



# Les buzz de l'ESMO 2021 en Oncologie Thoracique

Mardi 05 Octobre 2021

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**Bordeaux**

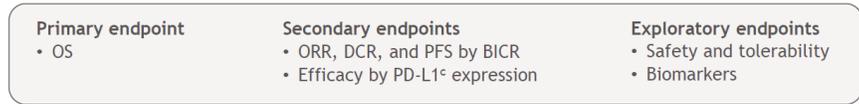
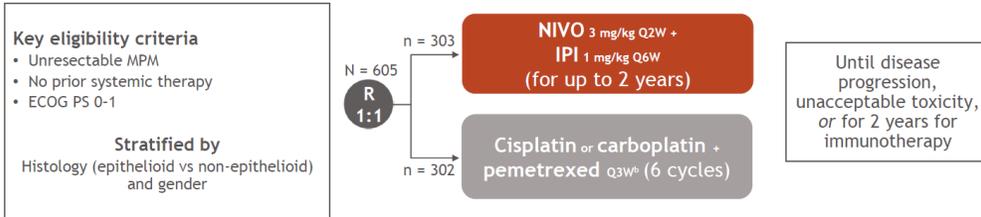
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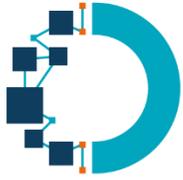
**Dr Charlotte Domblides**



# L'immunothérapie dans le mésothéliome pleural

## Etude CHECKMATE 743





# L'immunothérapie dans le mésothéliome pleural

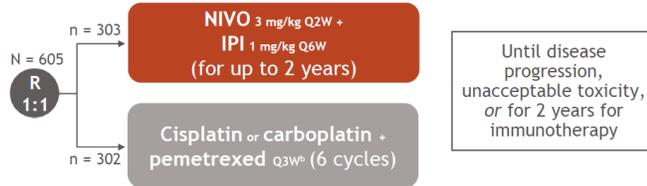
## Etude CHECKMATE 743

### Key eligibility criteria

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

### Stratified by

Histology (epithelioid vs non-epithelioid) and gender



### Primary endpoint

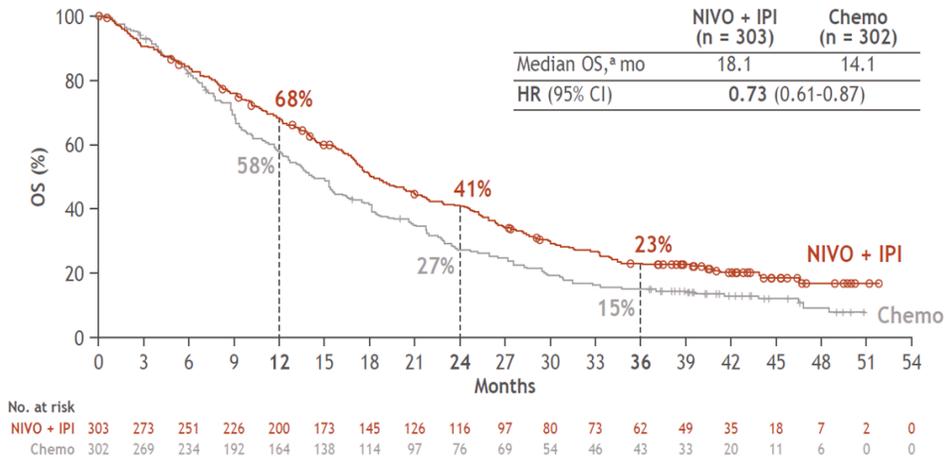
- OS

### Secondary endpoints

- ORR, DCR, and PFS by BICR
- Efficacy by PD-L1<sup>c</sup> expression

### Exploratory endpoints

- Safety and tolerability
- Biomarkers





# L'immunothérapie dans le mésothéliome pleural

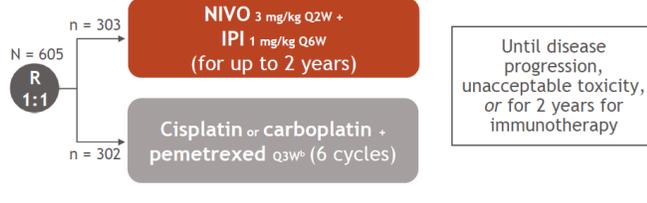
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### Primary endpoint

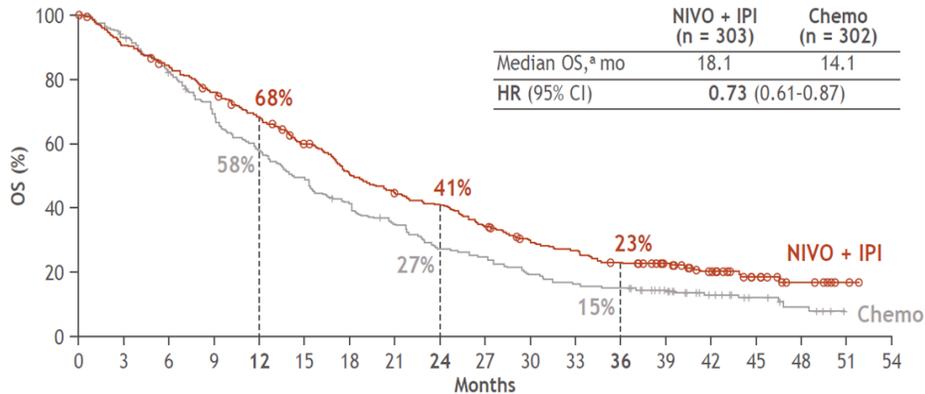
- OS

### Secondary endpoints

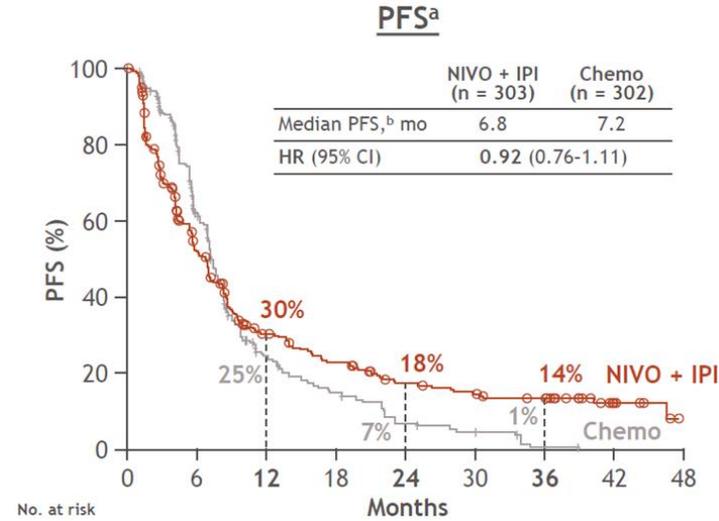
- ORR, DCR, and PFS by BICR
- Efficacy by PD-L1<sup>c</sup> expression

### Exploratory endpoints

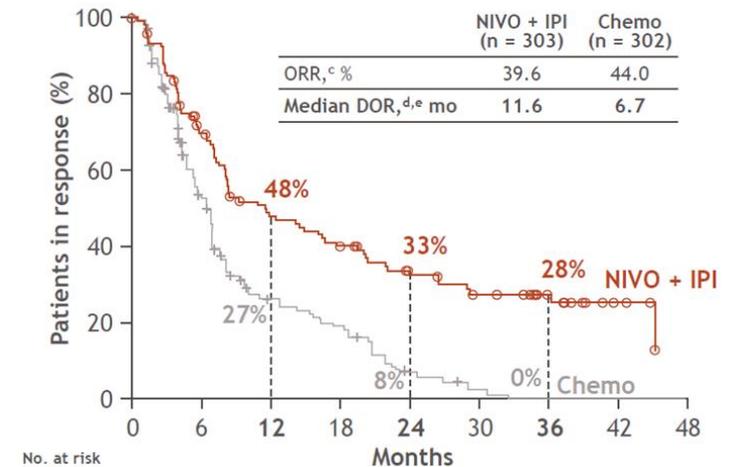
- Safety and tolerability
- Biomarkers



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



### ORR/DOR<sup>a</sup>





# L'immunothérapie dans le mésothéliome pleural

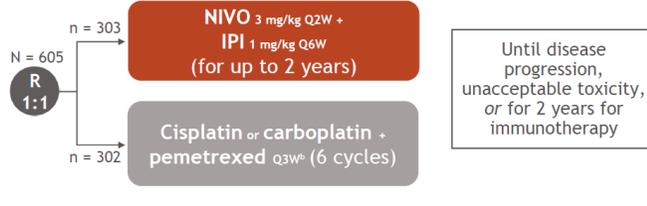
## Etude CHECKMATE 743

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- No prior systemic therapy
- ECOG PS 0-1

### Stratified by

Histology (epithelioid vs non-epithelioid) and gender



### Primary endpoint

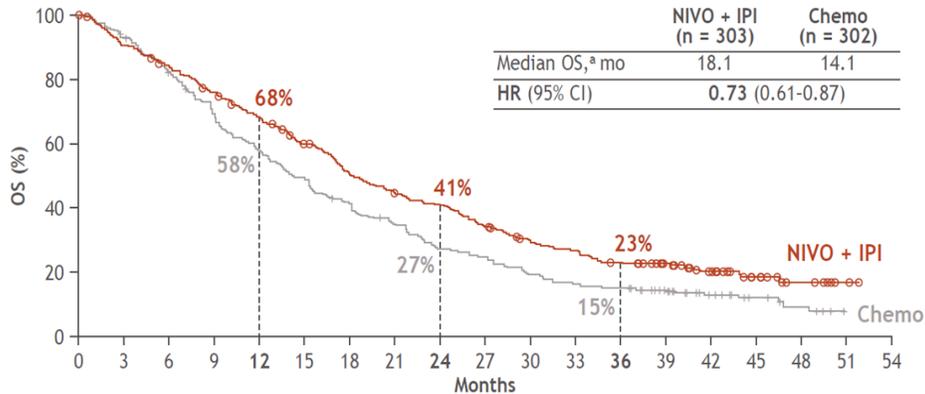
- OS

### Secondary endpoints

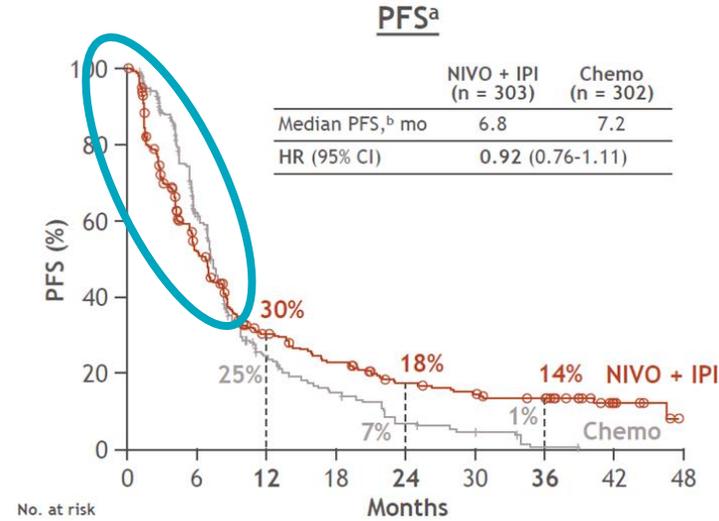
- ORR, DCR, and PFS by BICR
- Efficacy by PD-L1<sup>c</sup> expression

