Chimiothérapie de 1ère ligne des CBNPC métastatiques sans addiction oncogénique

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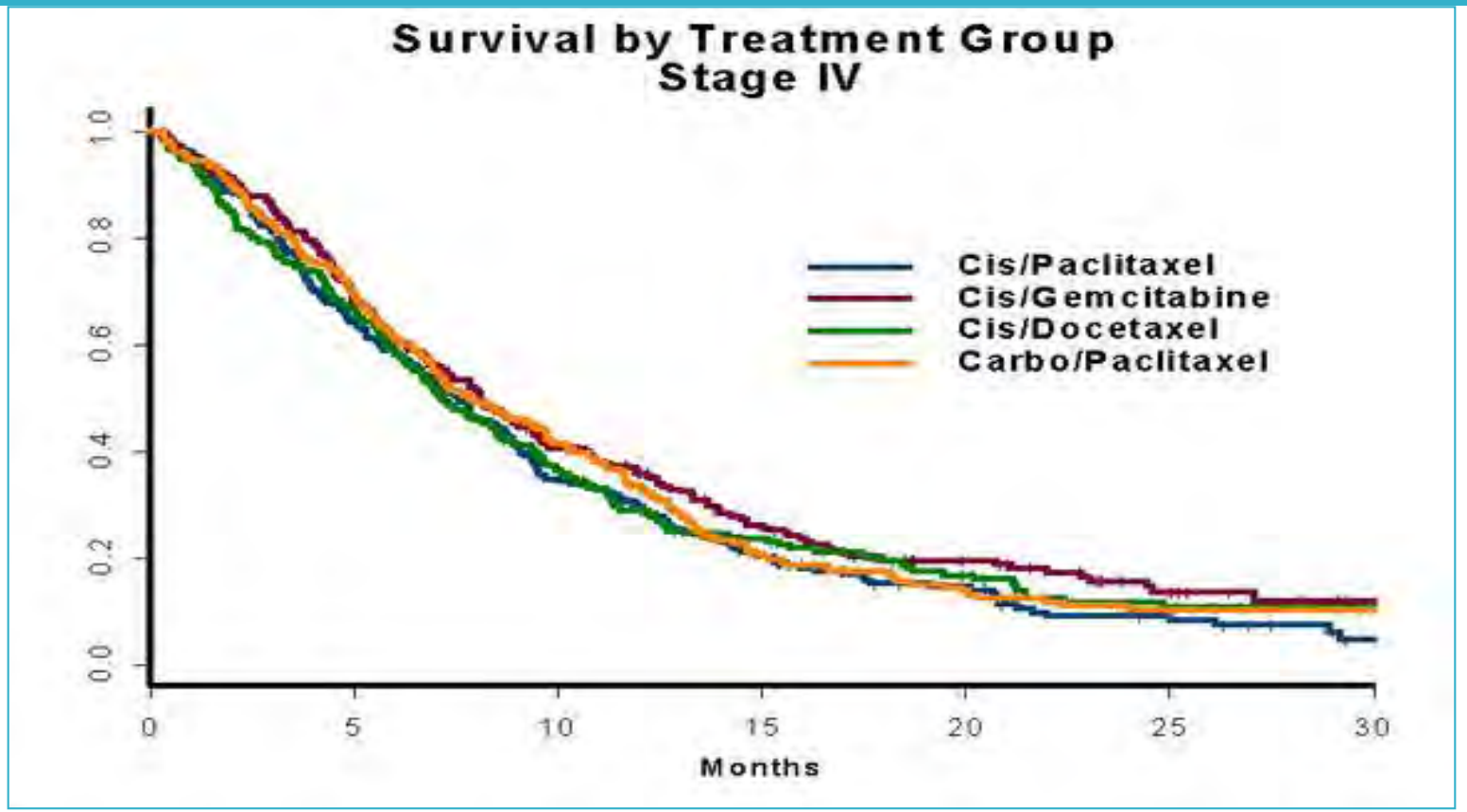
Liens d'intérêt

- Advisory Boards : Roche, Genentech, Eli Lilly, Pfizer, Boehringer-Ingelheim, Clovis Oncology, MSD, Bristol-Myers Squibb, Novartis, Pierre Fabre, Astra-Zeneca, Takeda
- Fonds de recherche institutionnels: Roche, Astra-Zeneca, Chugai
- Symposiums: Eli Lilly, Roche, Astra-Zeneca, Pfizer, Amgen, Boehringer-Ingelheim, Bristol-Myers Squibb, Takeda, Chugai

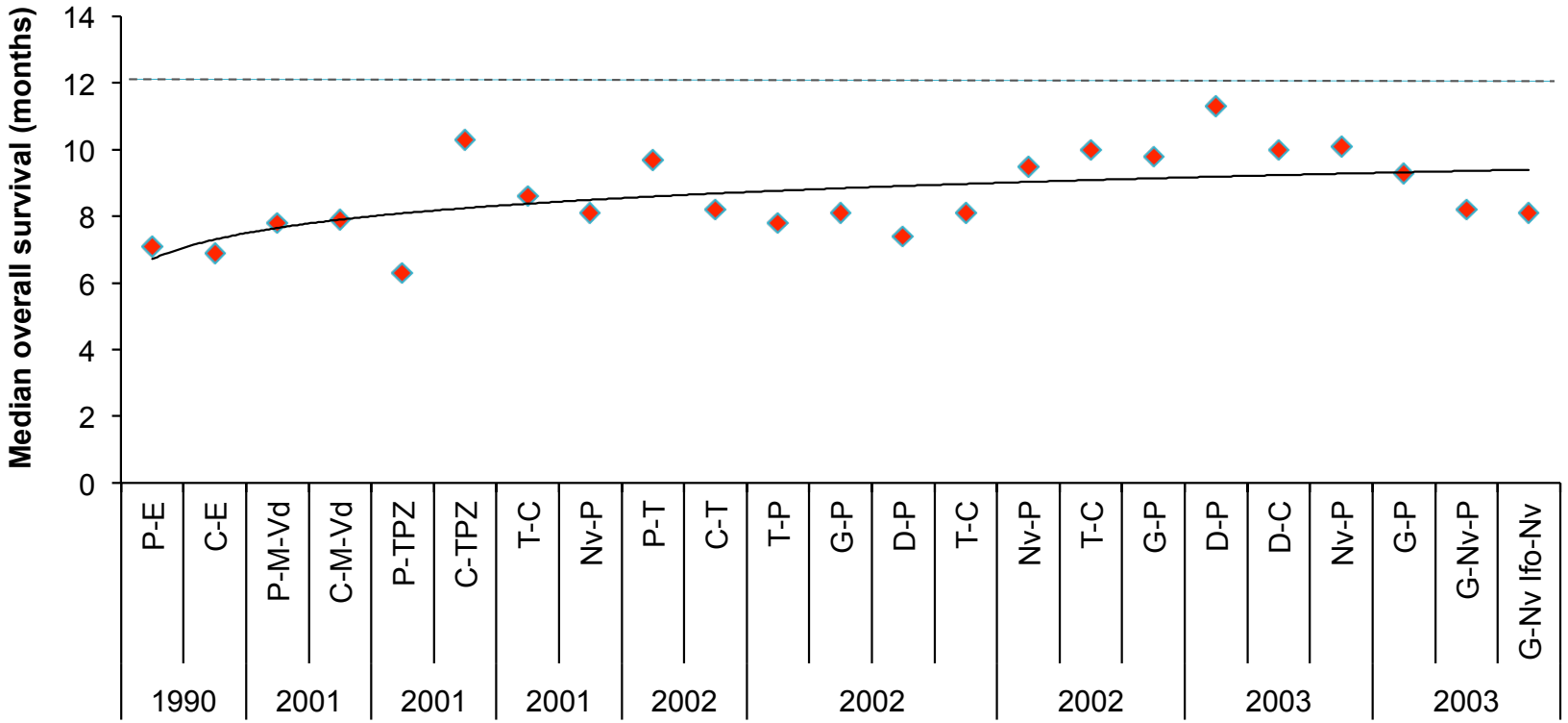
Le passé
Progrès incrémentaux
liés à la chimiothérapie cytotoxique

Bases de la chimiothérapie des CBNPC
Comparaison des doublets platine + drogue 3ème génération



ECOG 1594
Schiller, NEJM 2002

The Efficacy Plateau with Cytotoxic Chemotherapy at the Beginning of the 21st Century

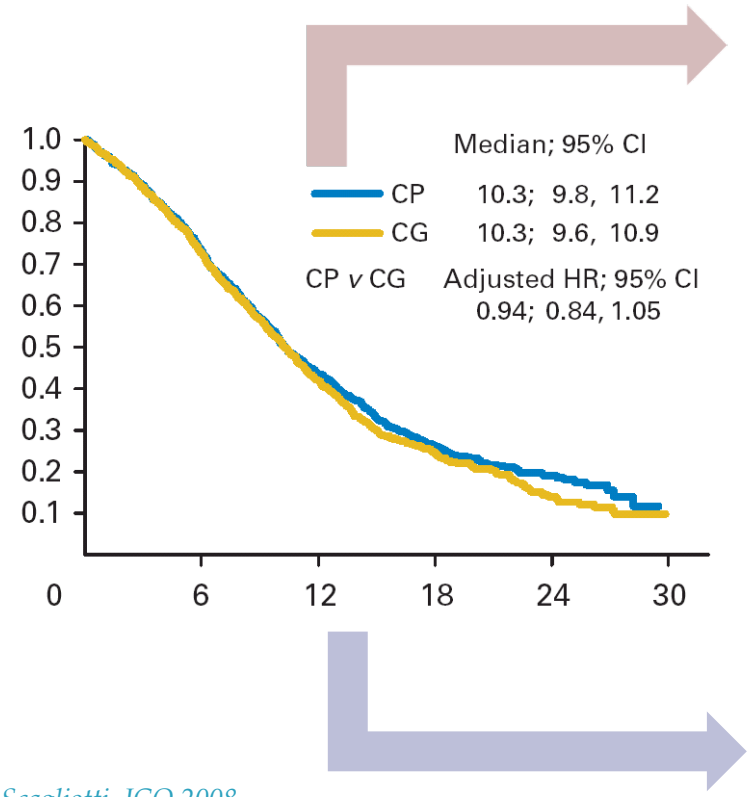


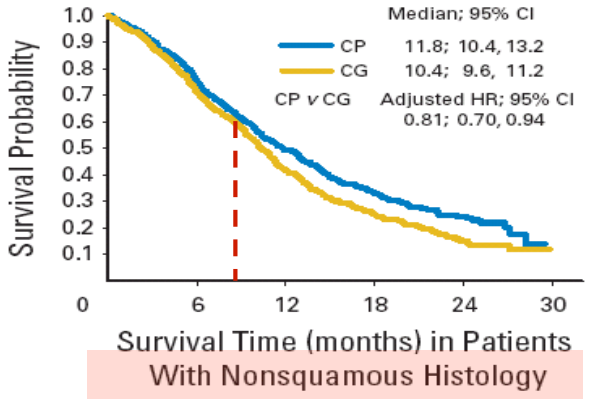
Courtesy of G. Scagliotti

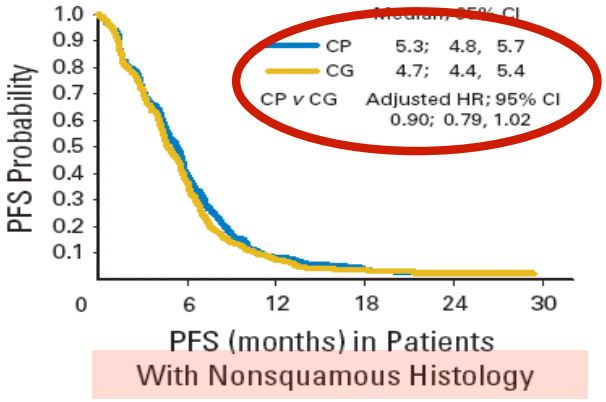
Les bases de la chimiothérapie de 1ère ligne des CBNPC avancés sans addiction oncogénique (PS 0-1)

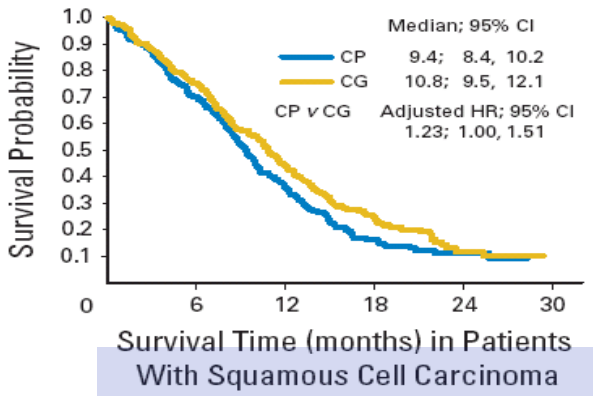
- Traitement fondé sur une chimiothérapie cytotoxique avec un doublet associant un sel de platine et un cytotoxique de 3ème génération
- Amélioration des résultats de la chimiothérapie (augmentation incrémentale de la survie) obtenue par
  - Prise en compte de l'histologie dans la décision thérapeutique
  - Pemetrexed dans les cancers non-épidermoïdes
  - Stratégie de maintenance, principalement avec le pemetrexed, dans les non-épidermoïdes
  - Blocage de la voie du VEGF par le bévacizumab dans les cancers non-épidermoïdes
  - Blocage de la voie de l'EGFR par le necitumumab dans les cancers épidermoïdes

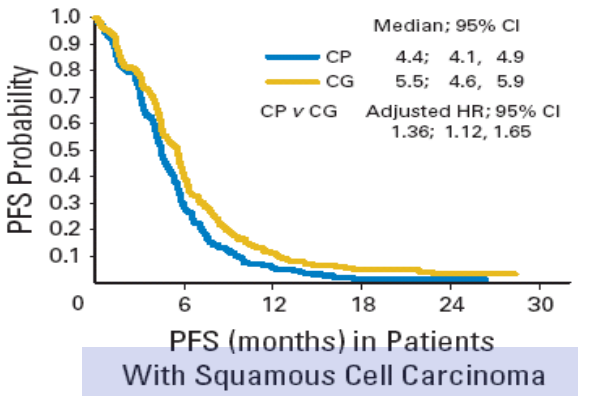
Cisplatine-gemcitabine *vs.* cisplatine-pemetrexed
Analyse de l'efficacité selon l'histologie





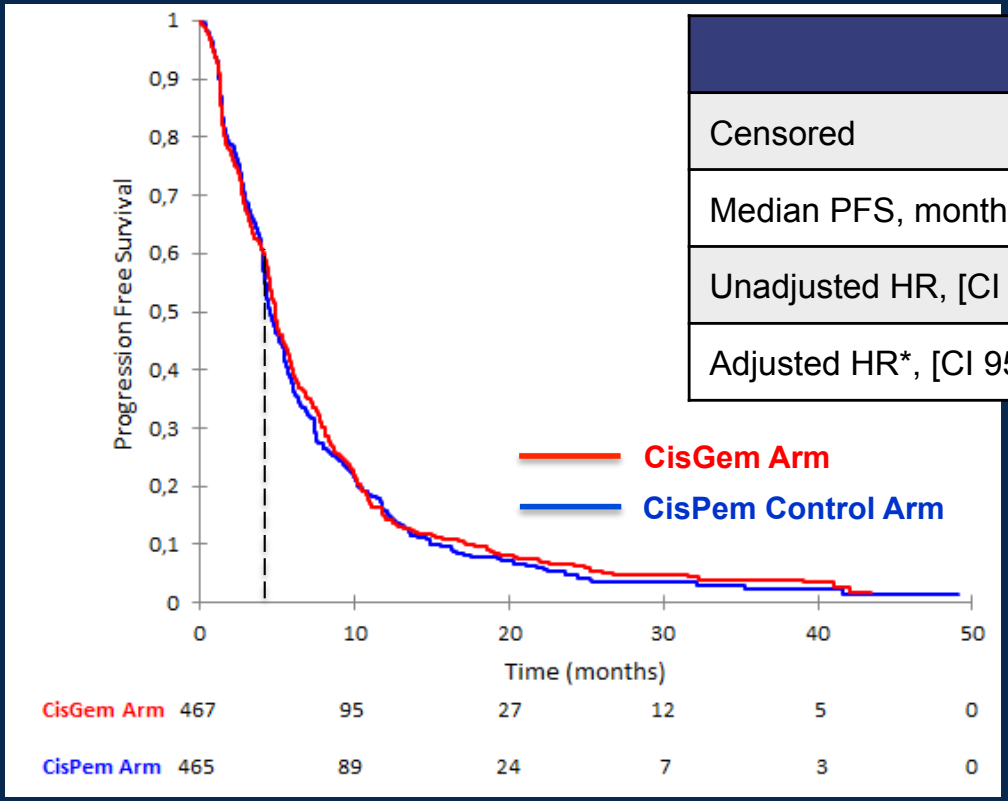






Scagliotti, JCO 2008

IFCT-GFPC-11.01: PFS and Response to Treatment



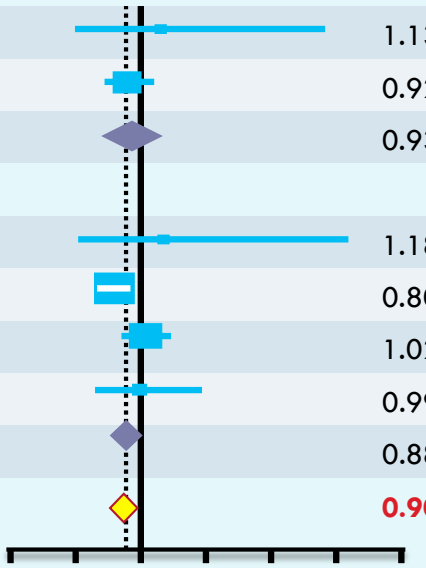
	CisGem Arm	CisPem Control Arm
Censored	7.9%	7.7%
Median PFS, months, [CI 95%]	**4.9 [4.5-5.3]**	**4.5 [4.3-5.1]**
Unadjusted HR, [CI 95%]	**0.96 [0.84-1.10], *P*=0.51**	
Adjusted HR*, [CI 95%]	**0.96 [0.84-1.10], *P*=0.54**	

