XXIV Simposio de Revisiones en Cáncer

"Tratamiento médico del cáncer en el año 2022"

Avanzando hacia estadios tempranos de la enfermedad con la OI

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ARÁN

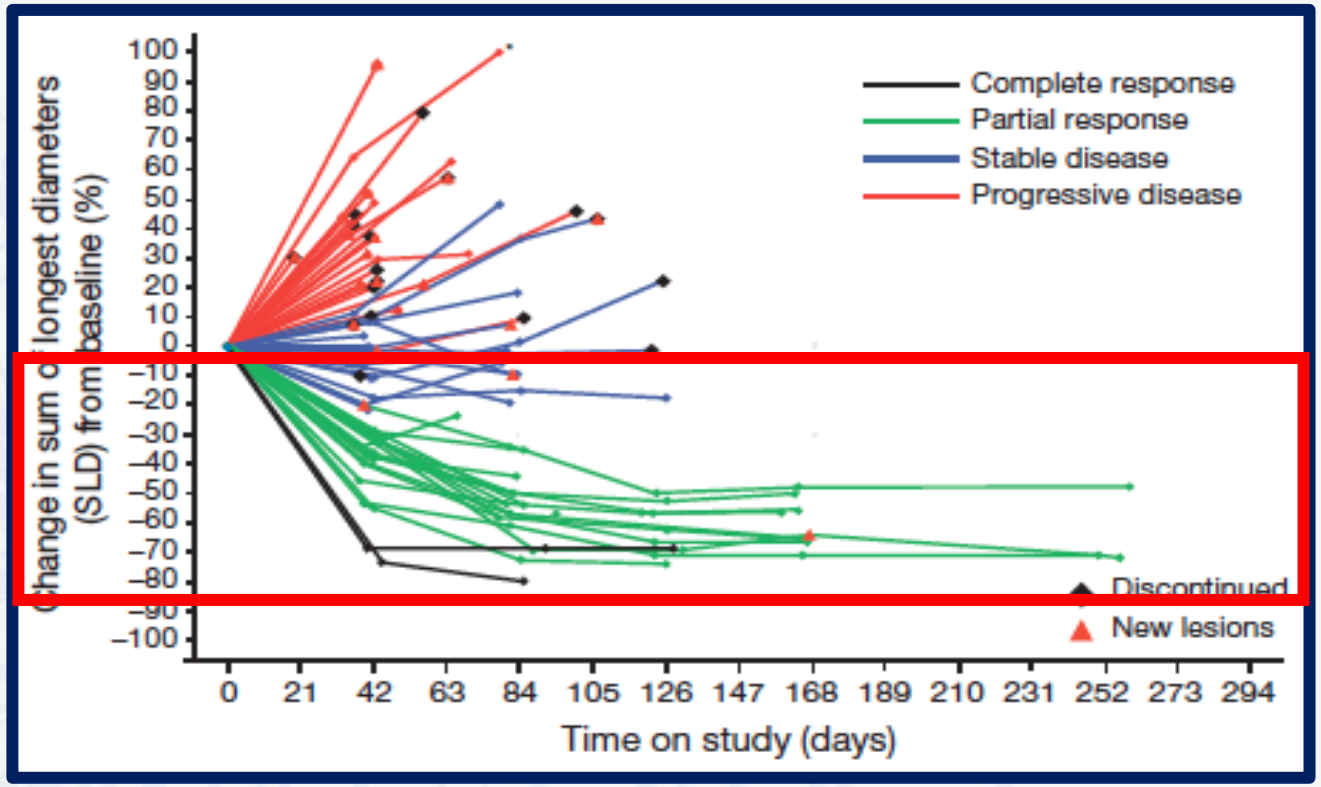
Conflictos de interés

- Honoraria for lectures or advisory boards from Pfizer, Roche, Ipsen, Merck, MSD, BMS, Astellas, Bayer, EUSA Pharma, Sanofi, PierreFabre

Avanzando hacia estadios tempranos: >2L

2014

A PHASE I EXPANSION STUDY OF ATEZOLIZUMAB



N=68

93% previous Carbo/Cisplatin based CT

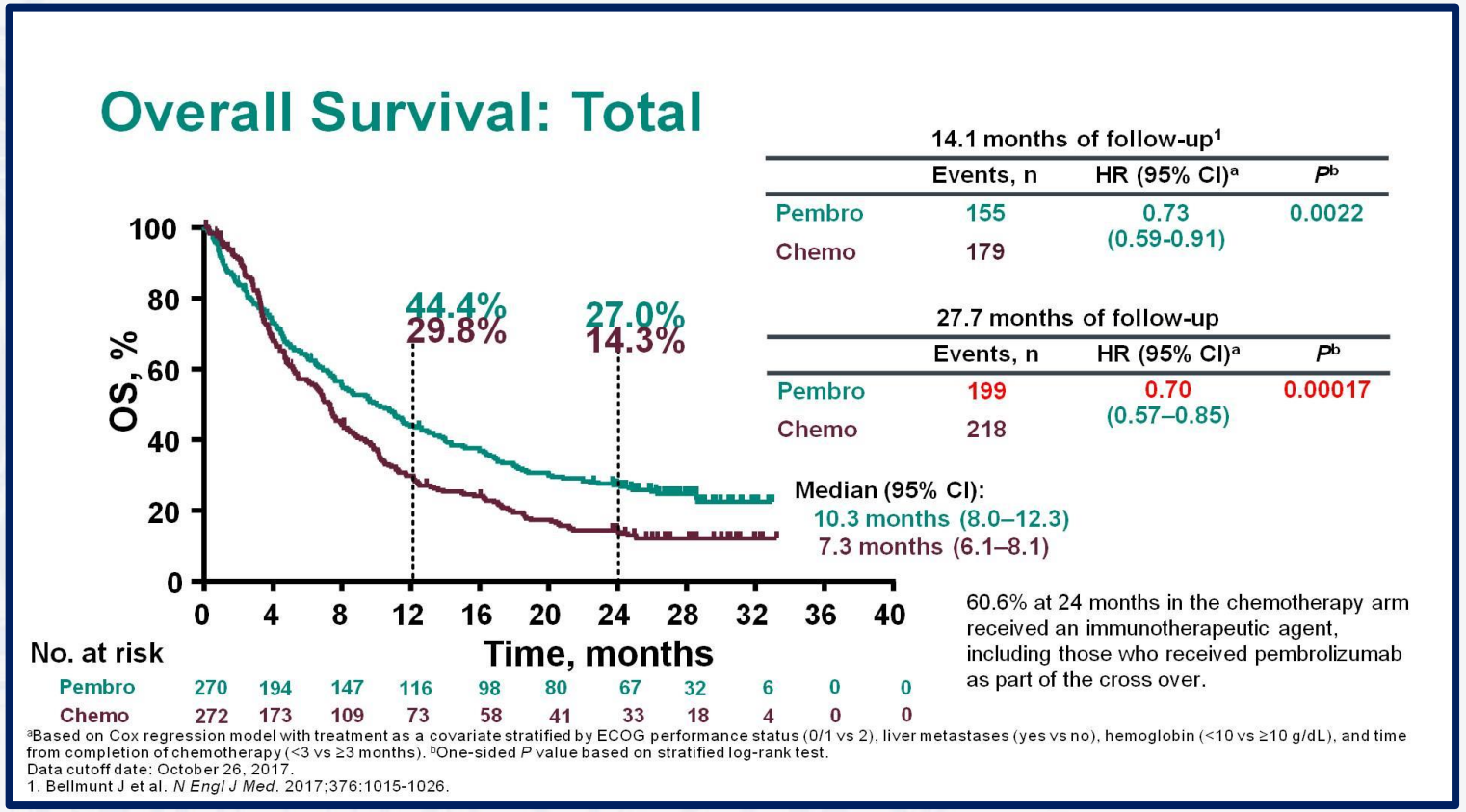
72% ≥ 2 previous systemic treatment lines

