Immunoprofiling, biomarqueurs et cibles moléculaires dans le cancer du poumon

Maurice Pérol
Centre Léon Bérard, Lyon

Avec le soutien du
Groupe Français de Cytogénomique Oncologique

Liens d'intérêt

- Advisory Boards : Roche, Genentech, Eli Lilly, Pfizer, Boehringer-Ingelheim, Clovis Oncology, MSD, Bristol-Myers Squibb, Novartis, Pierre Fabre, Astra-Zeneca
- Institutional Grants: Roche, Astra-Zeneca
- Symposiums: Eli Lilly, Roche, Astra-Zeneca, Pfizer, Amgen, Boehringer-Ingelheim, Bristol-Myers Squibb

Immunoprofiling, biomarqueurs et cibles moléculaires dans le cancer du poumon non à petites cellules

1. La révolution de la médecine de précision dans le CBNPC

- De la découverte des mutations de l'EGFR au changement de l'histoire naturelle de la maladie
- Evolution des techniques : du séquençage Sanger aux biopsies liquides
- Les biomarqueurs à rechercher en 2017

2. La seconde révolution de l'immunothérapie

- Impact des inhibiteurs des points de rétro-contrôle de la réponse immunitaire sur l'algorithme thérapeutique des CBNPC avancés
- La quête des biomarqueurs prédictifs : de PD-L1 à la personnalisation de l'immunothérapie

First Revolution of Treatment Personalization Oncogene Addiction Model: *EGFR* Mutations

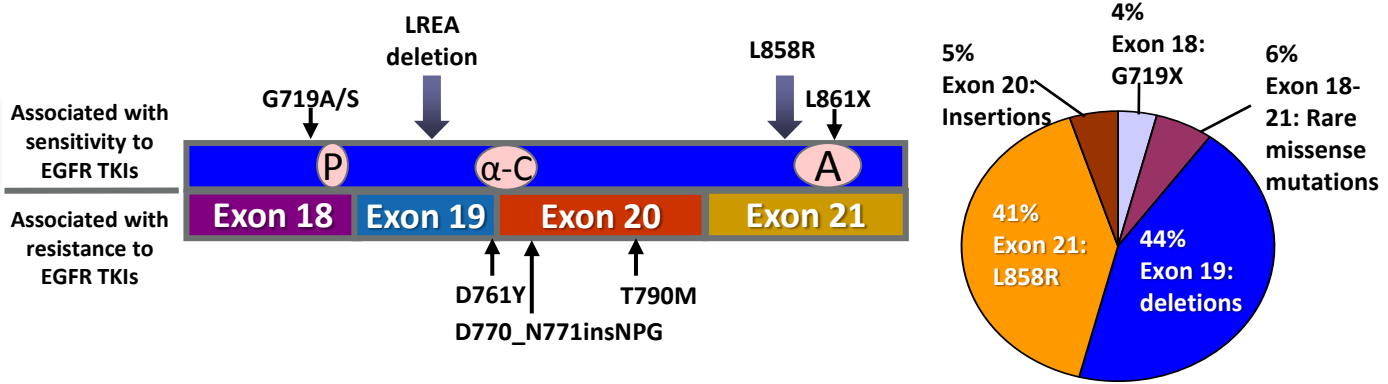
2010

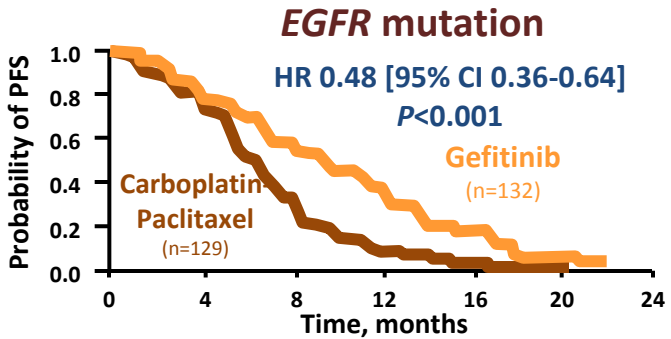
Targeting EGFR

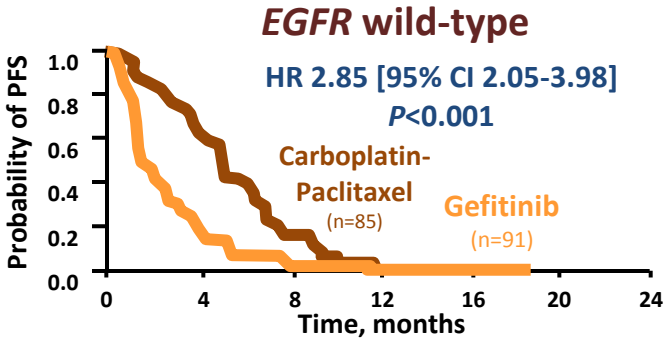
EGFR mutation

Non-squamous

Squamous



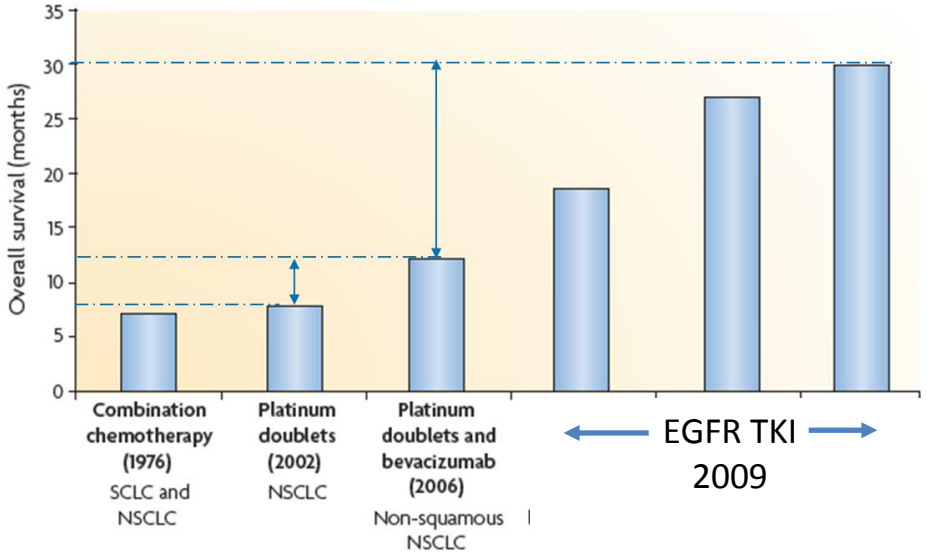




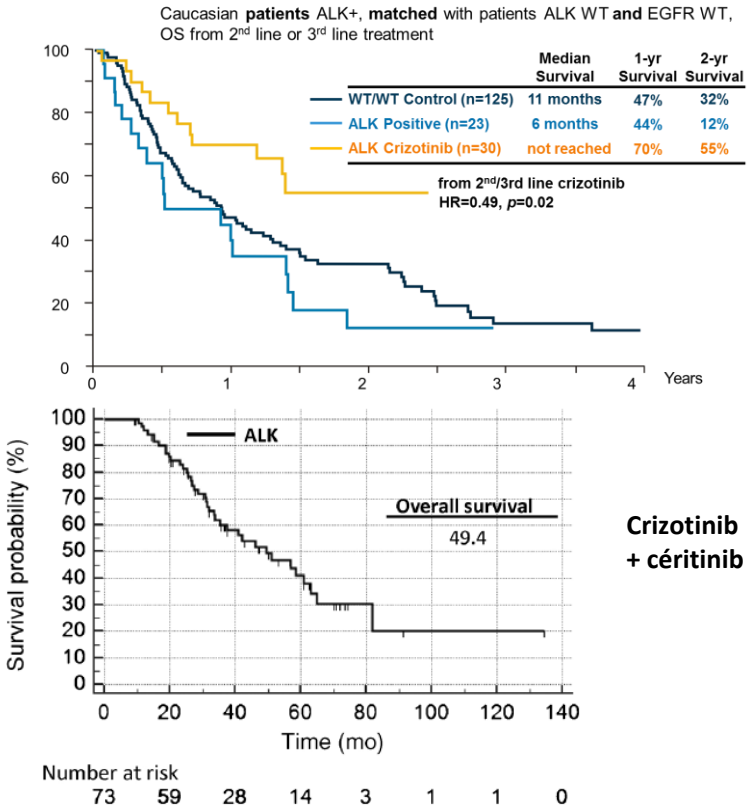
Mok TS, et al. *N Engl J Med*. 2009;361(10):947-957; Riely GJ, et al. *Clin Cancer Res*. 2006;12(24):7232-7241; Shigematsu H, Gazdar AF. *Int J Cancer*. 2006;118(2):257-262.

Impact des traitements ciblés sur l'histoire naturelle de la maladie

Mutations EGFR

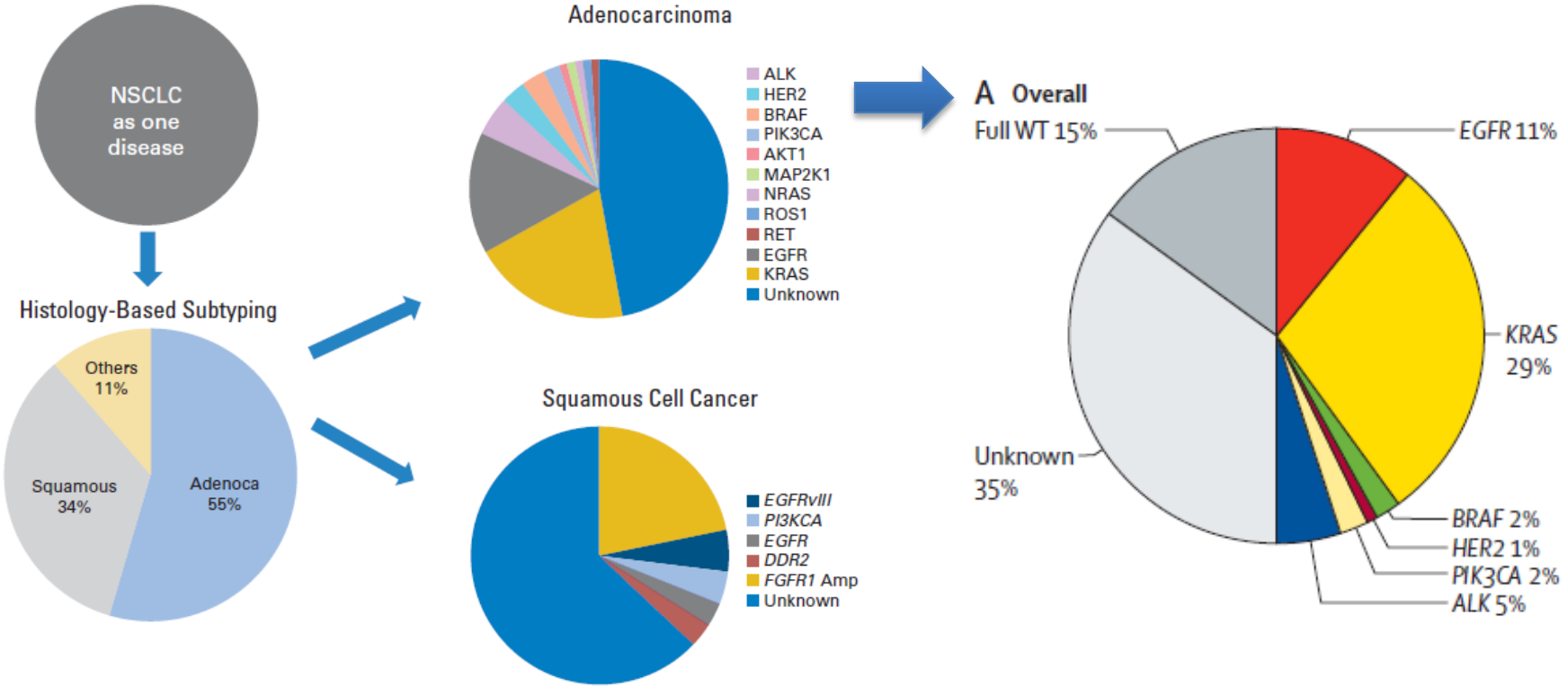


Réarrangement ALK



Crizotinib + céritinib

De la classification histologique à la classification génomique



Li et al., JCO 2013 ; Barlési F et al., Lancet 2016

Immunoprofiling, biomarqueurs et cibles moléculaires dans le cancer du poumon non à petites cellules

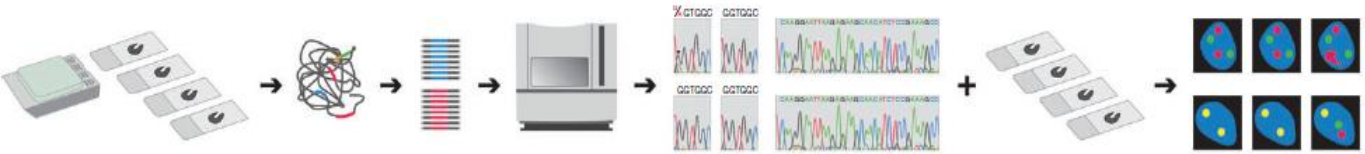
1. La révolution de la médecine de précision dans le CBNPC

- De la découverte des mutations de l'EGFR au changement de l'histoire naturelle de la maladie
- Evolution des techniques : du séquençage Sanger aux biopsies liquides
- Les biomarqueurs à rechercher en 2017

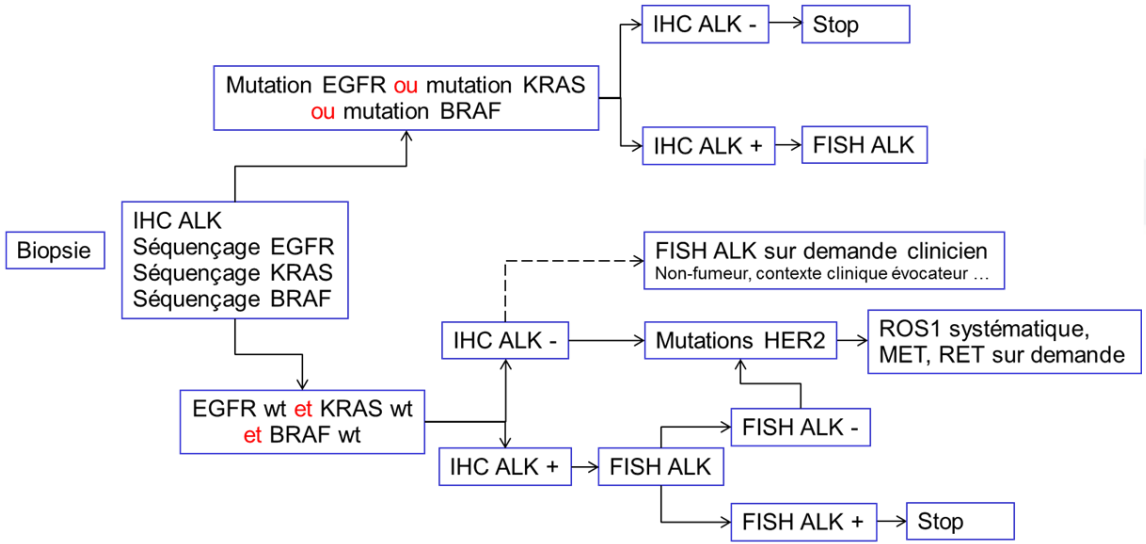
2. La seconde révolution de l'immunothérapie

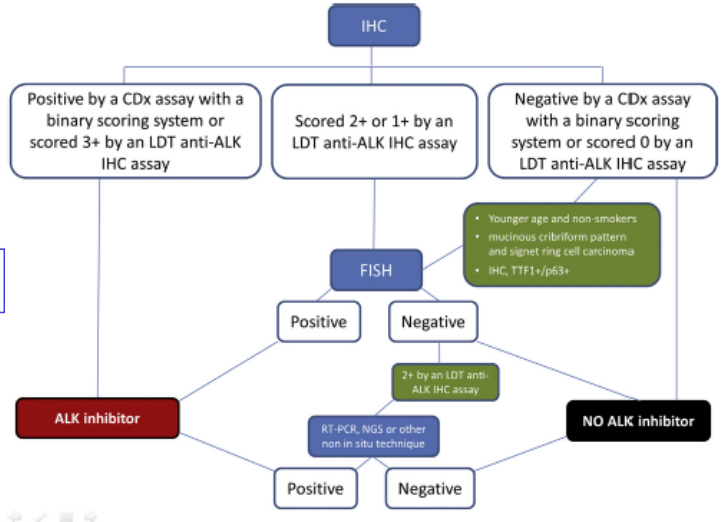
- Impact des inhibiteurs des points de rétro-contrôle de la réponse immunitaire sur l'algorithme thérapeutique des CBNPC avancés
- La quête des biomarqueurs prédictifs : de PD-L1 à la personnalisation de l'immunothérapie

Evolution des techniques de biologie moléculaire : séquençage Sanger



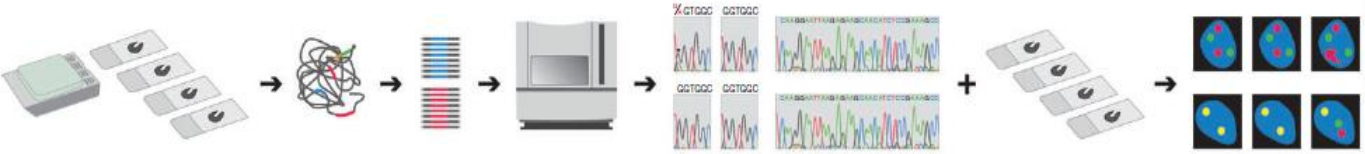
- Séquençage séparé de chaque région exonique d'intérêt : mutations ponctuelles, insertions, délétions
- Quantité importante tissu
- Sensibilité insuffisante si faible fréquence allélique
- FISH nécessaire pour réarrangements



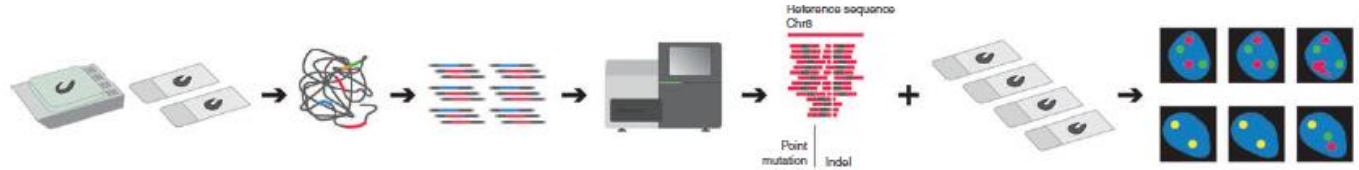


Heuckmann, Ann Oncol 2015; Marchetti, JTO 2016

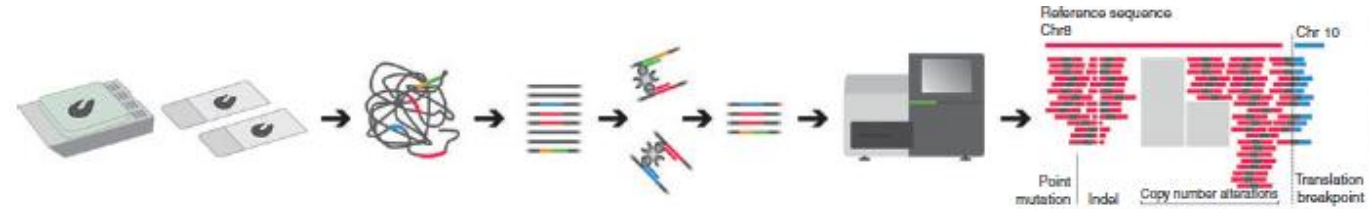
Evolution des techniques de biologie moléculaires



- Séquençage séparé de chaque région exonique d'intérêt : mutations ponctuelles, insertions, délétions
- Quantité importante tissu
- Sensibilité insuffisante si faible fréquence allélique
- FISH nécessaire pour réarrangements



- NGS par PCR amplicon "multiplexée"
- Faible quantité de tissu
- Haute sensibilité
- FISH nécessaire pour réarrangements



- NGS par capture d'hybrides : enrichissement des régions génomiques d'intérêt sans amplification par PCR
- Faible quantité de tissu
- Haute sensibilité
- Détecte toutes les altérations génomiques

Heuckmann, Ann Oncol 2015

Aujourd'hui : approche ciblée du NGS
Panel Inca

GENE	Targets	Molecules	Utility
AKT1	3	AKT inhibitors	clinical trials
ALK	23+24+25	Crizotinib, ALK inhibitors	AcSé, clinical trials
BRAF	11+15	vemurafenib, dabrafenib	AMM
EGFR	18+19+20+21	anti EGFR	AMM
ERBB2	20	trastuzumab, neratinib	clinical trials
ERBB4	E452K, R393W	Afatinib	clinical trials
FGFR2	S252, N549, K659	FGFR inhibitors	clinical trials
FGFR3	7+9+14 (R248 àS249 et G370 à Y3F7G3F)	FGFR inhibitors	clinical trials
HRAS	2+3+4	MEK inhibitor	clinical trials
KIT	8+9+11+13+17+18	imatinib	AMM
KRAS	2+3+4	panitumumab et cetuximab	AMM
MAP2K1 (MEK1)	2	MEK inhibitors	clinical trials
MET	2+14 to 20	crizotinib	AcSé
NRAS	2+3+4	panitumumab, MEK inhibitors, BRAF inhibitors	pré-AMM, clinical trials
PDGFRA	12+14+18	imatinib	AMM
PIK3CA	10 + 21	PI3K inhibitors	clinical trial

- Set de gènes d'intérêt
- Panels commerciaux/custom
- FFPE et 10-30 ng d'ADN
- Mutations et CNV
- Mise en place simple : conservation du même circuit de soins
- Volume de données réduit
- Augmentation du délai de résultats ?