Best response during induction CT	CisGem Arm	CisPem Control Arm
Objective response	**35.1%**	**33.8%**
Disease stabilization	**34.5%**	**40.9%**
Disease control rate	**69.6%**	**74.7%**
Disease progression	**15.6%**	**11.2%**
Not evaluable	14.8%	14.2%

*: adjusted on stratification factors:PS, gender, histology, center, stage

Bénéfice de survie avec le bevacizumab

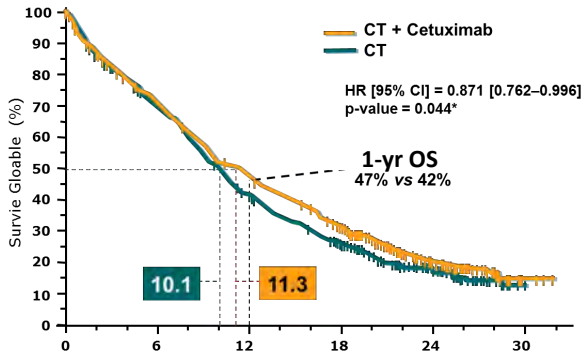
Trial	No. Deaths/No. Entered Bevacizumab	Control	O-E	Variance	HR	HR (95% CI)
Dose 7.5 mg/kg						
AVF-0757g 7.5	18/32	17/32	0.8	6.6		1.13 (0.52-2.42)
AVAiL 7.5	233/345	240/347	-7.5	90.4		0.92 (0.75-1.13)
Subtotal	251/377	257/379	-6.8	97.0		0.93 (0.76-1.14)
Dose 15 mg/kg						
AVF-0757g 15	16/34	17/32	1.0	6.2		1.18 (0.54-2.59)
ECOG 4599	335/434	363/444	-38.5	172.5		0.80 (0.69-0.93)
AVAiL 15	242/351	240/347	1.7	88.1		1.02 (0.83-1.26)
JO19907	66/117	33/58	-0.2	22.0		0.99 (0.65-1.50)
Subtotal	659/936	653/881	-36.0	288.8		0.88 (0.79-0.99)
Total	910/1313	910/1260	-42.7	385.8		**0.90 (0.81-0.99)** p=0.03

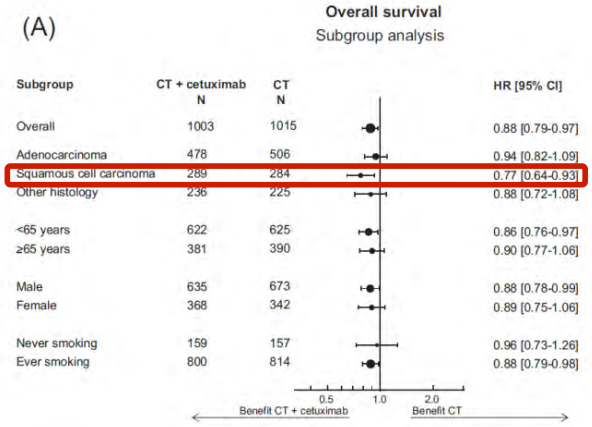


Test for heterogeneity: X^2=4.78; p=0.44; I^2=0%
Test for interaction: X^2=0.22; p=0.64

Soria JC, et al. Ann Oncol 2013;24:20–30.

Incremental Improvements: Targeting EGFR



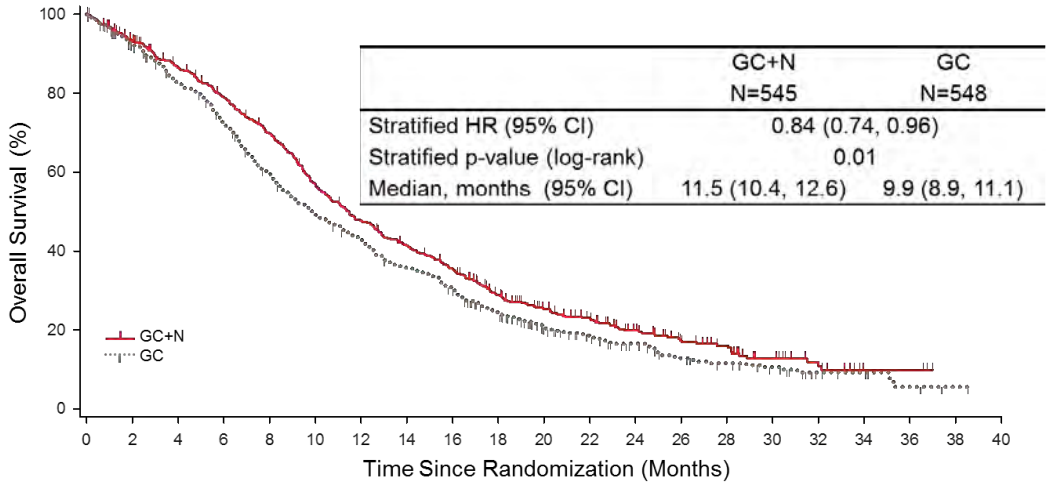


Pirker, Lancet 2009 ; Pujol, Lung Cancer 2014; Thatcher, Lancet Oncol 2015

FLEX

Cisplatin-Vinorelbine
+/- cetuximab

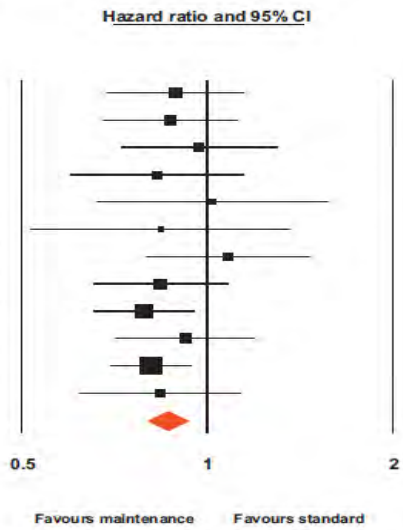
Squire



Cisplatin-Gemcitabine +/- necitumumab
(squamous cell carcinoma)

Le traitement de maintenance améliore la survie des patients conservant un PS 0-1 après le traitement d'induction

Study name	Hazard ratio	Lower limit	Upper limit	Maintenance Therapy	Standard Therapy
Perol-1 2010	0.890	0.689	1.149	154	155
Perol-2 2010	0.870	0.675	1.122	155	155
Belani 2010	0.970	0.722	1.303	128	127
Gaafar 2010	0.830	0.600	1.149	86	87
Belani 2003	1.020	0.661	1.573	65	65
Brodowicz 2006	0.840	0.516	1.368	138	68
Westeel 2005	1.080	0.792	1.473	91	90
Fidias 2009	0.840	0.652	1.083	153	156
Ciuleanu 2009	0.790	0.653	0.955	441	222
Johnson 2008	0.921	0.708	1.198	94	92
Cappuzzo 2010	0.810	0.695	0.944	437	447
Zhang 2011	0.840	0.619	1.139	148	148
	0.862	0.800	0.928		

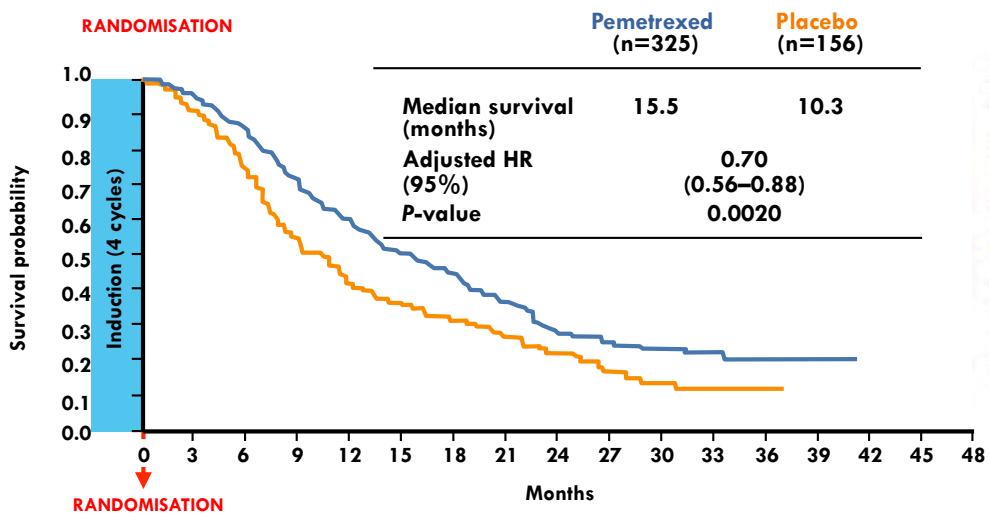


Overall survival: HR 0.86 (CI 0.80 0.92) ; P Value 0.0003

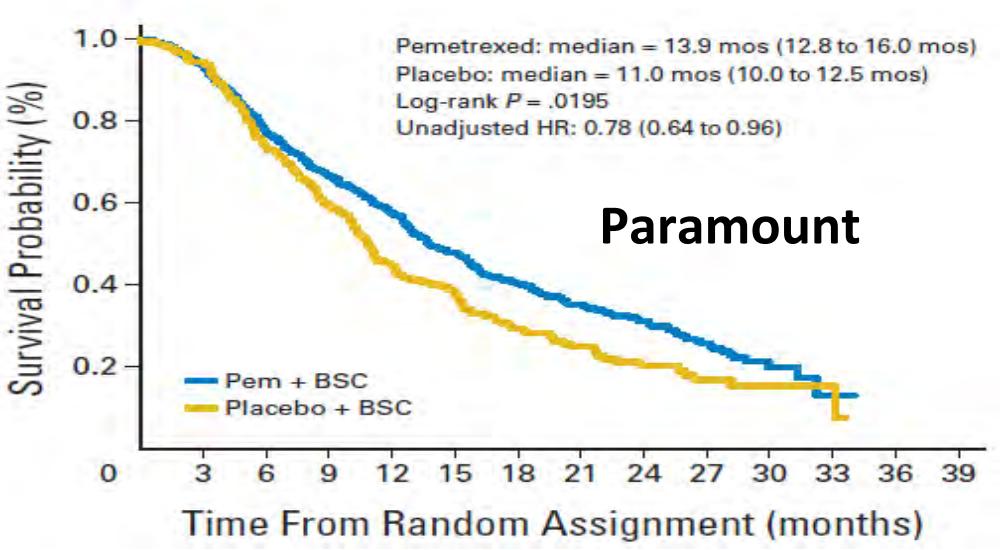
Etude	HR OS (maintenance *vs* obs./placebo) PS = 0	PS = 1	PS ≥ 2	Interaction
Continuation				
Gemcitabine (Brodowicz)	0.80		2.10	NR
Gemcitabine (IFCT-GFPC)	0.65	0.97	2.10	NR
Pemetrexed (Paramount)	0.72	0.83	-	NR
Switch				
Pemetrexed (JMEN)	0.68	0.86	-	NR
Erlotinib (Saturn)	0.59	0.77	-	NR
Erlotinib (IFCT-GFPC)	0.63	0.96	1.41	NR
Gefitinib (EORTC)	0.80		1.25	NR

Behera, Lung Cancer 2012, Brodowicz et al. 2006 Lung Cancer; Pérol et al. JCO 2012 ; Belani et al. ASCO 2009 ; Gaafar et al. 2011 EJC; Cappuzzo et al. Lancet Oncol 2010

Impact du pemetrexed en maintenance sur la survie des CBNPC non-épidermoïdes



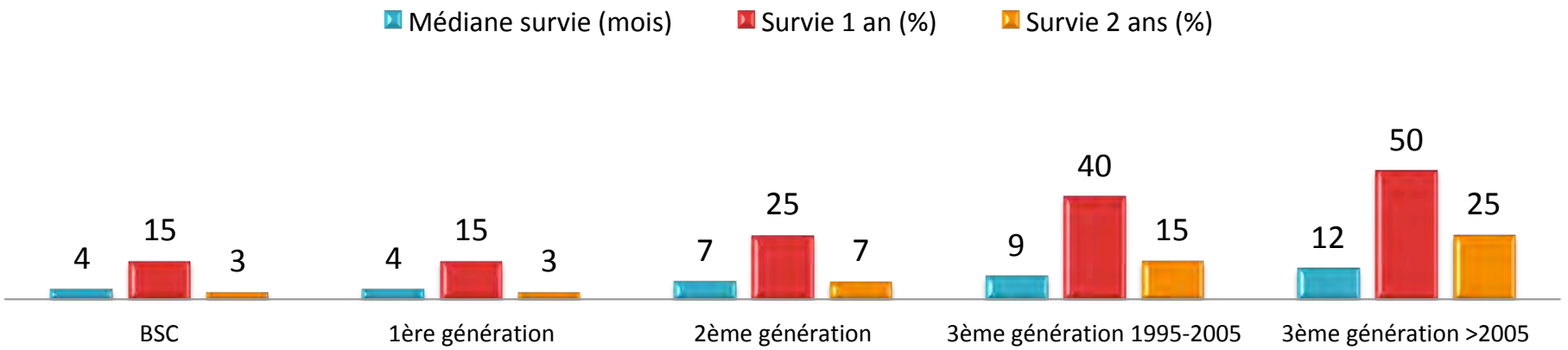
JMEN



	Pemetrexed	Placebo
Taux de survie (%)		
1 an	58	45
2 ans	32	21

Ciuleanu et al. , Lancet 2009; 374:1432 ; Paz-Ares, JCO 2013

Progrès incrémentaux 1980-2010 dans la survie des CBNPC avancés



Les raisons de l'amélioration de la survie …

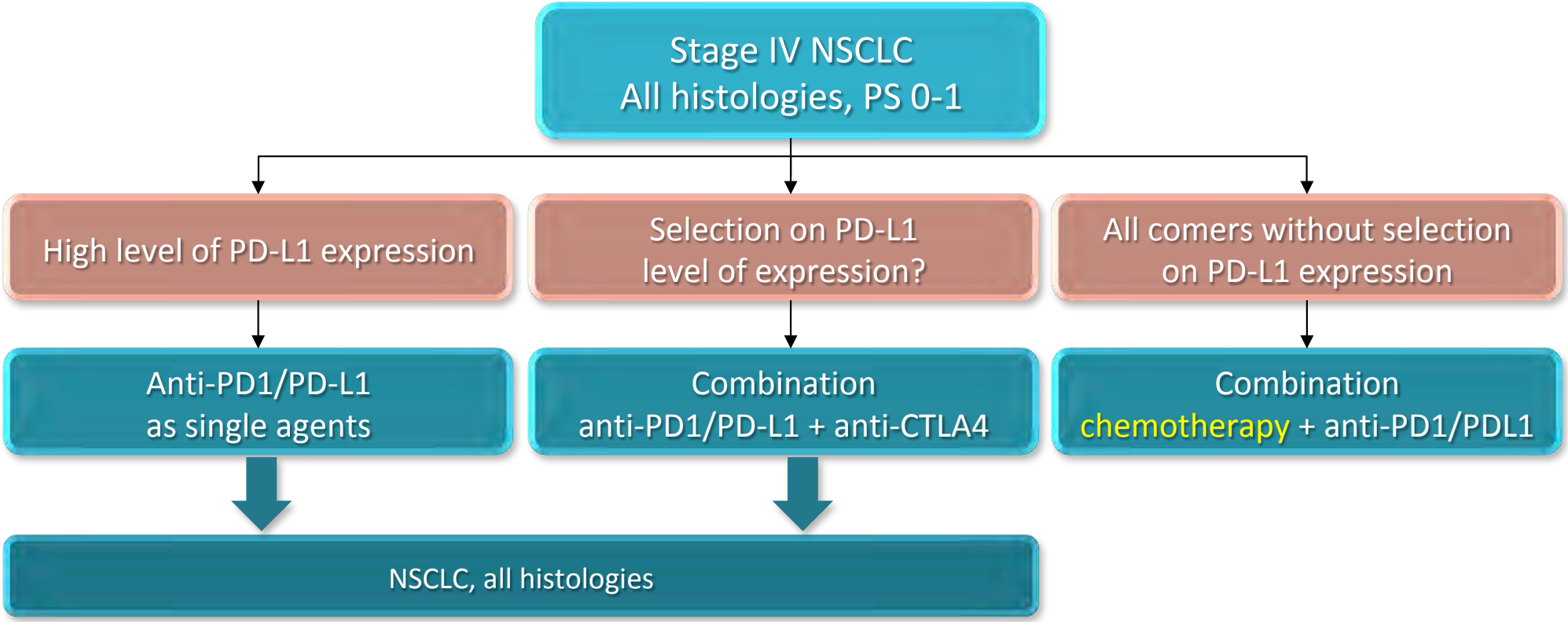
- Cytotoxiques de 3ème génération, bevacizumab
- Lignes ultérieures de chimiothérapie
- Traitement de maintenance, pemetrexed dans les adénocarcinomes
- Sélection accrue dans les essais (PS 0-1)
- Migration des stades
- Proportion accrue de femmes
- Traitement plus efficace des métastases cérébrales
- Amélioration des soins de support

Noonan K, JTO 2015

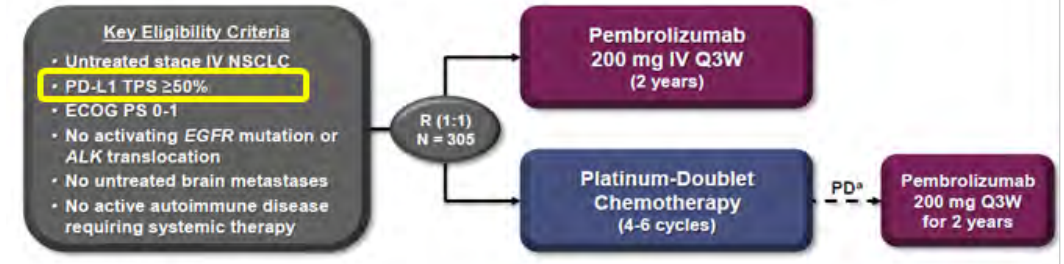
Le présent

La chimiothérapie face à l'immunothérapie, innovation de rupture : disparition ou partenaire de l'immunothérapie ?