Powles, T. Nature, 2014

Avanzando hacia estadios tempranos: 2 Línea

2017

KN-045 Ph3 RCT Pembrolizumab vs Ch

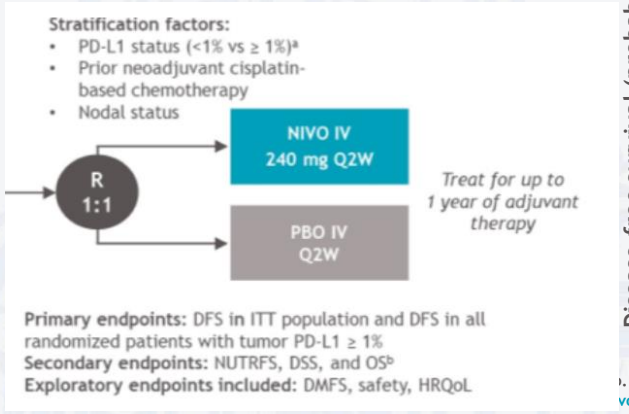


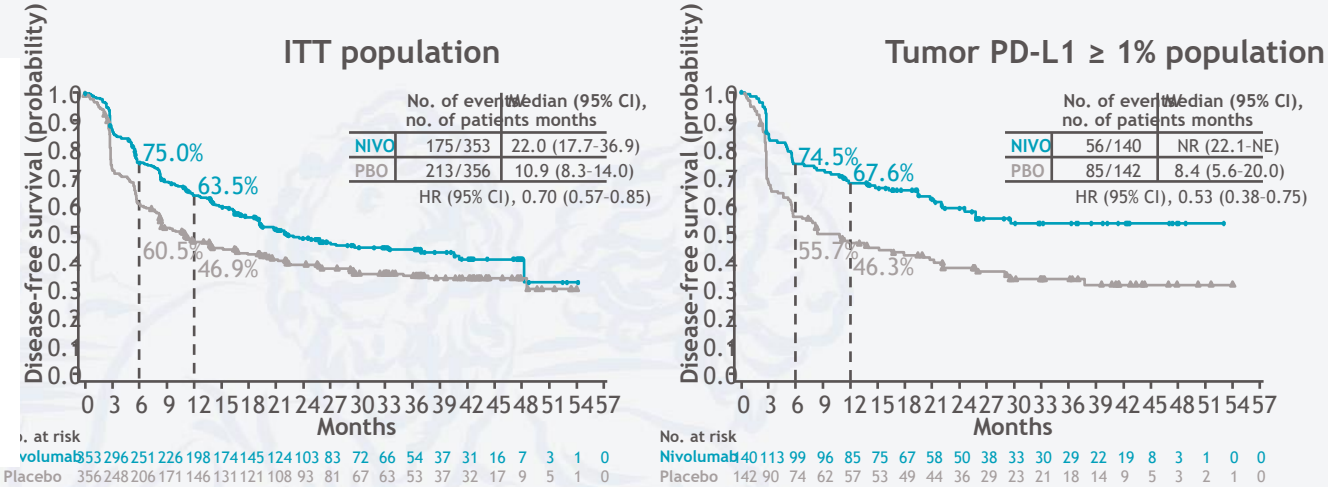
Bellmunt et al. NEJM 2017

Avanzando hacia estadios tempranos: ADYUVANCIA

CM 275

2021





Powles et al. NEJM 2021

Study design

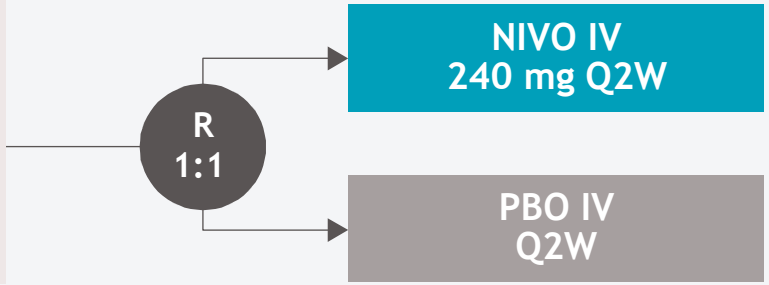
N = 709

Key inclusion criteria

- Patients with ypT2-ypT4a or ypN+ MIUC who had neoadjuvant cisplatin chemotherapy
- Patients with pT3-pT4a or pN+ MIUC without prior neoadjuvant cisplatin chemotherapy and not eligible/refuse adjuvant cisplatin chemotherapy
- Radical surgery within the past 120 days
- Disease-free status within 4 weeks of dosing

Stratification factors

- Tumor PD-L1 status (< 1% vs ≥ 1%)[a]
- Prior neoadjuvant cisplatin-based chemotherapy
- Nodal status



Primary endpoints: DFS (defined as the time between the date of randomization and the date of first recurrence [local urothelial tract, local non-urothelial tract, or distant] or death) in the ITT population and DFS in all randomized patients with tumor PD-L1 ≥ 1%

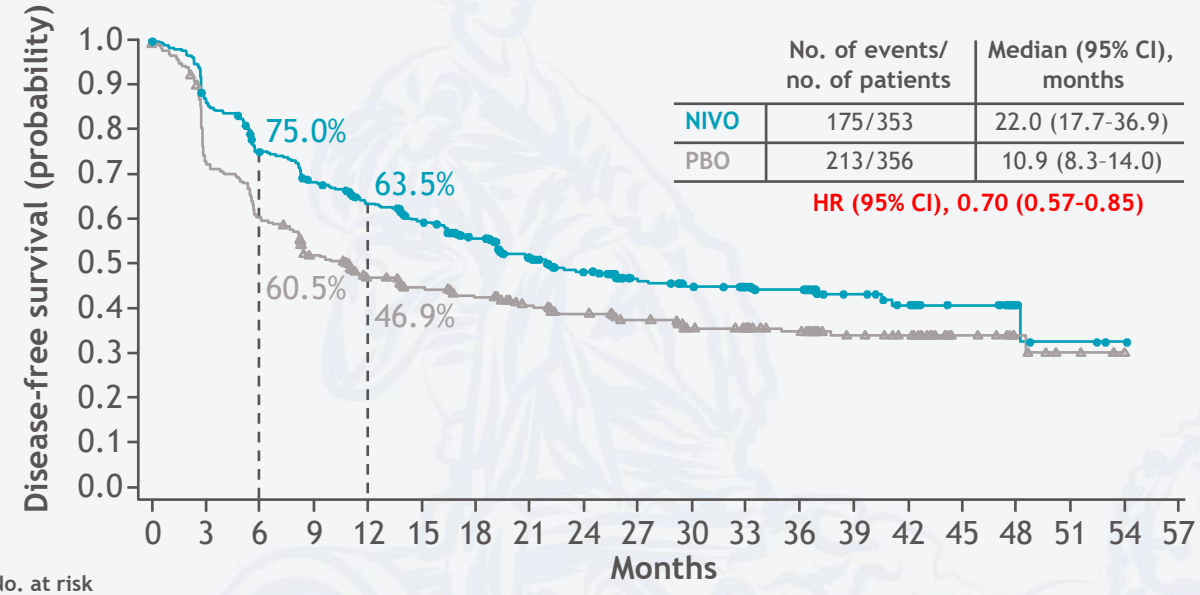
Secondary endpoints: NUTRFS (defined as the time between the date of randomization and the date of first local non-urothelial tract or distant recurrence or death), DSS (defined as the time between the date of randomization and the date of death due to urothelial carcinoma), and OS (defined as the time between the date of randomization and the date of death due to any cause)[b]

Exploratory endpoints: include DMFS (defined as the time between the date of randomization and the date of first distant recurrence [non-local] or date of death) and TTR (defined as the time between the date of randomization and the date of first recurrence or death due to disease, whichever occurred first)

[a]Defined by the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells using the Dako PD-L1 IHC 28-8 pharmDx assay.
[b]OS data were not mature at the time of this analysis. OS and DSS data are not presented.
DSS, disease-specific survival; IHC, immunohistochemistry; OS, overall survival; R, randomized.

Main Objective: Disease-free survival

ITT population

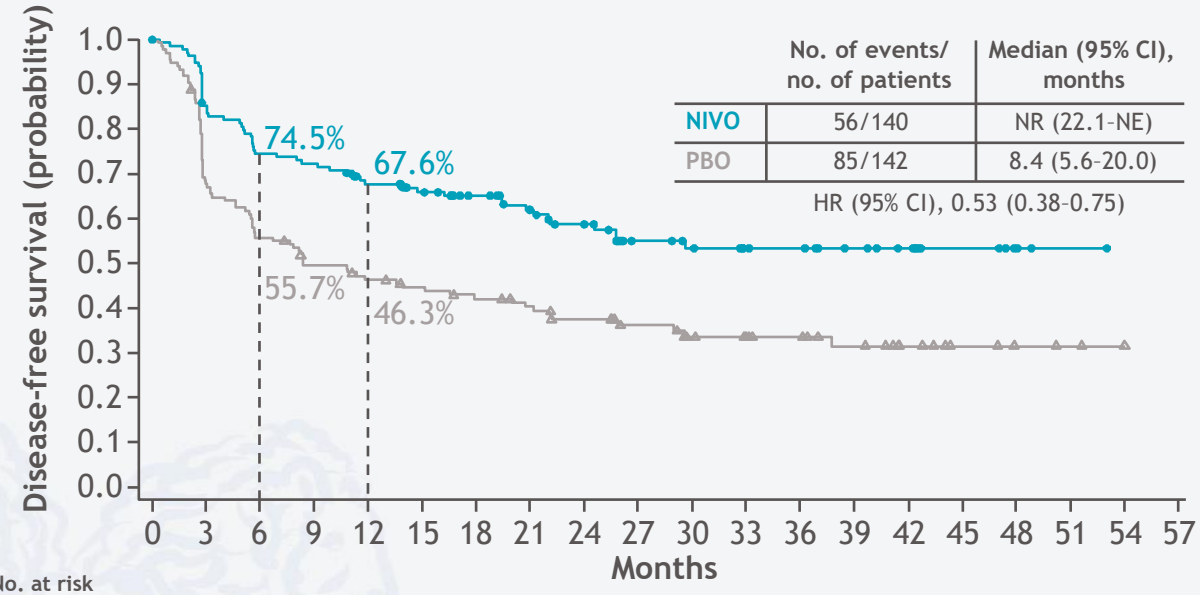


	No. of events/ no. of patients	Median (95% CI), months
NIVO	175/353	22.0 (17.7-36.9)
PBO	213/356	10.9 (8.3-14.0)

