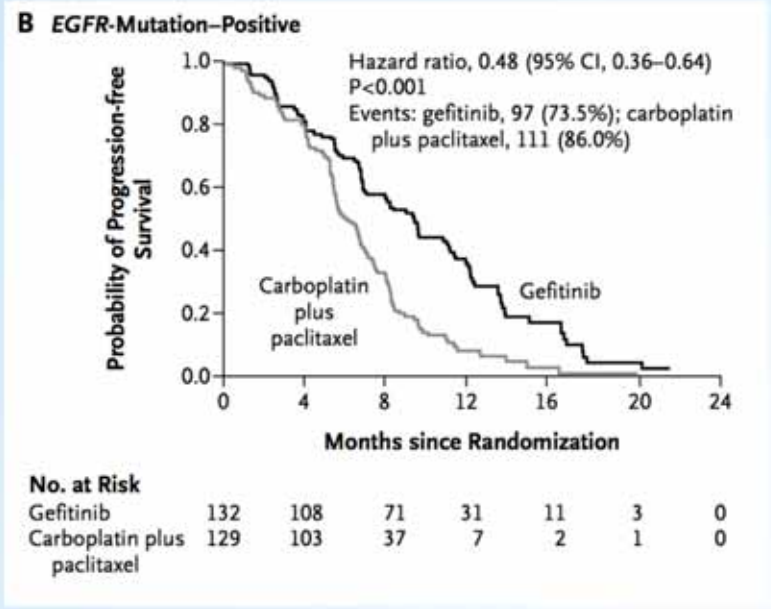
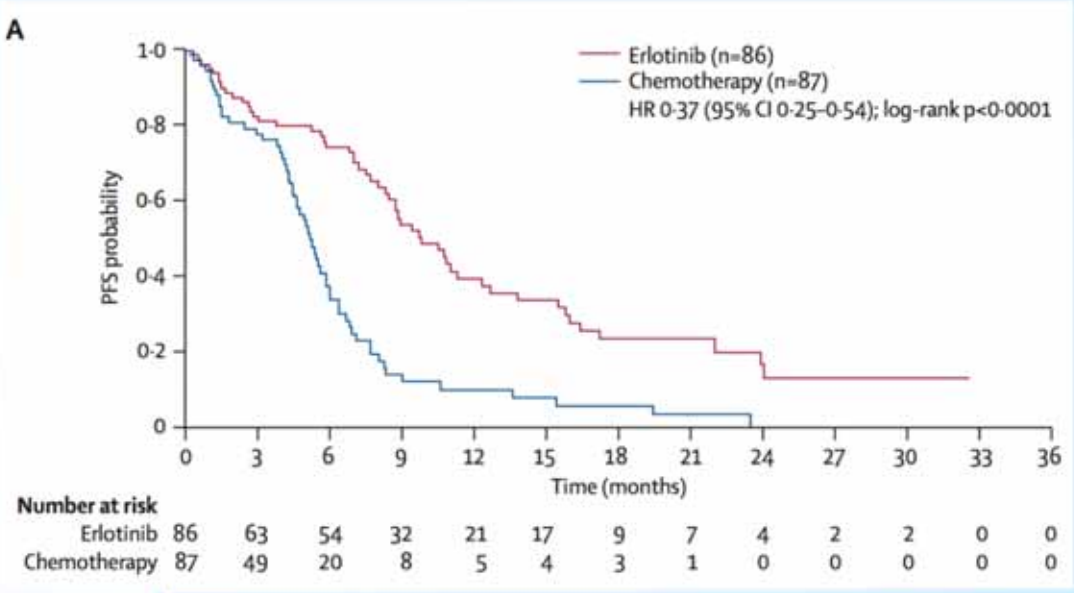
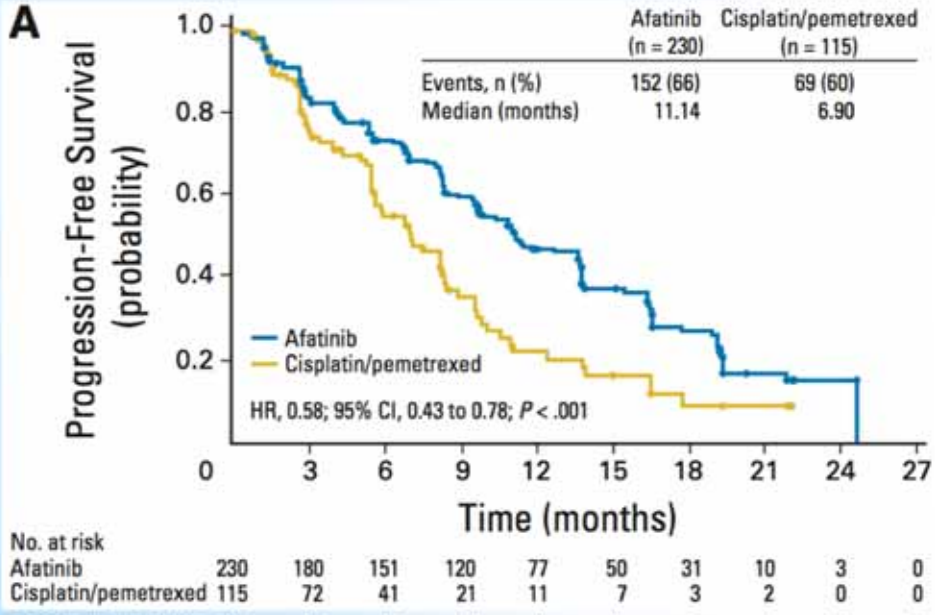
NSCLC métastatique, non muté, non réarrangé: 2ème ligne et au-delà

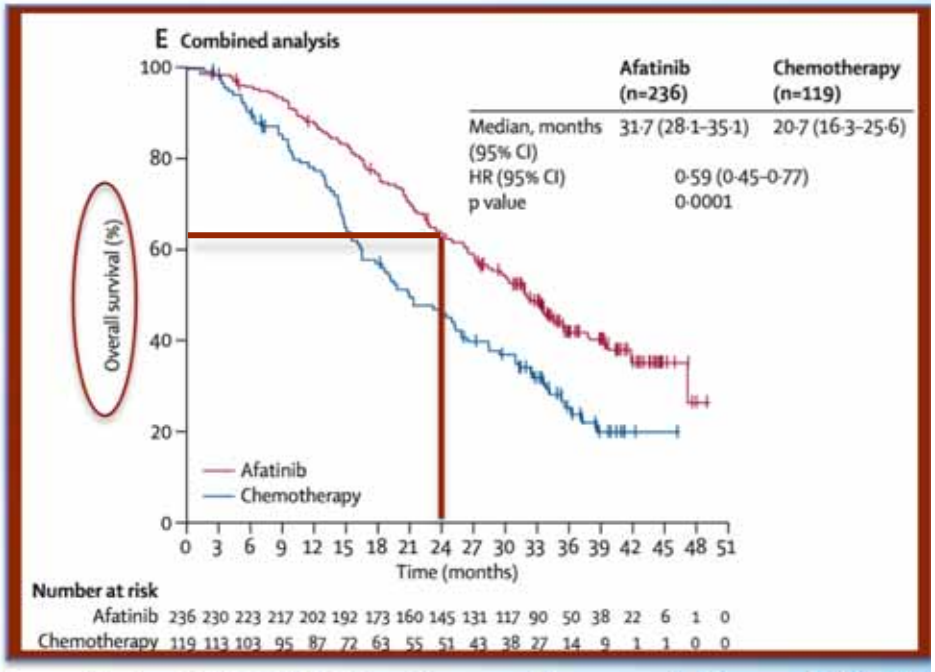
Stefano Kim

EGFR muté



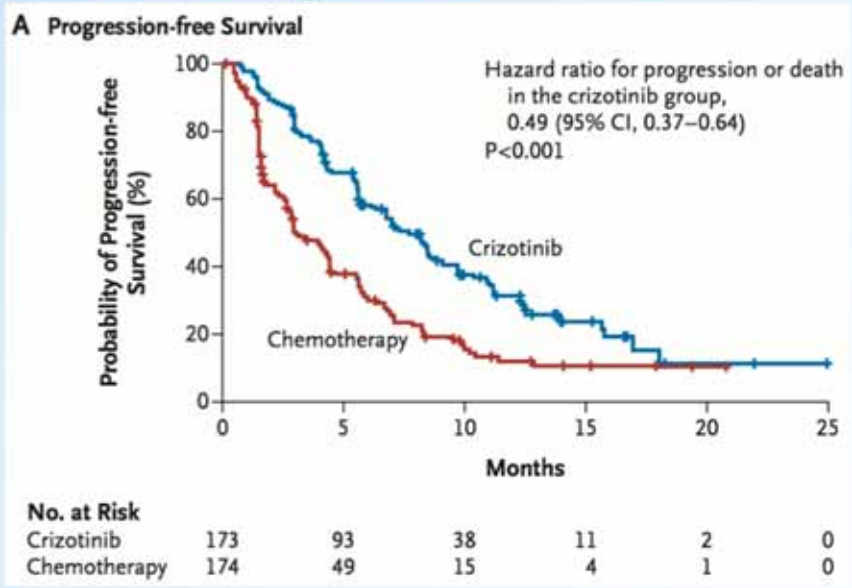


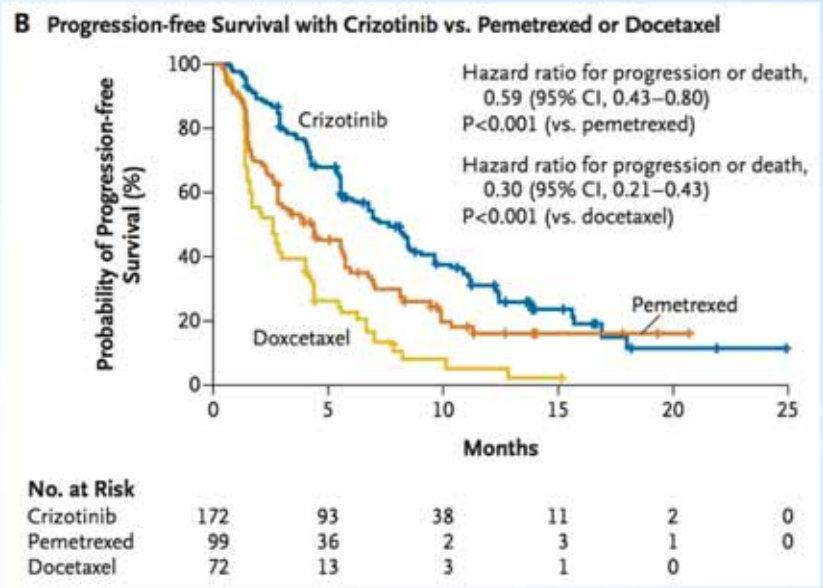


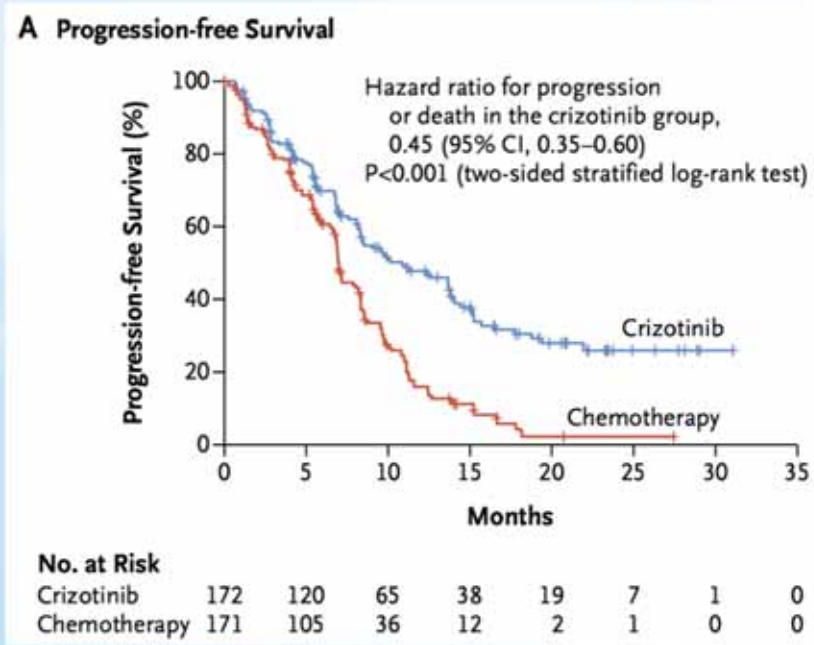


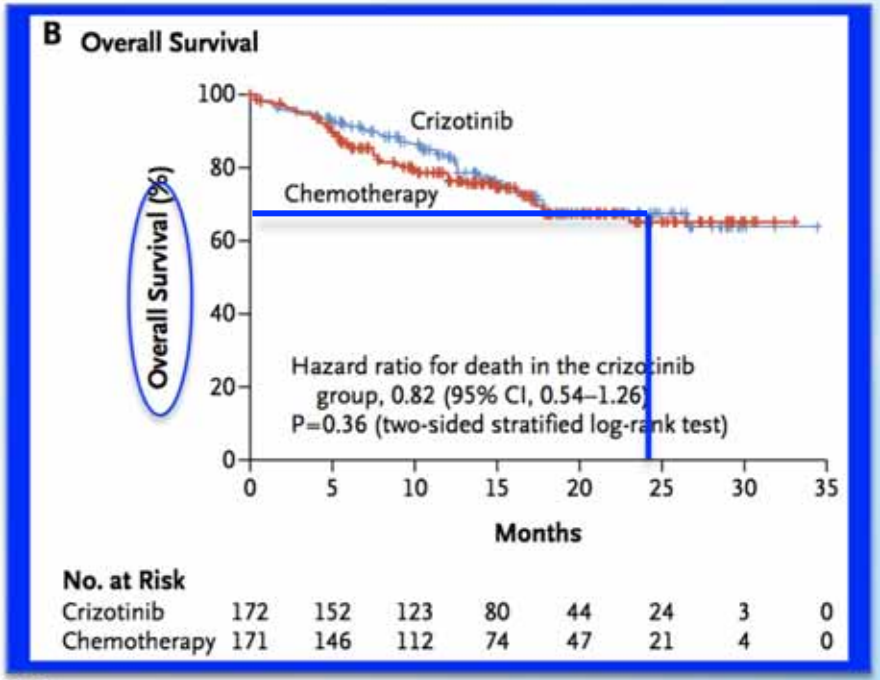
Mok, NEJM 2009. Rosell, Lancet Oncol 2012. Sequist, JCO 2013. Yang, Lancet Oncol 2013

Réarrangement EML4-ALK



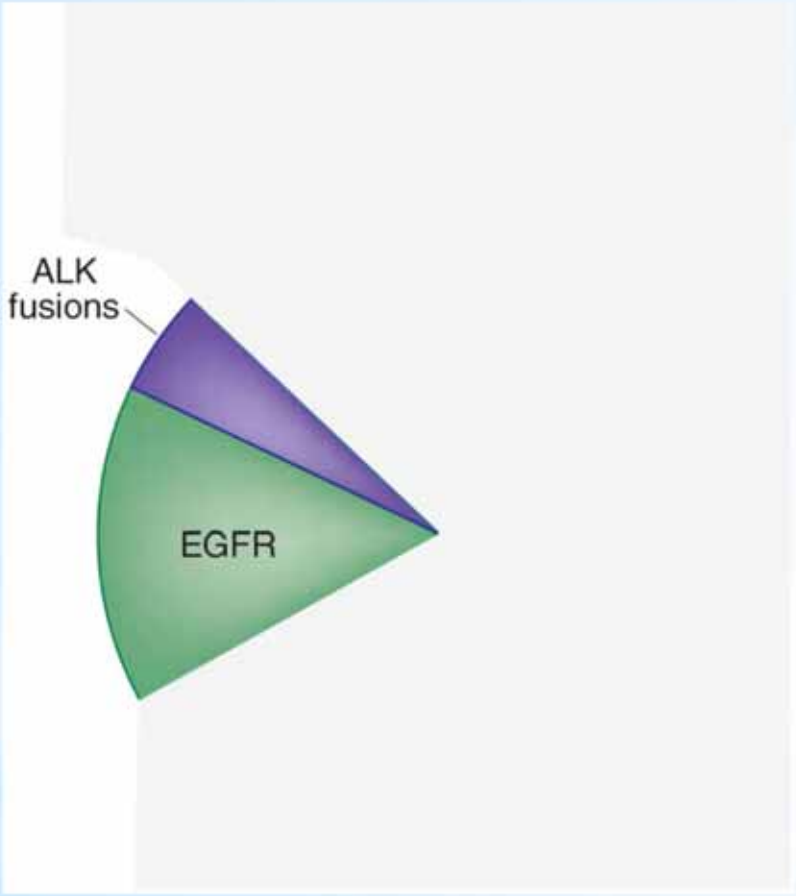






Shaw, NEJM 2013.

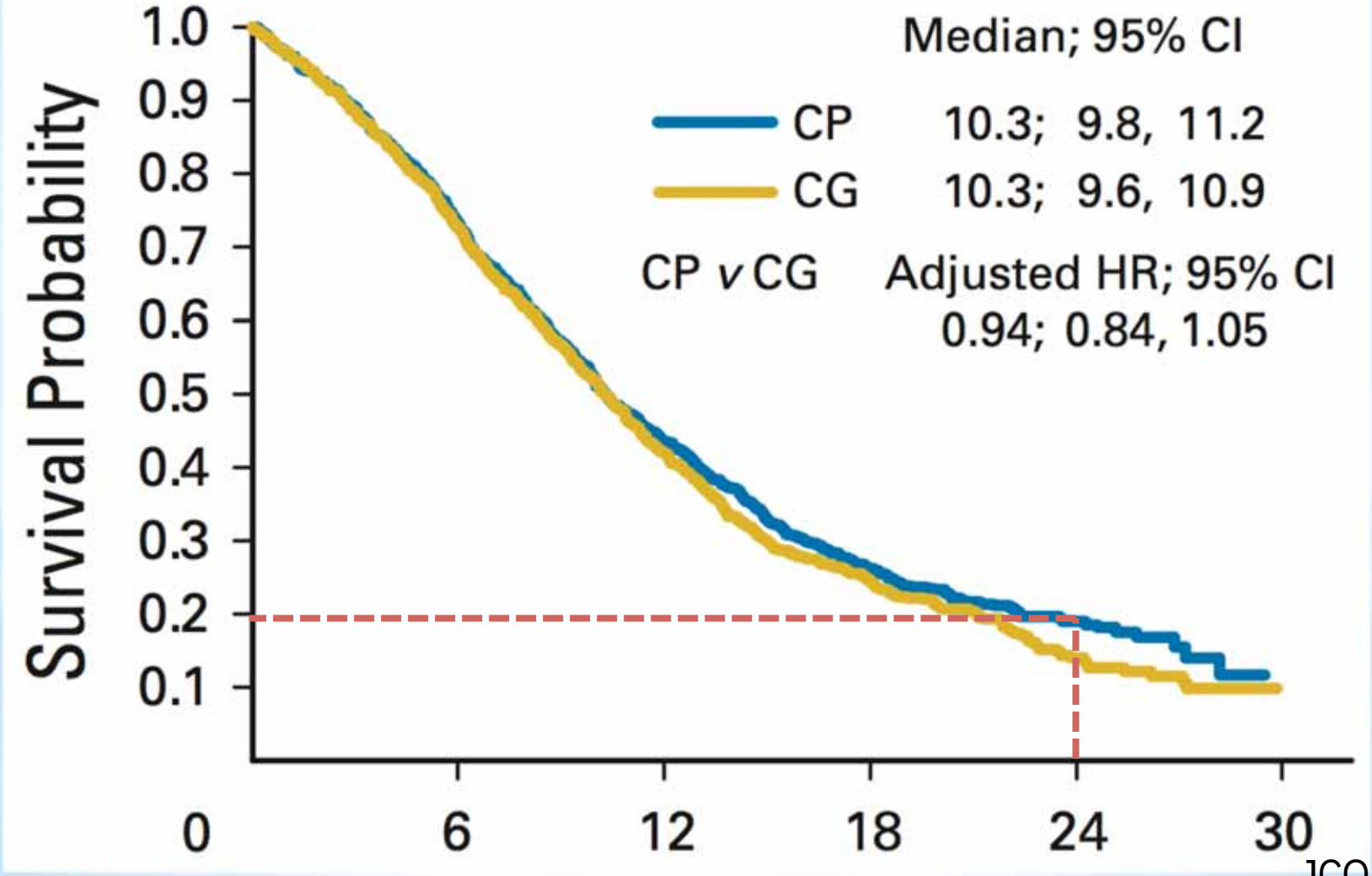
Solomon, NEJM 2014.


ALK
fusions
EGFR


Epidermoïde

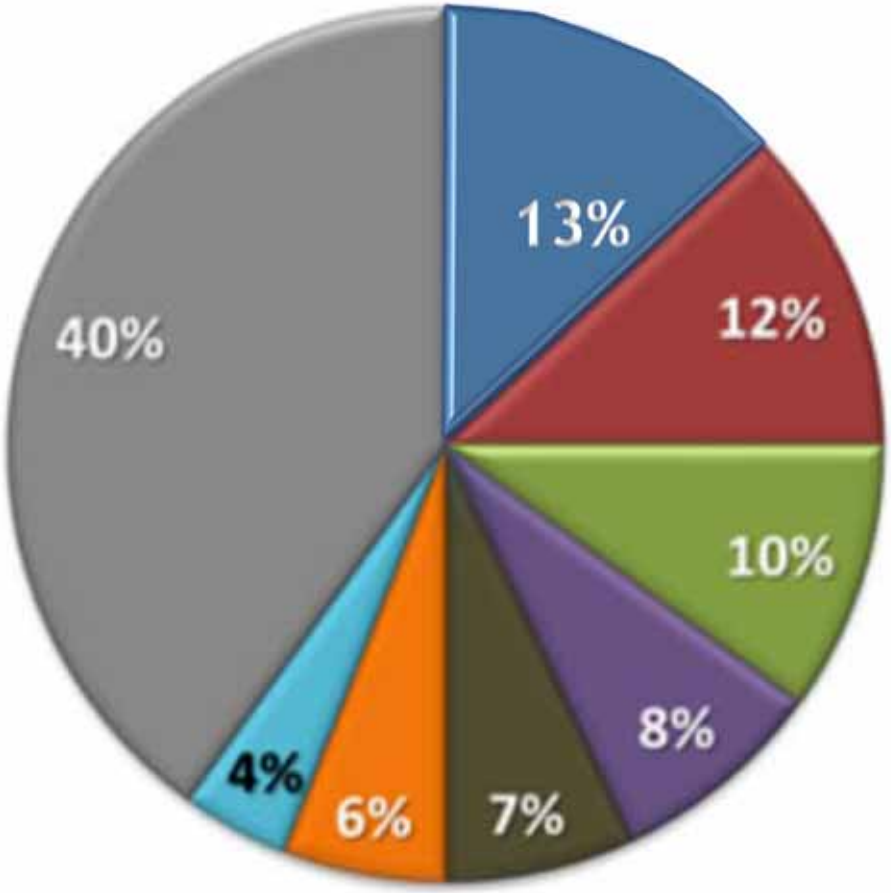
Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naive Patients With Advanced-Stage Non–Small-Cell Lung Cancer

Giorgio Vittorio Scagliotti, Purvish Parikh, Joachim von Pawel, Bonne Biesma, Johan Vansteenkiste,



JCO 2008

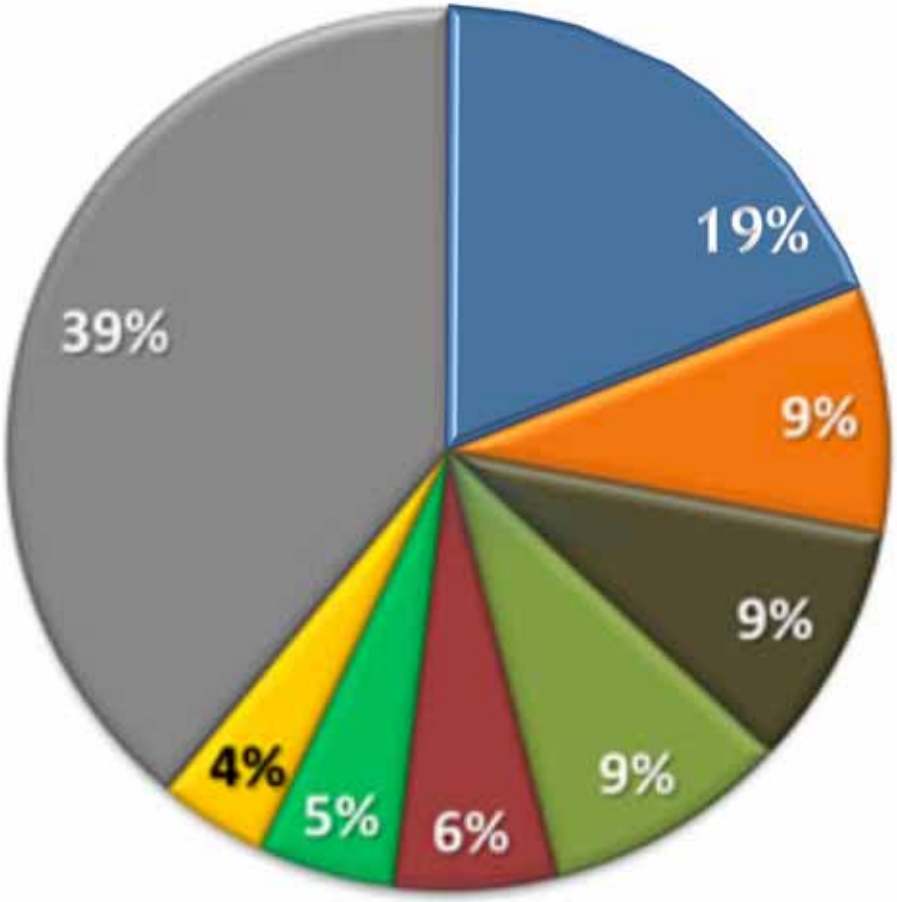
Most Common Cancers Worldwide in 2012



- Lung cancer
- Breast cancer
- Colorectal cancer
- Prostate cancer
- Stomach cancer
- Liver cancer
- Cervical cancer
- Other

