54 (0.37-0.80)	13.28
Heymach et al,[21] 2023	0.65 (0.43-0.98)	11.81
Wakelee et al,[14] 2023	0.54 (0.42-0.70)	30.27
Cascone et al,[16] 2023	0.51 (0.36-0.72)	16.44
Heterogeneity: $I^2 = 0.00\%$	0.55 (0.47-0.65)	
Test of heterogeneity: $Q_7 = 0.87$; $P = .83$		
Overall	**0.60 (0.52-0.69)**	

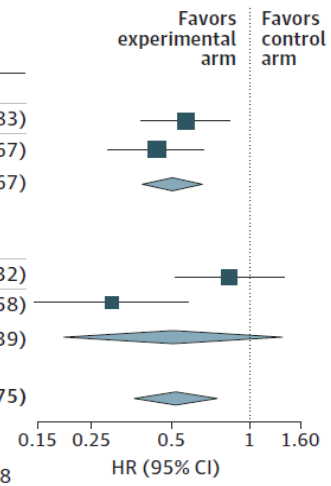
Heterogeneity: $I^2 = 0.00\%$
Test of heterogeneity: $Q_1 = 5.34$; $P = .62$
Test of group differences: $Q_{b1} = 3.74$; $P = .053$



B Stage III

Study	HR (95% CI)	Weight, %
Stage IIIA		
Heymach et al,[21] 2023	0.57 (0.39-0.83)	29.28
Zhang et al,[15] 2021	0.44 (0.29-0.67)	27.44
Heterogeneity: $I^2 = 0.00\%$	0.51 (0.38-0.67)	
Test of heterogeneity: $Q_1 = 0.81$; $P = .37$		
Stage IIIB		
Heymach et al,[21] 2023	0.83 (0.52-1.32)	25.28
Zhang et al,[15] 2021	0.30 (0.15-0.58)	18.00
Heterogeneity: $I^2 = 83.56\%$	0.51 (0.19-1.39)	
Test of heterogeneity: $Q_1 = 6.08$; $P = .01$		
Overall	**0.52 (0.36-0.75)**	

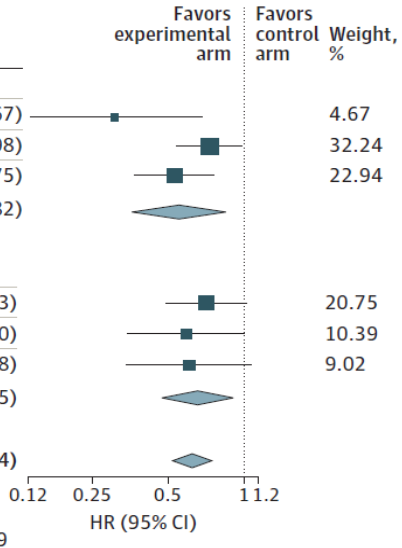
Heterogeneity: $I^2 = 60.65\%$
Test of heterogeneity: $Q_3 = 7.31$; $P = .06$
Test of group differences: $Q_{b1} = 0.00$; $P = .98$



D Platinum

Study	HR (95% CI)	Weight, %
Carboplatin		
Forde et al,[13] 2022	0.31 (0.14-0.67)	4.67
Heymach et al,[21] 2023	0.73 (0.54-0.98)	32.24
Cascone et al,[16] 2023	0.53 (0.37-0.75)	22.94
Heterogeneity: $I^2 = 60.09\%$	0.56 (0.38-0.82)	
Test of heterogeneity: $Q_2 = 4.87$; $P = .09$		
Cisplatin		
Forde et al,[13] 2022	0.71 (0.49-1.03)	20.75
Heymach et al,[21] 2023	0.59 (0.35-1.00)	10.39
Cascone et al,[16] 2023	0.61 (0.35-1.08)	9.02
Heterogeneity: $I^2 = 0.00\%$	0.65 (0.50-0.85)	
Test of heterogeneity: $Q_2 = 0.39$; $P = .82$		
Overall	**0.62 (0.53-0.74)**	

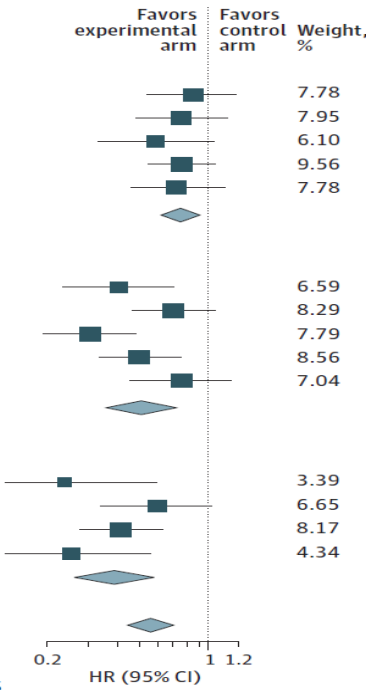
Heterogeneity: $I^2 = 0.00\%$
Test of heterogeneity: $Q_5 = 5.47$; $P = .36$
Test of group differences: $Q_{b1} = 0.47$; $P = .49$



C PD-L1

Study	HR (95% CI)	Weight, %
PD-L1 negative		
Forde et al,[13] 2022	0.85 (0.54-1.32)	7.78
Heymach et al,[21] 2023	0.76 (0.49-1.17)	7.95
Zhang et al,[15] 2021	0.59 (0.33-1.03)	6.10
Wakelee et al,[14] 2023	0.77 (0.55-1.07)	9.56
Cascone et al,[16] 2023	0.73 (0.47-1.15)	7.78
Heterogeneity: $I^2 = 0.00\%$	0.75 (0.62-0.91)	
Test of heterogeneity: $Q_4 = 1.01$; $P = .91$		
PD-L1 low		
Forde et al,[13] 2022	0.41 (0.24-0.70)	6.59
Heymach et al,[21] 2023	0.70 (0.46-1.05)	8.29
Zhang et al,[15] 2021	0.31 (0.20-0.48)	7.79
Wakelee et al,[14] 2023	0.51 (0.34-0.75)	8.56
Cascone et al,[16] 2023	0.76 (0.46-1.25)	7.04
Heterogeneity: $I^2 = 60.79\%$	0.51 (0.37-0.71)	
Test of heterogeneity: $Q_4 = 10.12$; $P = .04$		
PD-L1 high		
Forde et al,[13] 2022	0.24 (0.10-0.61)	3.39
Heymach et al,[21] 2023	0.60 (0.35-1.01)	6.65
Wakelee et al,[14] 2023	0.42 (0.28-0.65)	8.17
Cascone et al,[16] 2023	0.26 (0.12-0.55)	4.34
Heterogeneity: $I^2 = 35.56\%$	0.40 (0.27-0.58)	
Test of heterogeneity: $Q_3 = 4.72$; $P = .19$		
Overall	**0.56 (0.46-0.68)**	

Heterogeneity: $I^2 = 55.73\%$
Test of heterogeneity: $Q_{13} = 29.80$; $P = .005$
Test of group differences: $Q_{b2} = 10.68$; $P = .005$



Giuseppe Luigi Banna,. *JAMA Network Open. 2024;7(4):e246837. doi:10.1001/jamanetworkopen.2024.6837*

Study	Perioperative /Neoadjuvant	N	Percentage of PD-L1 > 1%	Percentage of Stage III %	Percentage of Surgery	pCR CT-ICB vs. CT	EFS HR [95% CI, *p*]	OS HR [95% CI, *p*]
CheckMate 816 [33,49]	Neoadjuvant	358	50%	63%	83%	24% vs. 2.2%	0.66 [0.49–0.9]	0.71 [0.47–1.07, $p = 0.045$] *
CheckMate 77T [34]	Perioperative	461	56%	64%	77%	25% vs. 5%	0.58 [0.42–0.81, $p < 0.00025$)	NR
KEYNOTE671 [35,47]	Perioperative	797	65%	70%	82%	18% vs. 4%	0.59 [0.48–0.72]	0.72 [0.56–0.93, $p < 0.01$)
AEGEAN [36]	Perioperative	802	67%	71%	81%	17% vs. 4%	0.68 [0.53–0.88, $p < 0.01$]	NR
NEOTORCH [37]	Perioperative	501	66%	100%	82%	25% vs. 1.0%	0.40 [0.28–0.57, $p < 0.01$]	0.62 [0.38–1.0, $p = 0.05$]
RATIONALE 315 [38]	Perioperative	453	58%	58%	84%	41% vs. 5.7%	0.56 [0.40–0.79, $p < 0.01$]	0.62 [0.39–0.98, $p = 0.02$]

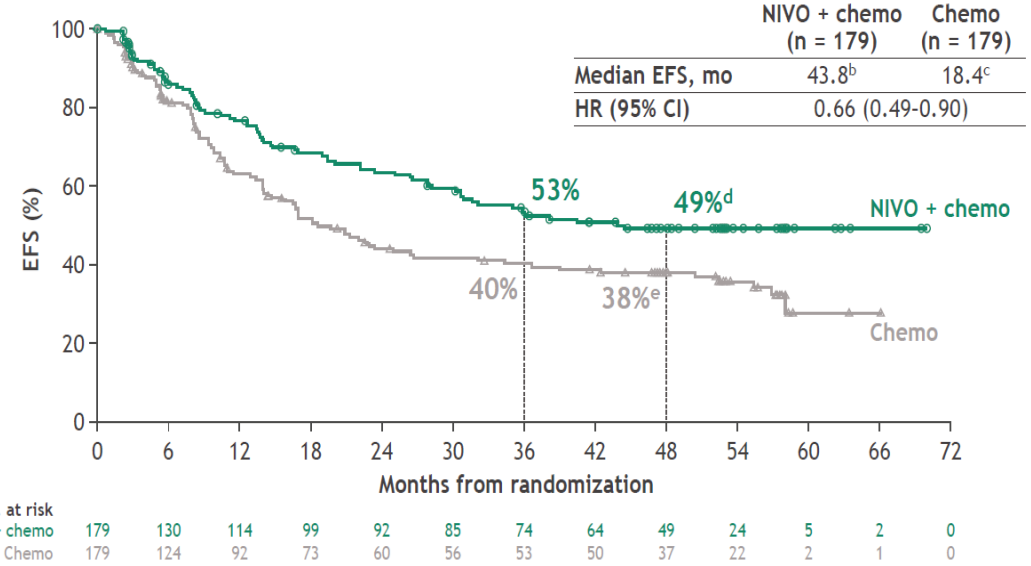
✚ Nivolumab x 3

ESTADIO III → **QT** → **CIRUGÍA**

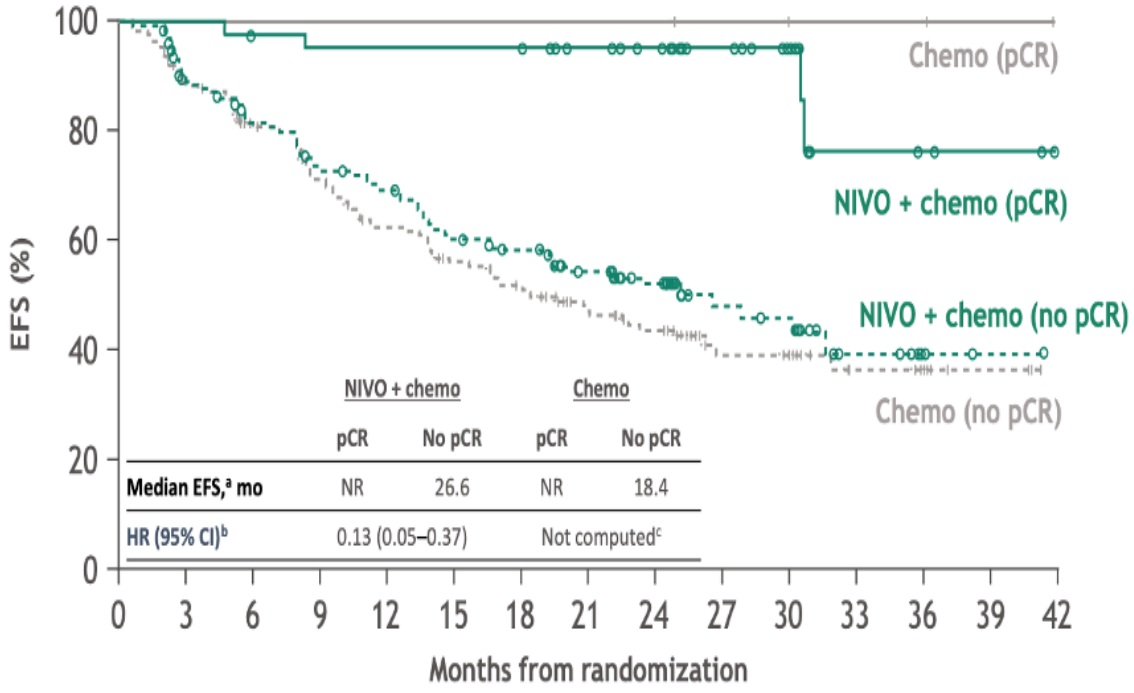
CHECKMATE 816

EFS: 4-year update[a]

- In CheckMate 816, neoadjuvant NIVO + chemo significantly improved the primary endpoints of EFS and pCR vs chemo and demonstrated a favorable OS trend in patients with resectable NSCLC[1,2]



	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS, mo	43.8[b]	18.4[c]
HR (95% CI)	0.66 (0.49-0.90)	