### Exploratory endpoints

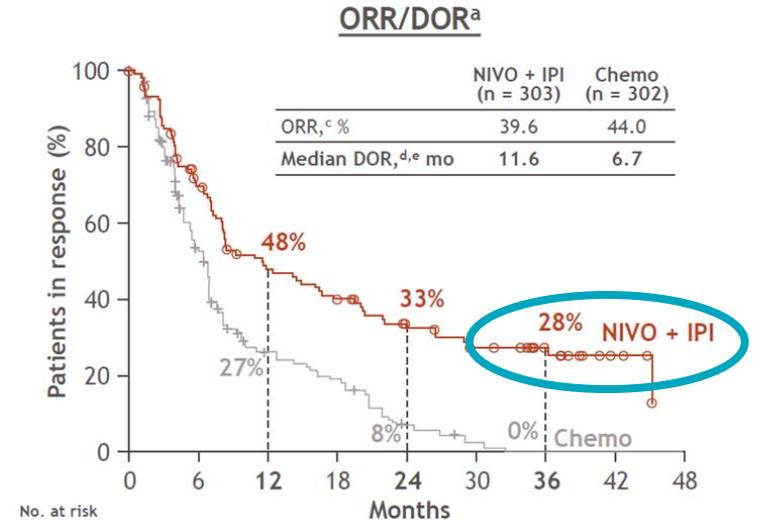
- Safety and tolerability
- Biomarkers



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 ?*

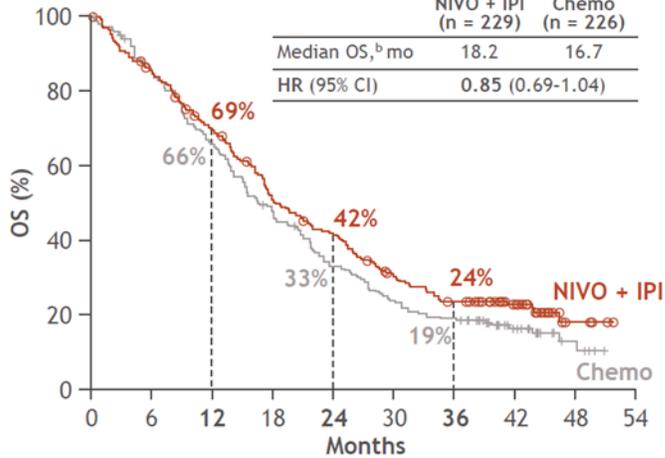




# L'immunothérapie dans le mésothéliome pleural

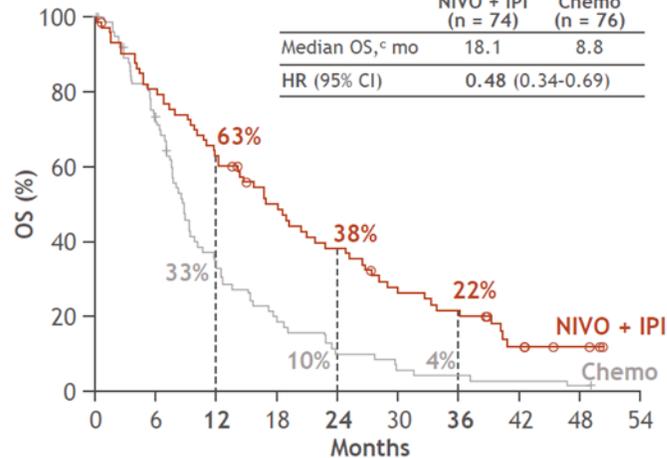
## Epithelioid

	NIVO + IPI (n = 229)	Chemo (n = 226)
Median OS, <sup>b</sup> 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, <sup>c</sup> mo	18.1	8.8
HR (95% CI)	0.48 (0.34-0.69)	

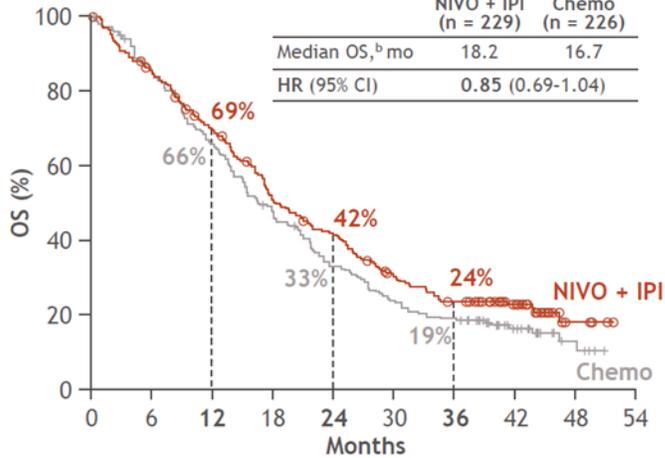




# L'immunothérapie dans le mésothéliome pleural

## Epithelioid

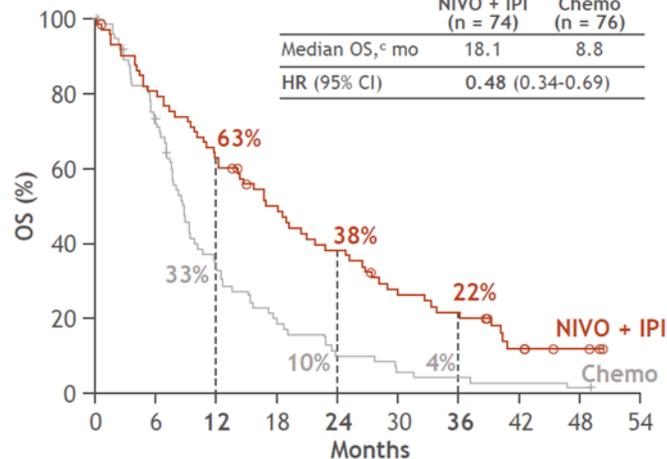
	NIVO + IPI (n = 229)	Chemo (n = 226)
Median OS, <sup>b</sup> mo	18.2	16.7
HR (95% CI)	0.85 (0.69-1.04)	



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

## Non-epithelioid

	NIVO + IPI (n = 74)	Chemo (n = 76)
Median OS, <sup>c</sup> mo	18.1	8.8
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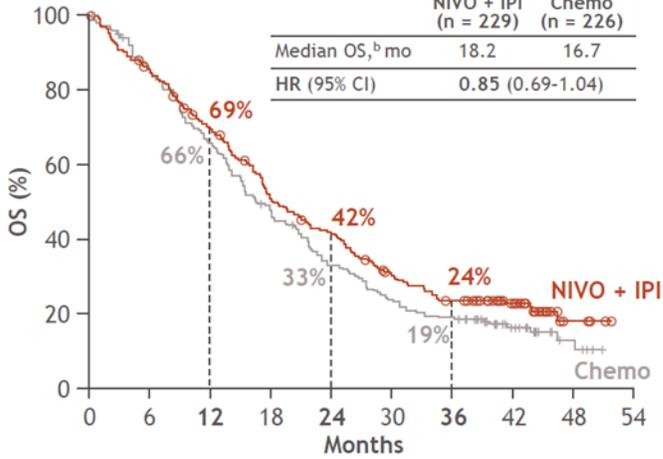




# L'immunothérapie dans le mésothéliome pleural

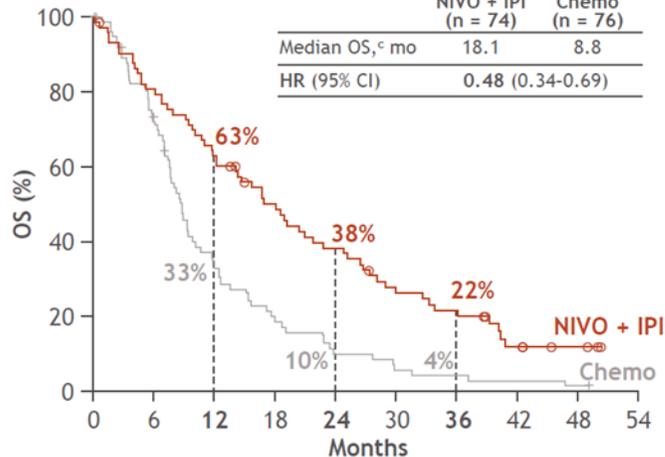
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	NIVO + IPI (n = 229)	Chemo (n = 226)
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## Non-epithelioid

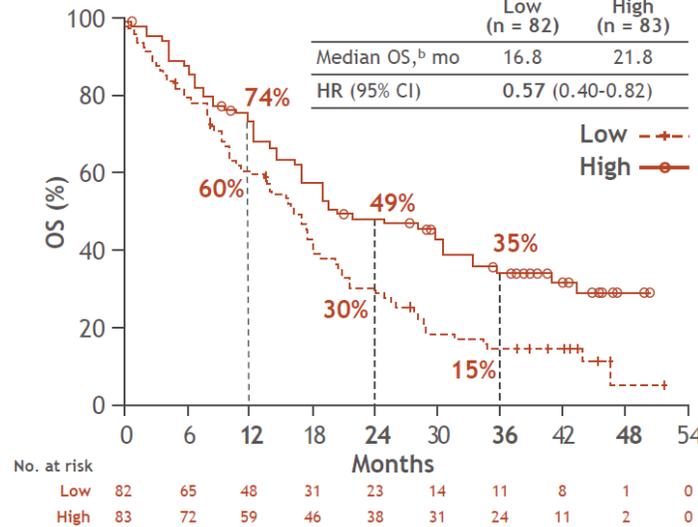
	NIVO + IPI (n = 74)	Chemo (n = 76)
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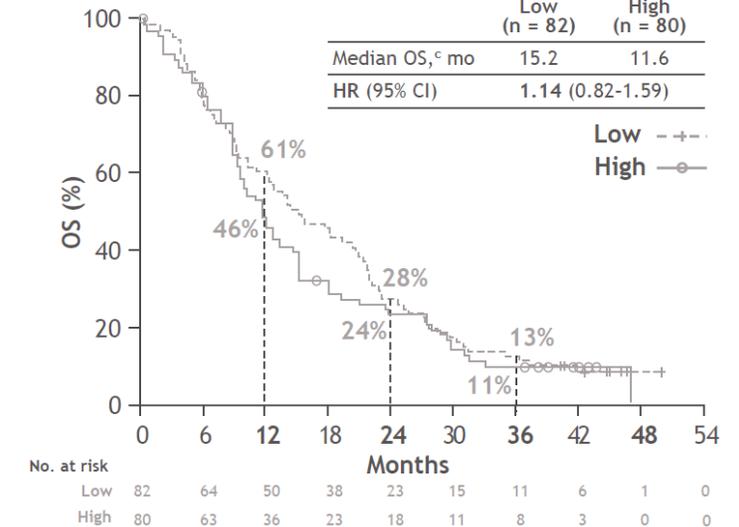
### NIVO + IPI