Source: GLOBOCAN 2012

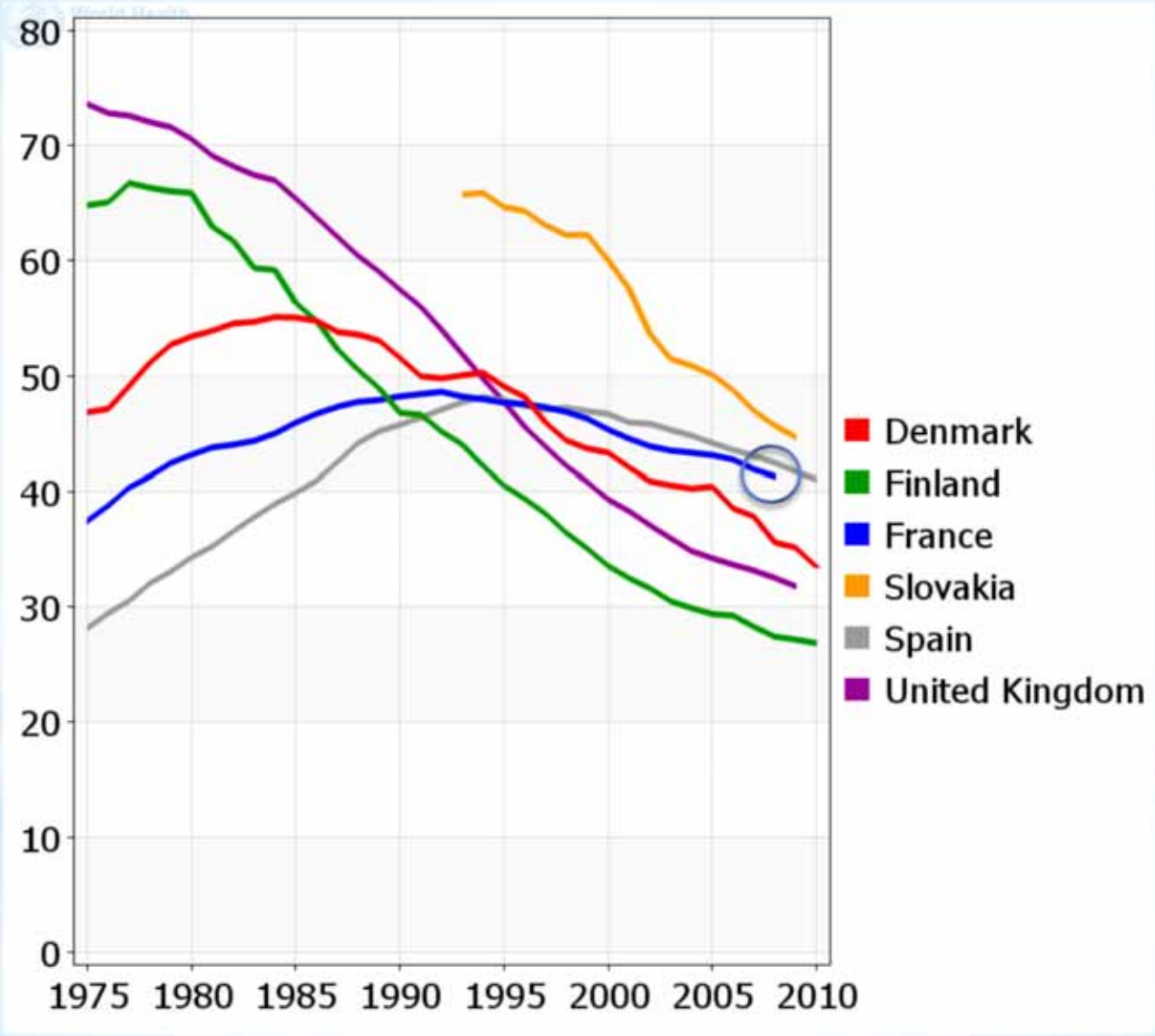
Most Common Causes of Cancer Death Worldwide in 2012



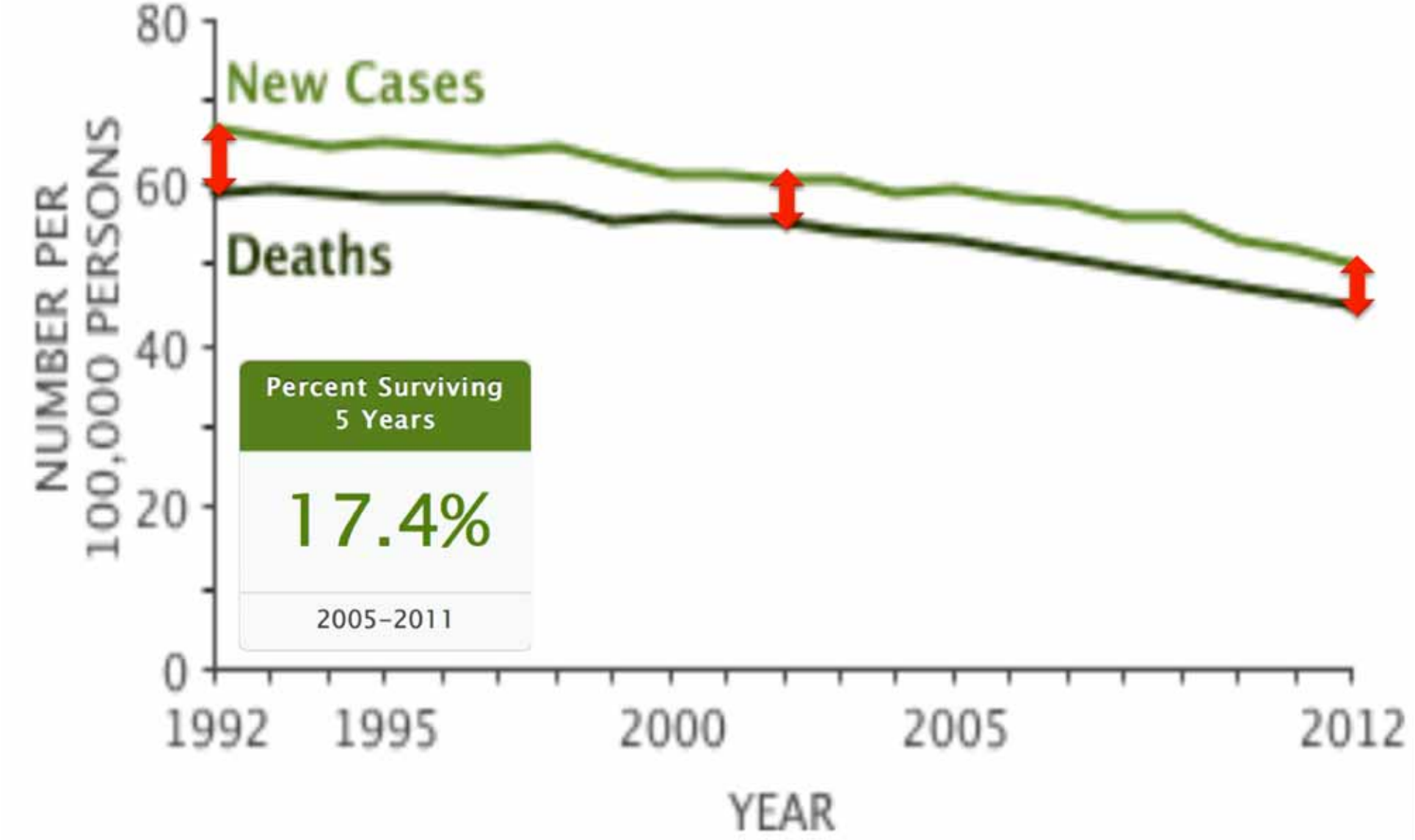
- Lung cancer
- Liver cancer
- Stomach cancer
- Colorectal cancer
- Breast cancer
- Esophagus cancer
- Pancreatic cancer
- Other

Source: GLOBOCAN 2012

Mortalité

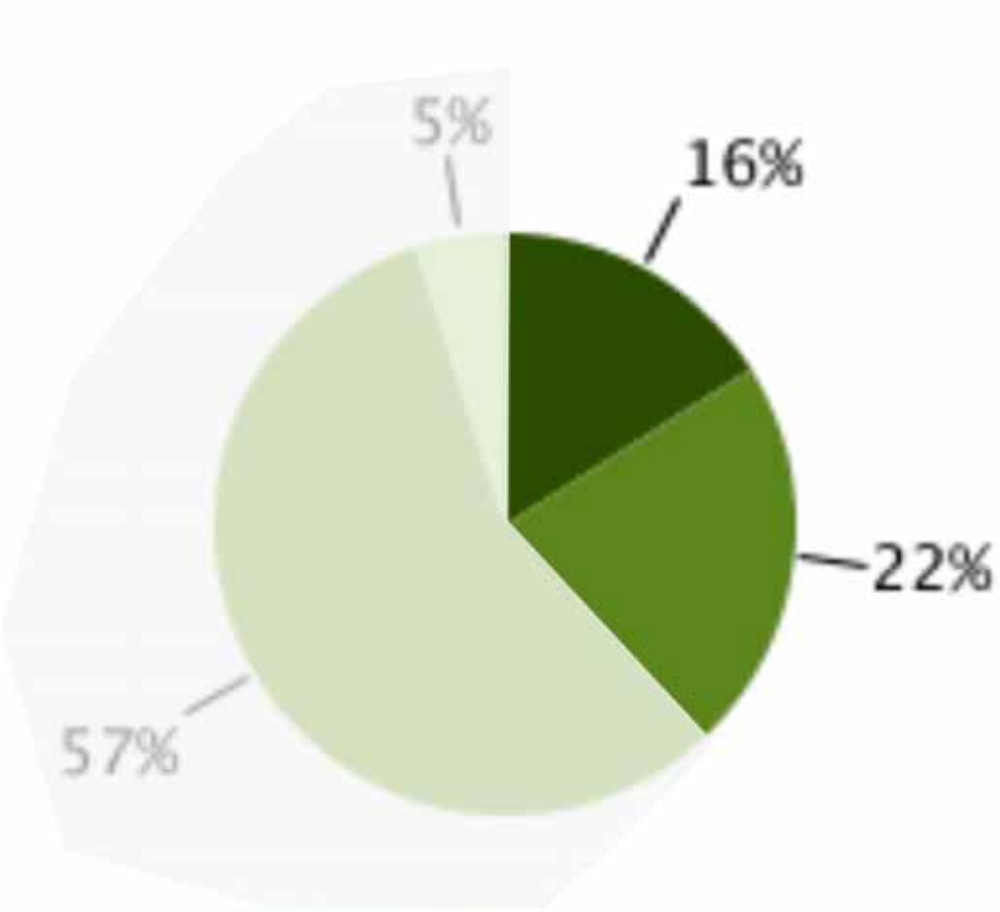


Global Cancer Statistics


New Cases
Deaths
NUMBER PER 100,000 PERSONS
80
60
40
20
0
1992
1995
2000
2005
2012
YEAR
Percent Surviving 5 Years
17.4%
2005-2011

SEER 2015

Stade localisé



Localized (16%)
Confined to Primary Site

Regional (22%)
Spread to Regional Lymph Nodes

Distant (57%)
Cancer Has Metastasized

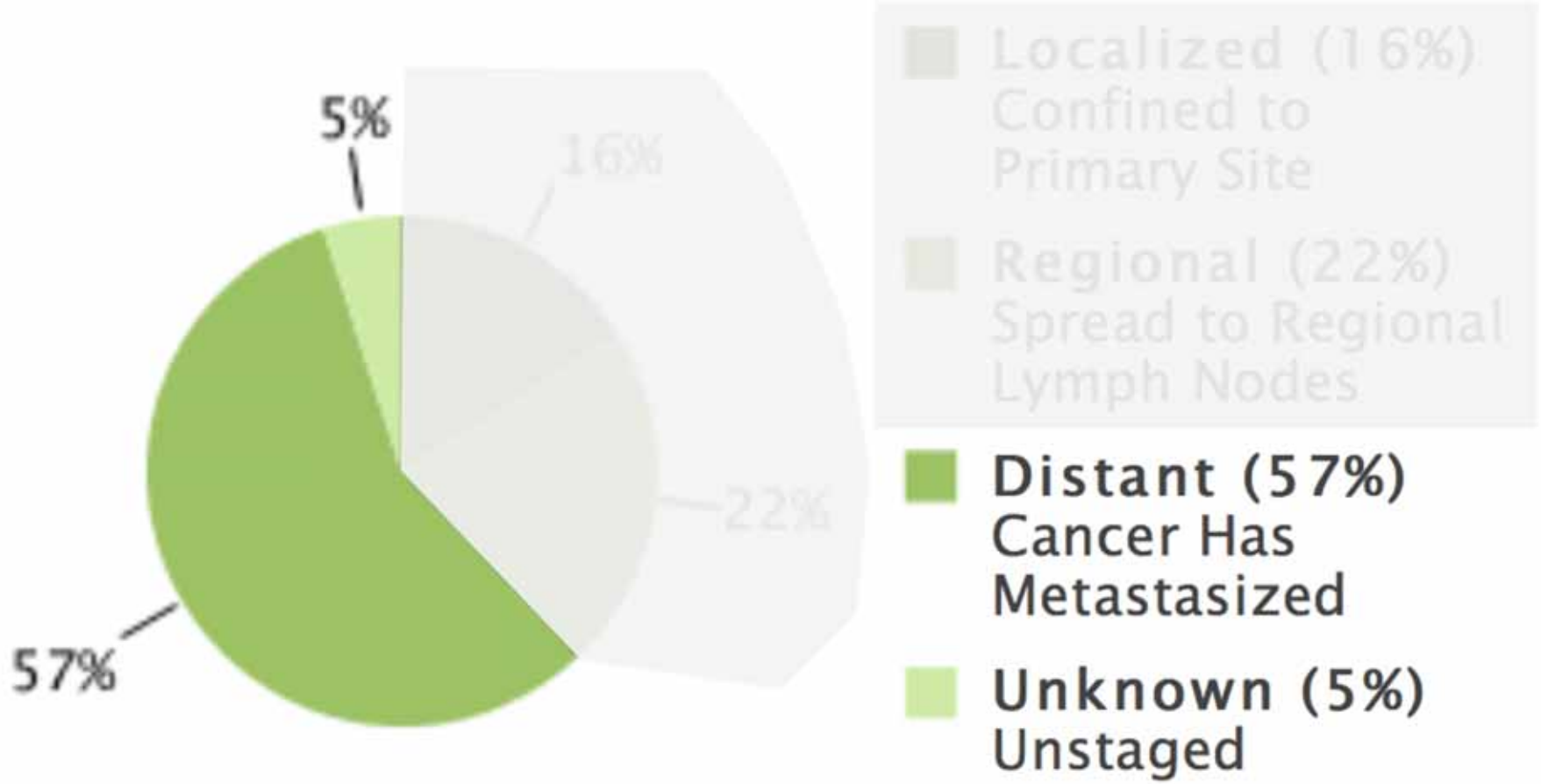
Unknown (5%)
Unstaged

SEER 2015

Stade	SG à 5 ans	Post CT	IC 95%	RRA	RRR
IA	**73**	**78,4**	76,4-80,3	**5,4%**	**20%**
IB	54	63,2	59,8-66,4	9,8%	21%
IIA	48	58,5	54,6-62,0	10,5%	20%
IIB	38	50,5	45,9-54,7	11,5%	19%
IIIA	**25**	**40,1**	34,5-45,3	**15,1%**	**20%**

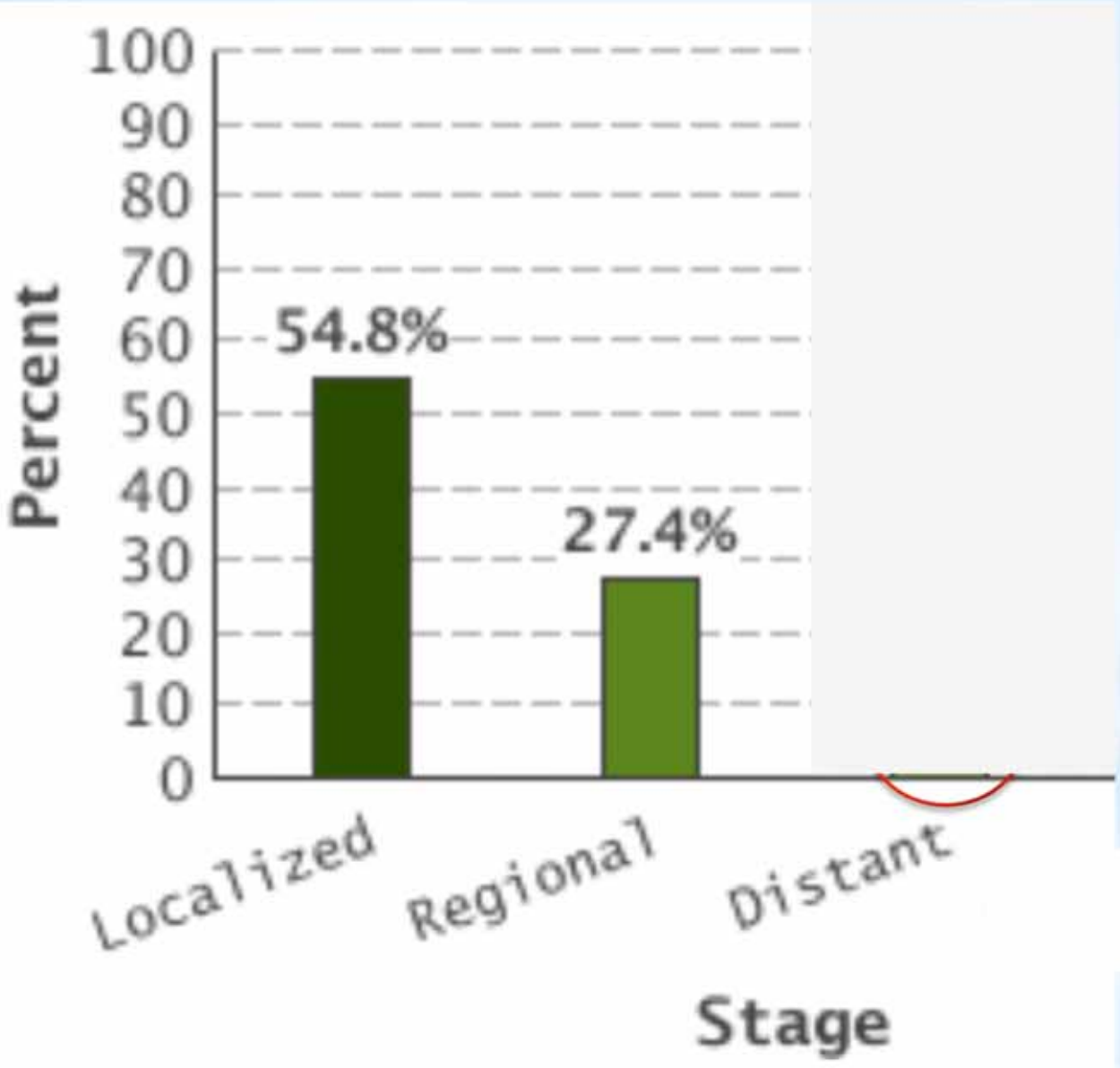
Chimiothérapie adjuvante

Stade métastatique



SEER 2015

Taux de survie à 5 ans



SEER 2015


2014
2015


NSCLC métastatique,
non muté, non réarrangé
Immunothérapie
2014
2015

* Chimiothérapie
* TKI anti EGFR
* Antiangiogénique
* Immunothérapie

NSCLC métastatique, non muté, non réarrangé: 2ème ligne et au-delà

Stefano Kim

Inserm

CHRU Besançon
centre hospitalier régional universitaire

FRANCHE-COMTÉ
IRFC
INSTITUT RÉGIONAL FÉDÉRATIF DU CANCER

CIC B
Centre d'Investigation Clinique de Besançon

* Chimiothérapie
* TKI anti EGFR
* Antiangiogénique
* Immunothérapie

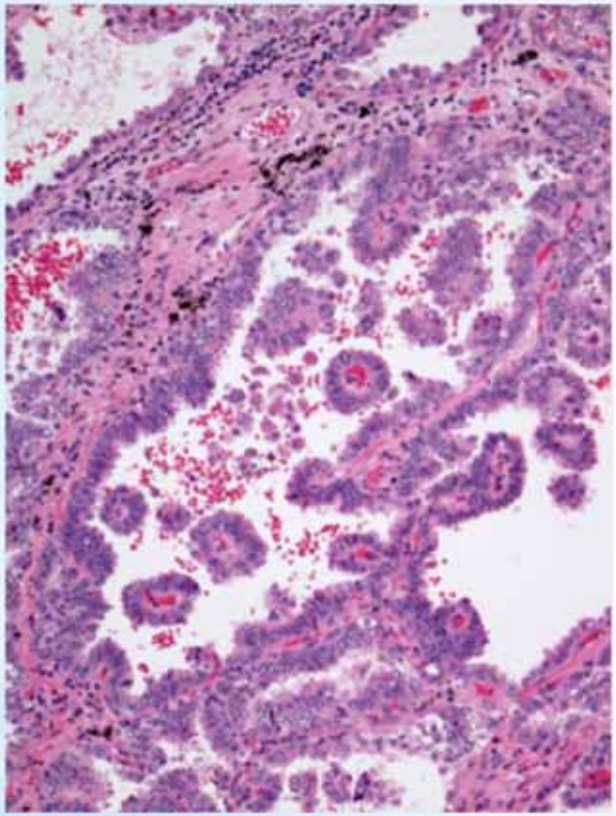
Traitements en 2ème/3ème ligne

	Docetaxel /3 sem Vs BSC Vs ifo ou vinorelbine Vs TKI	**Pemetrexed 500 mg/ 3 sem Vs docetaxel Vs 900 mg/m²**
RR	5,5-8,8 % (12,8 %)	7,1-9,1 %
PFS médiane	2-2,9 mois (2)	2,6-2,9 mois
Survie médiane	5,7-8 (14 mois*)	6,7-8,3 mois
Survie à 1 an	29,7-37 % (53,7 %*)	29,7 %

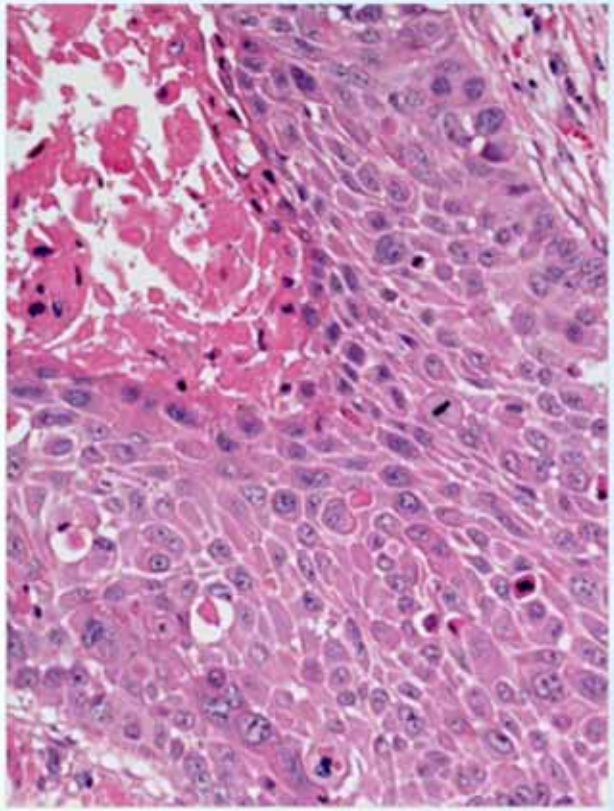
Docetaxel : Shepherd + Fossella JCO 2000 - Kim, Lancet 2008 - *Maruyama, JCO 2008

Pemetrexed : Hanna, JCO 2004 – Cullen, Ann Oncol 2008

Histologie



TTF1 +
CK7 +



P63 +
CK5/6 +

2ème ligne non muté, non réarrangé

Non épidermoïde

Pemetrexed

Docetaxel

Epidermoïde

Pemetrexed

Docetaxel

Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naive Patients With Advanced-Stage Non–Small-Cell Lung Cancer