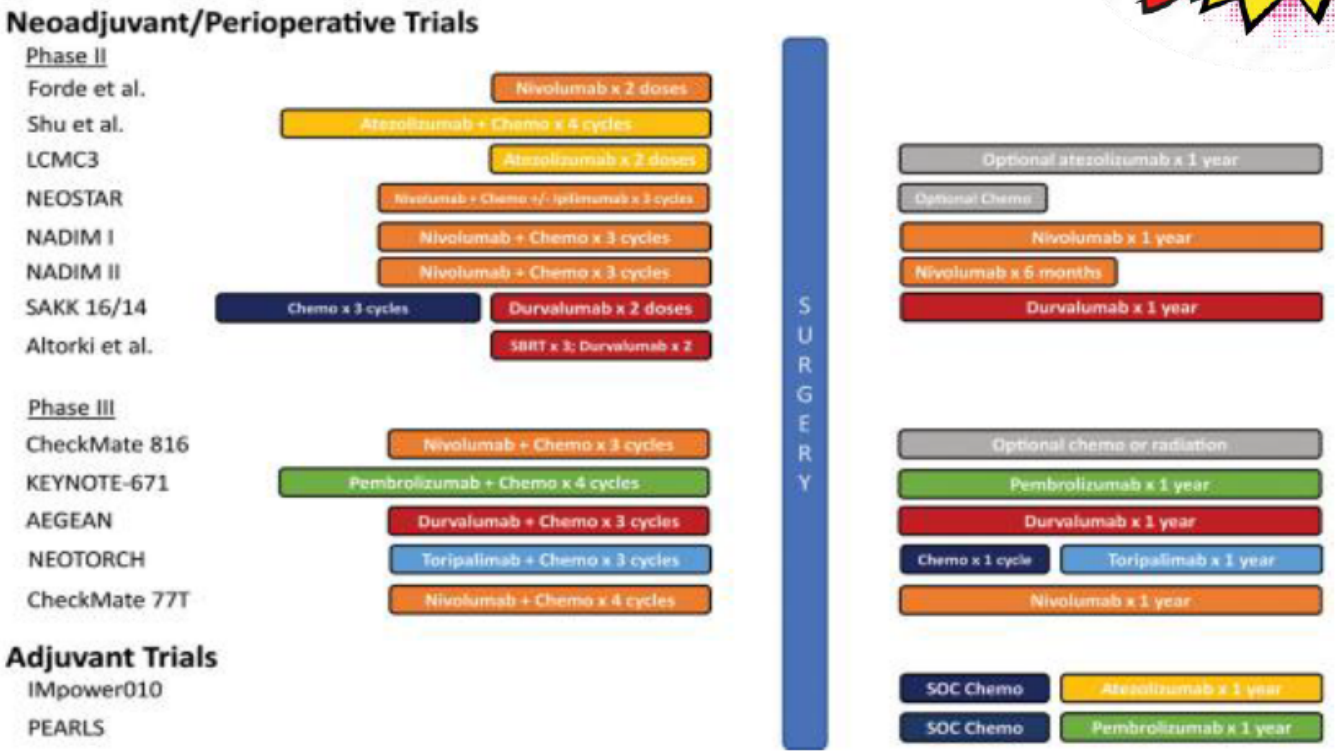


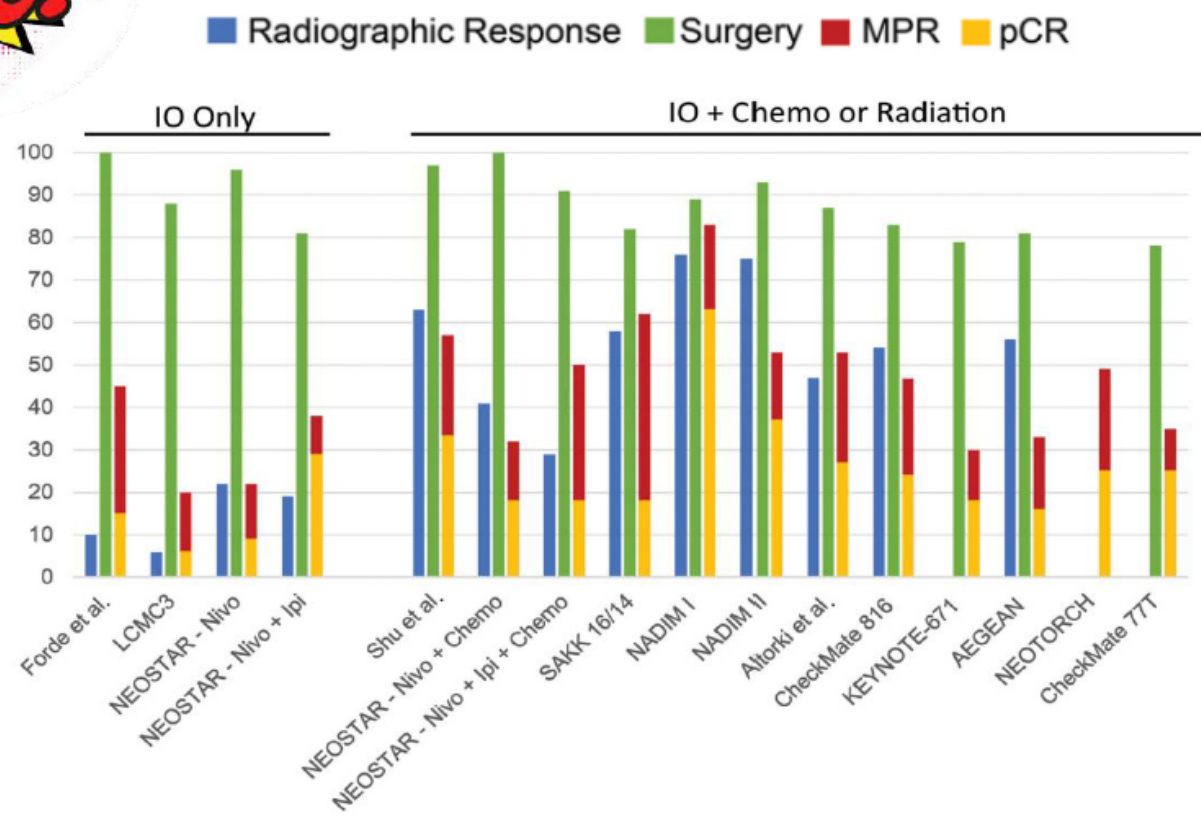
	NIVO + chemo		Chemo	
	pCR	No pCR	pCR	No pCR
Median EFS,[a] mo	NR	26.6	NR	18.4
HR (95% CI)[b]	0.13 (0.05–0.37)		Not computed[c]	

Database lock date, February 23, 2024; minimum/median follow-up, 49.1/57.6 months.

[a]Exploratory analysis. [b-e]95% CI: [b]30.6-NR; [c]14.0-26.7; [d]41-57; [e]30-46. 1. Forde PM, et al. *N Engl J Med* 2022;386:1973-1985. 2. Forde PM, et al. Oral presentation at European Lung Cancer Congress (ELCC); March 29-April 1, 2023; Copenhagen, Denmark. Presentation 840.

Neoadjuvant and perioperative chemo-IO





Pathological Complete Response (pCR) after chemo-IO -17% to 25%

5-10 x increase in pCR with neo-adjuvant chemo-immunotherapy vs chemo

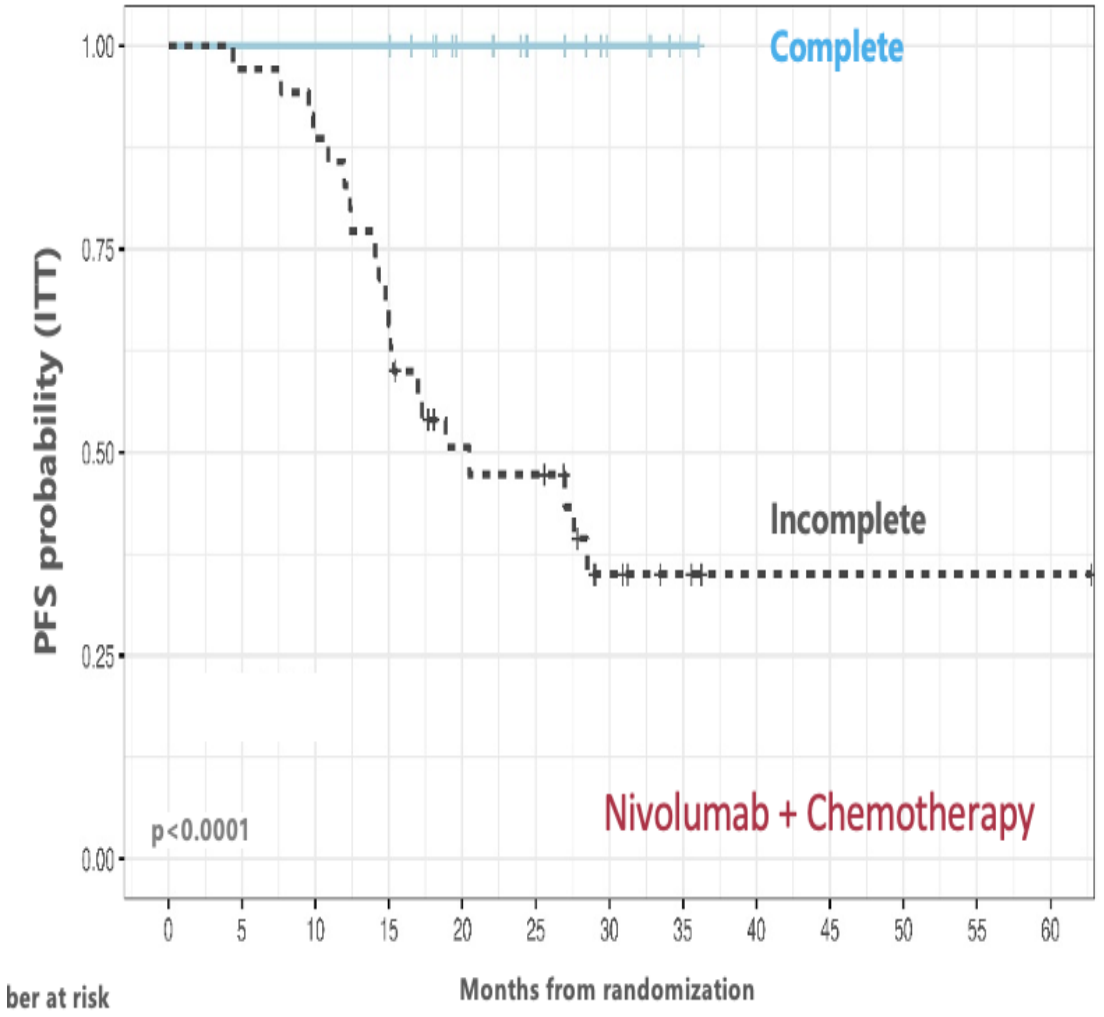
Neoadjuvant and adjuvant chemo-IO → standard of care in resectable stage III NSCLC

Dunne. Ann Thorac Surg 2024

Respuesta Patológica completa (PCR)

Complete Pathologic Response (PCR)	Ch-ImmunoT	Placebo arm
NADIM II Stage IIIA/B	36.8 %	6.9%
Neotorch Stage IIIA/B	24.8%	1%
CM 816	24.0%	2.2%
77T	25.3%	4.7%
KN671	18.1%	4%
AEGEAN	17.2%	4.3%
Lei	32.6%	8.9%
RATIONALE 315	40.7%	5.7%
Total	**27.4% (17.2-40.7%)**	**4.6% (1-8.9%)**

PCR in neoadjuvant/perioperative randomized trials



*Provencio M NEJM 2023; Lu S Oral-ASCO 2023; Provencio M Oral-ESMO 2023; Cascone T Oral-ESMO 2023 *18 mo; Wakelee H NEJM 2023; Lei JAMA Onco 2023; Yue D ESMO 2024*

ADYUVANCIA

- **Ib – II → 53.9% y 70%**
- **IIIA → 46.1% y 30%**

ESTUDIO	N	mSEG	mSLE	SLE 2a (%)	SLE 3a (%)	HR	SG 3a (%)	SG 5a (%)	HR
IMPOWER 010	1005	45	NA vs 37.2	**71.4** vs 63.6	**57.9** vs 52.6	0.81	**82.1** vs 78.9	76.8 vs 67.5	0.71
PEARLS	1177	35	53.6 vs 42	**67** vs 59	**58** vs 50	0.76	**82** vs 80	NA	0.87
CHECKMATE816	358	41	NA vs 21	**65** vs 47	**57** vs 43	0.68	**85** vs 66%	NA	0.62

NEOADYUVANCIA

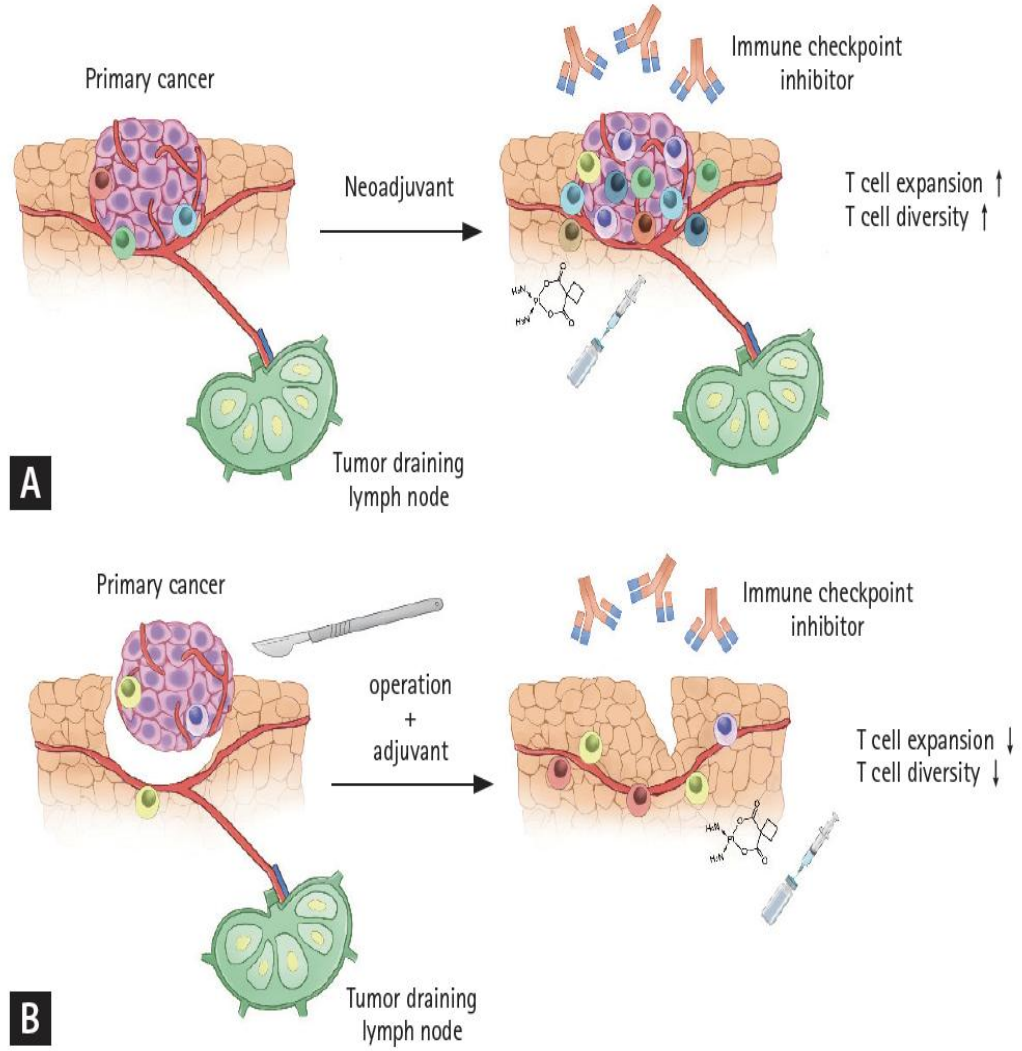
- **Ib – II → 36.3**
- **IIIA → 63.1**

Why do we use neoadjuvant treatment?

Neoadjuvant CTx-IO treatment

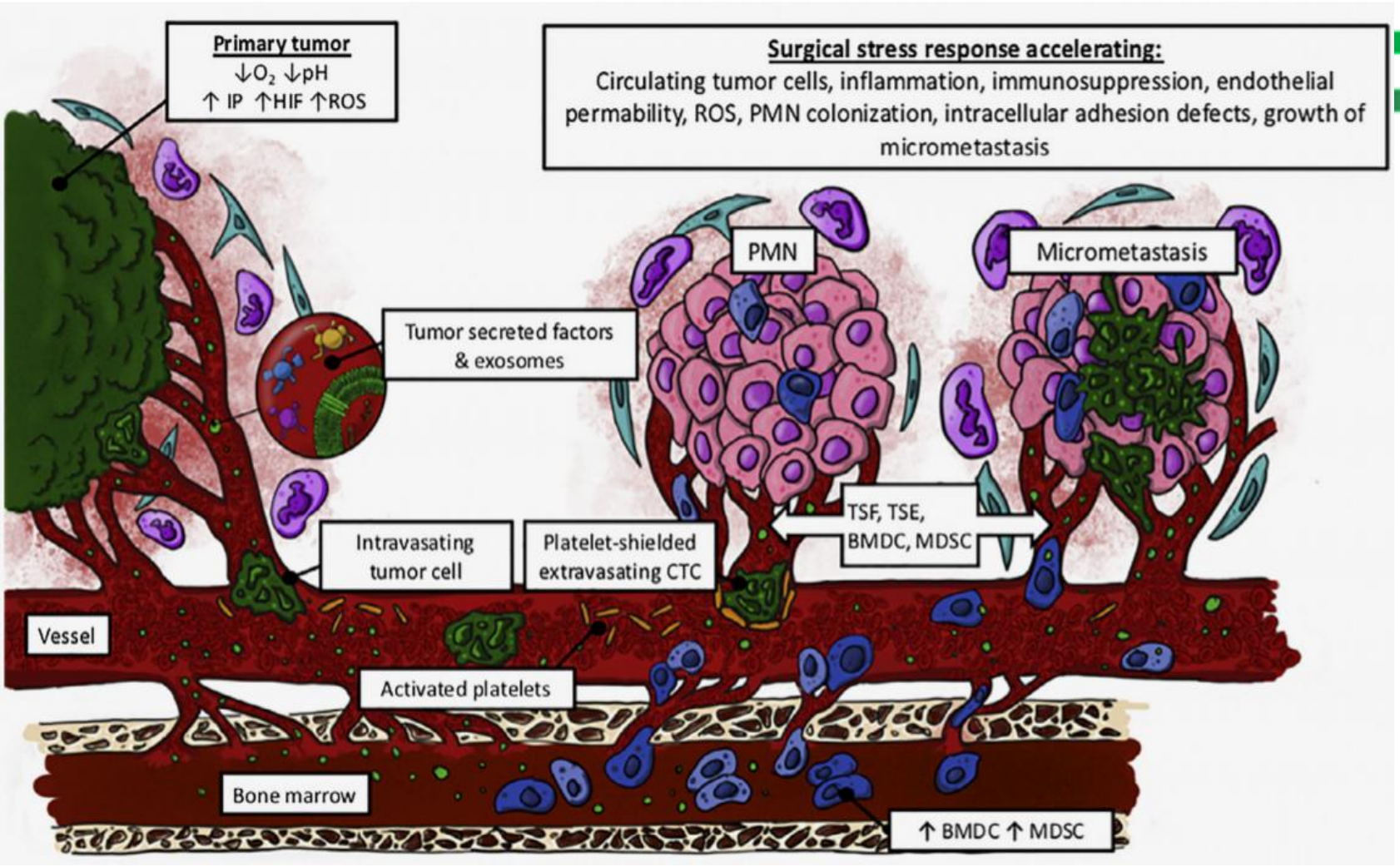
→ Surgery

- Front-line attack of micrometastases
- Better compliance
- Achieve downstaging
- Improved resectability
- Increase R0
- Better priming of immune system
- No significant clonal evolution
- Integrity of immune system
- Presence of whole tumour allows a larger repertoire of tumc antigen exposure
- Allows the study of tumour biology and treatment effects



