



Les buzz de l'ESMO 2021 en Oncologie Thoracique

Mardi 05 Octobre 2021

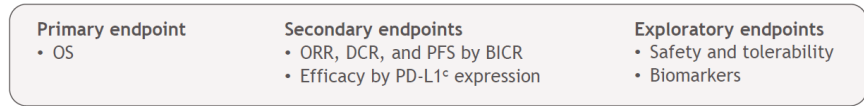
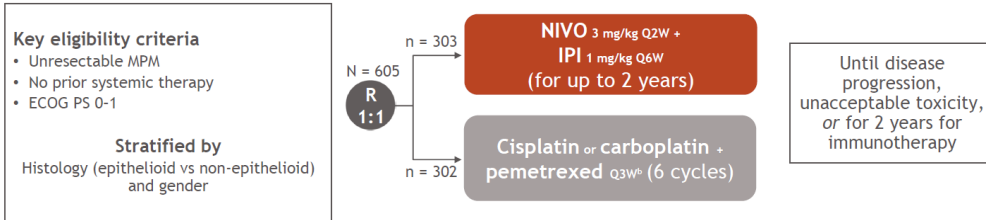
Bordeaux

Dr Charlotte Domblides



L'immunothérapie dans le mésothéliome pleural

Etude CHECKMATE 743





L'immunothérapie dans le mésothéliome pleural

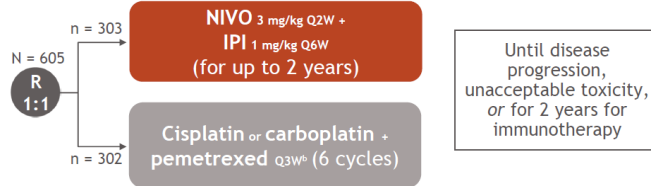
Etude CHECKMATE 743

Key eligibility criteria

- Unresectable MPM
- No prior systemic therapy
- ECOG PS 0-1

Stratified by

Histology (epithelioid vs non-epithelioid) and gender



Primary endpoint

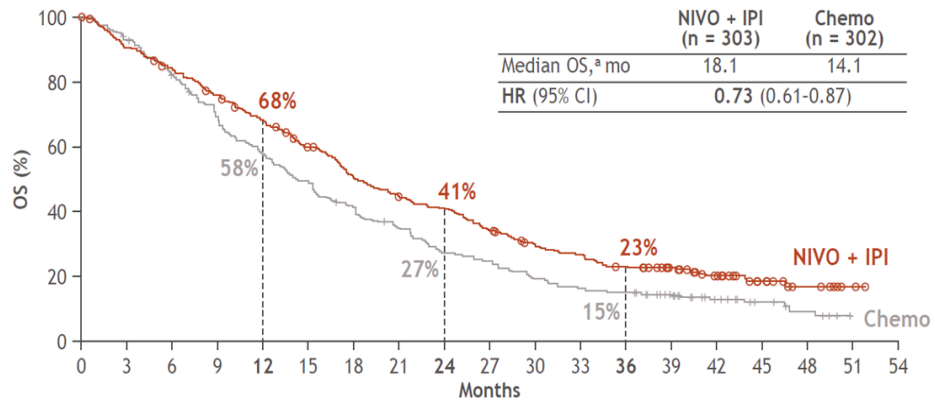
- OS

Secondary endpoints

- ORR, DCR, and PFS by BICR
- Efficacy by PD-L1^c expression

Exploratory endpoints

- Safety and tolerability
- Biomarkers



No. at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
NIVO + IPI	303	273	251	226	200	173	145	126	116	97	80	73	62	49	35	18	7	2	0
Chemo	302	269	234	192	164	138	114	97	76	69	54	46	43	33	20	11	6	0	0



L'immunothérapie dans le mésothéliome pleural

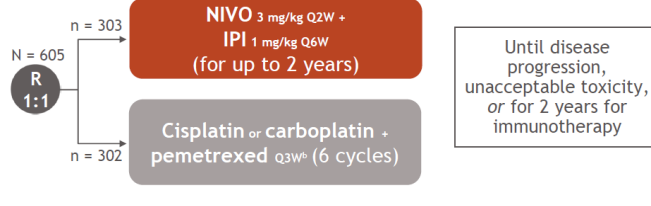
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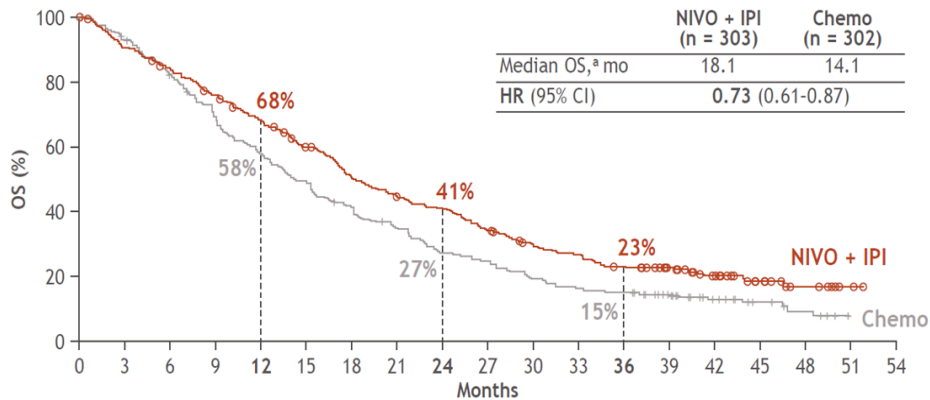
- OS

Secondary endpoints

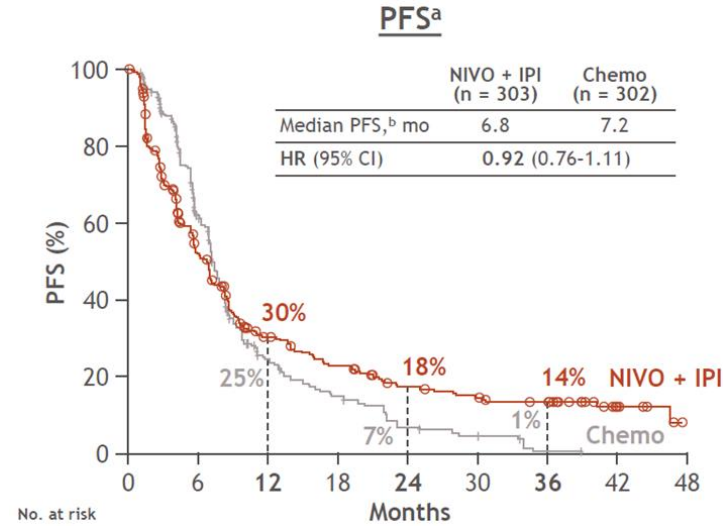
- ORR, DCR, and PFS by BICR
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Exploratory endpoints

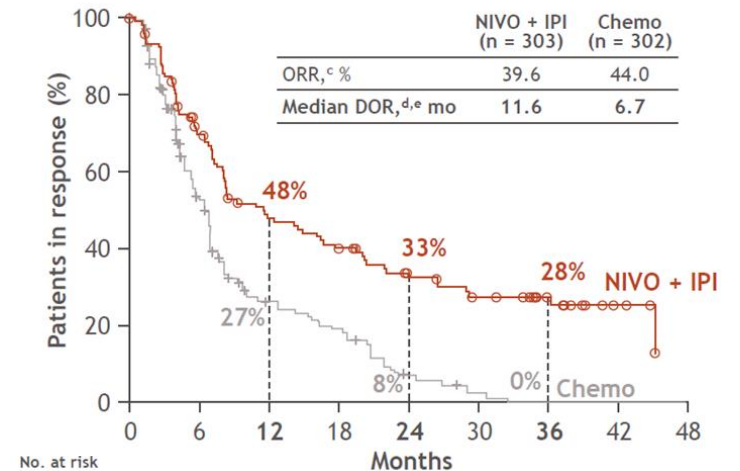
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No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
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ORR/DOR^a





L'immunothérapie dans le mésothéliome pleural

Etude CHECKMATE 743

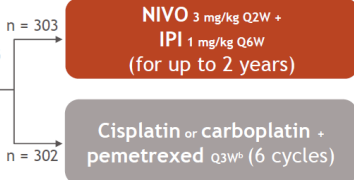
Key eligibility criteria

- Unresectable MPM
- No prior systemic therapy
- ECOG PS 0-1

Stratified by

Histology (epithelioid vs non-epithelioid) and gender

N = 605
R
1:1



Until disease progression, unacceptable toxicity, or for 2 years for immunotherapy

Primary endpoint

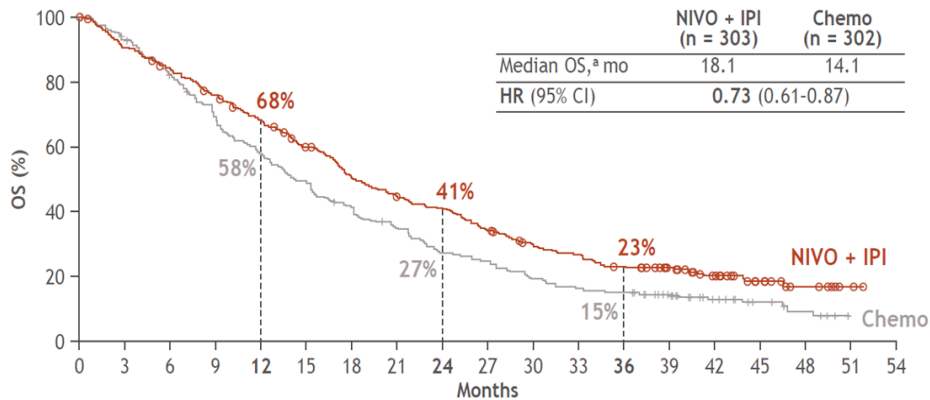
- OS

Secondary endpoints

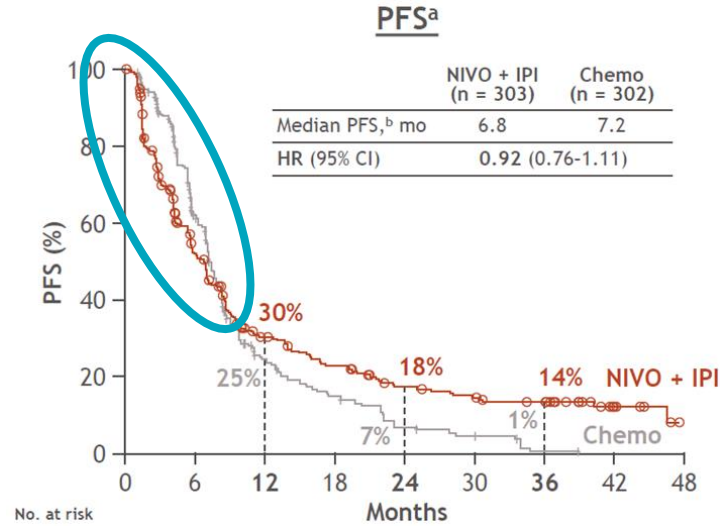
- ORR, DCR, and PFS by BICR
- Efficacy by PD-L1^c expression

Exploratory endpoints

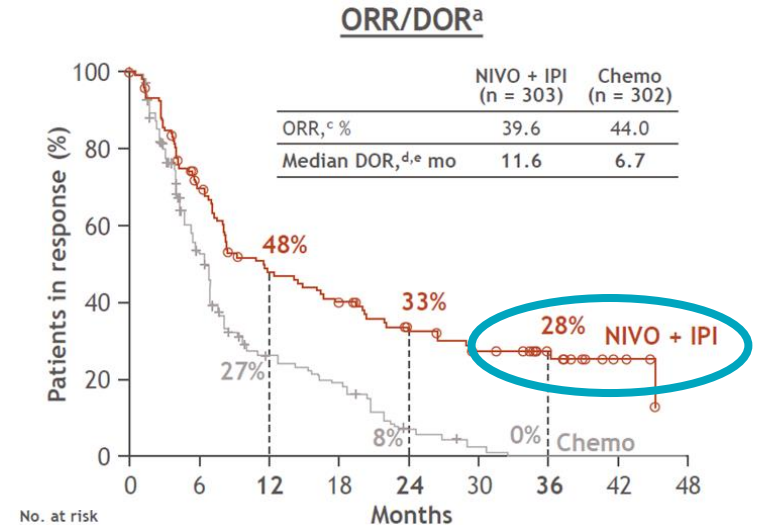
- Safety and tolerability
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No. at risk	NIVO + IPI	303	273	251	226	200	173	145	126	116	97	80	73	62	49	35	18	7	2	0
Chemo	302	269	234	192	164	138	114	97	76	69	54	46	43	33	20	11	6	0	0	0



Biomarqueurs prédictifs de (longue) réponse ?