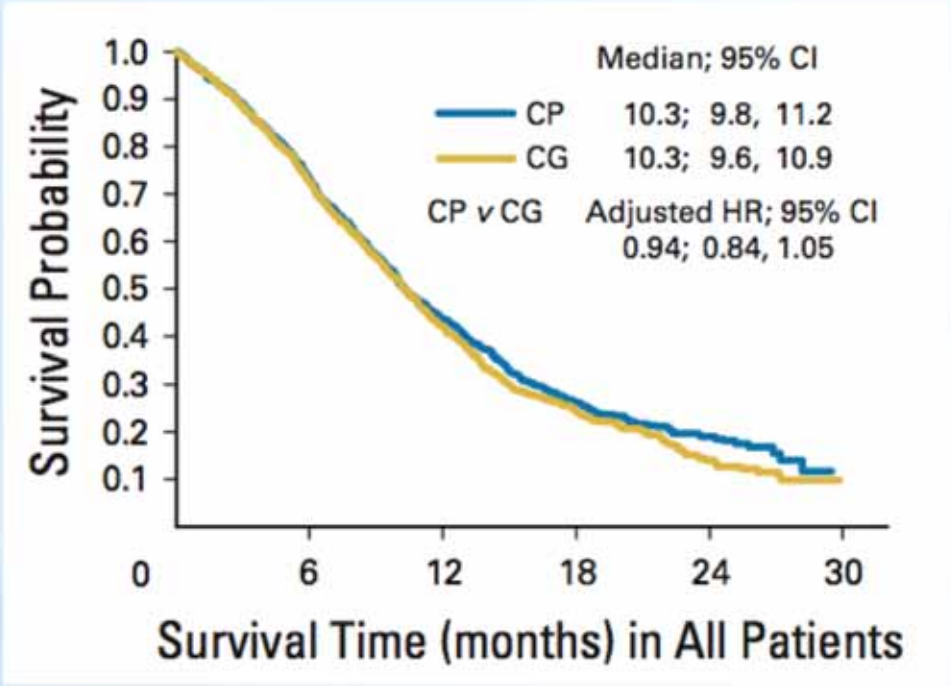
Giorgio Vittorio Scagliotti, Purvish Parikh, Joachim von Pawel, Bonne Biesma, Johan Vansteenkiste, Christian Manegold, Piotr Serwatowski, Ulrich Gatzemeier, Raghunadharao Digumarti, Mauro Zukin, Jin S. Lee, Anders Mellemgaard, Keunchil Park, Shehkar Patil, Janusz Rolski, Tuncay Goksel, Filippo de Marinis, Lorinda Simms, Katherine P. Sugarman, and David Gandara

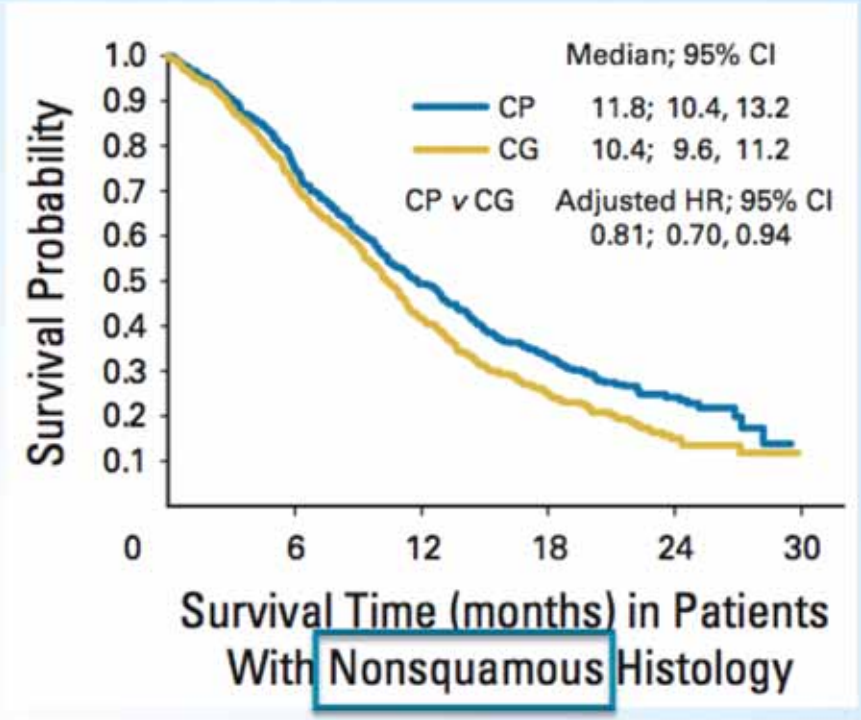
Table 1. Baseline Patient and Disease Characteristics for Randomly Assigned Patients

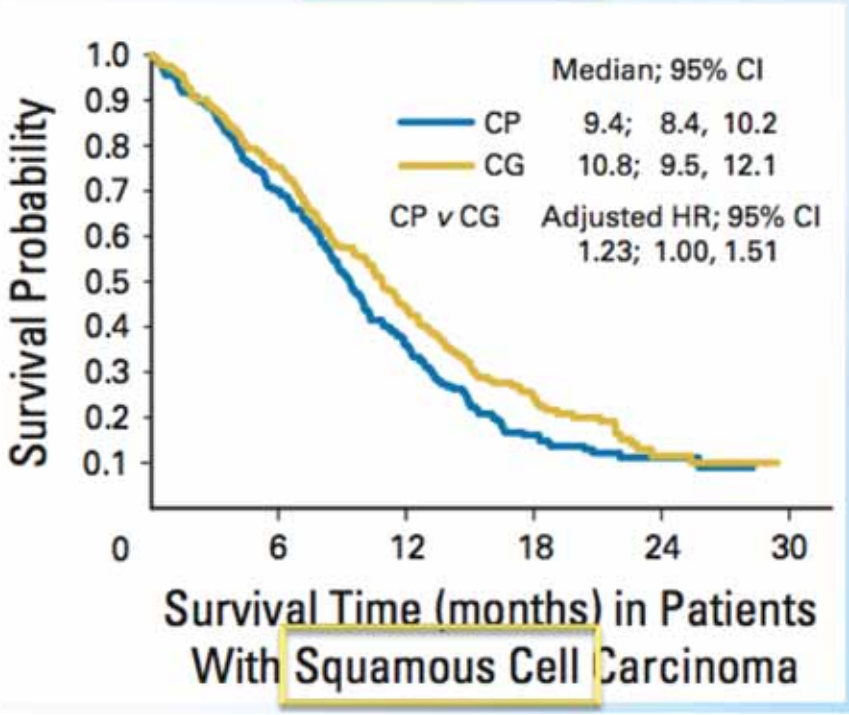
Characteristic	Cisplatin/ Pemetrexed (n = 862) No. of Patients	%	Cisplatin/ Gemcitabine (n = 863) No. of Patients	%
Age, years				
Median	61.1		61.0	
Range	28.8-83.2		26.4-79.4	
Age < 65 years	541	62.8	577	66.9
Age ≥ 65 years	321	37.2	286	33.1
Sex				
Female	257	29.8	258	29.9
Male	605	70.2	605	70.1
Smoking status				
Former/current smoker	629	73.0	637	73.8
Never-smoker	128	14.8	122	14.1
Unknown	105			
Stage of disease				
Stage IIIB, dry	138			
Stage IIIB, wet	67			
Stage IV	657			
ECOG performance status				
0	305			
1	556			
Unknown	1			
Pathologic diagnosis				
Histologic	573			
Cytologic	289			
Race				
African descent	18			
White	669			
East/South East Asian	116	13.5	104	12.1
Other	59	6.8	61	7.1
Histologic type*				
Adenocarcinoma	436	50.6	411	47.6
Large-cell carcinoma	76	8.8	77	8.9
Squamous cell carcinoma	244	28.3	229	26.5
Other: NSCLC, NOS	106	12.3	146	16.9

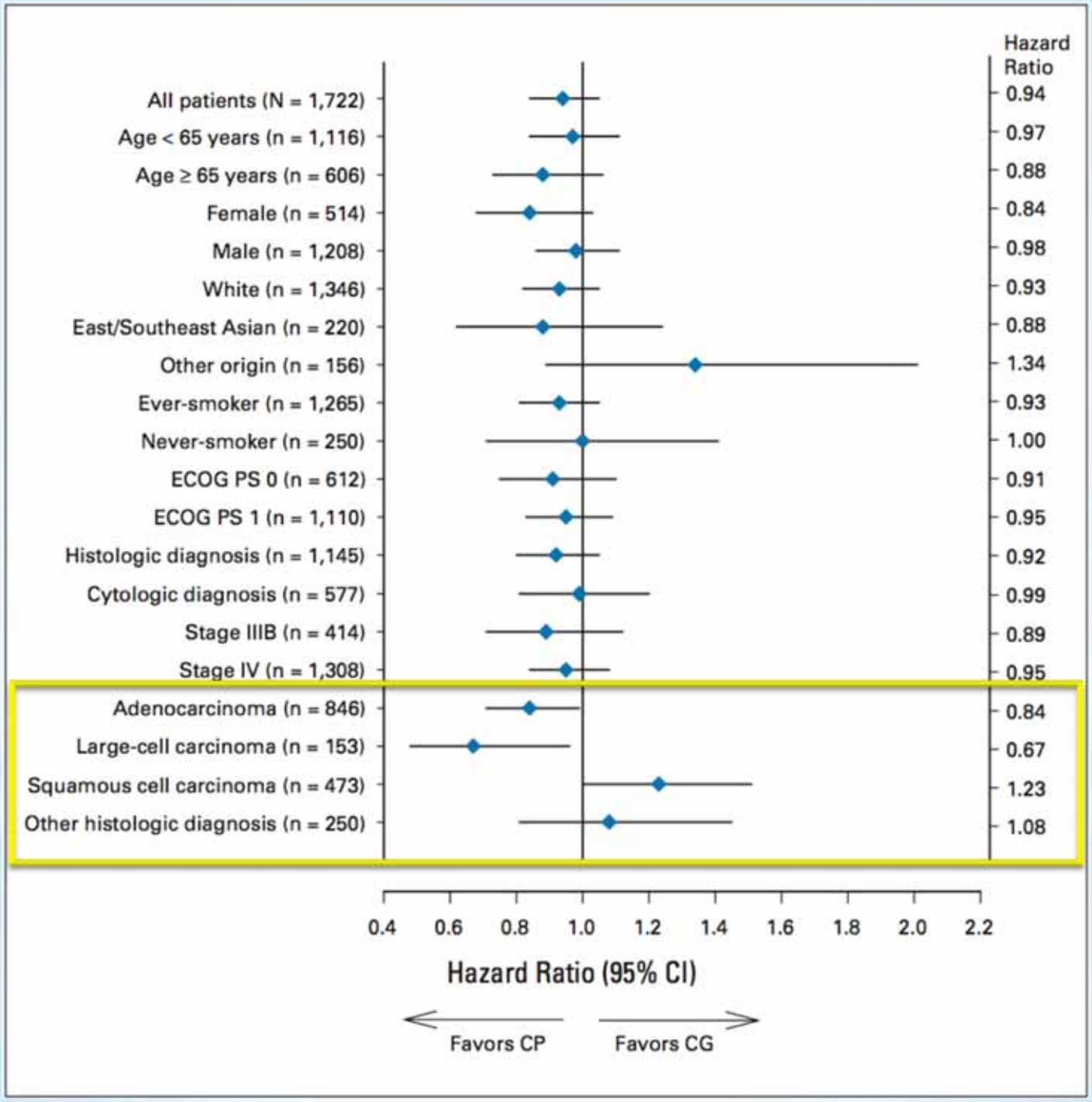
Histologic type*
Adenocarcinoma 436 50.6 411 47.6
Large-cell carcinoma 76 8.8 77 8.9
Squamous cell carcinoma 244 28.3 229 26.5
Other: NSCLC, NOS 106 12.3 146 16.9

Scagliotti G V et al, JCO 2008


Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
6
12
18
24
30
Median; 95% CI
CP 10.3; 9.8, 11.2
CG 10.3; 9.6, 10.9
CP v CG Adjusted HR; 95% CI
0.94; 0.84, 1.05
Survival Time (months) in All Patients


Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
6
12
18
24
30
Median; 95% CI
CP 11.8; 10.4, 13.2
CG 10.4; 9.6, 11.2
CP v CG Adjusted HR; 95% CI
0.81; 0.70, 0.94
Survival Time (months) in Patients With Nonsquamous Histology


Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
6
12
18
24
30
Median; 95% CI
CP 9.4; 8.4, 10.2
CG 10.8; 9.5, 12.1
CP v CG Adjusted HR; 95% CI
1.23; 1.00, 1.51
Survival Time (months) in Patients With Squamous Cell Carcinoma

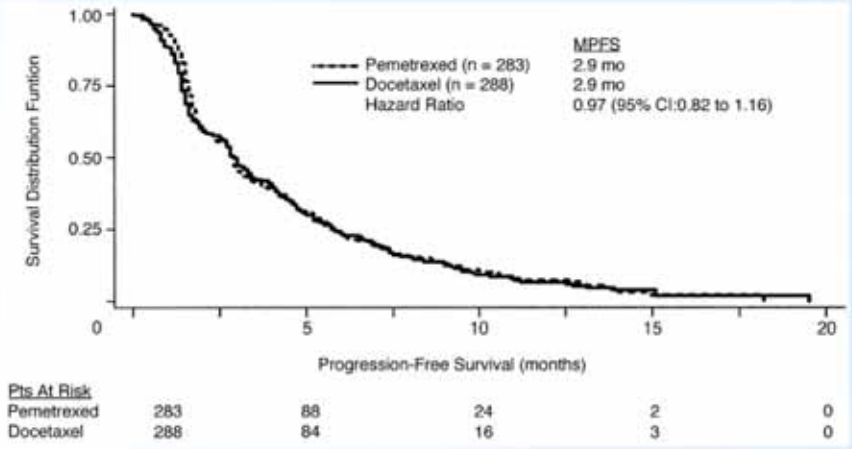

Hazard Ratio
All patients (N = 1,722)
Age < 65 years (n = 1,116)
Age ≥ 65 years (n = 606)
Female (n = 514)
Male (n = 1,208)
White (n = 1,346)
East/Southeast Asian (n = 220)
Other origin (n = 156)
Ever-smoker (n = 1,265)
Never-smoker (n = 250)
ECOG PS 0 (n = 612)
ECOG PS 1 (n = 1,110)
Histologic diagnosis (n = 1,145)
Cytologic diagnosis (n = 577)
Stage IIIB (n = 414)
Stage IV (n = 1,308)
Adenocarcinoma (n = 846)
Large-cell carcinoma (n = 153)
Squamous cell carcinoma (n = 473)
Other histologic diagnosis (n = 250)
0.94
0.97
0.88
0.84
0.98
0.93
0.88
1.34
0.93
1.00
0.91
0.95
0.92
0.99
0.89
0.95
0.84
0.67
1.23
1.08
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
Hazard Ratio (95% CI)
Favors CP
Favors CG

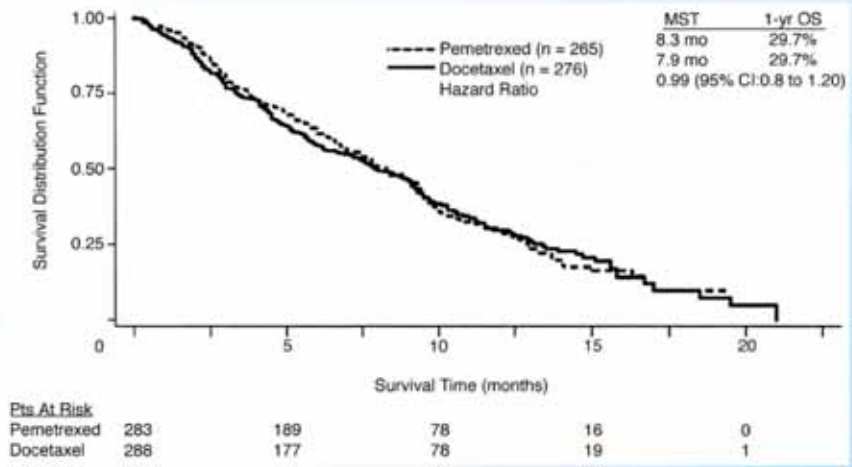
Randomized Phase III Trial of Pemetrexed Versus Docetaxel in Patients With Non–Small-Cell Lung Cancer Previously Treated With Chemotherapy

Nasser Hanna, Frances A. Shepherd, Frank V. Fossella, Jose R. Pereira, Filippo De Marinis, Joachim von Pawel, Ulrich Gatzemeier, Thomas Chang Yao Tsao, Miklos Pless, Thomas Muller, Hong-Liang Lim, Christopher Desch, Klara Szondy, Radj Gervais, Shaharyar, Christian Manegold, Sofia Paul, Paolo Paoletti, Lawrence Einhorn, and Paul A. Bunn Jr.

Table 1. Baseline Patient and Disease Characteristics

Characteristic	% of Patients: Pemetrexed Group (n = 283)	% of Patients: Docetaxel Group (n = 288)
Sex		
Male	68.6	75.3
Female	31.4	24.7
Age, years		
Median	59	57
Range	22-81	28-87
Performance status		
0 or 1	88.6	87.6
2	11.4	12.4
Stage IV	74.9	74.7
Prior Platinum	92.6	89.9
CR/PR to prior platinum	34.7	37.5
Prior paclitaxel	25.8	27.8
CR/PR to prior paclitaxel	39.7	35.0
Best response, any prior chemotherapy		
CR/PR	35.7	36.5
SD	37.5	32.3
PD/unknown or not evaluable	26.9	31.3
Histology		
Adenocarcinoma	54.4	49.3
Squamous cell carcinoma	27.6	32.3
< 12 μmol/L	71.4	68.9
Prior radiation	44.2	45.5





Hanna N et al, JCO 2006

The Differential Efficacy of Pemetrexed According to NSCLC Histology: A Review of Two Phase III Studies

GIORGIO SCAGLIOTTI,[a] NASSER HANNA,[b] FRANK FOSSELLA,[c] KATHERINE SUGARMAN,[d] JOHANNES BLATTER,[e] PATRICK PETERSON,[d] LORINDA SIMMS,[f] FRANCES A. SHEPHERD[g]

Table 3. Treatment-by-histology interactions for overall survival and progression-free survival for the pemetrexed versus docetaxel and cisplatin plus pemetrexed versus cisplatin plus gemcitabine studies

	Pemetrexed versus docetaxel (n = 571)		Cisplatin plus pemetrexed versus cisplatin plus gemcitabine (n = 1,725)	
Efficacy parameter	**Nonsquamous[a] (n = 399)**	**Squamous (n = 172)**	**Nonsquamous[a] (n = 1,252)**	**Squamous (n = 473)**
OS adjusted HR[b] (95% CI)	0.78 (0.61–1.00)	1.56 (1.08–2.26)	0.84 (0.74–0.96)	1.23 (1.00–1.51)
Superiority p-value	.047	.018	.011	.050
Treatment-by-histology interaction test p-value[c]	.001		.002	
PFS adjusted HR[b] (95% CI)	0.82 (0.66–1.02)	1.40 (1.01–1.96)	0.95 (0.84–1.06)	1.36 (1.12–1.65)
Superiority p-value	.076	.046	.349	.002
Treatment-by-histology interaction test p-value[c]	.004		.002	

[a]Nonsquamous histology comprises adenocarcinoma, large cell carcinoma, and other histologies.
[b]HR <1.0 favors pemetrexed study arm; HR >1.0 favors comparator.
[c]Tests for statistically significant treatment-by-histology interactions were performed for PFS and OS using cofactor-adjusted Cox proportional hazards models.
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Scagliotti G V et al, The Oncologist 2009

The Differential Efficacy of Pemetrexed According to NSCLC Histology: A Review of Two Phase III Studies

GIORGIO SCAGLIOTTI,[a] NASSER HANNA,[b] FRANK FOSSELLA,[c] KATHERINE SUGARMAN,[d] JOHANNES BLATTER,[e] PATRICK PETERSON,[d] LORINDA SIMMS,[f] FRANCES A. SHEPHERD[g]

* Conclusion : « pemetrexed should not be recommended for the treatment of squamous cell carcinoma »

Scagliotti G V et al, The Oncologist 2009

2ème ligne non muté, non réarrangé

Non épidermoïde

Pemetrexed

Docetaxel

Epidermoïde

~~Pemetrexed~~

Docetaxel

Docetaxel

	Pemetrexed versus docetaxel (n = 571)	
Histologic subgroup	**Pemetrexed**	**Docetaxel**
Nonsquamous (n)	205	194
Median OS (mos)	9.3	8.0
HR (95% CI)	0.78 (0.61–1.00)	
p-value	.048	
Median PFS (mos)	3.1	3.0
HR (95% CI)	0.82 (0.66–1.02)	
p-value	.076	
Response rate (%)[b]	11.5	9.0

Scagliotti G V et al, The Oncologist 2009

2ème ligne non muté, non réarrangé

Non épidermoïde

- Pemetrexed
- Docetaxel

Epidermoïde

- Docetaxel

* Chimiothérapie
* TKI anti EGFR
* Antiangiogénique
* Immunothérapie

2ème ligne non muté, non réarrangé

Non épidermoïde

- Pemetrexed
- Docetaxel

Epidermoïde

- Docetaxel

- Erlotinib
- Afatinib

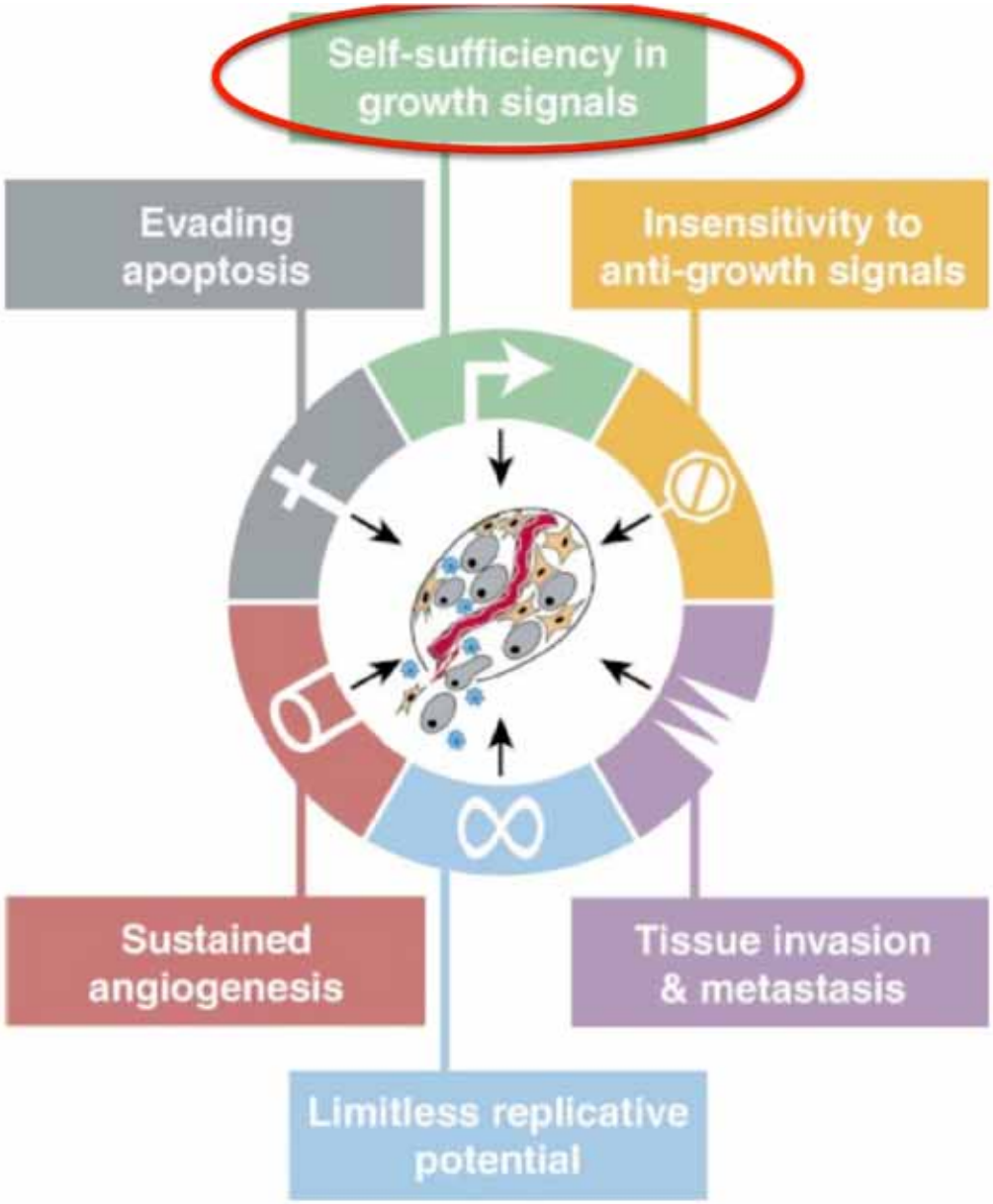


Figure 1. Acquired Capabilities of Cancer

We suggest that most if not all cancers have acquired the same set of functional capabilities during their development, albeit through various mechanistic strategies.