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



### Chemo

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

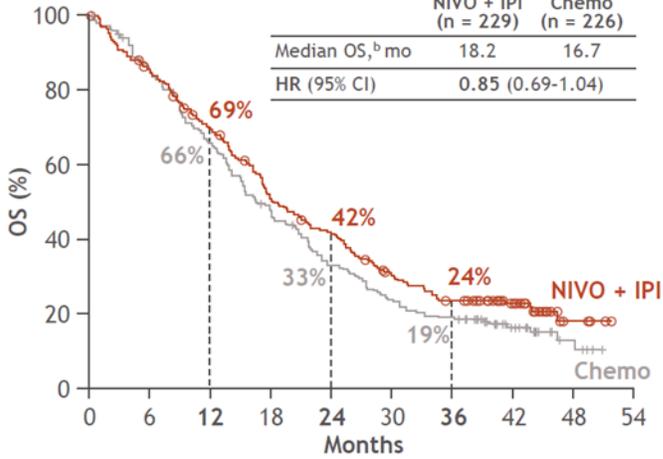




# L'immunothérapie dans le mésothéliome pleural

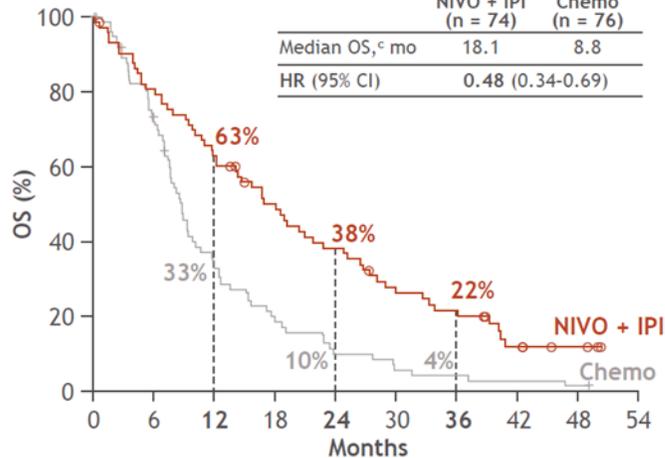
## Epithelioid

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



## Non-epithelioid

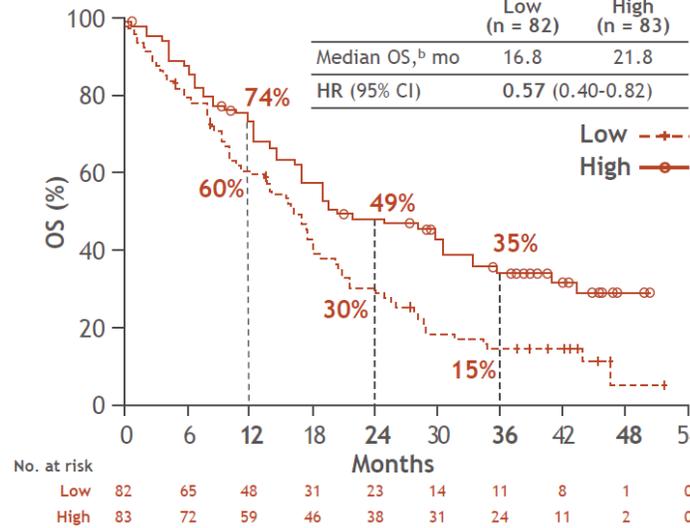
	NIVO + IPI (n = 74)	Chemo (n = 76)
Median OS, <sup>c</sup> mo	18.1	8.8
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## Signature de 4 gènes : CD8A, LAG3, STAT1 et PD-L1

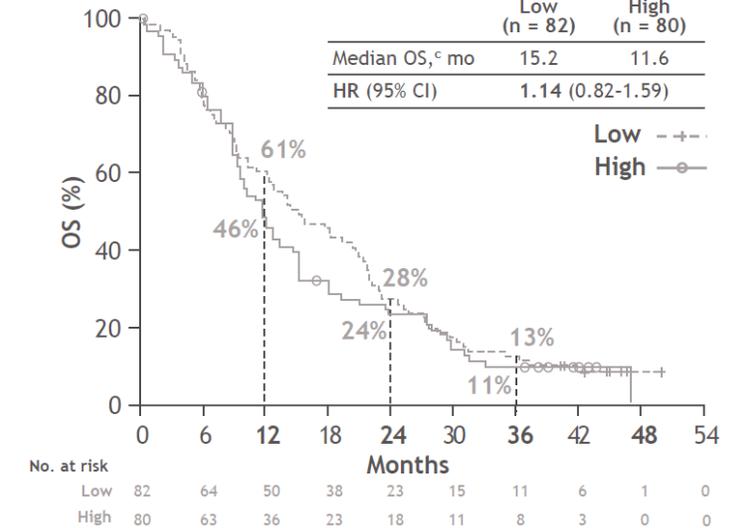
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	Low (n = 82)	High (n = 80)
Median OS, <sup>c</sup> mo	15.2	11.6
HR (95% CI)	1.14 (0.82-1.59)	



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



# L'immunothérapie dans le mésothéliome pleural

## Etude CHECKMATE 743

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

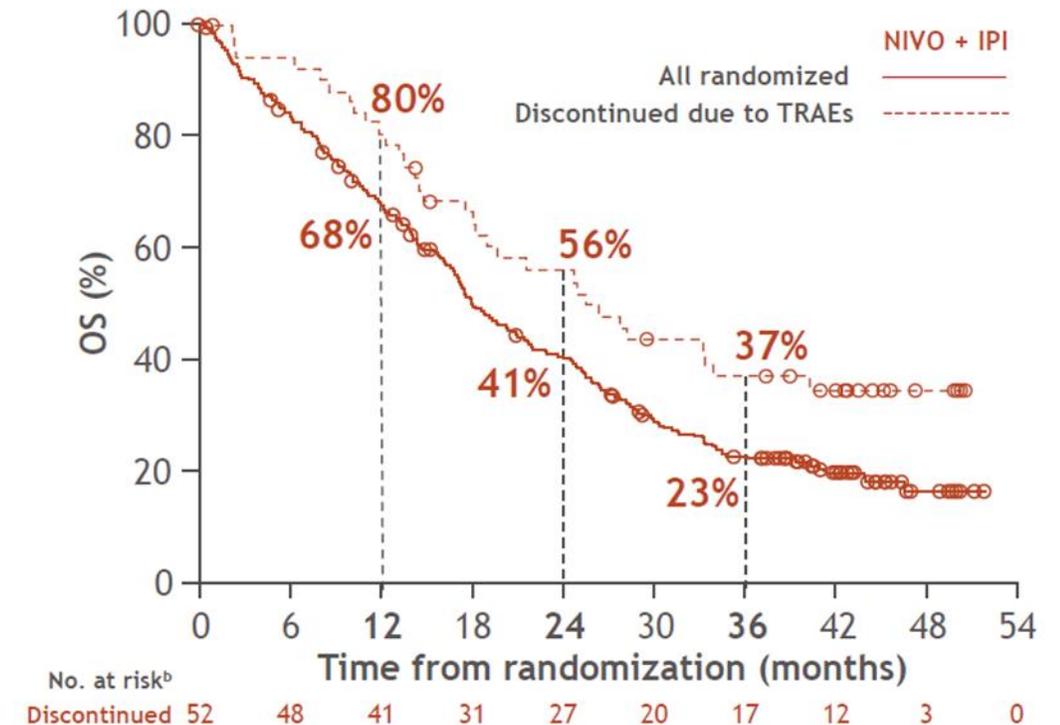


# L'immunothérapie dans le mésothéliome pleural

## Etude CHECKMATE 743

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

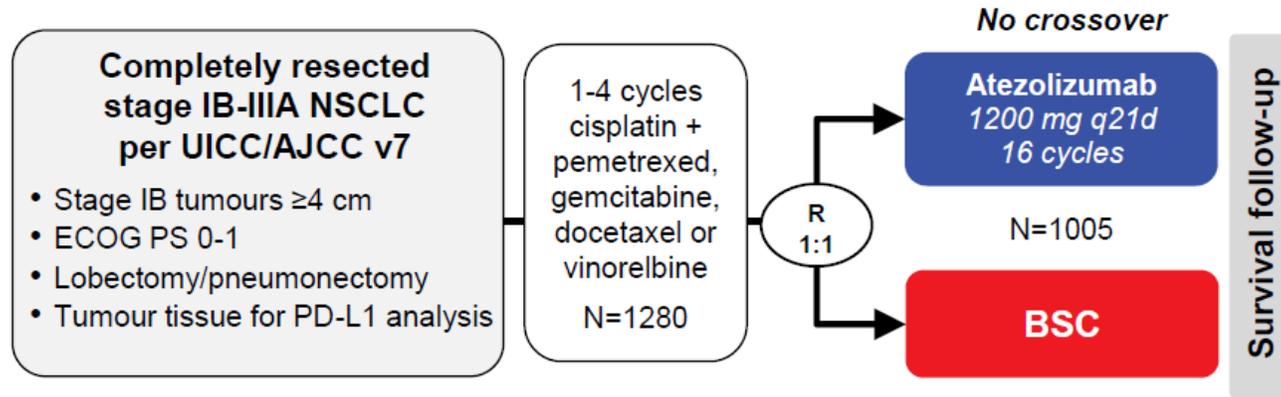
*Réponse maintenue même en cas d'arrêt pour toxicité*





# 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)<sup>a</sup>

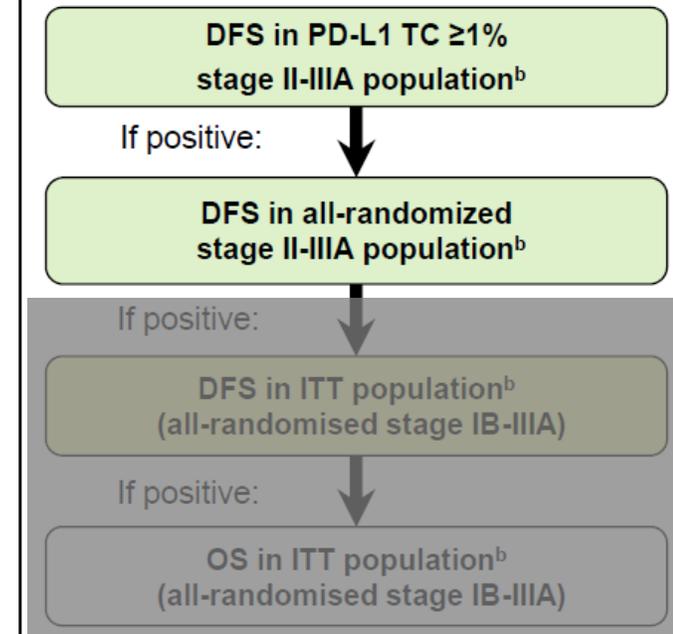
### Primary endpoints

- 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

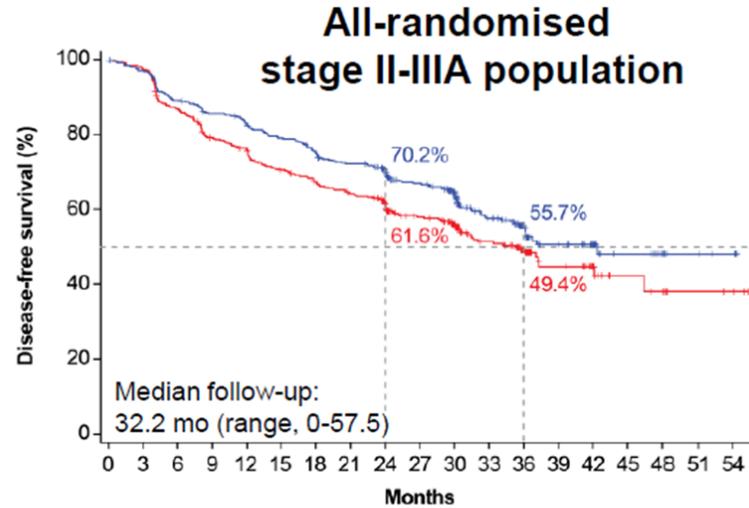


- Endpoint was met at DFS IA
- Endpoint was not met at DFS IA, and follow-up is ongoing
- OS data were immature, and endpoint was not formally tested