CTx, chemotherapy; IO, immunotherapy

Kyeom J KJIL 2023

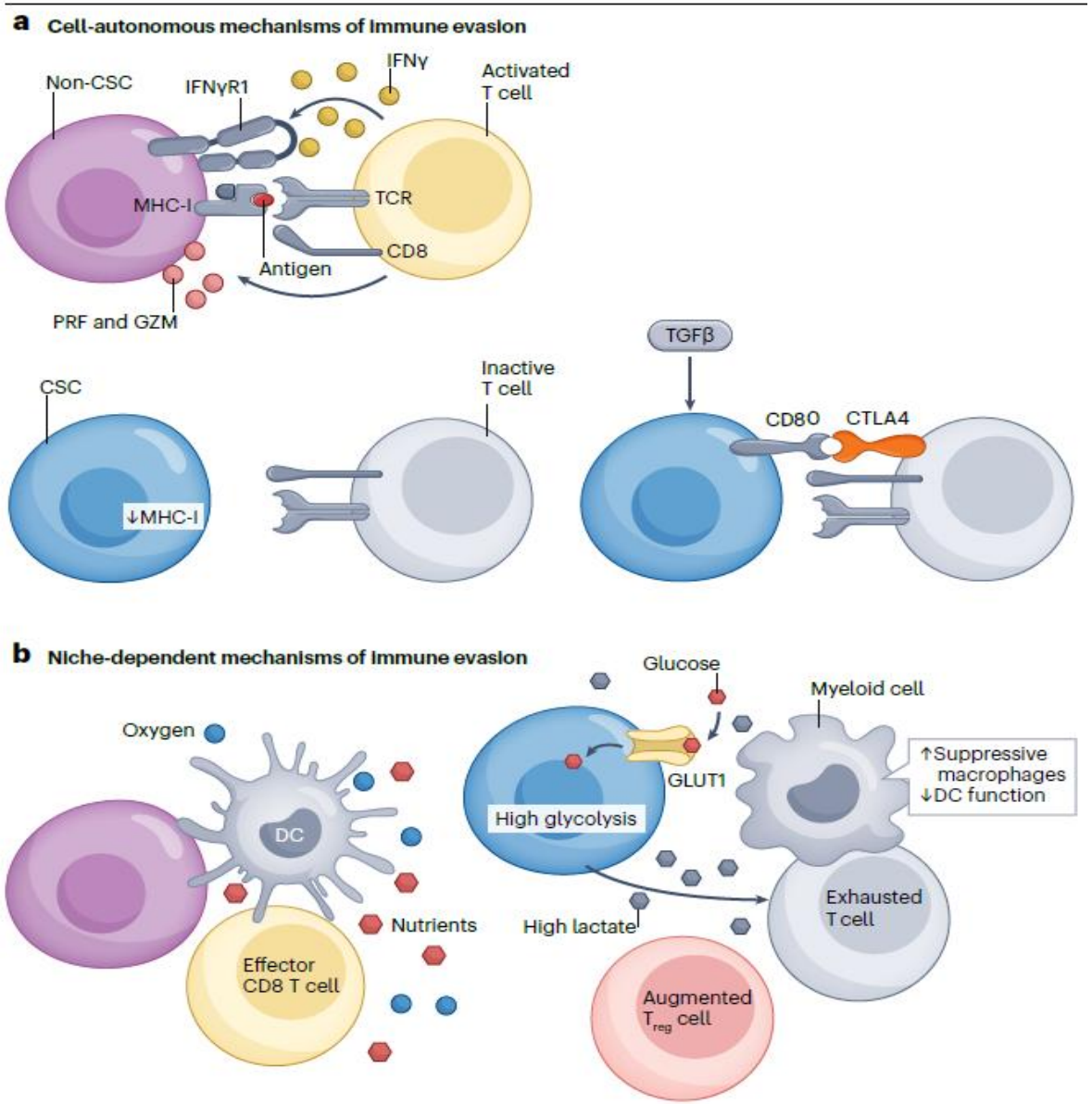


Establishment of premetastatic niches and micrometastases may be accelerated by surgery

.- Establishment of premetastatic niches and micrometastases may be accelerated by surgery. Within the primary tumor, hypoxia, acidity, lack of nutrition and a high interstitial pressure promote tumor cells to migrate and intravasate.
.- Tumor-secreted factors and tumor-secreted exosomes mobilize bone marrow-derived cells and myeloid suppressor cells, transforming the local microenvironment in the predestined premetastatic niche to receive and support incoming tumor cells. Surgery, inflammation and subsequent immunosuppression may increase the number and survival of circulating and disseminated tumor cells, and activated platelets may protect them from killer cells and the physics of circulation.

Raskov H, Orhan A, Salanti A, Gögenur I. Premetastatic niches, exosomes and circulating tumor cells: Early mechanisms of tumor dissemination and the relation to surgery. *Int J Cancer*. 2020;146(12):3244-3255. doi:10.1002/ijc.32820

Cancer stem cells (CSCs) exploit a combination of cellintrinsic and cell-extrinsic mechanisms to evade T cell immunity

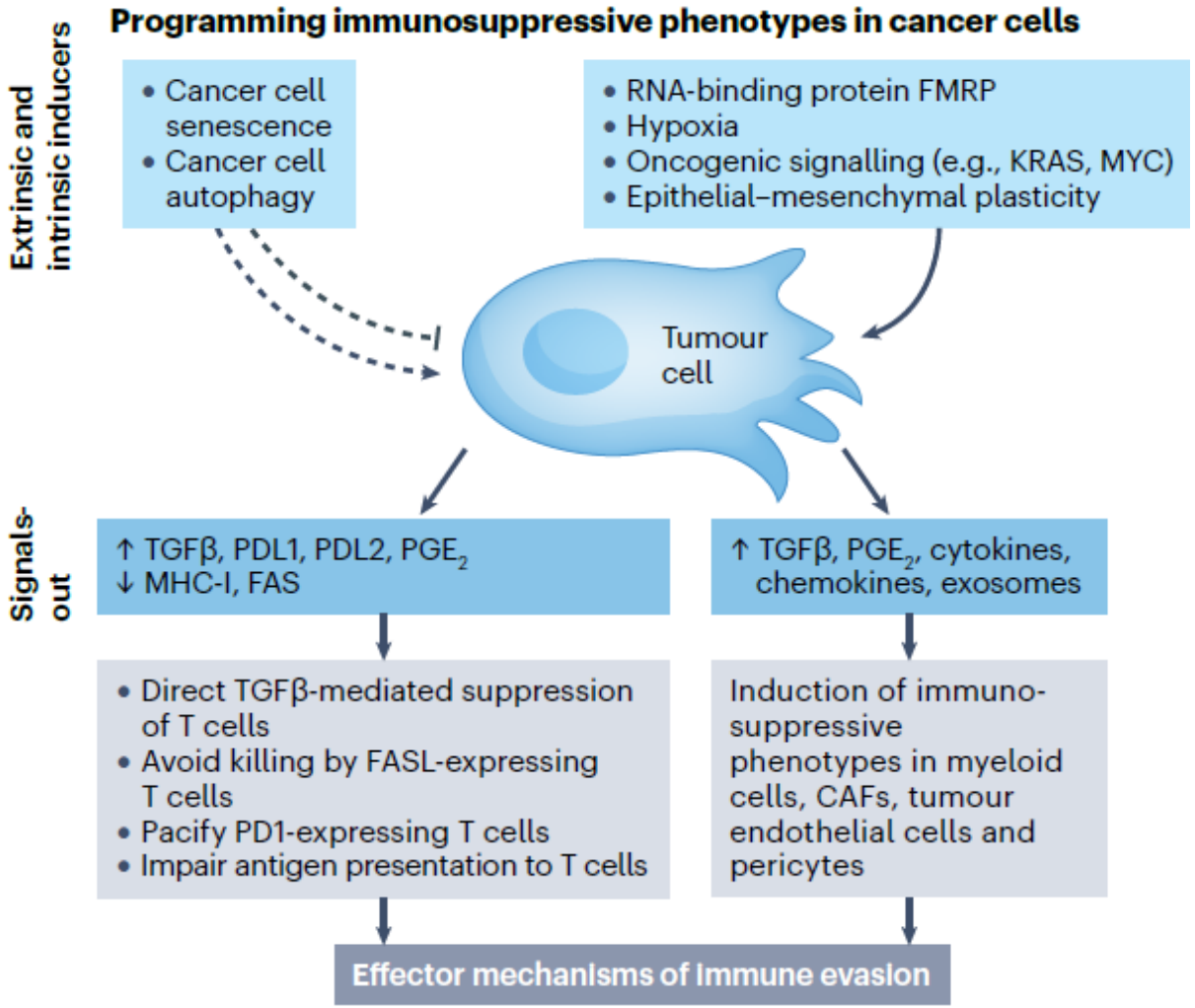


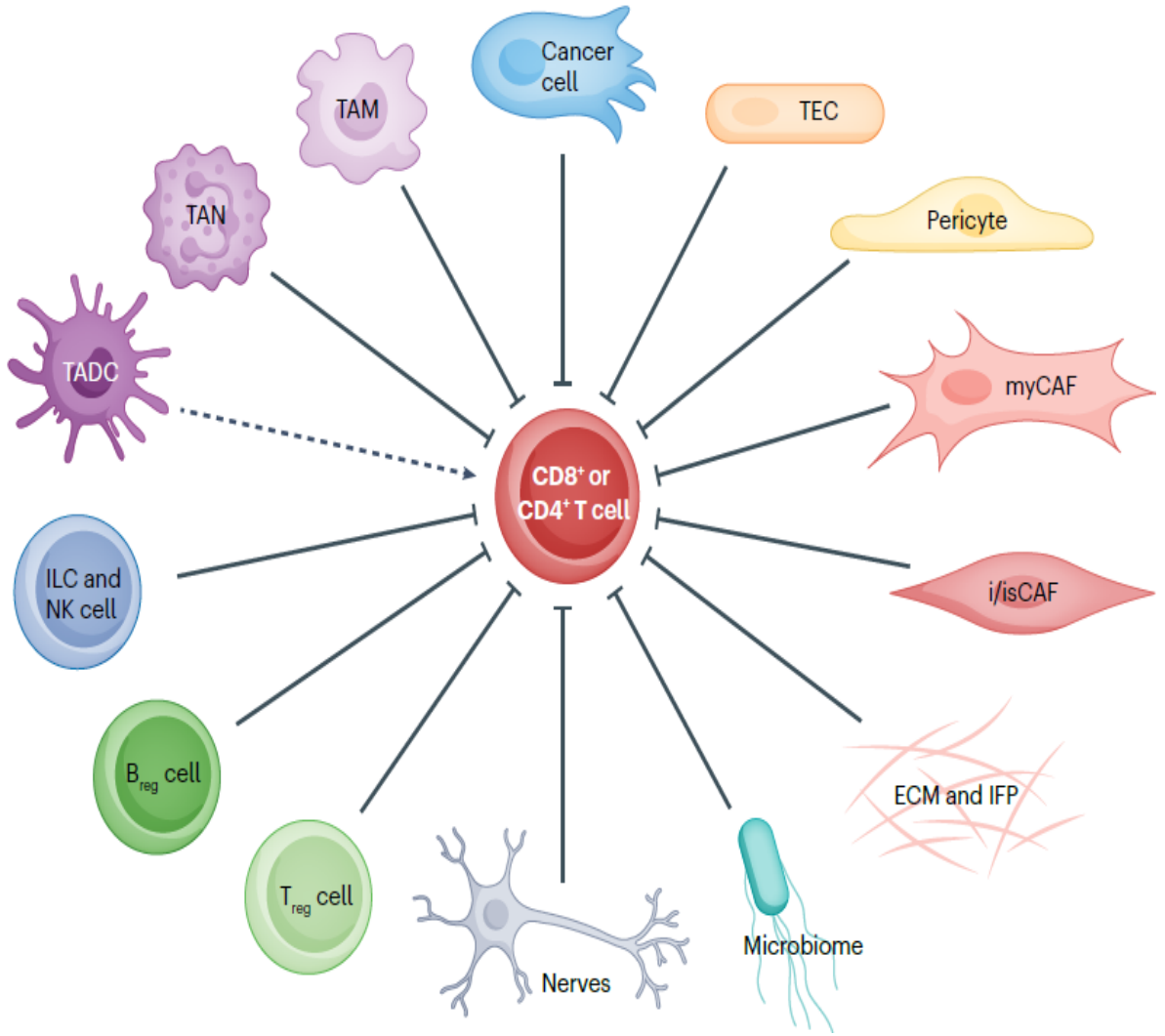
Ligand	Resistance mechanism	Tumour cell markers
PDL1 upregulation	Suppresses T cells	$CD44^{+}ALDH1^{+}$
		MYC^{HI}
CD80 upregulation	Suppresses T cells	TGFβ-responding $CD44^{+}CD34^{+}$
		$p53^{HI}$
CD86 upregulation	Increases levels of regulatory T cells	$ABCB5^{+}$
B7-H3 upregulation	Suppresses T cells	$BMI1^{+}$
B7x upregulation	Suppresses T cells	$SOX9^{HI}K8^{+}K14^{+}$
CD200 upregulation	Suppresses T cells	$CD44^{+}CD24^{-}$
		$CD133^{+}$
		$CD133^{+}$
CD59 upregulation	Blocks the complement system	$CD44^{+}CD24^{-}$
MIF upregulation	Modulates MDSCs	$CD133^{+}SOX2^{+}$
Periostin upregulation	Recruits TAMs	$SOX2^{+}$
WISP1 upregulation	Promotes TAM survival	$CD133^{+}CD15^{+}$
TAP1 downregulation	Reduces T cell killing	$ALDH1^{HI}$
TLR4 downregulation	Reduces innate stimulation	$SOX2^{HI}OCT4^{HI}$
MICA or MICB downregulation	Reduces natural killer cell killing	$ALDH1^{HI}$

ABCB5, ATP-binding cassette subfamily B member 5; ALDH1, aldehyde dehydrogenase 1; CSC, cancer stem cell; MDSC, myeloid-derived sequence; MIF, migration inhibitory factor; TAM, tumour-associated macrophage; TAP1, transporters associated with antigen processing receptor 4; WISP1, WNT-induced signalling protein 1.