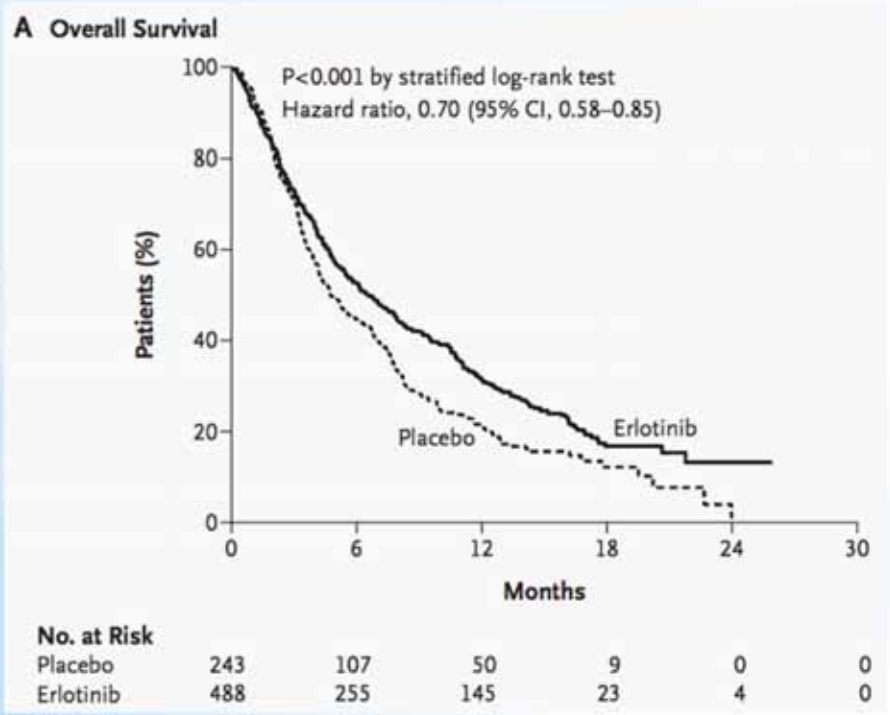
Hanahan, Cell 2000

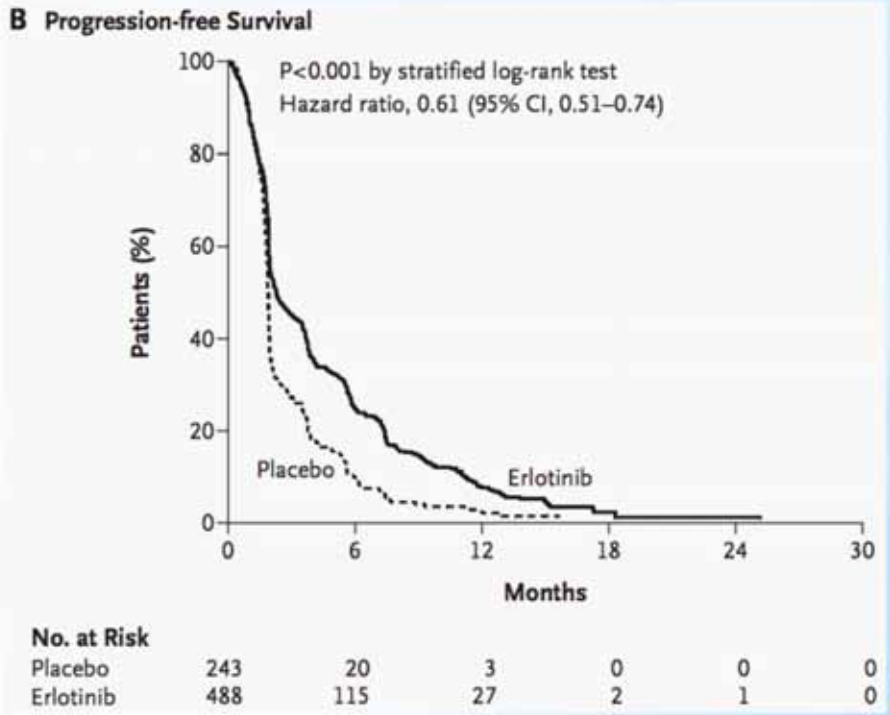
Erlotinib >= 2ème ligne

ESTABLISHED IN 1812 JULY 14, 2005 VOL. 353 NO. 2

Erlotinib in Previously Treated Non–Small-Cell Lung Cancer

Frances A. Shepherd, M.D., José Rodrigues Pereira, M.D., Tudor Ciuleanu, M.D., Eng Huat Tan, M.D.,





Shepherd, NEJM 2005

Table 3. Analysis of Survival.*

Factor	No. of Patients	Univariate Hazard Ratio (95% CI)†	P Value	Multivariate Hazard Ratio (CI)‡	P Value§
Treatment group					
Erlotinib	488	0.7 (0.6–0.9)	<0.001	0.7 (0.6–0.9)	0.002
Placebo	243				
Age				NI	
<60 yr	332	0.8 (0.6–1.0)	0.04		
≥60 yr	399	0.8 (0.6–1.0)	0.02		
Sex				NI	
Male	475	0.8 (0.6–0.9)	0.01		
Female	256	0.8 (0.6–1.1)	0.13		
Pathological subtype					
Adenocarcinoma	365	0.7 (0.6–0.9)	0.008	0.8 (0.6–0.9)	0.004
Other	366	0.8 (0.6–1.0)	0.07		
Performance status				NA	
0 or 1	486	0.7 (0.6–0.9)	0.003		
2	182	0.8 (0.5–1.1)	0.11		
3	63	0.8 (0.4–1.3)	0.33		

Table 3. Analysis of Survival.*

Factor	No. of Patients	Univariate Hazard Ratio (95% CI)†	P Value	Multivariate Hazard Ratio (CI)‡	P Value§
Treatment group					
Erlotinib	488	0.7 (0.6–0.9)	<0.001	0.7 (0.6–0.9)	0.002
Placebo	243				
Age				NI	
<60 yr	332	0.8 (0.6–1.0)	0.04		
≥60 yr	399	0.8 (0.6–1.0)	0.02		
Sex				NI	
Male	475	0.8 (0.6–0.9)	0.01		
Female	256	0.8 (0.6–1.1)	0.13		
Pathological subtype					
Adenocarcinoma	365	0.7 (0.6–0.9)	0.008	0.8 (0.6–0.9)	0.004
Other	366	0.8 (0.6–1.0)	0.07		
Performance status				NA	
0 or 1	486	0.7 (0.6–0.9)	0.003		
2	182	0.8 (0.5–1.1)	0.11		
3	63	0.8 (0.4–1.3)	0.33		

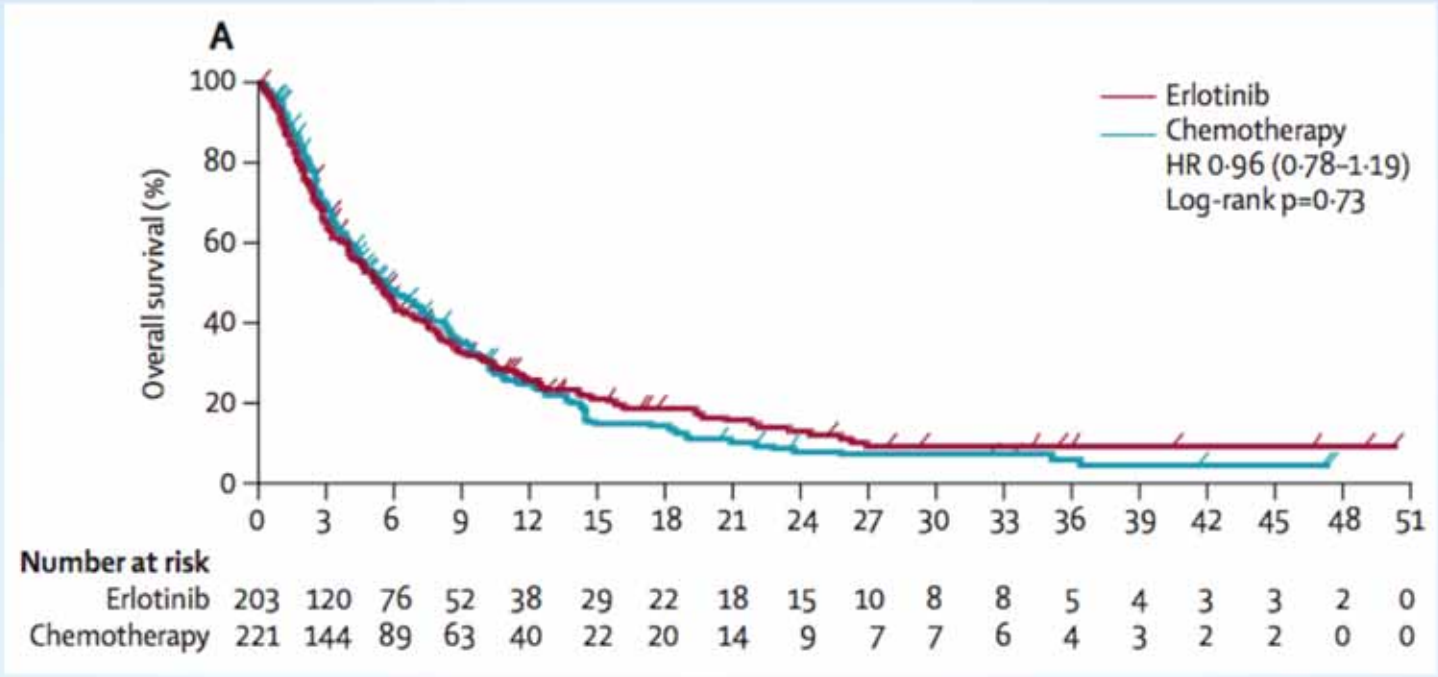
Response to prior therapy				NA	
Complete response or partial response	292	0.7 (0.5–0.9)	0.004		
Stable disease	287	0.8 (0.6–1.1)	0.18		
Progressive disease	152	0.9 (0.6–1.2)	0.34		
Prior regimens				NA	
1	369	0.8 (0.6–1.1)	0.03		
2 or 3	362	0.8 (0.6–1.1)	0.02		
Prior platinum-based therapy				NA	
Yes	672	0.7 (0.6–0.9)	<0.001		
No	59	1.7 (0.7–2.7)	0.30		
EGFR expression				NA	
Positive	184	0.7 (0.5–0.9)	0.02		
Negative	141	0.9 (0.6–1.4)	0.70		
Unknown	406	0.8 (0.6–1.0)	0.03		
Smoking status					
Current smoker or ever smoked	545	0.9 (0.7–1.0)	0.14	Reference group	
Never smoked	146	0.4 (0.3–0.6)	<0.001	0.8 (0.6–1.0)	0.048
Unknown	40	1.1 (0.5–2.6)	0.80	1.0 (0.7–1.5)	0.89
Race or ethnic group					
Asian	91	0.6 (0.4–1.0)	0.06	0.7 (0.5–0.9)	0.01
Other	640	0.8 (0.7–0.9)	0.01		

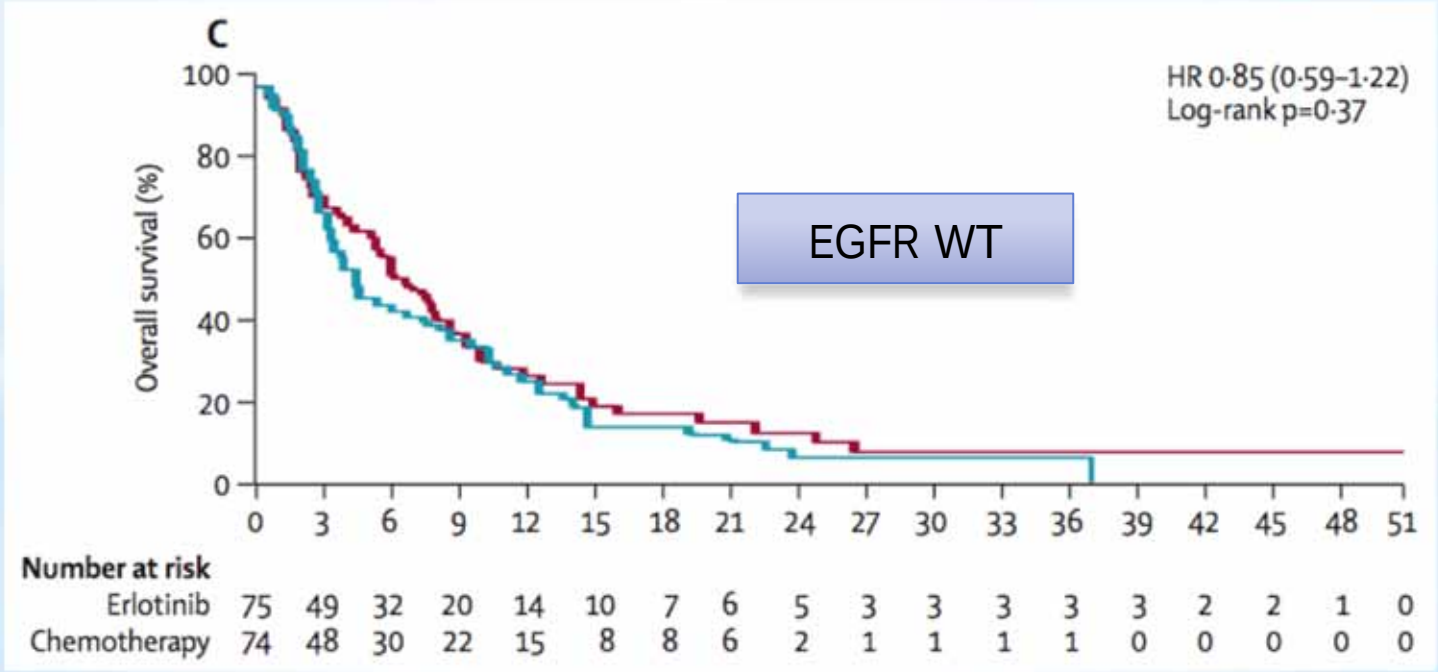
Erlotinib vs Chimiothérapie

Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study

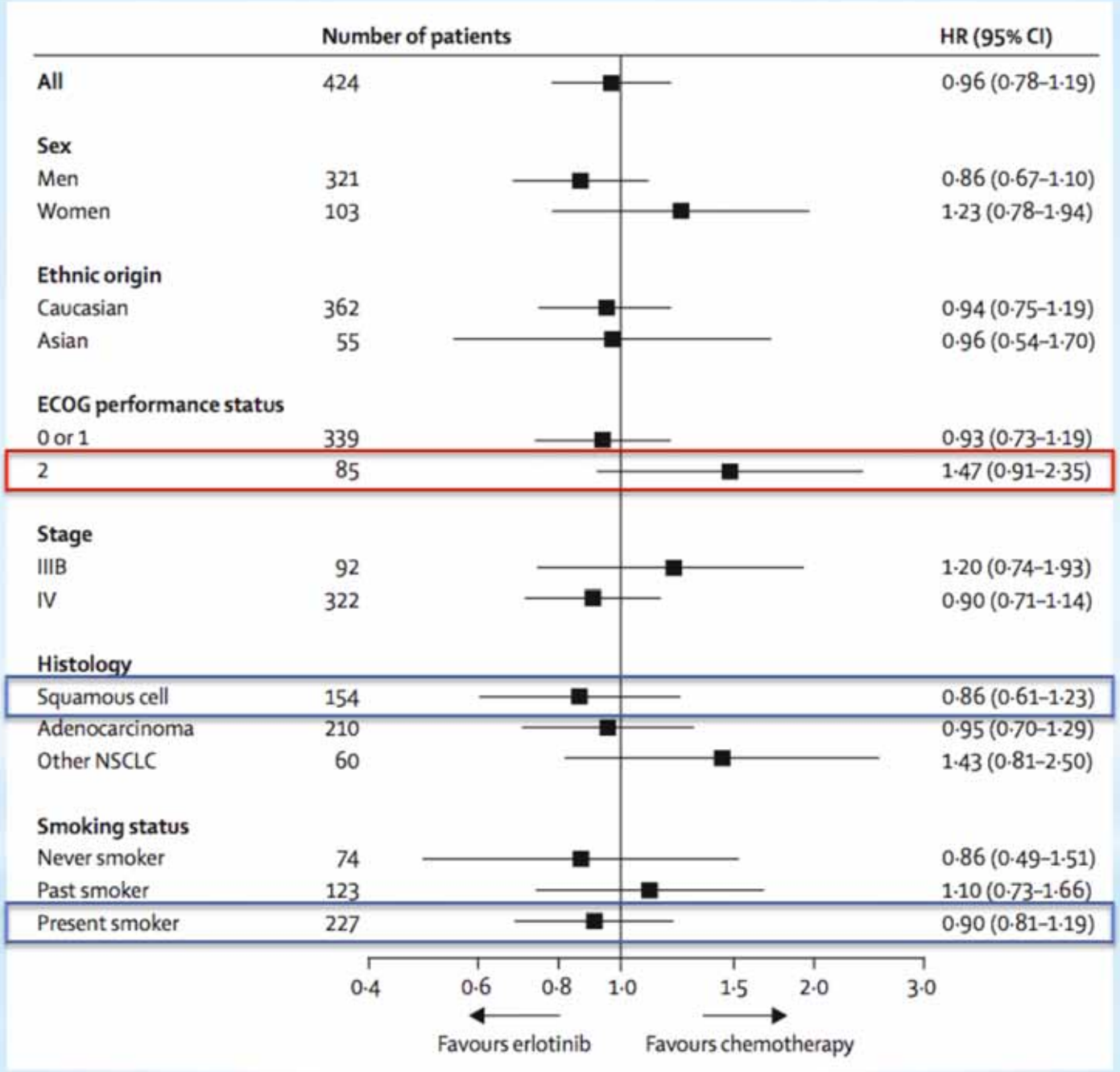
Tudor Ciuleanu, Lilia Stelmakh, Saulius Cicenas, Skaidrius Miliauskas, Alexandru Calin Grigorescu, Carina Hillenbach, Hrefna Kristin Johannsdottir, Barbara Klughammer, Emilio Esteban Gonzalez

	Erlotinib (n=203)	Chemotherapy (n=221)
Age (years)	59 (36–80)	59 (22–79)
Men	161 (79%)	160 (72%)
Ethnic origin		
Caucasian	172 (85%)	190 (86%)
Asian	28 (14%)	26 (12%)
Other*	3 (1%)	5 (2%)
ECOG performance status		
0	29 (14%)	23 (10%)
1	135 (67%)	152 (69%)
2	39 (19%)	46 (21%)
Disease stage		
IIIB	41 (20%)	51 (23%)
IV	162 (80%)	170 (77%)
Histology		
Adenocarconima	96 (47%)	114 (52%)
Squamous cell†	77 (38%)	77 (35%)
Other	30 (15%)	30 (14%)
Time since first diagnosis (months)	3·7 (1–50)	3·8 (1–223)
Smoking status		
Present	114 (56%)	113 (51%)
Past	59 (29%)	64 (29%)
Never	30 (15%)	44 (20%)
EGFR mutation status		
Activating mutation	7 (3%)	4 (2%)
Other mutation (including resistance mutation)	1 (<1%)	6 (3%)
Wild type	75 (37%)	74 (33%)
Indeterminate	32 (16%)	36 (16%)
Missing	88 (43%)	101 (46%)





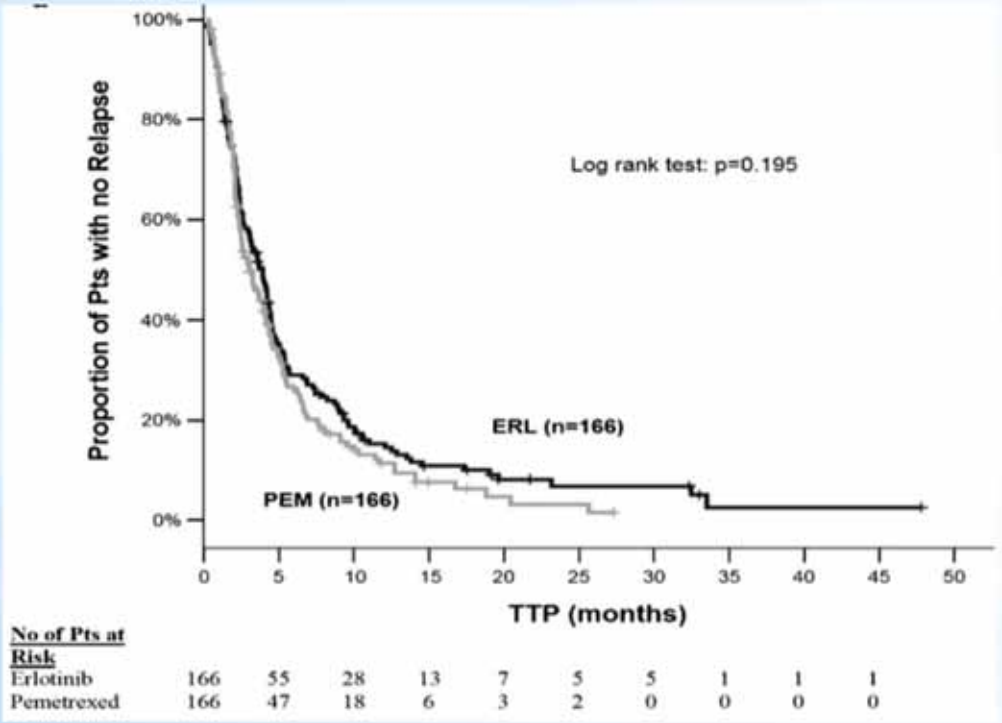
Ciuleanu, Lancet Oncol 2012

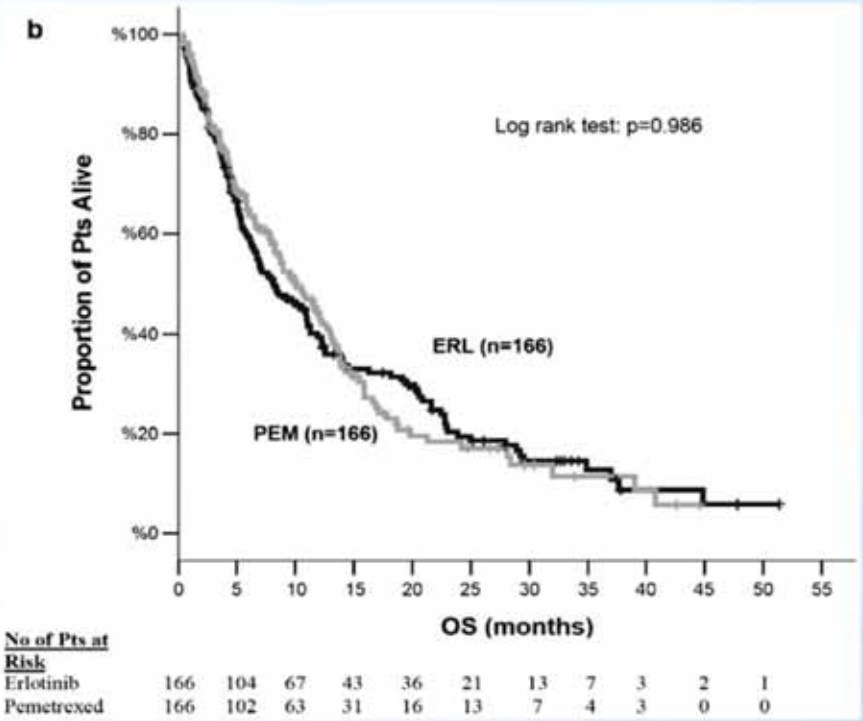


Ciuleanu, Lancet Oncol 2012

Pemetrexed Versus Erlotinib in Pretreated Patients With Advanced Non–Small Cell Lung Cancer: A Hellenic Oncology Research Group (HORG) Randomized Phase 3 Study

Athanasios Karampeazis, MD[1]; Alexandra Voutsina, PhD[2]; John Souglakos, MD, PhD[2,3]; Nikos Kentepozidis, MD[4];