# L'immunothérapie adjuvante

## Etude IMpower-010



No. at risk

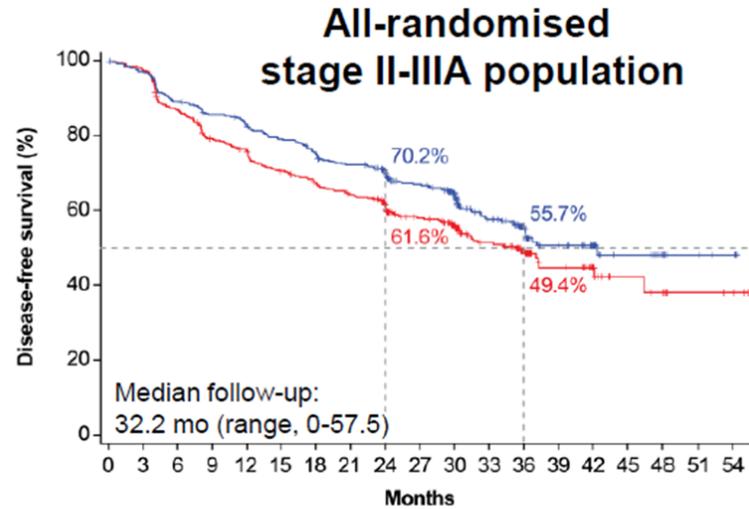
Atezolizumab	442	418	384	367	352	337	319	305	269	225	185	120	84	48	34	16	11	5	3
BSC	440	412	366	331	314	292	277	263	230	182	146	102	71	35	22	10	8	4	3

	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 <sup>b</sup>	0.02 <sup>c</sup>	



# L'immunothérapie adjuvante

## Etude IMpower-010

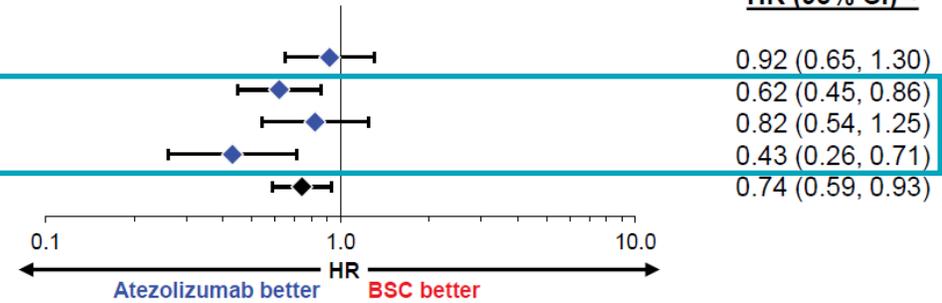


Subgroup (excluding EGFR/ALK+)<sup>e</sup>

PD-L1 status by SP263

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

HR (95% CI)<sup>f,g</sup>



No. at risk

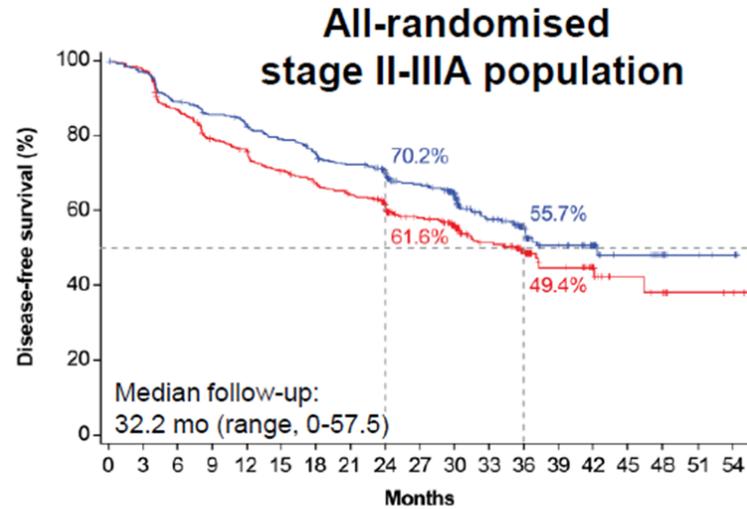
Months	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Atezolizumab	442	418	384	367	352	337	319	305	269	225	185	120	84	48	34	16	11	5	3
BSC	440	412	366	331	314	292	277	263	230	182	146	102	71	35	22	10	8	4	3

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# L'immunothérapie adjuvante

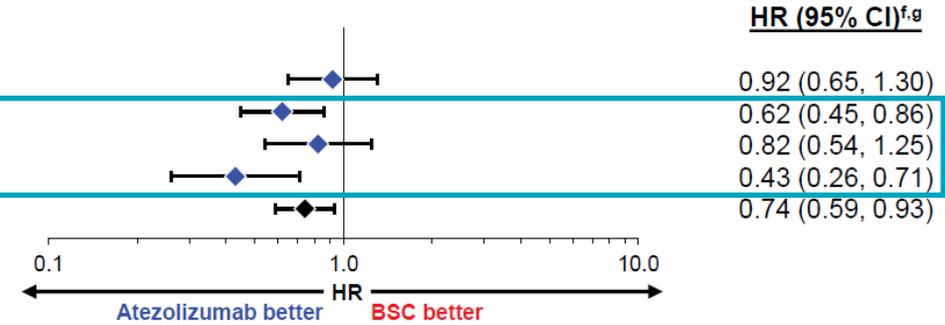
## Etude IMpower-010



Subgroup (excluding EGFR/ALK+)<sup>e</sup>

PD-L1 status by SP263

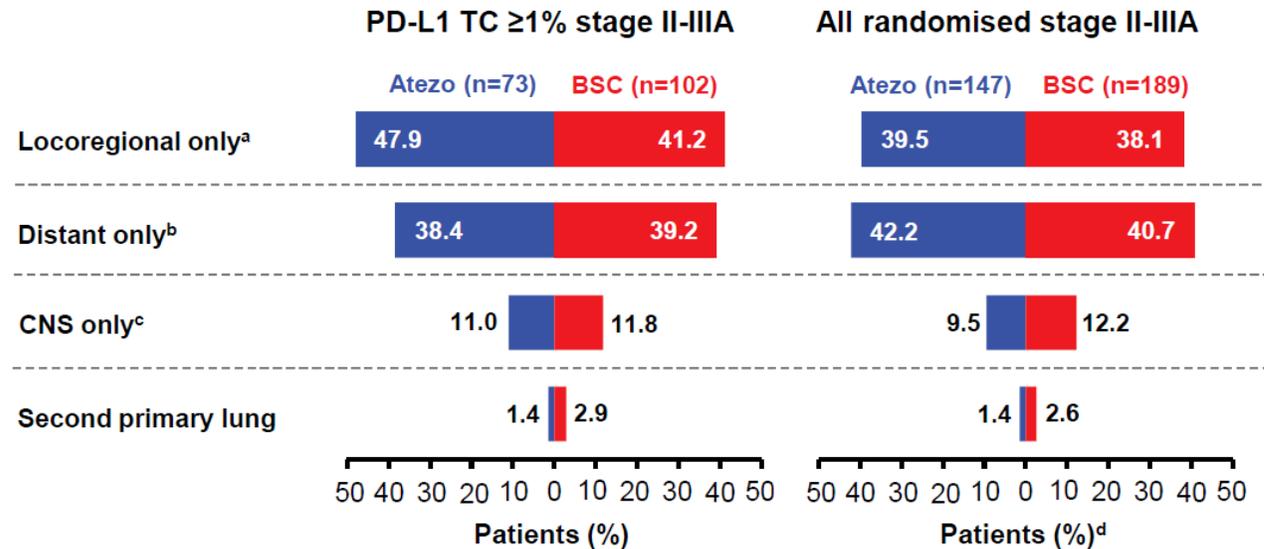
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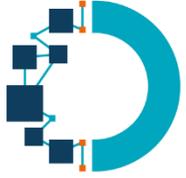


No. at risk

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
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P value <sup>b</sup>	0.02 <sup>c</sup>	





# L'immunothérapie adjuvante

## Etude IMpower-010

### PD-L1 TC ≥1% stage II-III A

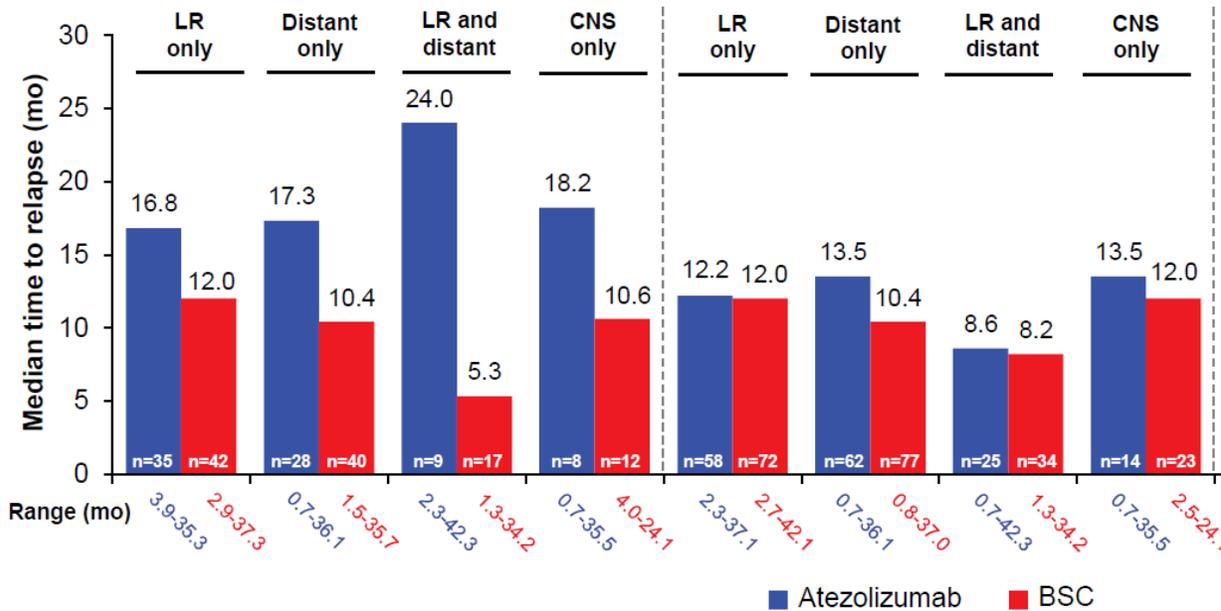
### All randomised stage II-III A

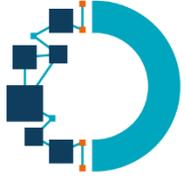
**Atezo:** Median (range) time to any relapse: 17.6 mo (0.7-42.3)