HR (95% CI), 0.70 (0.57-0.85)

No. at risk																				
Nivolumab	353	296	251	226	198	174	145	124	103	83	72	66	54	37	31	16	7	3	1	0
Placebo	356	248	206	171	146	131	121	108	93	81	67	63	53	37	32	17	9	5	1	0

Tumor PD-L1 ≥ 1% population



	No. of events/ no. of patients	Median (95% CI), months
NIVO	56/140	NR (22.1-NE)
PBO	85/142	8.4 (5.6-20.0)

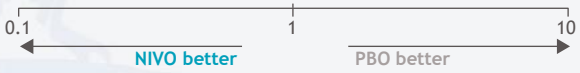
HR (95% CI), 0.53 (0.38-0.75)

No. at risk																				
Nivolumab	140	113	99	96	85	75	67	58	50	38	33	30	29	22	19	8	3	1	0	0
Placebo	142	90	74	62	57	53	49	44	36	29	23	21	18	14	9	5	3	2	1	0

DFS was defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death.
NE, not estimable; NR, not reached.

DFS in select subgroups

		NIVO Events/patients	PBO Events/patients	HR (95% CI)
Overall		175/353	213/356	0.70 (0.57-0.85)
Age, years	< 65	75/155	76/136	0.73 (0.53-1.01)
	≥ 65 and < 75	67/131	103/164	0.68 (0.49-0.93)
	≥ 75	33/67	34/56	0.66 (0.40-1.10)
Sex	Male	130/265	164/275	0.68 (0.54-0.86)
	Female	45/88	49/81	0.77 (0.50-1.17)
Race	White	131/264	168/272	0.65 (0.52-0.82)
	Asian	37/80	38/75	0.82 (0.51-1.32)
Region	United States	24/49	37/53	0.46 (0.26-0.81)
	Europe	91/170	100/171	0.86 (0.64-1.14)
	Asia	37/80	37/74	0.84 (0.52-1.36)
	Rest of world	23/54	39/58	0.41 (0.23-0.74)
ECOG PS	0	108/224	133/221	0.68 (0.52-0.88)
	1	66/122	73/125	0.79 (0.56-1.12)
Baseline hemoglobin	< 10 g/dL	9/19	18/27	0.27 (0.08-0.96)
	≥ 10 g/dL	166/332	193/321	0.71 (0.58-0.87)
Baseline creatinine clearance	< 60 mL/min	84/151	94/158	0.87 (0.64-1.17)
	≥ 60 mL/min	90/199	116/189	0.60 (0.45-0.79)
Initial tumor origin	Urinary bladder	133/279	173/281	0.61 (0.49-0.77)
	Renal pelvis	25/44	26/52	1.25 (0.70-2.25)
	Ureter	17/30	14/23	1.54 (0.69-3.44)
Minor histological variants	Present	74/145	80/141	0.73 (0.53-1.01)
	Absent	101/208	133/215	0.68 (0.52-0.88)
Pathological lymph node status	N+	97/167	121/168	0.63 (0.48-0.83)
	N0/x with < 10 nodes removed	48/94	53/99	0.85 (0.57-1.27)
	N0/x with ≥ 10 nodes removed	30/91	38/88	0.65 (0.40-1.07)
Pathological status	pT0-2	37/80	43/86	0.85 (0.53-1.36)
	pT3	98/206	122/204	0.62 (0.48-0.82)
	pT4a	38/57	44/62	0.74 (0.46-1.19)
Prior neoadjuvant cisplatin	Yes	73/153	102/155	0.52 (0.39-0.71)
	No	102/200	111/201	**0.90 (0.68-1.18)**
Time from MIUC surgery to randomization, days	> 30-60	43/79	42/70	0.64 (0.40-1.03)
	> 60-90	81/165	96/178	0.77 (0.56-1.04)
	> 90-120	49/103	66/94	0.63 (0.42-0.94)
Smoking status	Current/former	120/237	147/247	0.71 (0.56-0.91)
	Never smoked	53/111	64/104	0.66 (0.45-0.96)
PD-L1 status	≥ 1%	56/139	83/141	0.55 (0.39-0.77)
	< 1%	117/210	125/209	0.82 (0.63-1.05)



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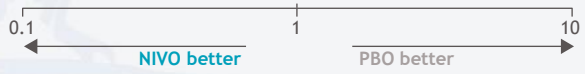

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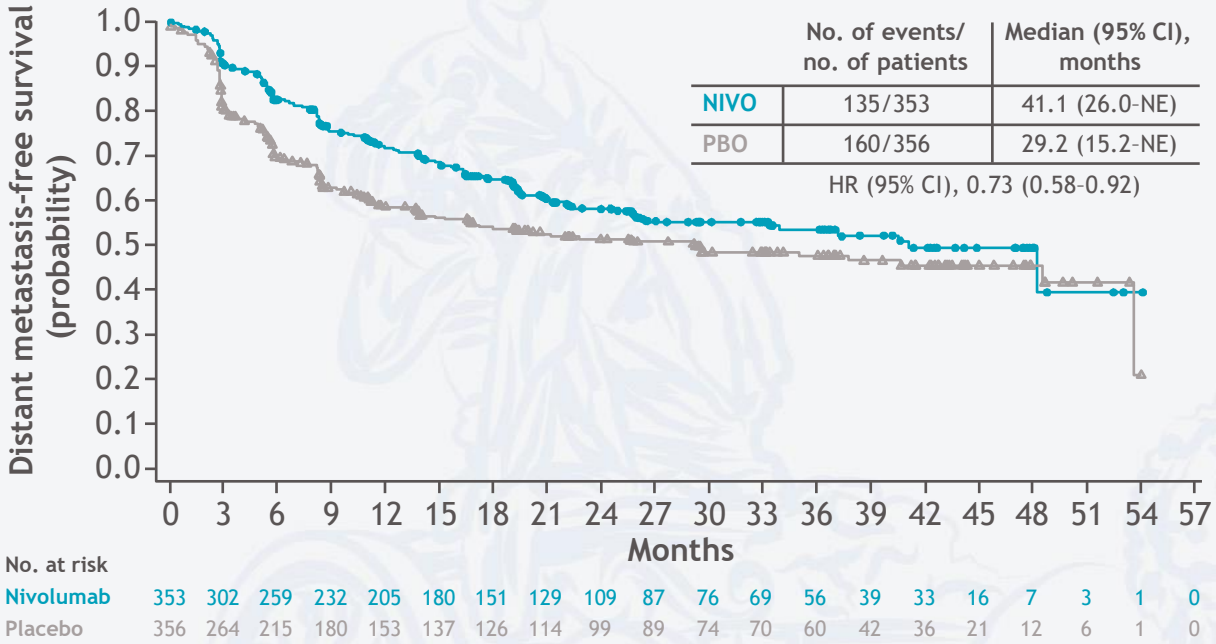
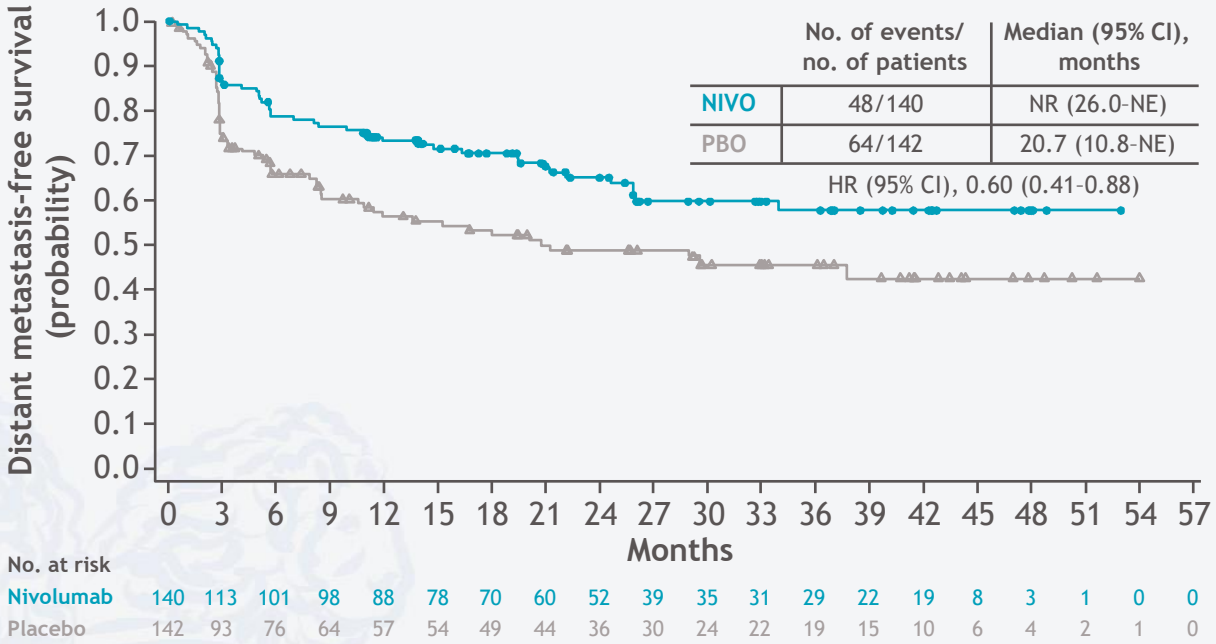
Distant metastasis-free survival