Judisth Agudo. Nature Rev Cancer 2025

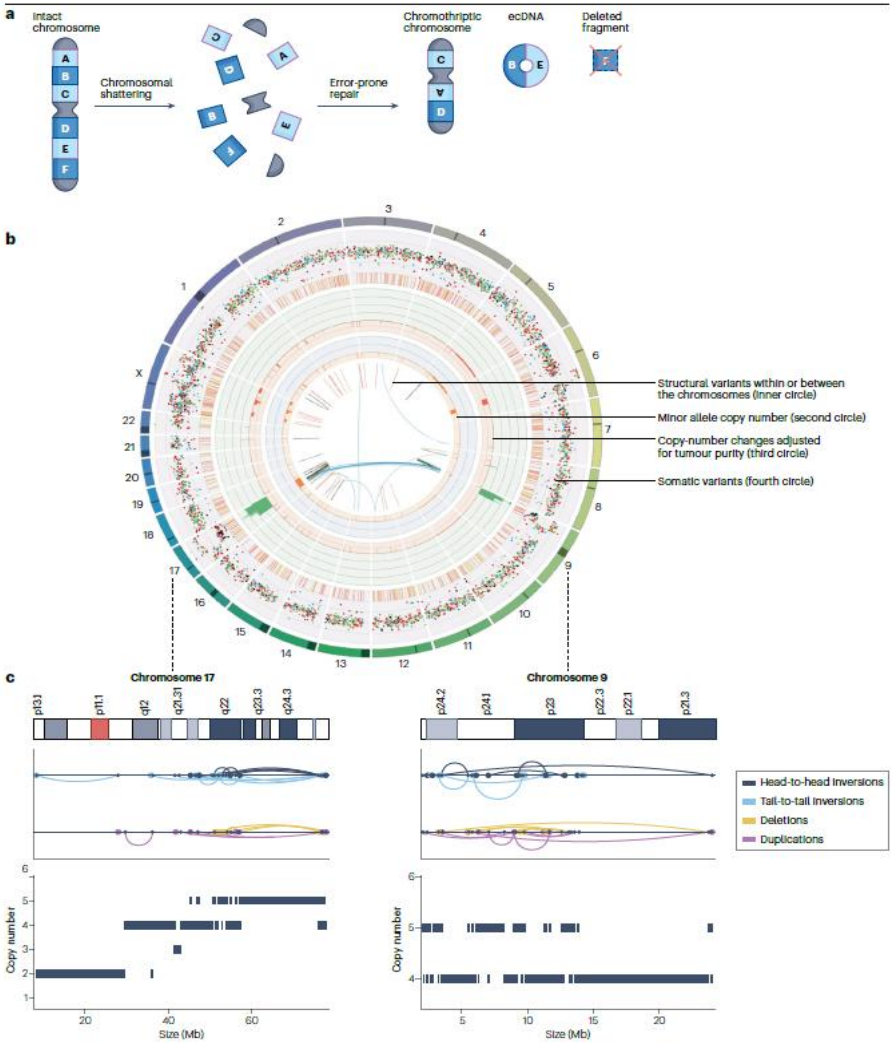
Cancer stem cell: Reprogramming: Convergent inducers and effectors of T cell paralysis in the tumour microenvironment

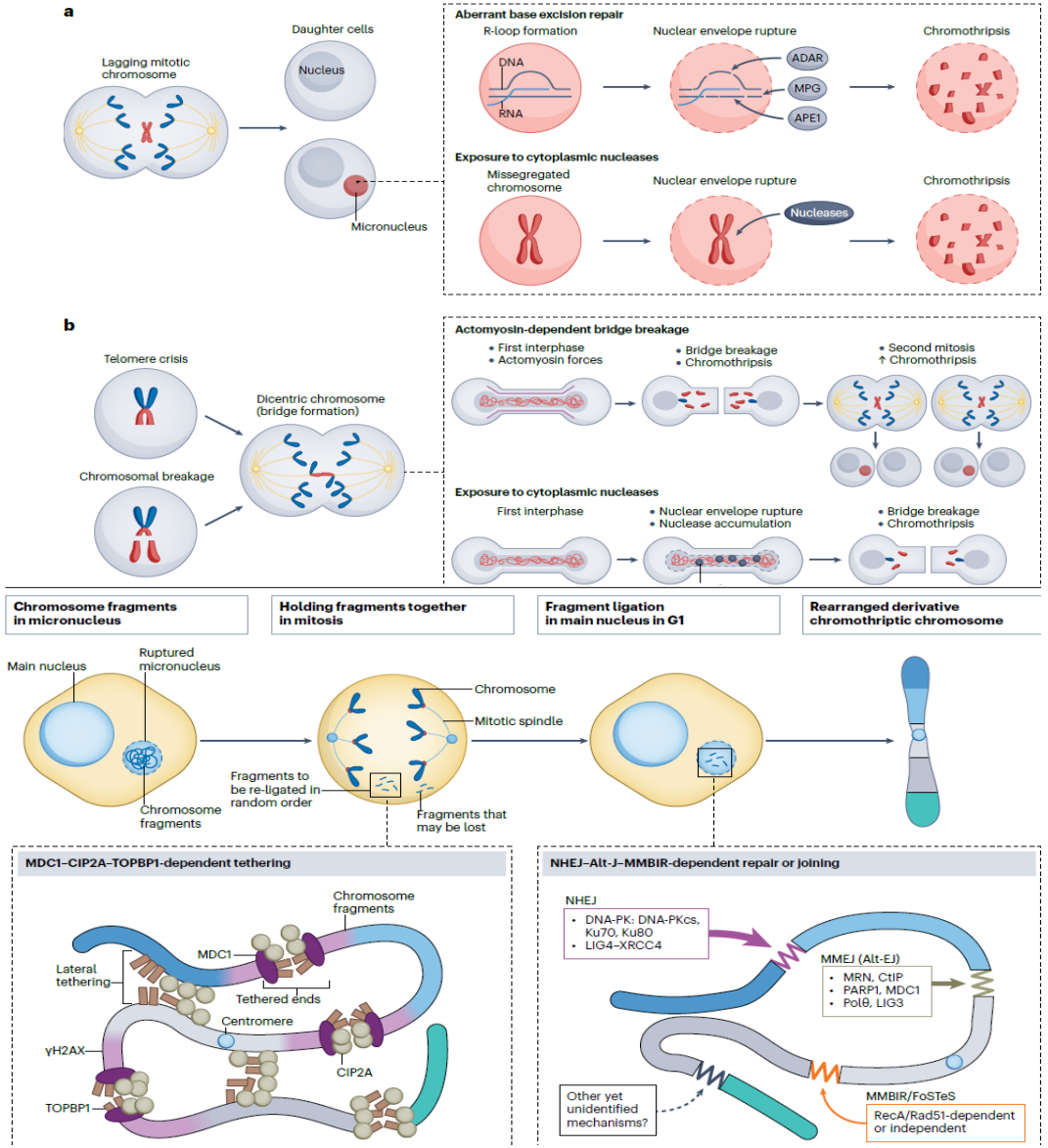




Douglas Hanahan. Nature Rev Cancer 2025

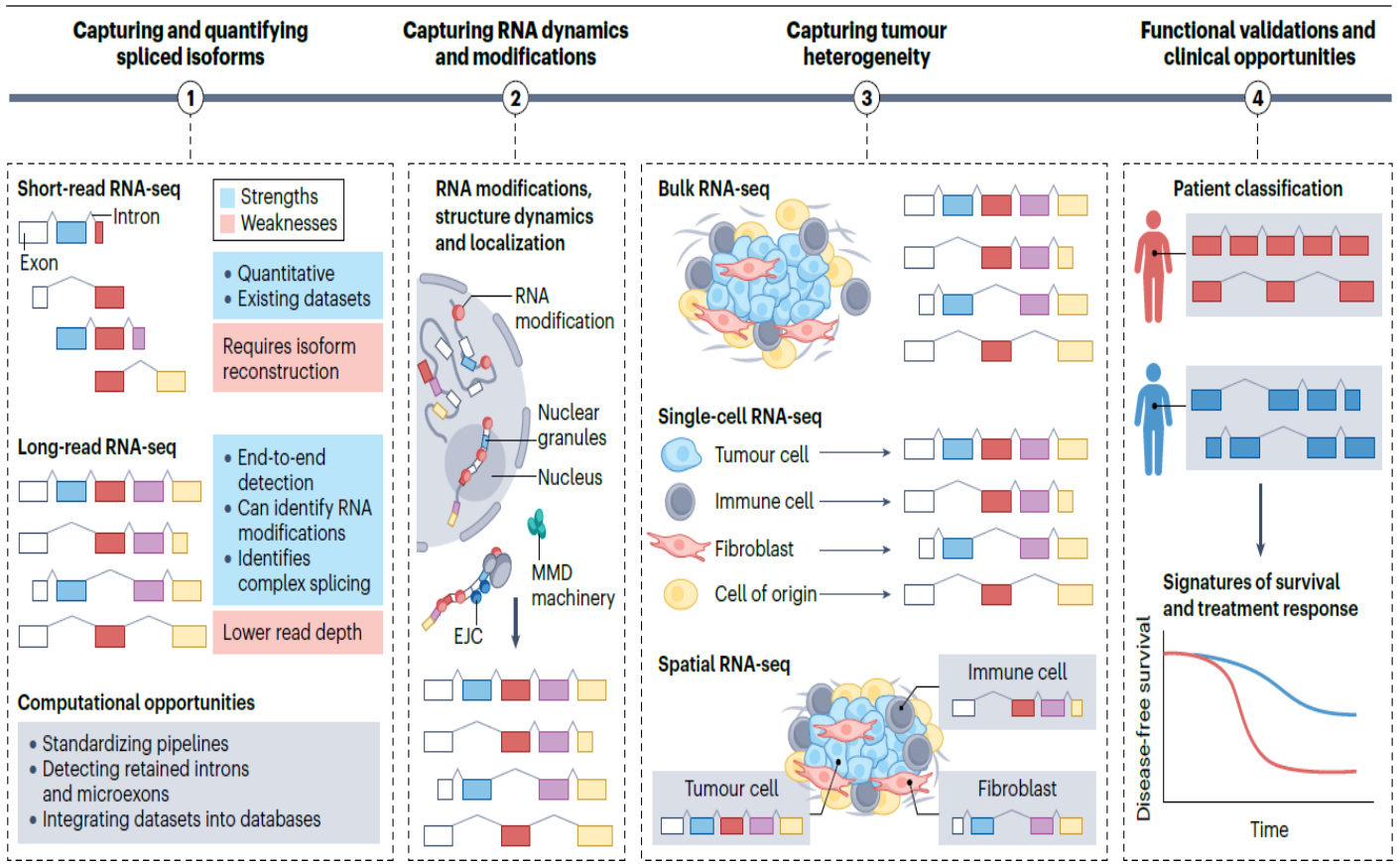
Inmunoterapia lo más precoz posible: Quimioterapia como fenómeno inductor de cromotripsis, y por tanto.. Aportación de ventajas evolutivas a las cél tumorales, incluida la inmunoresistencia…..” Nonetheless, many cancers evade immune detection by silencing cGAS–STING signalling wit Chromothripsis”

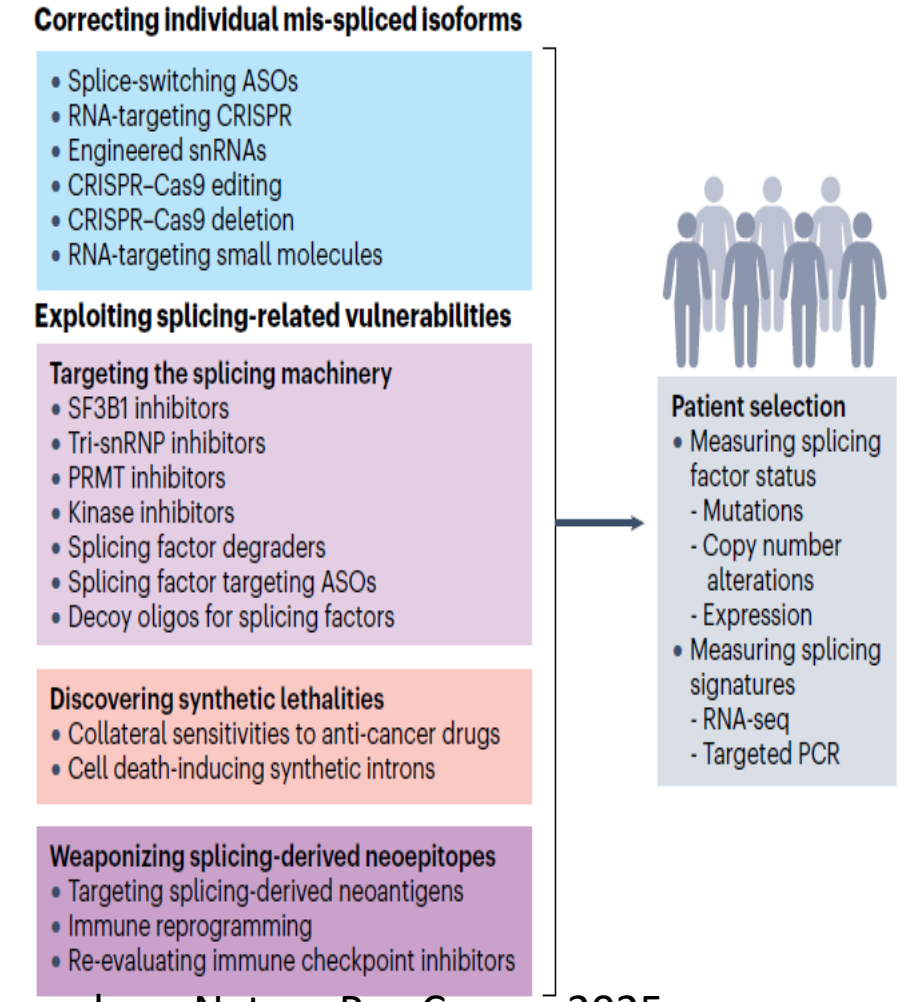




Milena Simovic-Lorenz. Nature Rev Cancer 2025

Inmunoterapia lo más precoz posible: Quimioterapia como fenómeno inductor de fenómenos re-splicing alternativos adaptativos, y por tanto.. Aportación de ventajas evolutivas a las cél tumorales, incluida la inmunoresistencia, al variar neoepitopos inmunogéticos “Steering research on mRNA splicing in cancer towards clinical translation”





Olga Anczukow. Nature Rev Cancer 2025

Neoadjuvant and perioperative P3 trials: Surgical resectability comparison

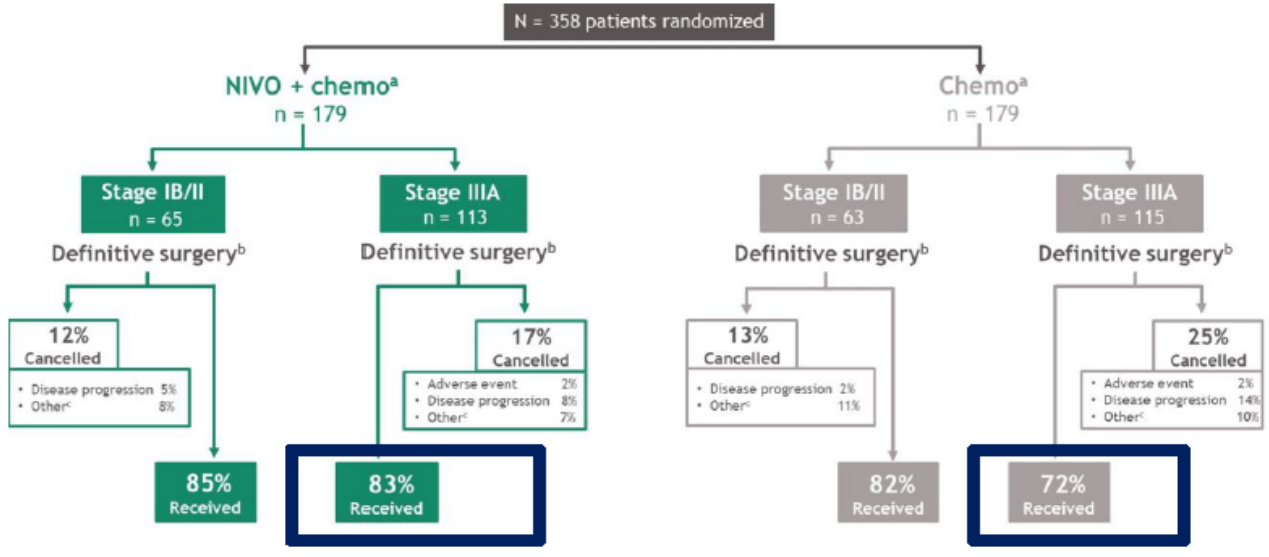
Neotorch[1]