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

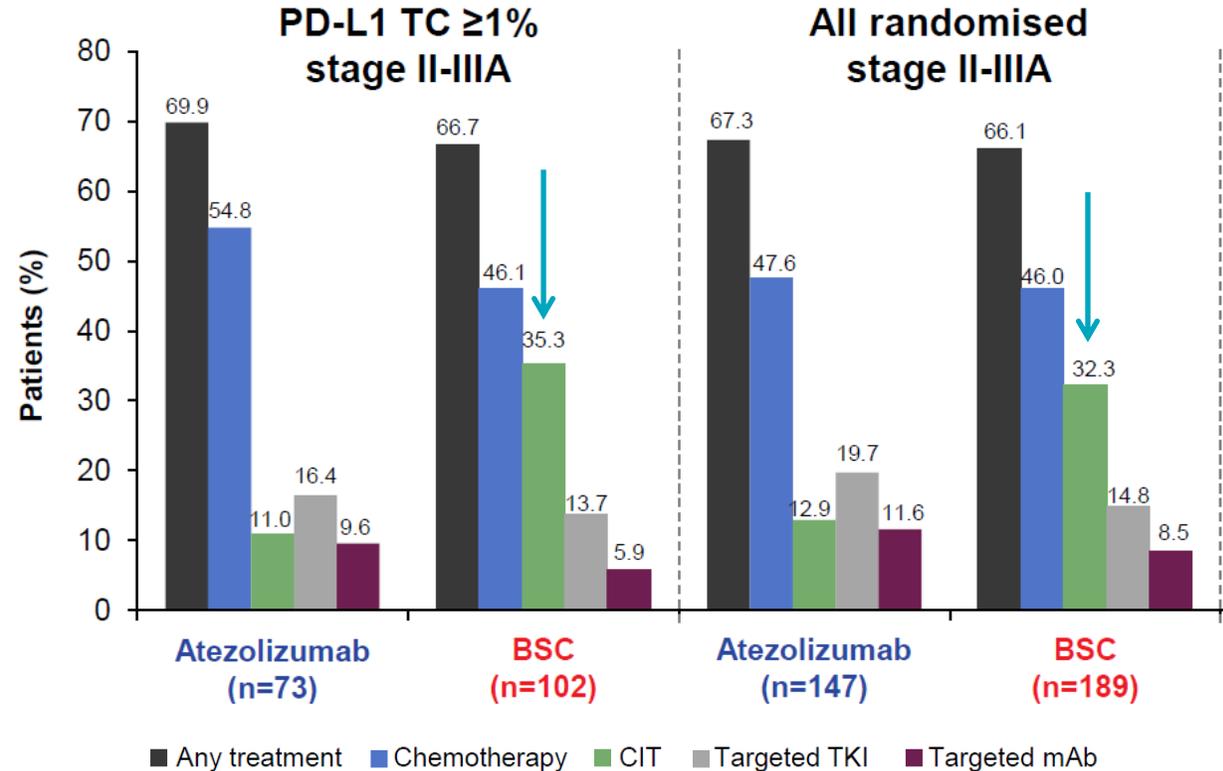
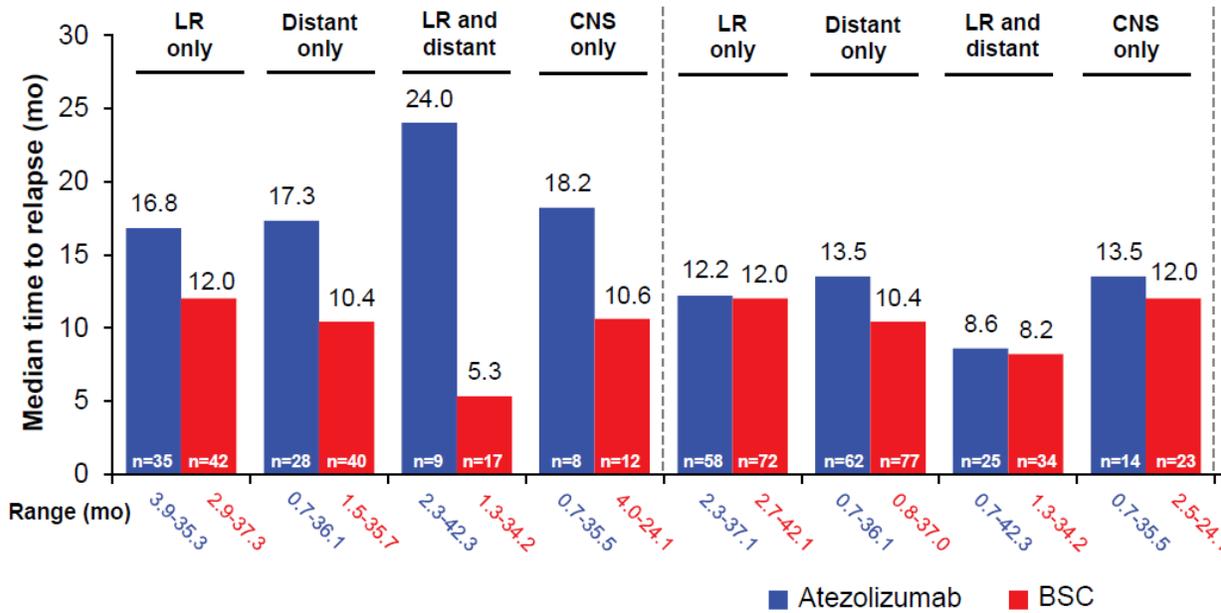
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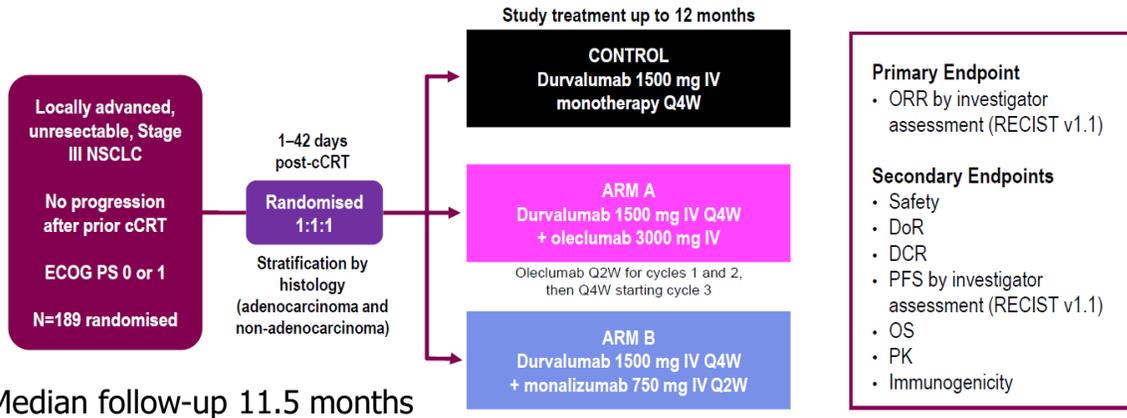
Median (range) time to any relapse: 11.1 mo (0.8-42.1)





# Association d'immunomodulateurs dans les stades III

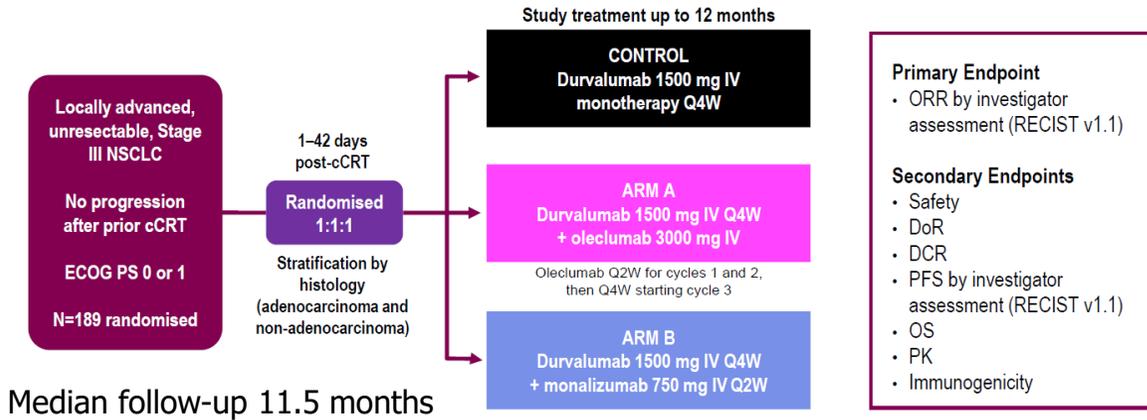
## Etude COAST





# Association d'immunomodulateurs dans les stades III

## Etude COAST

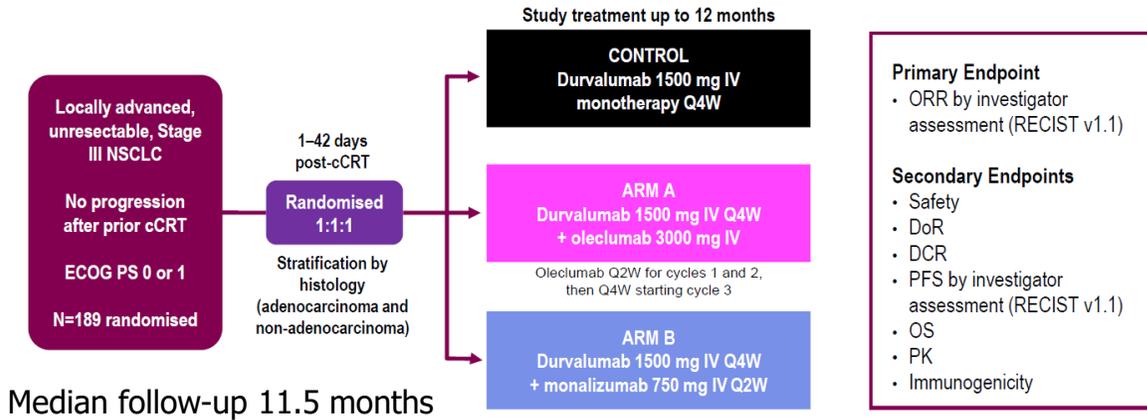


Characteristic <sup>a</sup>	D (N=67)	D+O (N=60)	D+M (N=62)
<b>Histology, %</b>			
Squamous / Non-squamous	44.8 / 55.2	40.0 / 60.0	43.5 / 56.5
<b>Disease stage at study entry, %</b>			
IIIA / IIIB / IIIC	40.3 / 50.7 / 9.0	45.0 / 48.3 / 6.7	51.6 / 43.5 / 4.8
<b>PD-L1 status, %<sup>b</sup></b>			
TC ≥1%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