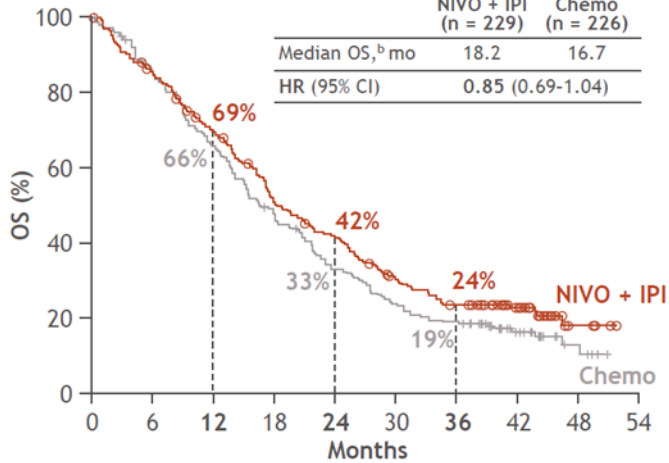




L'immunothérapie dans le mésothéliome pleural

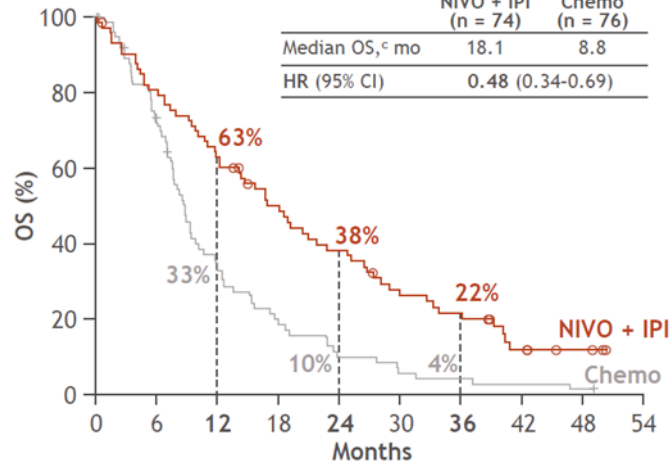
Epithelioid

	NIVO + IPI (n = 229)	Chemo (n = 226)
Median OS, ^b mo	18.2	16.7
HR (95% CI)	0.85 (0.69-1.04)	



Non-epithelioid

	NIVO + IPI (n = 74)	Chemo (n = 76)
Median OS, ^c mo	18.1	8.8
HR (95% CI)	0.48 (0.34-0.69)	

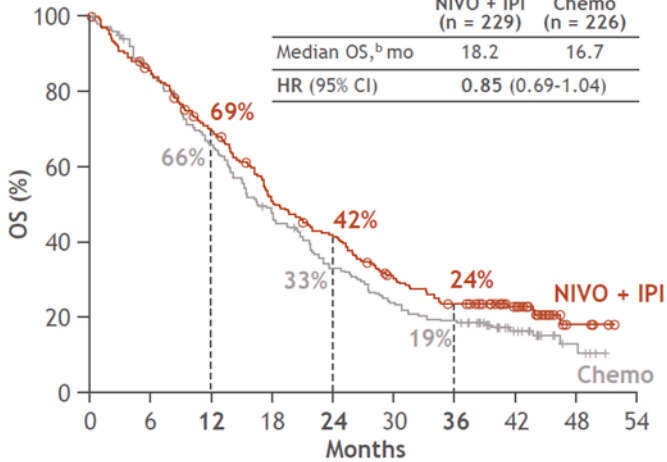




L'immunothérapie dans le mésothéliome pleural

Epithelioid

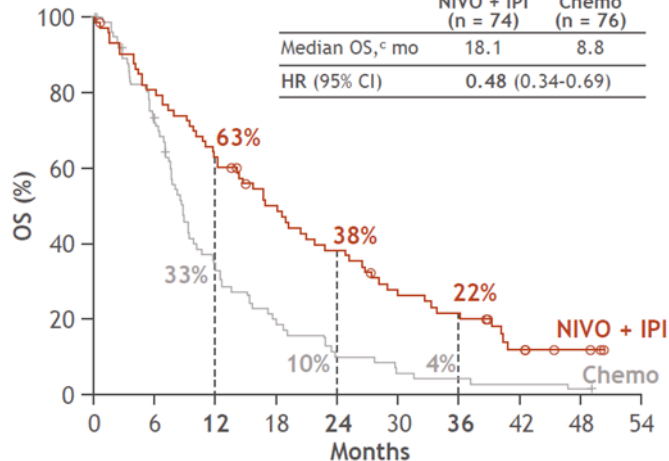
	NIVO + IPI (n = 229)	Chemo (n = 226)
Median OS, ^b mo	18.2	16.7
HR (95% CI)	0.85 (0.69-1.04)	



Signature de 4 gènes : CD8A, LAG3, STAT1 et PD-L1

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	NIVO + IPI (n = 74)	Chemo (n = 76)
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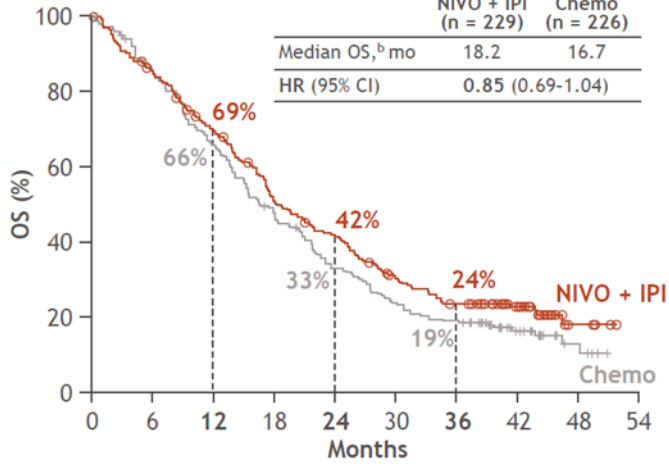




L'immunothérapie dans le mésothéliome pleural

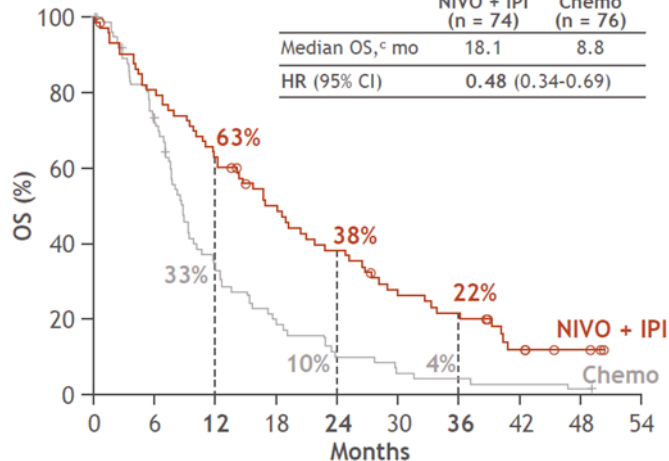
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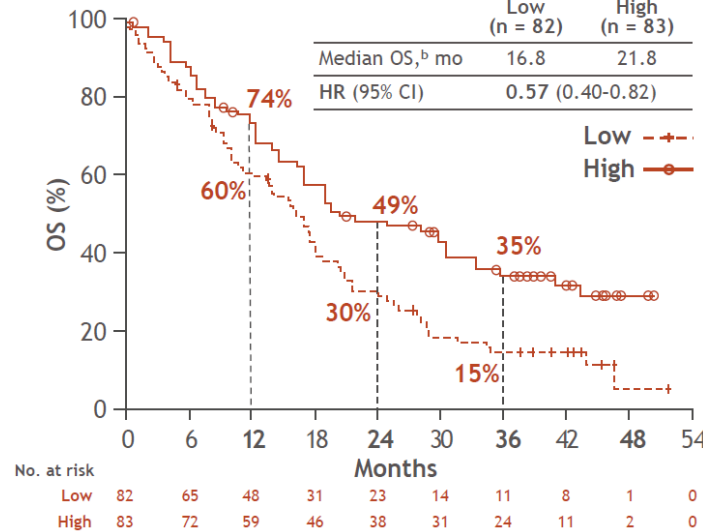
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Signature de 4 gènes : *CD8A*, *LAG3*, *STAT1* et *PD-L1*

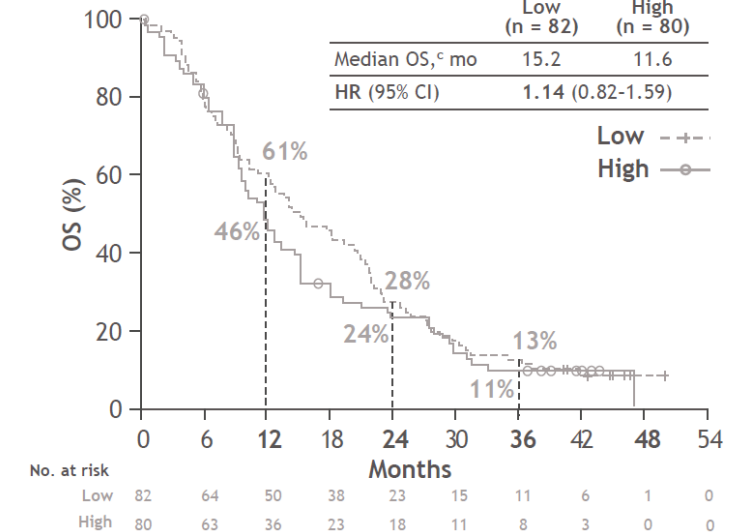
NIVO + IPI

	Low (n = 82)	High (n = 83)
Median OS, ^b mo	16.8	21.8
HR (95% CI)	0.57 (0.40-0.82)	