Turnaround time, days	18,679*	From sample collection to initiation of analysis	8.0 (4.0-16.0)	-
(median, Q1-Q3)		From initiation of analysis to report of results	11.0 (7.0-16.0)	-

*, the turnaround times were reported by analysts and not by patients.

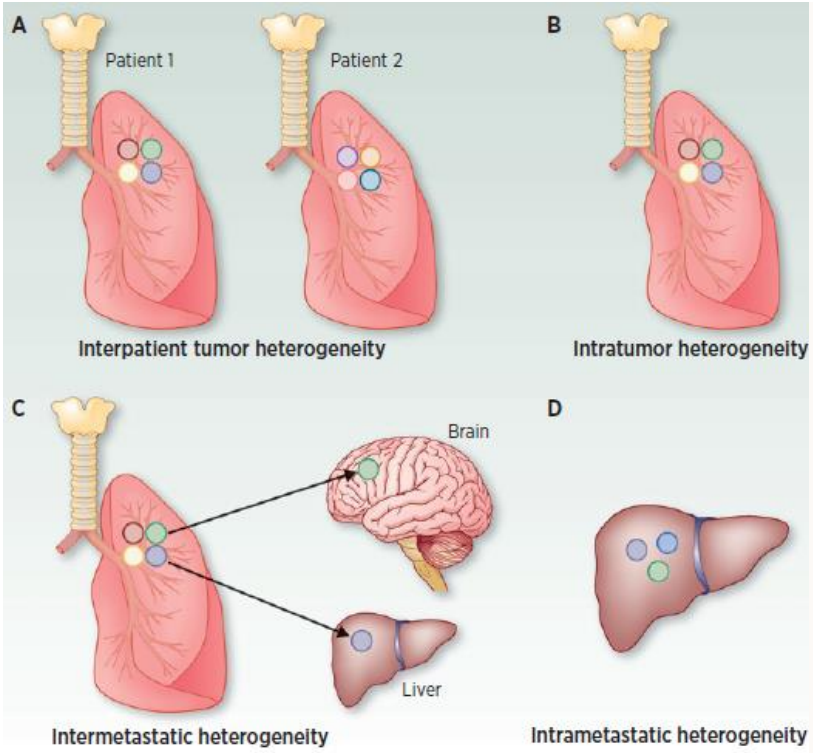
	Illumina					Ion Torrent (Life Technologies)	
	HiSeq 4000	HiSeq 3000	HiSeq 2500	NextSeq 500	MiSeq	Ion Proton	Ion PGM
Maximum data yield	1,500 Gb	750 Gb	1,000 Gb	120 Gb	15 Gb	10 Gb	2 Gb
Maximum run time	3.5 days	3.5 days	6 days	29 hours	55 hours	4 hours	7.3 hours

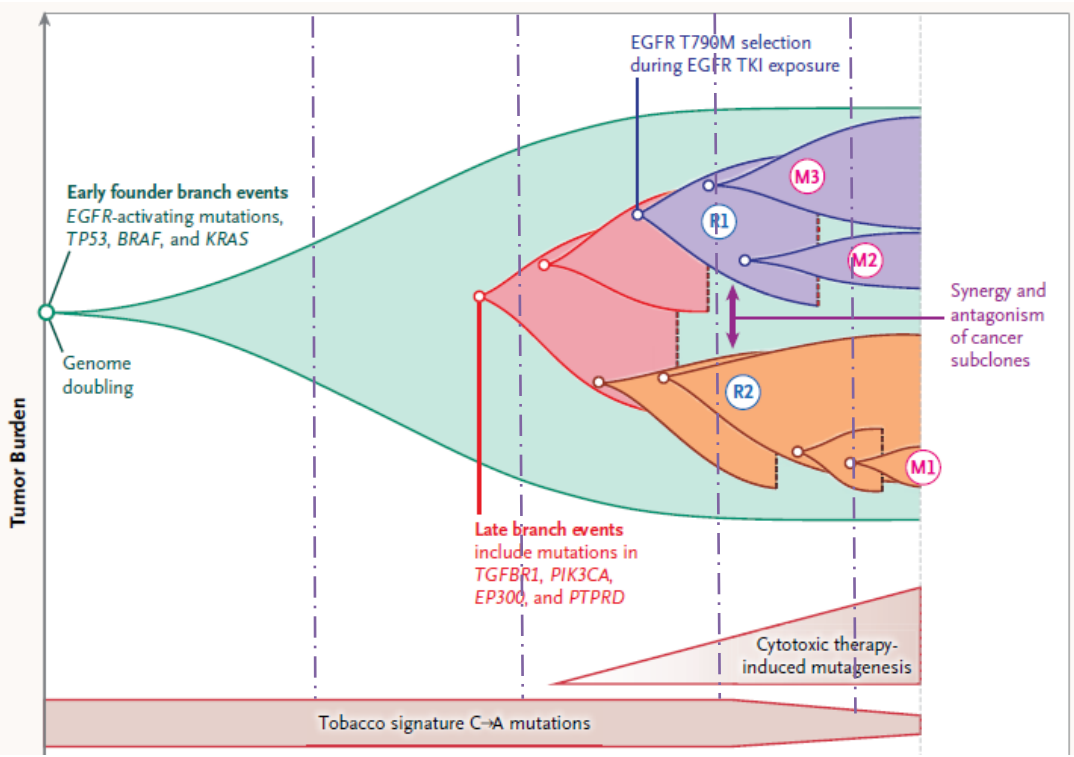
Parikh, F et al, Lancet 2016

Les limites de l'approche "génomique" des CBNPC

- La présence de "drivers" oncogéniques concerne une minorité des CBNPC (tabagisme)
- Matériel tumoral disponible en quantité faible
  - Gestion des prélèvements de petite taille
  - Fixation en paraffine : artéfacts si amplification par PCR
  - Différents types d'altérations génétiques : challenge technologique
  - Marqueurs de substitution +++ : CTC, cfDNA
- Sensibilité accrue des techniques : interprétation des clones minoritaires ?
- Coût des nouvelles technologies, structuration en bio-informatique
- Hétérogénéité tumorale, spatiale et temporelle : limite à la représentativité des prélèvements

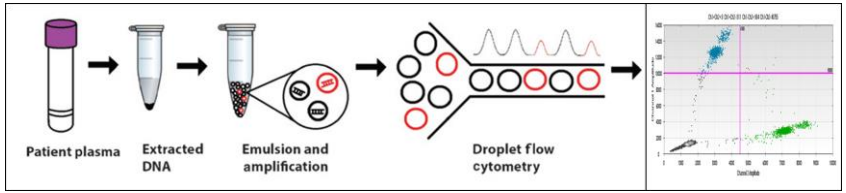
Hétérogénéité tumorale spatiale et temporelle

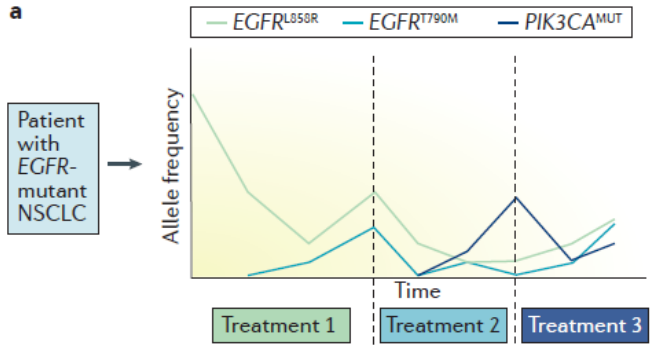


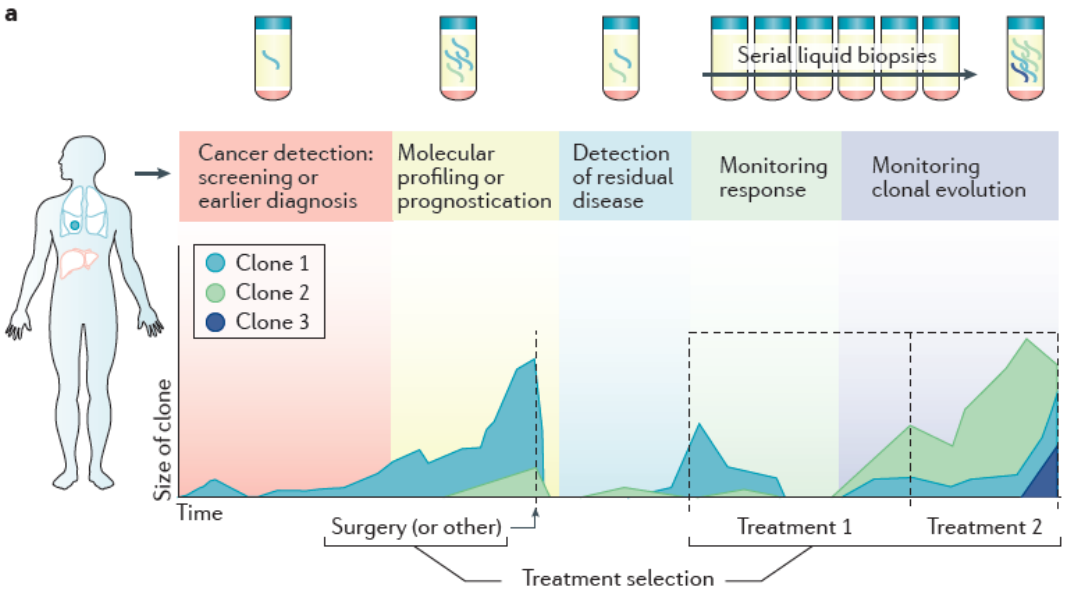


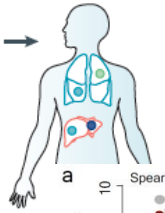
Jamal-Hanjani M et al., CCR 2015; Swanton C , Govindan R, NEJM 2016

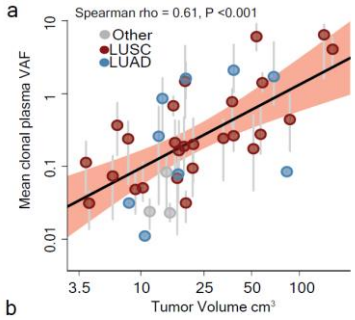
Applications de l'utilisation de l'ADN tumoral circulant

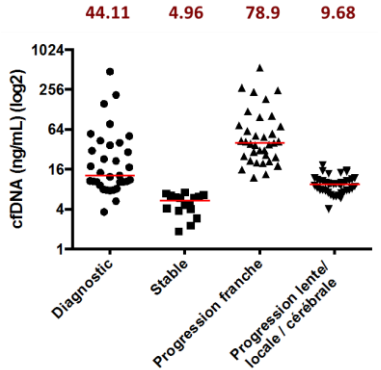












Wan, Nat Rev Cancer 2017; Haddad V, Swalduz A et al. in preparation; Abbosh, Nature 2017

Immunoprofiling, biomarqueurs et cibles moléculaires dans le cancer du poumon non à petites cellules

1. La révolution de la médecine de précision dans le CBNPC

- De la découverte des mutations de l'EGFR au changement de l'histoire naturelle de la maladie
- Evolution des techniques : du séquençage Sanger aux biopsies liquides
- Les biomarqueurs à rechercher en 2017

2. La seconde révolution de l'immunothérapie

- Impact des inhibiteurs des points de rétro-contrôle de la réponse immunitaire sur l'algorithme thérapeutique des CBNPC avancés
- La quête des biomarqueurs prédictifs : de PD-L1 à la personnalisation de l'immunothérapie

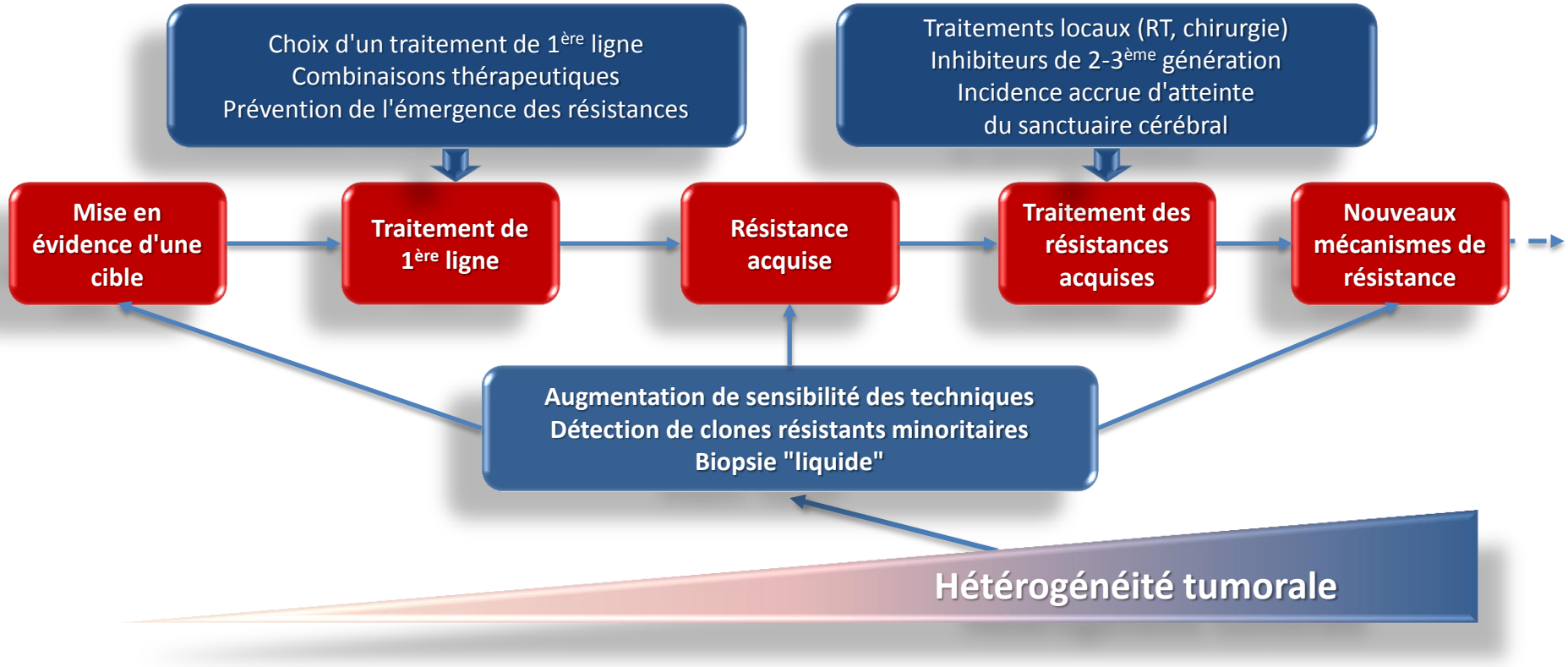
Targetable Genetic Alterations in Lung Adenocarcinoma Affecting First-Line Therapy

	Genetic alteration		Targeted drugs	Resistance to 1st generation	Resistance to 2nd generation
1st line	EGFR mutations	Del 19, L858R, G719, L861Q, T790M, S768I, exon 20 ins.	Gefitinib, erlotinib, afatinib, dacomitinib, …	T790M, MET amplification or HER2 amplification, bypass, SCLC …	C797S, L798I, L718Q … MET amplification, HER2, bypass, SCLC …
	ALK rearrangement		Crizotinib, ceritinib, alectinib, brigatinib, lorlatinib, entrectinib …	ALK mutations, bypass	ALK mutations ++, bypass
	ROS1 rearrangement		Crizotinib, ceritinib, lorlatinib, entrectinib, brigatinib	ROS1 mutations	?
	BRAF mutation	V600E	Dabrafenib + trametinib Vemurafenib,	?	?

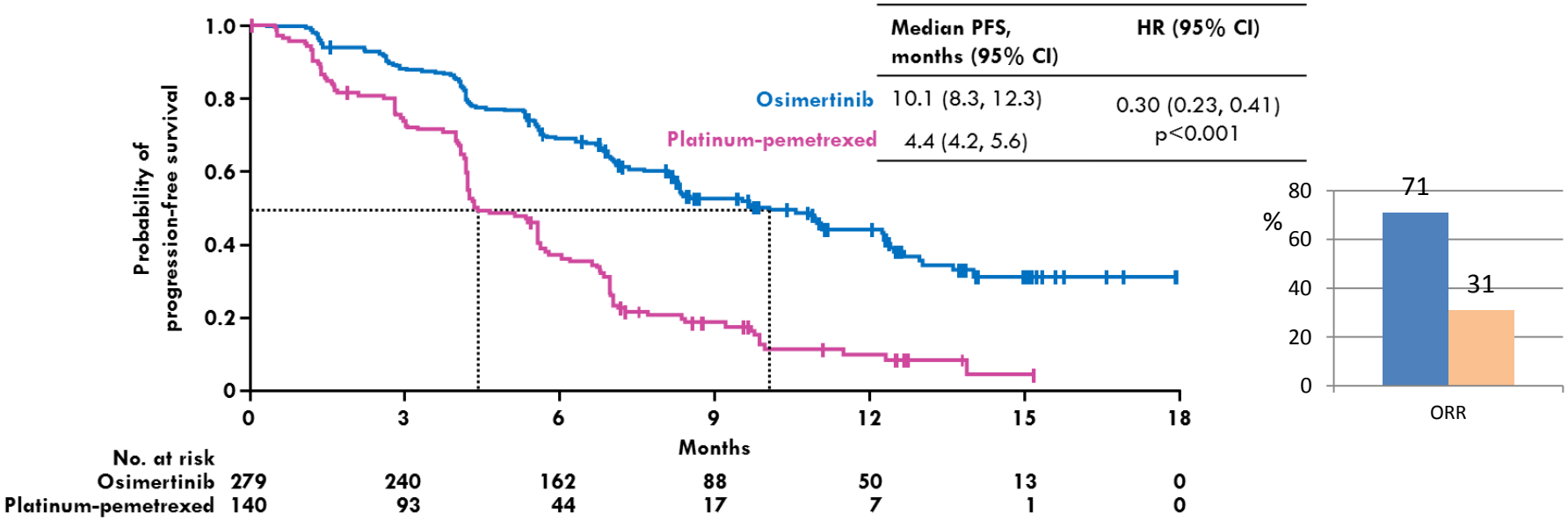
Targetable Genetic Alterations in Lung Adenocarcinoma Affecting 2nd and Further Lines of Treatment

	Genetic alteration		Targeted drugs	Resistance to 1st generation
2nd line and further	HER2 mutation	Exon 20 mutations	Trastuzumab, TDM1, afatinib, dacomitinib, lapatinib, …	?
	MET exon 14 mutation	"Skipping" exon 14 mutation	Crizotinib, capmatinib, savolitinib, cabozantinib …	?
	MET amplification		Crizotinib, capmatinib, savolitinib, cabozantinib …	?
	RET rearrangement		Vandetanib, cabozantinib, alectinib, lenvatinib	?
	NTRK rearrangement		Entrectinib, larotrectinib	?