ITT population



No. at risk																				
Nivolumab	353	302	259	232	205	180	151	129	109	87	76	69	56	39	33	16	7	3	1	0
Placebo	356	264	215	180	153	137	126	114	99	89	74	70	60	42	36	21	12	6	1	0

Tumor PD-L1 ≥ 1% population



No. at risk																				
Nivolumab	140	113	101	98	88	78	70	60	52	39	35	31	29	22	19	8	3	1	0	0
Placebo	142	93	76	64	57	54	49	44	36	30	24	22	19	15	10	6	4	2	1	0

DMFS was defined as the time between the date of randomization and the date of first distant recurrence (non-local) or death.

Avanzando hacia estadios tempranos: ADYUVANCIA

IMVIGOR 010

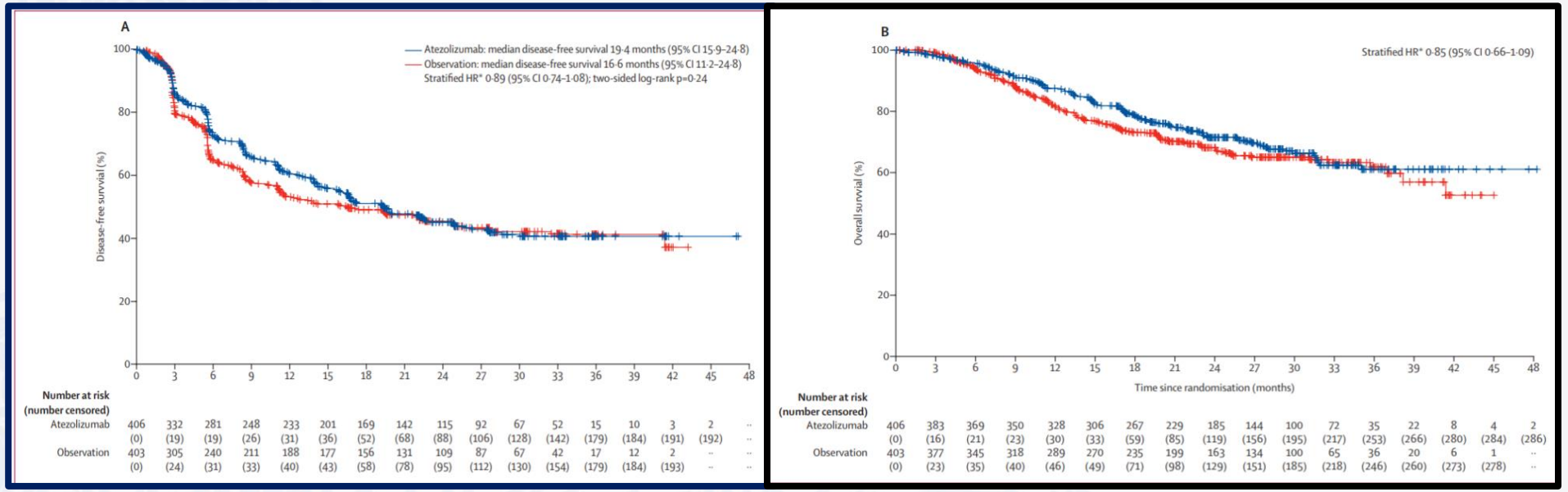
2021

Bellmunt al. Lancet 2021

Avanzando hacia estadios tempranos: ADYUVANCIA

IMVIGOR 010

2021

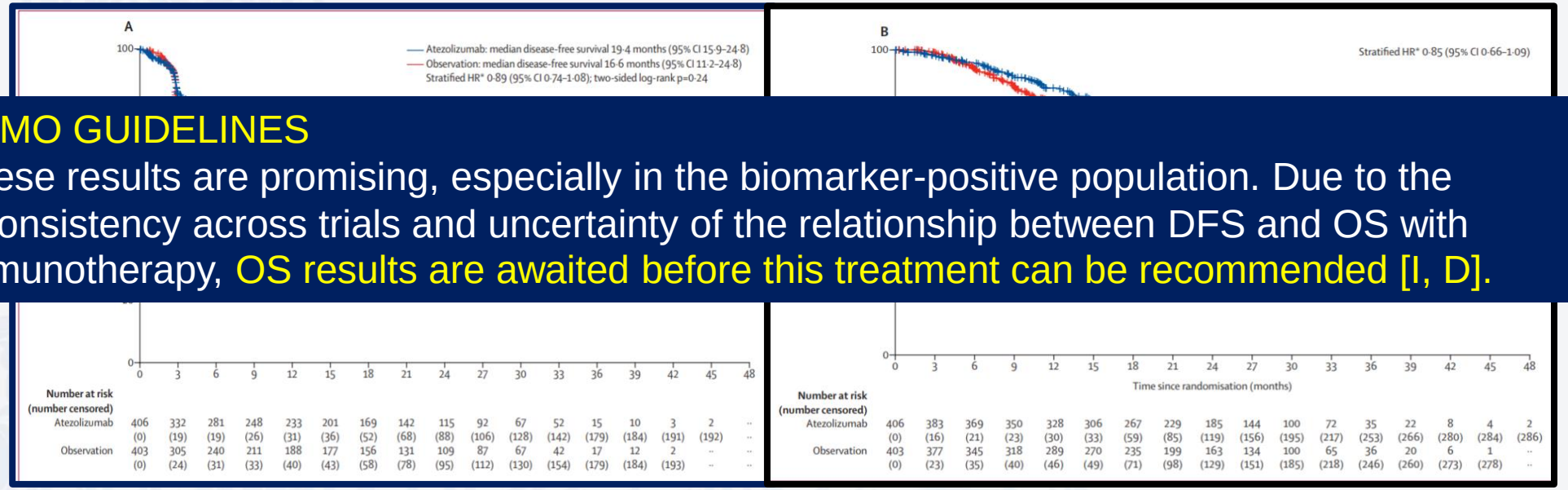


Bellmunt al. Lancet 2021

Avanzando hacia estadios tempranos: ADYUVANCIA

IMVIGOR 010

2021



ESMO GUIDELINES

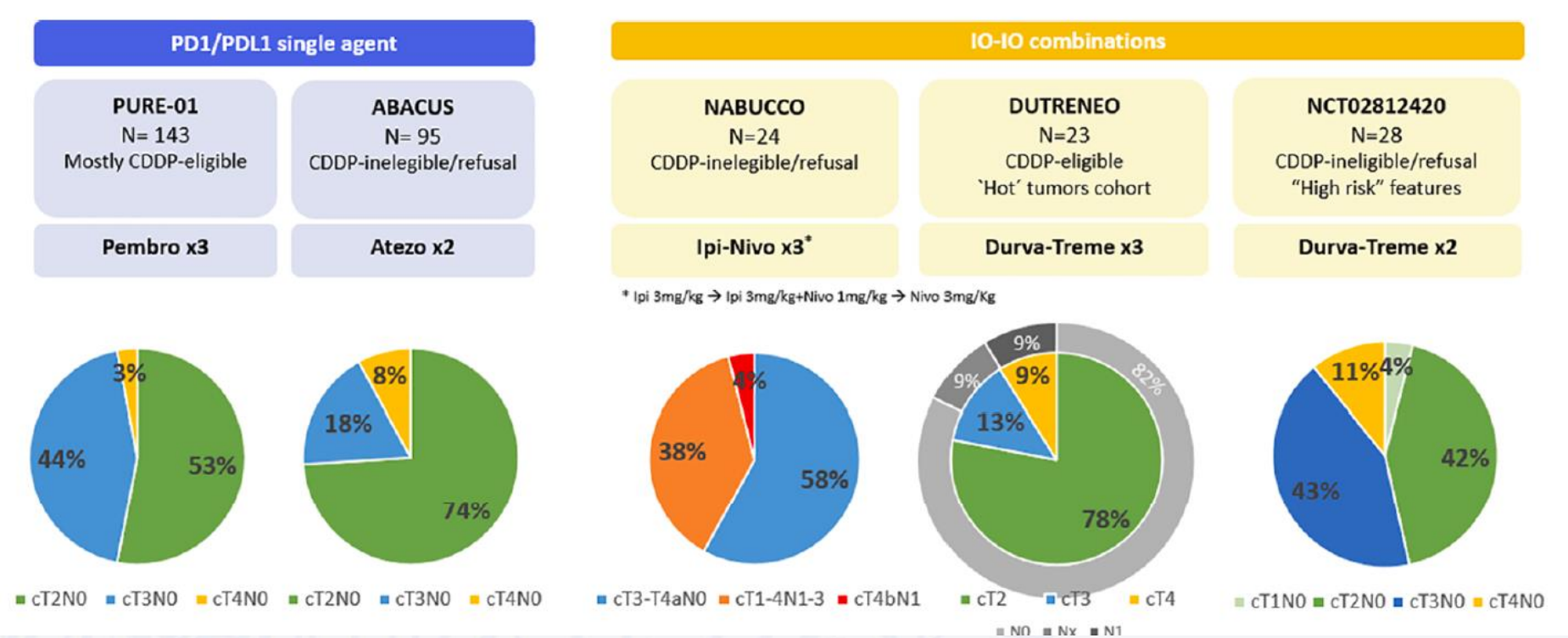
These results are promising, especially in the biomarker-positive population. Due to the inconsistency across trials and uncertainty of the relationship between DFS and OS with immunotherapy, OS results are awaited before this treatment can be recommended [I, D].