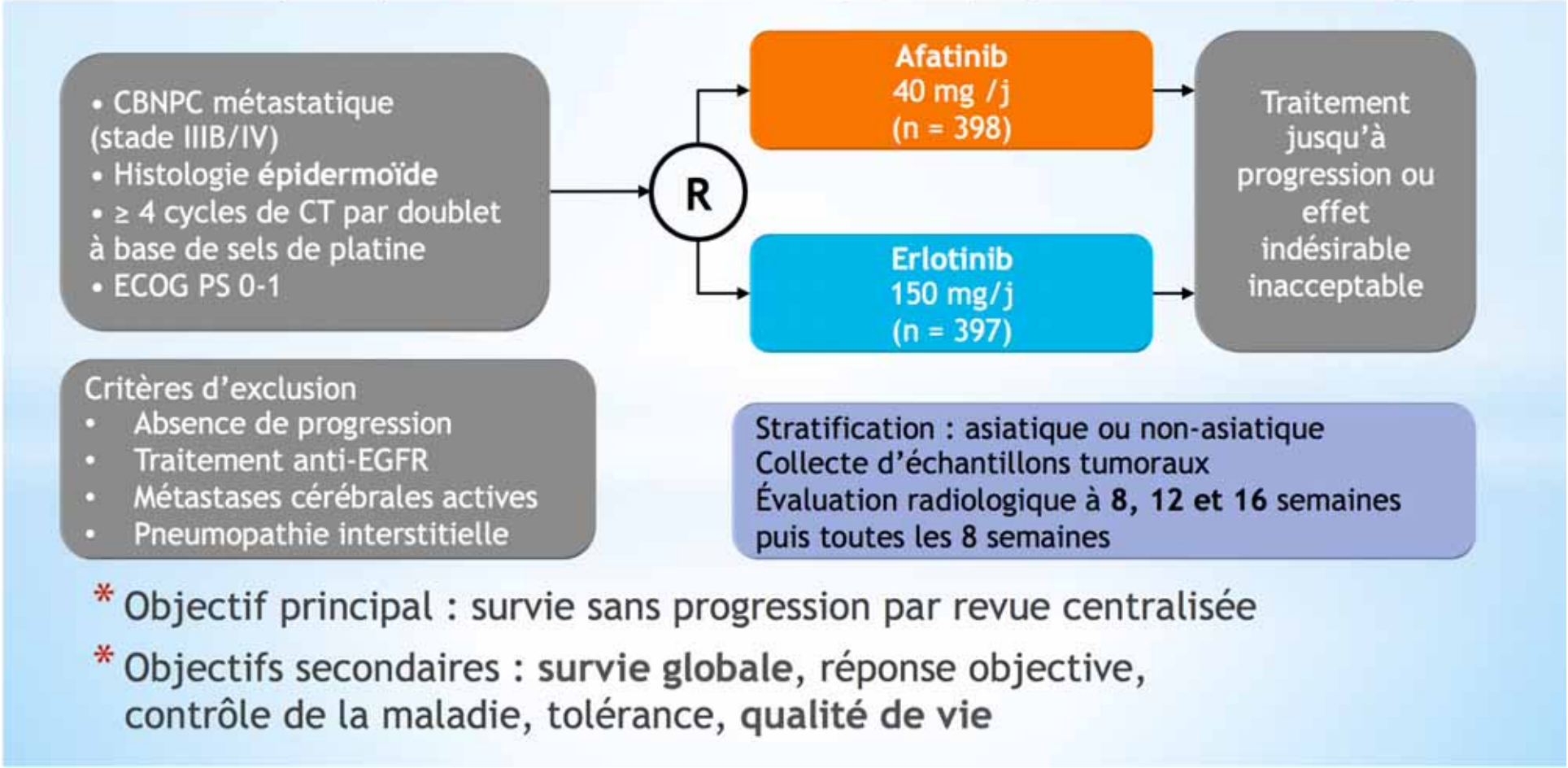




Karampeazis, Cancer 2013

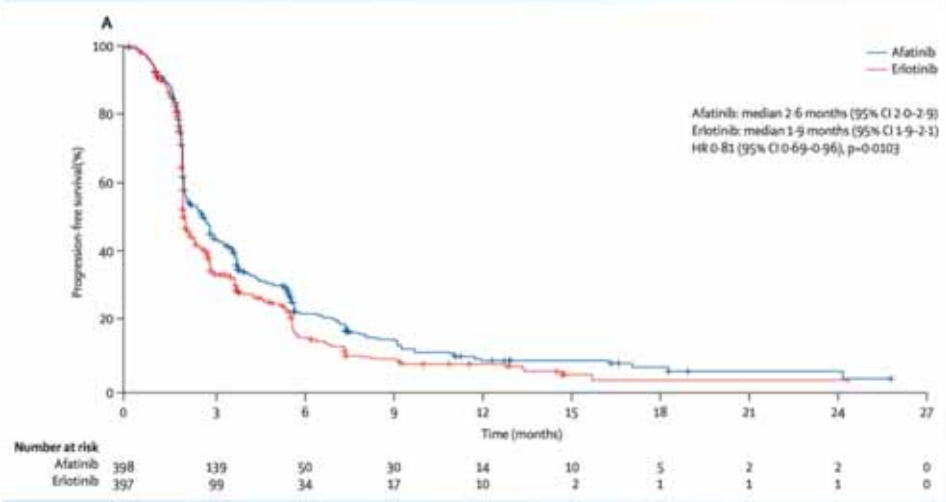
Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial

Jean-Charles Soria, Enriqueta Felip, Manuel Cobo, Shun Lu, Konstantinos Syrigos, Ki Hyeong Lee, Erdem Göker, Vassilis Georgoulias, Wei Li,

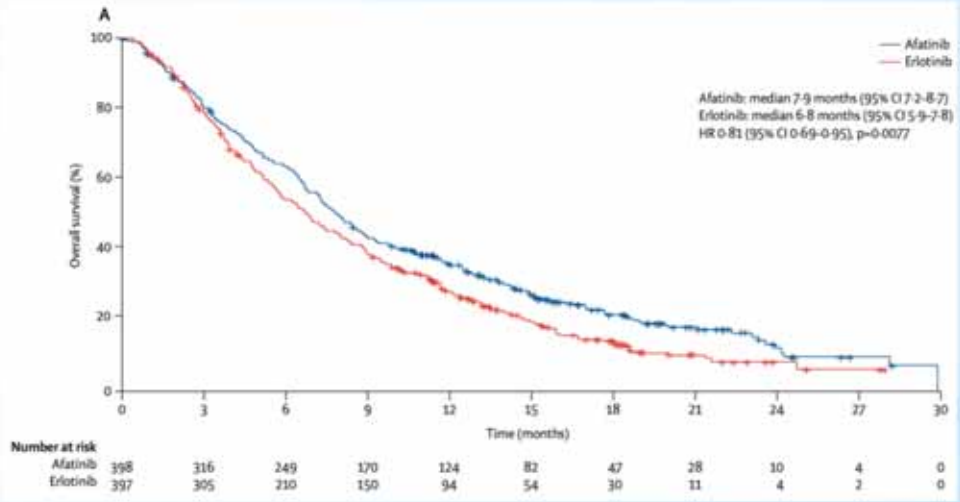


Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial

Jean-Charles Soria, Enriqueta Felip, Manuel Cobo, Shun Lu, Konstantinos Syrigos, Ki Hyeong Lee, Erdem Göker, Vassilis Georgoulias, Wei Li,



PFS: HR 0.81 (95%CI 0.69-0.96), p=0.0103



OS: HR 0.81 (95%CI 0.69-0.95), p=0.0077

Soria, Lancet Oncol 2015

2ème ligne non muté, non réarrangé

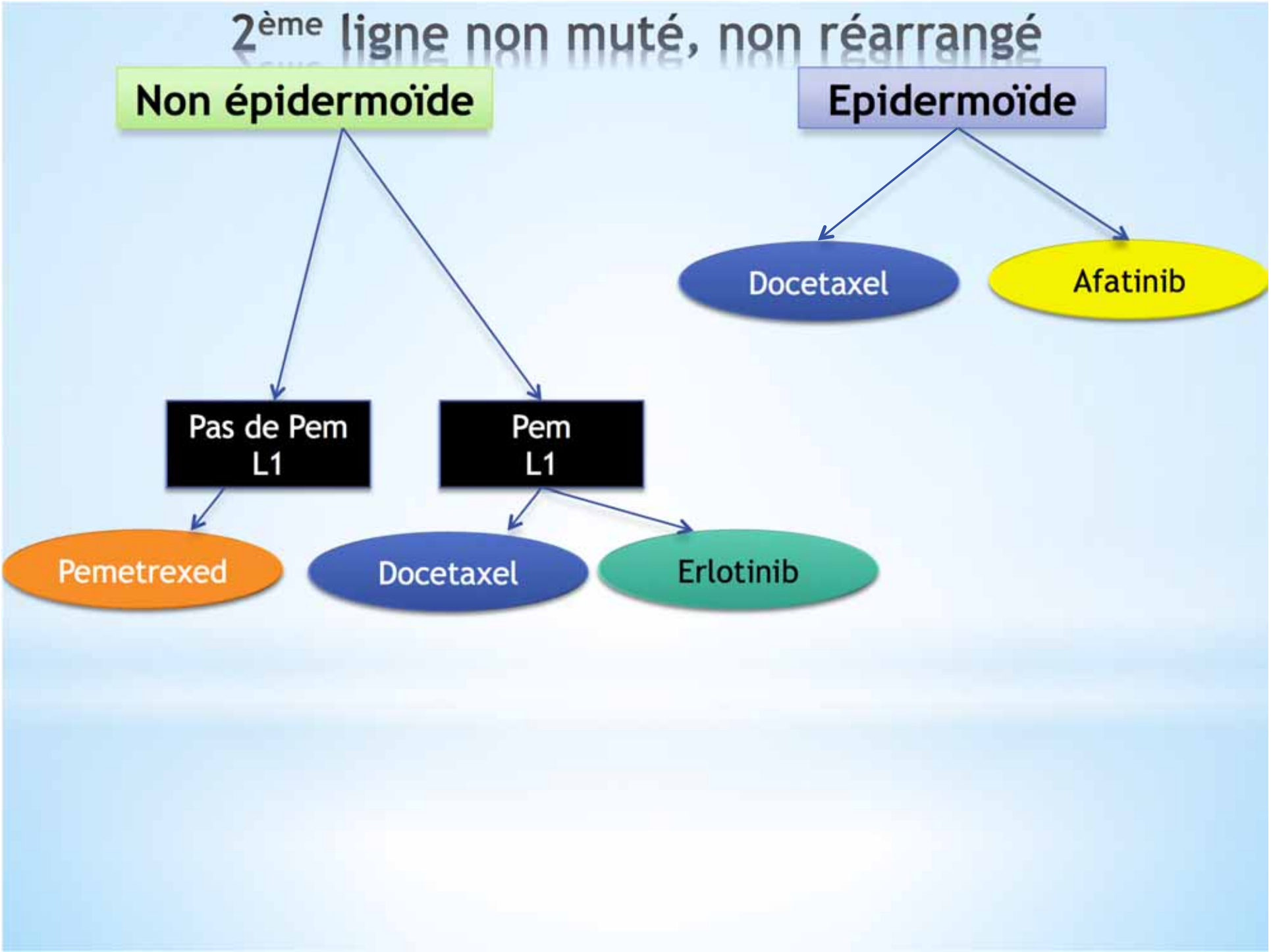
Non épidermoïde

- Pemetrexed
- Docetaxel

Epidermoïde

- Docetaxel

- Erlotinib
- Afatinib


2ème ligne non muté, non réarrangé
Non épidermoïde
Epidermoïde
Docetaxel
Afatinib
Pas de Pem L1
Pem L1
Pemetrexed
Docetaxel
Erlotinib

* Chimiothérapie
* TKI anti EGFR
* Antiangiogénique
* Immunothérapie

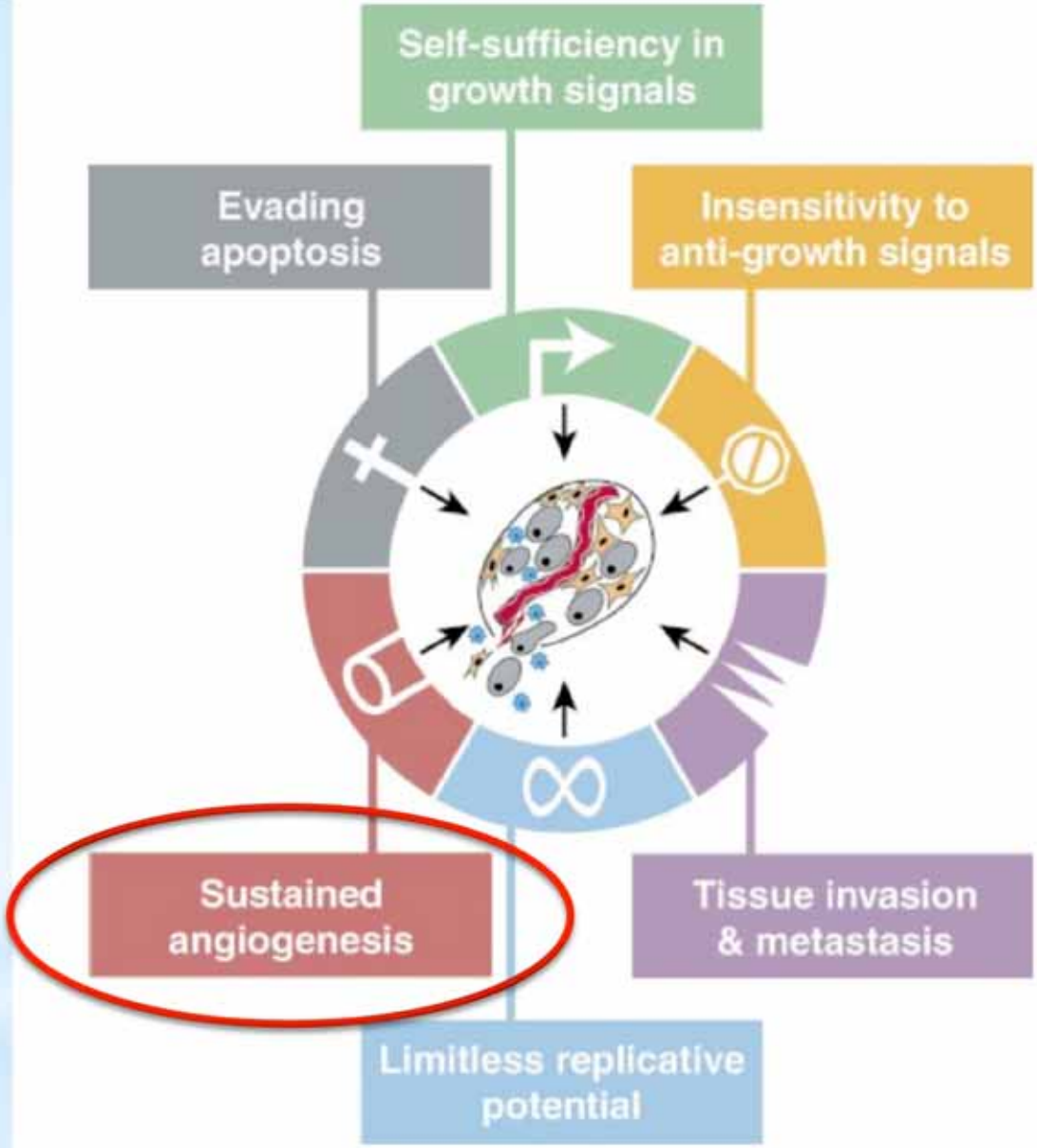
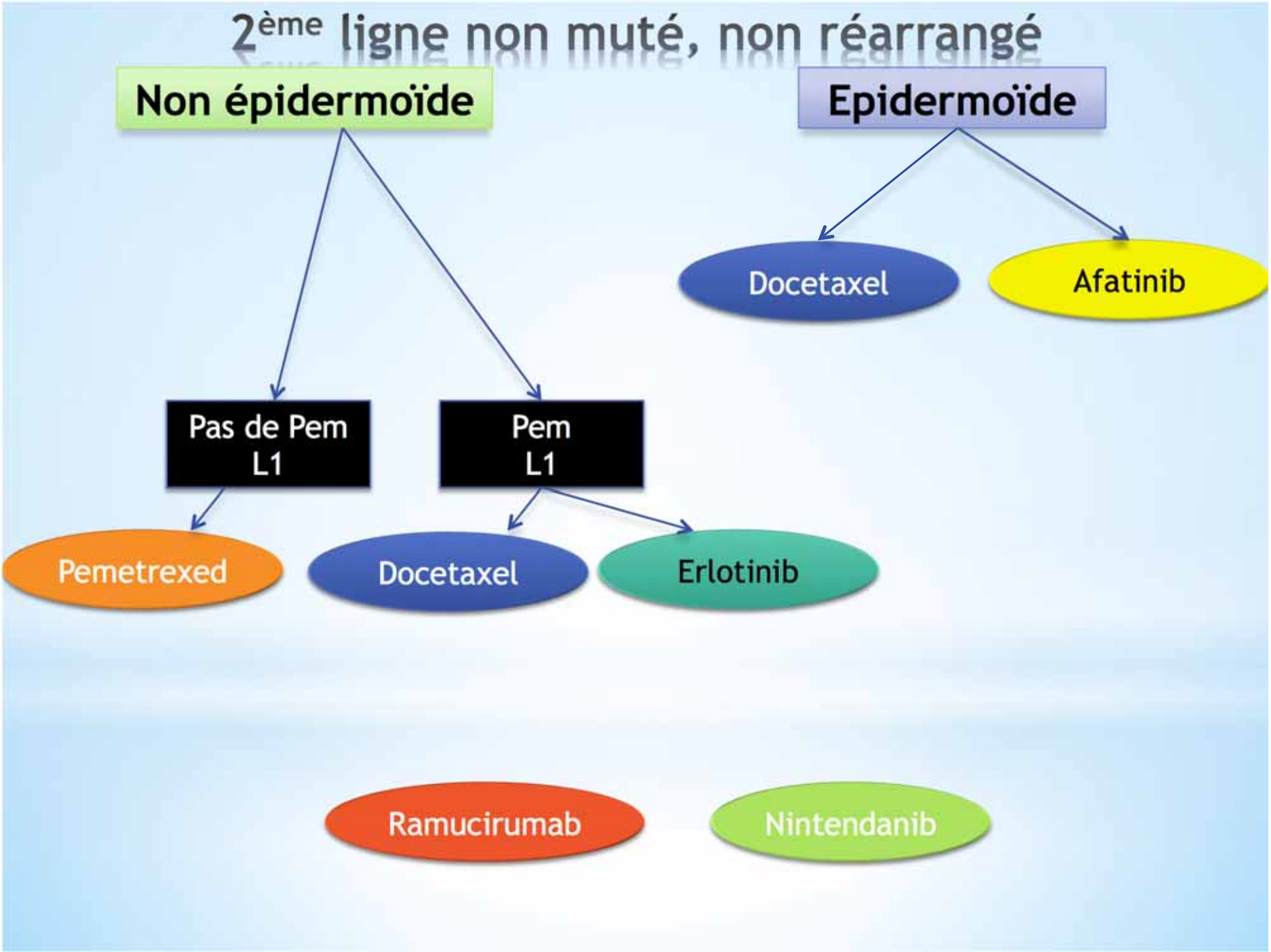


Figure 1. Acquired Capabilities of Cancer

We suggest that most if not all cancers have acquired the same set of functional capabilities during their development, albeit through various mechanistic strategies.

Hanahan, Cell 2000


2ème ligne non muté, non réarrangé
Non épidermoïde
Epidermoïde
Docetaxel
Afatinib
Pas de Pem L1
Pem L1
Pemetrexed
Docetaxel
Erlotinib
Ramucirumab
Nintendanib

Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial

Martin Reck, Rolf Kaiser, Anders Mellemgaard, Jean-Yves Douillard, Sergey Orlov, Maciej Krzakowski, Joachim von Pawel, Maya Gottfried,

Nintedanib Has a Highly Specific Kinase Selectivity Profile and Potently Inhibits VEGFR, PDGFR AND FGFR

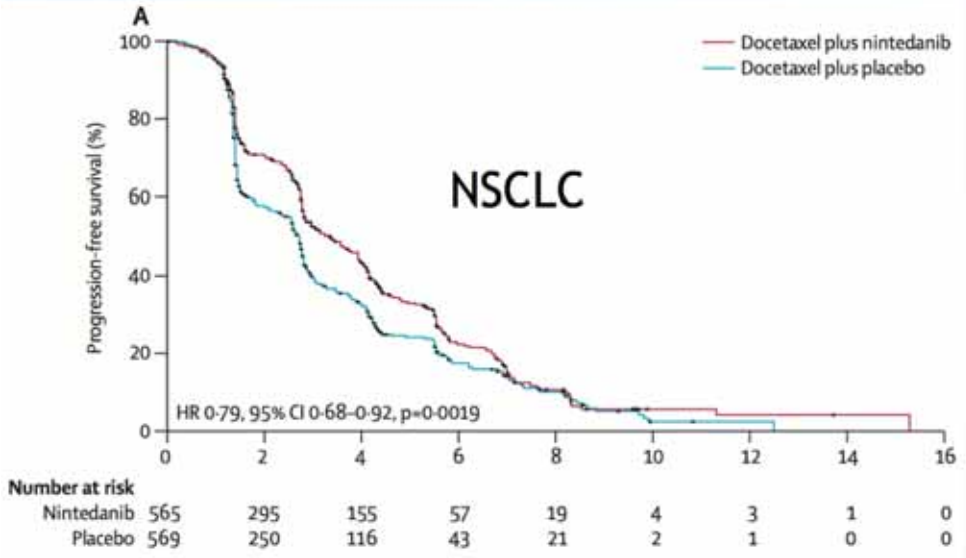
In vitro Kinase inhibition profile of Nintedanib

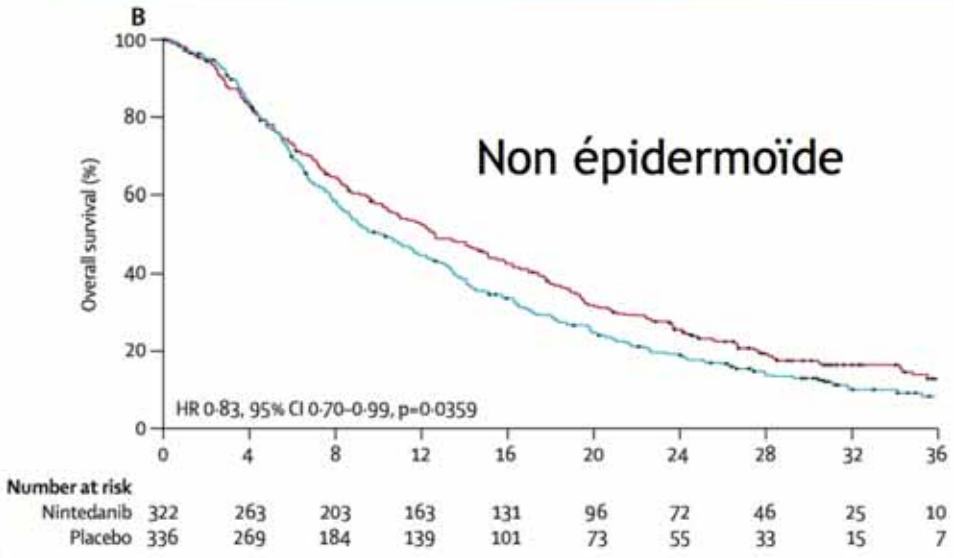
IC_{50} (nmol/L)	VEGFR 1 / 2 / 3	PDGFR α / β	FGFR 1 / 2 / 3
	34 / 21 / 13	59 / 65	69 / 37 /108

Reck, Lancet Oncol 2014

Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial

Martin Reck, Rolf Kaiser, Anders Mellemgaard, Jean-Yves Douillard, Sergey Orlov, Maciej Krzakowski, Joachim von Pawel, Maya Gottfried,