Immunotherapy in 1st Line Treatment of NSCLC
The three first options



Pembrolizumab in First-Line of Advanced NSCLC: Keynote 024



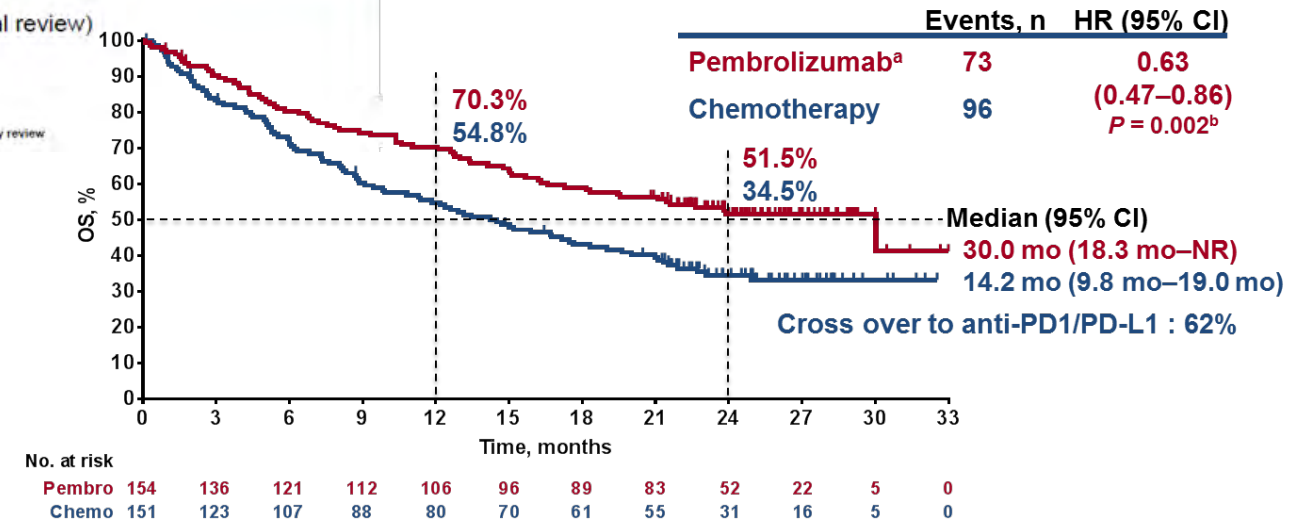
Key End Points

Primary: PFS (RECIST v1.1 per blinded, independent central review)

Secondary: OS, ORR, safety

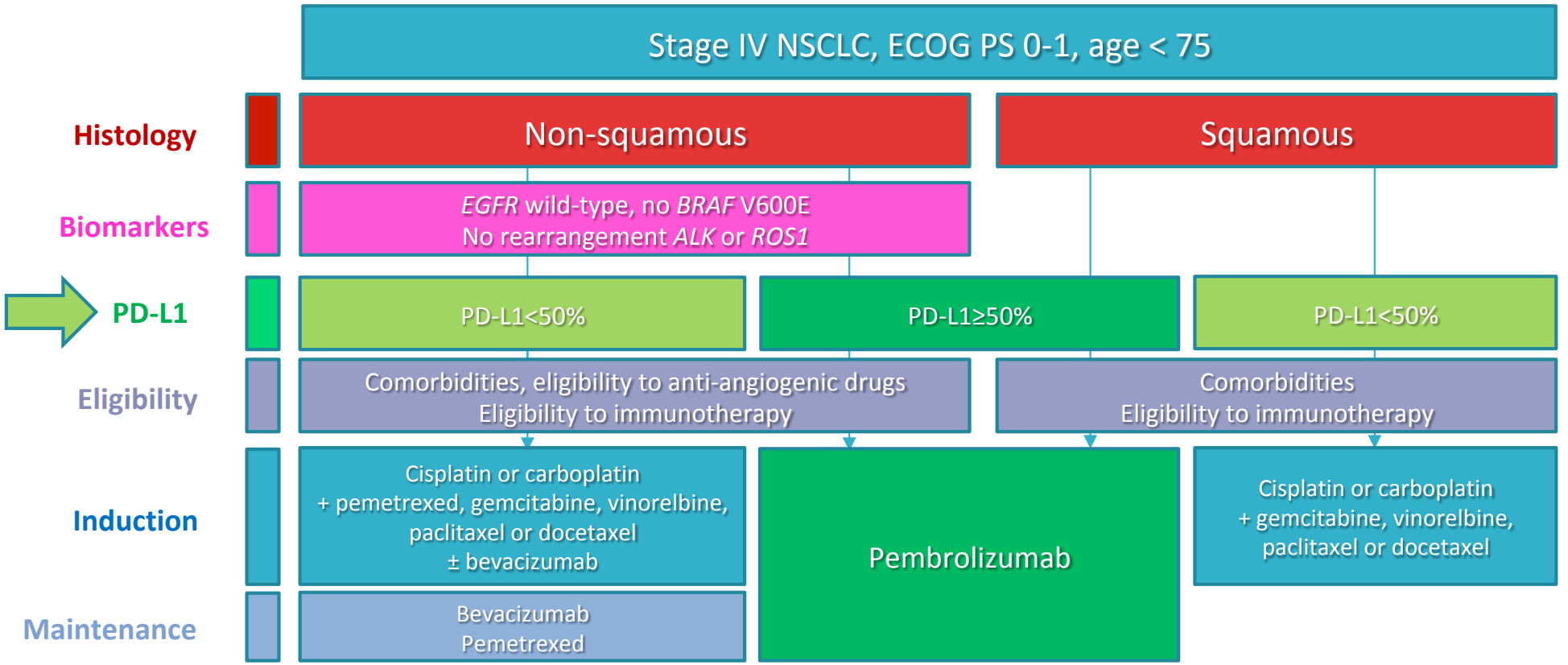
Exploratory: DOR

[a]To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.