Chemo

	Low (n = 82)	High (n = 80)
Median OS, ^c mo	15.2	11.6
HR (95% CI)	1.14 (0.82-1.59)	

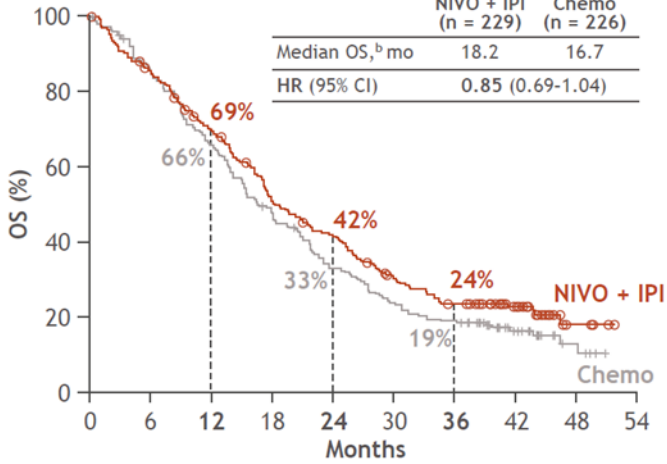




L'immunothérapie dans le mésothéliome pleural

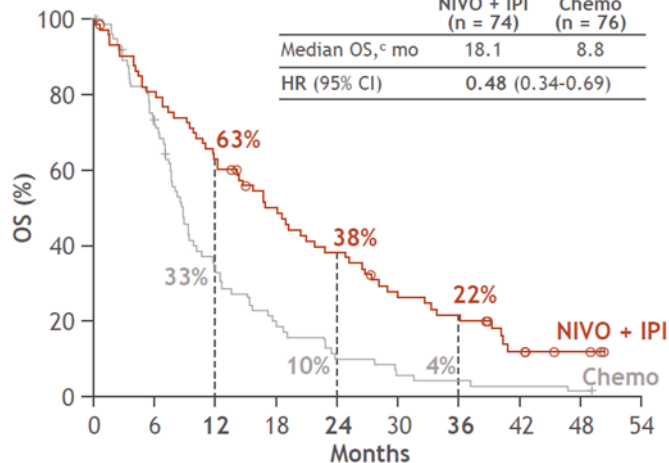
Epithelioid

	NIVO + IPI (n = 229)	Chemo (n = 226)
Median OS, ^b mo	18.2	16.7
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Non-epithelioid

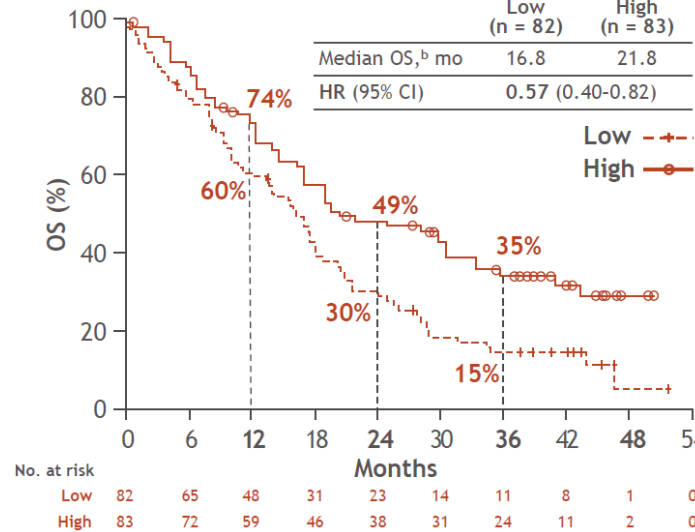
	NIVO + IPI (n = 74)	Chemo (n = 76)
Median OS, ^c mo	18.1	8.8
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Signature de 4 gènes : CD8A, LAG3, STAT1 et PD-L1

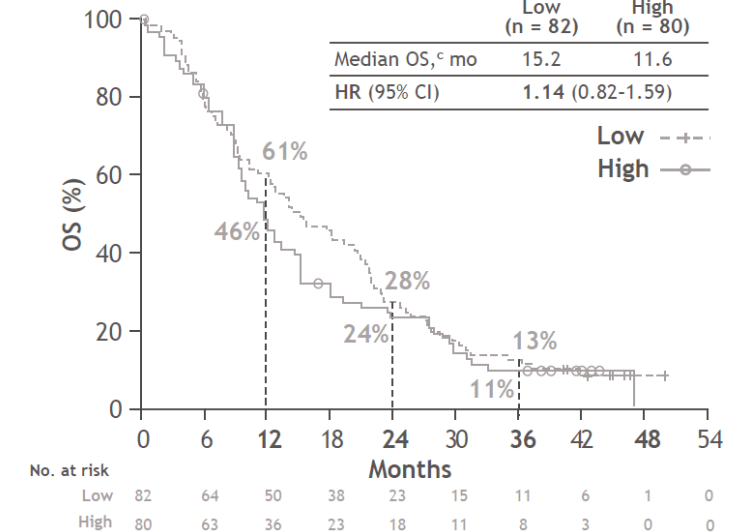
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Choix des gènes ?
Faisabilité en routine (54% exploitables) ?



L'immunothérapie dans le mésothéliome pleural

Etude CHECKMATE 743

TRAE, %	NIVO + IPI ^a (n = 300)		Chemo ^b (n = 284)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any TRAE ^c	80	31	82	32
TRAEs leading to discontinuation of any component of the regimen ^c	23	15	16	7
TRAEs leading to discontinuation of all components of the regimen	17	13	8	5
Serious TRAEs ^c	21	16	8	6
Treatment-related deaths	1 ^d		<1 ^e	

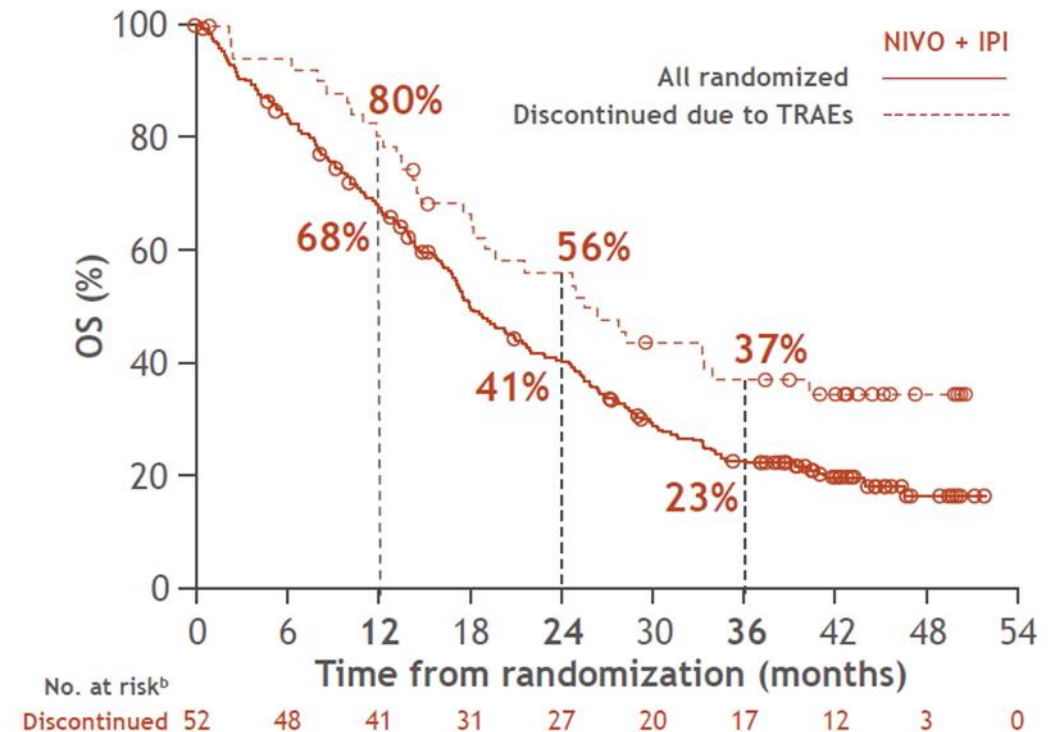


L'immunothérapie dans le mésothéliome pleural

Etude CHECKMATE 743

TRAE, %	NIVO + IPI ^a (n = 300)		Chemo ^b (n = 284)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any TRAE ^c	80	31	82	32
TRAEs leading to discontinuation of any component of the regimen ^c	23	15	16	7
TRAEs leading to discontinuation of all components of the regimen	17	13	8	5
Serious TRAEs ^c	21	16	8	6
Treatment-related deaths	1 ^d		<1 ^e	

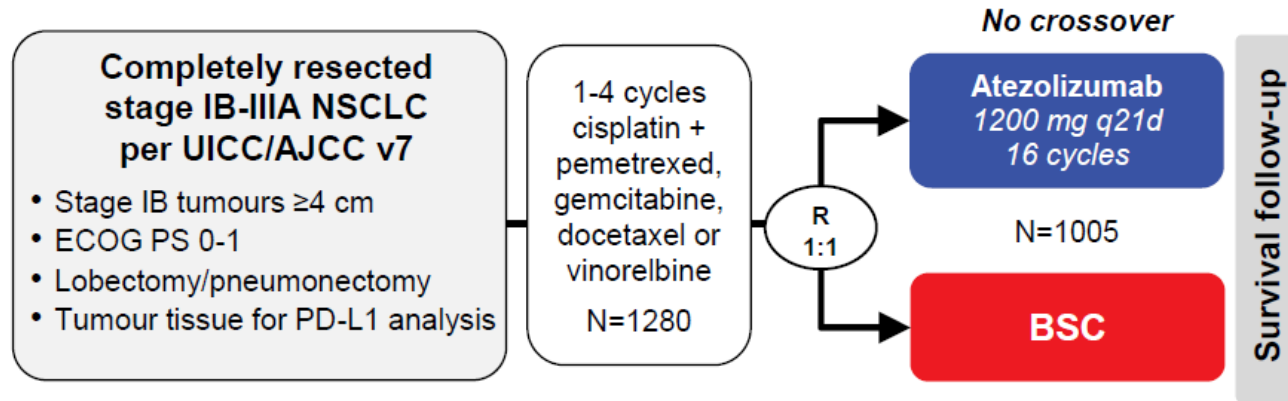
Réponse maintenue même en cas d'arrêt pour toxicité





L'immunothérapie adjuvante

Etude IMpower-010



Stratification factors

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

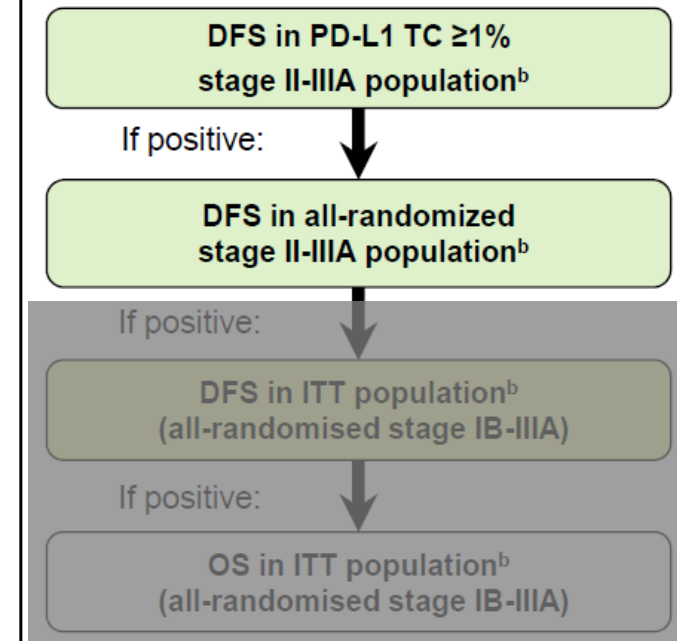
Primary endpoints

- Investigator-assessed DFS tested hierarchically:
 1. PD-L1 TC $\geq 1\%$ (SP263) stage II-IIIa population
 2. All-randomised stage II-IIIa population
 3. ITT (all-randomised stage IB-IIIa) population