Bellmunt al. Lancet 2021

Avanzando hacia estadios tempranos: NEOADYUVANCIA

Fases 2: IO o IOIO

2019-21

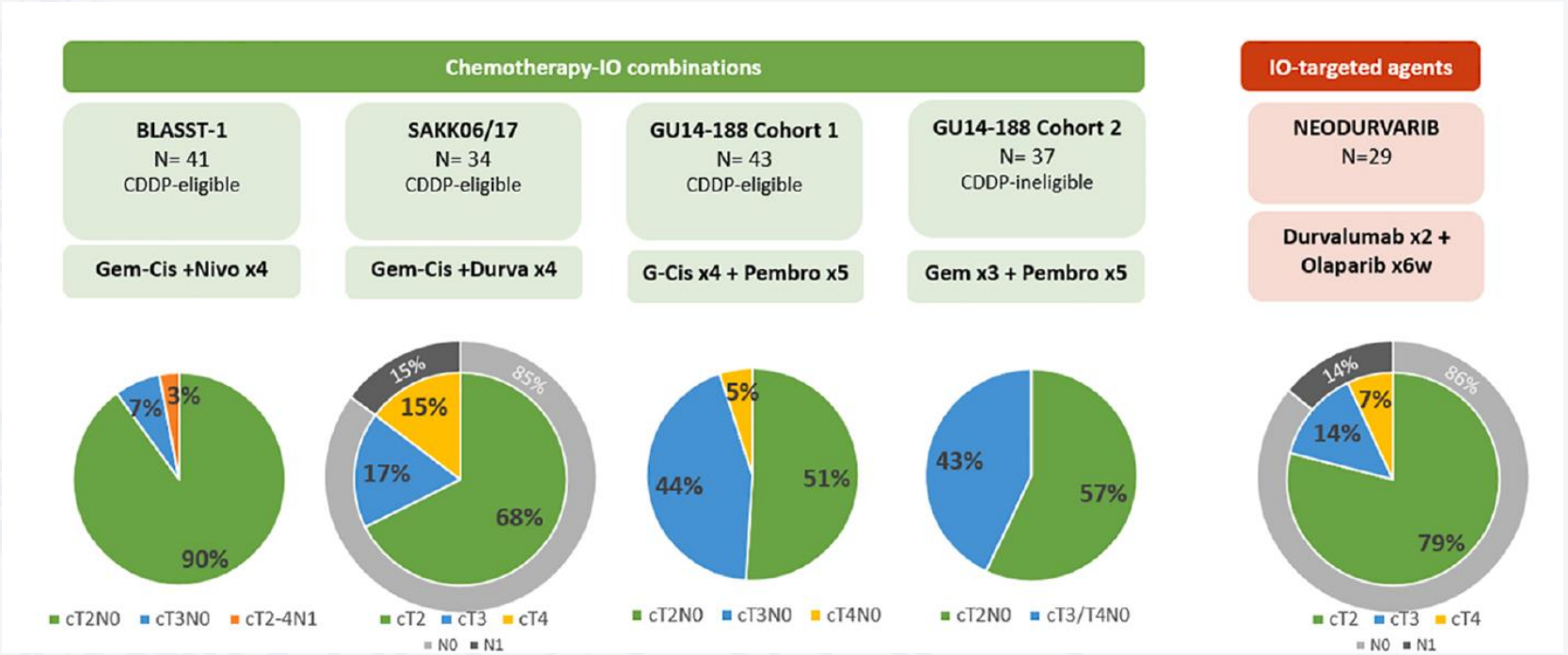


M. Rey-Cardenas et al.

Avanzando hacia estadios tempranos: NEOADYUVANCIA

Fases 2: Combinaciones IO/ChT

2019-21



M. Rey-Cardenas et al.

Avanzando hacia estadios tempranos: NEOADYUVANCIA

Análisis de repuesta en Fases 2. ypT0=30-50%

2019-21

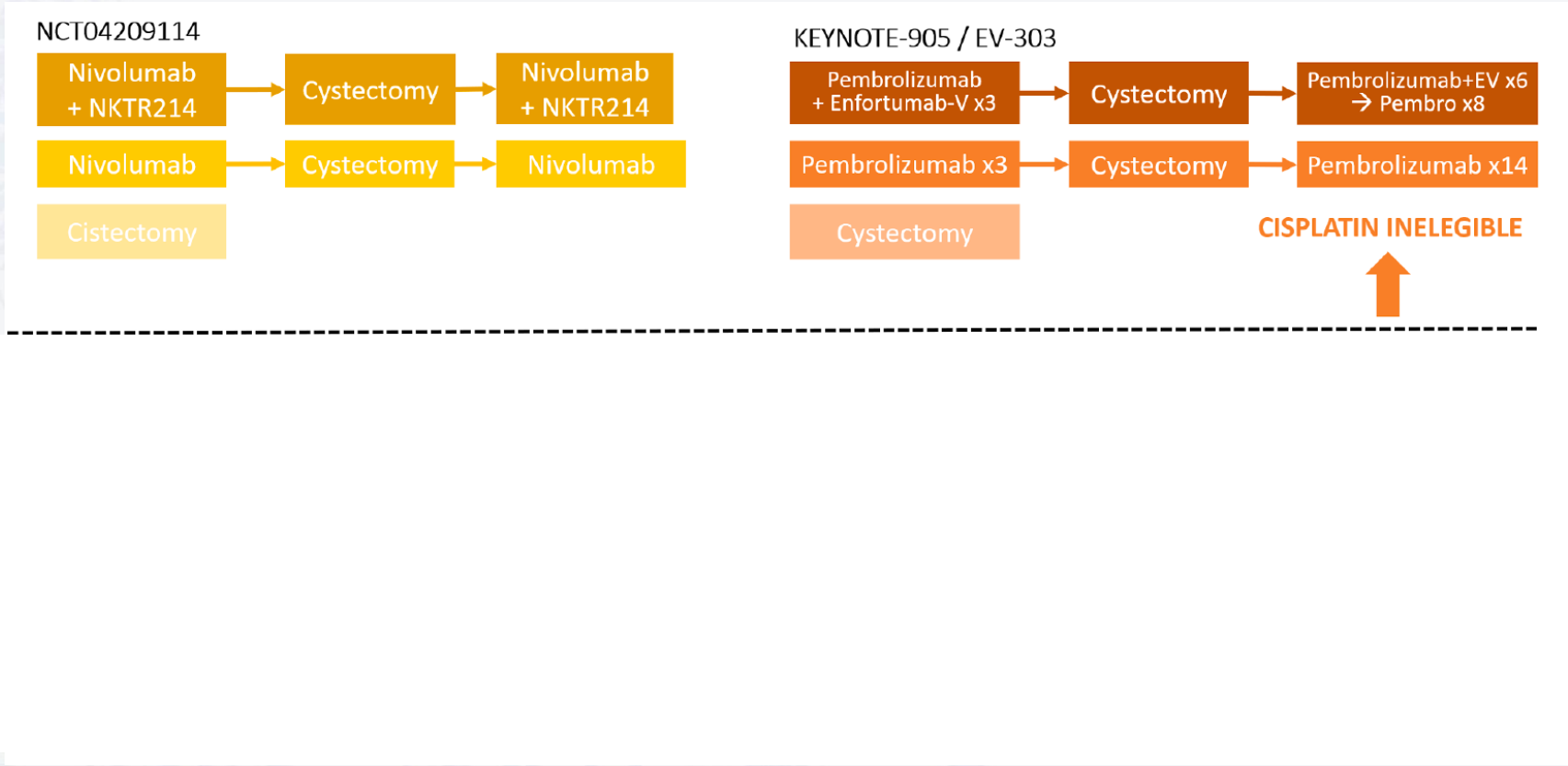
	PURE-01	ABACUS	NABUCCO	DUTRENEO	NCT02812420	BLASST-1	SAKK 06/17	GU14-188 C1	GU14-188 C2	NEODURVARIB
ypT0	38%	31% (pT0+pTis)	46%	35%	37% (pT0+pTis)	34%	33%	44%	45%	50%
<ypT2N0	56%	39%	58%	NR	58%	66%	60%	61%	52%	NR
ypT2-4 N0	20%	NR	NR	NR	21%	NR	NR	39%	48%	NR
ypN+	13%	24%	NR	NR	21%	NR	NR	14%	15%	NR
RC rate	94%	92%	100%	87%	86%	98%	88%	84%	92%	90%