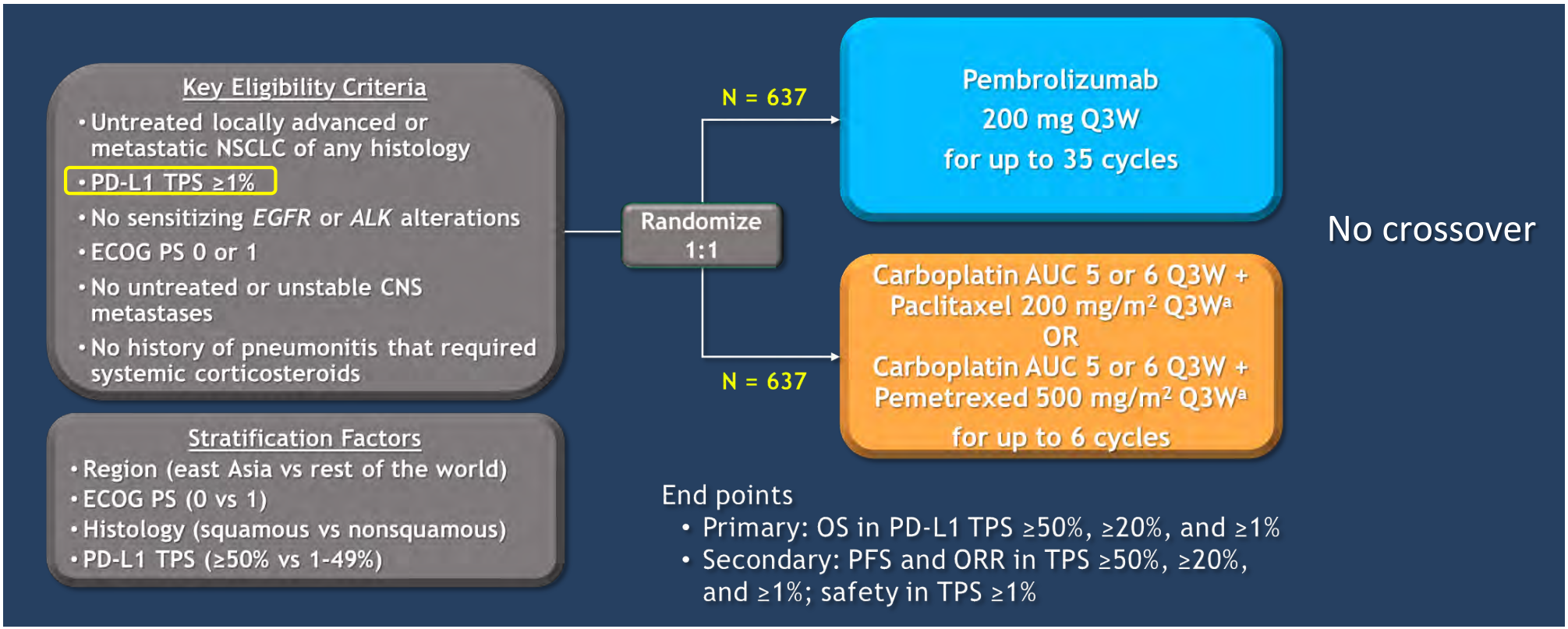


Reck, NEJM 2016; Brahmer, WCLC 2017

Stage IV NSCLC Without Oncogenic Addiction: A New Treatment Algorithm …

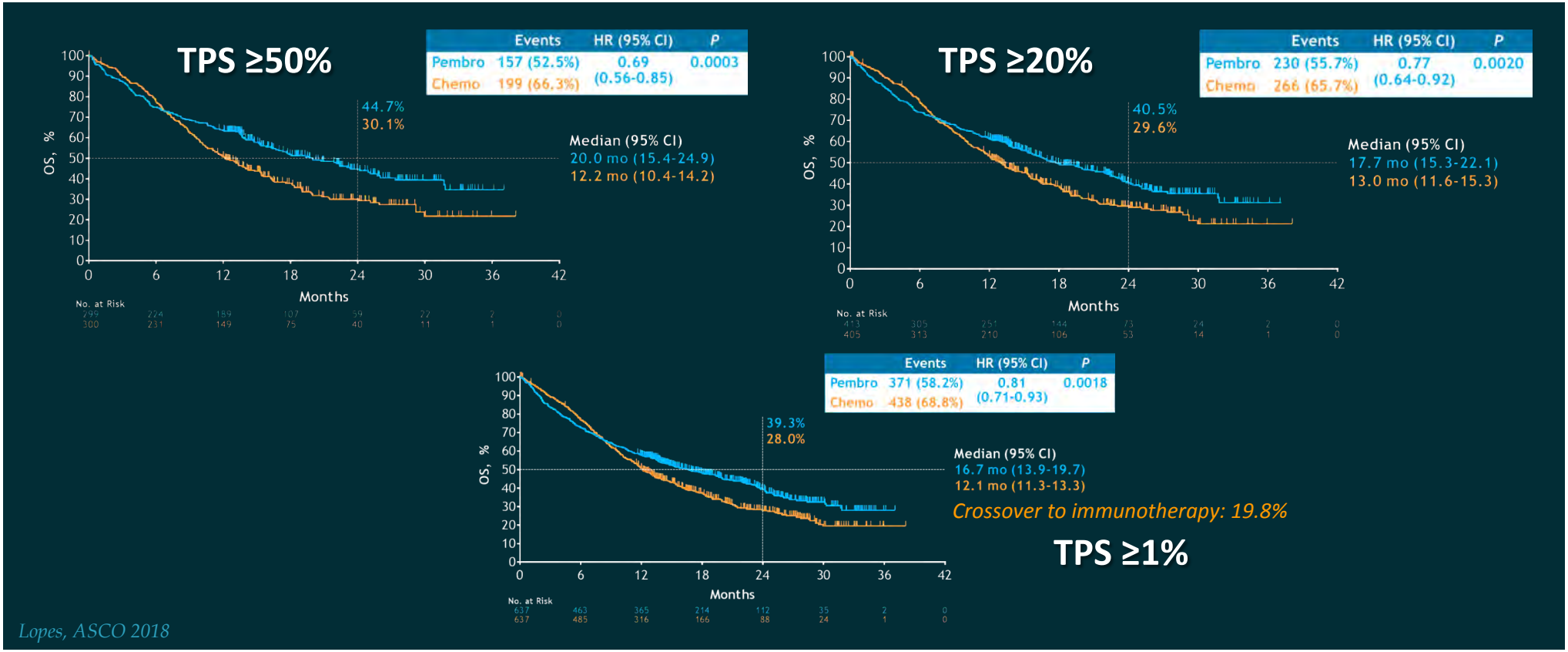


Should we Use Pembrolizumab in PD-L1 ≥1% NSCLC? Keynote 042



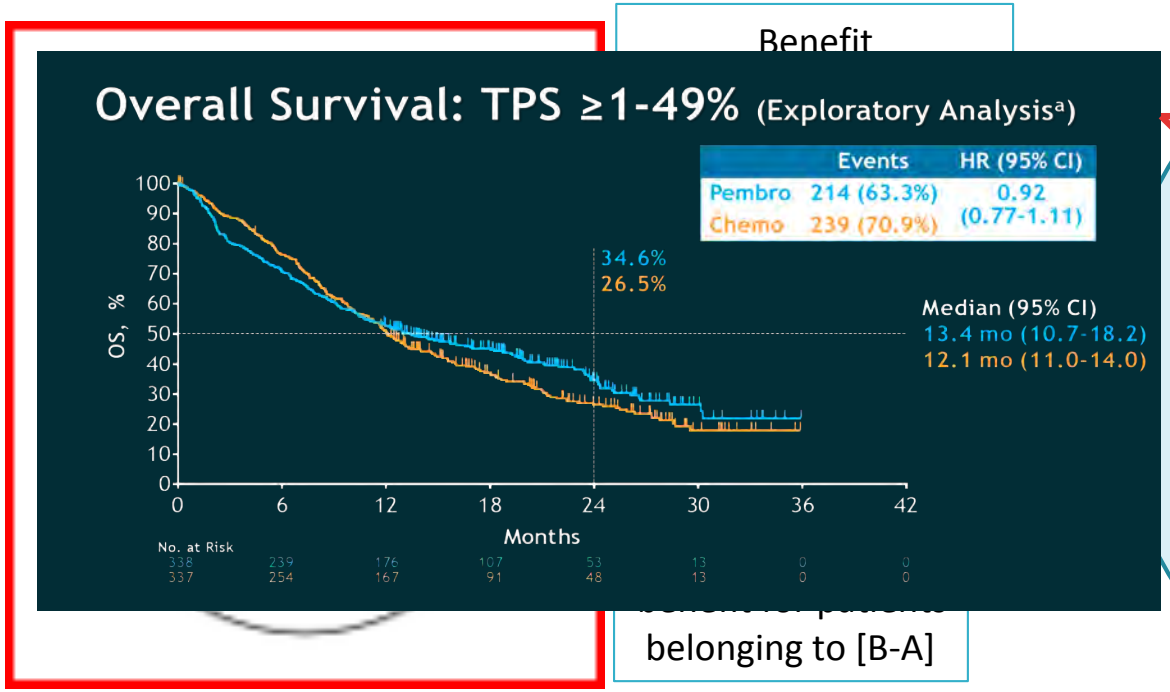
Lopes, ASCO 2018

Keynote 042: Pembrolizumab *vs*. Chemotherapy Overall Survival



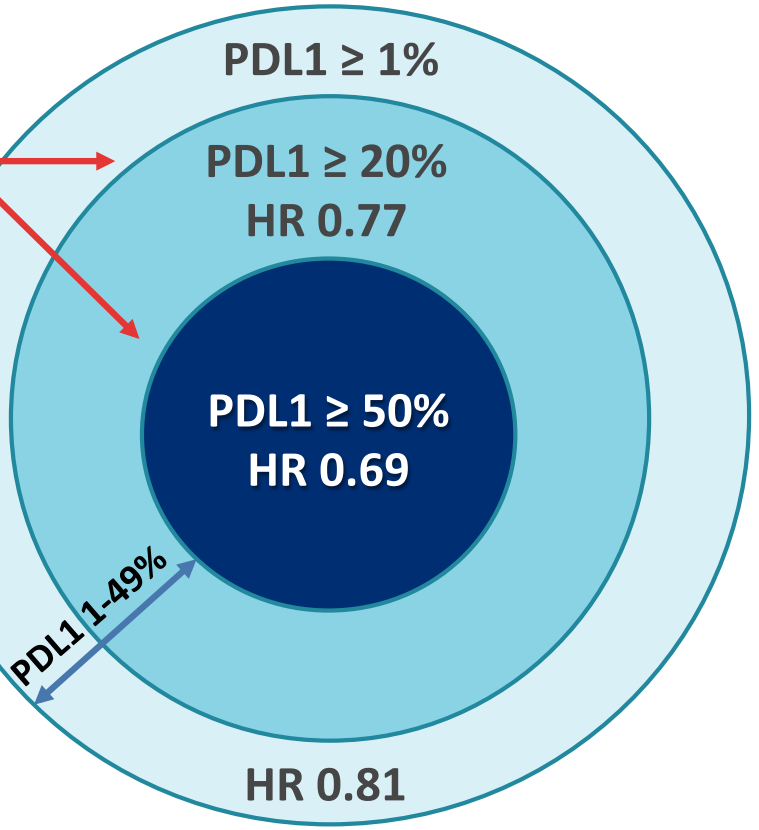
Lopes, ASCO 2018

Keynote 042: Hierarchical Analysis



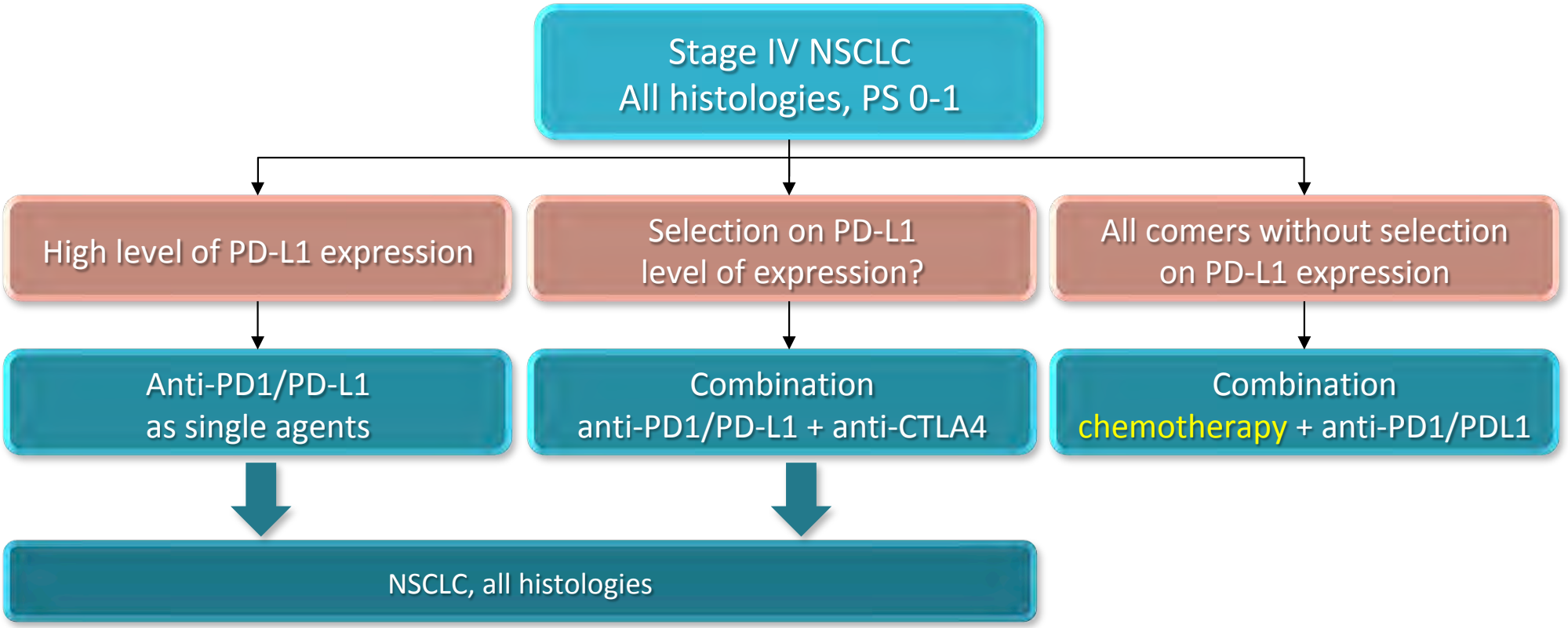
Benefit

belonging to [B-A]

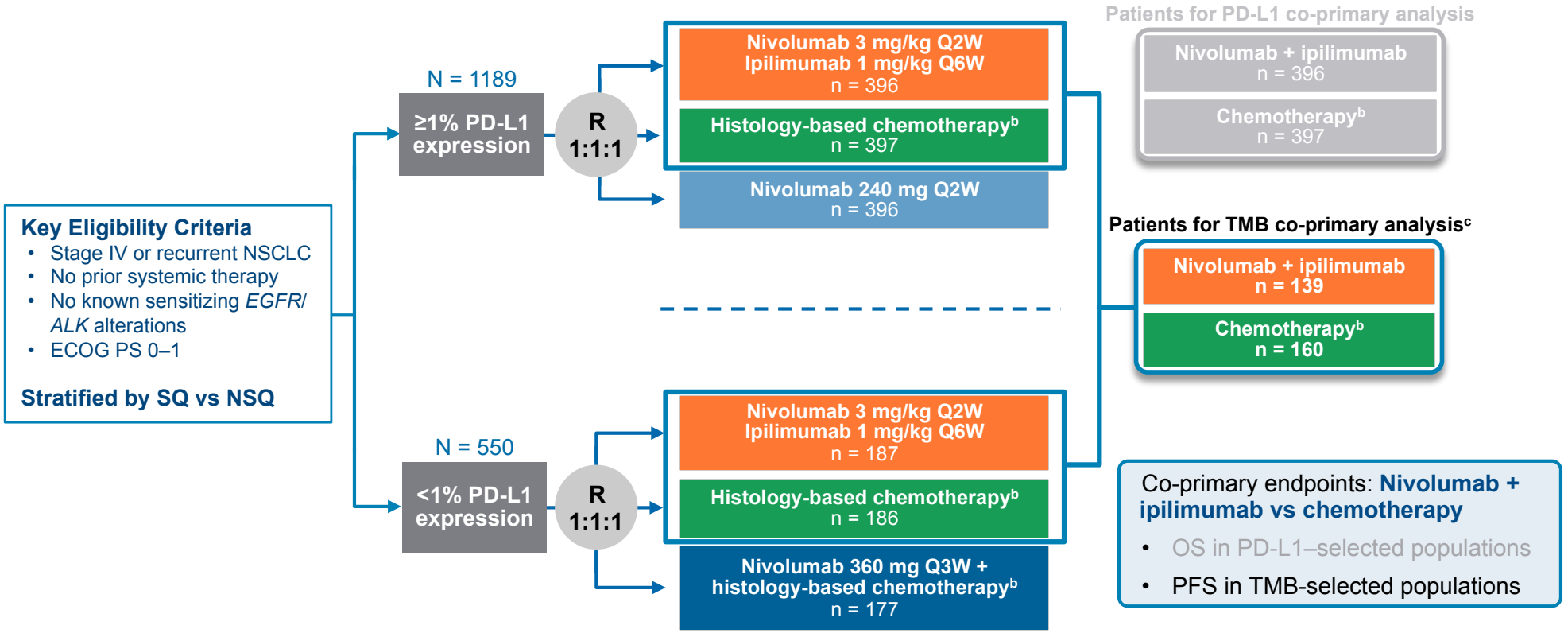


Adapted from Lopes, ASCO 2018

Immunotherapy in 1st Line Treatment of NSCLC
The three first options



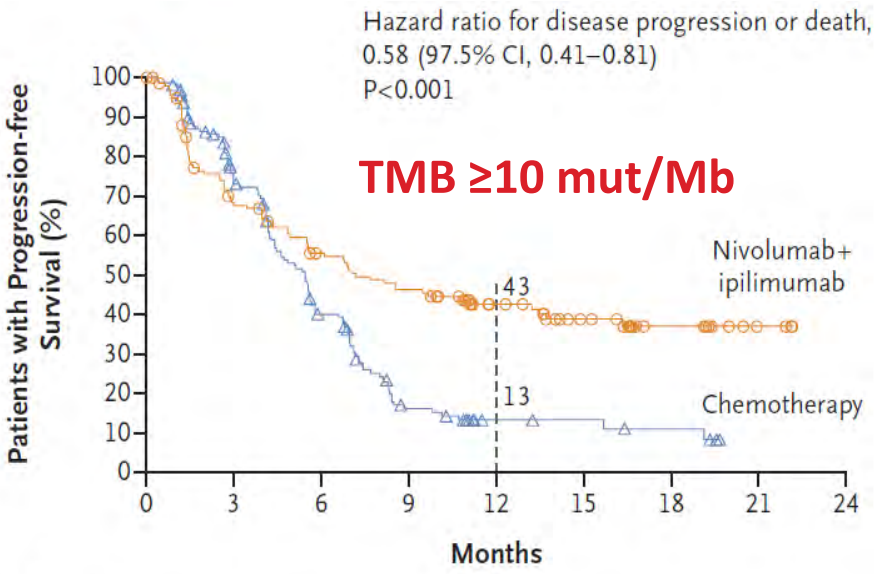
CheckMate 227 Part 1 Study Design[a]



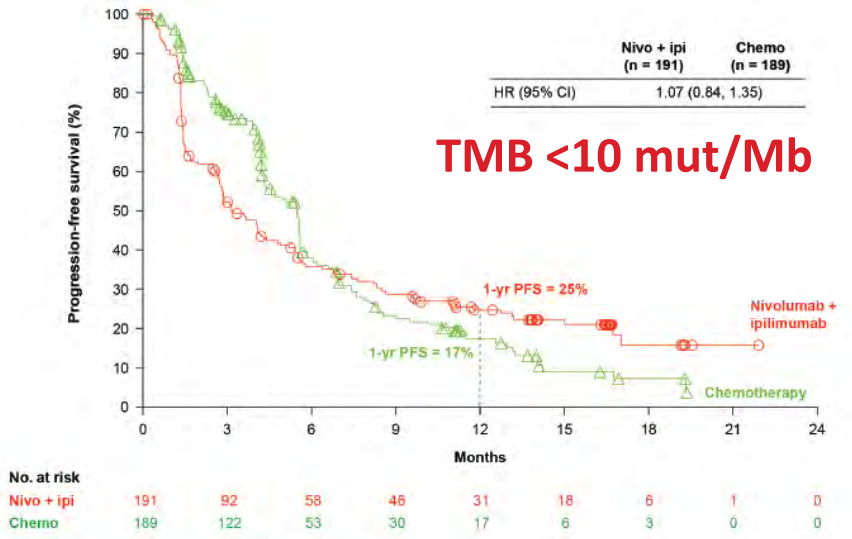
Database lock: January 24, 2018; minimum follow-up: 11.2 months

[a]NCT02477826 [b]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤4 cycles, with optional pemetrexed maintenance following chemotherapy or nivolumab + pemetrexed maintenance following nivolumab + chemotherapy; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤4 cycles; [c]The TMB co-primary analysis was conducted in the subset of patients randomized to nivolumab + ipilimumab or chemotherapy who had evaluable TMB ≥10 mut/Mb

CheckMate 227 Phase III Trial
Nivolumab + Ipilimumab in 1L NSCLC by TMB



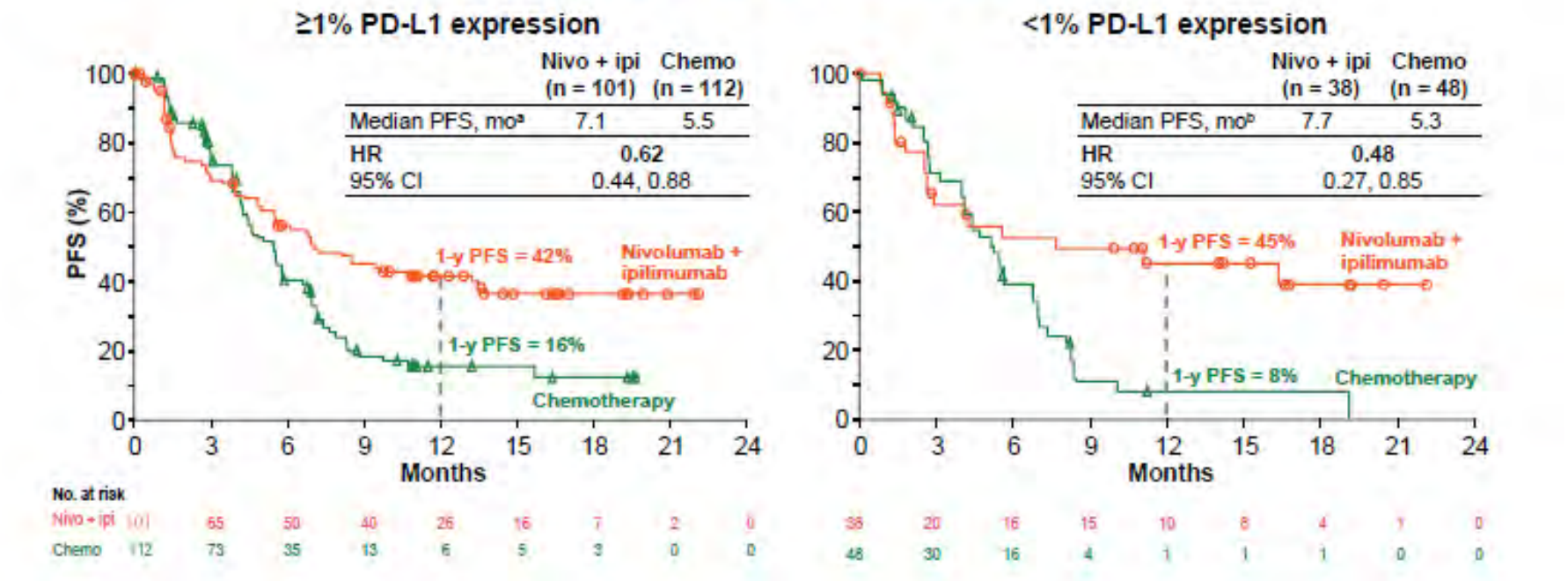
No. at Risk									
Nivolumab + ipilimumab	139	85	66	55	36	24	11	3	0
Chemotherapy	160	103	51	17	7	6	4	0	0



Hellmann M, NEJM 2018

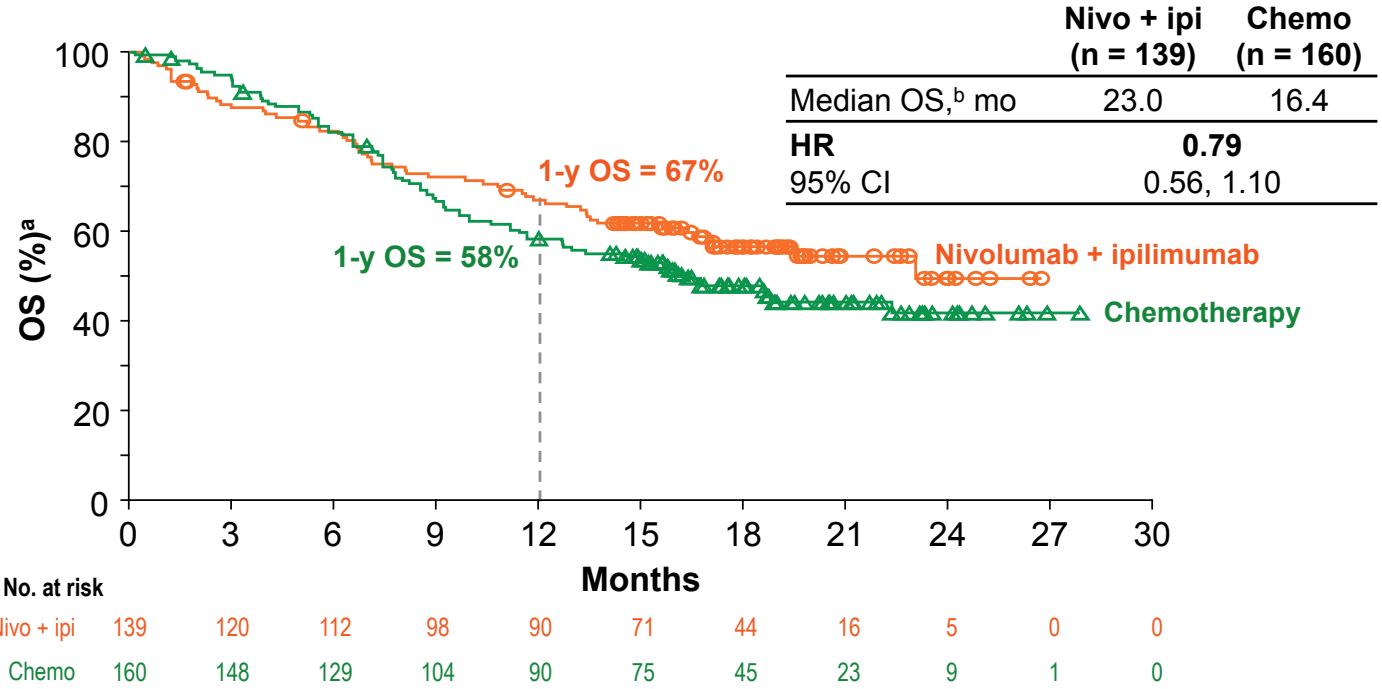
CheckMate 227 Phase III Trial
Nivolumab + Ipilimumab in 1L NSCLC with TMB ≥10 mut/Mb