Key secondary endpoints

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

Hierarchical statistical testing

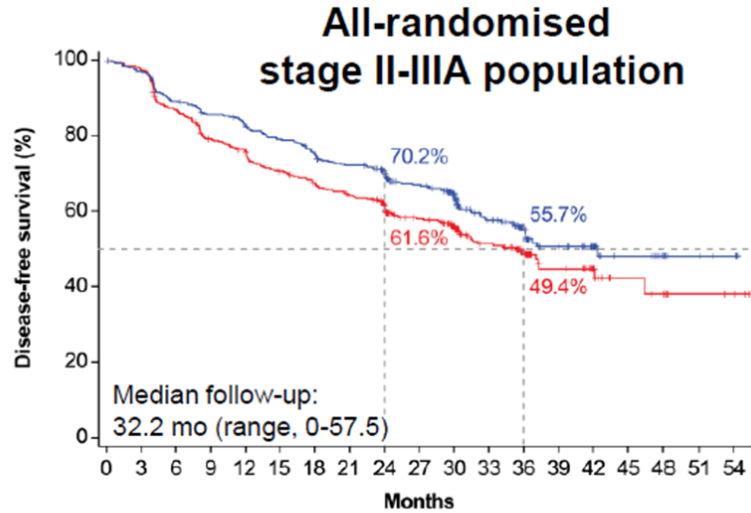


- Endpoint was met at DFS IA
- Endpoint was not met at DFS IA, and follow-up is ongoing
- OS data were immature, and endpoint was not formally tested



L'immunothérapie adjuvante

Etude IMpower-010



No. at risk

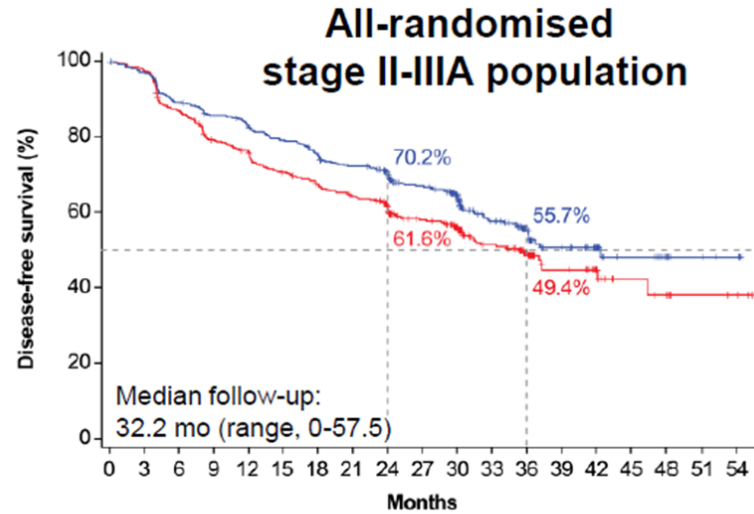
Atezolizumab 442 418 384 367 352 337 319 305 269 225 185 120 84 48 34 16 11 5 3
 BSC 440 412 366 331 314 292 277 263 230 182 146 102 71 35 22 10 8 4 3

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



L'immunothérapie adjuvante

Etude IMpower-010

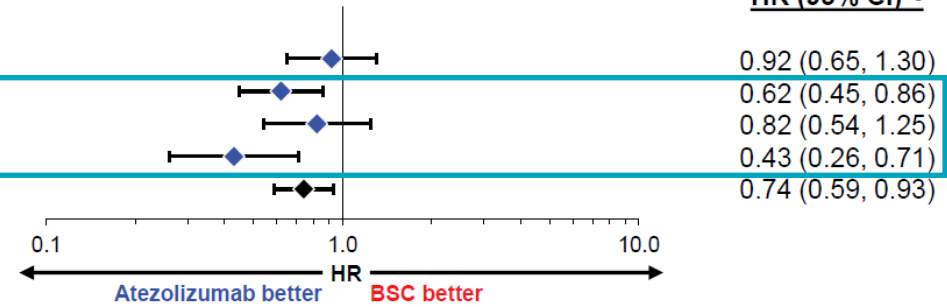


Subgroup (excluding EGFR/ALK+)^e

PD-L1 status by SP263

Subgroup	n
TC <1%	312
TC ≥1%	410
TC 1-49%	201
TC ≥50%	209
All patients ^h	743

HR (95% CI)^{f,g}



No. at risk

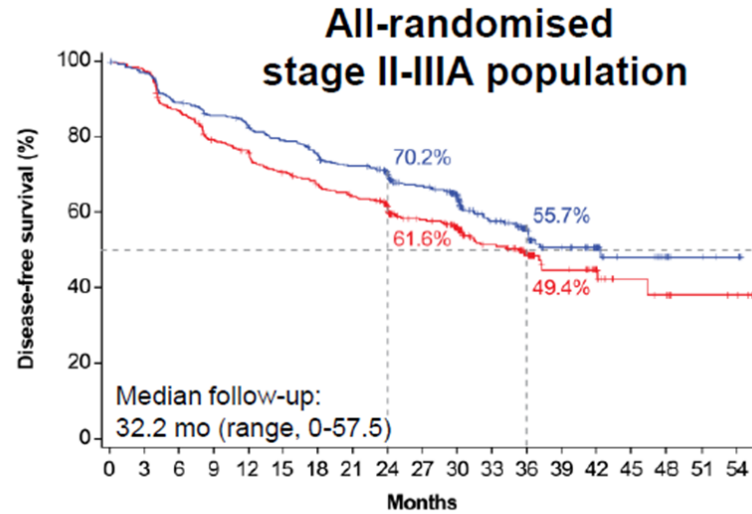
Months	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Atezolizumab	442	418	384	367	352	337	319	305	269	225	185	120	84	48	34	16	11	5	3
BSC	440	412	366	331	314	292	277	263	230	182	146	102	71	35	22	10	8	4	3

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L'immunothérapie adjuvante

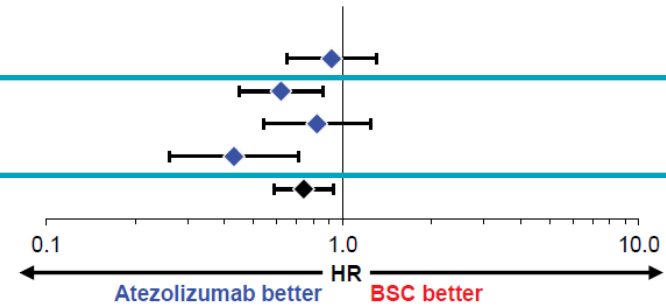
Etude IMpower-010



Subgroup (excluding EGFR/ALK+)^e

PD-L1 status by SP263

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



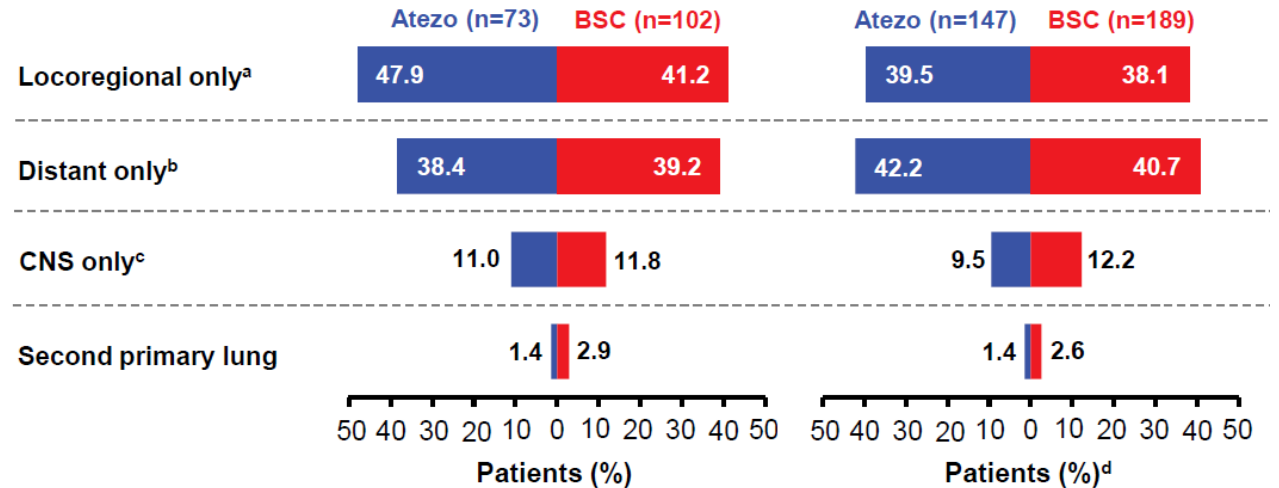
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PD-L1 TC ≥1% stage II-IIIa