# Association d'immunomodulateurs dans les stades III

## Etude COAST



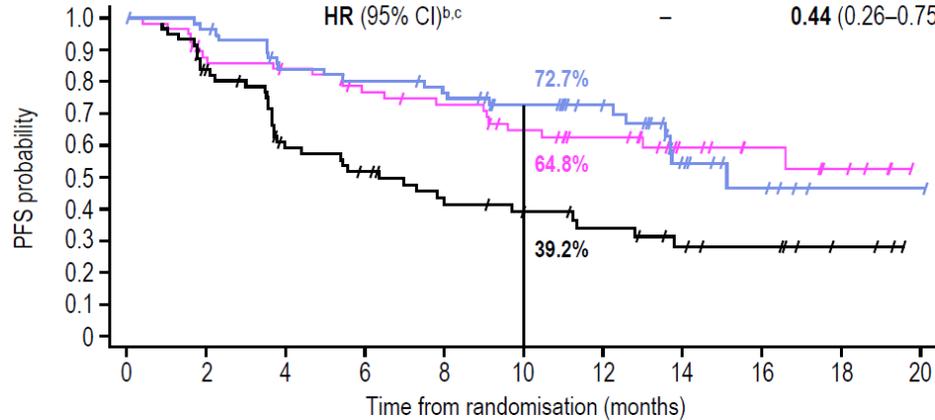
Characteristic <sup>a</sup>	D (N=67)	D+O (N=60)	D+M (N=62)
<b>Histology, %</b>			
Squamous / Non-squamous	44.8 / 55.2	40.0 / 60.0	43.5 / 56.5
<b>Disease stage at study entry, %</b>			
IIIA / IIIB / IIIC	40.3 / 50.7 / 9.0	45.0 / 48.3 / 6.7	51.6 / 43.5 / 4.8
<b>PD-L1 status, %<sup>b</sup></b>			
TC ≥1% / TC <1% / Unknown	37.3 / 20.9 / 41.8	38.3 / 11.7 / 50.0	29.0 / 19.4 / 51.6
<b>Prior RT dose, %</b>			
54-66 Gy / >66 Gy	92.5 / 7.5	90.0 / 10.0	91.9 / 8.1
<b>Time from last RT to randomisation, %</b>			
<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
<b>Prior platinum-based CT, %</b>			
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) <sup>a</sup>	6.3 (3.7–11.2)	NR (10.4–NE)	15.1 (13.6–NE)
HR (95% CI) <sup>b,c</sup>	–	0.44 (0.26–0.75)	0.65 (0.49–0.85)



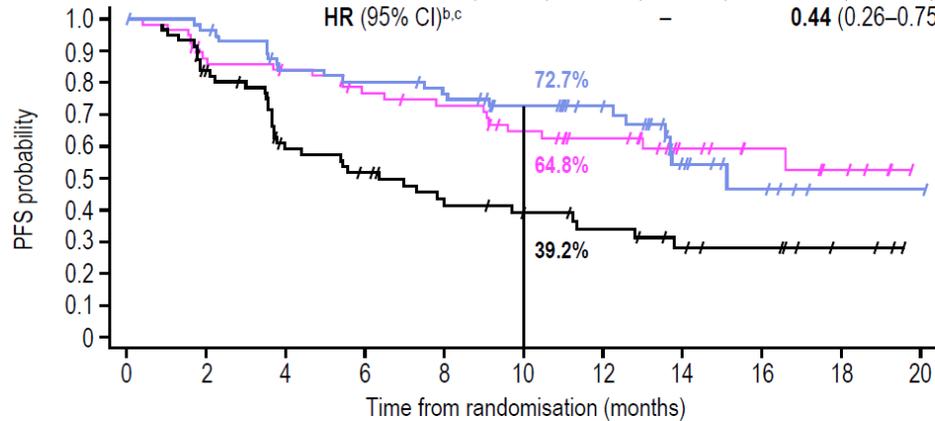
No. at risk	D	D+O	D+M
0	67	60	62
2	50	49	55
4	32	46	46
6	32	40	44
8	20	37	41
10	16	30	35
12	13	22	25
14	9	13	11
16	7	9	6
18	3	5	1
20	0	0	1



# Association d'immunomodulateurs dans les stades III

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	D	D+O	D+M
Events/patients, n	38/67	22/60	21/62
mPFS, months (95% CI) <sup>a</sup>	6.3 (3.7–11.2)	NR (10.4–NE)	15.1 (13.6–NE)
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6	32	40	40
8	20	37	37
10	16	30	30
12	13	22	22
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16	7	9	9
18	3	5	5
20	0	0	0

*Bras contrôle moins performant que dans PACIFIC*

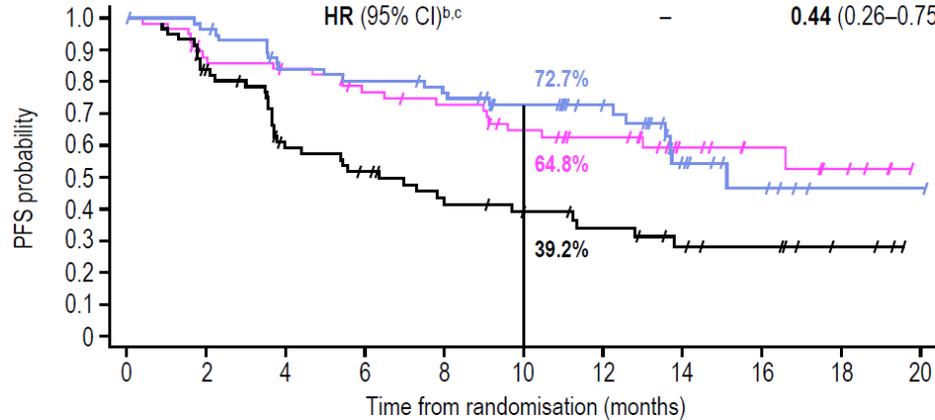
	No. of events/ total no. of patients (%)	Median PFS (95% CI), months	12-month PFS rate (95% CI) %
<b>Durvalumab</b>	266/476 (55.9)	17.2 (12.3–23.8)	55.3 (50.5–59.8)
<b>Placebo</b>	174/237 (73.4)	5.6 (4.6–7.7)	34.4 (28.2–40.7)



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16	7	9	25
18	3	5	21
20	0	0	17

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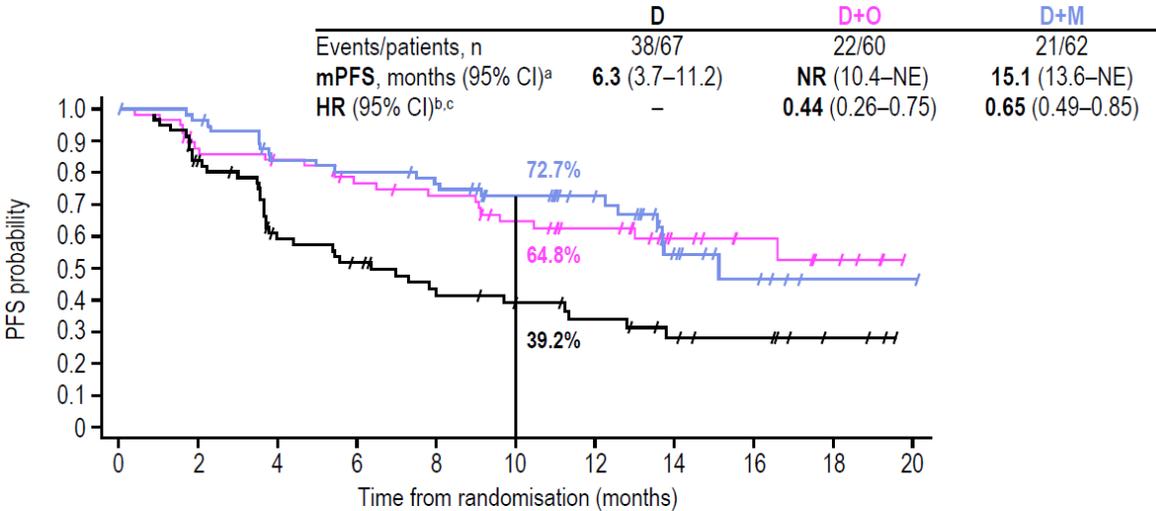
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Antitumour activity	D (N=67)	D+O (N=60)	D+M (N=62)
Confirmed ORR (95% CI) <sup>b</sup> % [n]	17.9 (9.6, 29.2) [12]	30.0 (18.8, 43.2) [18]	35.5 (23.7, 48.7) [22]
DCR at 16 weeks (95% CI) <sup>a,c</sup> % [n]	58.2 (45.5, 70.2) [39]	81.7 (69.6, 90.5) [49]	77.4 (65.0, 87.1) [48]
Median DoR (95% CI) <sup>a</sup> 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+



# Association d'immunomodulateurs dans les stades III

## Etude COAST

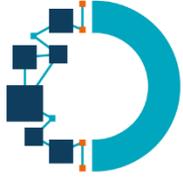


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Incidence, n (%)	D (N=66)	D+O (N=59)	D+M (N=61)
Any TEAEs	65 (98.5)	57 (96.6)	61 (100)
Grade ≥3 TEAEs	26 (39.4)	24 (40.7)	17 (27.9)
Study drug-related AEs	49 (74.2)	46 (78.0)	50 (82.0)
Study drug-related SAEs	6 (9.1)	7 (11.9)	5 (8.2)
AEs leading to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