PFS in patients with High TMB (≥10 mut/Mb) by Tumor PD-L1 Expression



Hellmann M, AACR 2018

Preliminary Overall Survival With Nivolumab + Ipilimumab vs Chemotherapy in Patients With High TMB (≥10 mut/Mb)

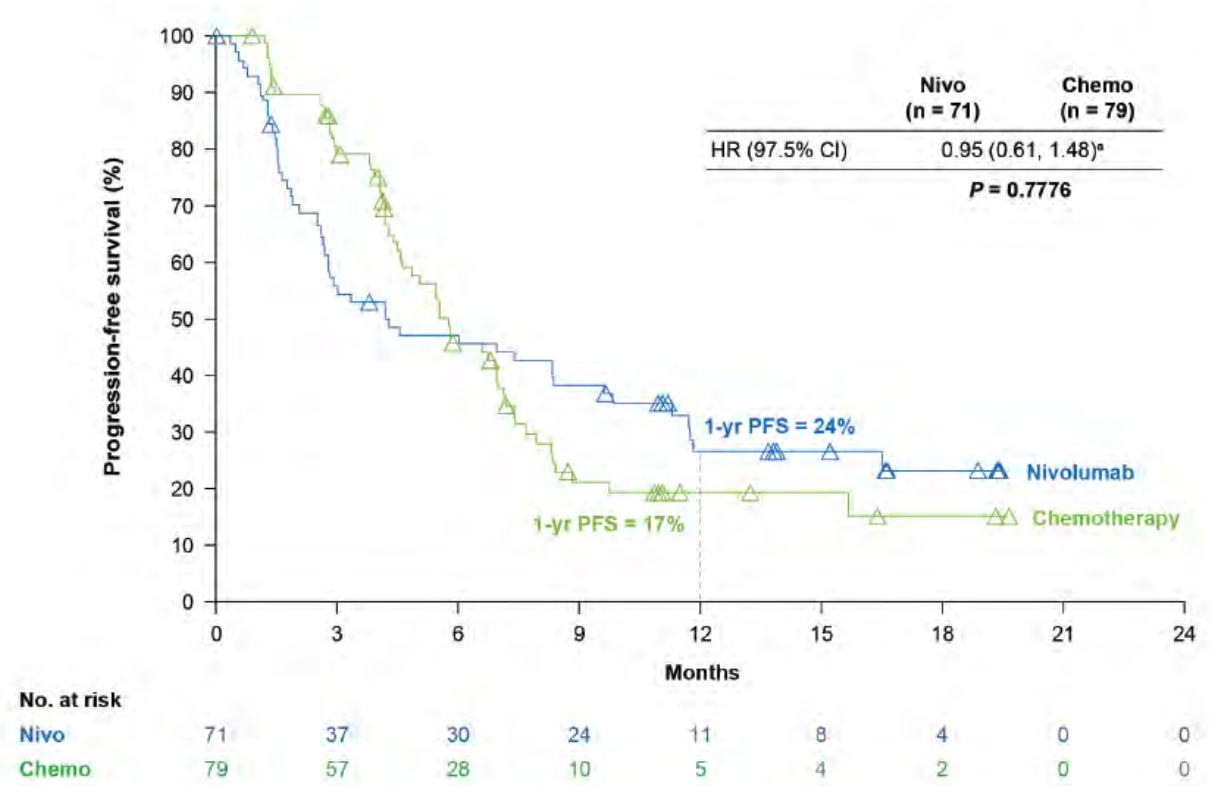


	Nivo + ipi (n = 139)	Chemo (n = 160)
Median OS,[b] mo	23.0	16.4
HR	**0.79**	
95% CI	0.56, 1.10	

- Database lock: March 15, 2018; minimum follow-up: 14.2 months; 53% of patients were censored
- In the chemotherapy arm, 31.3% received subsequent immunotherapy (38.3% among those with disease progression[c])

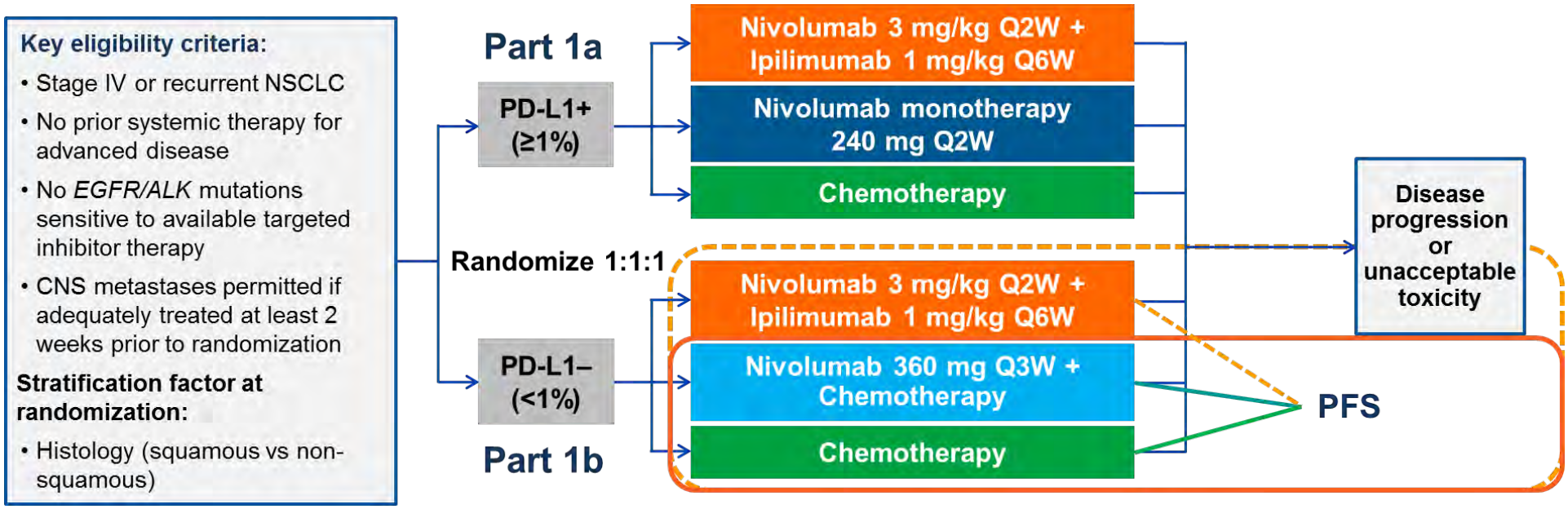
[a]In the first 1.5 months, 8 deaths occurred in the nivo + ipi arm (4 due to disease progression; 1 patient never treated [respiratory sepsis]; 2 due to AEs unrelated to study drug per investigator [thromboembolism, septic shock]; 1 due to myocarditis related to study drug), and 2 deaths occurred in the chemo arm (1 due to disease progression; 1 due to multiple brain infarctions related to carboplatin); [b]95% CI: nivo + ipi (16.5 mo, NR), chemo (12.6 mo, NR); [c]Per investigator

PFS with Nivolumab *vs*. Chemotherapy in Patients with TMB ≥13 Mutations/Mb and ≥1% Tumor PD-L1 Expression



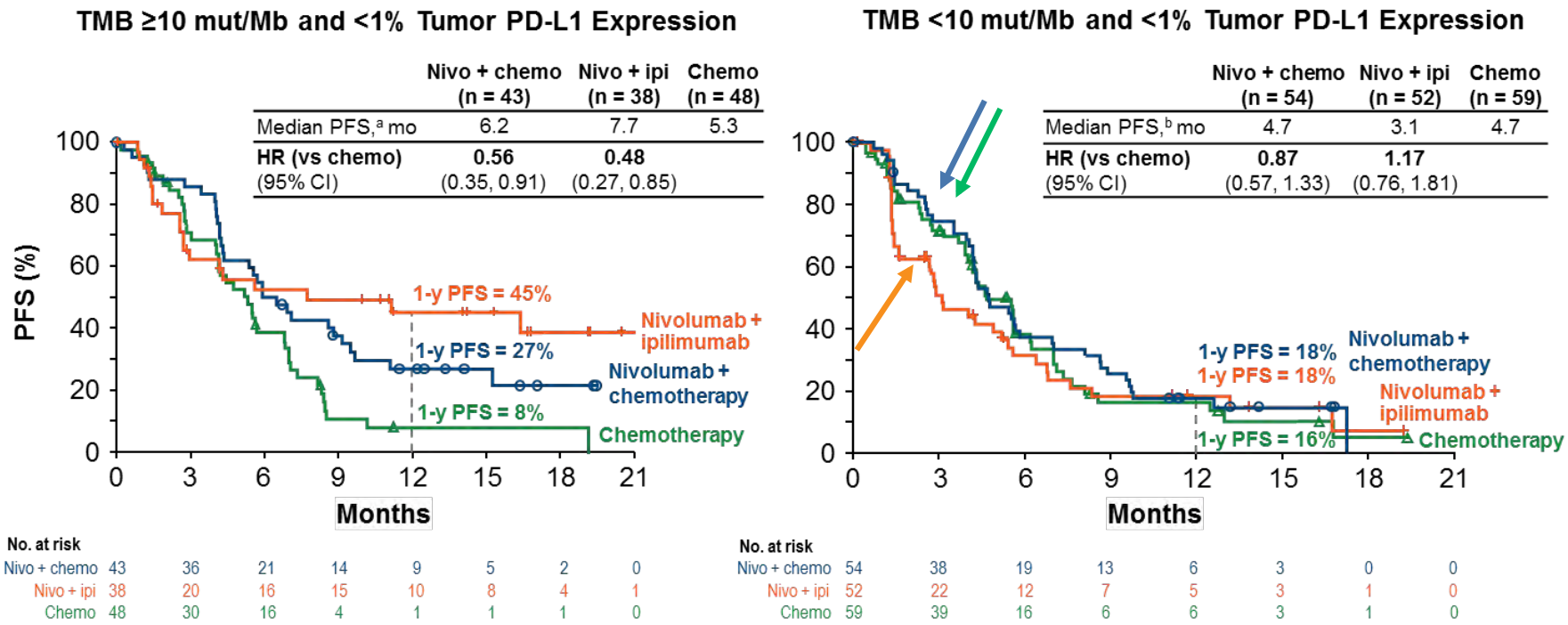
Hellmann, NEJM 2018

CheckMate 227: PD-L1<1% NSCLC (Part 1b) Chemotherapy + Nivolumab vs. Chemotherapy



Borghaei H, ASCO 2018

Checkmate 227: PFS
Nivolumab + Chemotherapy and Nivolumab + Ipilimumab By TMB

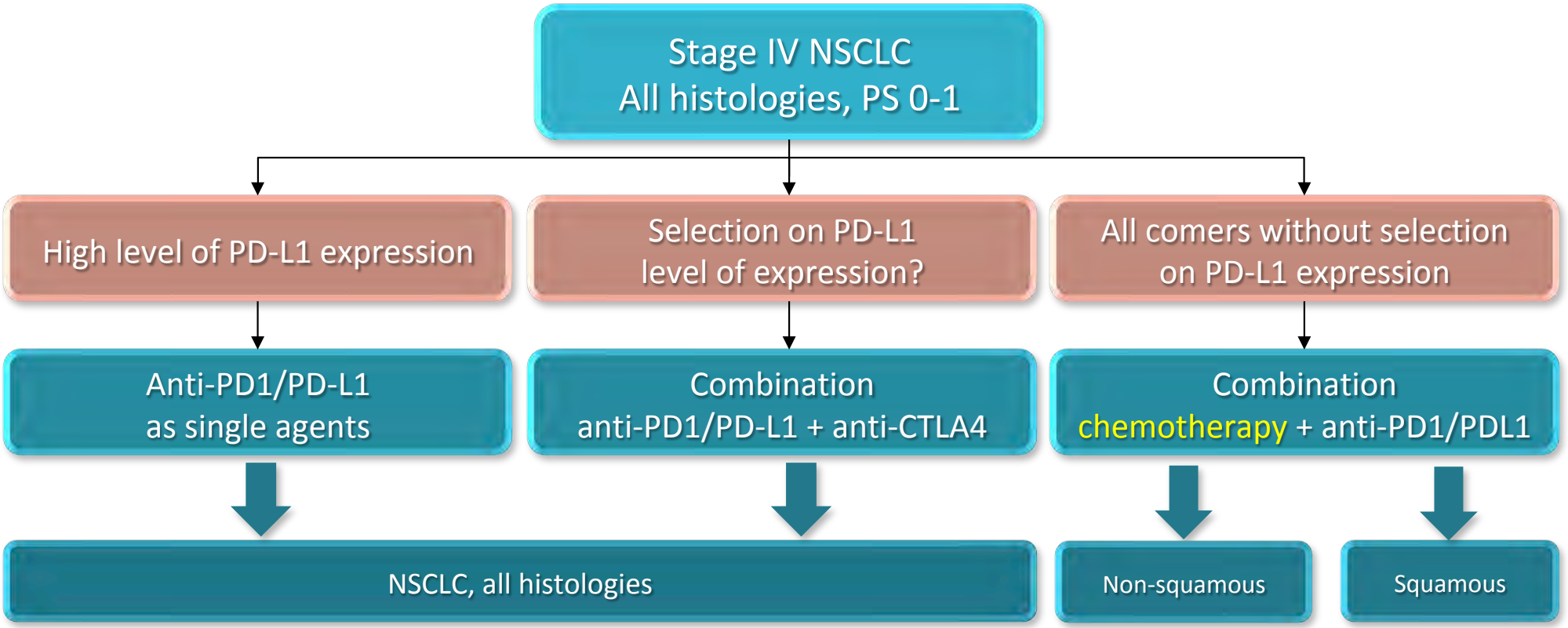


Exploratory analysis

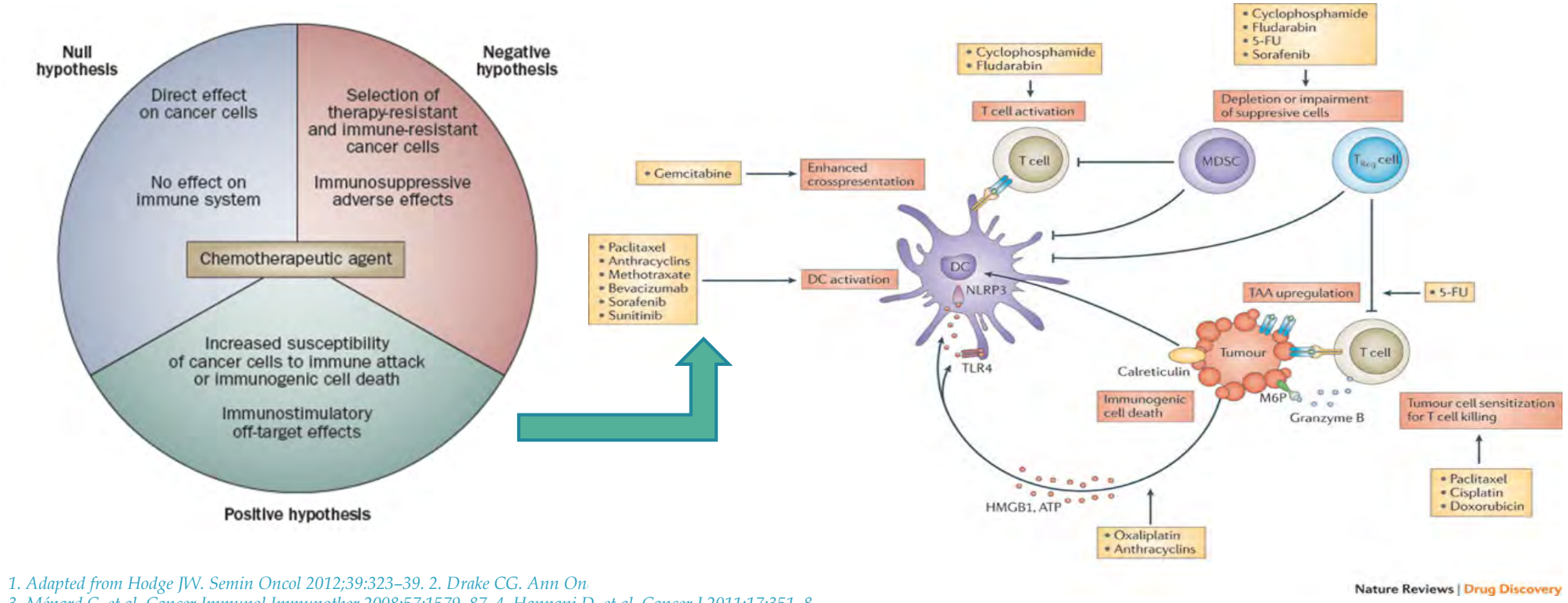
[a]95% CI: nivo + chemo (4.3, 9.1 mo), nivo + ipi (2.7, NR mo), chemo (4.0, 6.8 mo); [b]95% CI: nivo + chemo (4.2, 6.9 mo), nivo + ipi (1.6, 5.4 mo), chemo (3.9, 6.2 mo)