All randomised stage II-IIIa





L'immunothérapie adjuvante

Etude IMpower-010

PD-L1 TC ≥1% stage II-IIIa

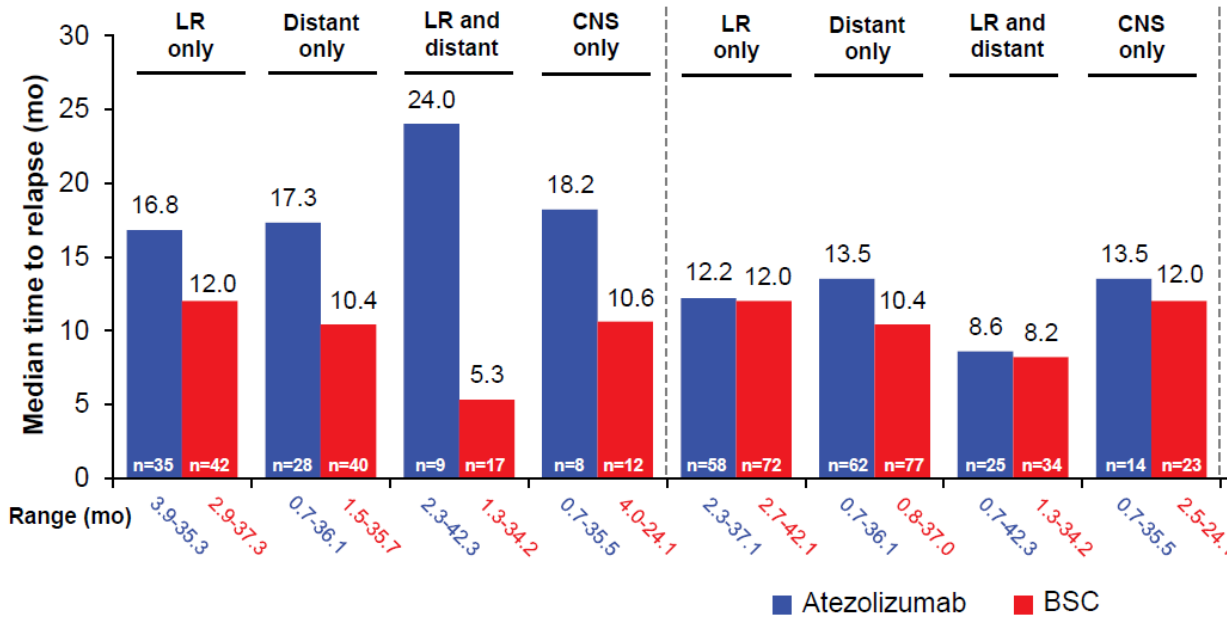
All randomised stage II-IIIa

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

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

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

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





L'immunothérapie adjuvante

Etude IMpower-010

PD-L1 TC ≥1% stage II-IIIa

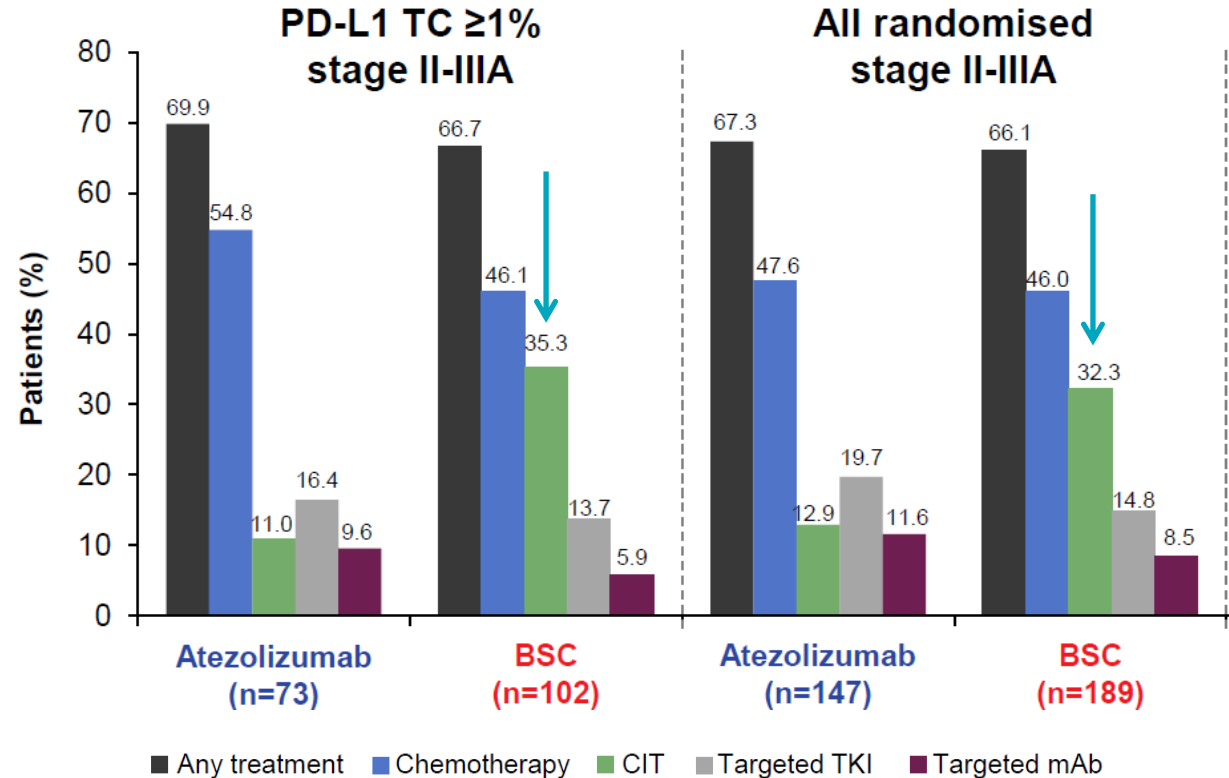
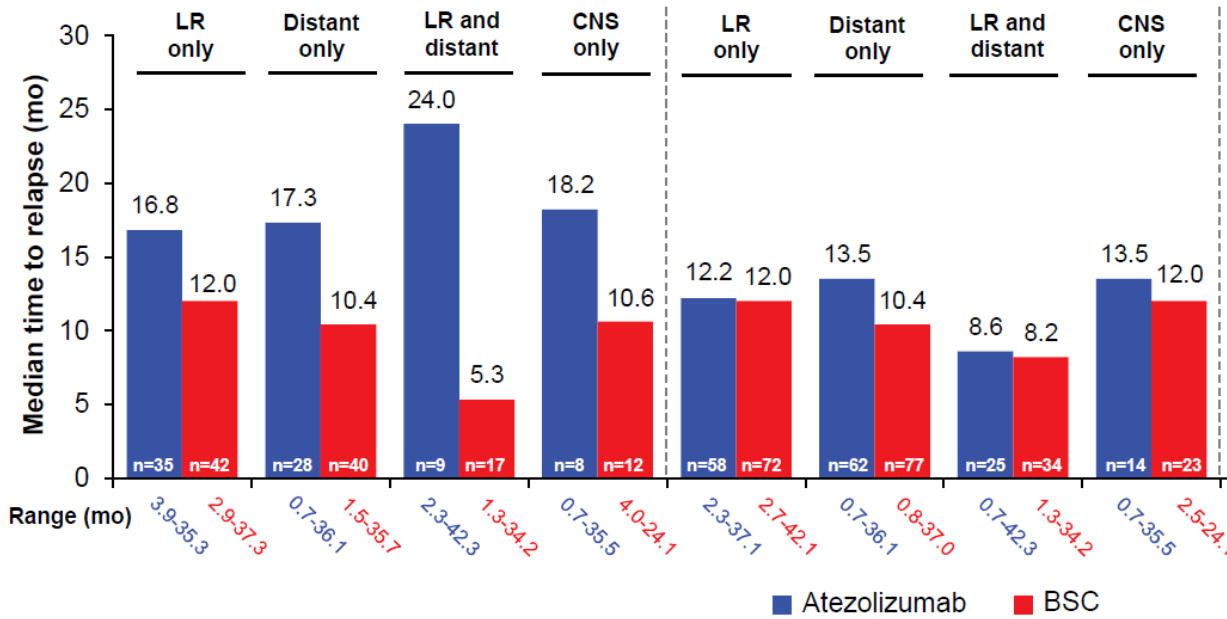
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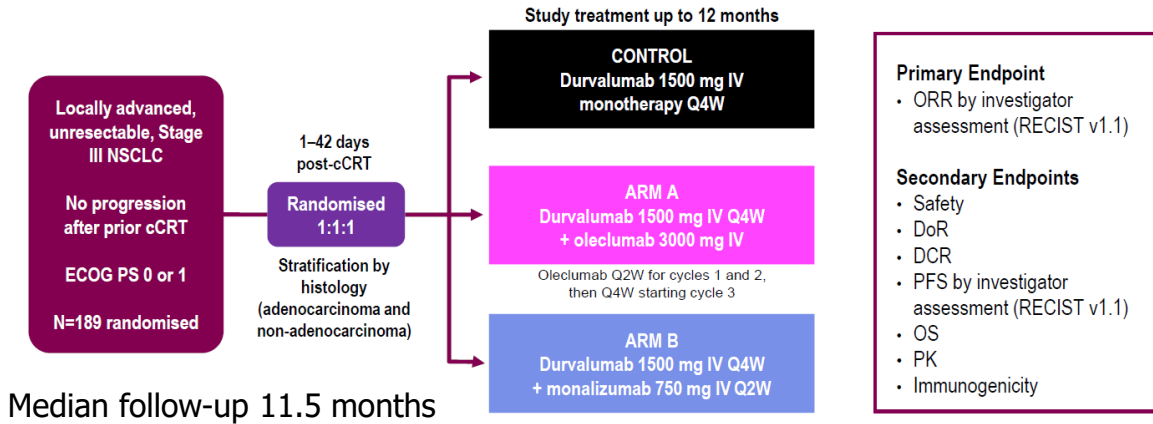
Median (range) time to any relapse: 11.1 mo (0.8-42.1)





Association d'immunomodulateurs dans les stades III

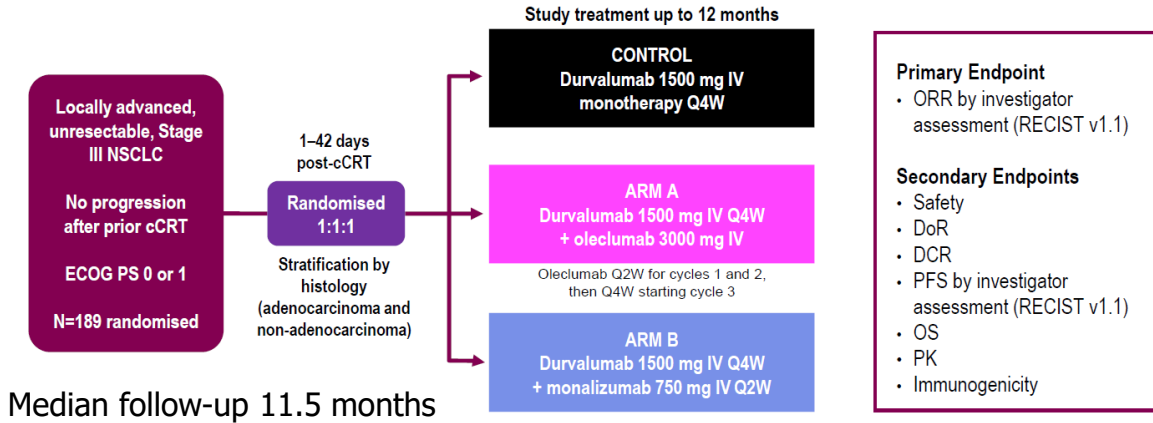
Etude COAST





Association d'immunomodulateurs dans les stades III

Etude COAST

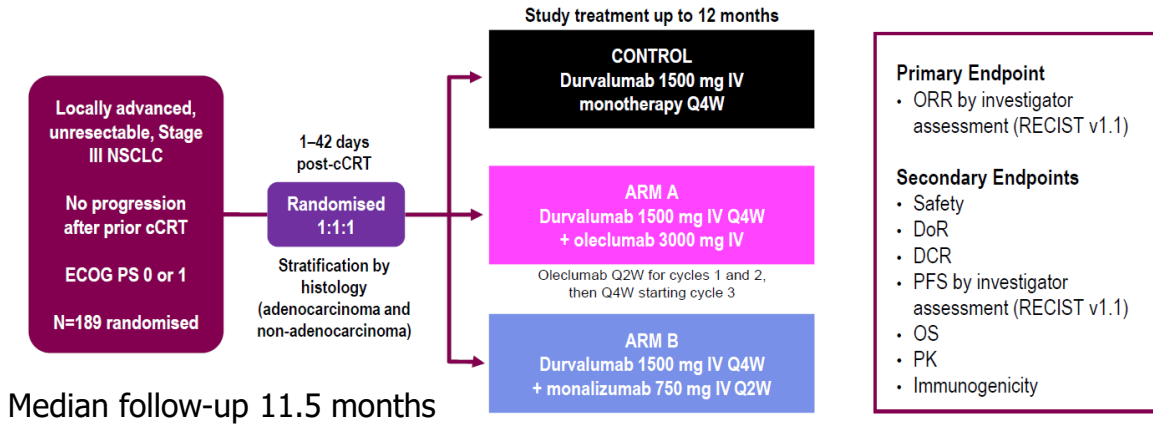


Characteristic ^a	D (N=67)	D+O (N=60)	D+M (N=62)
Histology, %			
Squamous / Non-squamous	44.8 / 55.2	40.0 / 60.0	43.5 / 56.5
Disease stage at study entry, %			
IIIA / IIIB / IIIC	40.3 / 50.7 / 9.0	45.0 / 48.3 / 6.7	51.6 / 43.5 / 4.8
PD-L1 status, %^b			
TC ≥1% / TC <1% / Unknown	37.3 / 20.9 / 41.8	38.3 / 11.7 / 50.0	29.0 / 19.4 / 51.6
Prior RT dose, %			
54-66 Gy / >66 Gy	92.5 / 7.5	90.0 / 10.0	91.9 / 8.1
Time from last RT to randomisation, %			
<14 days / 14-28 days / 29-42 days	13.4 / 40.3 / 46.3	6.7 / 45.0 / 48.3	9.7 / 48.4 / 41.9
Prior platinum-based CT, %			
Cisplatin / Carboplatin	34.3 / 64.2	46.7 / 46.7	24.2 / 71.0