M. Rey-Cardenas et al.

Avanzando hacia estadios tempranos: NEOADYUVANCIA

Ensayos Clínicos FASES 3 en neoadyuvancia

2019-21

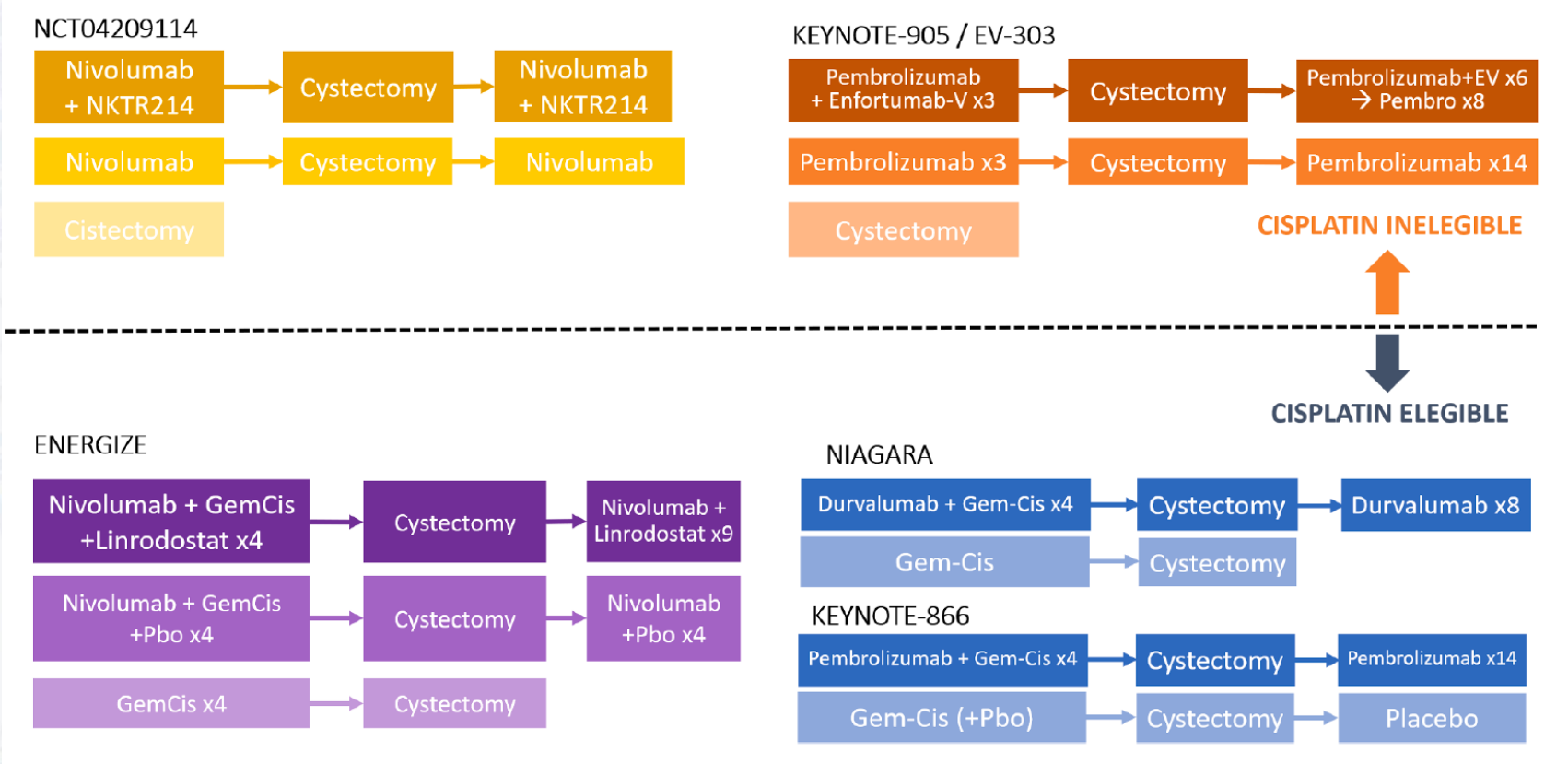


M. Rey-Cardenas et al.

Avanzando hacia estadios tempranos: NEOADYUVANCIA

Ensayos Clínicos FASES 3 en neoadyuvancia

2019-21



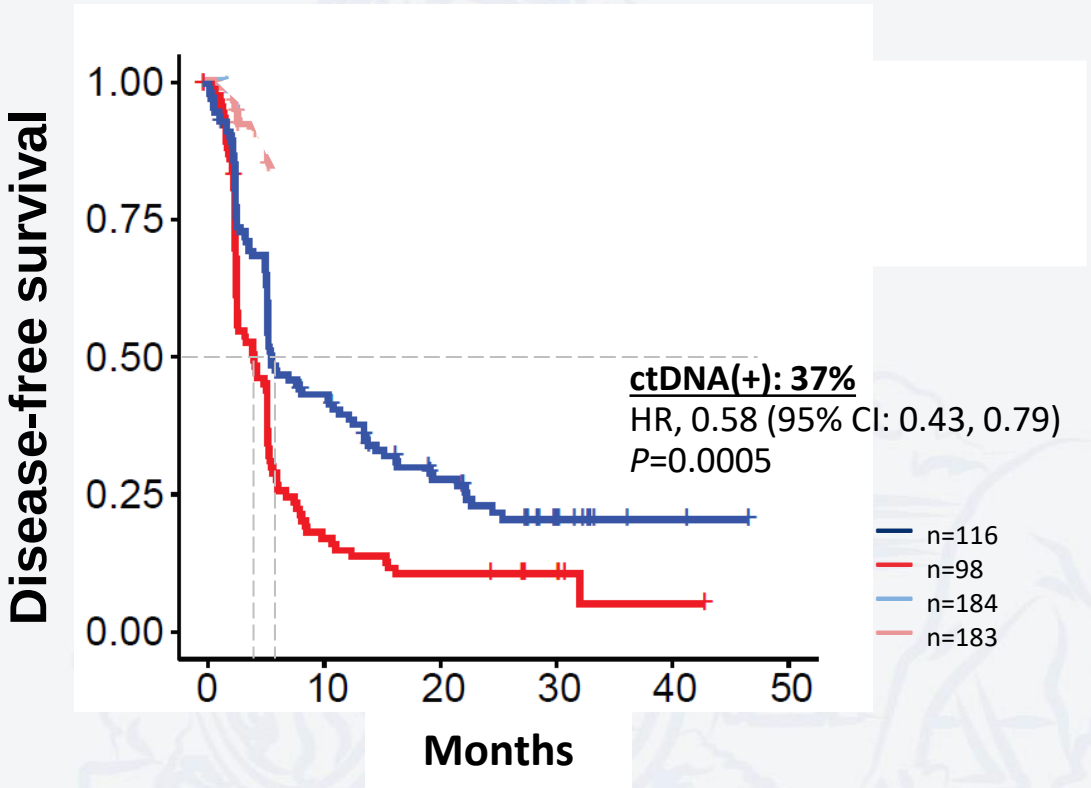
M. Rey-Cardenas et al.