	Toripalimab +Chemo (N=202)	Placebo + Chemo (N=202)
No surgery performed n(%)	36 (17.8)	54 (26.7)
Patient underwent surgery n(%)	166 (82.2)	148 (73.3)
R0 resection n(%*)	159 (95.8)	137 (92.6)
95% CI	91.5, 98.3	87.1, 96.2
Differences between arms	3.2	
95% CI	-2.0, 8.4	

AEGEAN[3]

Study phase*		D arm (N=366)	PBO arm (N=374)
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)

CheckMate 816[2]

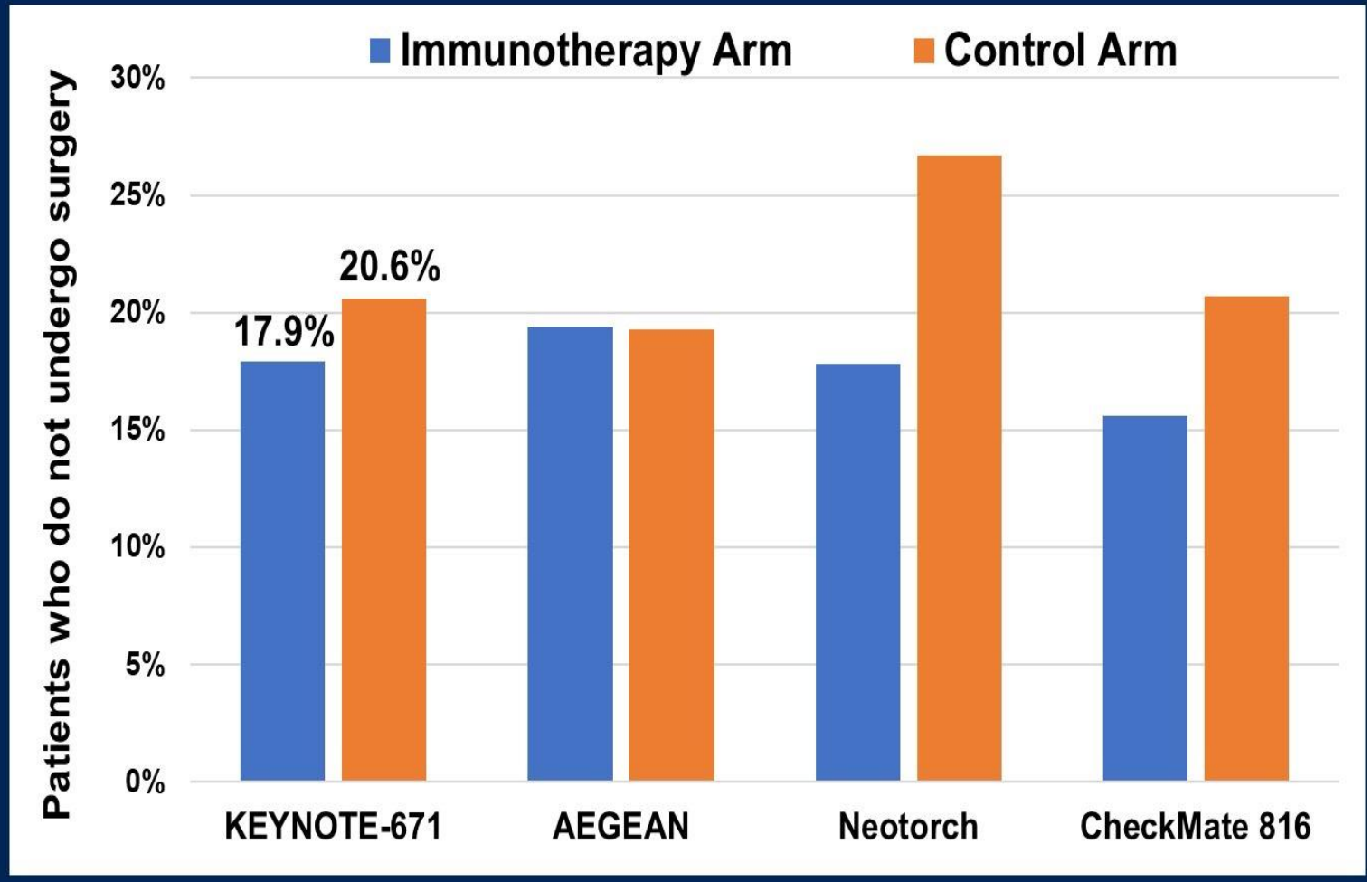


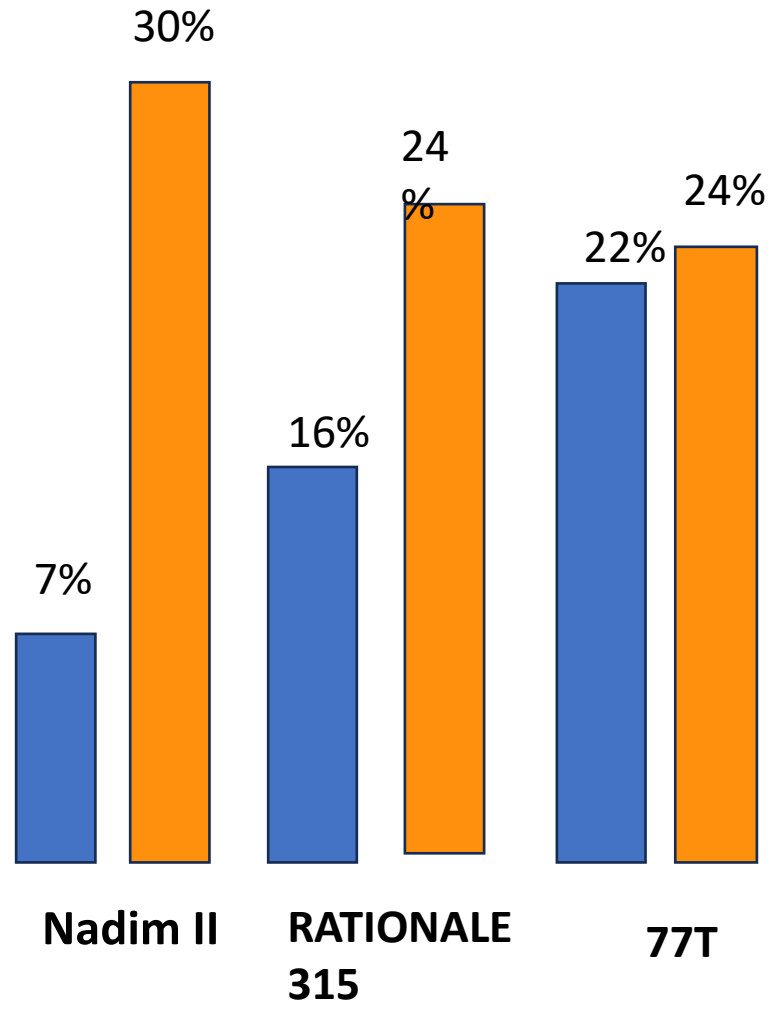
KEYNOTE 671[4]

	Pembro Arm	Placebo Arm
Underwent in-study surgery	325 (82.1%)	317 (79.4%)

1. Lu S, Oral Presentation ASCO Plenary Series 2023; 2. Spicer Oral Presentation ASCO Annual Meeting 2022; 3. Heymach JV, Oral Presentation AACR Annual Meeting 2023; 4. Wakelee H, Oral Presentation ASCO Annual Meeting 2023

Canceled Surgeries





Wakelee H, et al, ASCO Annual Meeting, 2023; Heymach JV, et al, AA

Eligibility - Checkmate 816

- Stage I, II, or IIIA NSCLC. Deemed to be surgically resectable before enrolment
- ECOG performance status 0-1
- Normal organ function. Adequate pulmonary function
- No immunodeficiency, immunosuppressive therapy, active autoimmune disease
- No clinically significant concurrent cancer

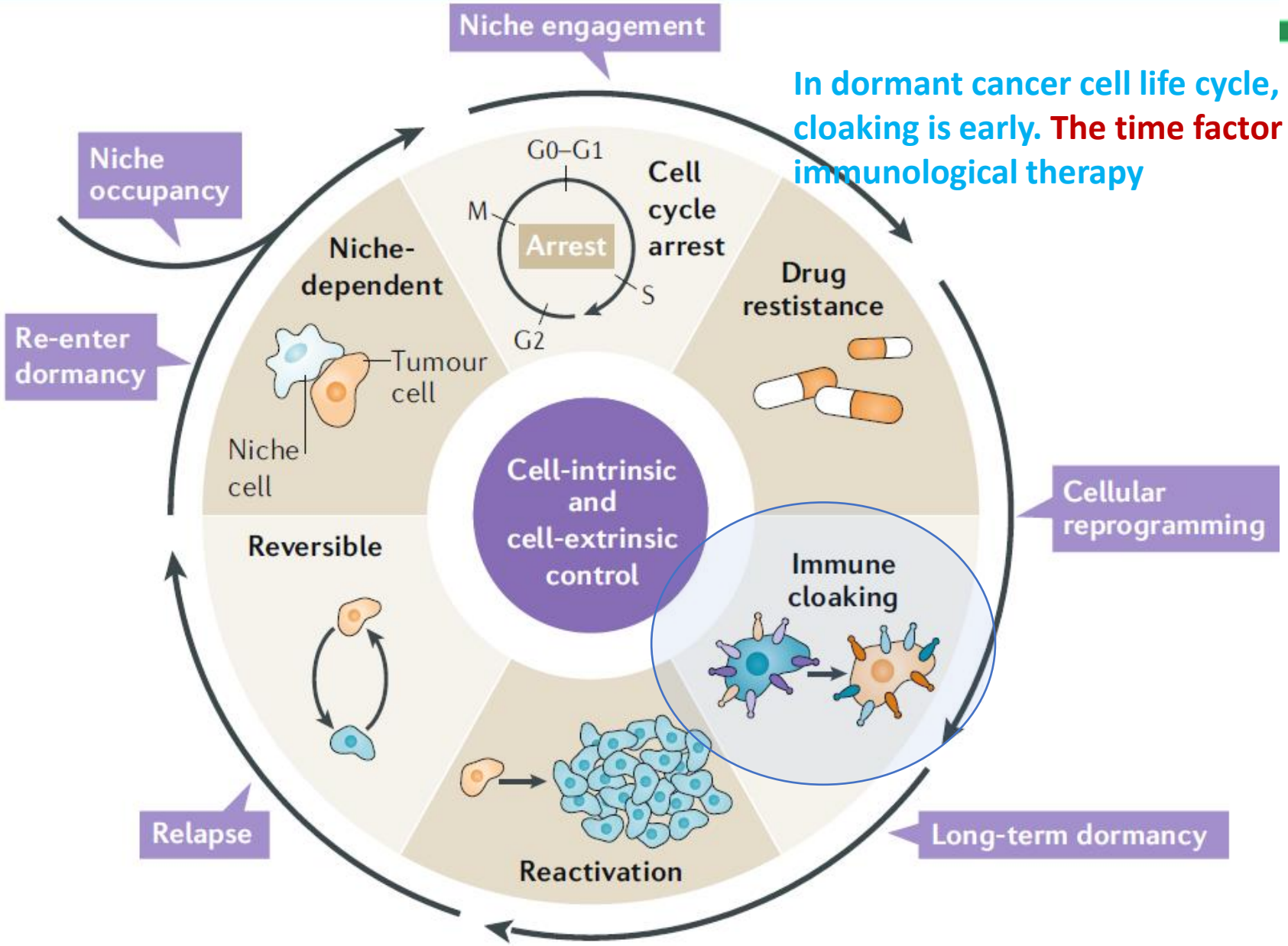
Very selected population - only 40-60% of the patients included in these trials are finally randomized
e.g. CM816 773→358 (46%); NEOTORCH 926→ 404 (43%)

Areas de controversia

.- Estadio II y IIIa resecables y operables: QT –inmuno Neoadyuvante vs QT-inmuno adyuvante

.- Estadio II y IIIa resecables y operables: QT –inmuno Neoadyuvante vs QT –inmuno Perioperatoria

.- Estadio IIIa/b potencialmente operables: QT –inmuno Neoadyuvante vs QT+RT radical y durvalumab



In dormant cancer cell life cycle, cellular reprogramming to immune cloaking is early. The time factor is key in the approach of an immunological therapy

Dormant cancer cell life cycle

.- Dormant cancer cells are subject to both cell- intrinsic control and cell- extrinsic control by the niche.

.- In the dormant cancer cell life cycle, cancer cells first occupy the niche. Upon engagement of cells with receptors in the niche, dormant cancer cells undergo G0–G1 cell cycle arrest and cellular reprogramming to adapt to the niche and survive.

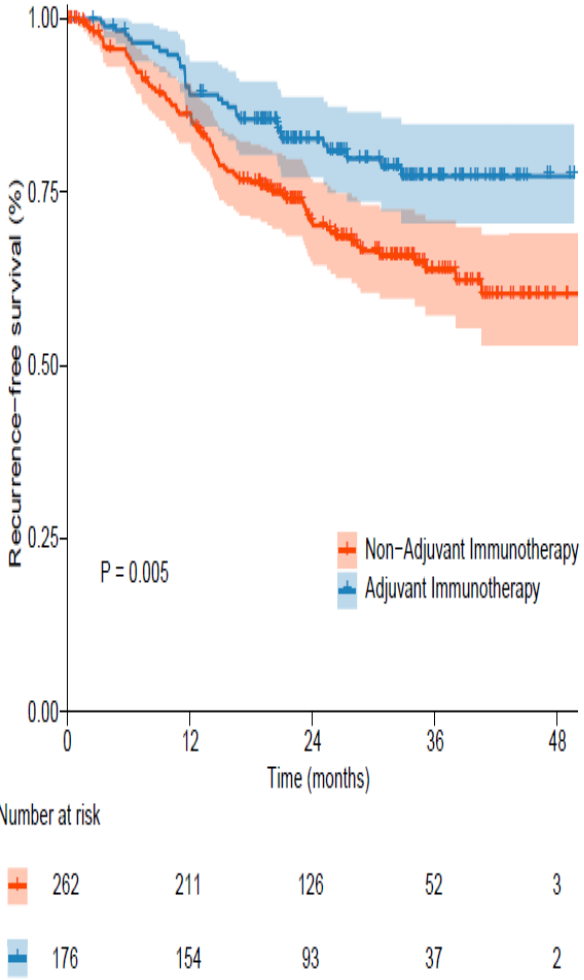
.- As part of this adaptation, dormant cancer cells activate immune evasion mechanisms, which we call **'immune cloaking',** to hide from the immune system to enable long- term dormancy.

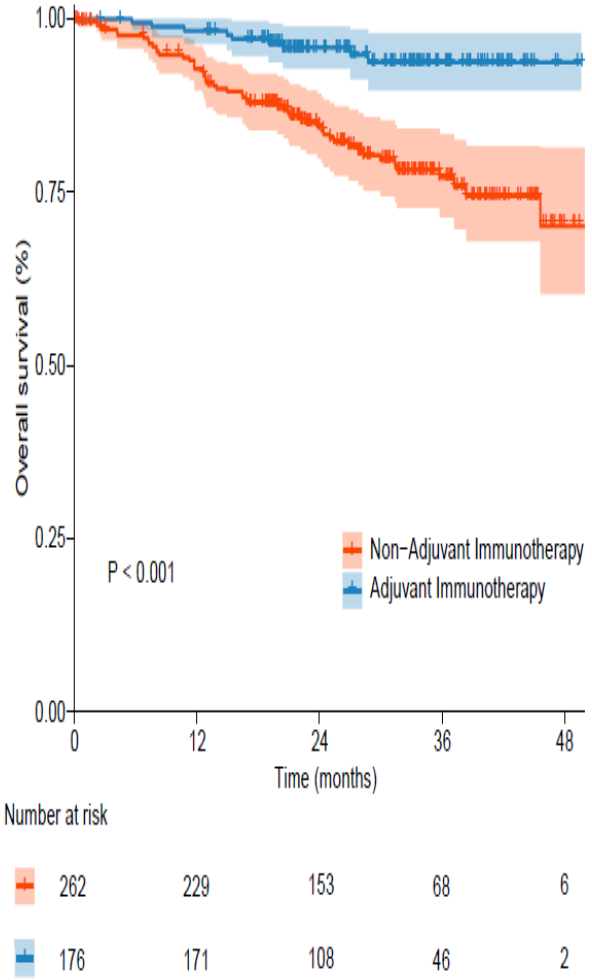
.- Subsequently, these dormant cancer cells are reactivated by changes in the niche, proliferate and manifest as metastatic relapse.