Association d'immunomodulateurs dans les stades III

Etude COAST



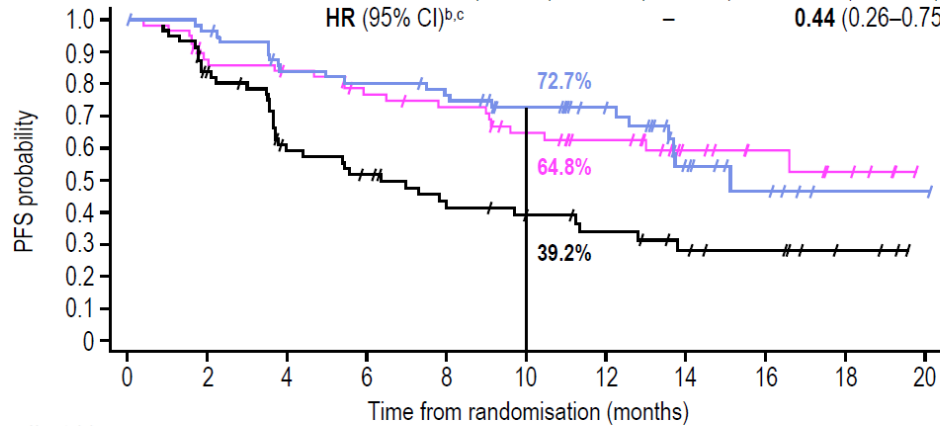
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IIIA / IIIB / IIIC	40.3 / 50.7 / 9.0	45.0 / 48.3 / 6.7	51.6 / 43.5 / 4.8
PD-L1 status, %^b			
TC ≥1% / TC <1% / Unknown	37.3 / 20.9 / 41.8	38.3 / 11.7 / 50.0	29.0 / 19.4 / 51.6
Prior RT dose, %			
54-66 Gy / >66 Gy	92.5 / 7.5	90.0 / 10.0	91.9 / 8.1
Time from last RT to randomisation, %			
<14 days / 14-28 days / 29-42 days	13.4 / 40.3 / 46.3	6.7 / 45.0 / 48.3	9.7 / 48.4 / 41.9
Prior platinum-based CT, %			
Cisplatin / Carboplatin	34.3 / 64.2	46.7 / 46.7	24.2 / 71.0



Association d'immunomodulateurs dans les stades III

Etude COAST

	D	D+O	D+M
Events/patients, n	38/67	22/60	21/62
mPFS, months (95% CI) ^a	6.3 (3.7–11.2)	NR (10.4–NE)	15.1 (13.6–NE)
HR (95% CI) ^{b,c}	–	0.44 (0.26–0.75)	0.65 (0.49–0.85)



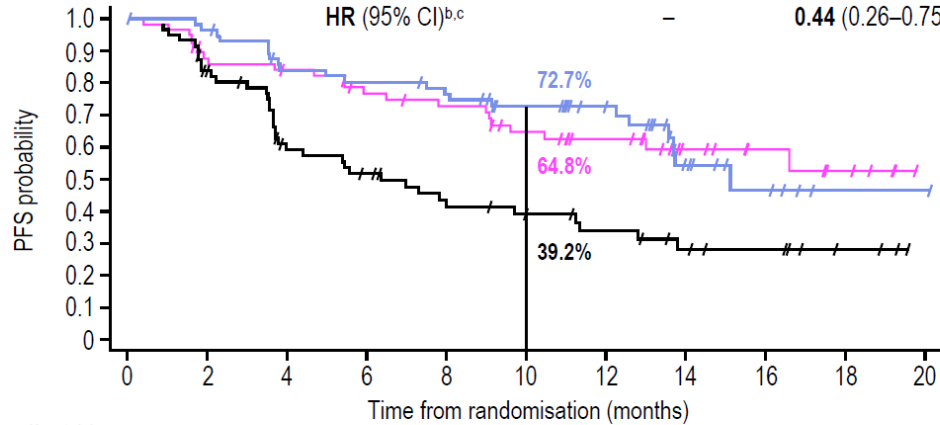
No. at risk	D	D+O	D+M
0	67	60	62
2	50	49	55
4	32	46	46
6	32	40	44
8	20	37	41
10	16	30	35
12	13	22	25
14	9	13	11
16	7	9	6
18	3	5	1
20	0	0	1



Association d'immunomodulateurs dans les stades III

Etude COAST

	D	D+O	D+M
Events/patients, n	38/67	22/60	21/62
mPFS, months (95% CI) ^a	6.3 (3.7–11.2)	NR (10.4–NE)	15.1 (13.6–NE)
HR (95% CI) ^{b,c}	–	0.44 (0.26–0.75)	0.65 (0.49–0.85)



No. at risk	D	D+O	D+M
0	67	60	62
2	50	49	50
4	32	46	46
6	32	40	40
8	20	37	37
10	16	30	30
12	13	22	22
14	9	13	13
16	7	9	9
18	3	5	5
20	0	0	0

Bras contrôle moins performant que dans PACIFIC

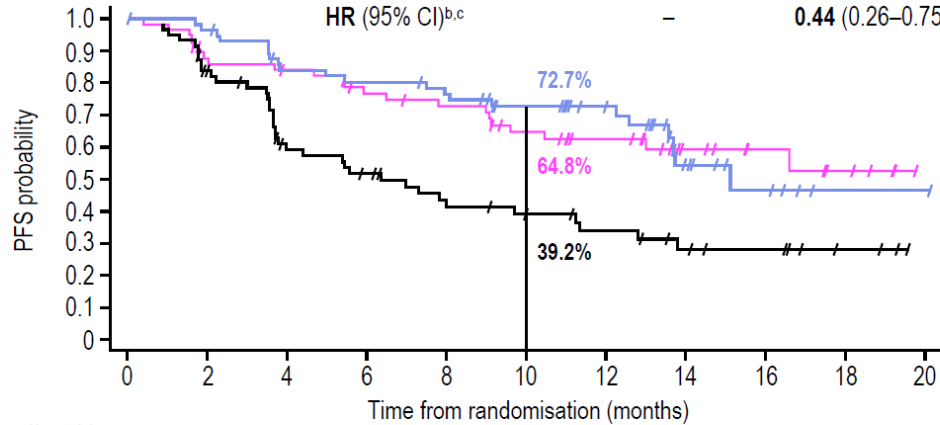
	No. of events/ total no. of patients (%)	Median PFS (95% CI), months	12-month PFS rate (95% CI) %
Durvalumab	266/476 (55.9)	17.2 (12.3–23.8)	55.3 (50.5–59.8)
Placebo	174/237 (73.4)	5.6 (4.6–7.7)	34.4 (28.2–40.7)



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20	0	0	17

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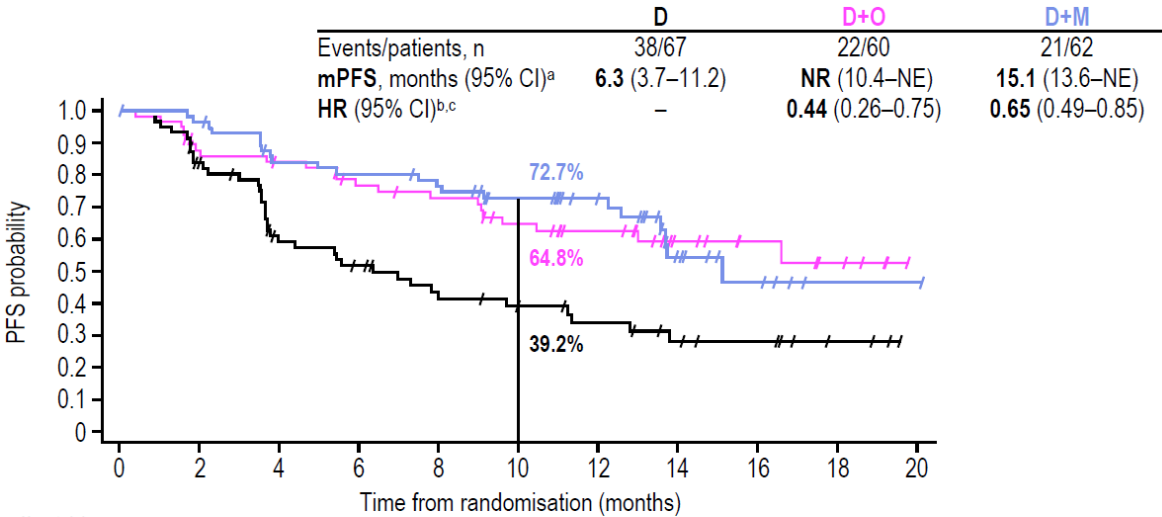
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Antitumour activity	D (N=67)	D+O (N=60)	D+M (N=62)
Confirmed ORR (95% CI) ^b % [n]	17.9 (9.6, 29.2) [12]	30.0 (18.8, 43.2) [18]	35.5 (23.7, 48.7) [22]
DCR at 16 weeks (95% CI) ^{a,c} % [n]	58.2 (45.5, 70.2) [39]	81.7 (69.6, 90.5) [49]	77.4 (65.0, 87.1) [48]
Median DoR (95% CI) ^a months Range	NR (2.3, NA) 0.0+, 17.5+	12.9 (6.7, NA) 0.0+, 16.9+	NR (9.0, NA) 1.9+, 18.4+



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Etude COAST



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Incidence, n (%)	D (N=66)	D+O (N=59)	D+M (N=61)
Any TEAEs	65 (98.5)	57 (96.6)	61 (100)
Grade ≥3 TEAEs	26 (39.4)	24 (40.7)	17 (27.9)
Study drug-related AEs	49 (74.2)	46 (78.0)	50 (82.0)
Study drug-related SAEs	6 (9.1)	7 (11.9)	5 (8.2)
AEs leading to discontinuation	11 (16.7)	9 (15.3)	9 (14.8)
Deaths ^{a,b}	7 (10.6)	4 (6.8)	3 (4.9)