# Place du pembrolizumab seul chez les PD-L1 élevés

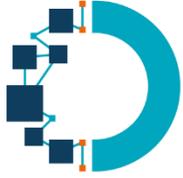
Etude sur la base de données FLATIRON



# Place du pembrolizumab seul chez les PD-L1 élevés

## Etude sur la base de données FLATIRON

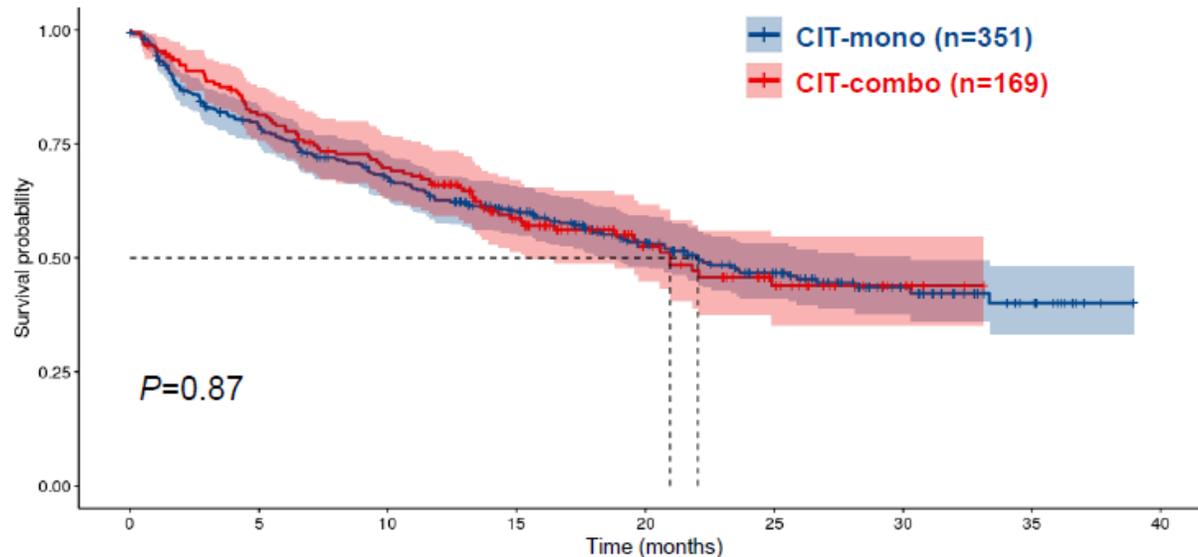
Characteristic, n (%)	CIT-mono (n=351)	CIT-chemo (n=169)
Age group, years		
< 65	109 (31)	77 (46)
65-74	112 (32)	58 (34)
≥75	130 (37)	34 (20)

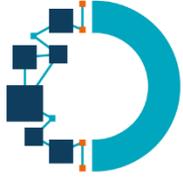


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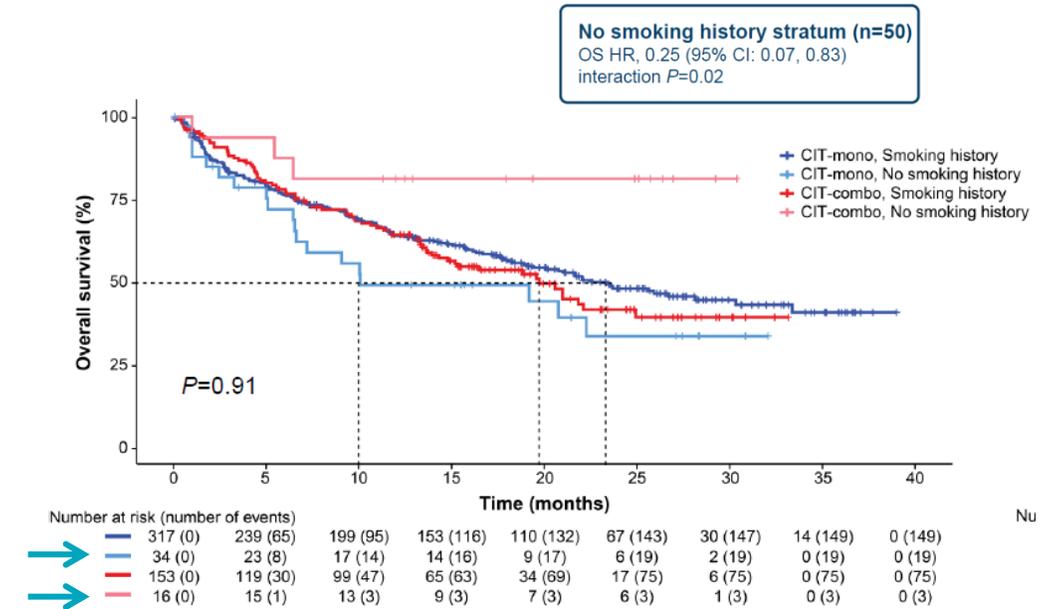
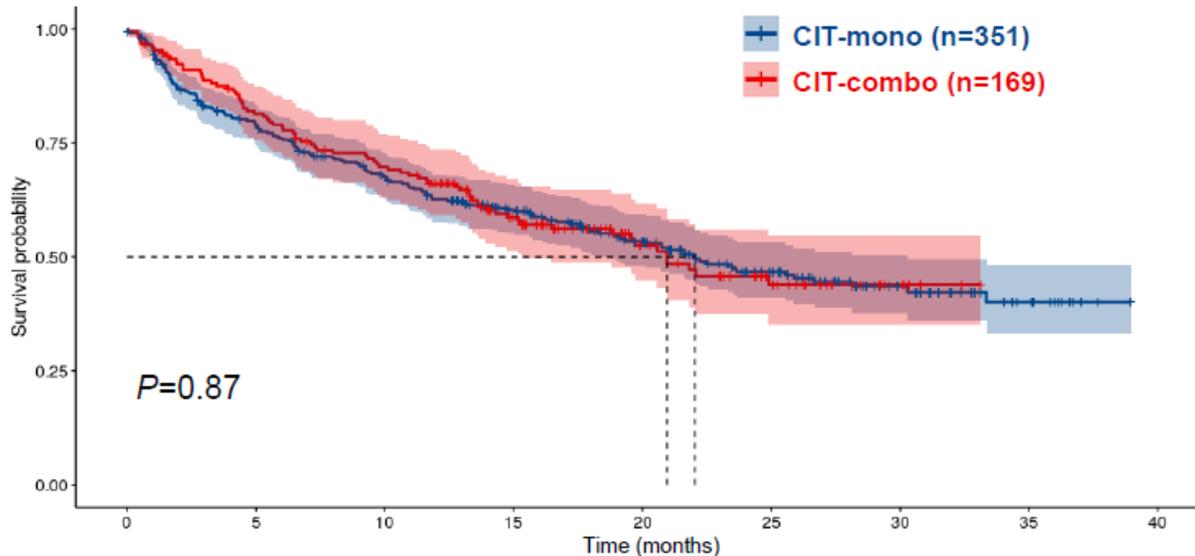




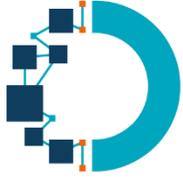
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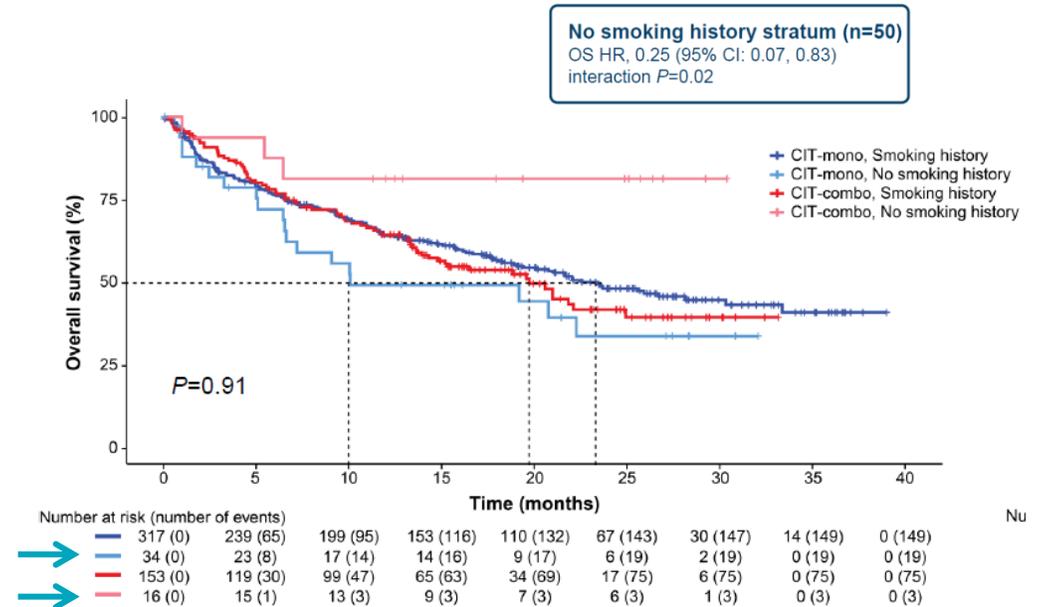
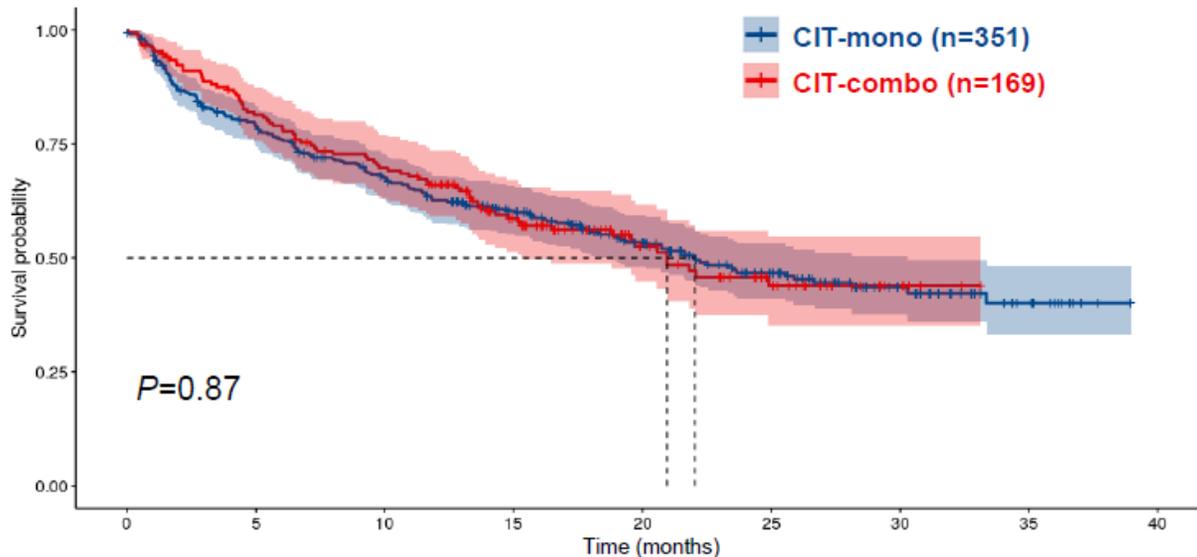
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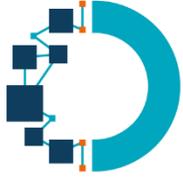
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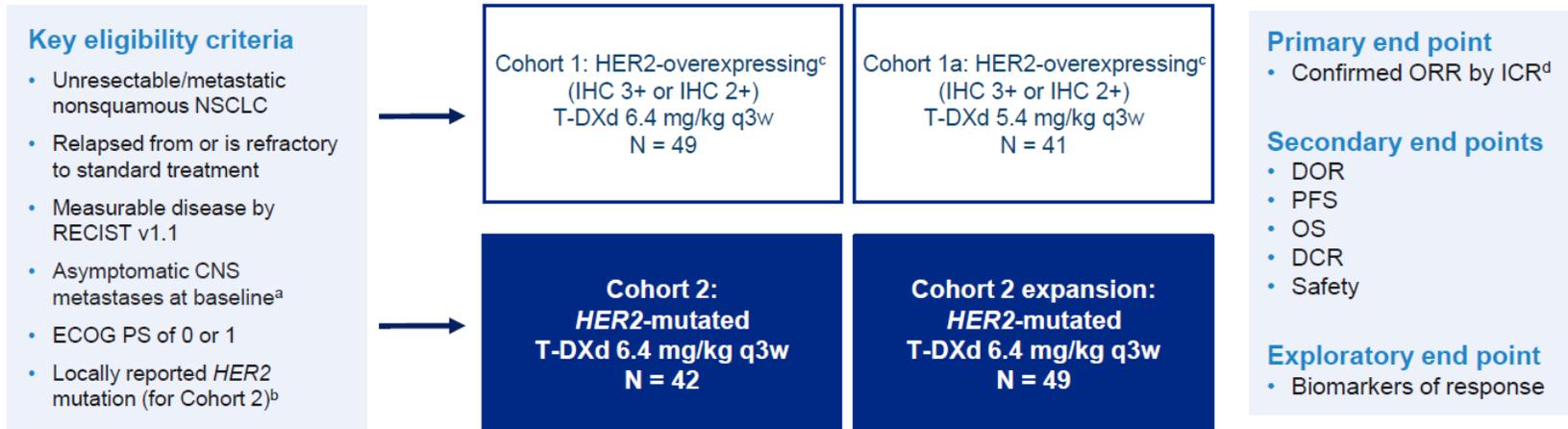
*Manquent des facteurs pronostics : nombre de sites, localisations à risque, évolutivité de la maladie*