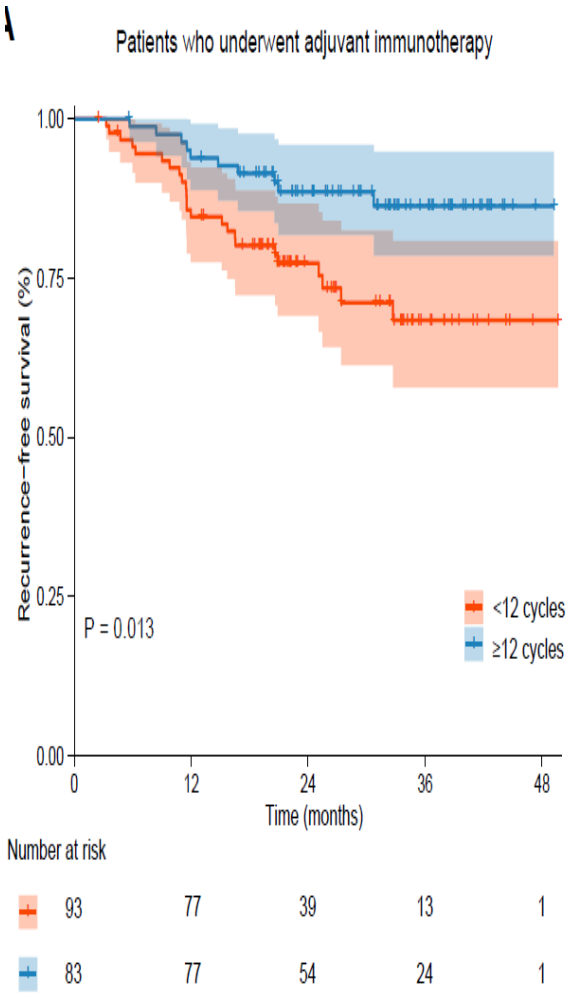
.- These stages are accompanied by hallmarks that define cancer cell dormancy: niche dependence; cell cycle arrest; drug resistance; immune cloaking; reactivation; and reversibility.

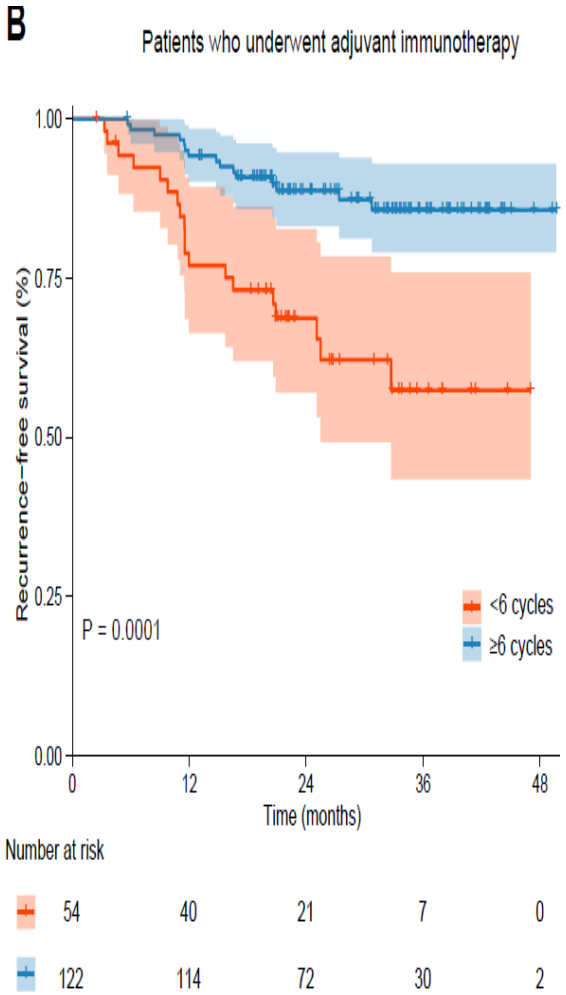
Phan TG, Croucher PI. The dormant cancer cell life cycle. *Nat Rev Cancer*. 2020;20(7):398-411. doi:10.1038/s41568-020-0263-0

Prognostic Impact of Adjuvant Immunotherapy in Patients With Resectable NSCLC After Neoadjuvant Chemoimmunotherapy: A Brief Report





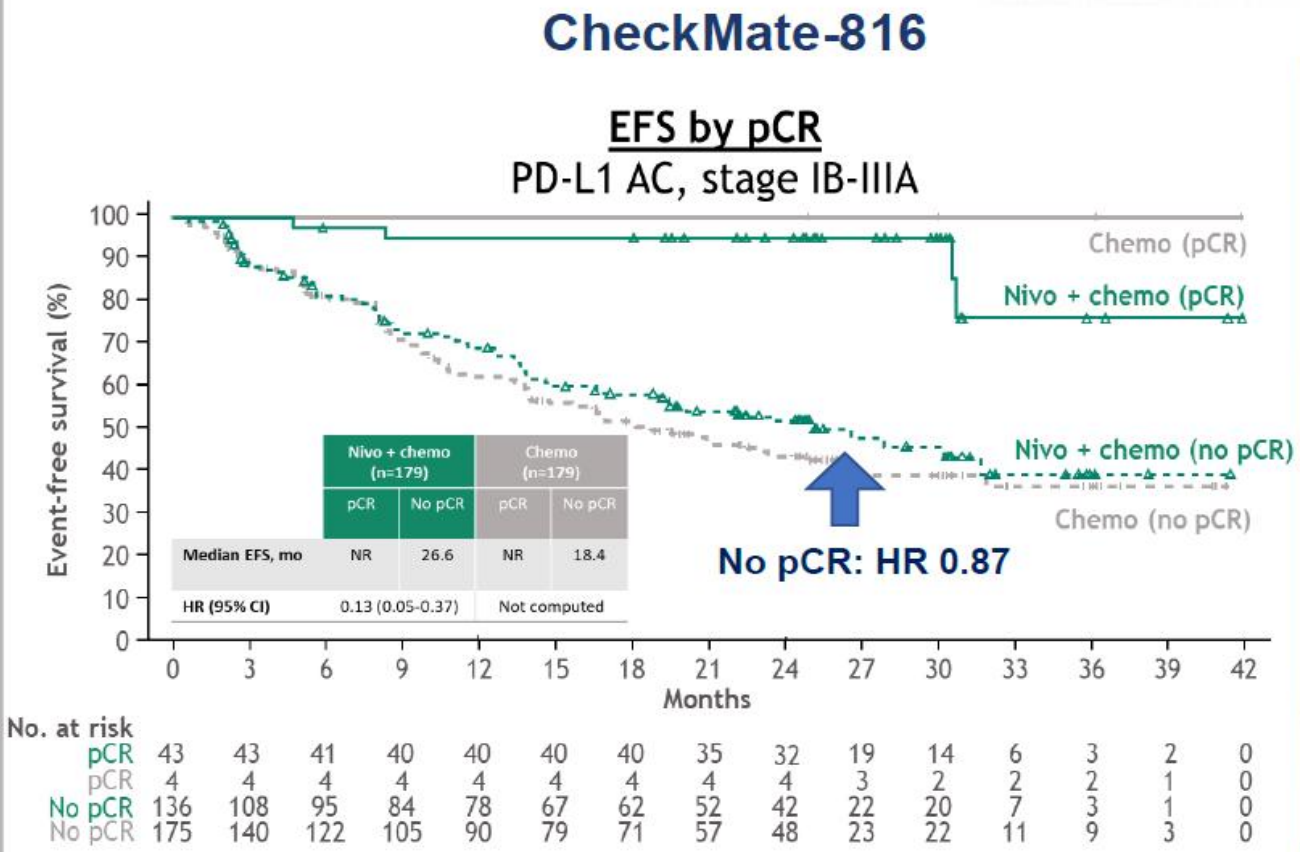




Yichen Dong, et al. JTO 2024

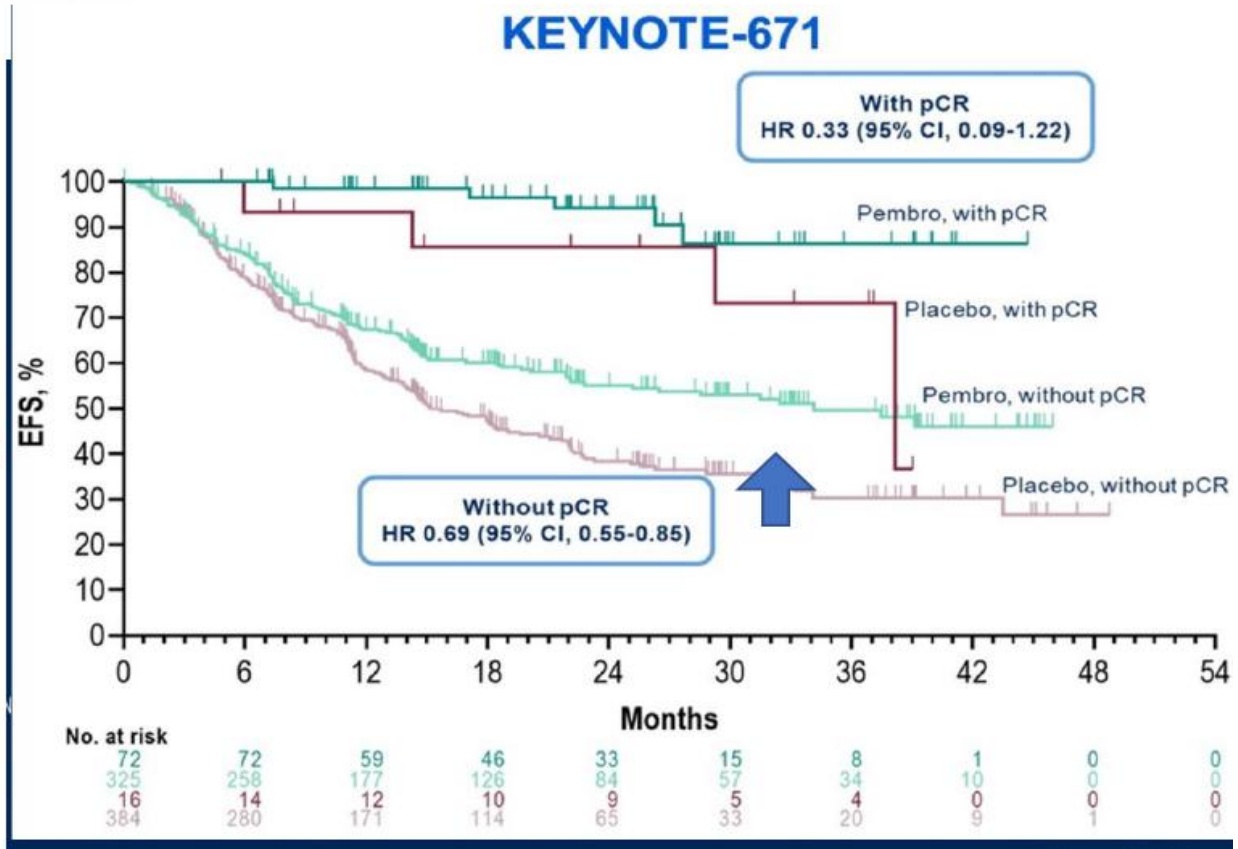
EFS benefit by pCR: Is the adjuvant ICI component needed following neoadjuvant chemo-ICI therapy?

CheckMate-816



Forde PM et al. *N Engl J Med*. 2022

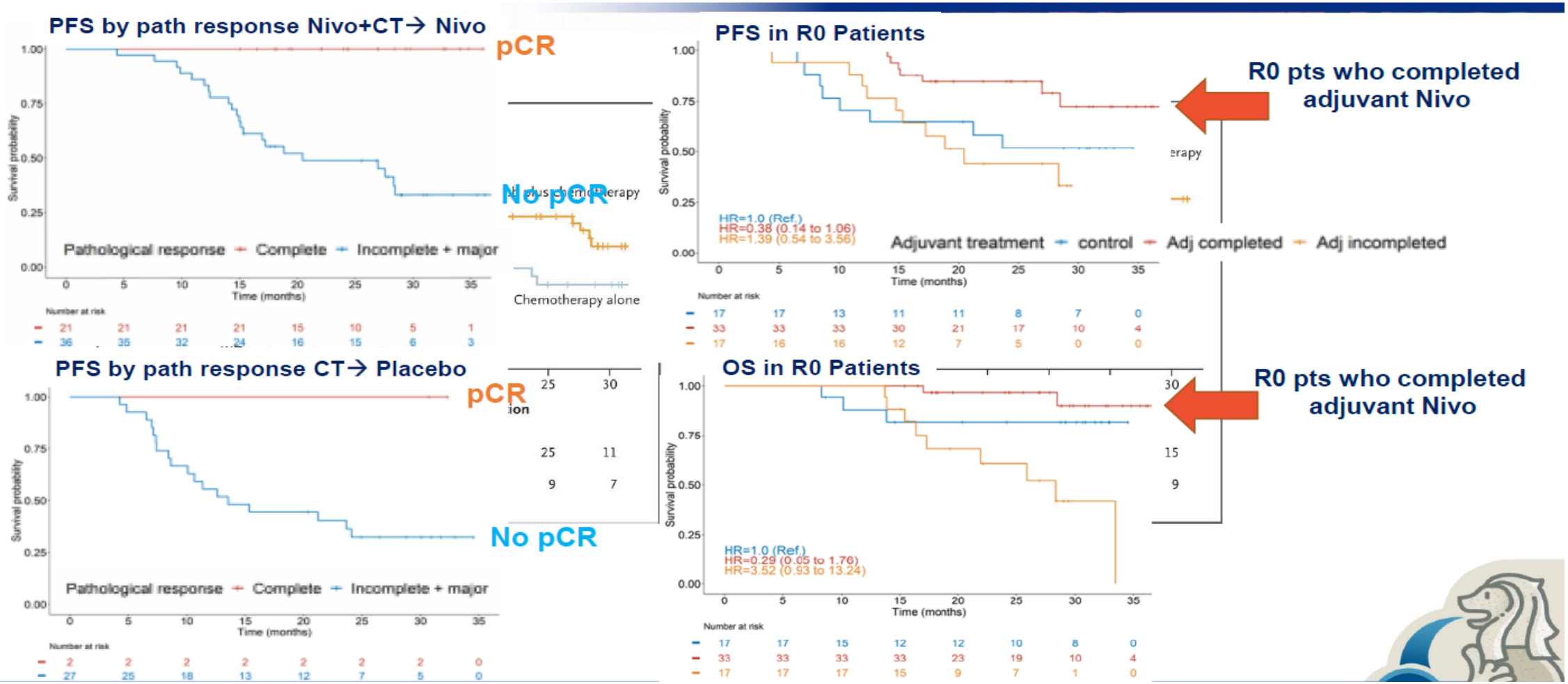
KEYNOTE-671



Lu S, Oral Presentation ASCO/Engl J Med 2023

Wakelee H et al. *N Engl J Med* 2023

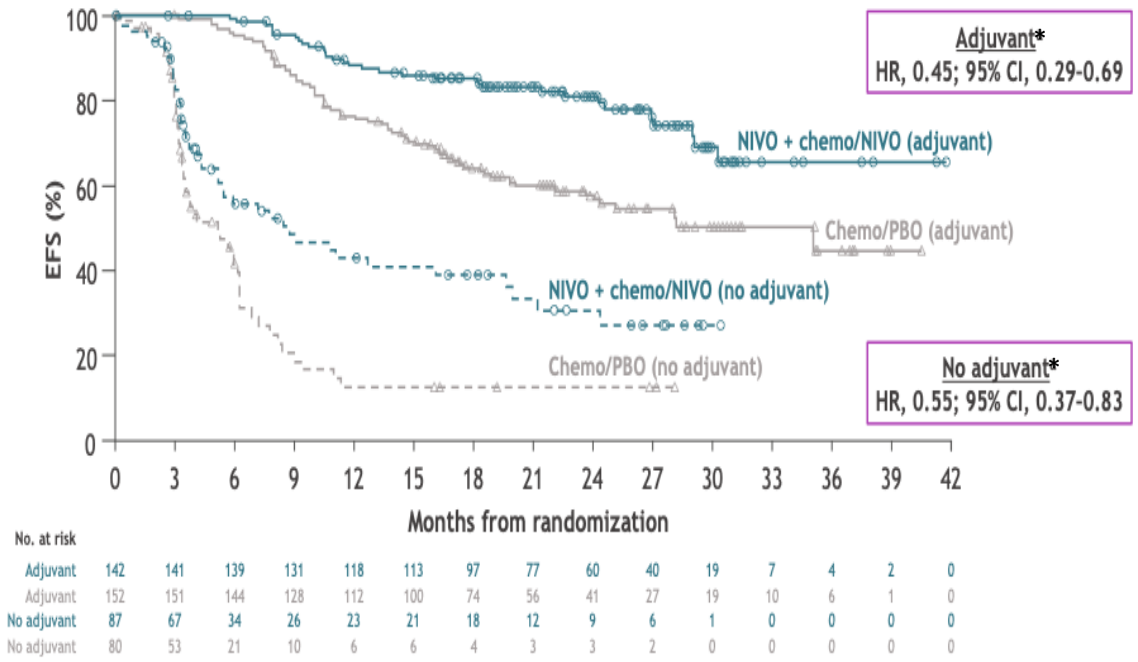
NADIM 2: Neoadjuvant Nivo + CT followed by 6 months of adjuvant Nivo in stage III NSCLC (AJCC 8th)