Stratégie thérapeutique en cas de driver oncogénique impactant la 1ère ligne



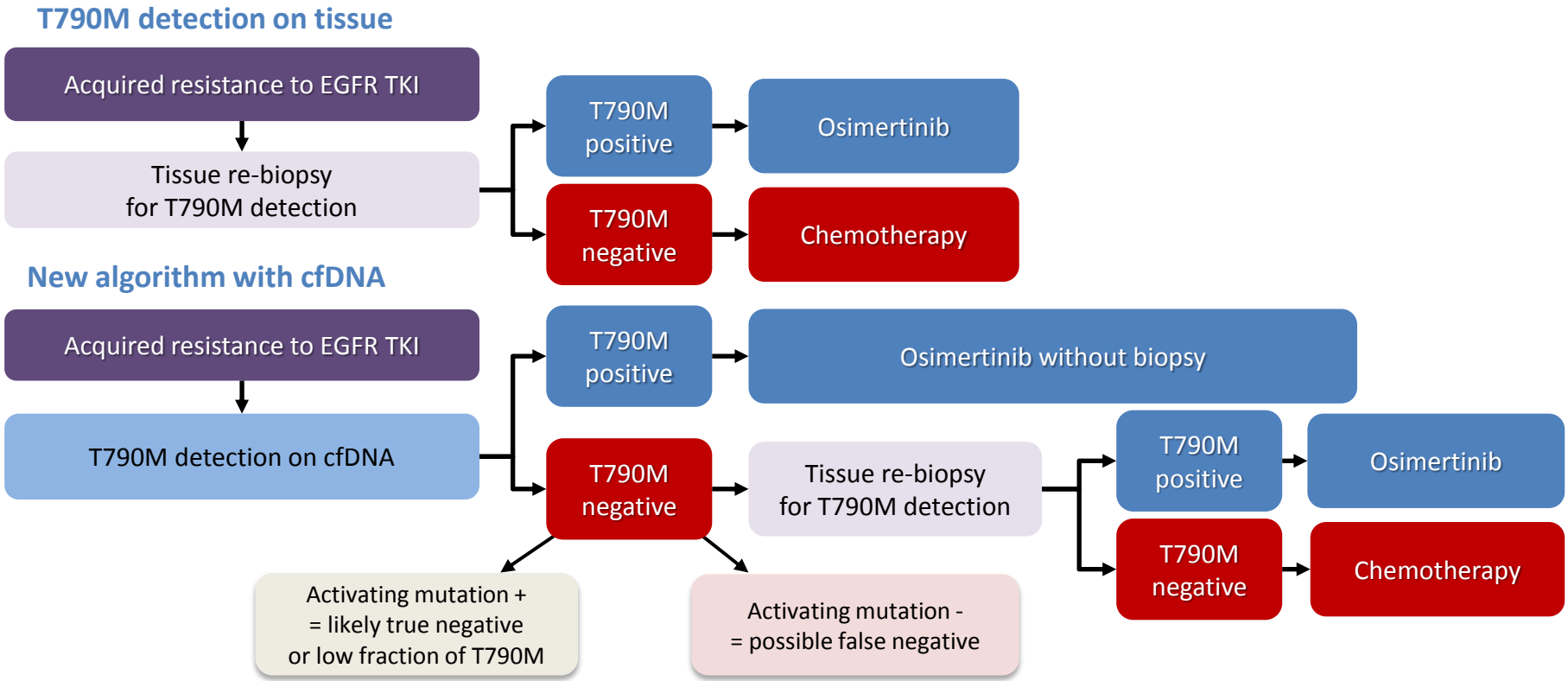
AURA3 Primary Endpoint: Osimertinib *vs.* Chemotherapy in T790M+ Patients: PFS by Investigator Assessment



- Analysis of PFS by BICR was consistent with the investigator-based analysis: **HR 0.28** (95% CI 0.20, 0.38), p<0.001; median PFS 11.0 vs 4.2 months.

Mok, NEJM 2016

Impact of plasma cfDNA on T790M Detection Algorithm



Adapted from Oxnard *et al.*, ELCC 2016

Immunoprofiling, biomarqueurs et cibles moléculaires dans le cancer du poumon non à petites cellules

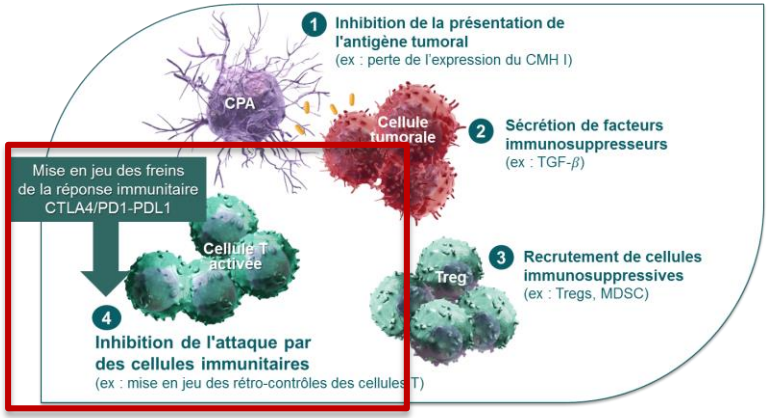
1. La révolution de la médecine de précision dans le CBNPC

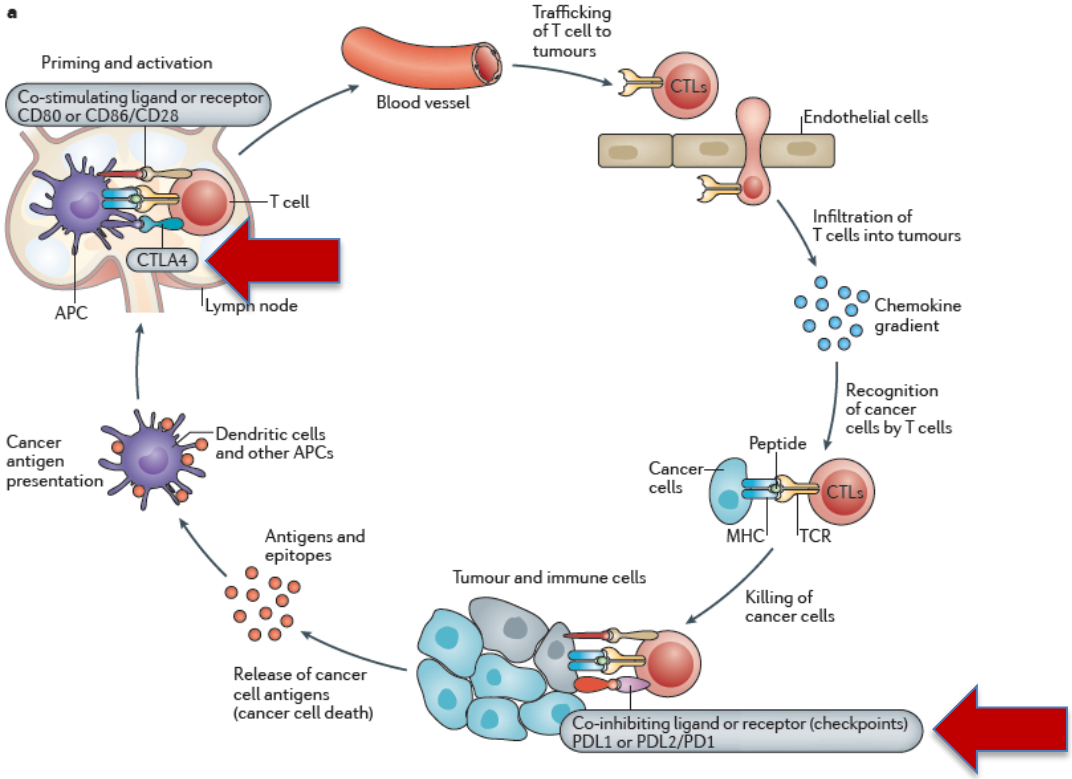
- De la découverte des mutations de l'EGFR au changement de l'histoire naturelle de la maladie
- Evolution des techniques : du séquençage Sanger aux biopsies liquides
- Les biomarqueurs à rechercher en 2017

2. La seconde révolution de l'immunothérapie

- Impact des inhibiteurs des points de rétro-contrôle de la réponse immunitaire sur l'algorithme thérapeutique des CBNPC avancés
- La quête des biomarqueurs prédictifs : de PD-L1 à la personnalisation de l'immunothérapie

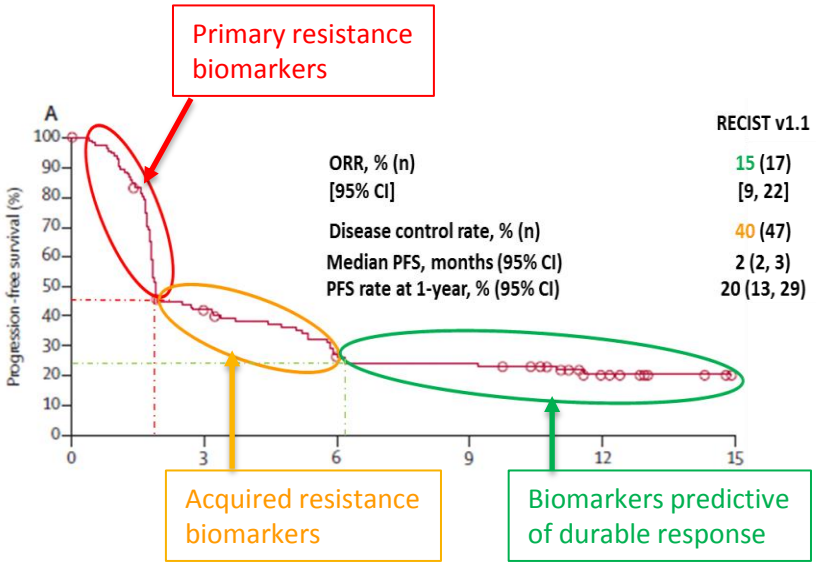
Le cycle de l'immunité anti-tumorale
Site d'action des inhibiteurs de checkpoints



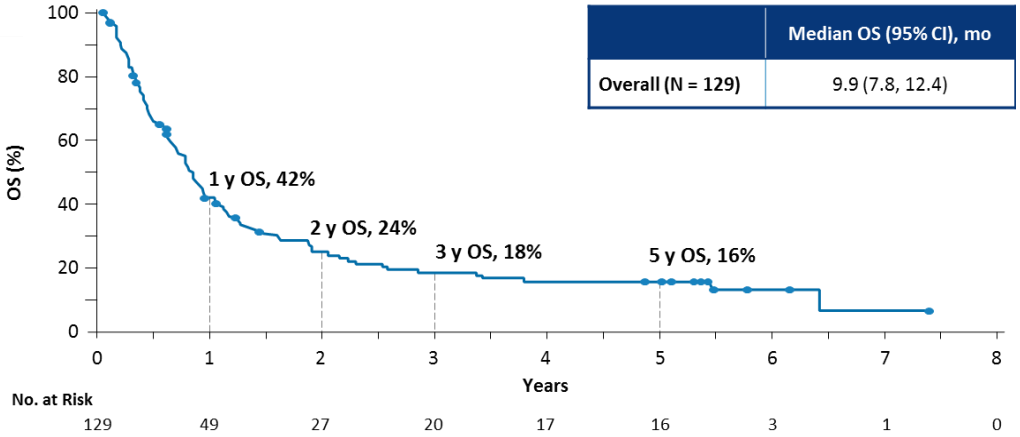


Hackl et al., Nat Rev Genetics 2016

Nivolumab: PFS and Long Term Survival in NSCLC



Checkmate 063: Nivolumab as ≥ 3rd Line
in Advanced Squamous Cell Carcinoma



5-Year Estimates of OS
CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC

Rizvi, Lancet Oncol 2015; Brahmer, AACR 2017

Comparative Analysis of Phase III Studies in Pre-Treated Patients

	CheckMate 017 Nivolumab vs. docetaxel	CheckMate 057 Nivolumab vs. docetaxel	KEYNOTE-010 Pembrolizumab (10mg/kg or 2mg/kg) vs. docetaxel	OAK Atezolizumab vs. docetaxel
PD-L1 selected	No	No	**Yes (TPS ≥1%)**	No
Study size, n	272 (135 *vs.* 137)	582 (292 *vs.* 290)	1,033 (346 *vs.* 344 *vs.* 343)	1,225 (425 *vs.* 425)*
Histology	**Squamous**	**Non-squamous**	**All-comers**	**All-comers**
Line of therapy, % 2L 3L >3L	 100 0 0	 88 **11** <1	 69 **20** **9**	 75 **25** 0
Crossover from chemo arm to study IO, %	4	4	Not permitted	Not permitted
Median OS, months HR *vs.* docetaxel (p value)	**9.2** *vs.* 6.0 **0.62** (p=0.0004)	**12.2** *vs.* 9.5 **0.75** (p<0.001)	**12.7** *vs.* **10.4** vs. 8.5 2mg/kg: **0.71** (p=0.0008) 10mg/kg: **0.61** (p<0.0001)	**13.8** *vs.* 9.6 **0.73** (p=0.0003)
18-months survival	**28%** *vs.* 13%	**39%** *vs.* 23%	**43%** *vs.* **38%** *vs.* 23%	**40%** *vs.* 27%
24-months survival	**23%** *vs.* 8%	**29%** *vs.* 16%	**37.5%** *vs.* **30.1%** *vs.* 14.5%	

Adapted from Paz-Ares, WCLC 2016; Borghei, NEJM 2015; Barlesi , ESMO 2016; Rittmeyer, Lancet 2016; Herbst, WCLC 2016

Atezolizumab is not approved in NSCLC in EU

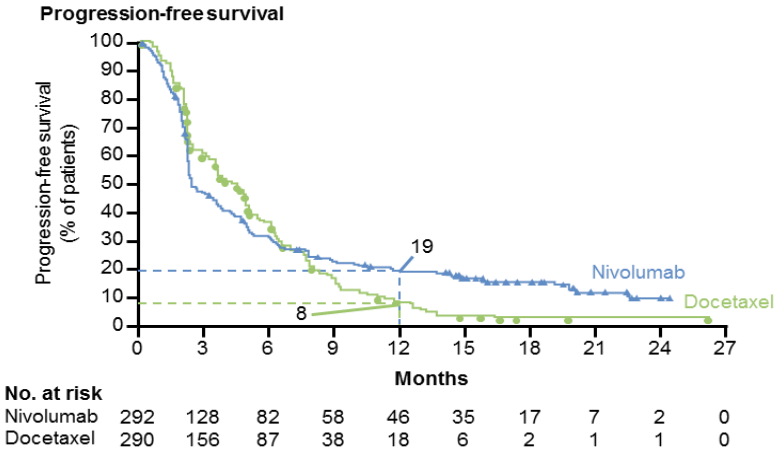
ORR and PFS in CheckMate-057 Study
Non-Squamous Carcinoma

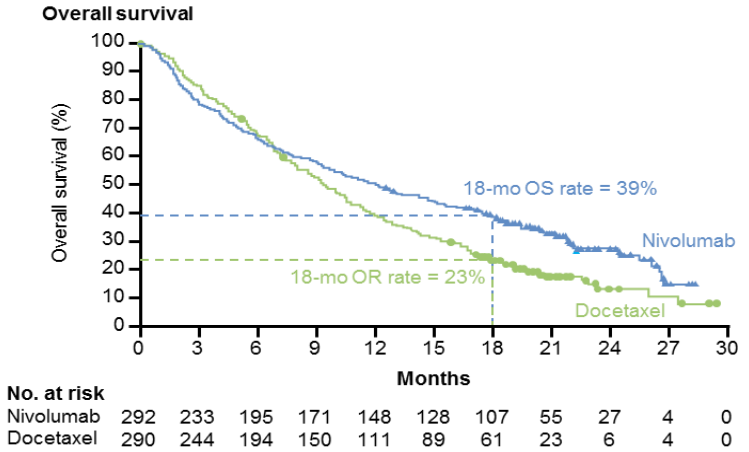
ORR and PFS

	Nivolumab (n=292)	Docetaxel (n=290)
ORR, %	19	12
Median, months	2.3	4.2
HR 0.92; 95% CI 0.77-1.11; p=0.3932		

OS

	Nivolumab (n=292)	Docetaxel (n=290)
Median, months	12.2	9.4
18-month OS, %	39	23
HR 0.73; 95%CI 0.59-0.89; p=0.0015		





Paz-Ares L et al. *J Clin Oncol* 2015;33(suppl):abstr LBA109;
Borghaei H et al. *N Engl J Med* 2015;373:1627-39

Immunoprofiling, biomarqueurs et cibles moléculaires dans le cancer du poumon non à petites cellules

1. La révolution de la médecine de précision dans le CBNPC

- De la découverte des mutations de l'EGFR au changement de l'histoire naturelle de la maladie
- Evolution des techniques : du séquençage Sanger aux biopsies liquides
- Les biomarqueurs à rechercher en 2017

2. La seconde révolution de l'immunothérapie

- Impact des inhibiteurs des points de rétro-contrôle de la réponse immunitaire sur l'algorithme thérapeutique des CBNPC avancés
- La quête des biomarqueurs prédictifs : de PD-L1 à la personnalisation de l'immunothérapie

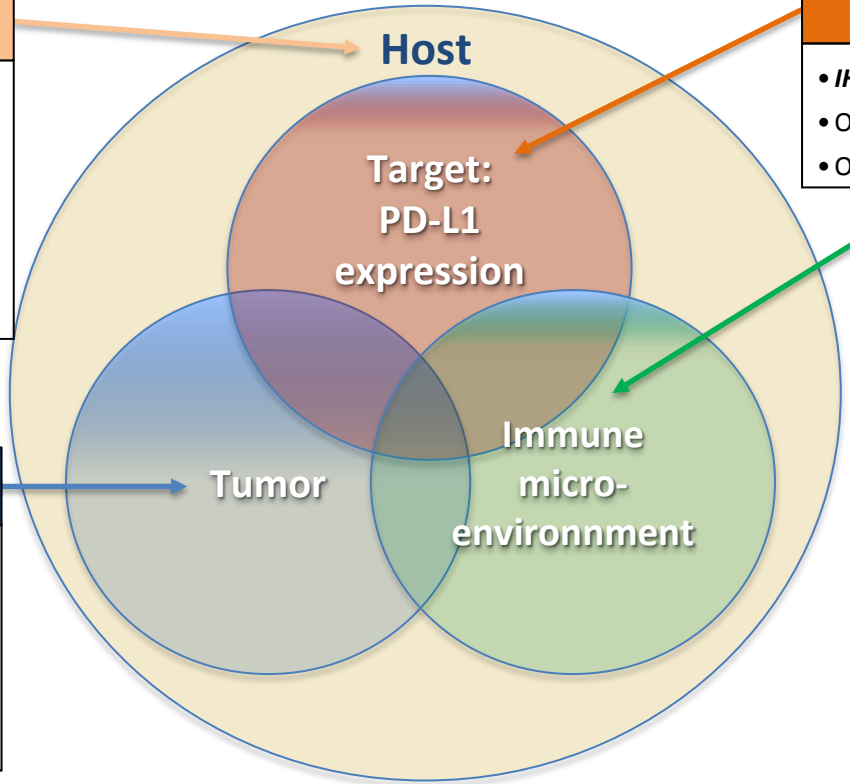
Parameters and potential biomarkers of anti-tumor immune response