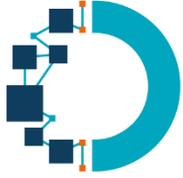


# Les adénocarcinomes avec mutation *HER2*

## Essai DESTINY-Lung01

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

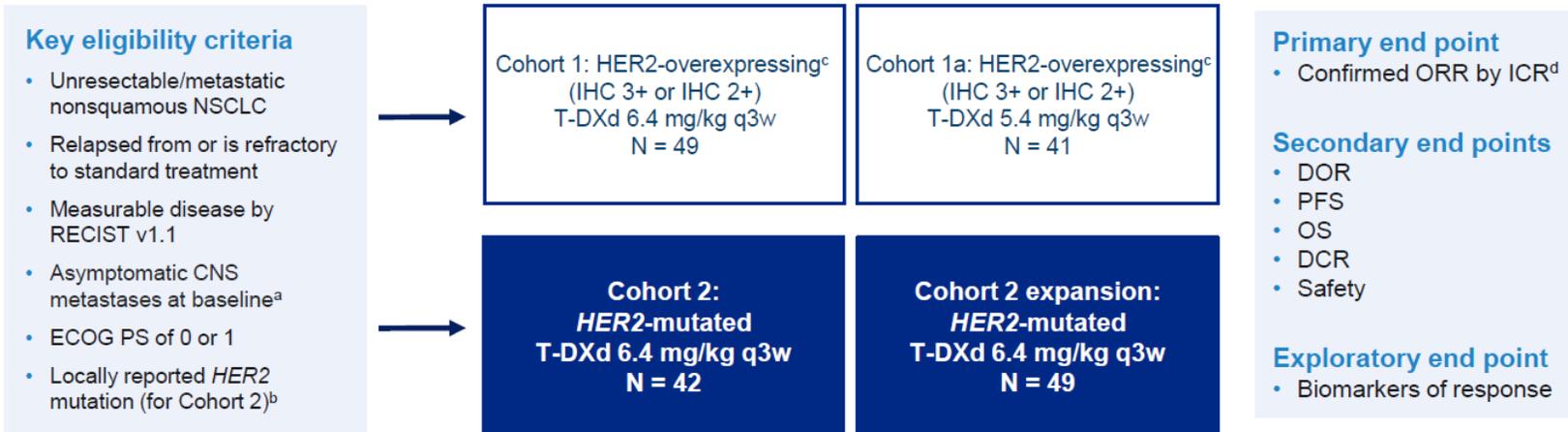




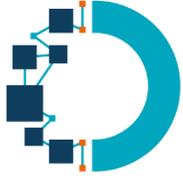
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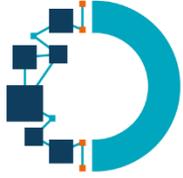
	Patients (N = 91)
History of any prior systemic cancer therapy, n (%)	90 (98.9)
Prior lines of treatment, median (range)	2 (0-7) <sup>a</sup>
<b>Prior treatment, n (%)</b>	
Platinum-based therapy	86 (94.5)
Anti-PD-(L)1 therapy	60 (65.9)
Platinum-based and anti-PD-(L)1 therapy <sup>b</sup>	57 (62.6)
Docetaxel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



# Les adénocarcinomes avec mutation *HER2*

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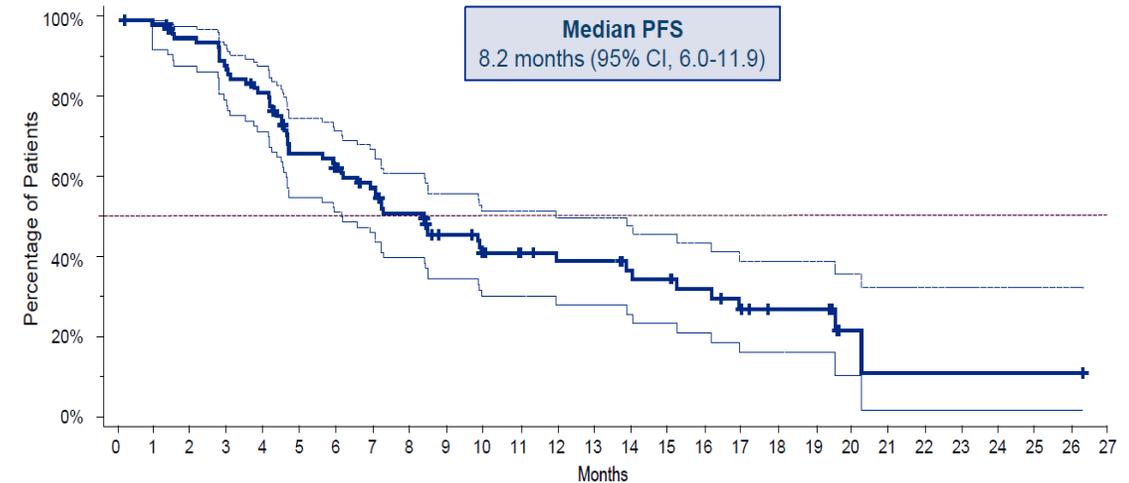
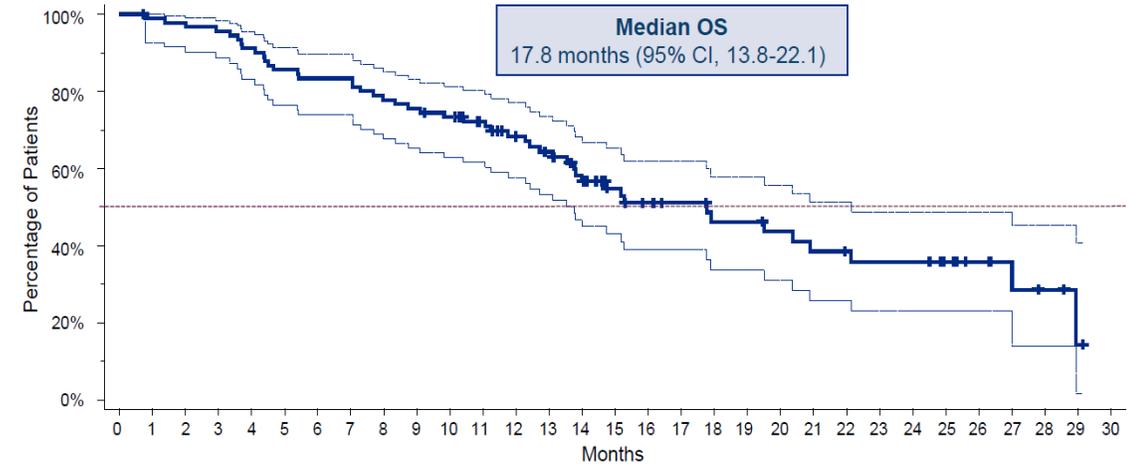
	Patients (N = 91)
Confirmed ORR <sup>a</sup> , n (%)	<b>50 (54.9)</b> (95% CI, 44.2-65.4)
Best overall response, n (%)	
CR	<b>1 (1.1)</b>
PR	<b>49 (53.8)</b>
SD	<b>34 (37.4)</b>
PD	<b>3 (3.3)</b>
Not evaluable	<b>4 (4.4)</b>
DCR, n (%)	84 (92.3) (95% CI, 84.8-96.9)
Median DoR, months	9.3 (95% CI, 5.7-14.7)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

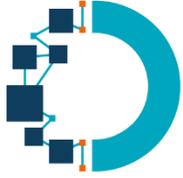


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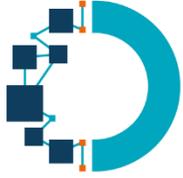




# Les adénocarcinomes avec mutation *HER2*

## Essai DESTINY-Lung01

n (%)	Patients (N = 91)
Any drug-related TEAE	88 (96.7)
Drug-related TEAE Grade $\geq 3$	42 (46.2)
Serious drug-related TEAE	18 (19.8)
Drug-related TEAE associated with discontinuation <sup>a</sup>	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) <sup>c</sup>



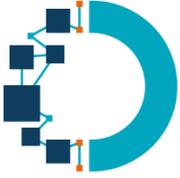
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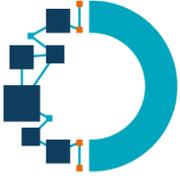
- TRAE le plus fréquent : atteinte pulmonaire (13.2%)
- Délai médian de survenue : 4.6 mois [0.5-15.1]
- 88% traités par corticoïdes

	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)



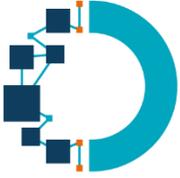
# En conclusion, encore beaucoup d'interrogations !

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



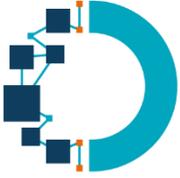
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  - *guérison ou contrôle de la maladie ?*
  - *bénéfice en OS ?*
  - *adjuvant versus néoadjuvant ?*
  - *biomarqueurs prédictifs pour mieux sélectionner les patients ?*



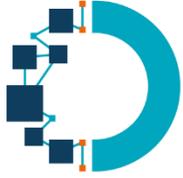
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  - *biomarqueurs prédictifs pour mieux sélectionner les patients ?*
- **CBNPC de stades III** : intérêt d'améliorer les (longues) réponses avec des combinaisons d'immunomodulateurs
  - *sélection des patients qui bénéficient le plus de l'intensification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



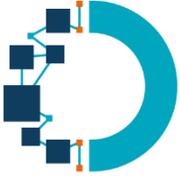
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  - place pour les autres molécules : essai *EMPower-Lung3*
  - Essais *INSIGNA* et *PERSEE*



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  - place par rapport aux TKI : ZENITH20 ?



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  - place par rapport aux TKI : ZENITH20 ?
- Beaucoup d'autres données notamment sur les stratégies chez **les EGFR et les ALK**