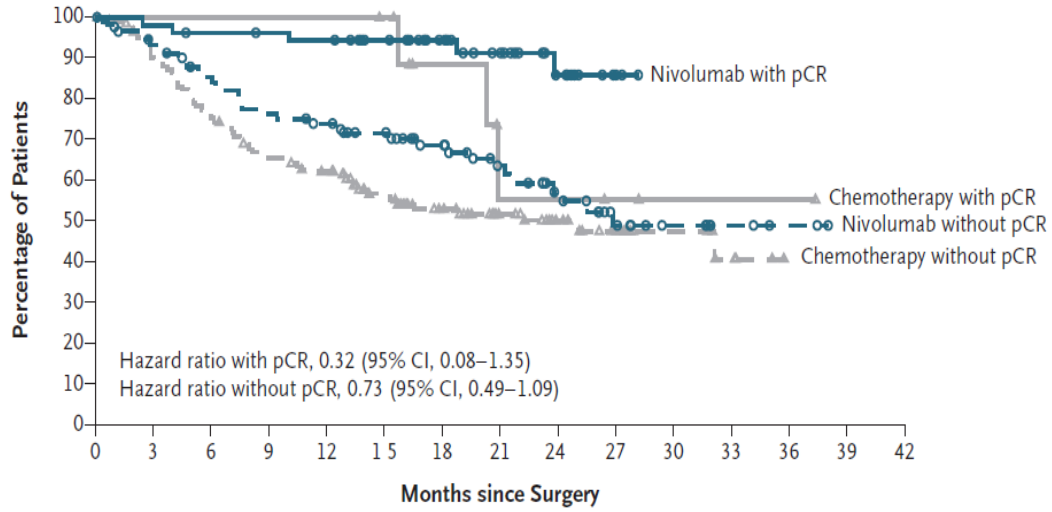
Provencio et al. NEJM 2023

CheckMate 77T: Phase 3 study of neoadjuvant nivolumab + chemo and adjuvant nivolumab in patients with resectable Stage II–IIIB NSCLC

Exploratory analysis: EFS by adjuvant treatment status



Analysis of Event-free Survival from Definitive Surgery, According to Pathological Complete Response



No. at Risk															
With pCR															
Nivolumab	58	56	54	53	52	45	35	25	14	2	0	0	0	0	0
Chemotherapy	11	11	11	11	11	10	6	3	3	2	1	1	1	0	0
Without pCR															
Nivolumab	98	85	74	67	62	54	45	33	23	14	7	4	2	0	0
Chemotherapy	148	129	109	93	84	61	45	33	22	14	9	5	0	0	0

- NIVO + chemo/NIVO improved EFS versus chemo/PBO with numerically higher benefit in patients who received adjuvant treatment (HR [95% CI], 0.45 [0.29, 0.69]) vs those who did not (HR [95% CI], 0.55 [0.37, 0.83])†

Median follow-up (range): 25.4 months (15.7–44.2). *HR (95% CI) with NIVO + chemo/NIVO vs chemo/PBO; †HR (95% CI), 0.17 (0.11, 0.27) in patients who received adjuvant treatment versus those who did not in the NIVO + chemo/NIVO arm and 0.15 (0.10, 0.22) in the chemo/PBO arm

Chemo, chemotherapy; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; NIVO, nivolumab; NSCLC, non-small cell lung cancer; PBO, placebo

Cascone T, et al. Presented at ESMO 2023 (Abstract LBA1) and information provided Professor Provencio

Areas de controversia

.- Estadio II y IIIa resecables y operables: QT –inmuno Neoadyuvante vs QT-inmuno adyuvante

.- Estadio II y IIIa resecables y operables: QT –inmuno Neoadyuvante vs QT –inmuno Perioperatoria

.- Estadio IIIa/b potencialmente operables: QT –inmuno Neoadyuvante vs QT+RT radical y durvalumab

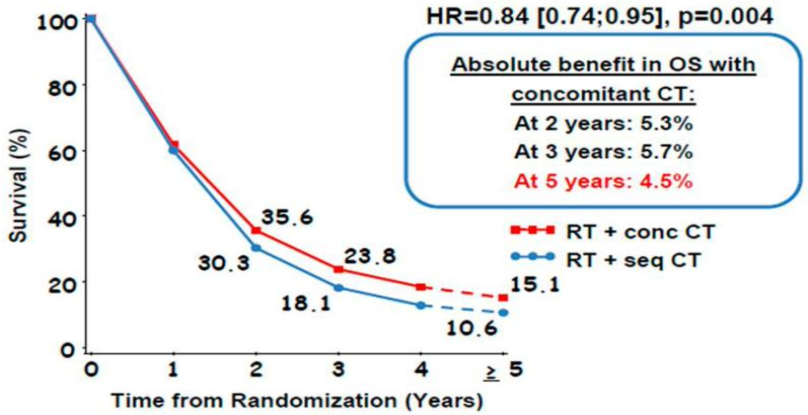
ESTADIO I, II → **CIRUGÍA** → **QT**

- **PDL1>50% →Atezolizumab x 1a**
- **. PD-L1 all: Pembrolizumab x 1ª (aun sin financ**
- **EGFR →Osimertinib x 3a**

ESTADIO III

→ **QT-IO** → **CIRUGÍA**

Meta-analysis of concomitant versus sequential radiochemotherapy



Aupérin, JCO 2010

→ **QT** → **RT**

- **PDL1>1% →Durvalumab x 1a**

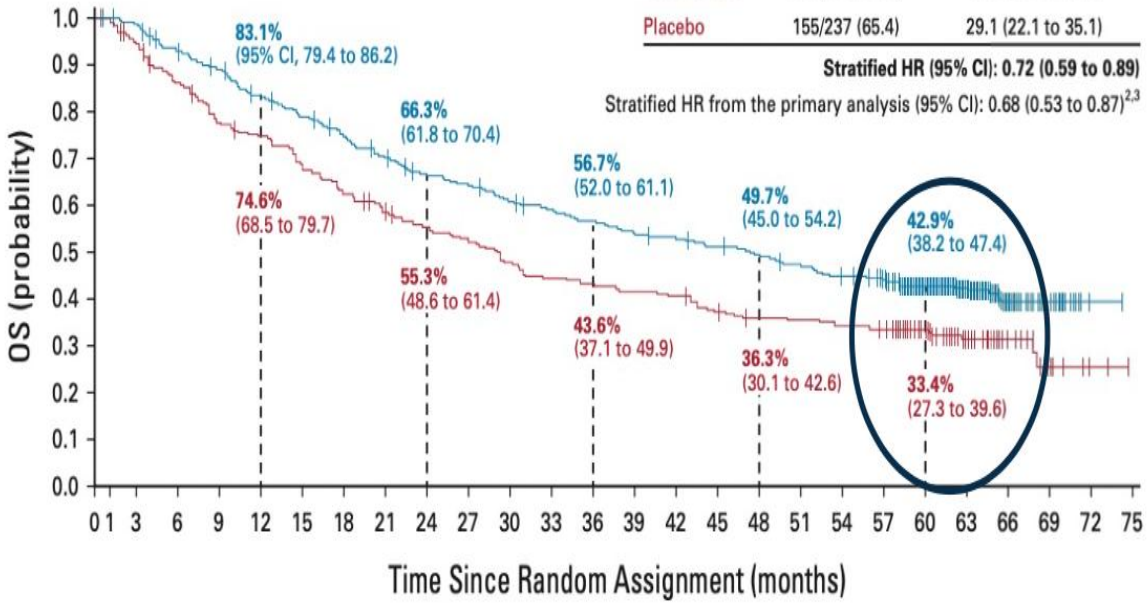
ESTADIO III → **QT** → **RT** → • **PDL1>1% →Durvalumab x 1a**

PACIFIC

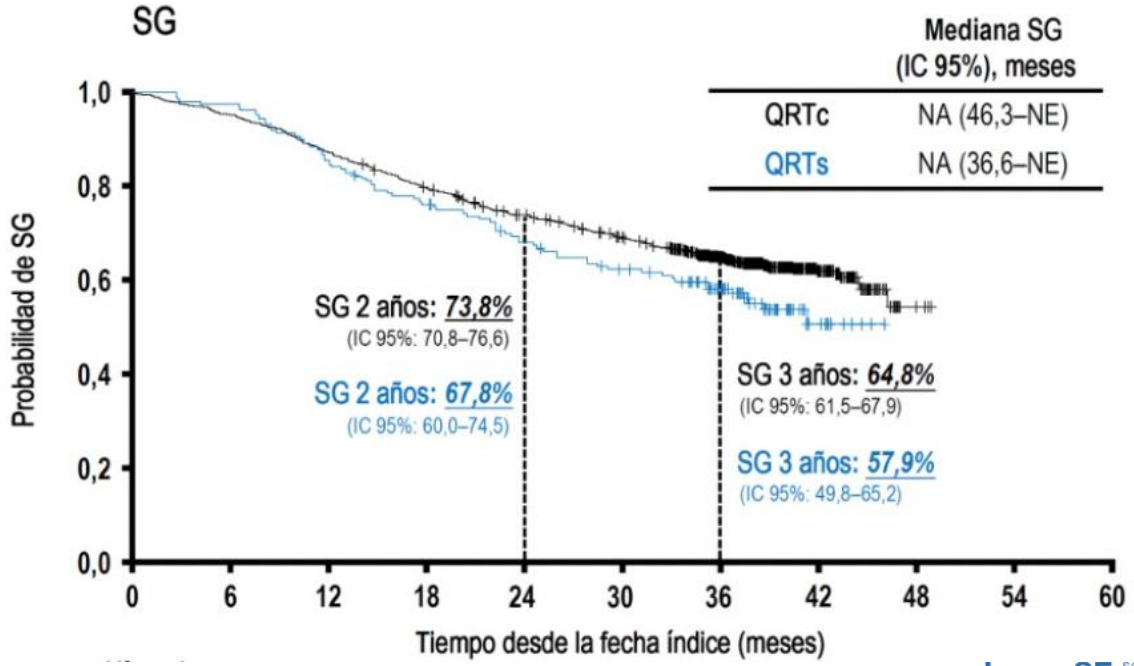
Arm	No. of Events/ Total No. of Patients (%)	Median OS (95% CI), Months
Durvalumab	264/476 (55.5)	47.5 (38.1 to 52.9)
Placebo	155/237 (65.4)	29.1 (22.1 to 35.1)

Stratified HR (95% CI): 0.72 (0.59 to 0.89)

Stratified HR from the primary analysis (95% CI): 0.68 (0.53 to 0.87)[2,3]



PACIFIC-R

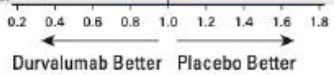


Spiegel et al. J Clin Oncol 2021; Girard et al. ESMO IO 2022

Nuestro tratamiento estándar actual: PACIFIC

Análisis exploratorio de SG

Group	No. of Events / No. of Patients (%) Durvalumab	Placebo	Unstratified HR (95% CI)
All patients	264/476 (55.5)	155/237 (65.4)	0.72 (0.59 to 0.87)
Sex			
Male	192/334 (57.5)	112/166 (67.5)	0.75 (0.59 to 0.95)
Female	72/142 (50.7)	43/71 (60.6)	0.64 (0.44 to 0.94)
Age at random assignment			
< 65 years	130/261 (49.8)	79/130 (60.8)	0.66 (0.50 to 0.87)
≥ 65 years	134/215 (62.3)	76/107 (71.0)	0.79 (0.60 to 1.05)
Smoking status			
Smoker	244/433 (56.4)	140/216 (64.8)	0.75 (0.61 to 0.93)
Nonsmoker	20/43 (46.5)	15/21 (71.4)	0.42 (0.21 to 0.82)
NSCLC disease stage			
IIIA	136/252 (54.0)	91/125 (72.8)	0.61 (0.47 to 0.80)
IIIB	121/212 (57.1)	61/107 (57.0)	0.86 (0.63 to 1.17)
Tumor histologic type			
Squamous	138/224 (61.6)	67/102 (65.7)	0.82 (0.61 to 1.09)
All other	126/252 (50.0)	88/135 (65.2)	0.62 (0.47 to 0.81)
Best response to prior treatment			
Complete response	6/9 (66.7)	3/7 (42.9)	Not calculated[a]
Partial response	118/237 (49.8)	68/112 (60.7)	0.71 (0.52 to 0.95)
Stable disease	135/223 (60.5)	81/115 (70.4)	0.70 (0.53 to 0.92)
Prior chemotherapy type			
Gemcitabine-based	5/9 (55.6)	2/5 (40.0)	Not calculated[a]
Non–gemcitabine-based	259/467 (55.5)	153/232 (65.9)	0.70 (0.58 to 0.86)
Cisplatin	134/266 (50.4)	81/129 (62.8)	0.65 (0.50 to 0.86)
Carboplatin	121/199 (60.8)	69/102 (67.6)	0.81 (0.60 to 1.09)
Cisplatin and carboplatin	6/8 (75.0)	4/5 (80.0)	Not calculated[a]
Last radiation to random assignment			
< 14 days	64/120 (53.3)	43/62 (69.4)	0.54 (0.37 to 0.80)
≥ 14 days	200/356 (56.2)	112/175 (64.0)	0.79 (0.63 to 1.00)
WHO PS			
0 – Normal	121/234 (51.7)	65/114 (57.0)	0.84 (0.62 to 1.14)
1 – Restricted[b]	143/242 (59.1)	90/123 (73.2)	0.62 (0.47 to 0.80)
Region			
Asia	54/109 (49.5)	37/68 (54.4)	0.79 (0.52 to 1.20)
Europe	125/217 (57.6)	64/102 (62.7)	0.84 (0.62 to 1.14)
North and South America	85/150 (56.7)	54/67 (80.6)	0.47 (0.34 to 0.67)
Race			
White	200/337 (59.3)	110/157 (70.1)	0.72 (0.57 to 0.91)
Black or African American	5/12 (41.7)	2/2 (100)	Not calculated[a]
Asian	56/120 (46.7)	39/72 (54.2)	0.73 (0.48 to 1.09)
Other[c]	3/8 (50.0)	4/6 (66.7)	Not calculated[a]
EGFR or *ALK* aberration status			
Positive[d]	17/29 (58.6)	8/14 (57.1)	0.85 (0.37 to 1.97)
Negative	166/317 (52.4)	109/165 (66.1)	0.66 (0.52 to 0.84)
Unknown	81/130 (62.3)	38/58 (65.5)	0.85 (0.57 to 1.24)
PD-L1 expression level			
≥ 25%	51/115 (44.3)	27/44 (61.4)	0.52 (0.32 to 0.82)
< 25%	111/187 (59.4)	64/105 (61.0)	0.90 (0.67 to 1.23)
Unknown	102/174 (58.6)	64/88 (72.7)	0.68 (0.50 to 0.93)
1%-24% (post hoc analysis)	52/97 (53.6)	29/47 (61.7)	0.73 (0.46 to 1.14)
≥ 1% (post hoc analysis)	103/212 (48.6)	56/91 (61.5)	0.61 (0.44 to 0.85)
< 1% (post hoc analysis)	59/90 (65.6)	35/58 (60.3)	1.15 (0.75 to 1.75)