Borghaei H, ASCO 2018

Immunotherapy in 1st Line Treatment of NSCLC
The three first options

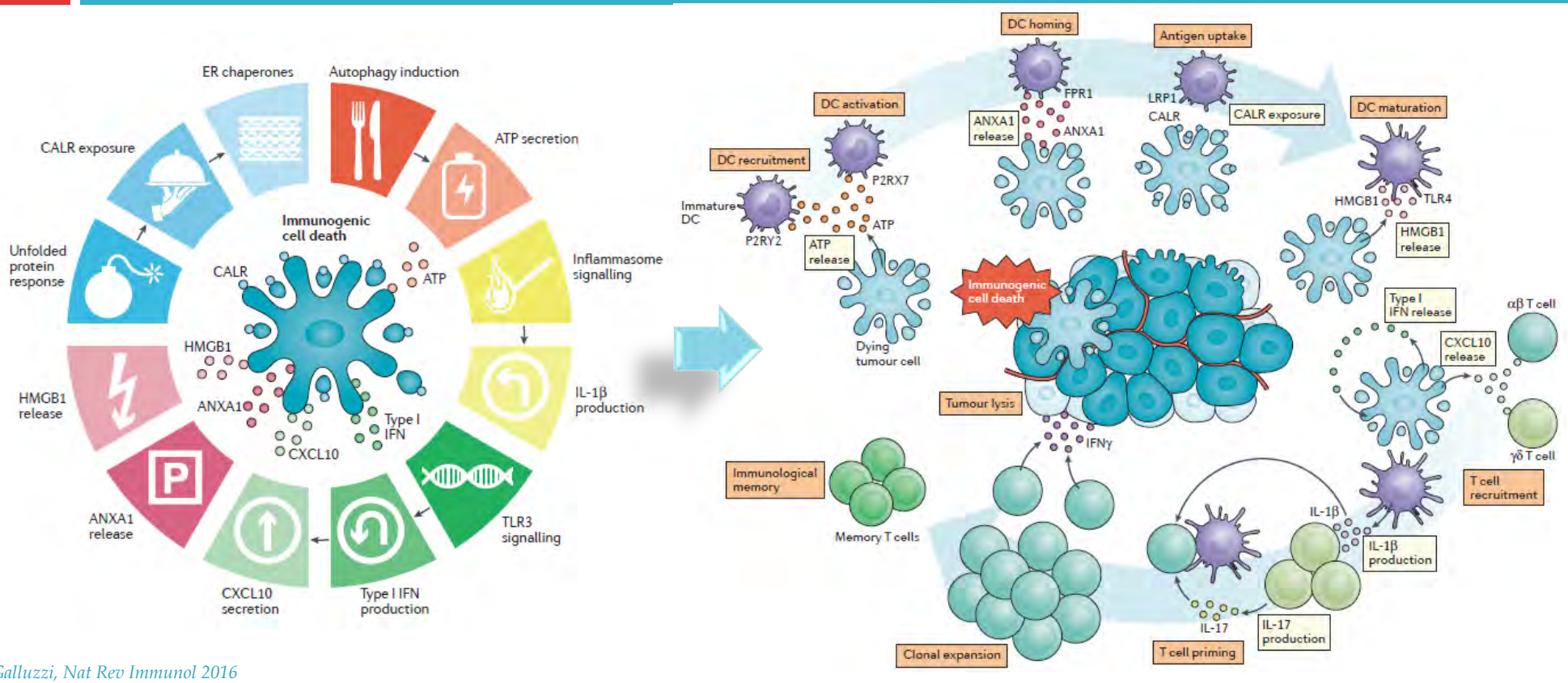


Rationale of Combination of Chemotherapy and IOs



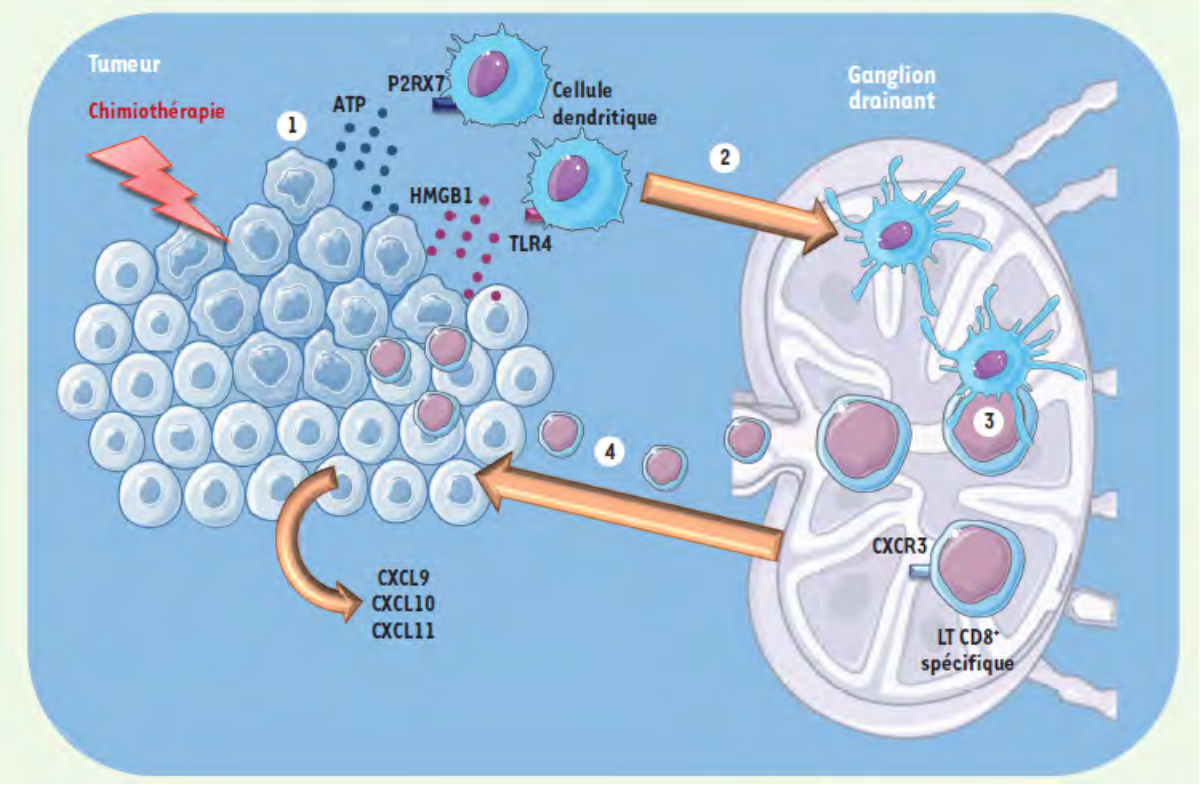
1. Adapted from Hodge JW. Semin Oncol 2012;39:323–39. 2. Drake CG. Ann On
3. Ménard C, et al. Cancer Immunol Immunother 2008;57:1579–87. 4. Hannani D, et al. Cancer J 2011;17:351–8.
5. Ribas A at al. Curr Opin Immunol. 2013:25:291–6. 6. Zitvogel, Nat Rev Clin Oncol 2011

Mort cellulaire immunogénique



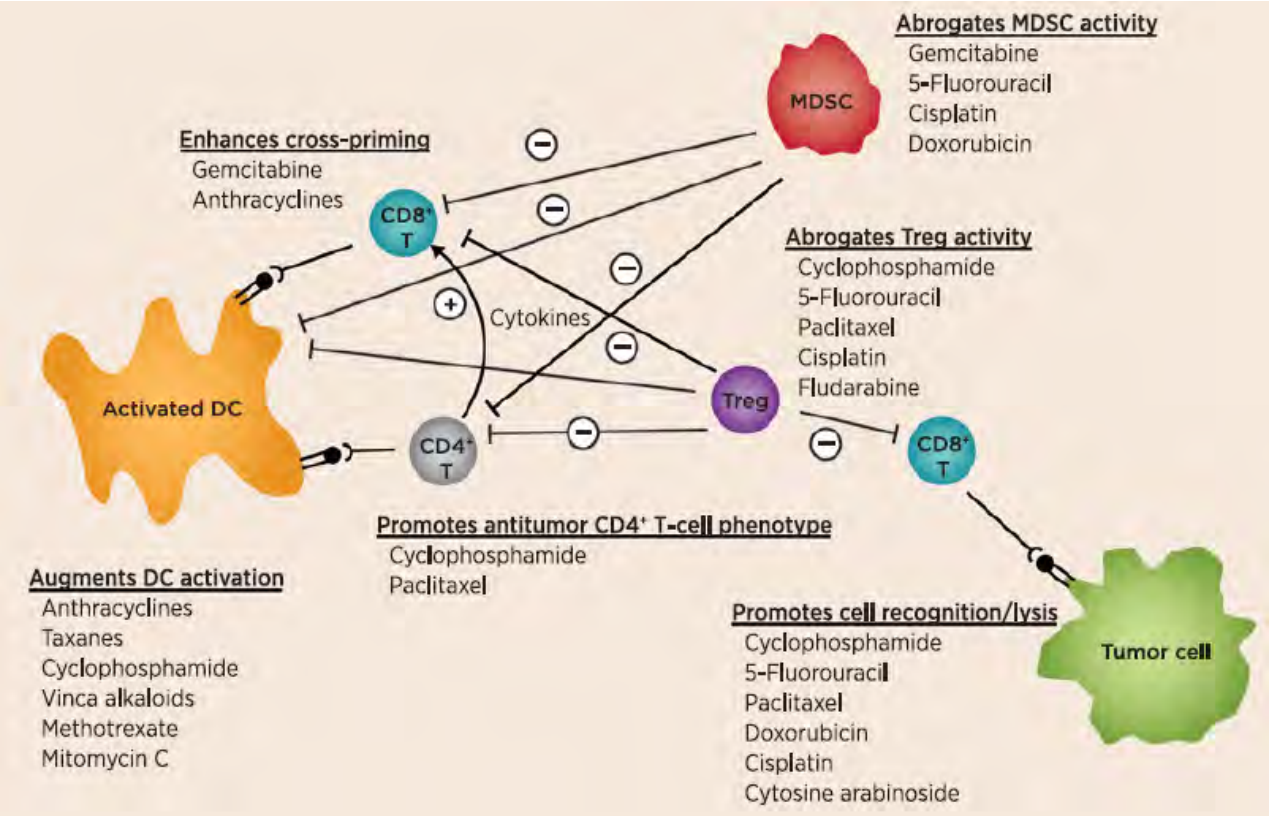
Galluzzi, Nat Rev Immunol 2016

Impact de la mort cellulaire immunogène sur le cycle de l'immunité anti-tumorale



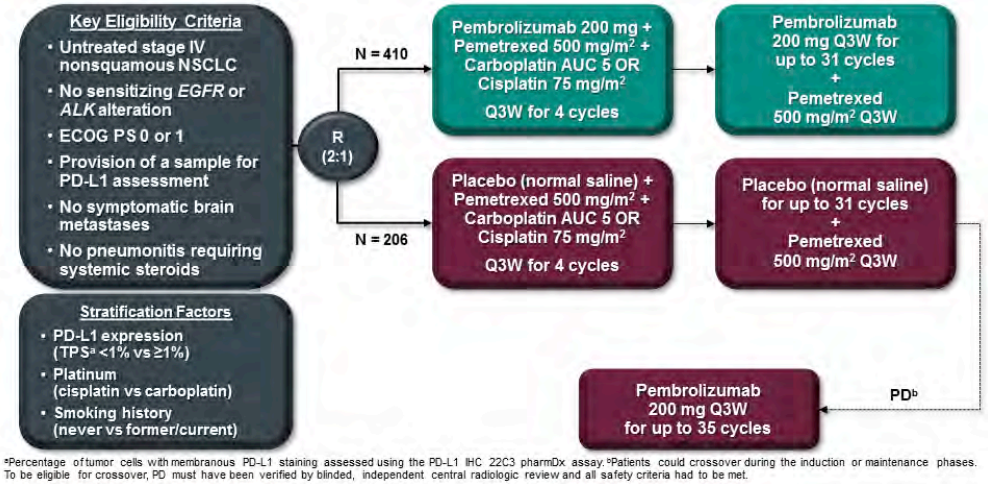
Hanoteau, Med Sci 2016

Rôle des différents cytotoxiques dans la réponse immunitaire anti-tumorale

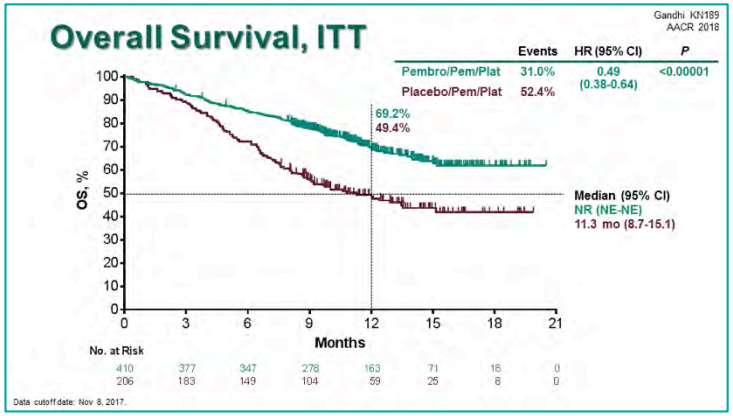


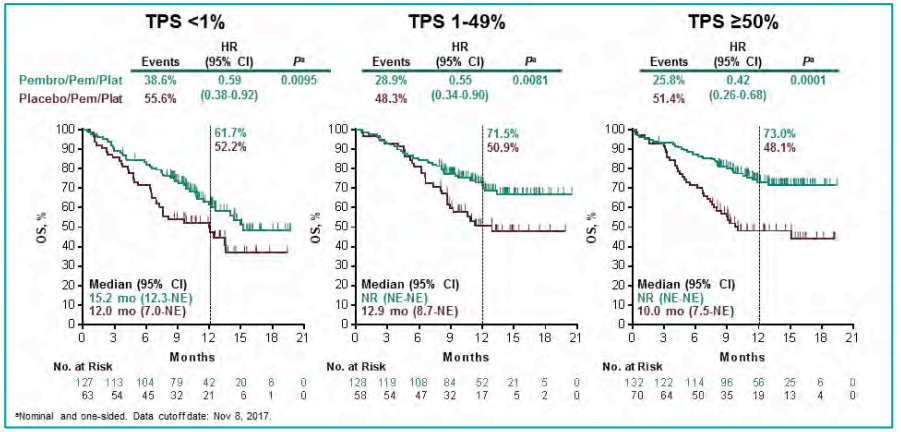
Emmens, CCR 2015

Chemotherapy ± Anti-PD-1
Keynote 189 (Non-Squamous Carcinoma)



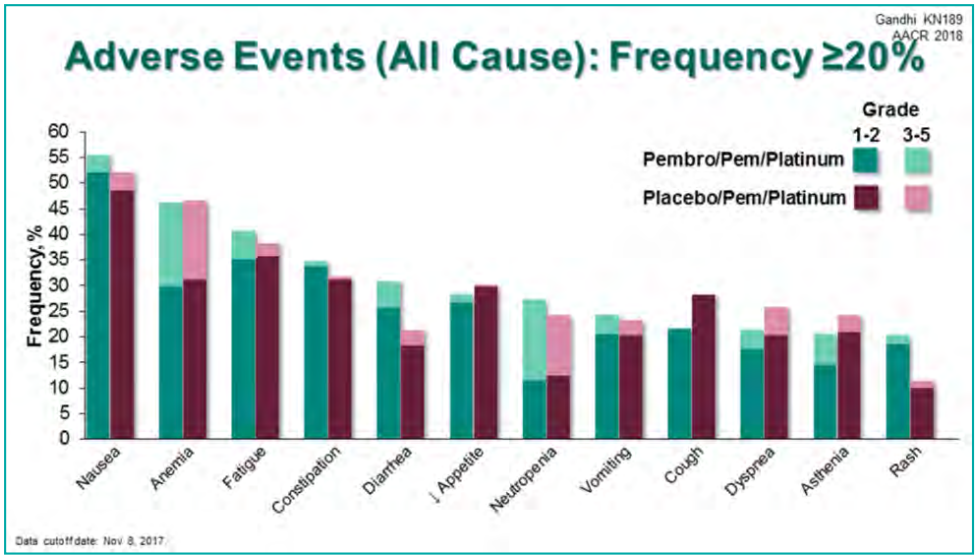
[a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay. [b]Patients could crossover during the induction or maintenance phases. To be eligible for crossover, PD must have been verified by blinded, independent central radiologic review and all safety criteria had to be met.