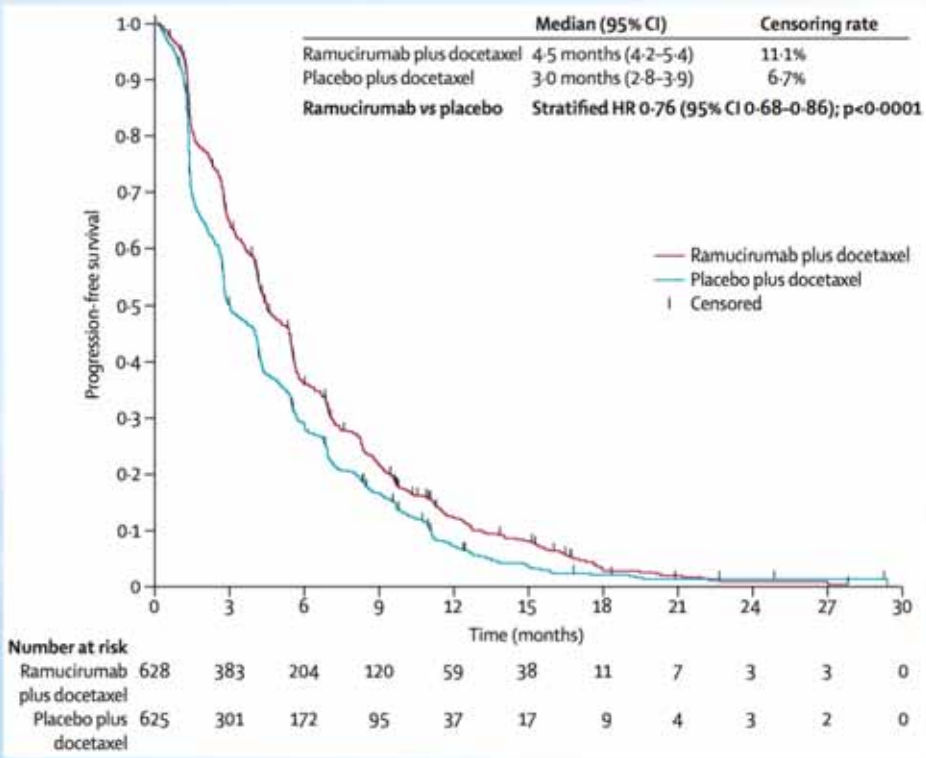
HR 0.79, 95%CI 0.68-0.92, p=0.0019

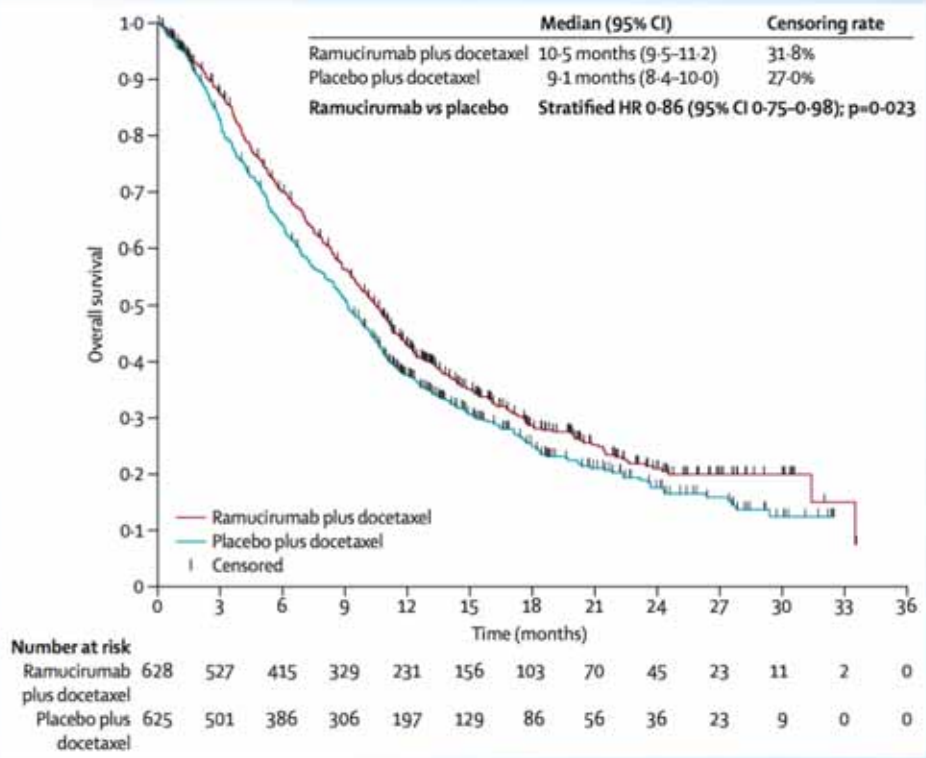
HR 0.83, 95%CI 0.70-0.99, p=0.0359

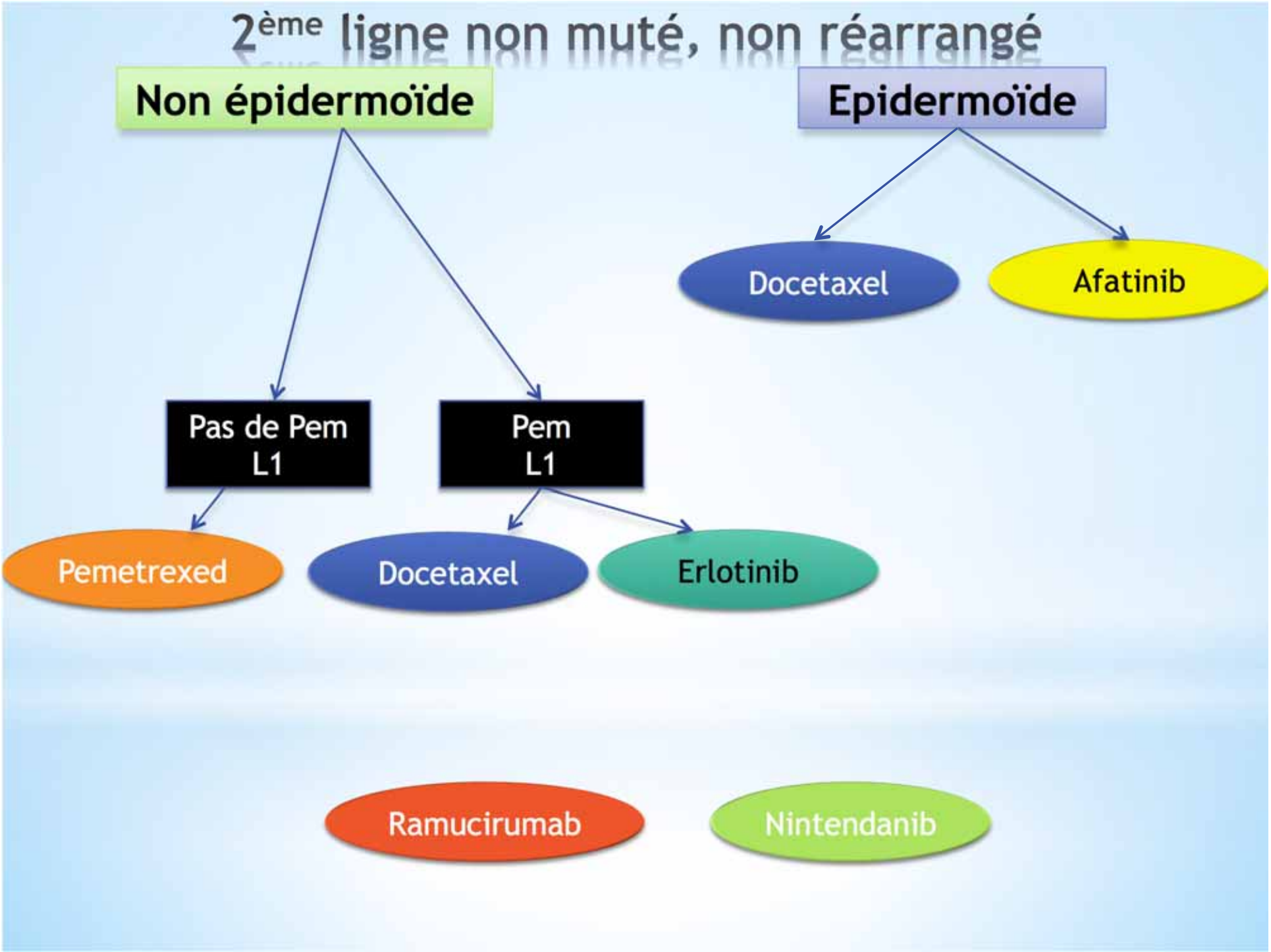
Reck, Lancet Oncol 2014

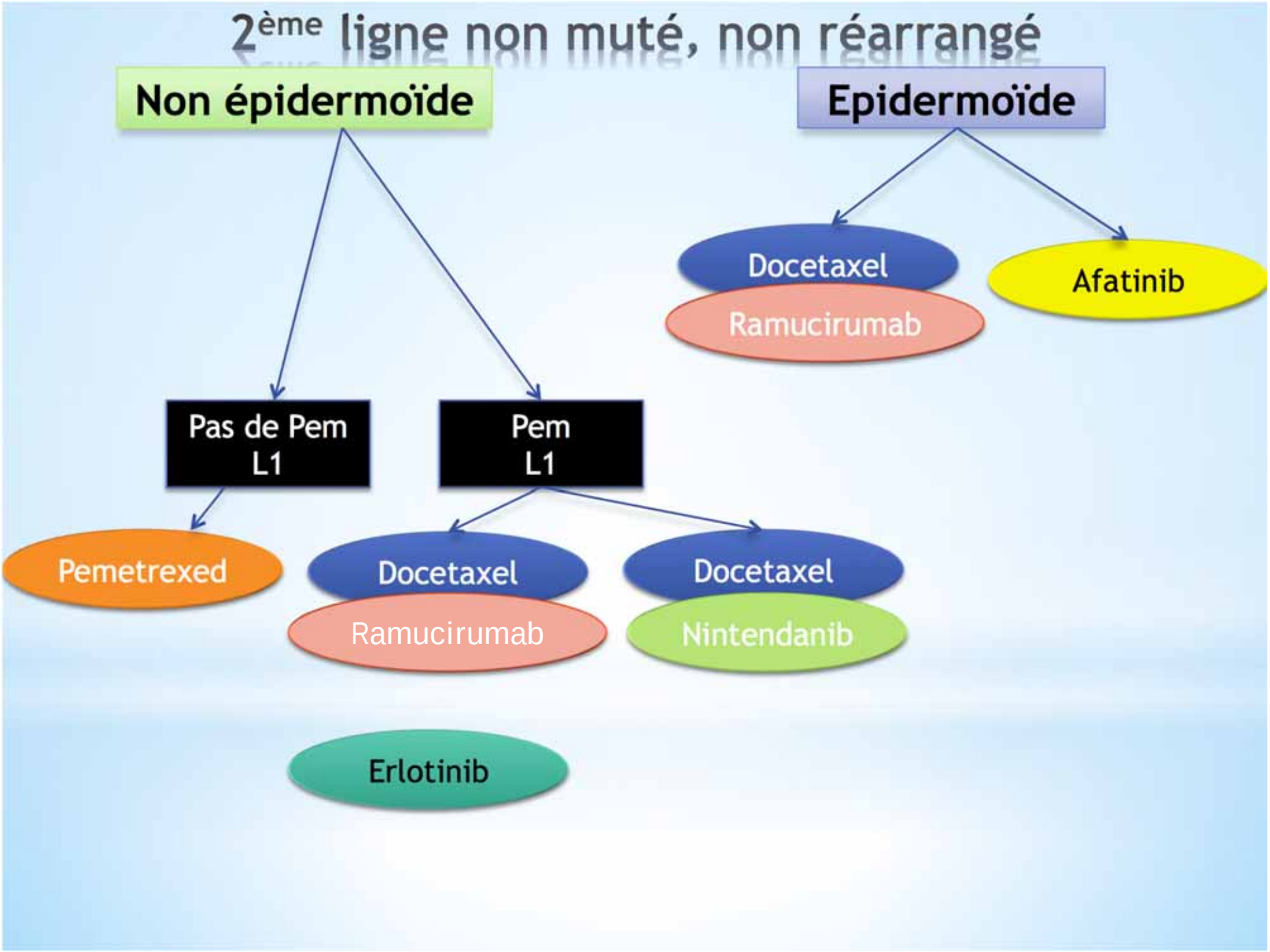
Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial

Edward B Garon, Tudor-Eliade Ciuleanu, Oscar Arrieta, Kumar Prabhash, Konstantinos N Syrigos, Tuncay Goksel, Keunchil Park, Vera Gorbunova,

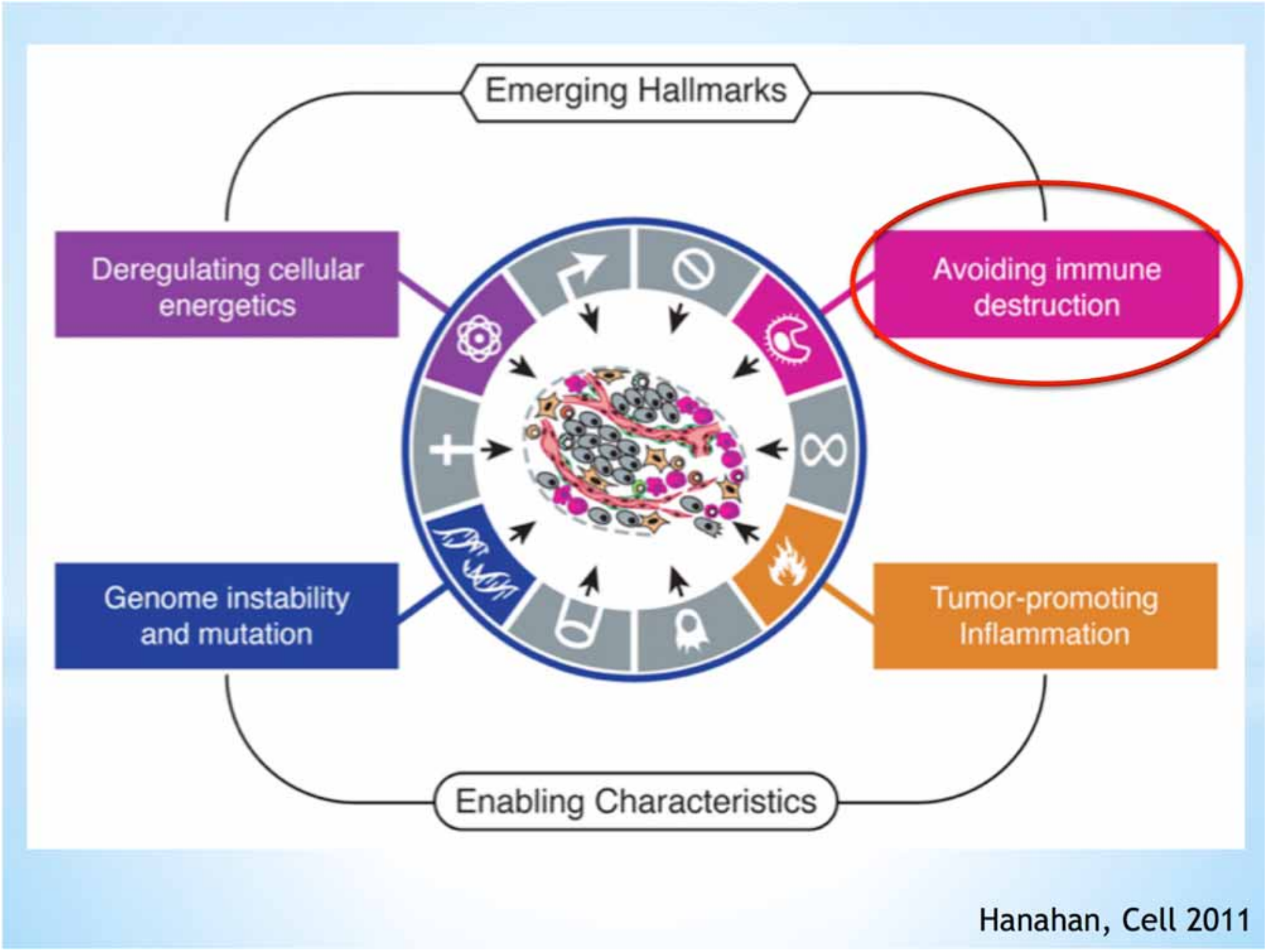




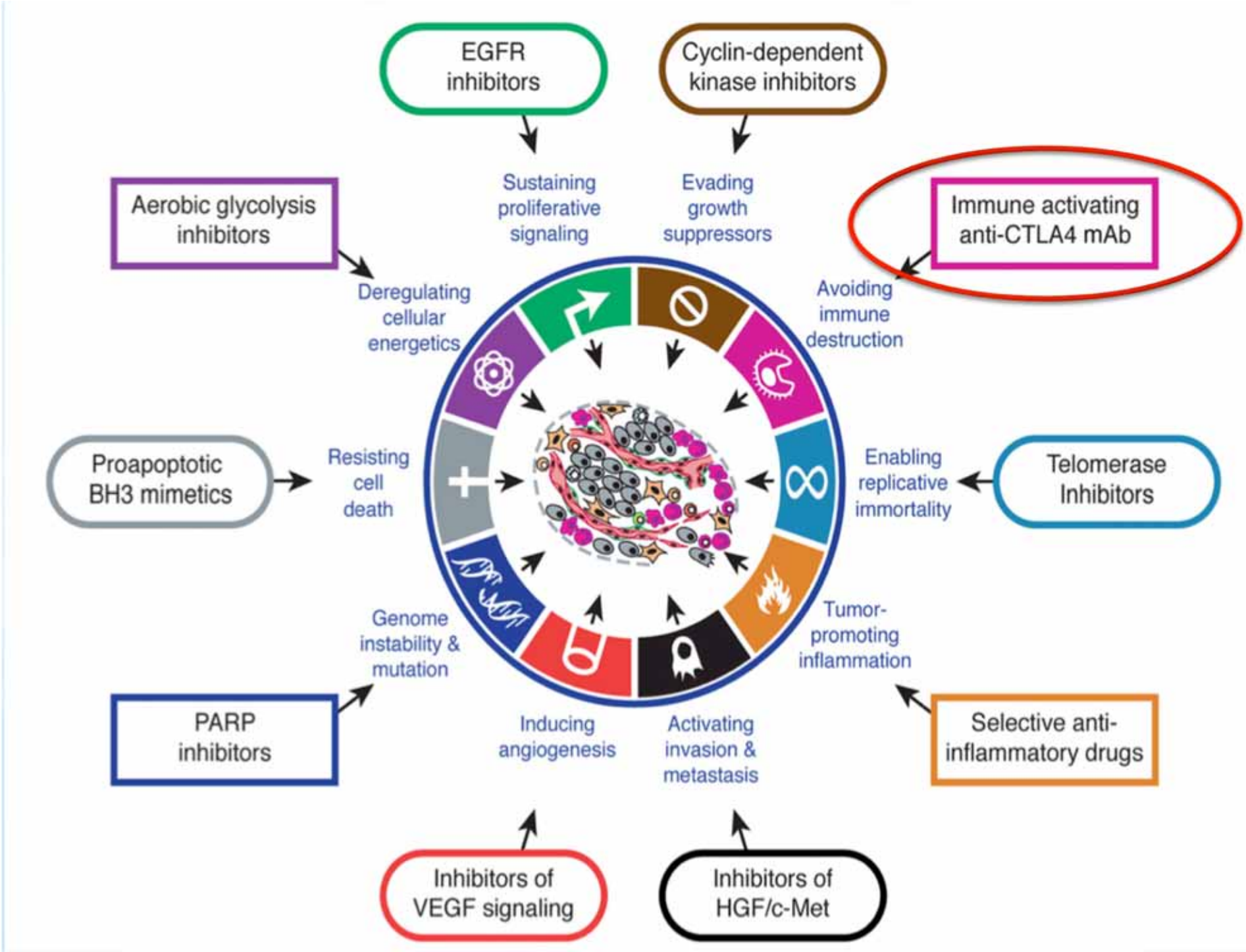

2ème ligne non muté, non réarrangé
Non épidermoïde
Epidermoïde
Docetaxel
Afatinib
Pas de Pem L1
Pem L1
Pemetrexed
Docetaxel
Erlotinib
Ramucirumab
Nintendanib


2ème ligne non muté, non réarrangé
Non épidermoïde
Epidermoïde
Docetaxel
Ramucirumab
Afatinib
Pas de Pem L1
Pem L1
Pemetrexed
Docetaxel
Ramucirumab
Docetaxel
Nintendanib
Erlotinib

* Chimiothérapie
* TKI anti EGFR
* Antiangiogénique
* Immunothérapie



Hanahan, Cell 2011


EGFR inhibitors
Cyclin-dependent kinase inhibitors
Aerobic glycolysis inhibitors
Immune activating anti-CTLA4 mAb
Sustaining proliferative signaling
Evading growth suppressors
Deregulating cellular energetics
Avoiding immune destruction
Proapoptotic BH3 mimetics
Resisting cell death
Enabling replicative immortality
Telomerase Inhibitors
Genome instability & mutation
Tumor-promoting inflammation
PARP inhibitors
Inducing angiogenesis
Activating invasion & metastasis
Selective anti-inflammatory drugs
Inhibitors of VEGF signaling
Inhibitors of HGF/c-Met

Check-point inhibitors

Anti PD-1

* Nivolumab
* Pembrolizumab

Anti PD-L1

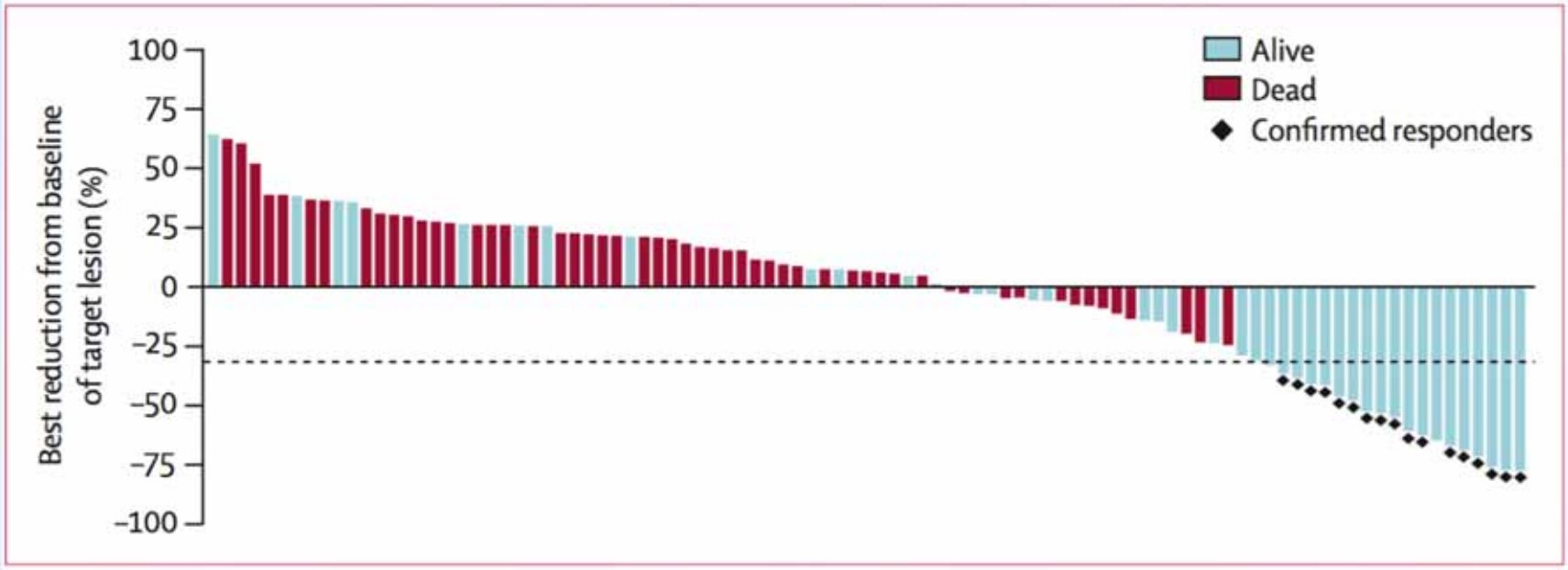
* Atezolizumab
* Avelumab

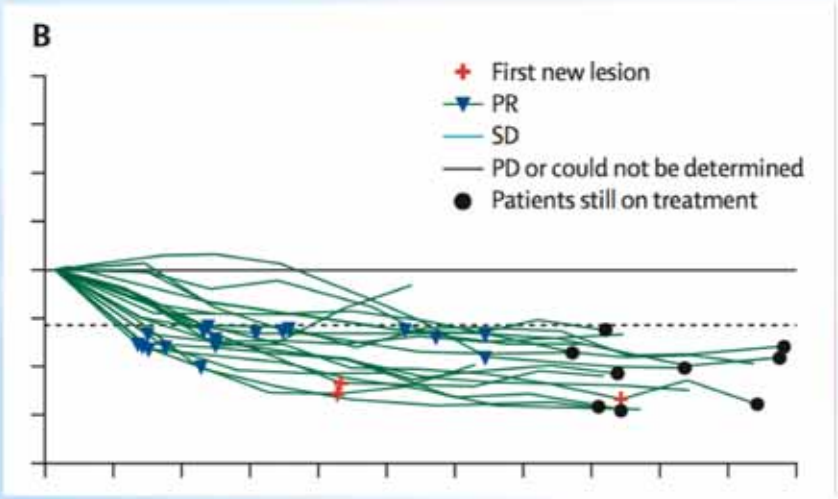
Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial

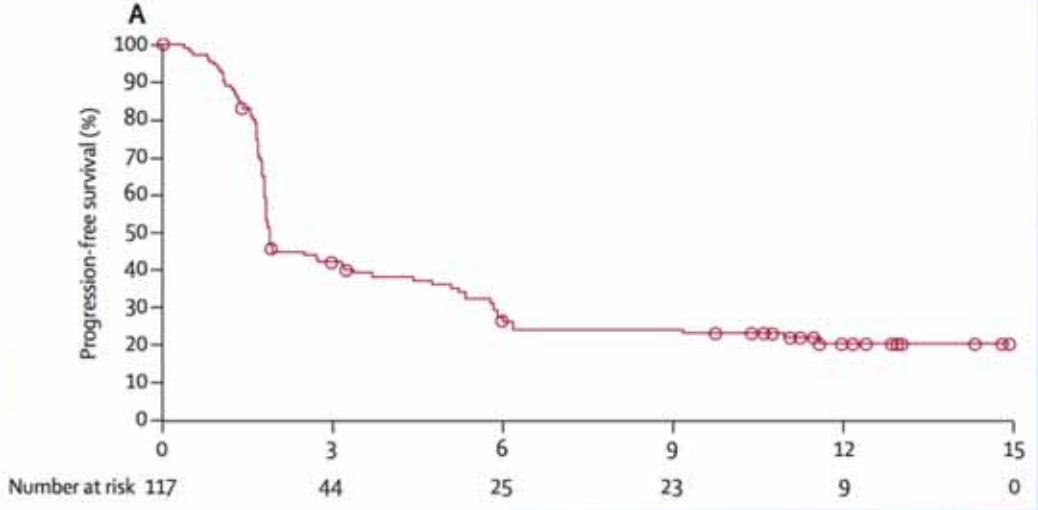
Naiyer A Rizvi, Julien Mazières, David Planchard, Thomas E Stinchcombe, Grace K Dy, Scott J Antonia, Leora Horn, Hervé Lena, Elisa Minenza,

	Patients (n=117)
Previous systemic therapy	
Platinum-based therapy	117 (100%)
Other	117 (100%)
EGFR TKI	39 (33%)
Experimental treatment	13 (11%)
Number of previous systemic treatments	
2	41 (35%)
3	52 (44%)
≥4	24 (21%)
Previous radiotherapy	87 (74%)
Best response to most recent previous treatment	
CR or PR	5 (4%)
SD	32 (27%)
Progressive disease	71 (61%)