Host Characteristics and Environment

- Biomarkers which characterize the host environment, beyond tumor microenvironment, may predict response to IO treatment
- ***Clinical factors: gender, age, PS, histology, smoking status***
- ***Microbiome, Germline Genetics***

Tumor Antigens

- Biomarkers indicative of hypermutation & neo-antigens may predict response to IO treatment
- ***EGFR, KRAS mutations, ALK+***
- ***TMB, MSI-High, Neo-Antigens, clonality***



PD-L1 expression

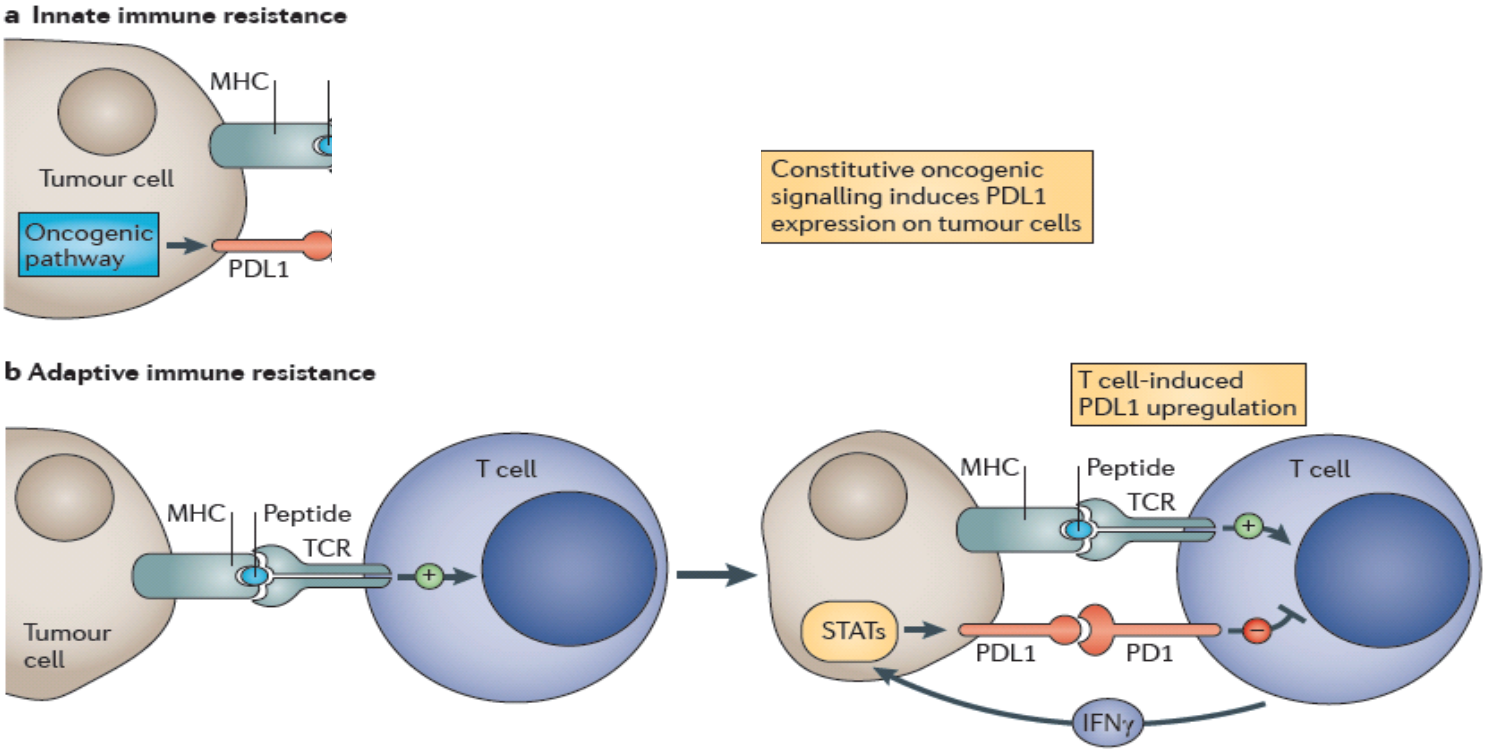
- ***IHC, gene expression, mRNA***
- On tumor cells
- On immune infiltrating cells

Tumor Immune Microenvironment

- Biomarkers that identify tumor immune system evasion beyond PD-1/CTLA-4
- ***Tregs, MDSCs, IDO, LAG3, …***
- Inflamed tumor, immune desert, immune excluded **phenotypes**
- Biomarkers (intra- or peri-tumoral) indicative of an inflamed phenotype may predict response to IO treatment
- ***CD8+T cell infiltration and functionality***
- ***TCR clonality***
- ***Immune gene signatures***

Modified from Peters, AACR 2017; Topalian, Nat Rev Cancer 2016

Mécanismes
de surexpression tumorale de PD-L1



Pardoll, Nat Rev Cancer 2012

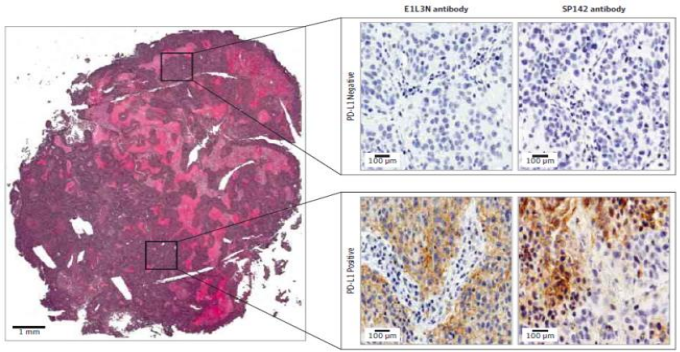
Challenges for PD-L Expression as a Biomarker

PD-L1 Biology

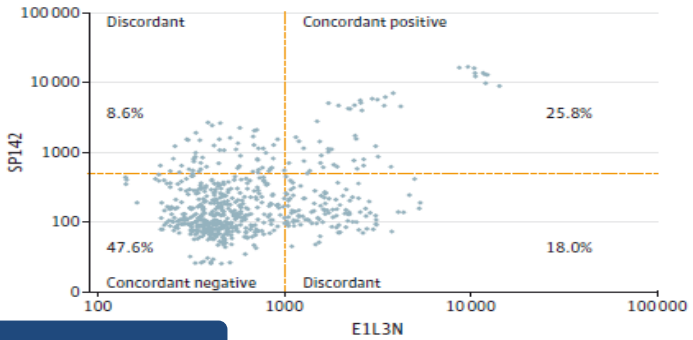
- Intra-tumor heterogeneity
- Dynamic of expression (IFN, treatment)
- Tumor cells *vs.* immune cells
- Membrane *vs.* cytoplasmic expression

Test

- Different epitopes and antibodies
- Different platforms
- Different cut-offs
- Reproducibility?



PD-L1



Sample

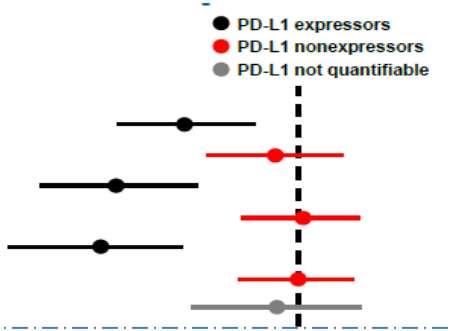
- Primary tumor *vs.* metastases
- Archived biopsy *vs.* fresh biopsy
- Age, representability of the sample

Adapted from Martin Reck, ESMO Asia 2015; McLaughlin, JAMA Oncol 2015

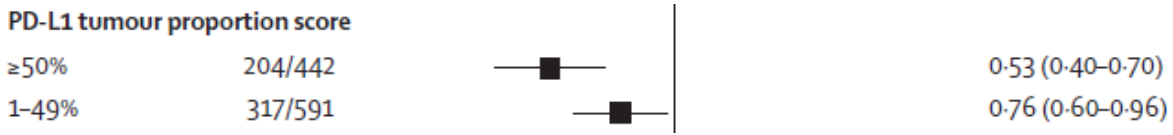
Impact of PD-L1 Expression Level on OS in Phase III Trials

Checkmate 057
Non-Squamous
Dako 28-8

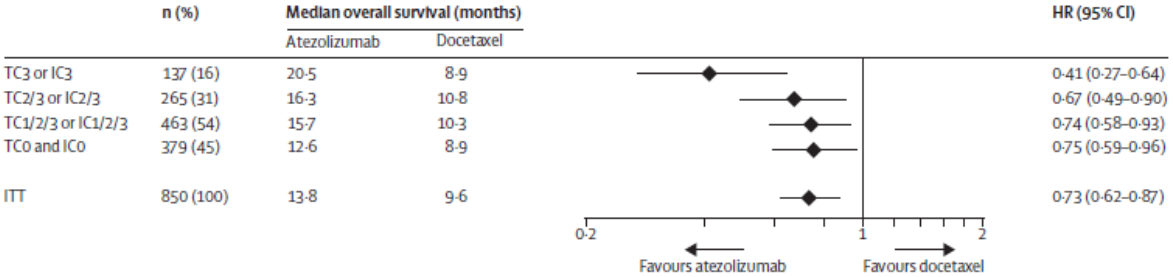
PD-L1 expression level	Nivo n	Doc n	Unstratified HR (95% CI)	Interaction *P*-value[a]
OS				
≥1%	123	123	0.59 (0.43, 0.82)	0.0646
<1%	108	101	0.90 (0.66, 1.24)	
≥5%	95	86	0.43 (0.30, 0.63)	0.0004
<5%	136	138	1.01 (0.77, 1.34)	
≥10%	86	79	0.40 (0.26, 0.59)	0.0002
<10%	145	145	1.00 (0.76, 1.31)	
Not quantifiable	61	66	0.91 (0.61, 1.35)	



Keynote-010
All histologies; PD-L1 TPS ≥1%
Dako 22C3

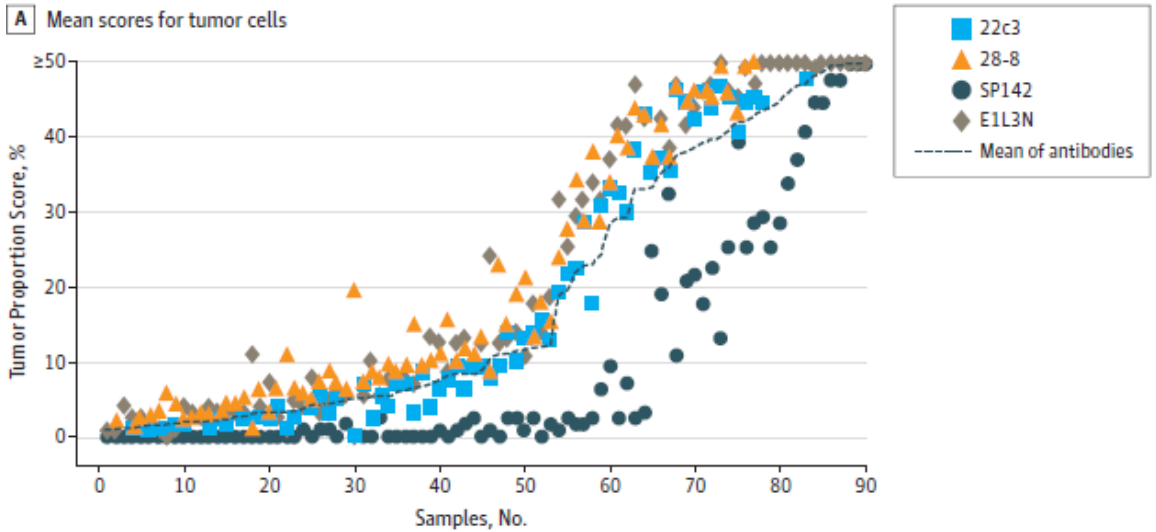


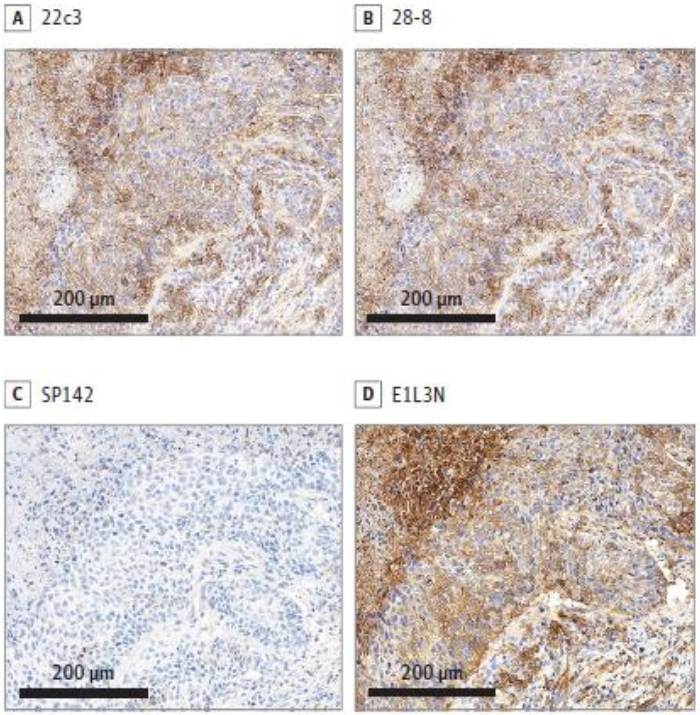
OAK
All comers
Ventana SP142



Borghaei H et al. *N Engl J Med* 2015;373:1627-39; Fehrenbacher, Lancet 2016; Herbst, Lancet 2015;

PD-L1 Staining of Tumor Cells
Concordance of Different Tests





Rimm, JAMA Oncol 2017

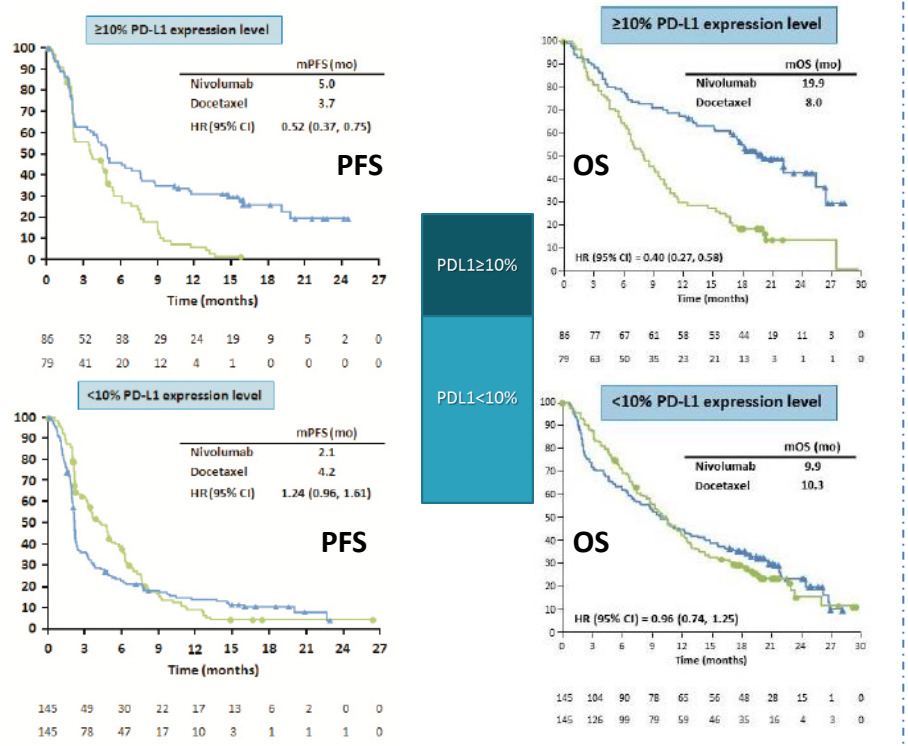
Response Rate for PD-L1 Negative Patients

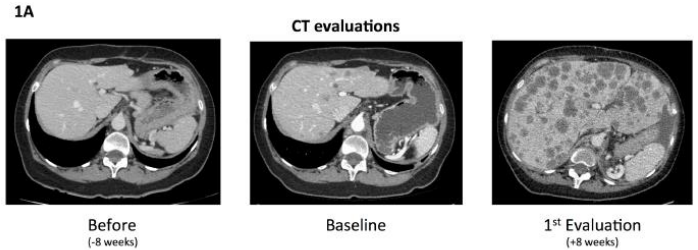
Drug	Histology	Testing	Cut-off PD-L1 -	% PD-L1-	ORR
Nivolumab (Checkmate 017)	Squamous	Dako 28.8	<1%	40%	17%
Nivolumab (Checkmate 057)	Non-squamous	Dako 28.8	<1%	46%	9%
Atezolizumab (Poplar)	All histologies	Ventana SP142	TC0 + IC0	32%	7.8%
Atezolizumab (Oak)	All histologies	Ventana SP142	TC0 + IC0	45%	8%
Durvalumab (phase I-II)	All histologies	Ventana SP263	<25%	45%	6.1%
Pembrolizumab (phase I)	All histologies	Dako 22C3	<1%	39%	8.1%
Avelumab (phase Ib)	All histologies	Dako 73.10	<1%	14%	10%

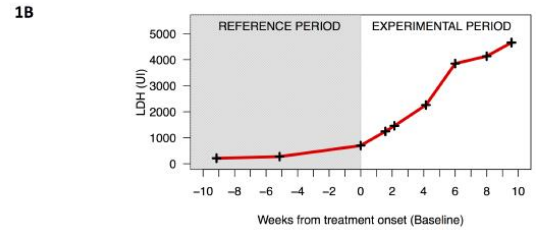
Brahmer, NEJM 2015; Borghaei H et al. *N Engl J Med* 2015;373:1627-39; Fehrenbacher; Lancet 2016; Garon, Lancet 2015; Rizvi, Science 2015; Herbst, Lancet 2015; Antonia, ASCO 2015; Gettinger, ASCO 2015

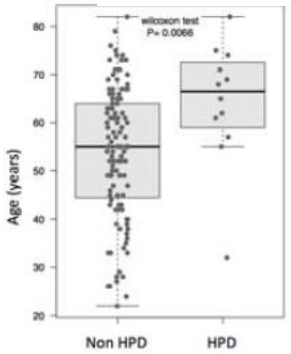
Durvalumab and atezolizumab are not approved in NSCLC in EU

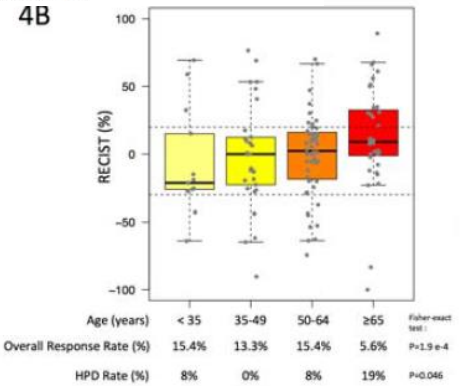
Checkmate 057: PFS and OS by PD-L1 Expression Level
Risk of "Hyperprogression" with anti-PD1/PD-L1 Therapy