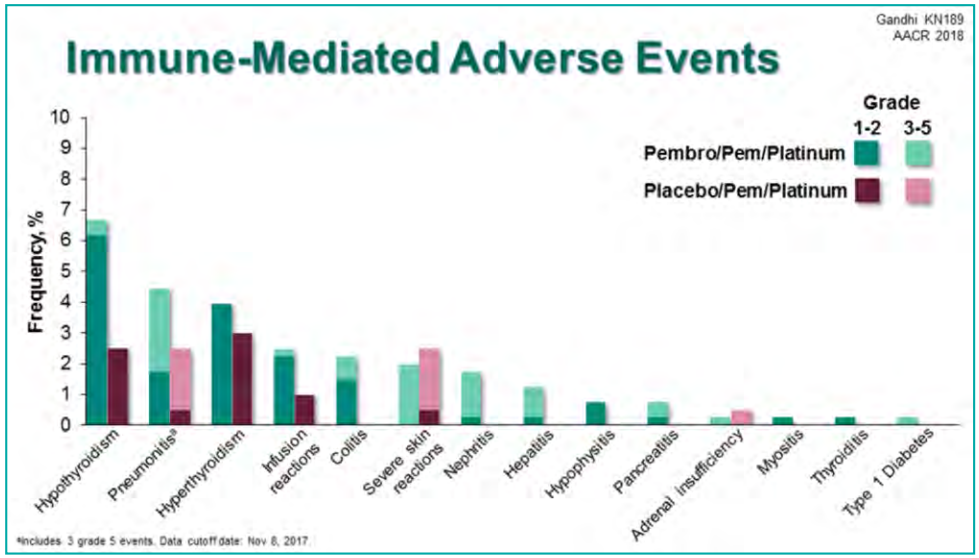




Gandhi KN189, AACR 2018 and NEJM 2018

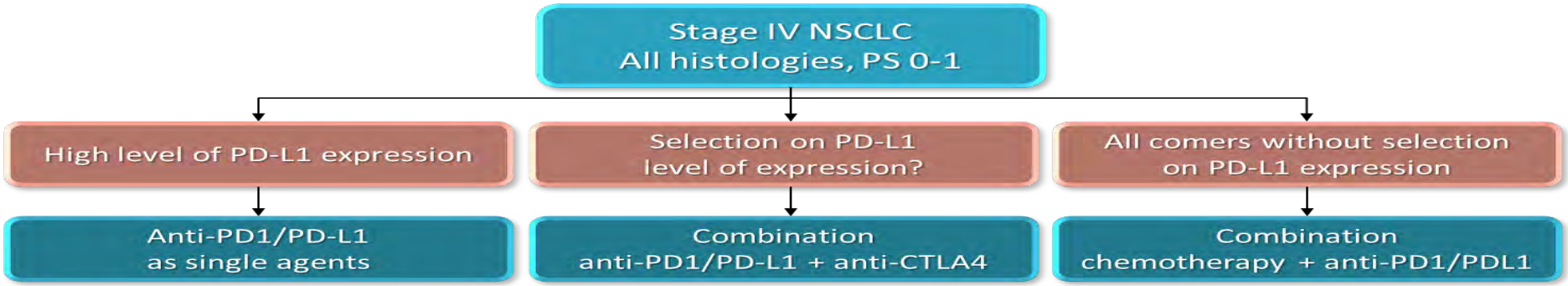
Keynote 189: Tolerance Profile





Gandhi L, NEJM 2018

Immunotherapy in 1st Line Treatment of NSCLC
The three first options



Keynote 024 (PD-L1 ≥50%) (OS)

Checkmate 026 (PD-L1≥5%) (PFS-OS)

Mystic (PD-L1 ≥25%) (PFS)

Keynote 042 (PD-L1 ≥1%) (OS)

Checkmate 227 (PD-L1 ≥1%)

Checkmate 227 (TMB ≥10) (PFS)

Mystic (PD-L1 ≥25%) (PFS)

Neptune

Poseidon

Keynote 21G (Non-Sq) (PFS, OS)

Keynote 189 (Non-Sq) (PFS, OS)

IMPower 150 (Non-Sq) (PFS, OS)

IMPower 130 (Non-Sq) (PFS, OS)

IMPower 132 (Non-Sq) (PFS, OS)

IMPower 131 (Sq) (PFS, OS)

Keynote 407 (Sq) (ORR, PFS, OS)

Checkmate 227 (PD-L1<1%, PFS)

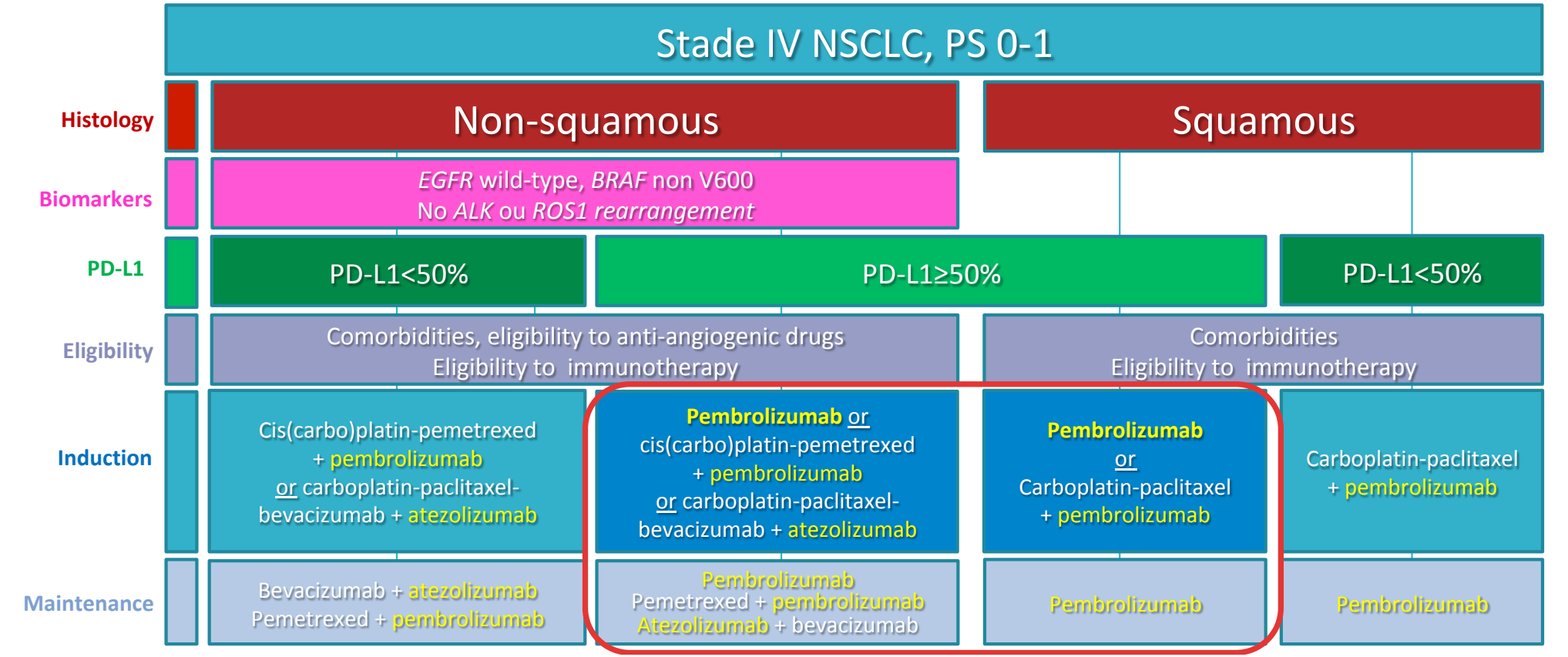
Poseidon

Ongoing study
Positive trial
Negative trial

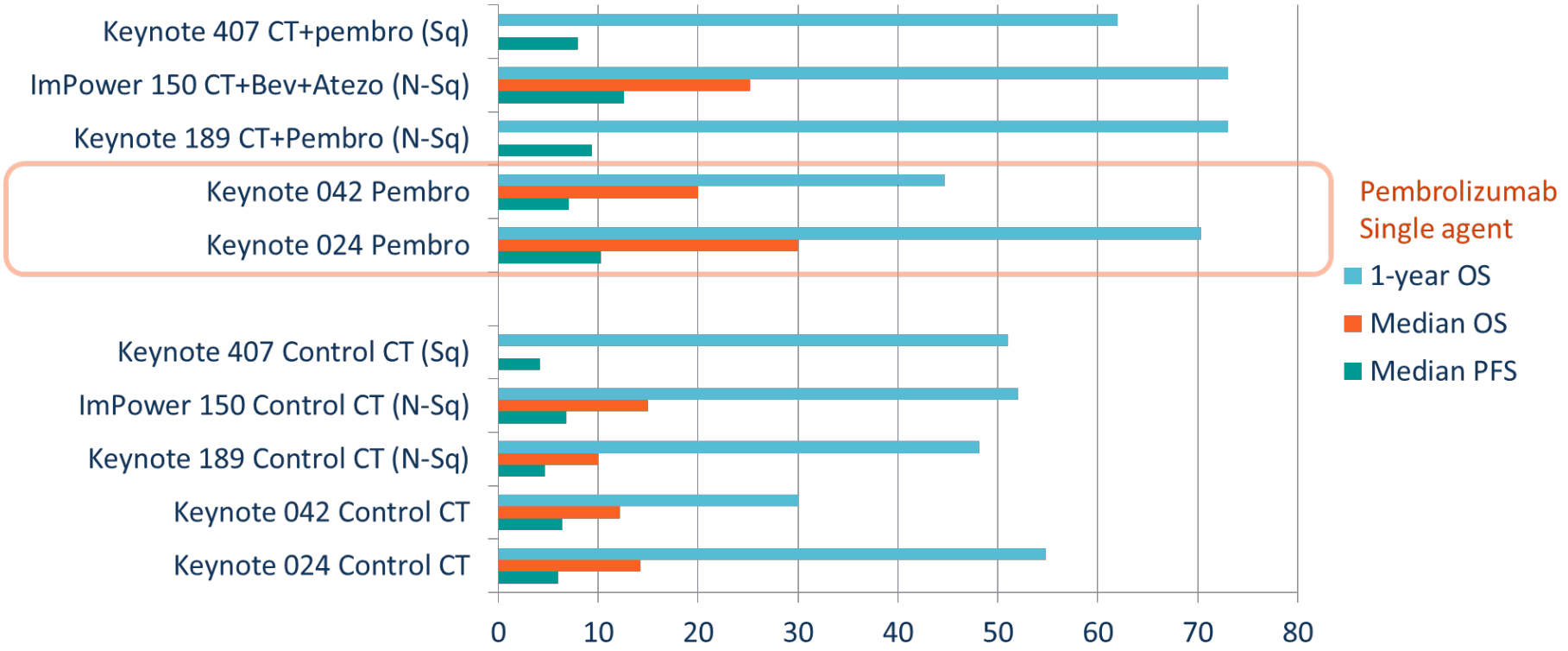
Which Treatment Strategy in 1st Line?

- Three potential strategies: single agent pembrolizumab, chemotherapy + anti-PD(L)-1, ipilimumab + nivolumab
  - Either "one size fits all" : chemotherapy + anti-PD(L)-1PD-L1, regardless of PD-L1 status
  - Or strategy adapted to biomarkers/disease characteristics
    - In order to avoid toxicity from chemotherapy and keep platinum-based doublet for 2nd line
- Histology does not seem to matter for selecting the optimal treatment strategy
  - Only impacts the selection of chemotherapy regimen
- Two independent biomarkers: PD-L1 expression level and TMB

Advanced NSCLC without Oncogenic Addiction
2019 Treatment Algorithm?

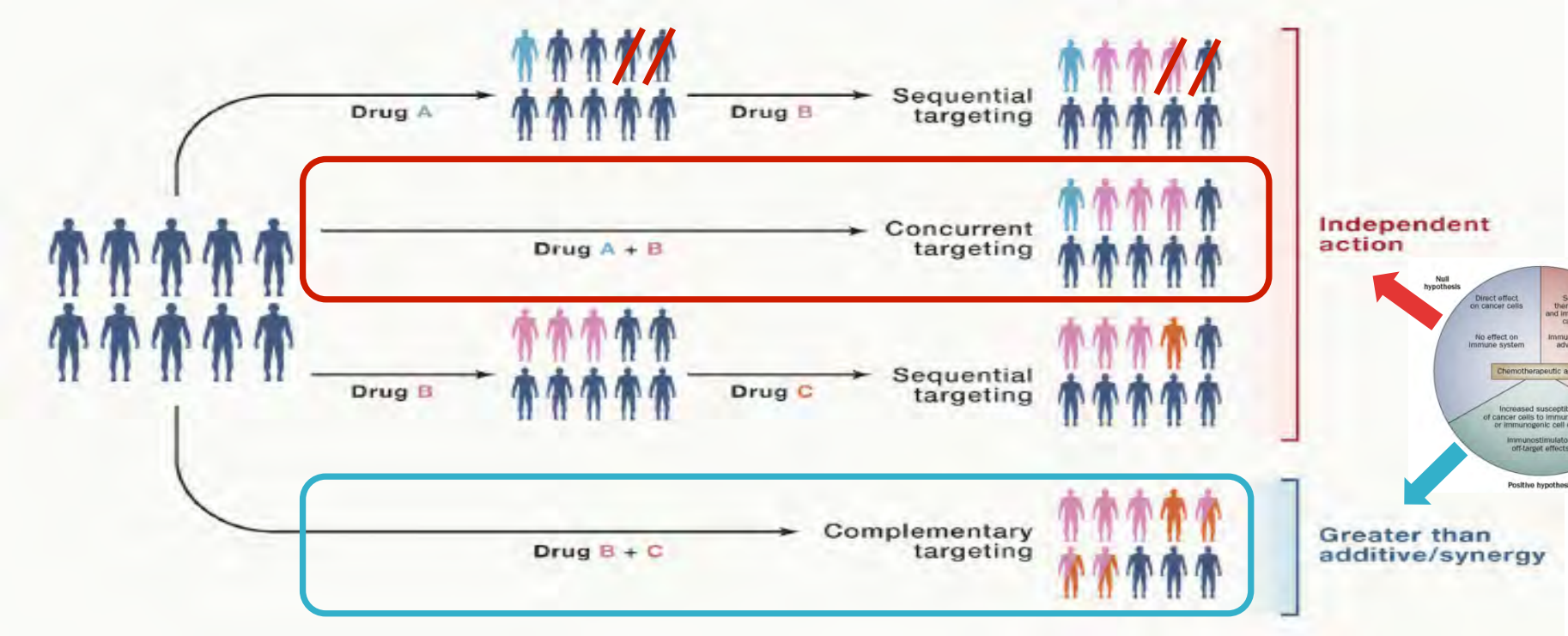


CT + Anti-PD(L)-1 or Anti-PD-1 monotherapy *vs*. CT in **PD-L1 High** NSCLC



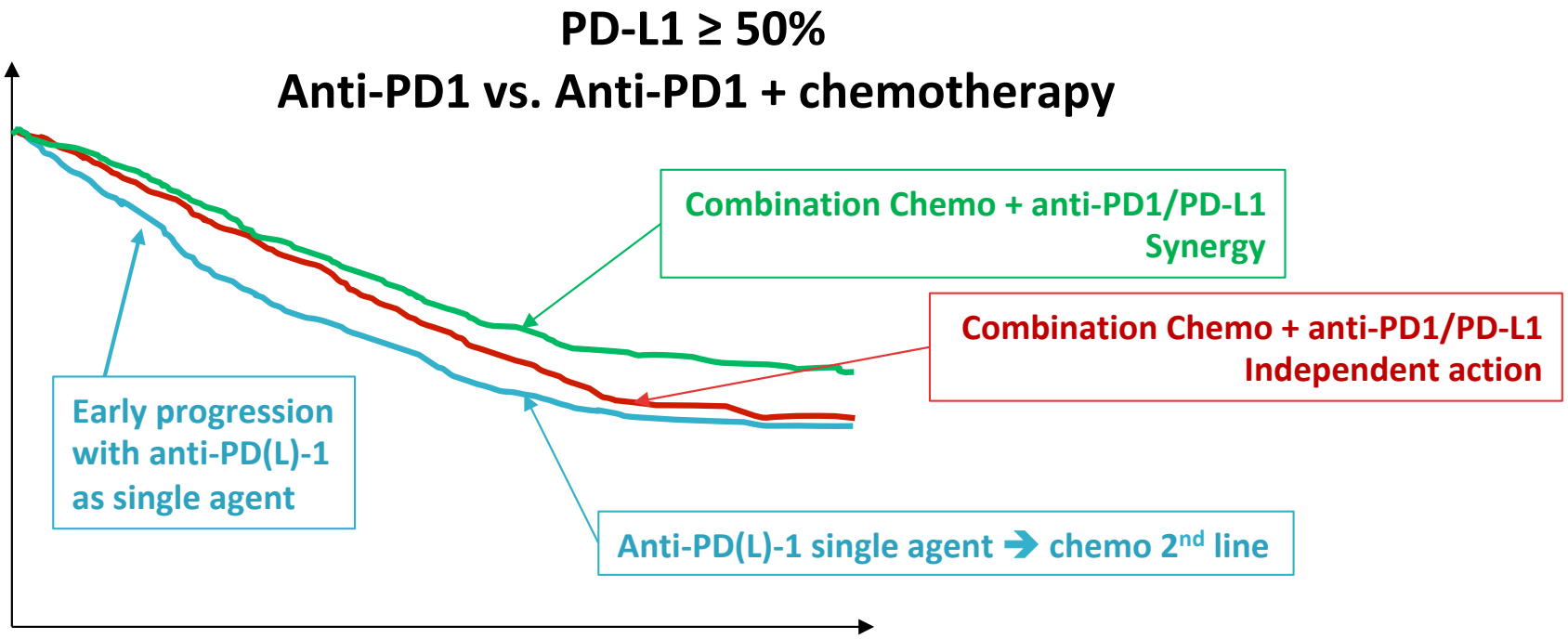
Socinski, NEJM 2018; Gandhi, NEJM 2018; Paz-Ares, ASCO 2018; Jotte, ASCO 2018; Lopes, ASCO 2018; Reck, NEJM 2016

Combination IO + CT
Independent Action or Synergy?