Place du pembrolizumab seul chez les PD-L1 élevés

Etude sur la base de données FLATIRON



Place du pembrolizumab seul chez les PD-L1 élevés

Etude sur la base de données FLATIRON

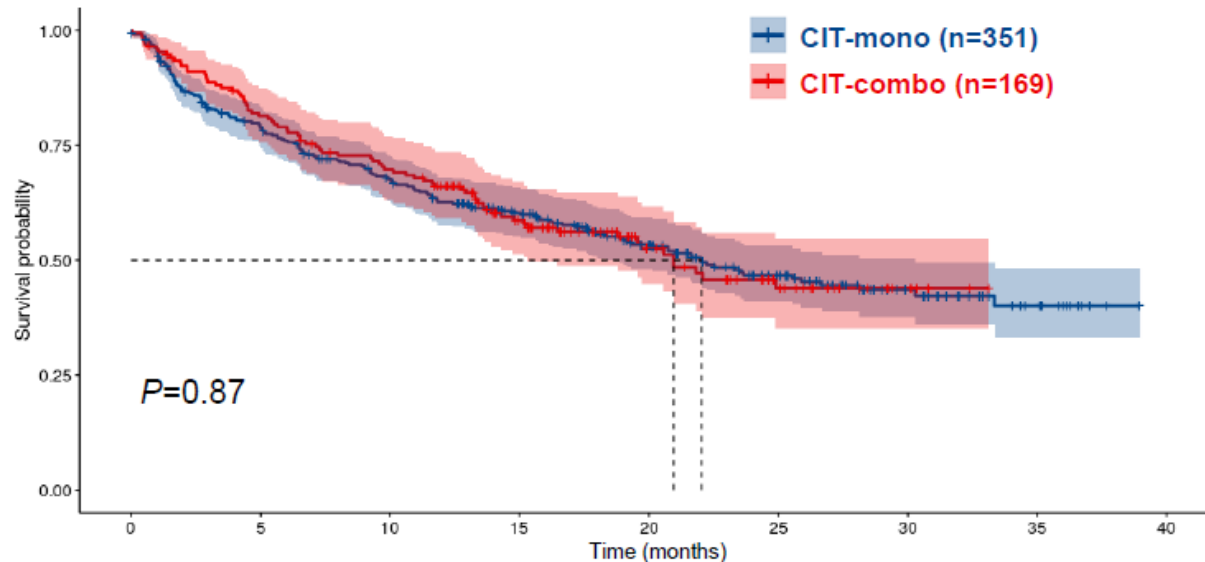
Characteristic, n (%)	CIT-mono (n=351)	CIT-chemo (n=169)
Age group, years		
< 65	109 (31)	77 (46)
65-74	112 (32)	58 (34)
≥75	130 (37)	34 (20)



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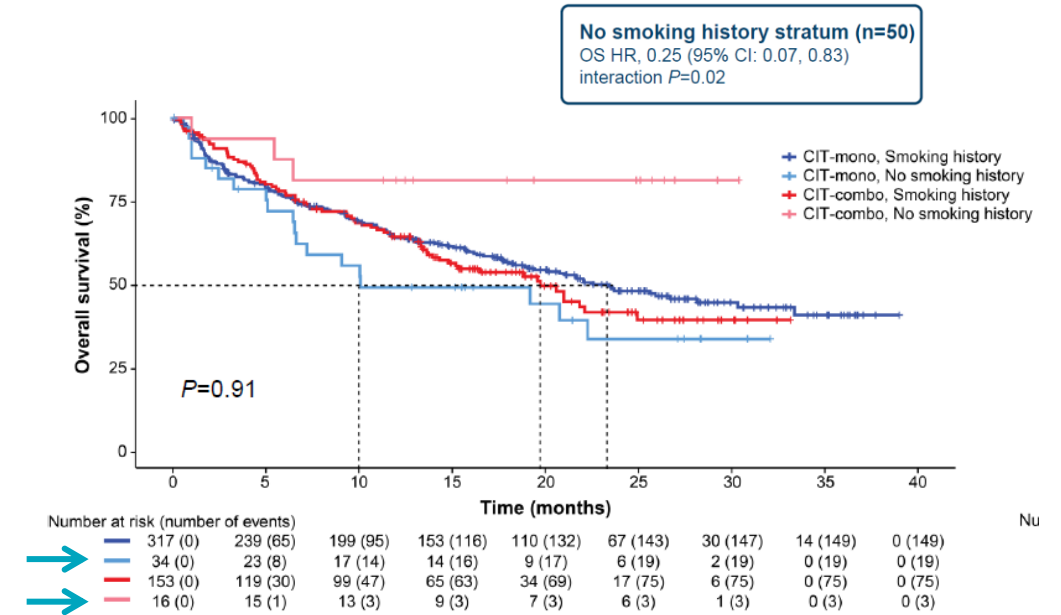
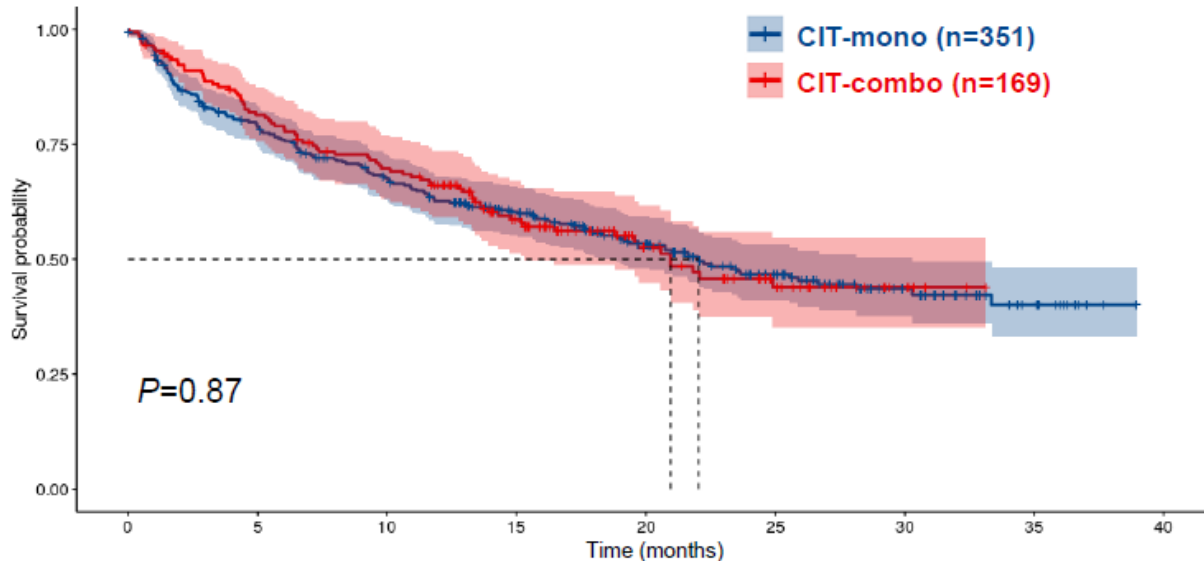




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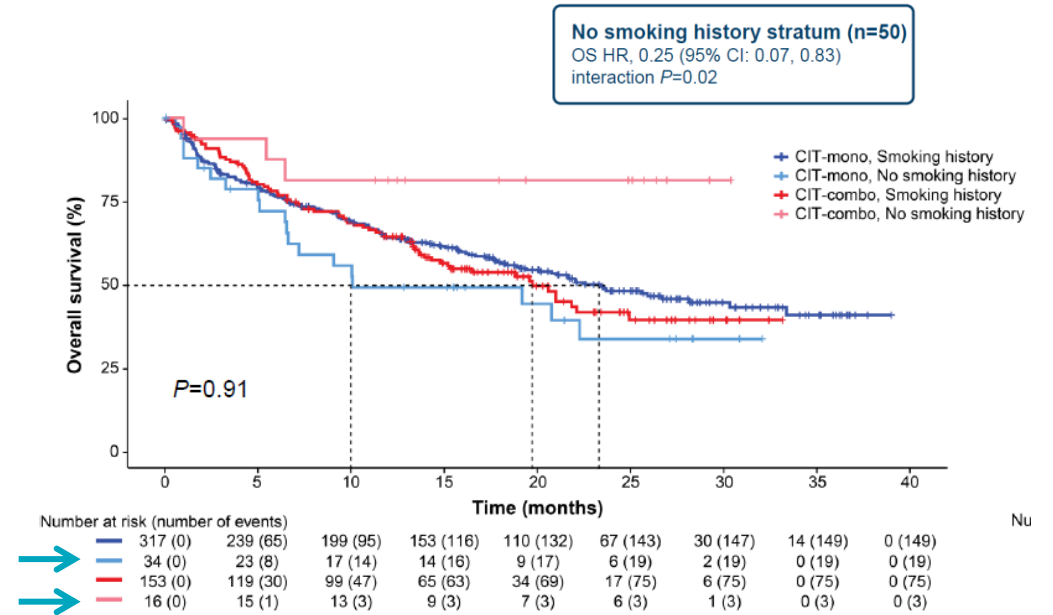
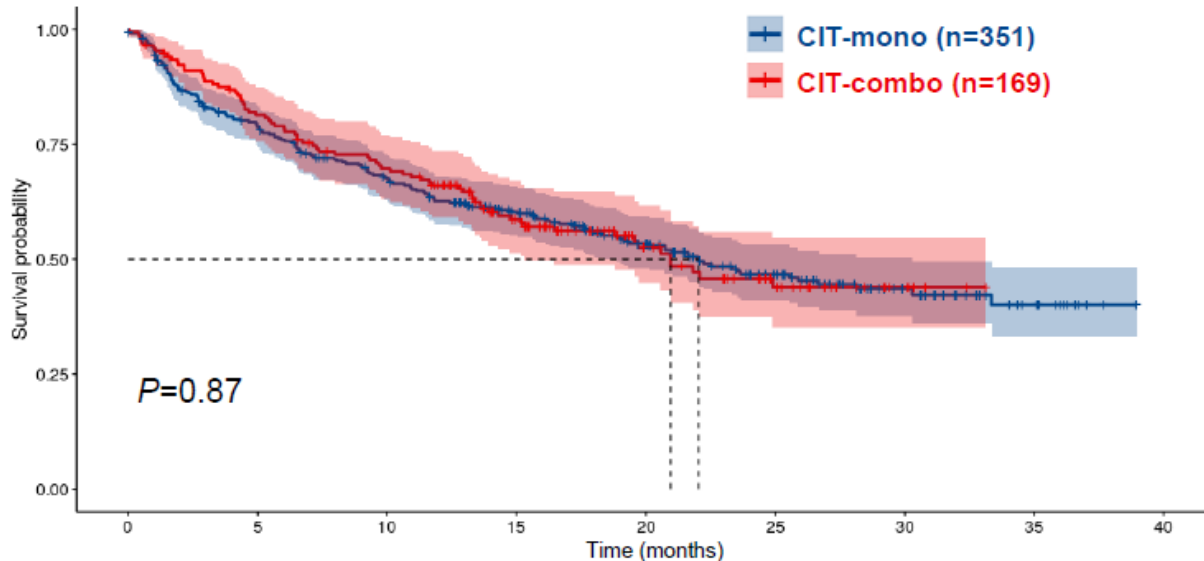
Pas de différence selon la présence de métastases cérébrales ou hépatiques