Lancet Oncol 2015


Best reduction from baseline of target lesion (%)
100
75
50
25
0
−25
−50
−75
−100
Alive
Dead
Confirmed responders


B
First new lesion
PR
SD
PD or could not be determined
Patients still on treatment


A
Progression-free survival (%)
100
90
80
70
60
50
40
30
20
10
0
0
3
6
9
12
15
Number at risk 117
44
25
23
9
0

ORIGINAL ARTICLE

CheckMate 017

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D.,

- PS 0-1
- Prétraité (une seule ligne à base de platine)
- Biopsie archivée disponible

(n = 272)

R

1:1

Nivolumab 3 mg/kg toutes les 2 semaines jusqu'à progression ou toxicité (n = 135)

Docétaxel 75 mg/m² toutes les 3 semaines jusqu'à progression ou toxicité (n = 137)

* Objectif principal : **SG**

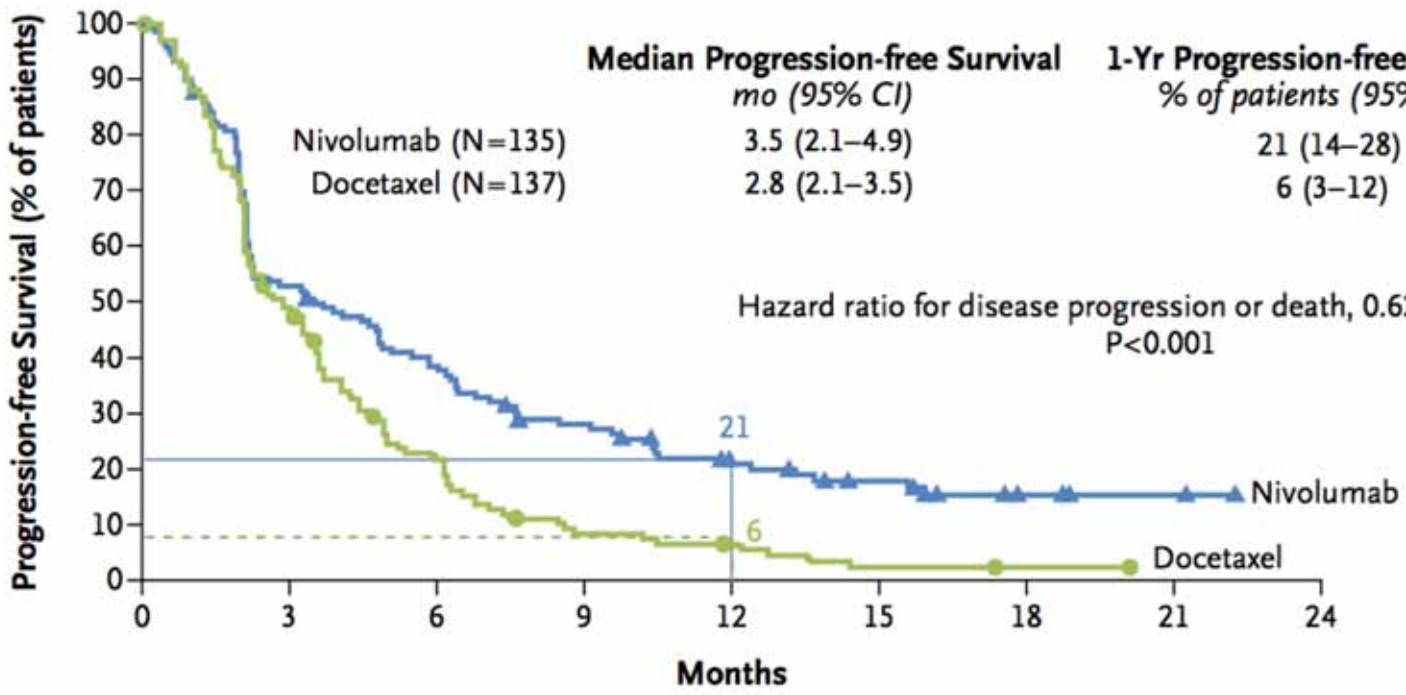
- Objectifs secondaires
  - RO RECIST 1.1
  - SSP
  - Qualité de vie
  - Tolérance
  - Efficacité selon l'expression du PD-L1

NEJM 2015

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D.,

B **Progression-free Survival**



	Median Progression-free Survival *mo (95% CI)*	1-Yr Progression-free Survival *% of patients (95% CI)*	No. of Events
Nivolumab (N=135)	3.5 (2.1–4.9)	21 (14–28)	105
Docetaxel (N=137)	2.8 (2.1–3.5)	6 (3–12)	122

Hazard ratio for disease progression or death, 0.62 (0.47–0.81)
P<0.001

No. at Risk									
Nivolumab	135	68	48	33	21	15	6	2	0
Docetaxel	137	62	26	9	6	2	1	0	0

NEJM 2015

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D.,

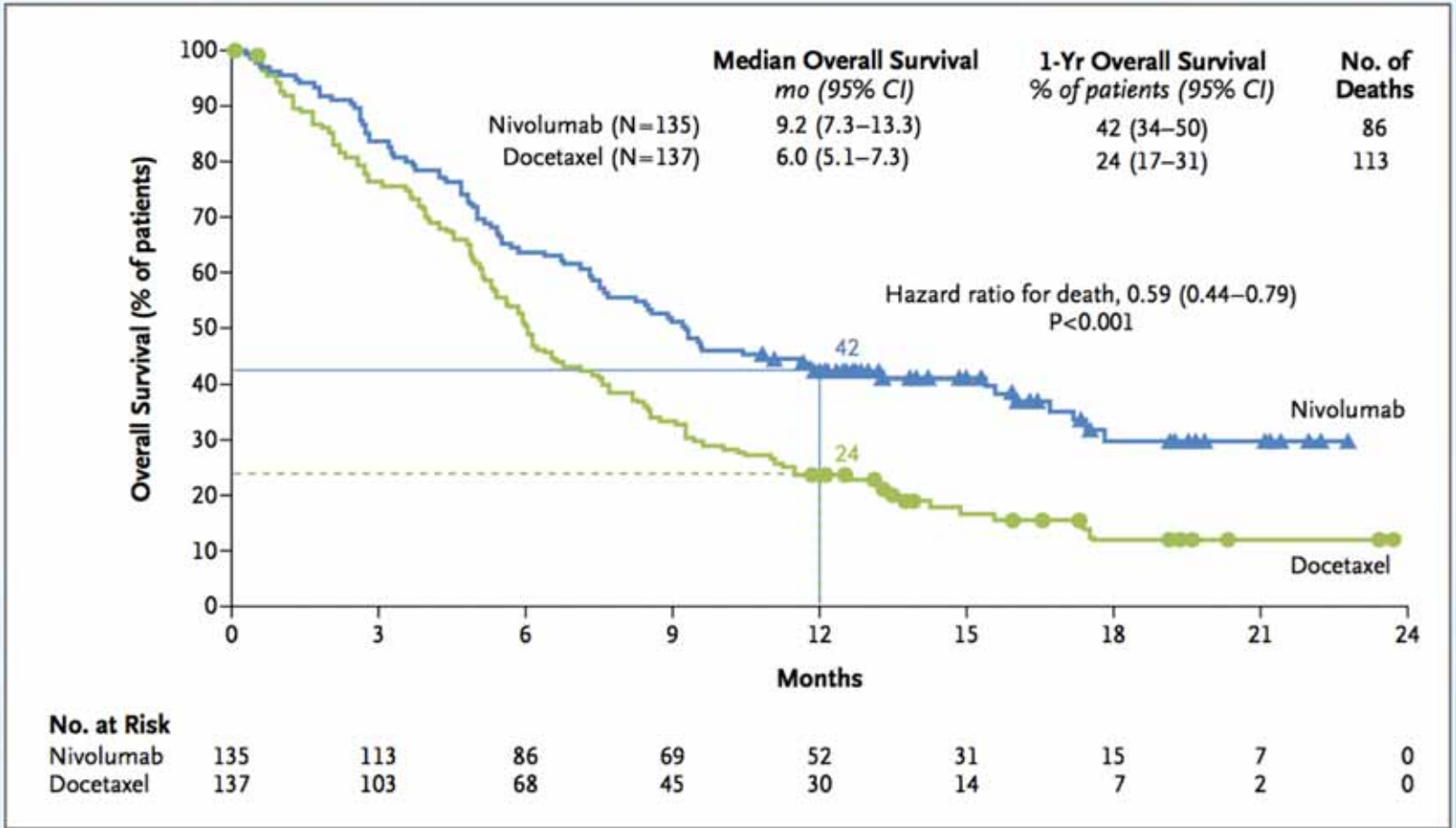


Figure 1. Kaplan–Meier Curves for Overall Survival.

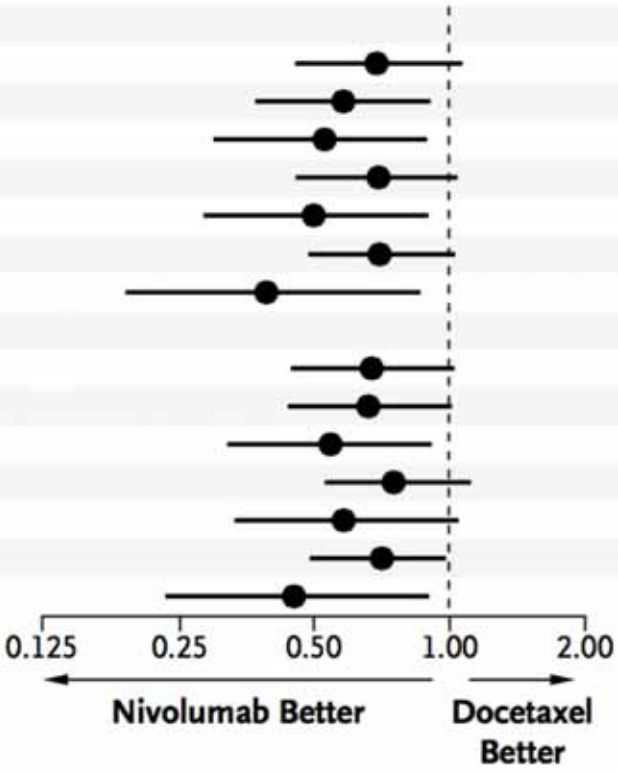
The analysis included all the patients who underwent randomization. Symbols indicate censored observations, and horizontal lines the rates of overall survival at 1 year.

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D.,

C Overall and Progression-free Survival According to PD-L1 Expression Level

PD-L1 Expression Level	Nivolumab	Docetaxel	Unstratified Hazard Ratio (95% CI)
	no. of patients		
Overall survival			
≥1%	63	56	0.69 (0.45–1.05)
<1%	54	52	0.58 (0.37–0.92)
≥5%	42	39	0.53 (0.31–0.89)
<5%	75	69	0.70 (0.47–1.02)
≥10%	36	33	0.50 (0.28–0.89)
<10%	81	75	0.70 (0.48–1.01)
Not quantifiable at baseline	18	29	0.39 (0.19–0.82)
Progression-free survival			
≥1%	63	56	0.67 (0.44–1.01)
<1%	54	52	0.66 (0.43–1.00)
≥5%	42	39	0.54 (0.32–0.90)
<5%	75	69	0.75 (0.52–1.08)
≥10%	36	33	0.58 (0.33–1.02)
<10%	81	75	0.70 (0.49–0.99)
Not quantifiable at baseline	18	29	0.45 (0.23–0.89)



NEJM 2015

Phase III, Randomizes Trial (CheckMate 057) of Nivolumab versus Docetaxel in Advanced Non-squamous Cell NSCLC

- Cancers non épidermoïdes
- Stades IIIB/IV
- ECOG PS 0-1
- Prétraités par un doublet à base de platine ± ITK

R

1:1

Nivolumab 3 mg/kg toutes les 2 semaines jusqu'à progression ou toxicité (n = 292)

Docétaxel 75 mg/m² toutes les 3 semaines jusqu'à progression ou toxicité (n = 290)

* Objectif principal : SG

- Objectifs secondaires
  - RO RECIST 1.1
  - SSP
  - Qualité de vie
  - Tolérance
  - Efficacité selon l'expression du PD-L1*

** IHC anti PD-L1 évaluée avec le système IHC Dako.*

Paz-Ares, ASCO 2015

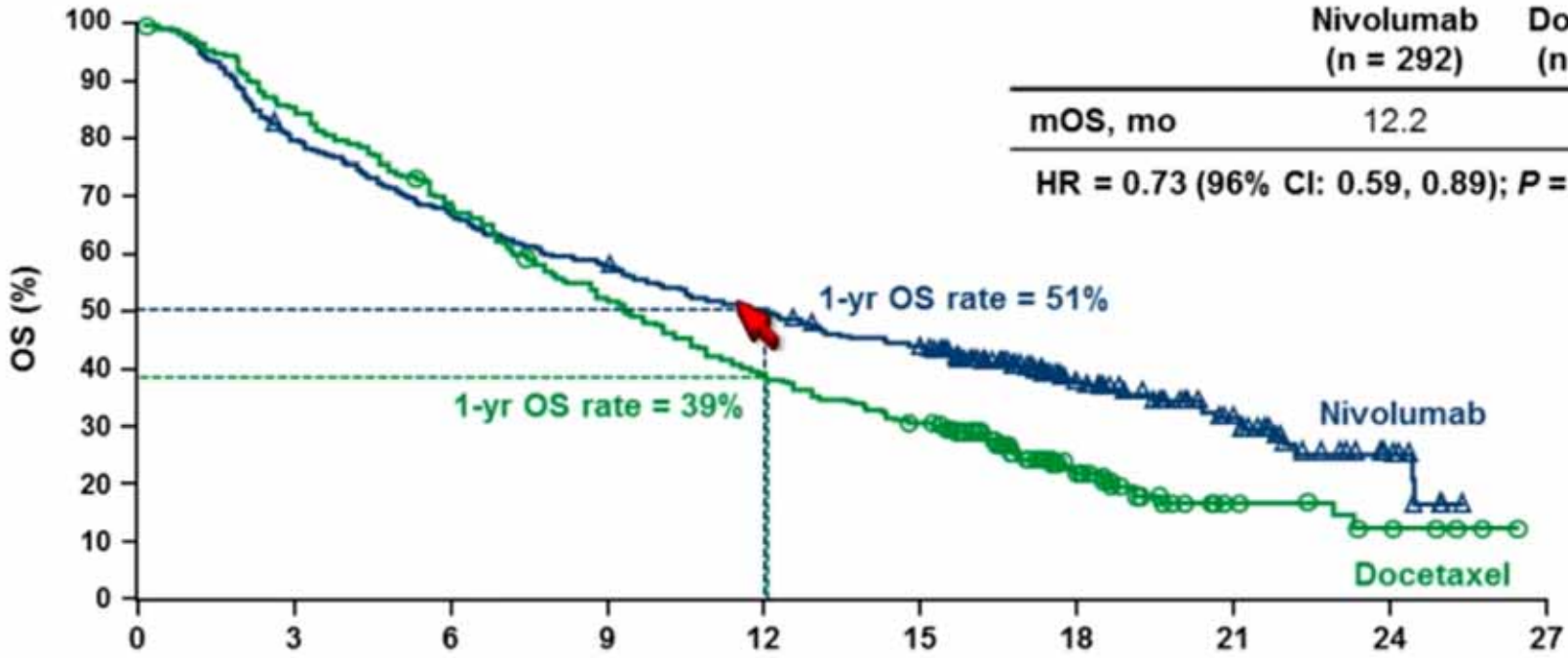
Phase III, Randomizes Trial (CheckMate 057) of Nivolumab versus Docetaxel in Advanced Non-squamous Cell NSCLC

	Nivolumab (n = 292)	**Docétaxel** (n = 290)
Âge médian (ans)	61	64
Homme (%)	52	58
ECOG PS 0/1 (%)	29/71	33/67
Nombre de lignes antérieures 1/2 (%)	88/12	89/11
ALK+/EGFR+ (%)	4/15	3/13
PDL-1* (%) **≥1%** **≥5%** **≥10**	 53 41 37	 55 38 35

* 455/582 (78%) patients évaluables pour l'expression de PD-L1

Phase III, Randomizes Trial (CheckMate 057) of Nivolumab versus Docetaxel in Advanced Non-squamous Cell NSCLC

Overall Survival



	Nivolumab (n = 292)	Docetaxel (n = 290)
mOS, mo	12.2	9.4

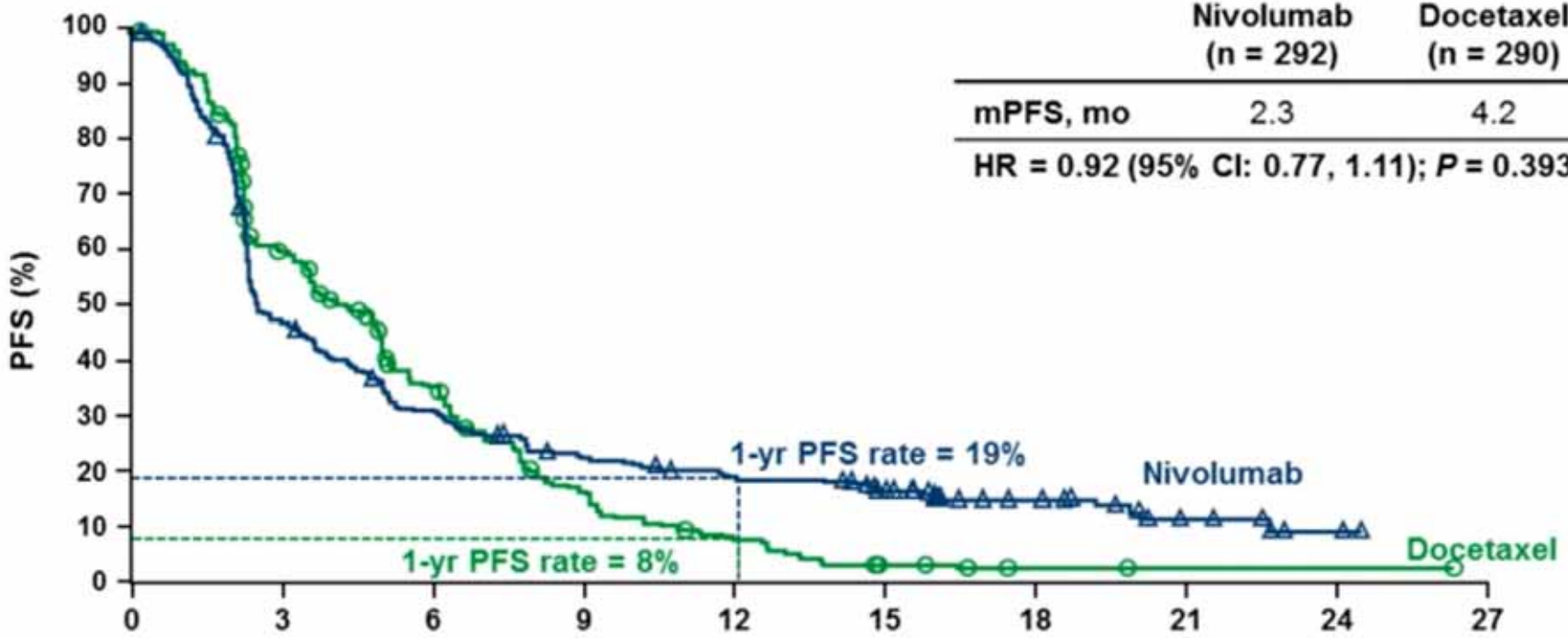
HR = 0.73 (96% CI: 0.59, 0.89); *P* = 0.0015

Number of Patients at Risk										
Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

Progression-free Survival

	Nivolumab (n = 292)	Docetaxel (n = 290)
mPFS, mo	2.3	4.2

HR = 0.92 (95% CI: 0.77, 1.11); *P* = 0.3932

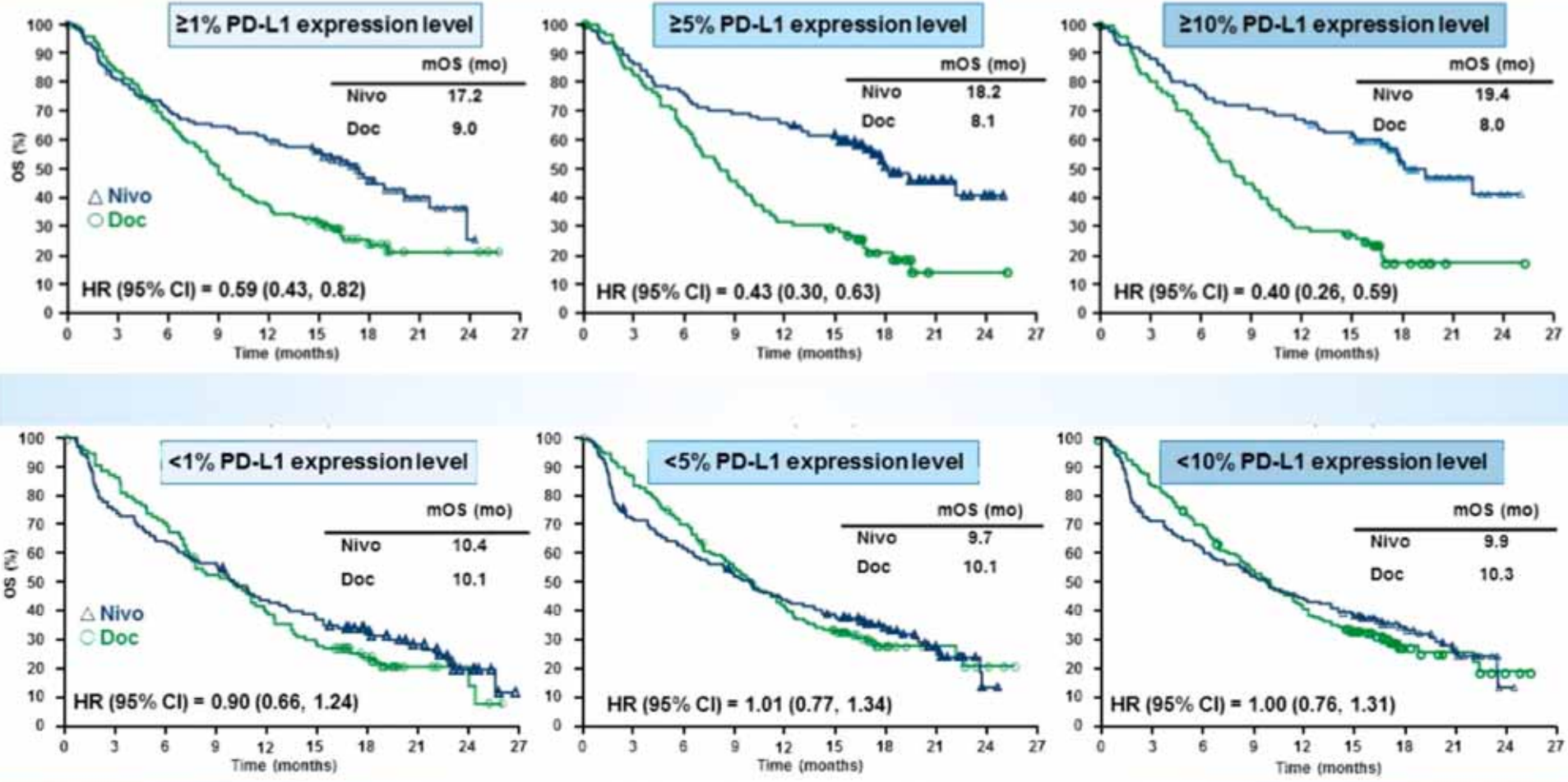


Number of Patients at Risk										
Nivolumab	292	128	82	58	46	35	17	7	2	0
Docetaxel	290	156	87	38	18	6	2	1	1	0