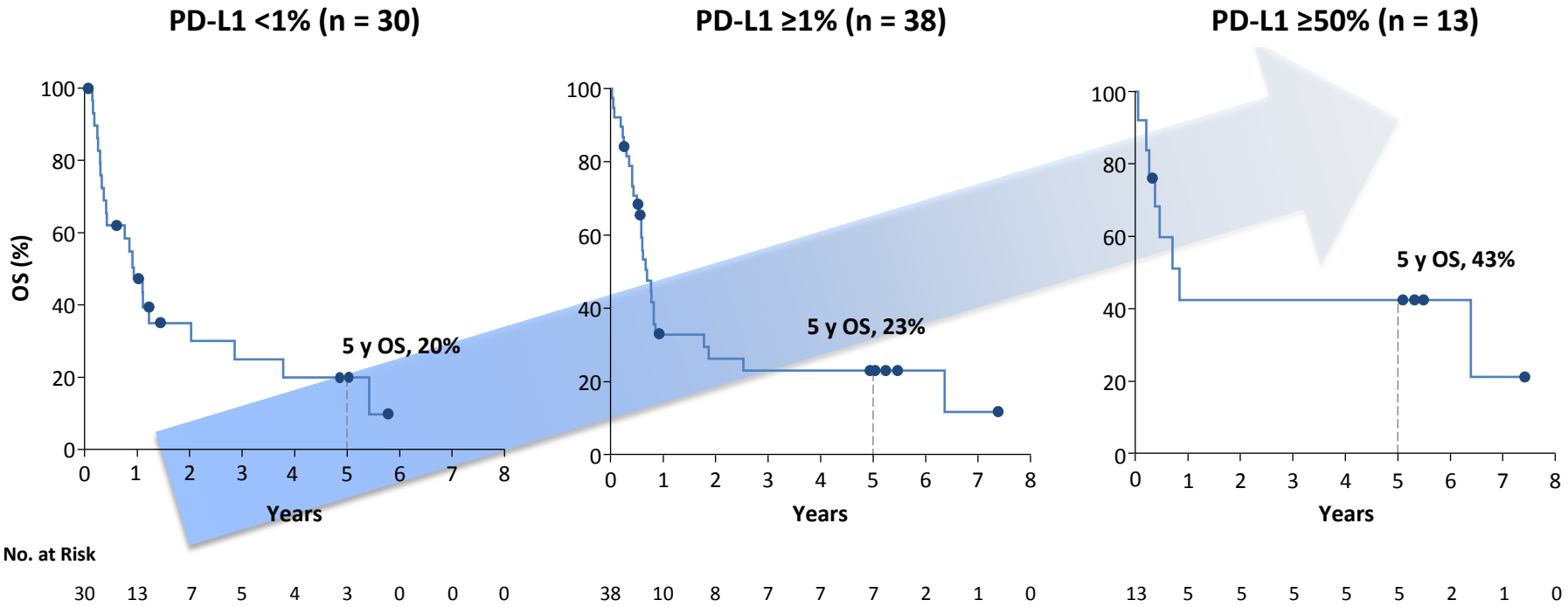


Borghaei H et al. , *N Engl J Med* 2015; Herbst, Lancet 2015

Dr.M.Pérol 16 juin

5-Year Estimates of OS by PD-L1 Status

CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC



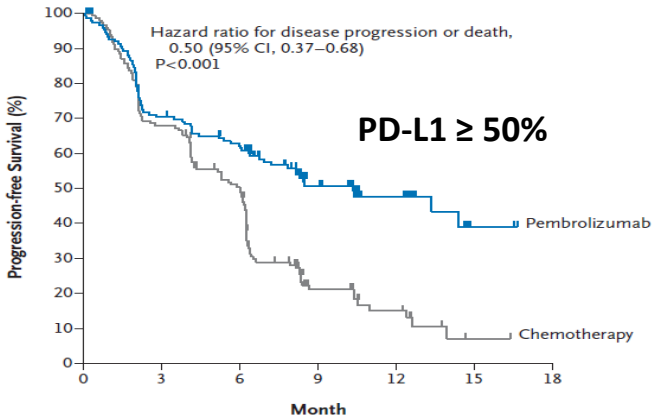
Brahmer, AACR 2017

Rôle de l'expression de PD-L1 dans la décision thérapeutique en 2ème ligne

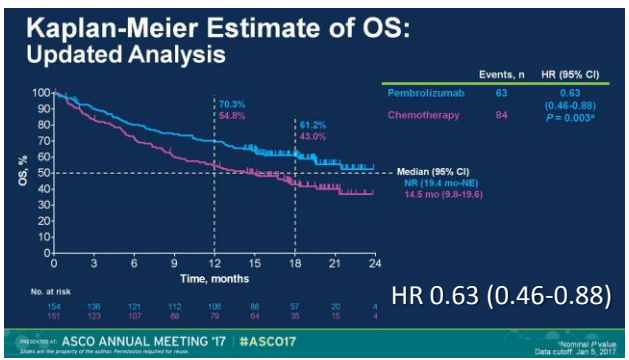
- PD-L1 est un biomarqueur d'enrichissement pour la probabilité de réponse aux anti-PD1/PD-L1
  - Biomarqueur continu (exprimé sur 0-100% des cellules tumorales), dont le niveau d'expression est corrélé à la probabilité de réponse
  - Réponse d'amplitude et de durée identique chez les patients PD-L1 + ou PD-L1 – s'ils sont répondeurs au traitement
- Valeur prédictive positive et négative imparfaites : pour PD-L1 ≥50%, VPP=37% et VPN=89%
- Standardisation du testing en cours en France
- Aide à la décision thérapeutique en 2ème ligne pour le nivolumab, requis (≥ 1%) pour le pembrolizumab
- Facteur décisionnel du traitement de 1ère ligne

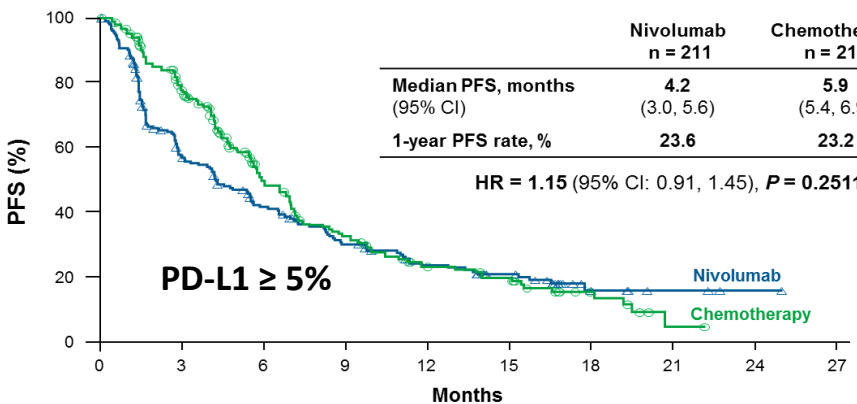
Garon E et al. , *N Engl J Med* 2015; Herbst, *Lancet* 2015

Keynote 024 *vs.* Checkmate 26
PD-L1 Level of Expression Does Matter



No. at Risk							
Pembrolizumab	154	104	89	44	22	3	1
Chemotherapy	151	99	70	18	9	1	0





	Nivolumab n = 211	Chemotherapy n = 212
Median PFS, months (95% CI)	4.2 (3.0, 5.6)	5.9 (5.4, 6.9)
1-year PFS rate, %	23.6	23.2

HR = 1.15 (95% CI: 0.91, 1.45), ***P* = 0.2511**

No. of patients at risk:										
Nivolumab	211	104	71	49	35	24	6	3	1	0
Chemotherapy	212	144	74	47	28	21	8	1	0	0

Reck, NEJM 2016; Brahmer, ASCO 2017, Abstr. 9000; Socinski, ESMO 2016

Positive CHMP opinion for pembrolizumab in 1st line therapy in NSCLC in EU
Nivolumab is not approved in first-line of advanced NSCLC

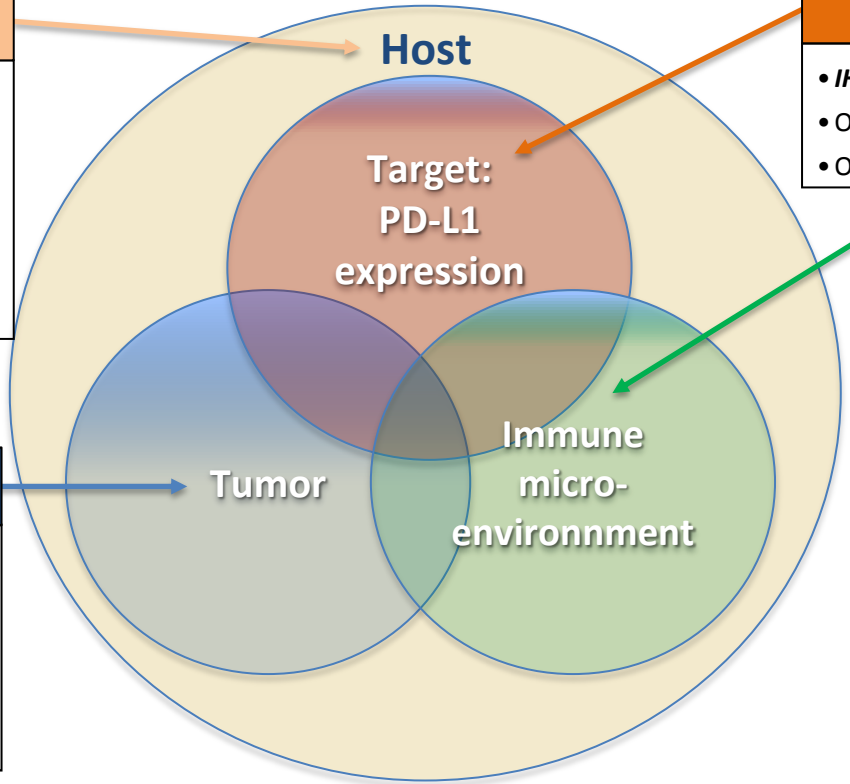
Parameters and potential biomarkers of anti-tumor immune response

Host Characteristics and Environment

- Biomarkers which characterize the host environment, beyond tumor microenvironment, may predict response to IO treatment
- ***Clinical factors: gender, age, PS, histology, smoking status***
- ***Microbiome, Germline Genetics***

Tumor Antigens

- Biomarkers indicative of hypermutation & neo-antigens may predict response to IO treatment
- ***EGFR, KRAS mutations, ALK+***
- ***TMB, MSI-High, Neo-Antigens, clonality***



PD-L1 expression

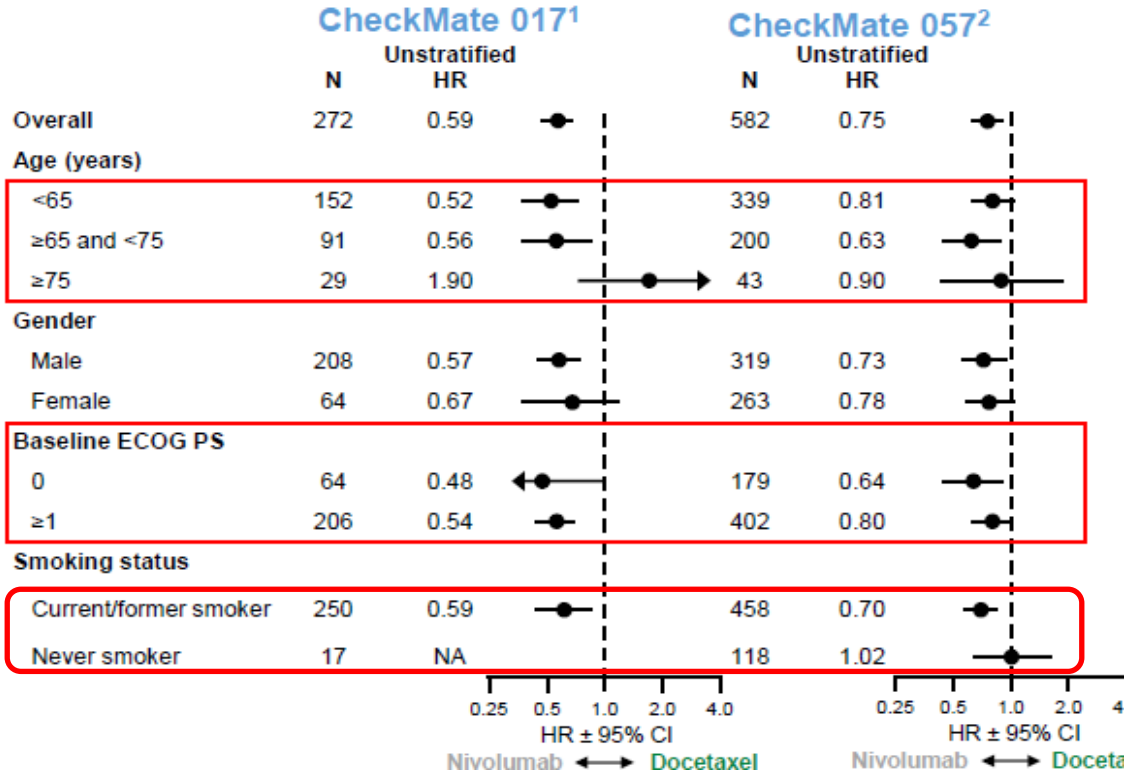
- ***IHC, gene expression, mRNA***
- On tumor cells
- On immune infiltrating cells

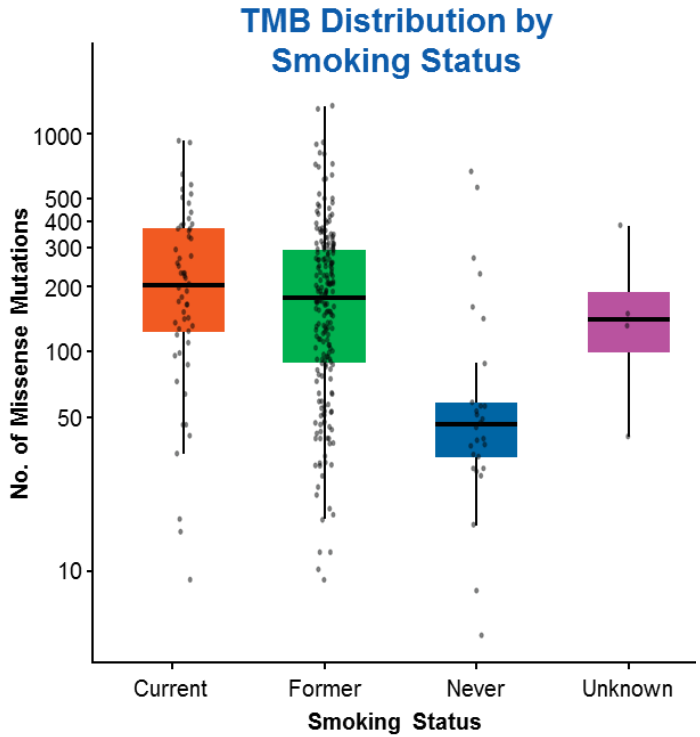
Tumor Immune Microenvironment

- Biomarkers that identify tumor immune system evasion beyond PD-1/CTLA-4
- ***Tregs, MDSCs, IDO, LAG3, …***
- Inflamed tumor, immune desert, immune excluded **phenotypes**
- Biomarkers (intra- or peri-tumoral) indicative of an inflamed phenotype may predict response to IO treatment
- ***CD8+T cell infiltration and functionality***
- ***TCR clonality***
- ***Immune gene signatures***

Modified from Peters, AACR 2017; Topalian, Nat Rev Cancer 2016

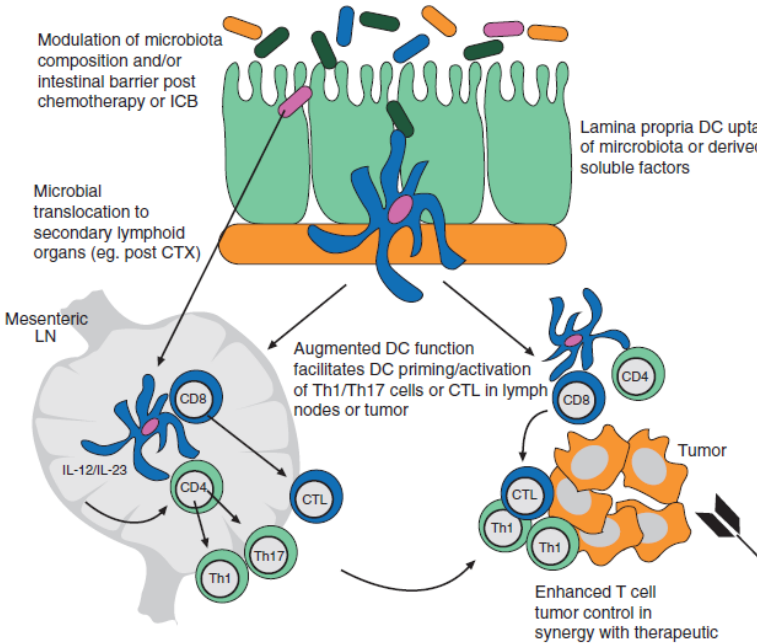
Can We Select Patients on Clinical Factors?