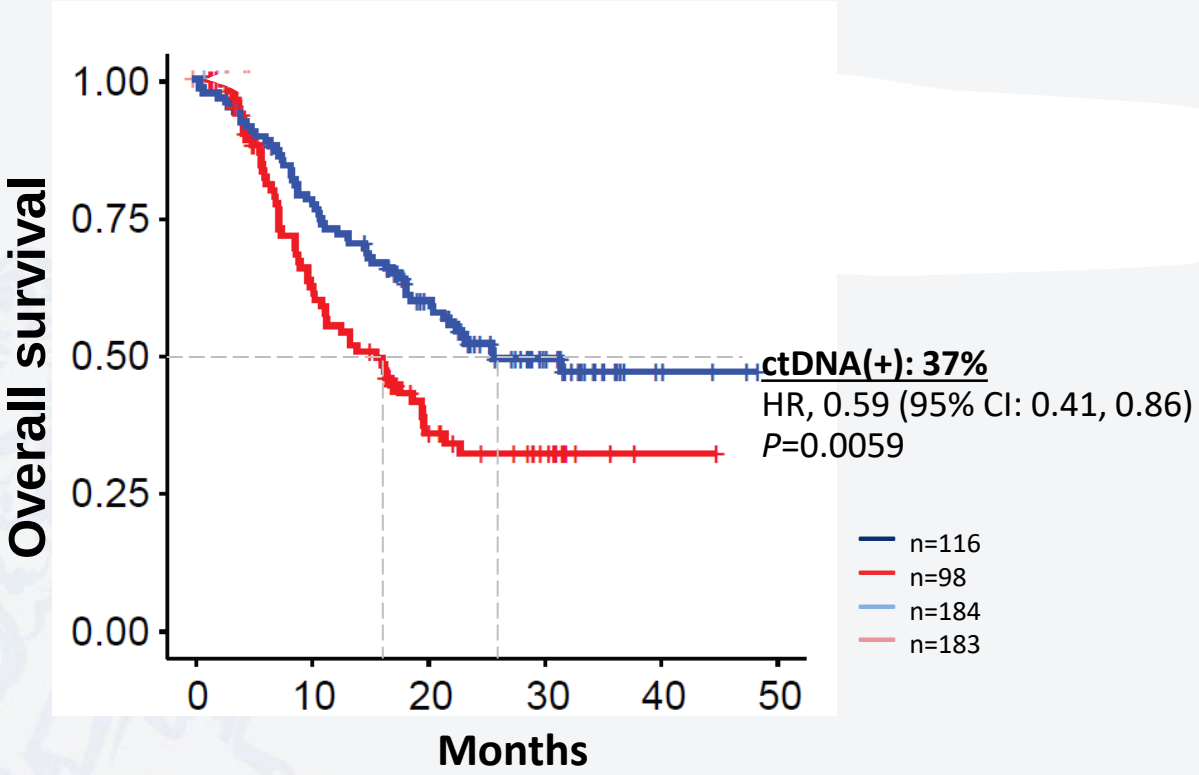
Avanzando hacia estadios tempranos: ctDNA

Avanzando hacia estadios tempranos: ctDNA

IMVIGOR 010

ctDNA(+) ctDNA(-)
Atezolizumab
Observation





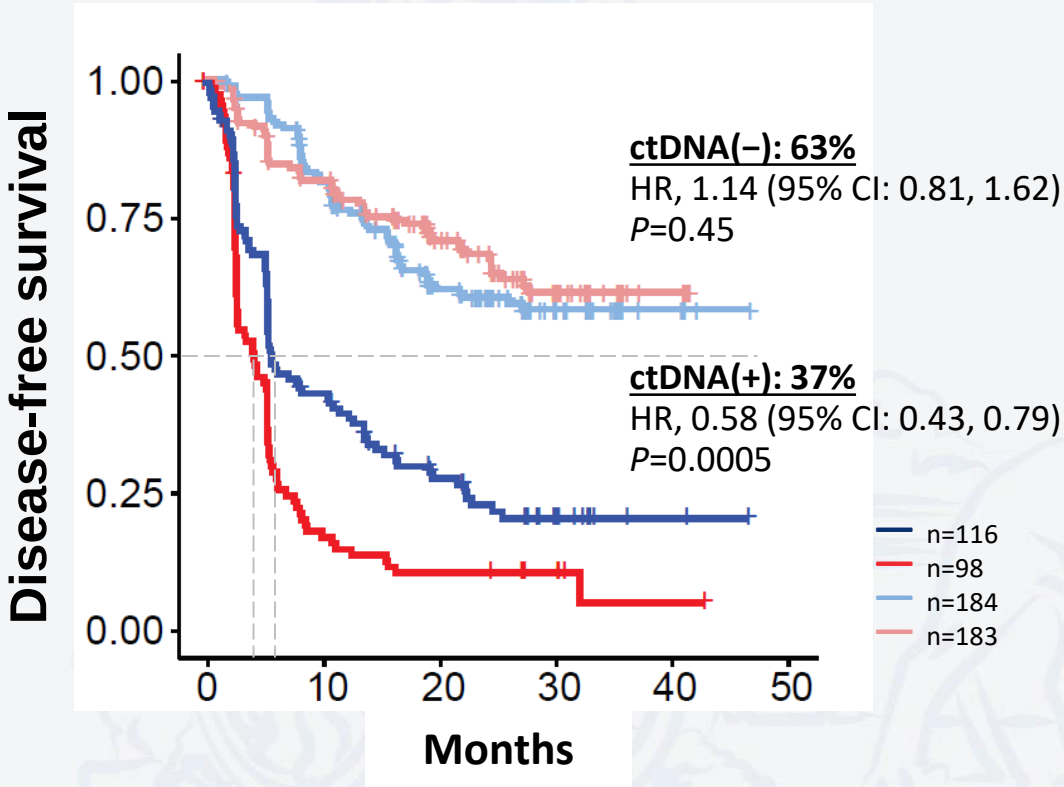
NR, not reached.

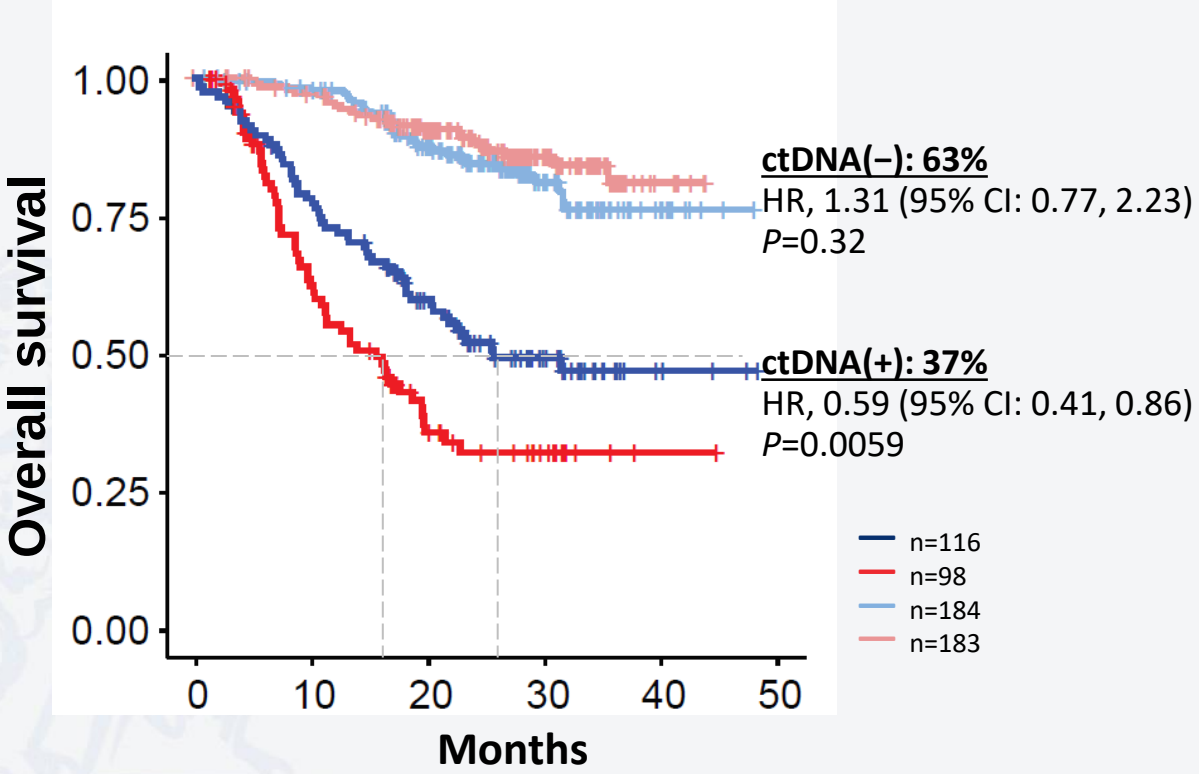
Powles et al. IMvigor010 ctDNA
https://bit.ly/2IxYllE

Avanzando hacia estadios tempranos: ctDNA

IMVIGOR 010

ctDNA(+) ctDNA(-)
Atezolizumab
Observation





NR, not reached.