Post hoc exploratory analysis showed no OS benefit in

- **EGFR / ALK positive (HR=0.85, 95% CI 0.37-1.97)**
- **PD-L1 negative (HR = 1.15, 95% CI 0.75 -1.75)**

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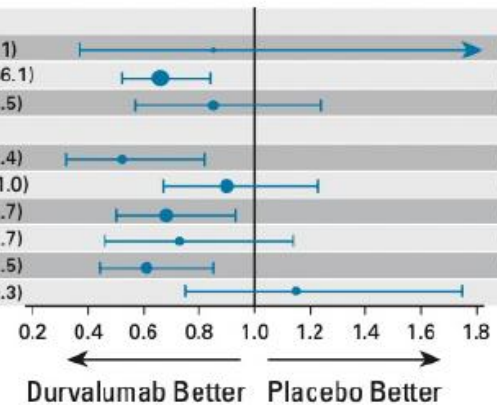
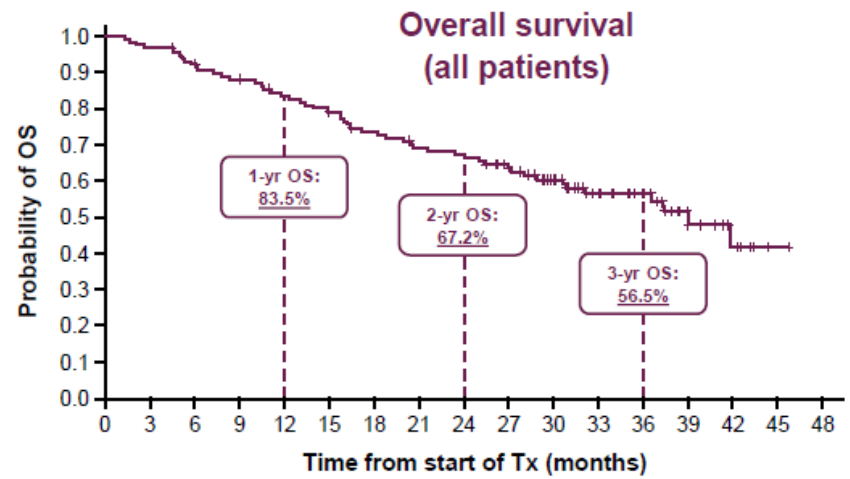


Spiegel et al. J Clin Oncol 2021

PACIFIC-6 - durvalumab consolidation post sequential CTRT (phase 2)

AE Category (N=117)	All-cause	PRAE*
Any AE, n (%)	111 (94.9)	90 (76.9)
Grade 3/4§	32 (27.4)	7 (6.0)
SAE	32 (27.4)	7 (6.0)
Outcome of death¶	3 (2.6)	1 (0.9)
Leading to Tx discontinuation	32 (27.4)	19 (16.2)
AESI	89 (76.1)	75 (64.1)

Incidence grade 3-4 AEs possibly-related to treatment
4.3% (95% CI: 1.4–9.7)



Similar safety profile to that seen in PACIFIC
Encouraging efficacy in a frailer population
>55% of patients estimated to remain alive at 3 years
PACIFIC 5 (phase III awaited)

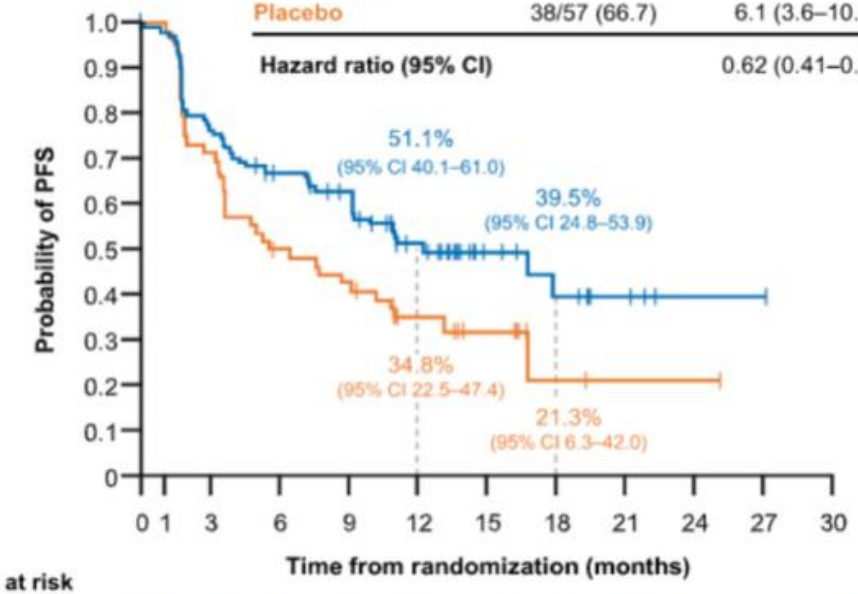
Garassino. JTO 2022, updated results ESMO 2023

¿Tiene sentido régimen PACIFIC en pacientes ancianos?

PACIFIC

A)

Aged ≥70 years	No. events/No. patients (%)	Median PFS (95% CI), months
Durvalumab	48/101 (47.5)	12.3 (9.2–NR)
Placebo	38/57 (66.7)	6.1 (3.6–10.9)
Hazard ratio (95% CI)		0.62 (0.41–0.95)



No. at risk											
Durvalumab	101	75	62	54	30	14	8	4	1	1	0
Placebo	57	40	27	23	12	7	2	1	1	0	0

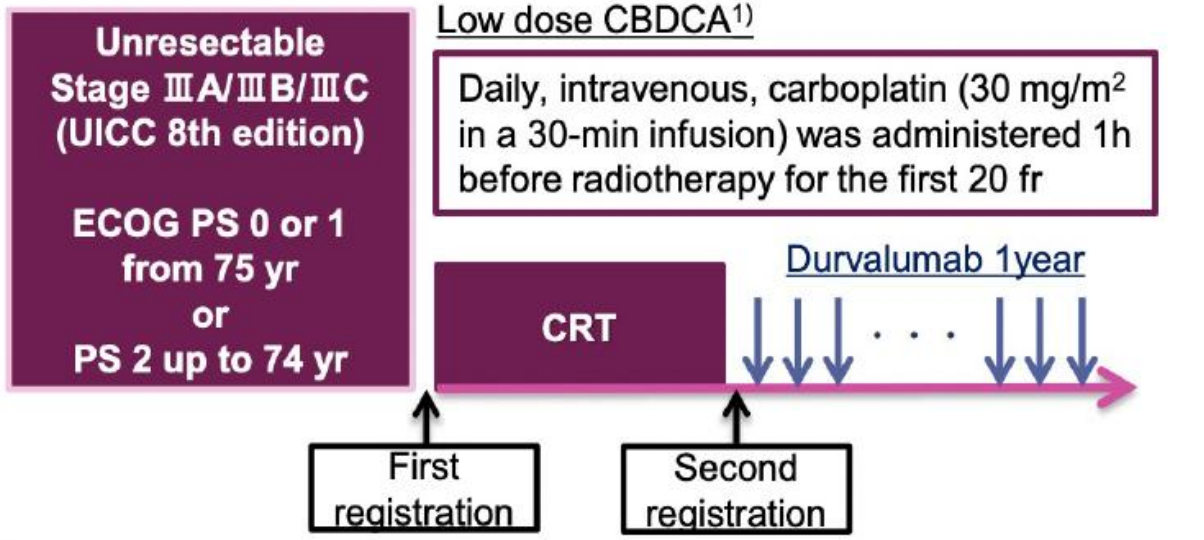
22% pts ≥ 70y

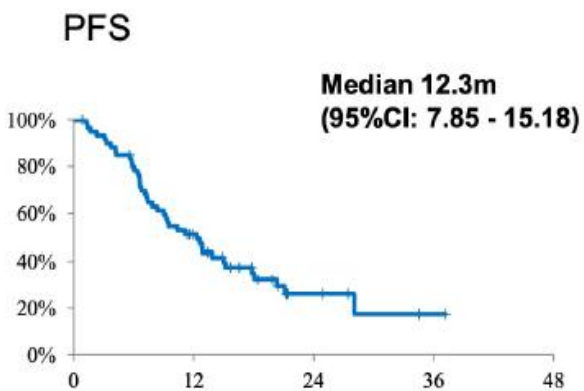
PFS HR = 0.62 (95% CI 0.41-0.95)

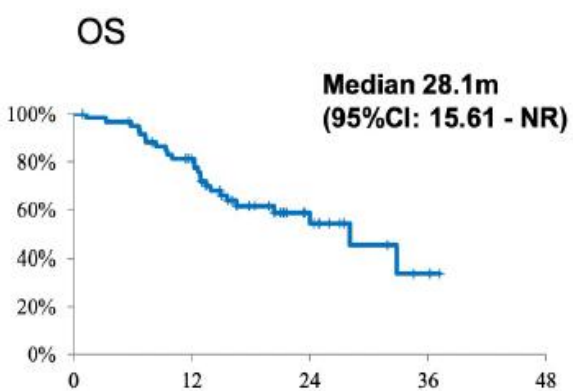
OS HR = 0.78 (95% CI 0.50-1.22)

Higher rate of AE G3-4 (41.6% vs. 25.5%) & SAEs (42.6% vs 25.5%)

NEJ039A







Socinski et al. Clin Lung Cancer 2021; Ko et al. ESMO 2023

¿Cómo podemos seguir mejorando los resultados de PACIFIC?

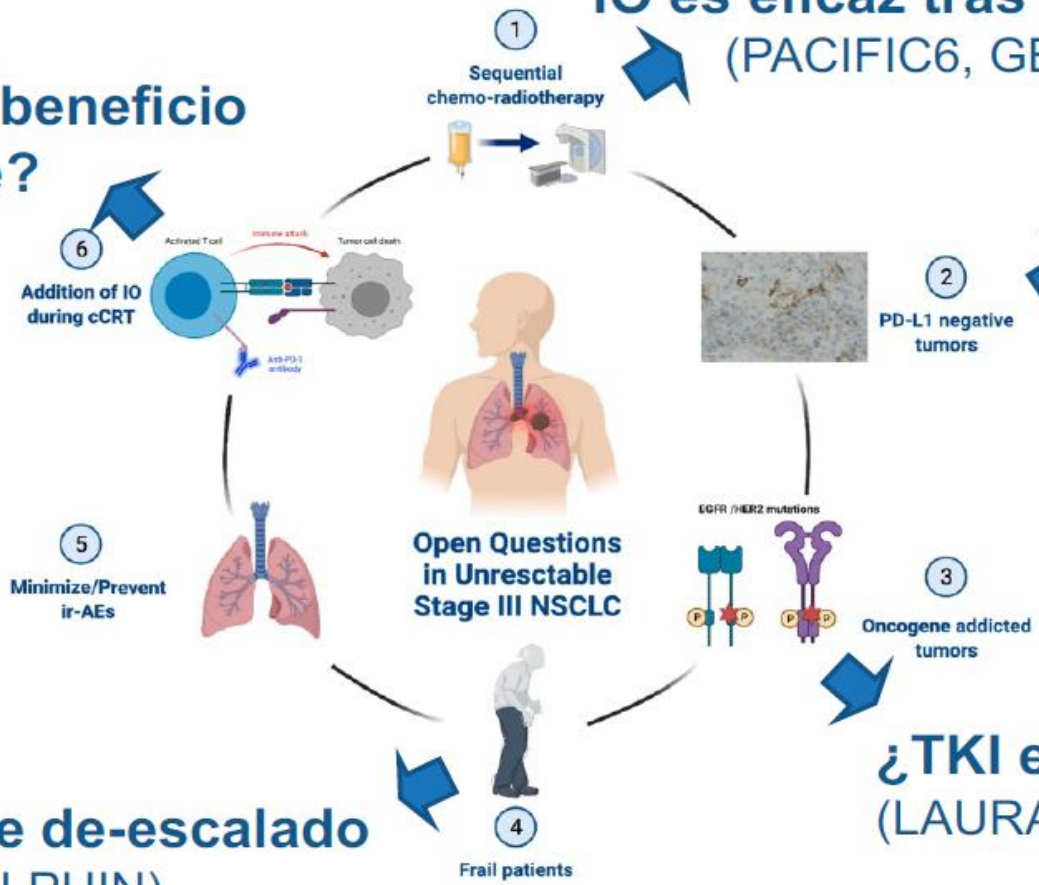
IO es eficaz tras QT-RT secuencial
(PACIFIC6, GEMSTONE-301)

Intensificar IO consolidación
(COAST)

¿TKI en lugar de ICI?
(LAURA, LIBRETTO-432)

Estudios de de-escalado
(DOLPHIN)

¿Balance riesgo/beneficio favorable?



Catania et al. Crit Rev Onc Hem 2022

Is induction chemo-IO followed by surgery the right strategy for this patient?

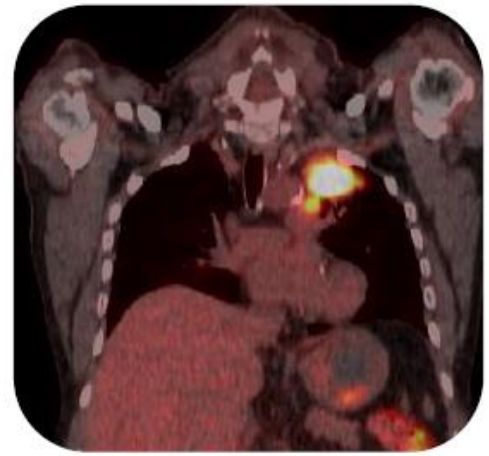
Clinical case

61 year old male
PS1
High blood pressure, controlled type 2 diabetes
FEV1 78% predicted; KCO 75% predicted

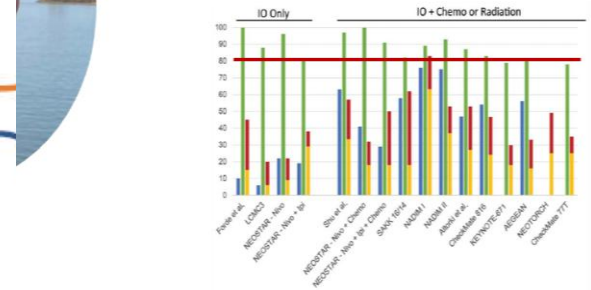
Adenocarcinoma
PD-L1 50%
No driver mutations

MR brain clear
PETCT/EBUS T2aN2M0

Contrast enhanced CT raised consideration of mediastinal invasion
T2aN2M0→T4 N2 M0



	N0	N1	N2	N3
T1	IA	IIB	IIIA	IIIB
T2a	IB	IIB	IIIA	IIIB
T2b	IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIB	IIIC
T4	IIIA	IIIA	IIIB	IIIC
M1a	IVA	IVA	IVA	IVA
M1b	IVA	IVA	IVA	IVA
M1c	IVB	IVB	IVB	IVB



CM816 Ib-IIIA (TNM7)
NADIM2 IIIa-IIIb [N2] (TNM8)
AGEAN IIa-IIIb [N2] (TNM8)
NEOTORCH II-IIIb [N2] (TNM8)

18-22% of patients in phase III trials of neoA chemo-IO fail to undergo surgery

Rates likely higher in patients borderline/not considered resectable upfront

Is this always the right strategy?

Risk of applying neo-adjuvant chemo-IO to patients not suitable for upfront surgery?

	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

GRACIAS!

II JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN: A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 6 Y 7 DE FEBRERO DE 2025