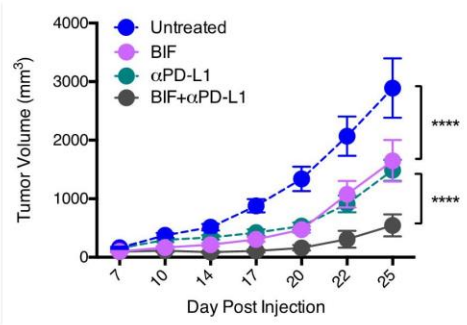


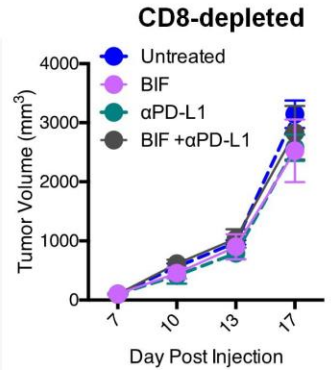
Brahmer, NEJM 2015; Borghaei, NEJM 2015; Peters, AACR 2017

Impact of Gut Microbiota on Host Anti-cancer Immunity



Commensal microbiota: *Bifidobacterium* species can improve anti-tumor immunity and response to anti-PD-L1 antibody in vivo





Sivan, Corrales et al; Science. 2015

Pitt, Ann Oncol 2016; Sivan, Science 2015; Gajewski, ASCO 2017

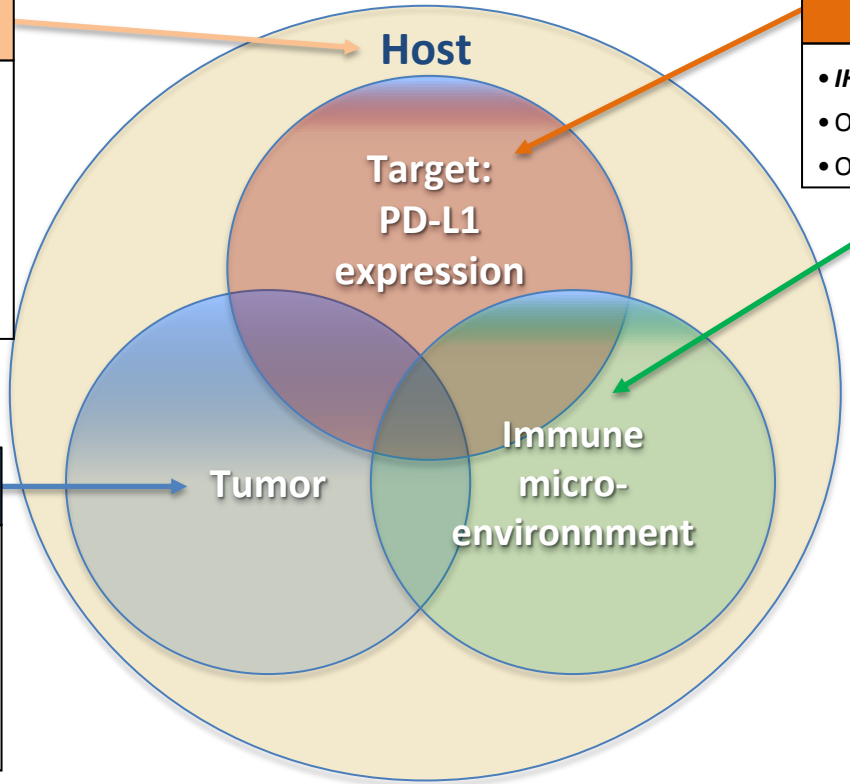
Parameters and potential biomarkers of anti-tumor immune response

Host Characteristics and Environment

- Biomarkers which characterize the host environment, beyond tumor microenvironment, may predict response to IO treatment
- ***Clinical factors: gender, age, PS, histology, smoking status***
- ***Microbiome, Germline Genetics***

Tumor Antigens

- Biomarkers indicative of hypermutation & neo-antigens may predict response to IO treatment
- ***EGFR, KRAS mutations, ALK+***
- ***TMB, MSI-High, Neo-Antigens, clonality***



PD-L1 expression

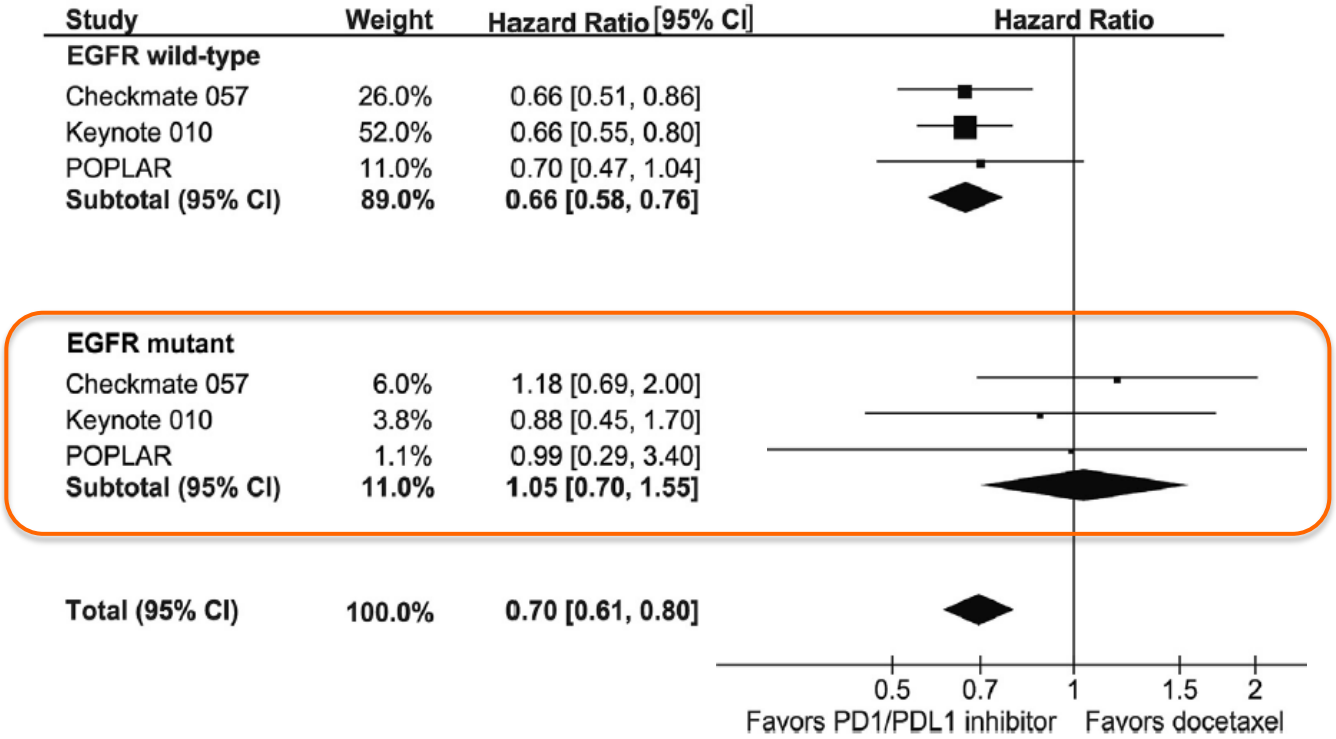
- ***IHC, gene expression, mRNA***
- On tumor cells
- On immune infiltrating cells

Tumor Immune Microenvironment

- Biomarkers that identify tumor immune system evasion beyond PD-1/CTLA-4
- ***Tregs, MDSCs, IDO, LAG3, …***
- Inflamed tumor, immune desert, immune excluded **phenotypes**
- Biomarkers (intra- or peri-tumoral) indicative of an inflamed phenotype may predict response to IO treatment
- ***CD8+T cell infiltration and functionality***
- ***TCR clonality***
- ***Immune gene signatures***

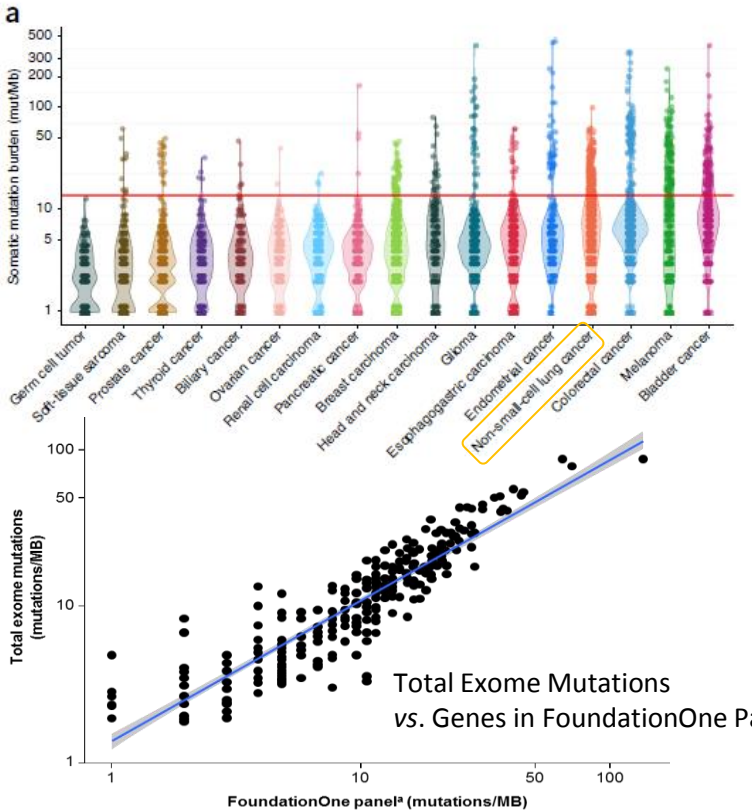
Modified from Peters, AACR 2017; Topalian, Nat Rev Cancer 2016

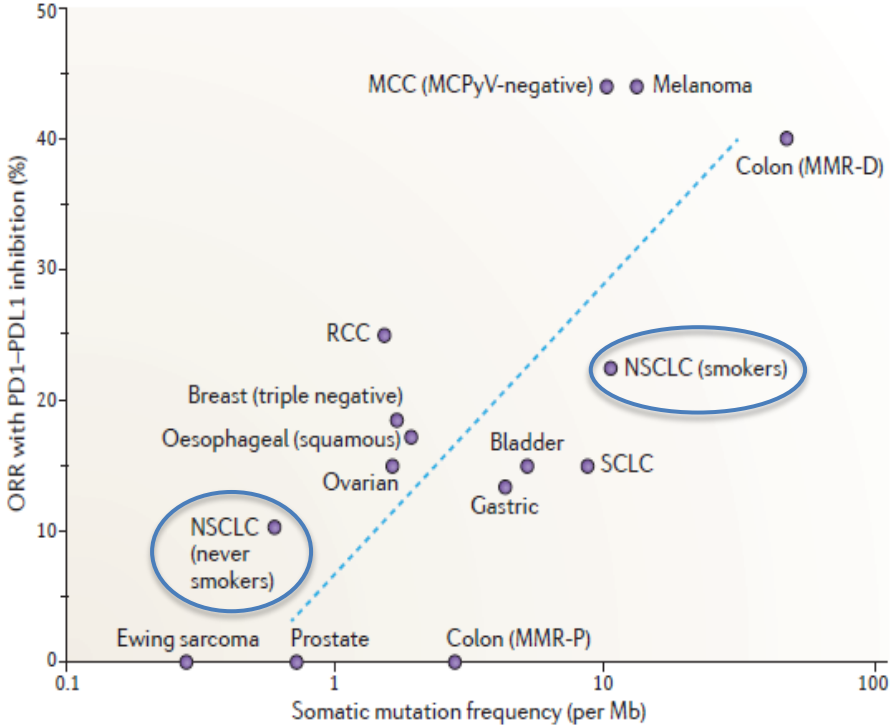
Impact des mutations EGFR sur la survie dans les essais anti-PD1/PD-L1 vs. docetaxel



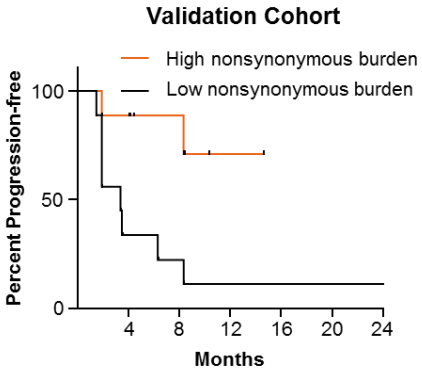
Lee CK, JTO 2017, 12:403

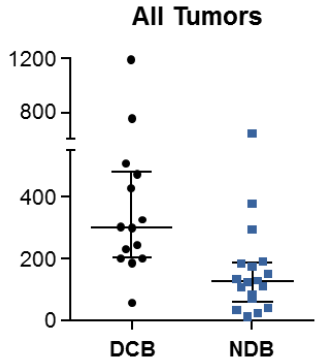
Correlation between somatic mutation frequency and response to anti-PD1/PD-L1

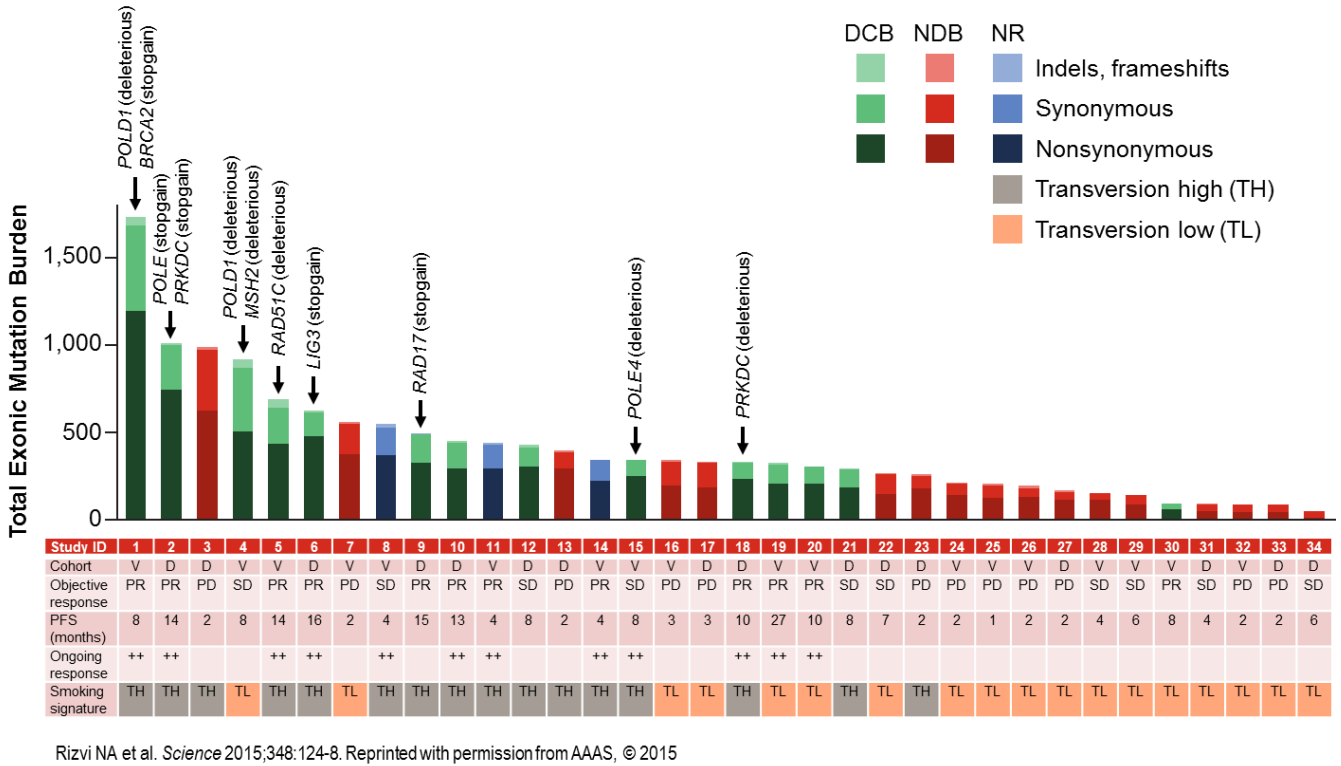




Mutational Load is Predictive of anti-PD1 Clinical Benefit



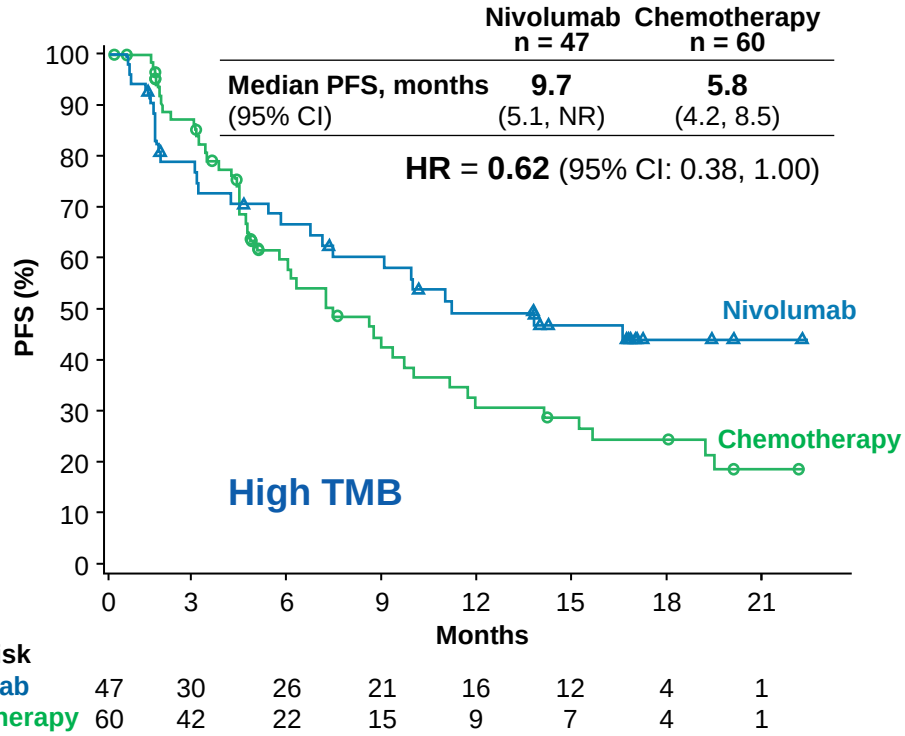


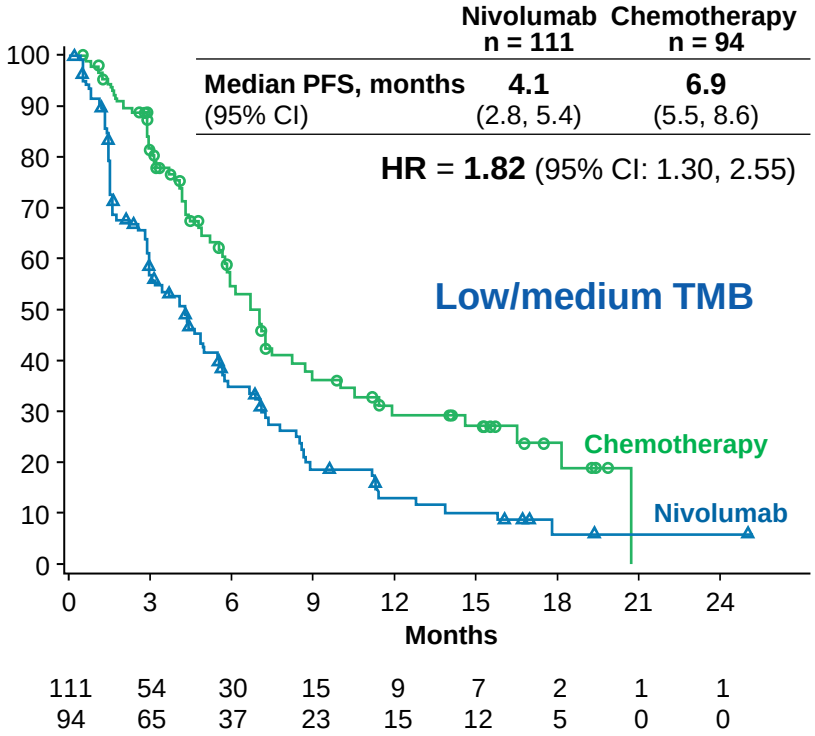


Study ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34
Cohort	V	D	D	V	V	D	V	V	D	D	V	D	D	V	V	V	D	D	V	V	D	D	D	V	V	V	D	V	V	V	D	V	D	D
Objective response	PR	PR	PD	SD	PR	PR	PD	SD	PR	PR	PR	SD	PD	PR	SD	PD	PD	PR	PR	PR	SD	SD	PD	PD	PD	PD	PD	SD	SD	PR	SD	PD	PD	SD
PFS (months)	8	14	2	8	14	16	2	4	15	13	4	8	2	4	8	3	3	10	27	10	8	7	2	2	1	2	2	4	6	8	4	2	2	6
Ongoing response	++	++			++	++		++		++	++			++	++			++	++	++														
Smoking signature	TH	TH	TH	TL	TH	TH	TL	TH	TH	TH	TH	TH	TH	TH	TH	TL	TL	TH	TL	TL	TH	TL	TH	TL	TL	TL	TL	TL	TL	TL	TL	TL	TL	TL

Rizvi NA et al. *Science* 2015;348:124-8. Reprinted with permission from AAAS, © 2015

PFS by Tumor Mutation Burden Subgroup
CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC