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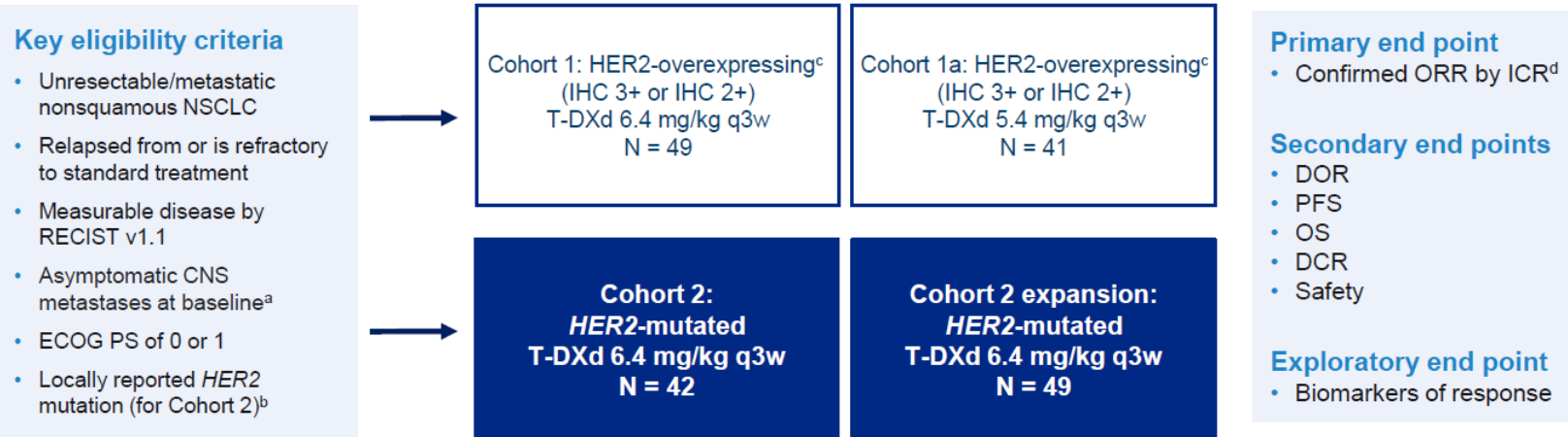
Manquent des facteurs pronostics : nombre de sites, localisations à risque, évolutivité de la maladie



Les adénocarcinomes avec mutation *HER2*

Essai DESTINY-Lung01

Multicenter, international, 2-cohort phase 2 trial (NCT03505710)

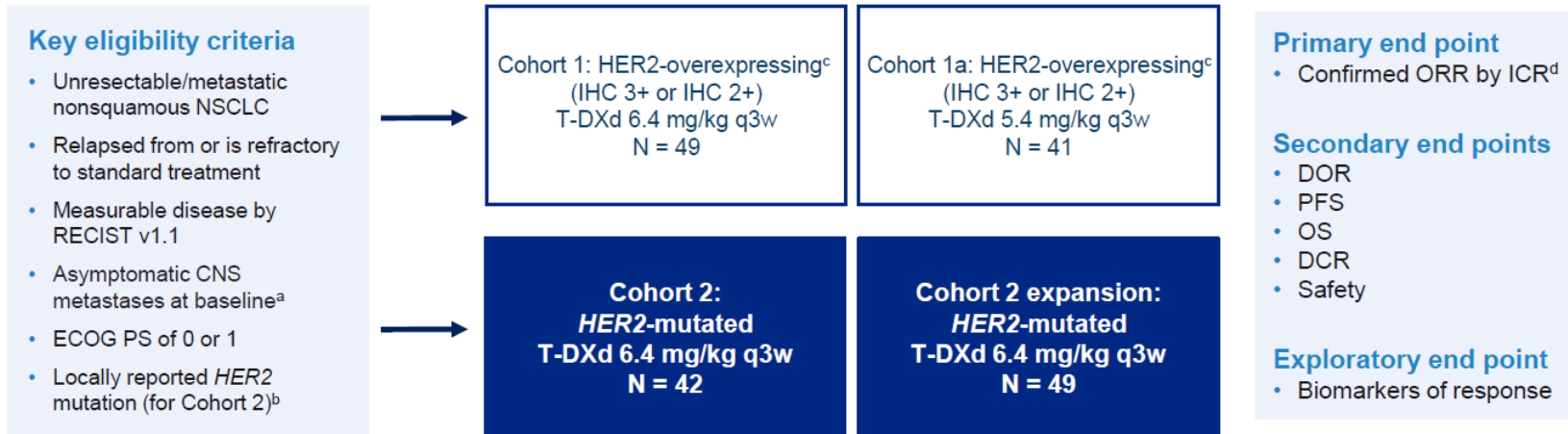




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	Patients (N = 91)
History of any prior systemic cancer therapy, n (%)	90 (98.9)
Prior lines of treatment, median (range)	2 (0-7) ^a
Prior treatment, n (%)	
Platinum-based therapy	86 (94.5)
Anti-PD-(L)1 therapy	60 (65.9)
Platinum-based and anti-PD-(L)1 therapy ^b	57 (62.6)
Docetaxel	18 (19.8)
<i>HER2</i> TKI ^c	13 (14.3)
Asymptomatic CNS metastases at baseline, %	36.3



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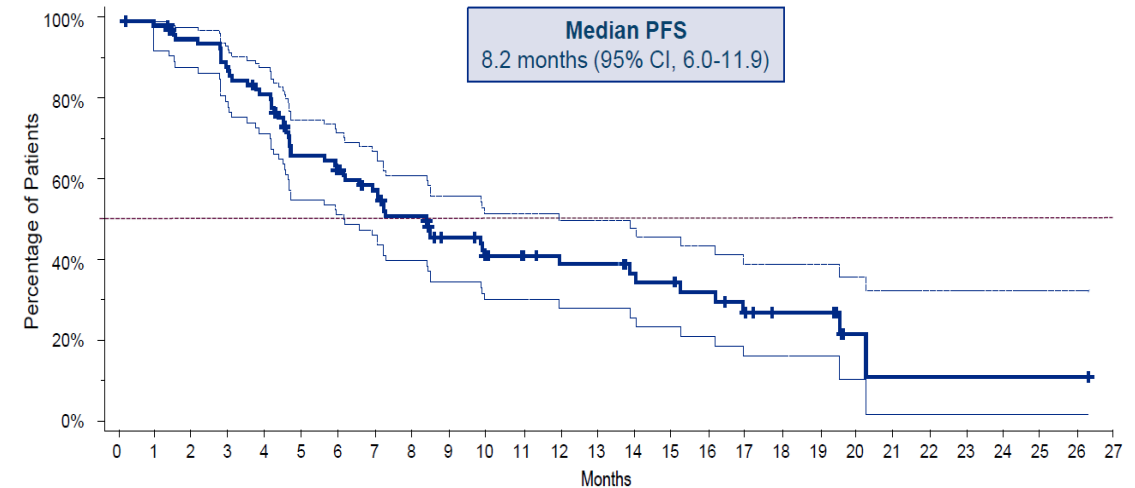
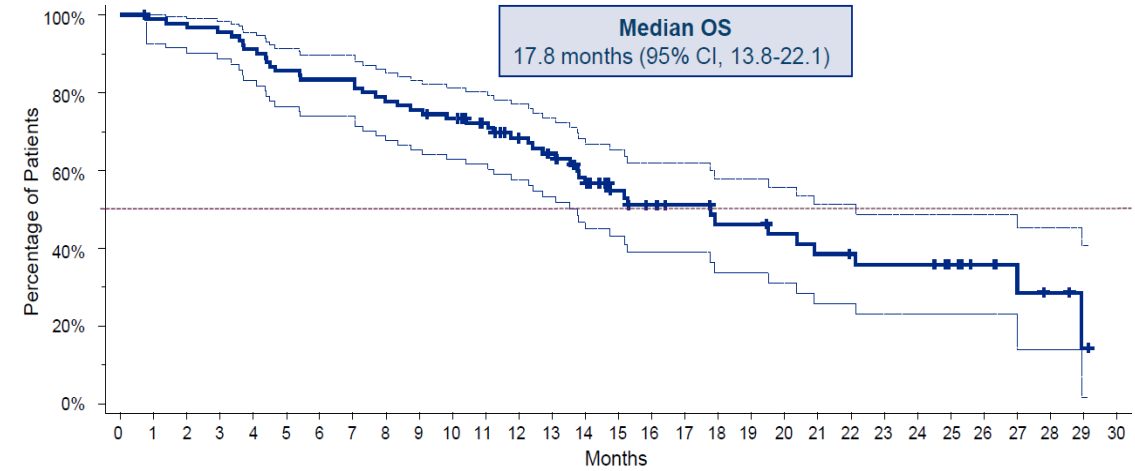
	Patients (N = 91)
Confirmed ORR ^a , n (%)	50 (54.9) (95% CI, 44.2-65.4)
Best overall response, n (%)	
CR	1 (1.1)
PR	49 (53.8)
SD	34 (37.4)
PD	3 (3.3)
Not evaluable	4 (4.4)
DCR, n (%)	84 (92.3) (95% CI, 84.8-96.9)
Median DoR, months	9.3 (95% CI, 5.7-14.7)
Median follow up, months	13.1 (range, 0.7-29.1)



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n (%)	Patients (N = 91)
Any drug-related TEAE	88 (96.7)
Drug-related TEAE Grade ≥ 3	42 (46.2)
Serious drug-related TEAE	18 (19.8)
Drug-related TEAE associated with discontinuation ^a	23 (25.3)
Drug-related TEAE associated with dose reduction	31 (34.1)
Drug-related TEAE associated with an outcome of death	2 (2.2) ^c



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Drug-related TEAE associated with an outcome of death	2 (2.2) ^c

- TRAE le plus fréquent : atteinte pulmonaire (13.2%)
- Délai médian de survenue : 4.6 mois [0.5-15.1]
- 88% traités par corticoïdes

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
n (%)	3 (3.3)	15 (16.5)	4 (4.4)	0	2 (2.2)	24 (26.4)



En conclusion, encore beaucoup d'interrogations !

- **Mésothéliome pleural** : nivolumab/ipilimumab est un nouveau standard en 1^{ère} ligne (ATU de cohorte)
→ *étude PEMBIB (pembrolizumab/nindétanib) ?*



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- **CBNPC de stades III** : intérêt d'améliorer les (longues) réponses avec des combinaisons d'immunomodulateurs
 - *sélection des patients qui bénéficient le plus de l'intensification ?*



En conclusion, encore beaucoup d'interrogations !

- Pembrolizumab +/- chimiothérapie dans le **CBNPC métastatique PD-L1 \geq 50%**
 - biomarqueurs prédictifs pour sélectionner et limiter les surtoxicités
 - place pour les autres molécules : essai *EMPower-Lung3*
 - Essais *INSIGNA* et *PERSEE*



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- Beaucoup d'autres données notamment sur les stratégies chez les **EGFR** et les **ALK**



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