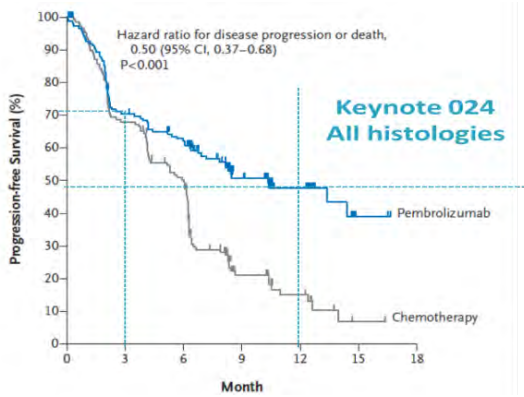


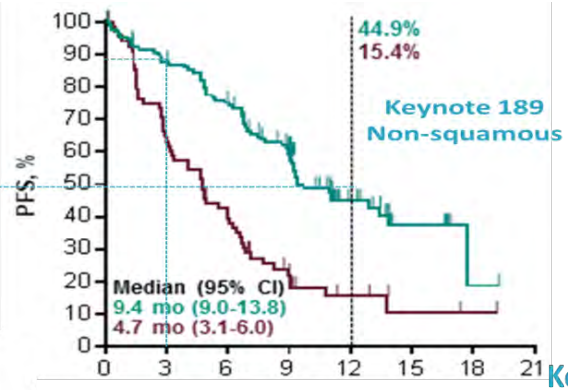
Doroshow, Simon, Cell 2017

Combination IO + CT
Independent Action or Synergy?



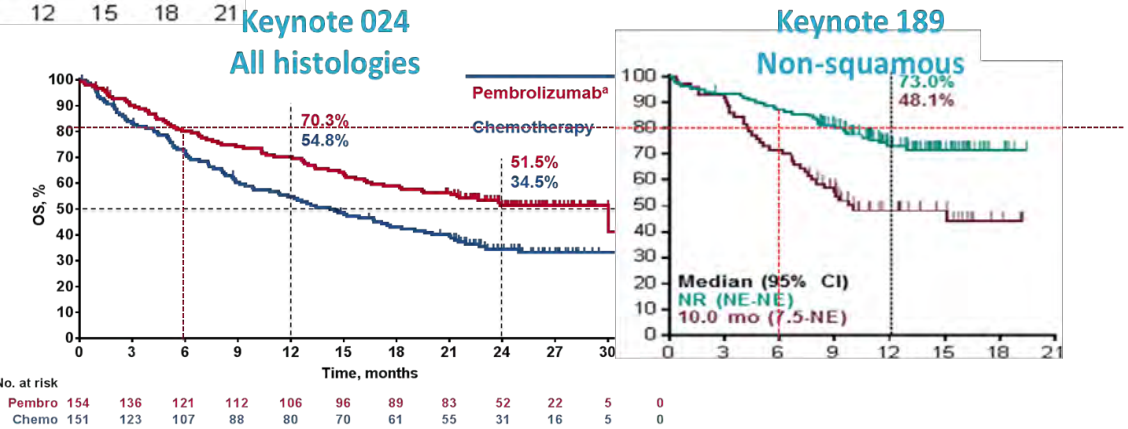
PD-L1 ≥50% : monotherapy or combination with CT?





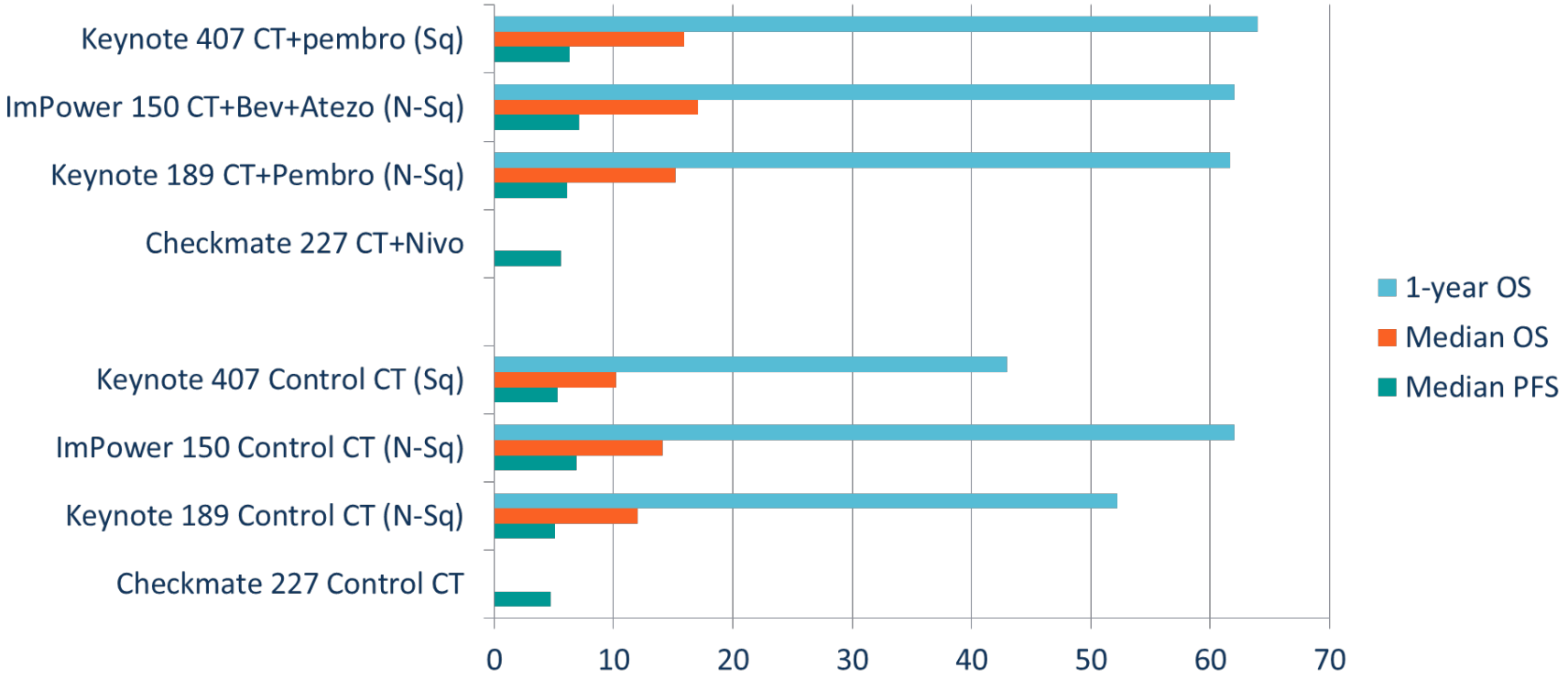
PFS

OS



Reck, NEJM 2016; Gandhi, NEJM 2018

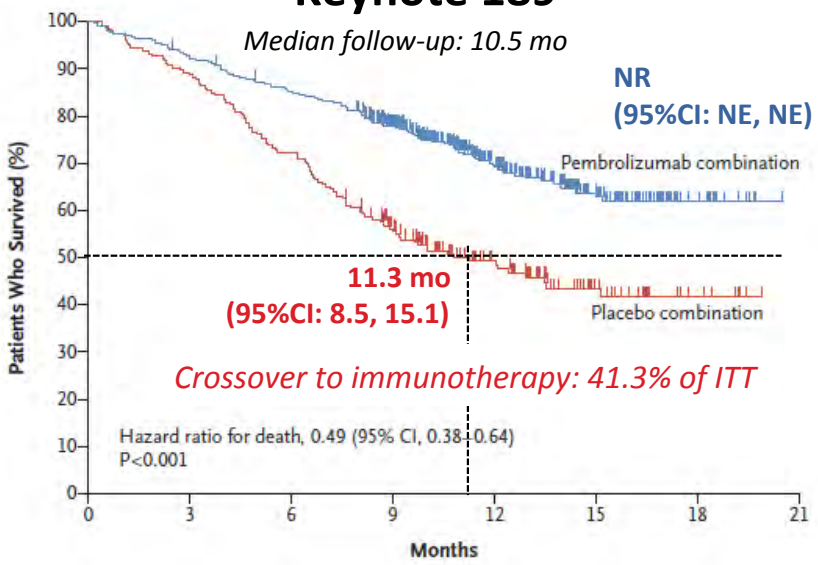
CT + Anti-PD-1/PD-L1 *vs*. CT in **PD-L1 <1%** NSCLC



Socinski, NEJM 2018; Gandhi, NEJM 2018; Paz-Ares, ASCO 2018; Jotte, ASCO 2018; Lopes, ASCO 2018; Reck, NEJM 2016; Borghaei, ASCO 2018

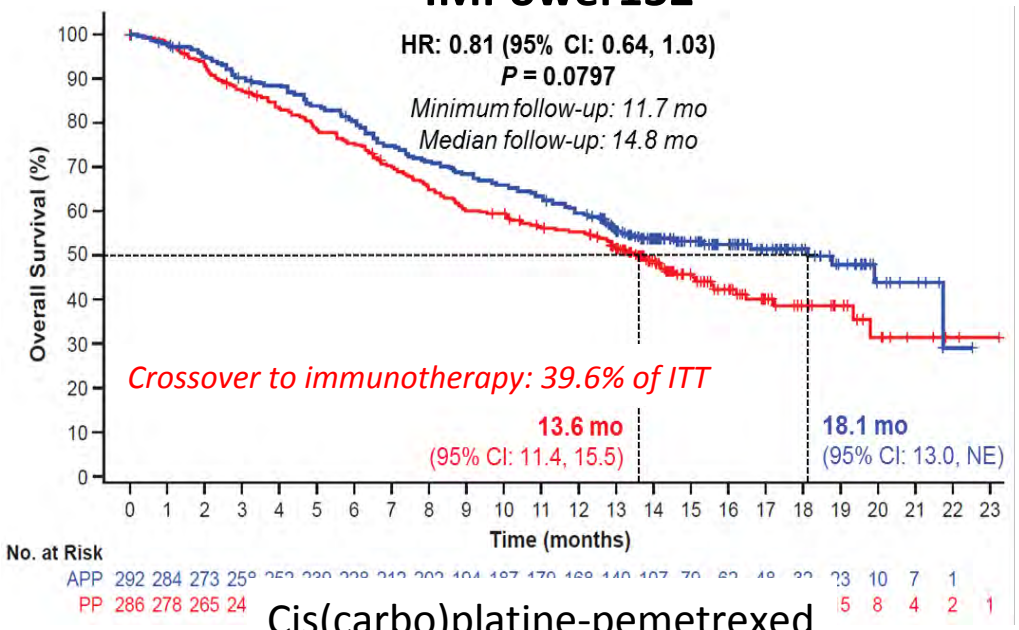
Anti-PD-1 *vs*. Anti-PD-L1?

Keynote 189



Cis(carbo)platine-pemetrexed
± pembrolizumab

IMPower132



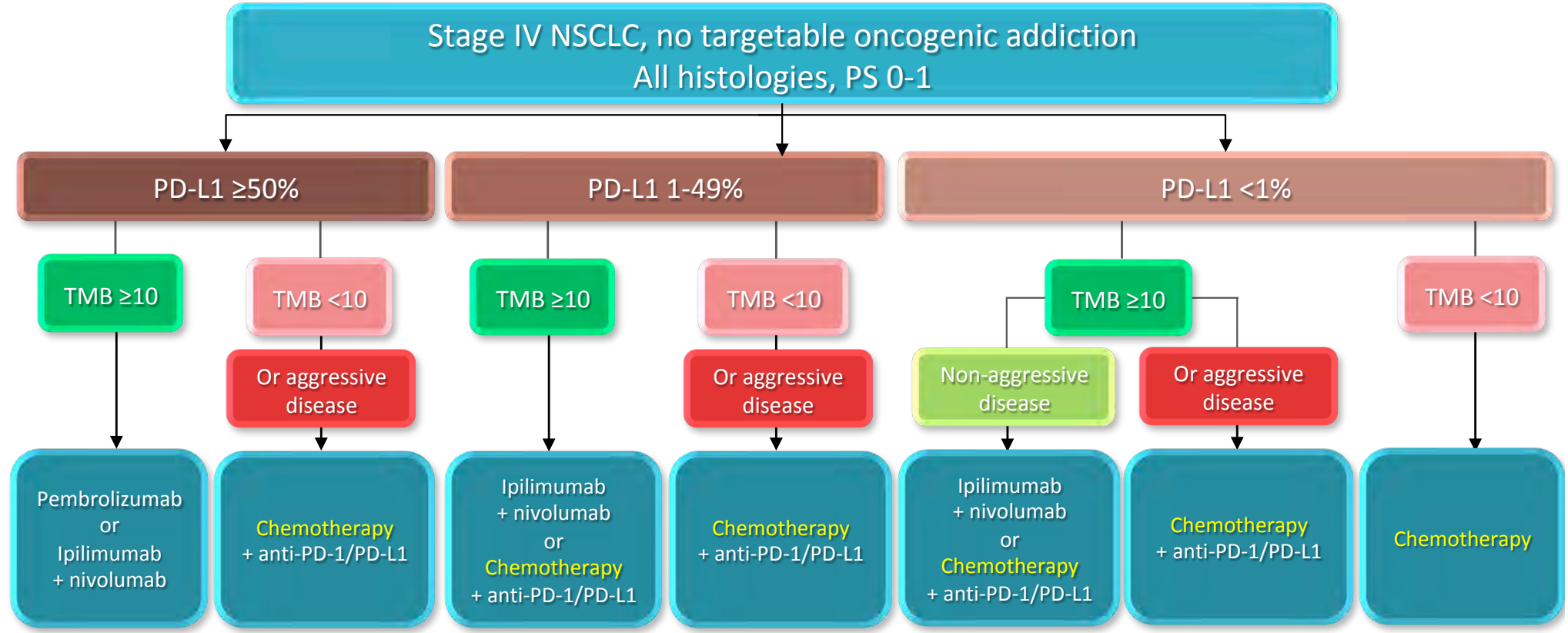
Cis(carbo)platine-pemetrexed
± atezolizumab

Gandhi, NEJM 2018; Papadimitrakopoulou, WCLC 2018

Quelle stratégie en 1ère ligne ?
Le rôle de la chimiothérapie cytotoxique

- Absence de synergie évidente entre CT et anti-PD(L)-1 : effet simplement additif ?
  - Proportion similaire de patients bénéficiant à long terme du pembrolizumab et de l'association CT + pembrolizumab pour les tumeurs PD-L1 ≥50%
  - Synergie possible pour les tumeurs exprimant faiblement ou n'exprimant pas PD-L1
  - Choix du cytotoxique au sein de l'association ? Anti-PD-1 *vs*. Anti-PD-L1 ?
- La chimiothérapie protège d'une progression précoce pour les tumeurs ne répondant pas aux IOs
  - Nécessité en cas de maladie menaçante, de charge mutationnelle faible ou si PD-L1 <50%
  - Pourrait être évitée en cas de haute probabilité de réponse aux anti-PD(L)-1 (TMB et PD-L1 élevés)
- Rôle de la charge mutationnelle dans les associations CT + anti-PD(L)-1 ?
  - Les tumeurs PD-L1 <1% avec TMB <10 mut/Mb pourraient être traitées par chimiothérapie seule

Which Role for Chemotherapy in First-Line Treatment for Stage IV NSCLC without Oncogenic Addiction ?



Improvement of OS in Advanced NSCLC without Targetable Oncogene Addiction