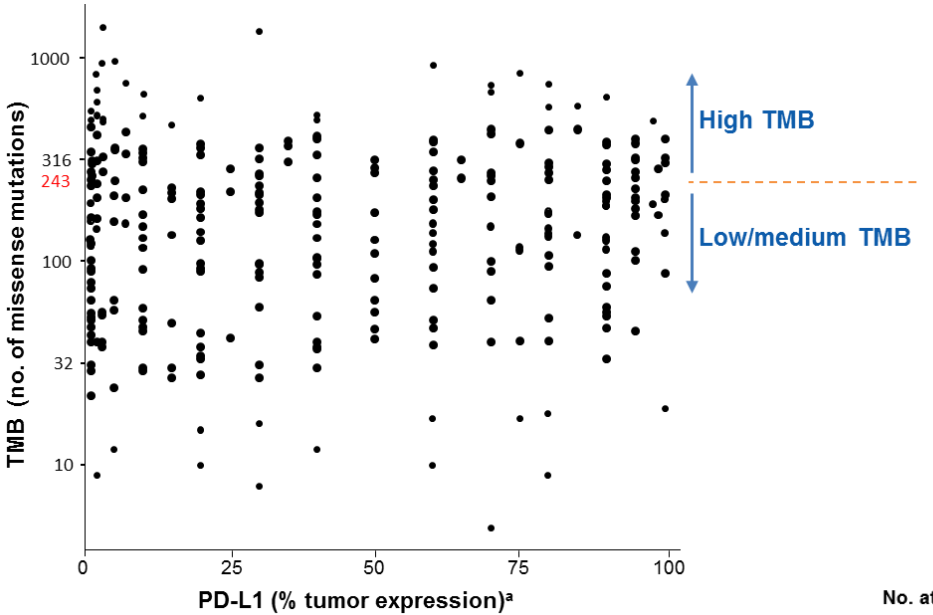




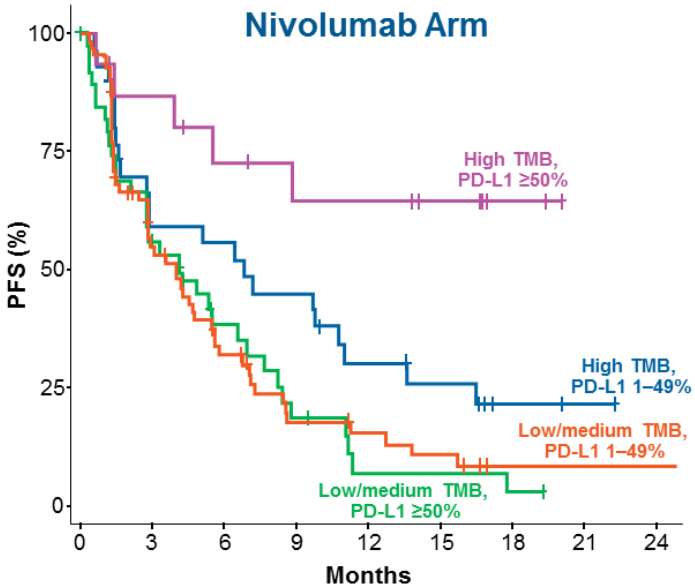
Peters S et al., AACR 2017

Analysis of the Association Between TMB and PD-L1 Expression

CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC



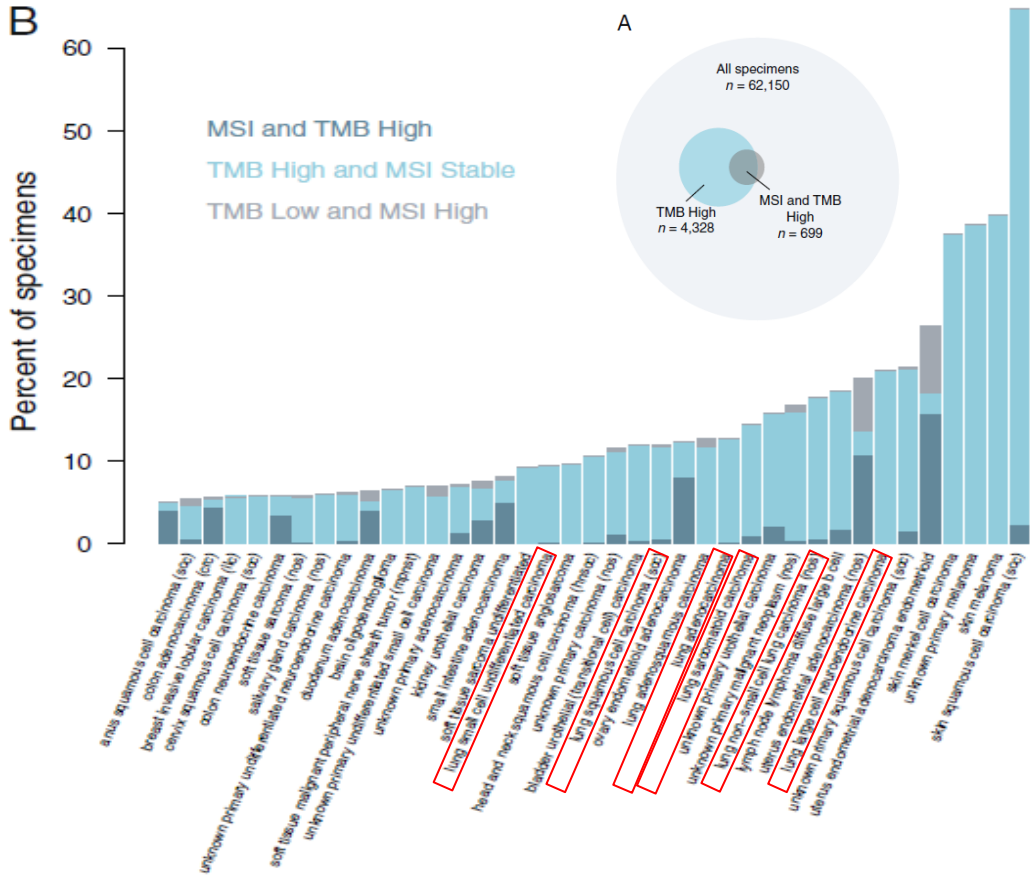
No association between TMB and PD-L1 expression in patients with ≥1% PD-L1 tumor expression

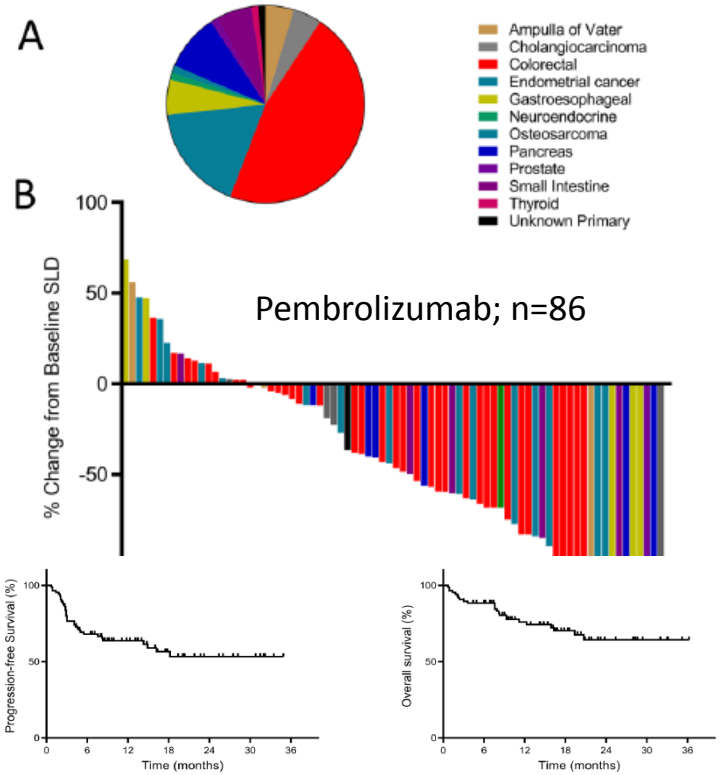


No. at Risk									
High TMB, PD-L1 ≥50%	16	13	10	8	8	6	2	0	0
High TMB, PD-L1 1–49%	31	17	16	13	8	6	2	1	0
Low/medium TMB, PD-L1 ≥50%	41	21	12	6	2	2	1	0	0
Low/medium TMB, PD-L1 1–49%	70	33	18	9	7	5	1	1	1

Peters S et al., AACR 2017

Mismatch-repair deficiency predicts response to anti-PD1 regardless of tumor type





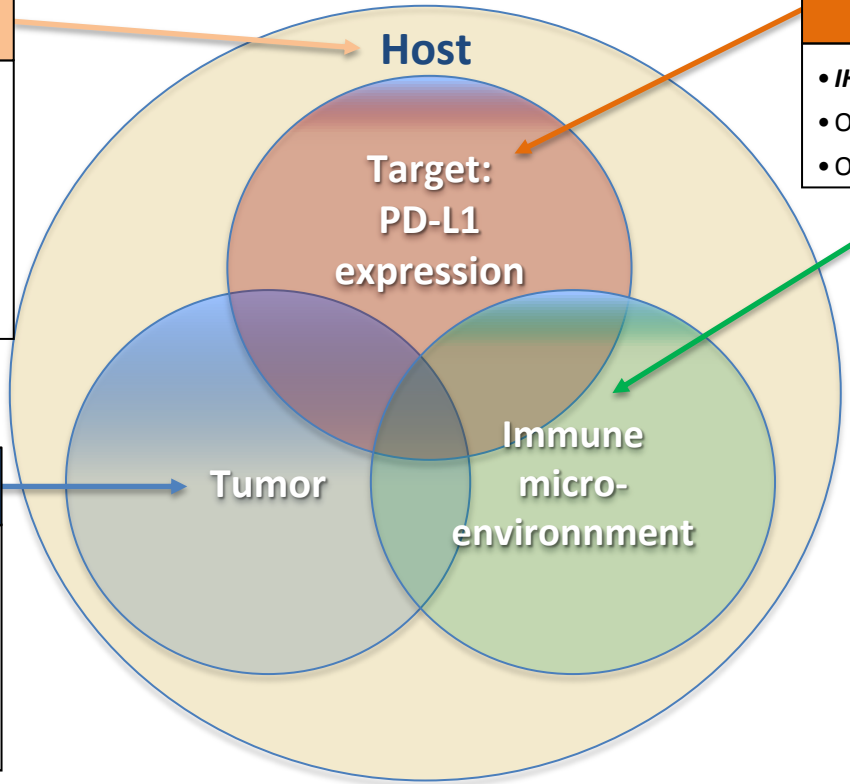
Parameters and potential biomarkers of anti-tumor immune response

Host Characteristics and Environment

- Biomarkers which characterize the host environment, beyond tumor microenvironment, may predict response to IO treatment
- ***Clinical factors: gender, age, PS, histology, smoking status***
- ***Microbiome, Germline Genetics***

PD-L1 expression

- ***IHC, gene expression, mRNA***
- On tumor cells
- On immune infiltrating cells



Tumor Immune Microenvironment

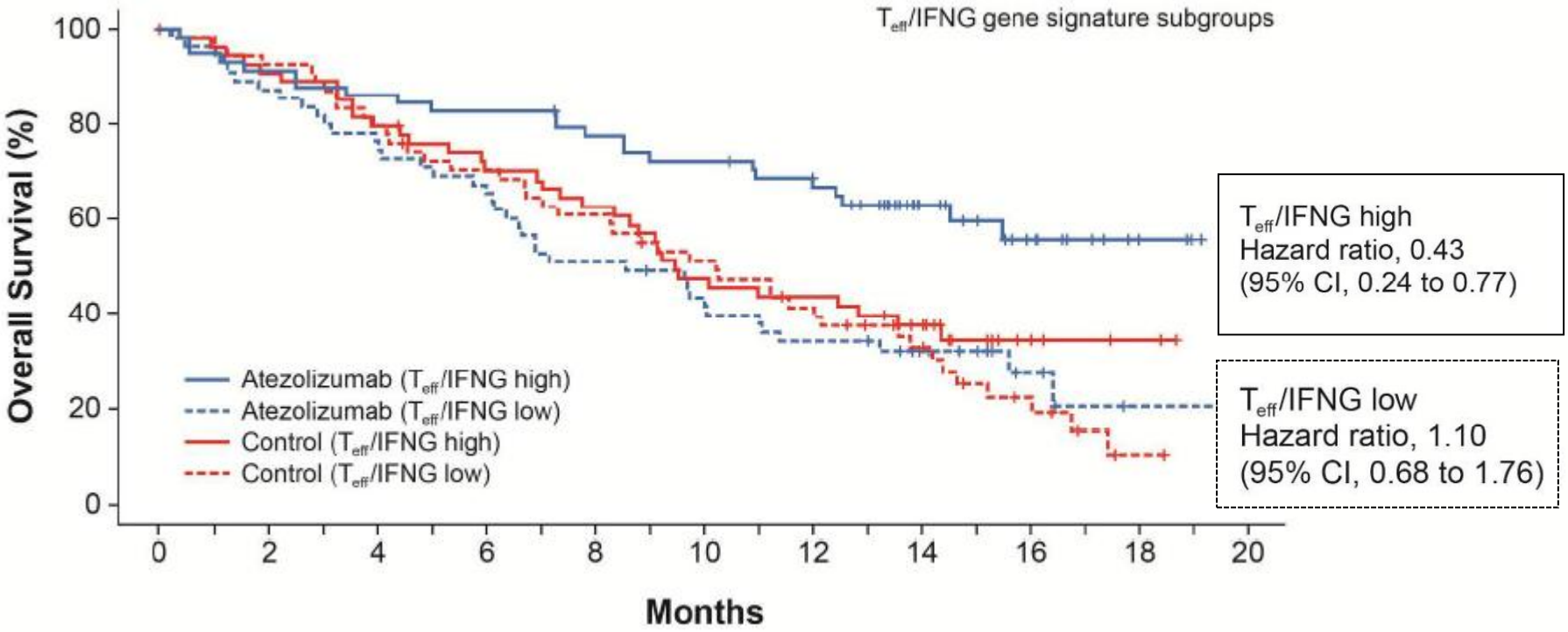
- Biomarkers that identify tumor immune system evasion beyond PD-1/CTLA-4
- ***Tregs, MDSCs, IDO, LAG3, …***
- Inflamed tumor, immune desert, immune excluded **phenotypes**
- Biomarkers (intra- or peri-tumoral) indicative of an inflamed phenotype may predict response to IO treatment
- ***CD8+T cell infiltration and functionality***
- ***TCR clonality***
- ***Immune gene signatures***

Tumor Antigens

- Biomarkers indicative of hypermutation & neo-antigens may predict response to IO treatment
- ***EGFR, KRAS mutations, ALK+***
- ***TMB, MSI-High, Neo-Antigens, clonality***

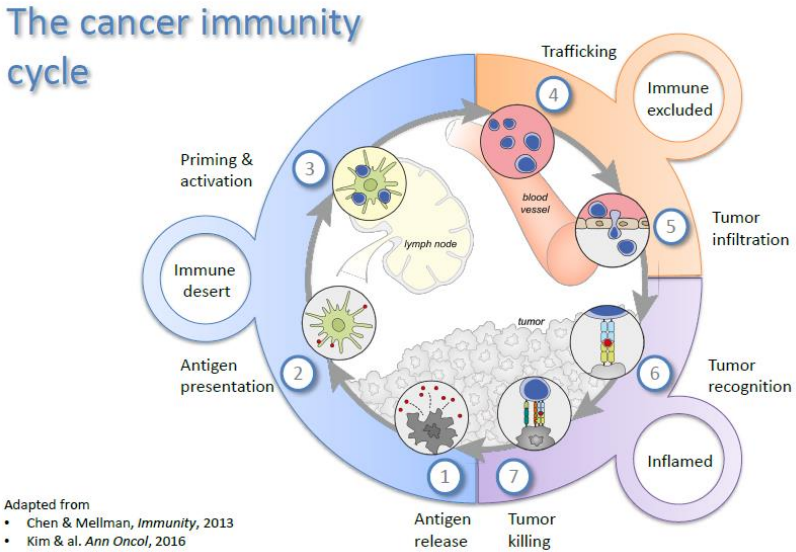
Modified from Peters, AACR 2017; Topalian, Nat Rev Cancer 2016

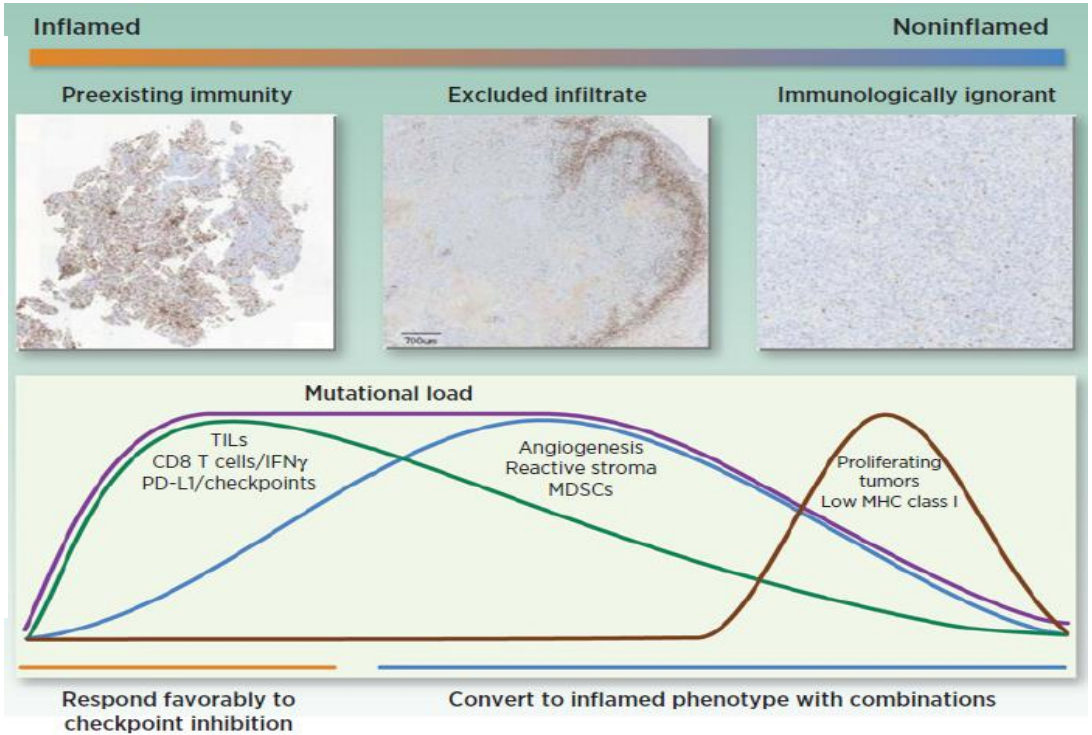
Existing Immune Response Does Matter: Immune Signatures



Fehrenbacher, Lancet 2016

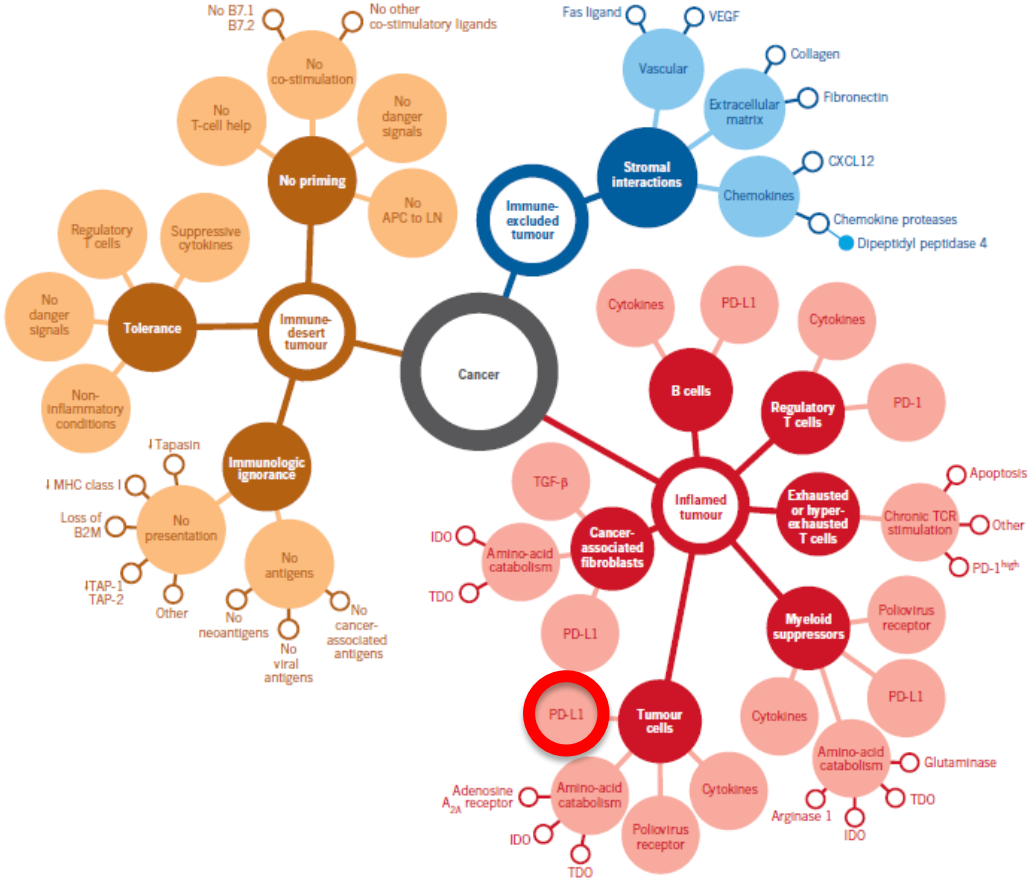
Tumors "Immunophenotype"