Powles et al. IMvigor010 ctDNA
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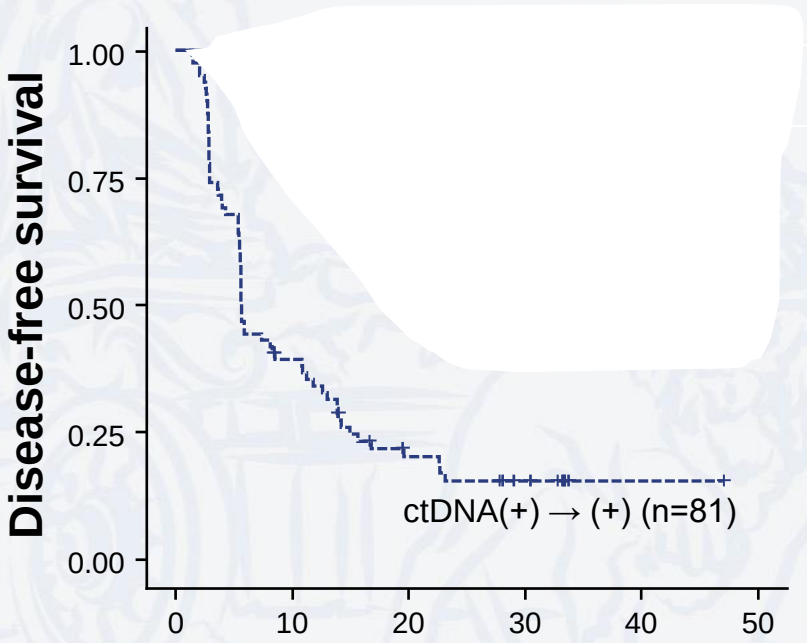
Avanzando hacia estadios tempranos: ctDNA

IMVIGOR 010

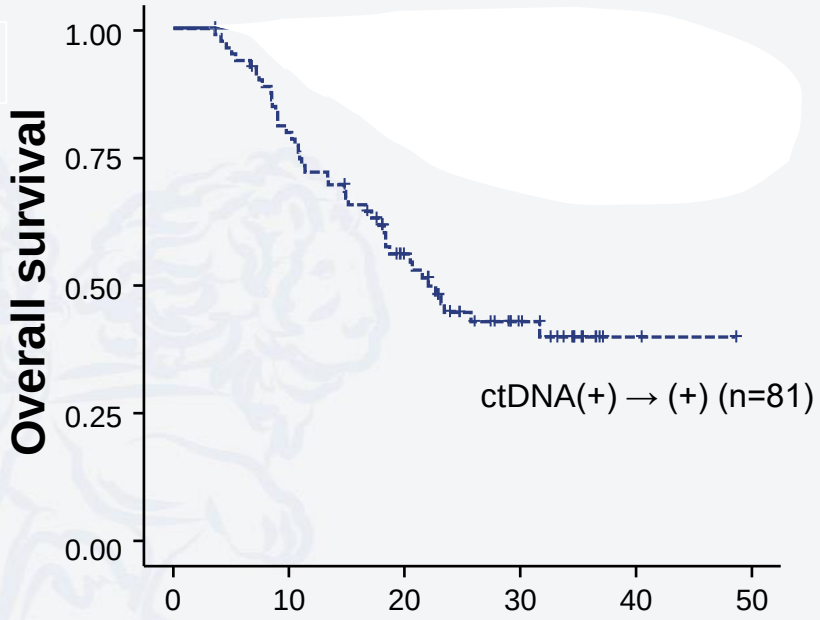
ctDNA(+) ctDNA(-)
Atezolizumab
Observation

ctDNA clearance was associated with improved outcomes

Atezolizumab arm



Atezolizumab arm



Powles et al. IMvigor010 ctDNA
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Avanzando hacia estadios tempranos: ctDNA

IMVIGOR 010

ctDNA(+) ctDNA(-)
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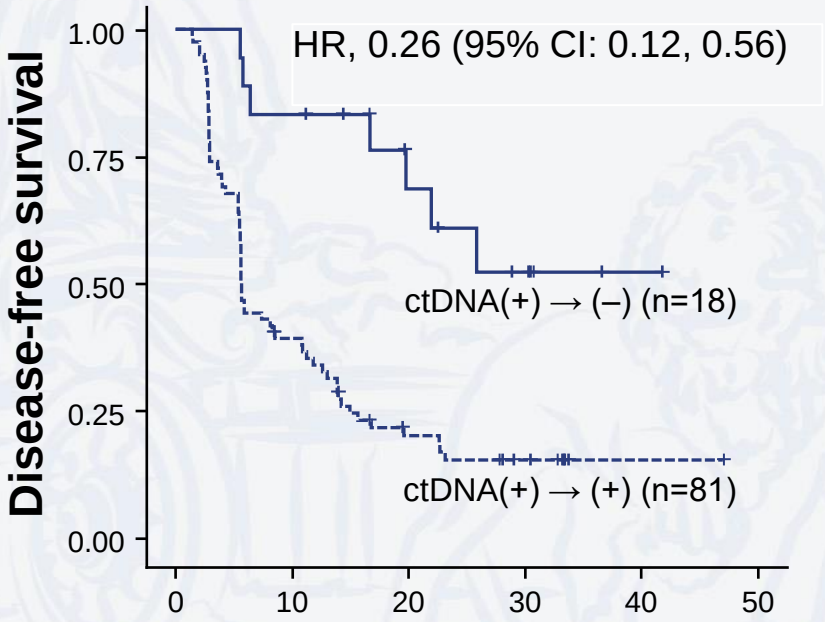

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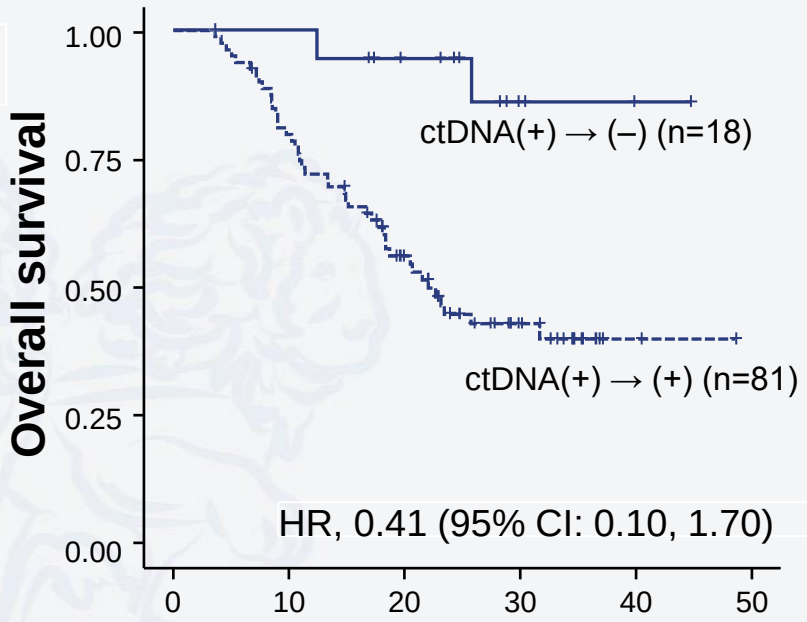
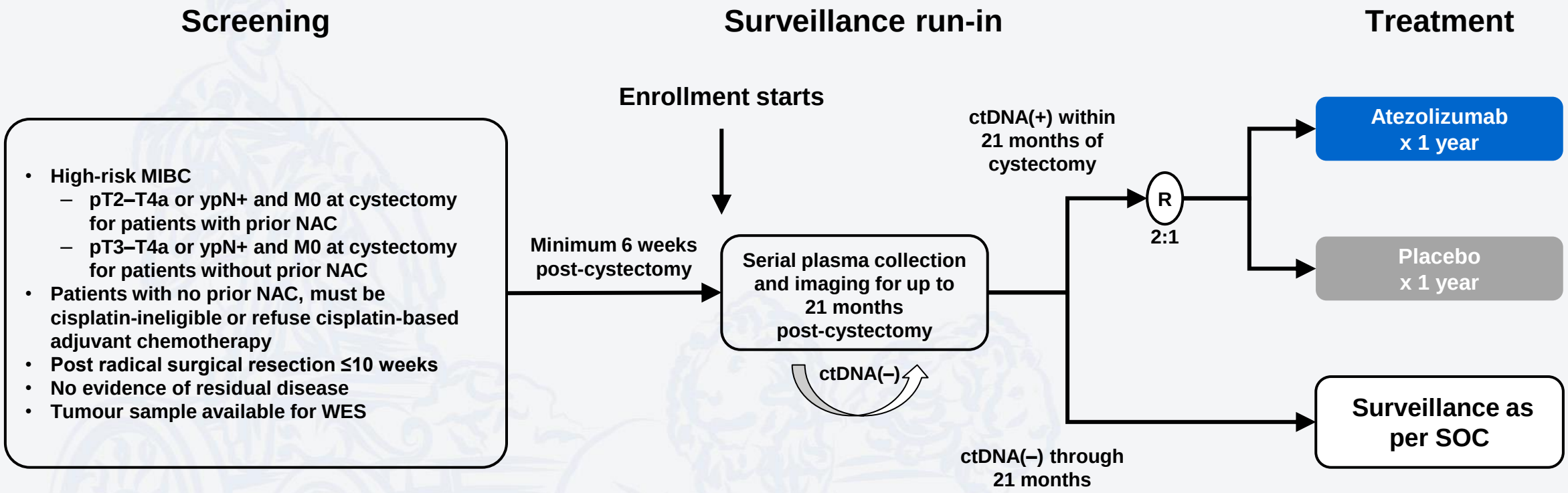


Powles et al. IMvigor010 ctDNA
https://bit.ly/2IxYllE

Avanzando hacia estadios tempranos: ctDNA

IMVIGOR 011



Conclusiones

- La inmunoterapia continua transformando el manejo del carcinoma urotelial
- Nivolumab ha sido el primer fármaco en demostrar impacto en supervivencia libre de enfermedad en pacientes con carcinoma urotelial localizado
- Quedan algunas cuestiones importantes por definir en la enfermedad localizada
- Muchos ensayos clínicos ayudarán a definir el manejo en los próximos años
- La biopsia líquida puede ser clave

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Gracias

ARÁN