Objective Response Rate

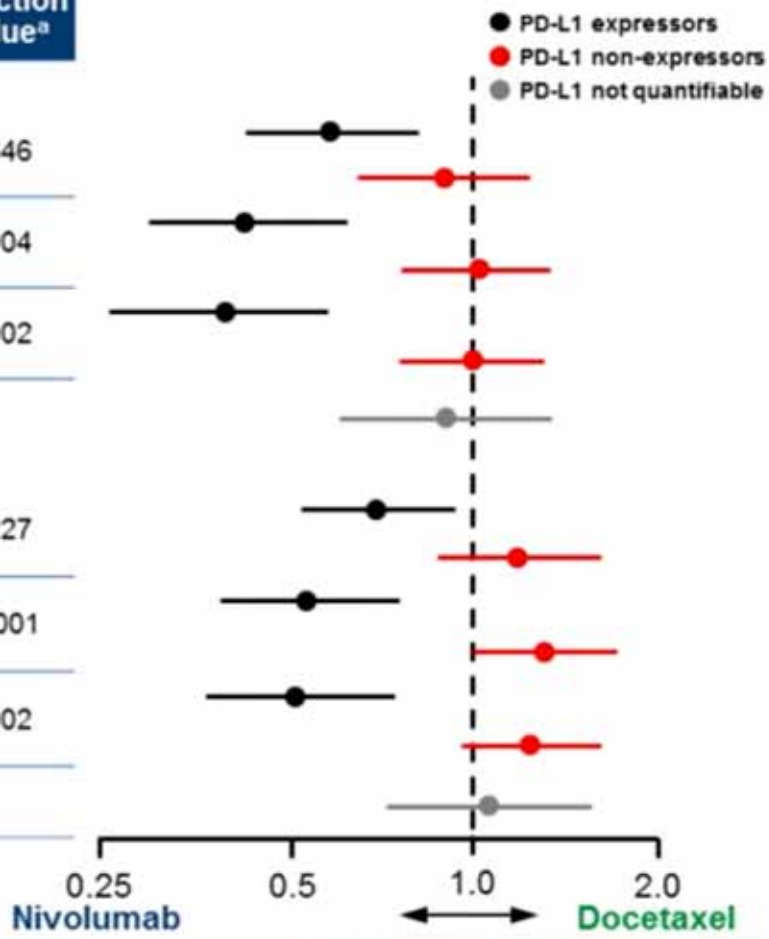
	Nivolumab (n = 292)	Docetaxel (n = 290)
ORR (95% CI)	**19%** (15, 24)	**12%** (9, 17)
***Odds Ratio* (95% CI)**	1.72 (1.1, 2.6)	
***P*-value[a]**	0.0246	
Best overall response, %		
Complete response	1	<1
Partial response	18	12
Stable disease	25	42
Progressive disease	44	29
Unable to determine	11	16
Median time to response,[b] mo (range)	2.1 (1.2, 8.6)	2.6 (1.4, 6.3)
Median DOR,[b] mo (range)	**17.2** (1.8, 22.6+)	**5.6** (1.2+, 16.2+)
Ongoing response,[c] %	52	14

Survie globale selon l'expression de PD-L1

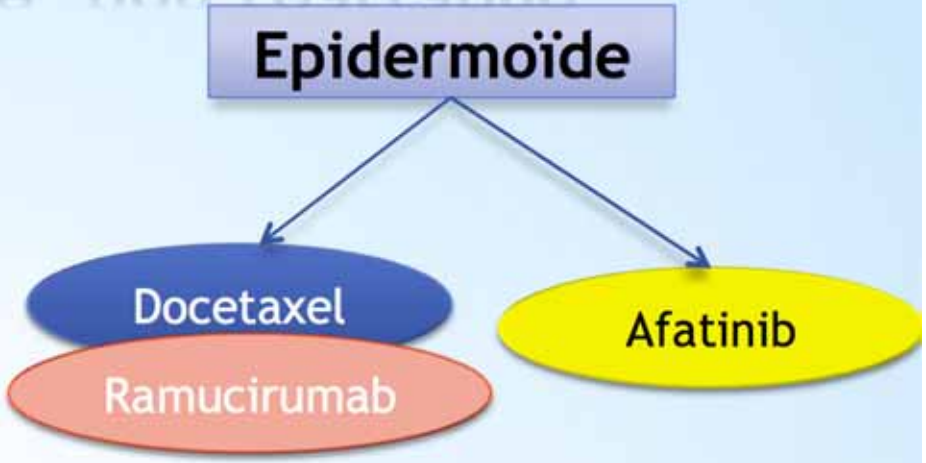


PD-L1expression level	Nivolumab n	Docetaxel n	Unstratified HR (95% CI)	Interaction *P*-value[a]
OS				
≥1%	123	123	0.59 (0.43, 0.82)	0.0646
<1%	108	101	0.90 (0.66, 1.24)	
≥5%	95	86	0.43 (0.30, 0.63)	0.0004
<5%	136	138	1.01 (0.77, 1.34)	
≥10%	86	79	0.40 (0.26, 0.59)	0.0002
<10%	145	145	1.00 (0.76, 1.31)	
Not quantifiable at baseline	61	66	0.91 (0.61, 1.35)	
PFS				
≥1%	123	123	0.70 (0.53, 0.94)	0.0227
<1%	108	101	1.19 (0.88, 1.61)	
≥5%	95	86	0.54 (0.39, 0.76)	<0.0001
<5%	136	138	1.31 (1.01, 1.71)	
≥10%	86	79	0.52 (0.37, 0.75)	0.0002
<10%	145	145	1.24 (0.96, 1.61)	
Not quantifiable at baseline	61	66	1.06 (0.73, 1.56)	

[a] Interaction p-value from Cox proportional hazard model with treatment, PD-L1 expression and treatment by PD-L1 expression interaction.

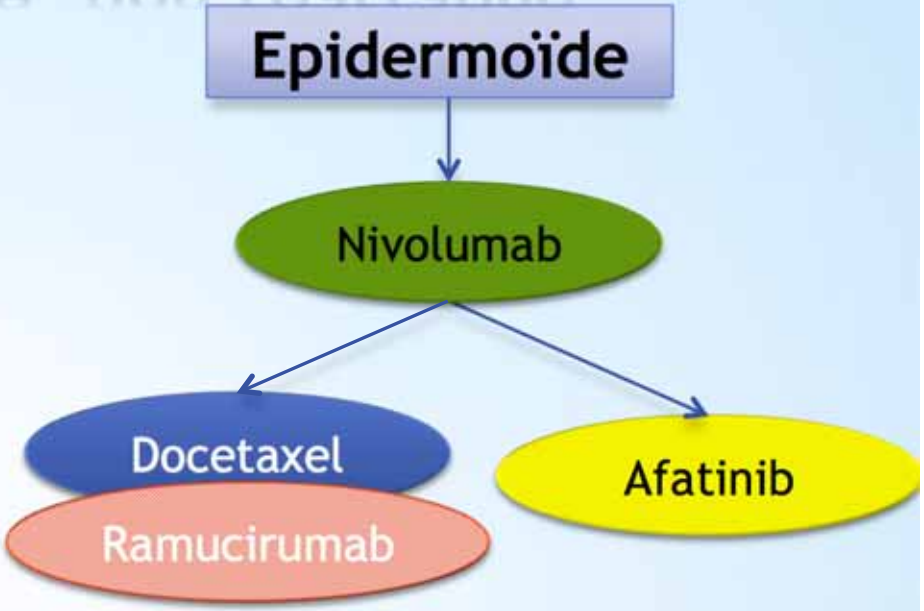


2ème ligne non muté, non réarrangé

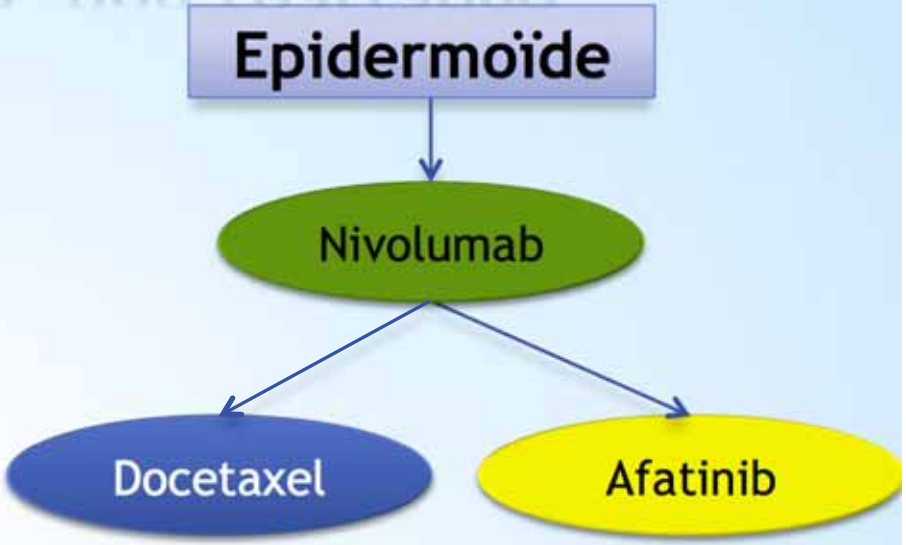


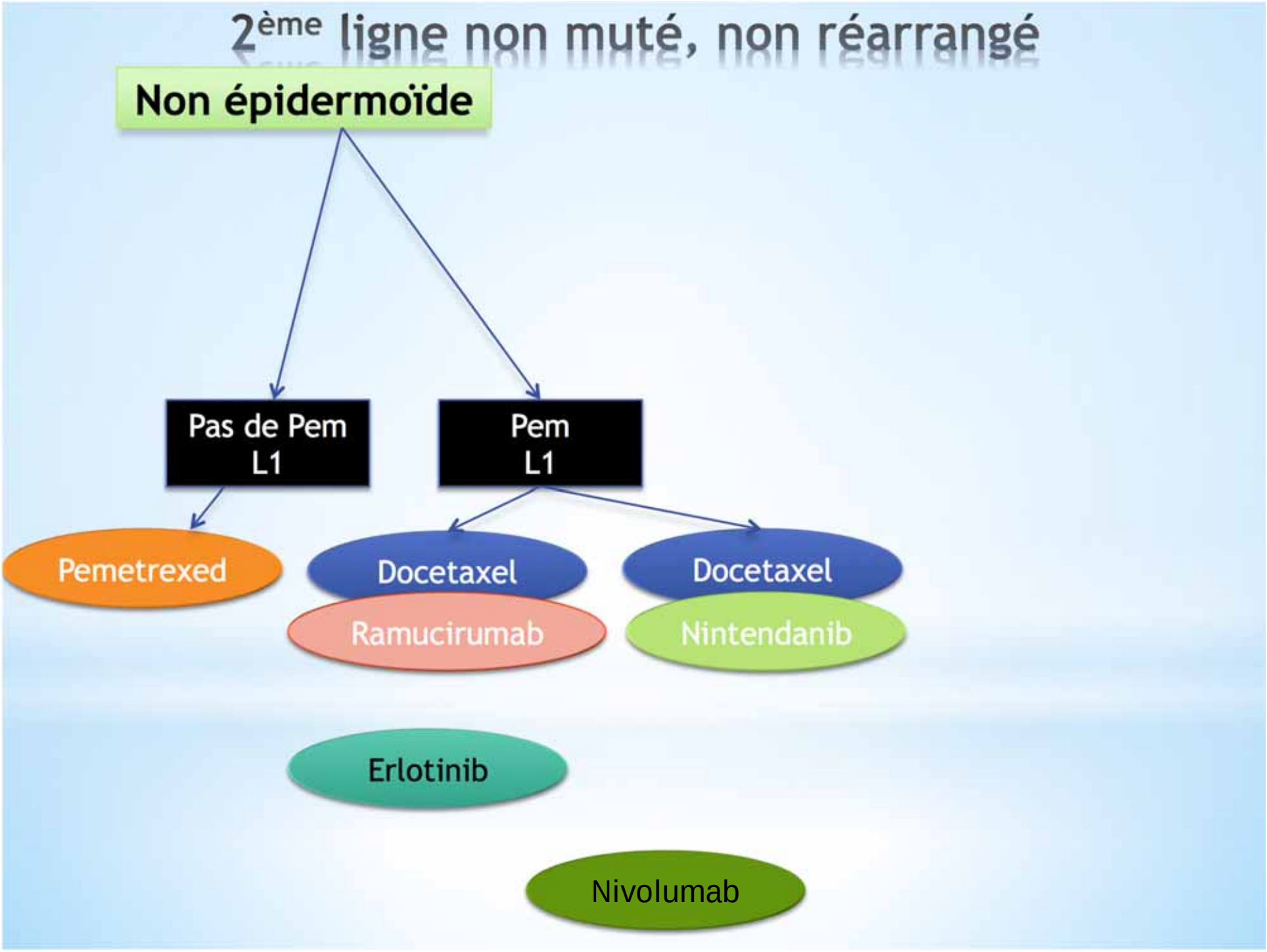
Nivolumab

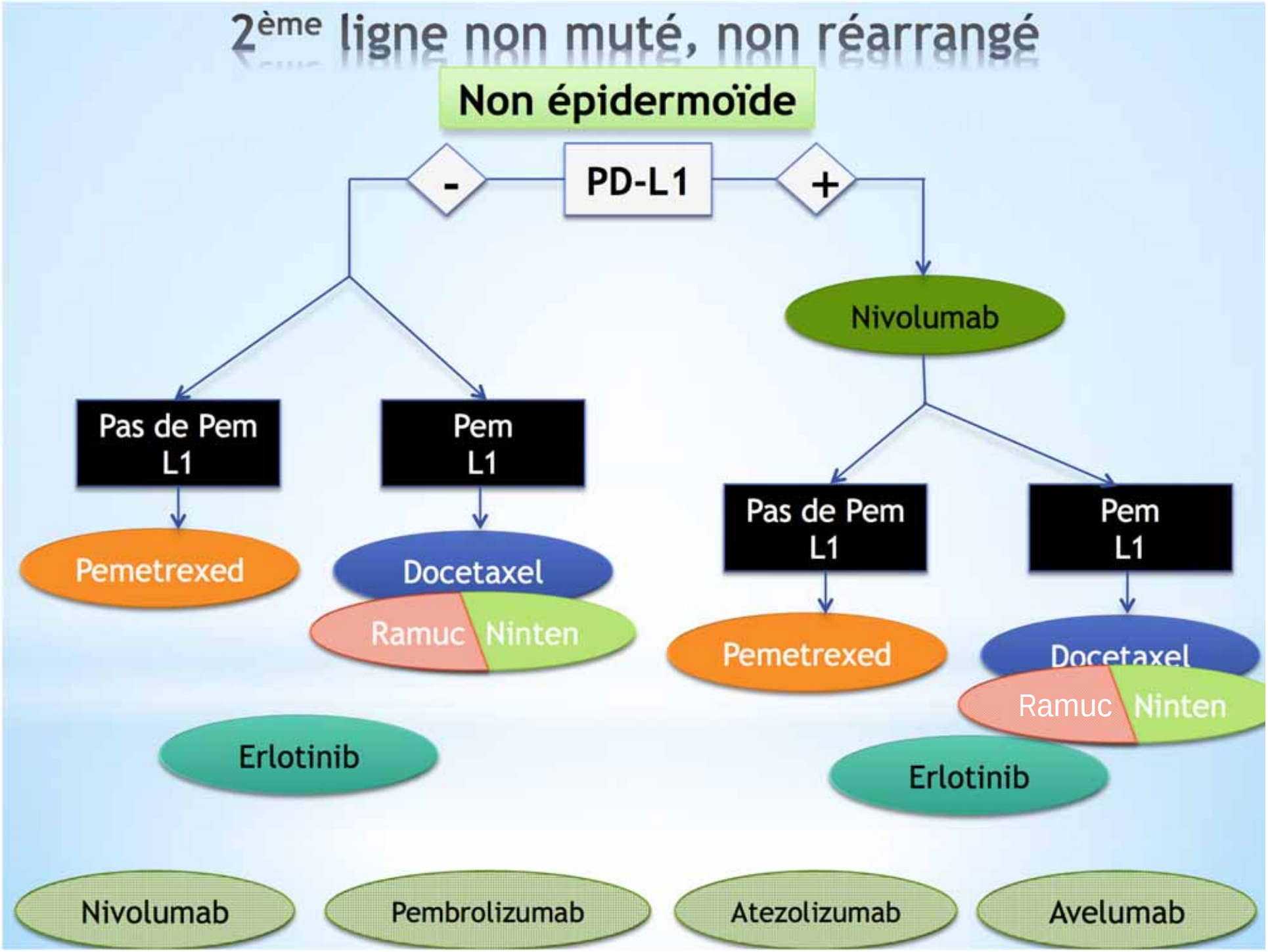
2ème ligne non muté, non réarrangé



2ème ligne non muté, non réarrangé




2ème ligne non muté, non réarrangé
Non épidermoïde
Pas de Pem L1
Pem L1
Pemetrexed
Docetaxel
Ramucirumab
Docetaxel
Nintendanib
Erlotinib
Nivolumab


2ème ligne non muté, non réarrangé
Non épidermoïde
PD-L1
-
+
Nivolumab
Pas de Pem L1
Pem L1
Pas de Pem L1
Pem L1
Pemetrexed
Docetaxel
Ramuc
Ninten
Pemetrexed
Docetaxel
Ramuc
Ninten
Erlotinib
Erlotinib
Nivolumab
Pembrolizumab
Atezolizumab
Avelumab

Check-point inhibitors

Anti PD-1

* Nivolumab
* Pembrolizumab

Anti PD-L1

* Atezolizumab
* Avelumab

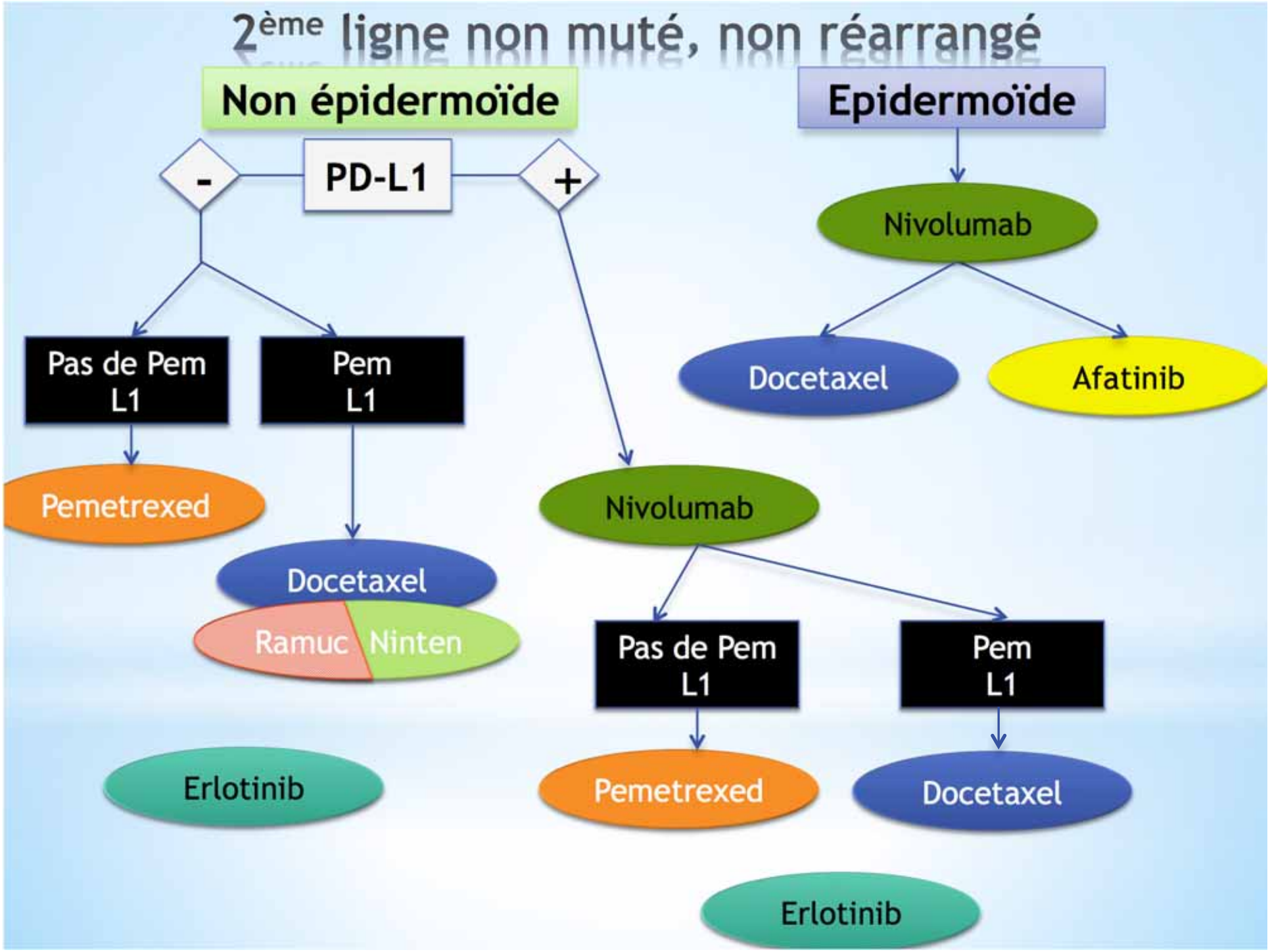
Check-point inhibitors (Phase 3)

Anti PD-1

* Nivolumab
  * L1 NSCLC (CheckMate 026)
  * Localement avancé post RTCT
* Pembrolizumab
  * Adjuvant (Keynote 091)
  * L1 NSCLC (vs chimio, Keynote 024)

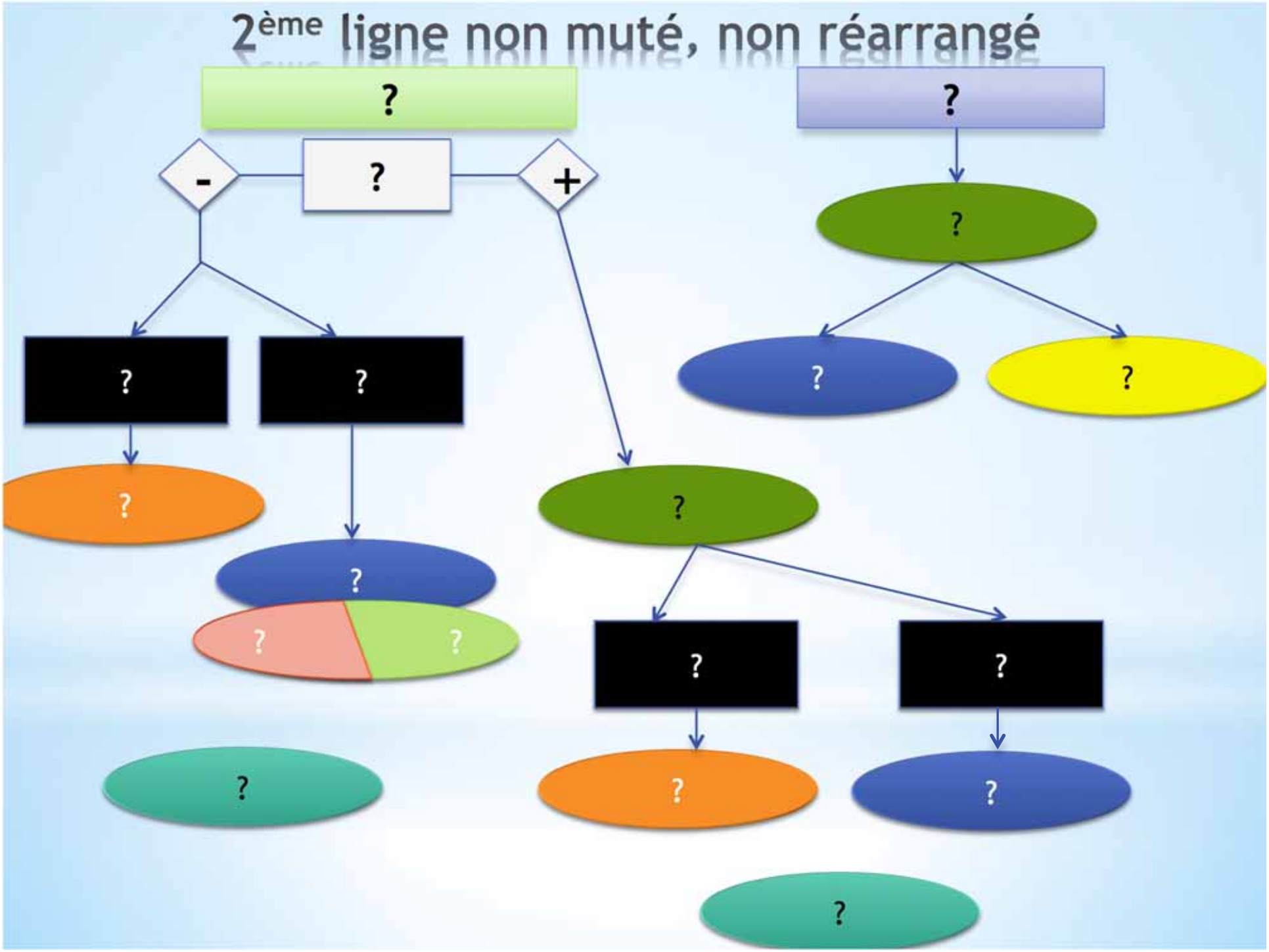
Anti PD-L1

* Atezolizumab
  * Adjuvant
  * L1 épidermoïde
    * Carbo/Taxol/Nab-pacli (IM power 131
    * Platine/Gem (IM power 111)
  * L1 non-épidermoïde
    * Carbo/Nab-pacli (IM power 130)
    * Platine/Pem (IM power 110)
    * Carbo/Taxol/Avastin (IM power 150)
* Avelumab
  * L2 NSCLC (JAVELIN Lung 200)


2ème ligne non muté, non réarrangé
Non épidermoïde
Epidermoïde
PD-L1
-
+
Nivolumab
Pas de Pem L1
Pem L1
Docetaxel
Afatinib
Pemetrexed
Nivolumab
Docetaxel
Ramuc
Ninten
Pas de Pem L1
Pem L1
Erlotinib
Pemetrexed
Docetaxel
Erlotinib


immunothérapie

2ème ligne non muté, non réarrangé



MERCI

Stefano Kim

Inserm

CHRU Besançon
centre hospitalier régional universitaire

FRANCHE-COMTÉ
IRFC
INSTITUT RÉGIONAL FÉDÉRATIF DU CANCER

CIC B
Centre d'Investigation Clinique de Besançon