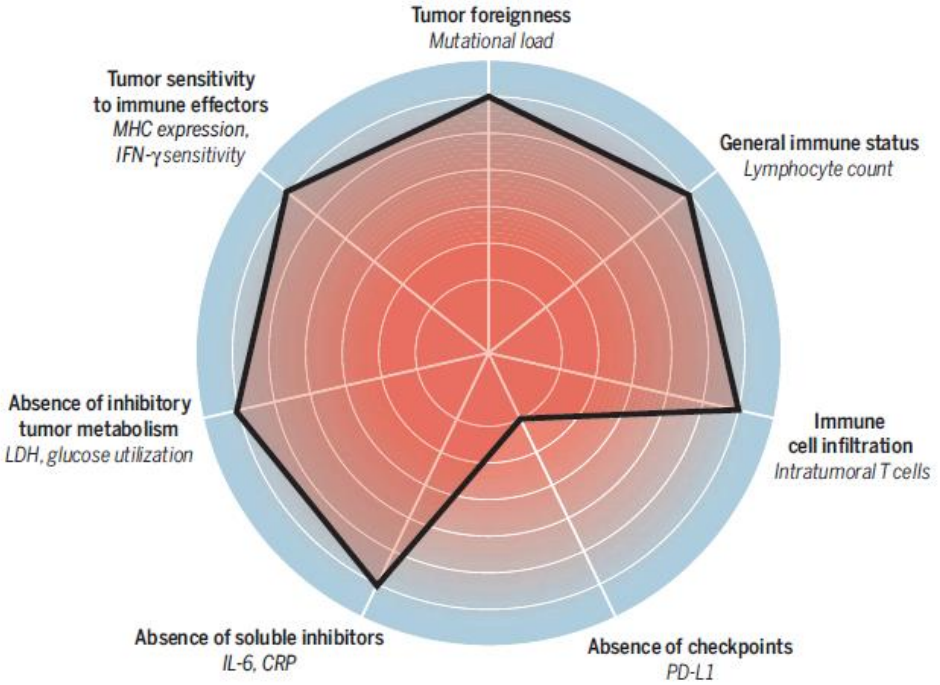


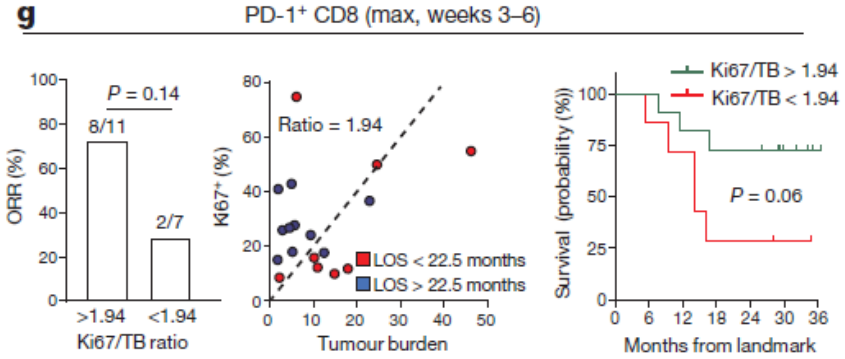
Hedge et al., CCR 2016; Courtesy of O. Michielin

Cancer Immune Phenotypes



Composite, Integrative Biomarkers
The Cancer Immunogram





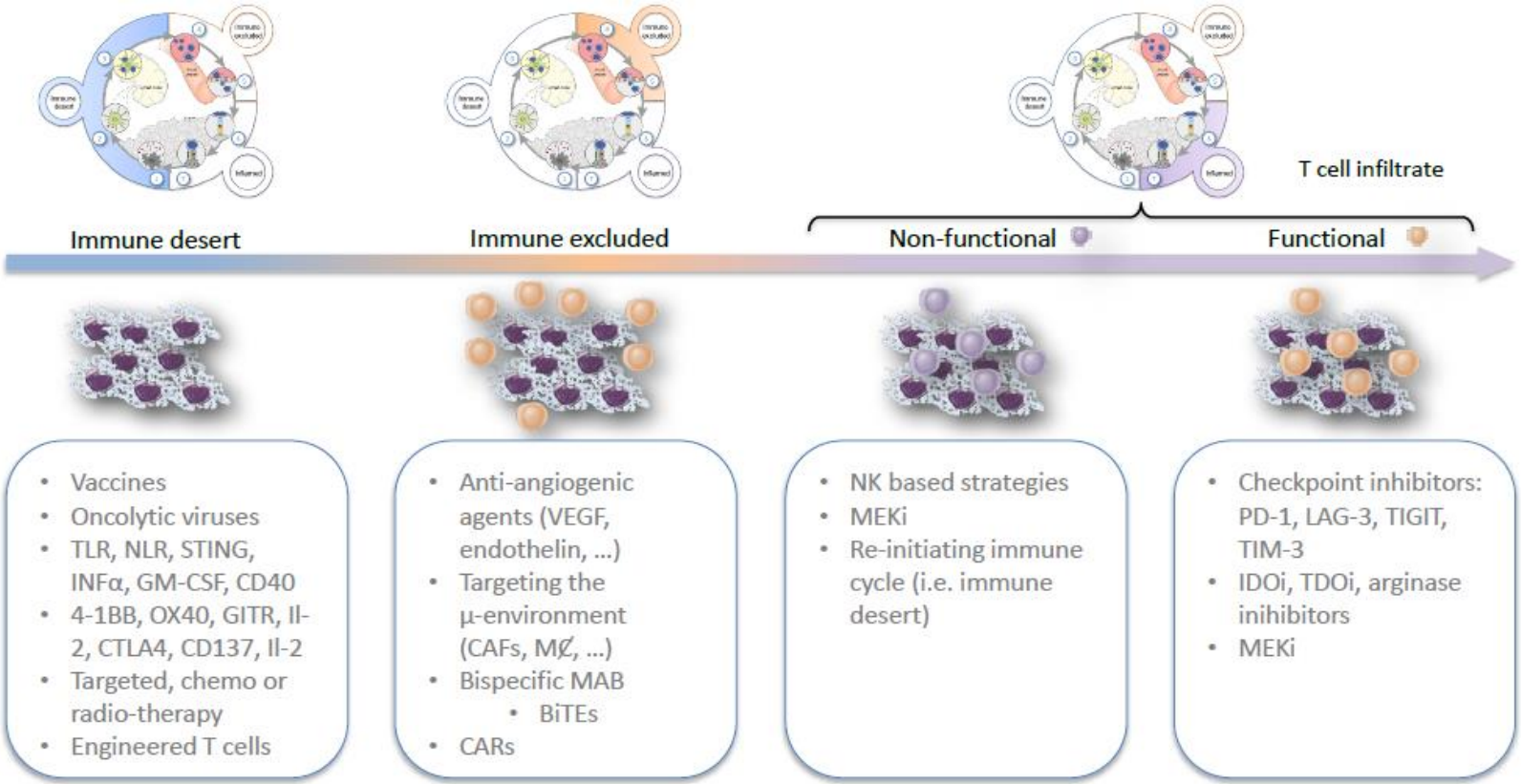
Blank, Science 2016; Huang, Nature 2017

Au-delà de PD-L1
De nouveaux biomarqueurs ?

- Il est peu probable qu'un biomarqueur unique puisse refléter la globalité de l'interaction entre la tumeur et le système immunitaire de l'hôte
  - PD-L1 est un reflet imparfait de cette interaction (anti-PD1/PD-L1)
  - Nécessité de biomarqueurs composites : TMB, PD-L1, signature IFN gamma, TILs …

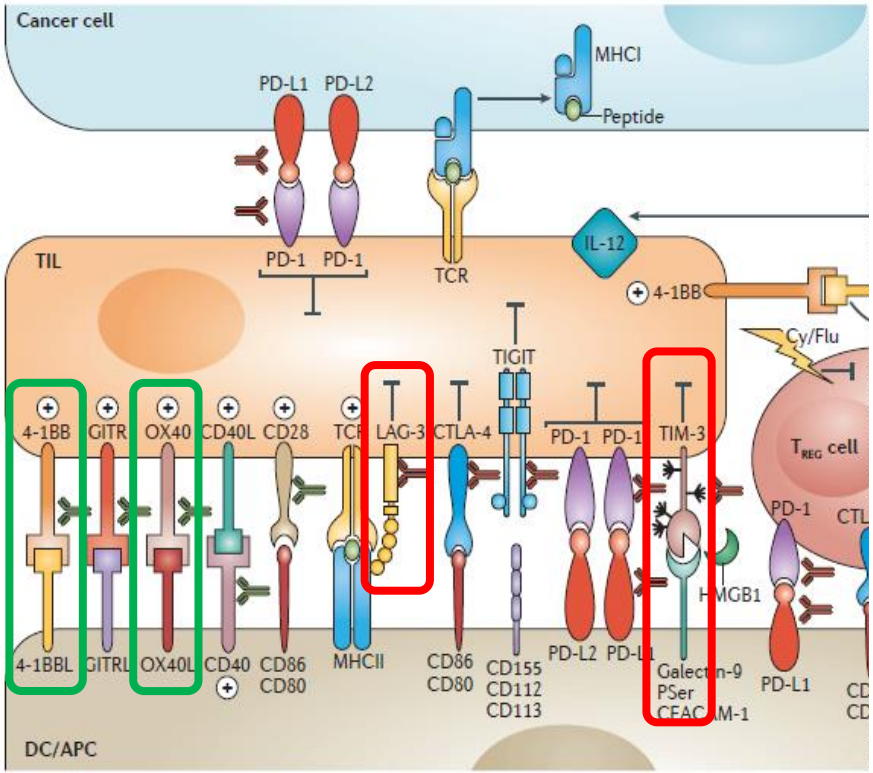
- Problématique des biomarqueurs potentiels
  - Identification rétrospective sur de petits sous-groupes de patients issus des essais cliniques
  - Absence de validation prospective
  - Valeur pronostique (infiltration lymphocytaire)
  - Standardisation ?
  - Applicabilité à la pratique clinique (technologie, bioinformatique, coût …)

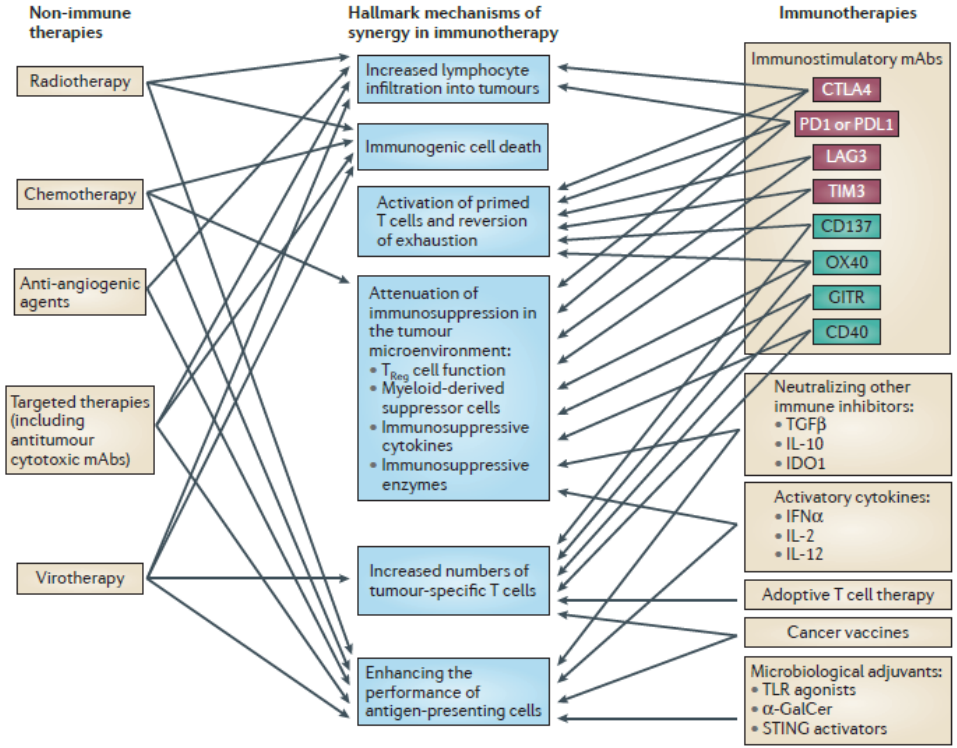
Potential Therapeutic Interventions



Courtesy of O. Michielin

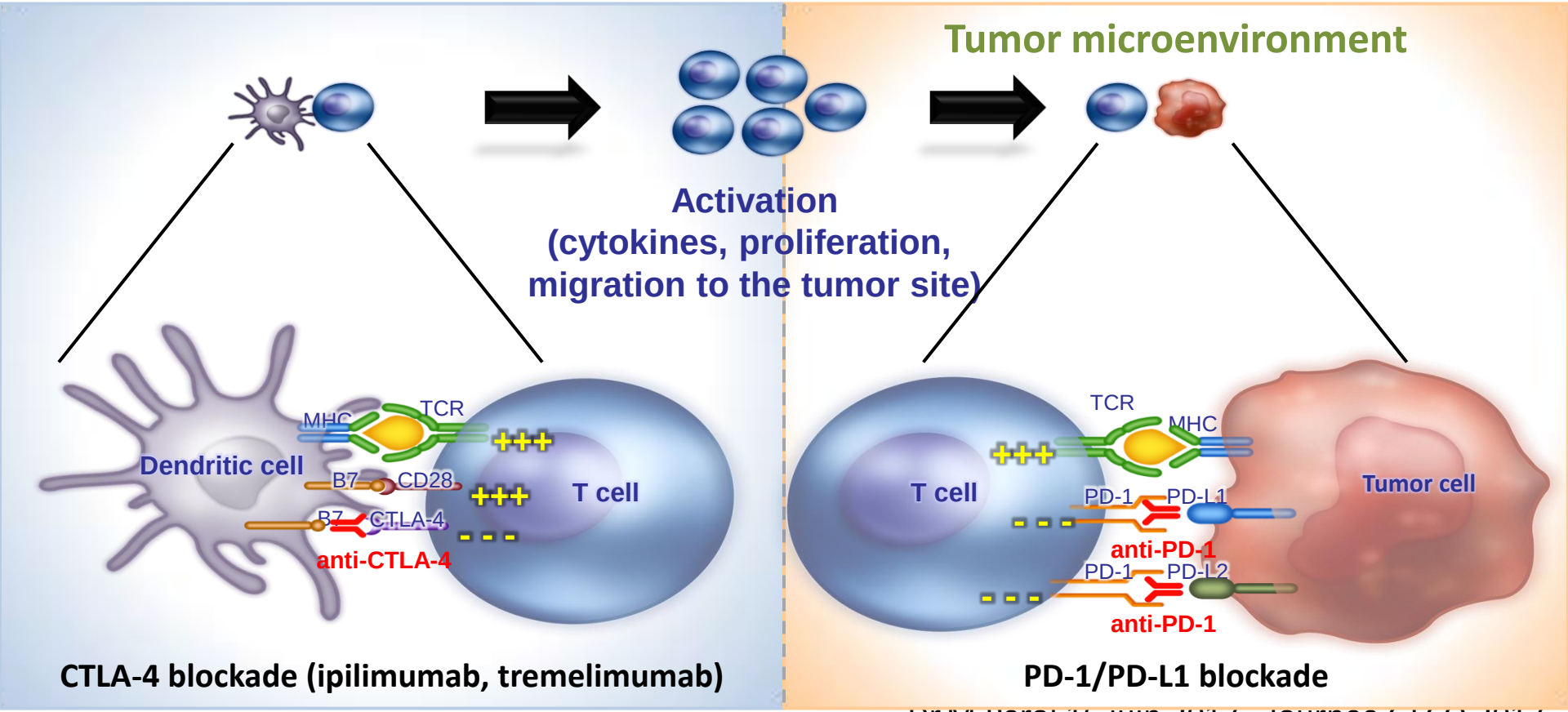
De nombreuses combinaisons et voies d'action sur la réponse immunitaire



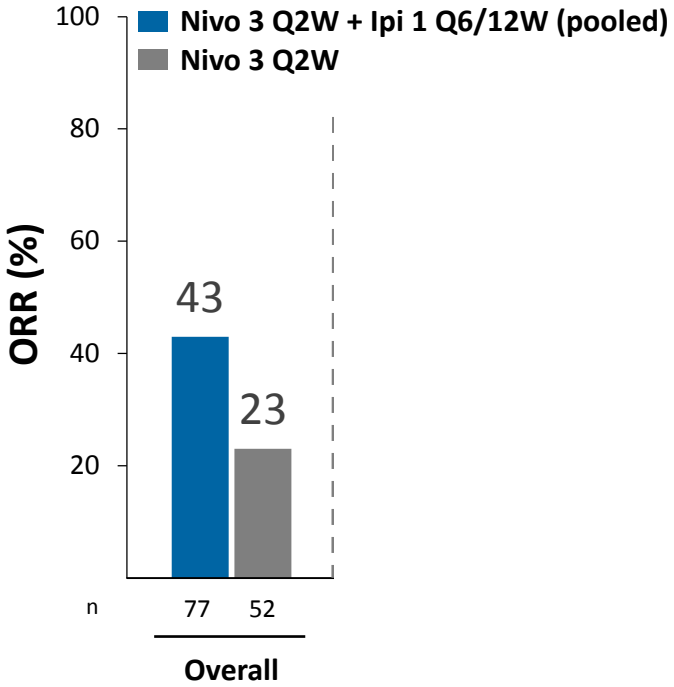


Khalil, Nat Rev Clin Oncol 2016; Melero, Nat Rev Cancer 2015

Combination of Anti-CTLA4 and Anti-PD1/PD-L1

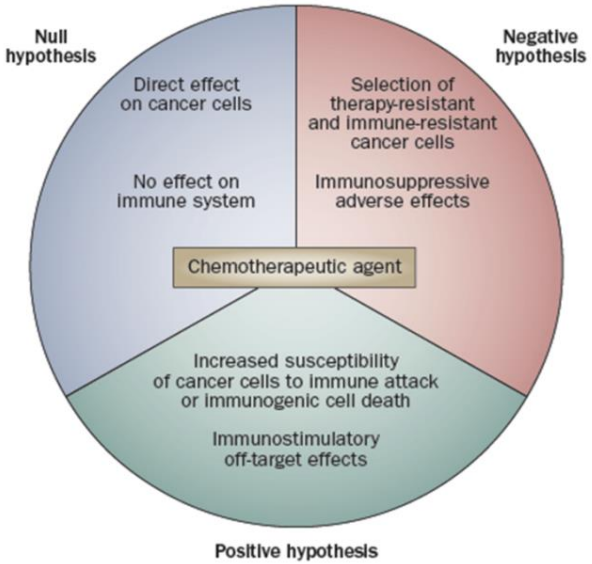


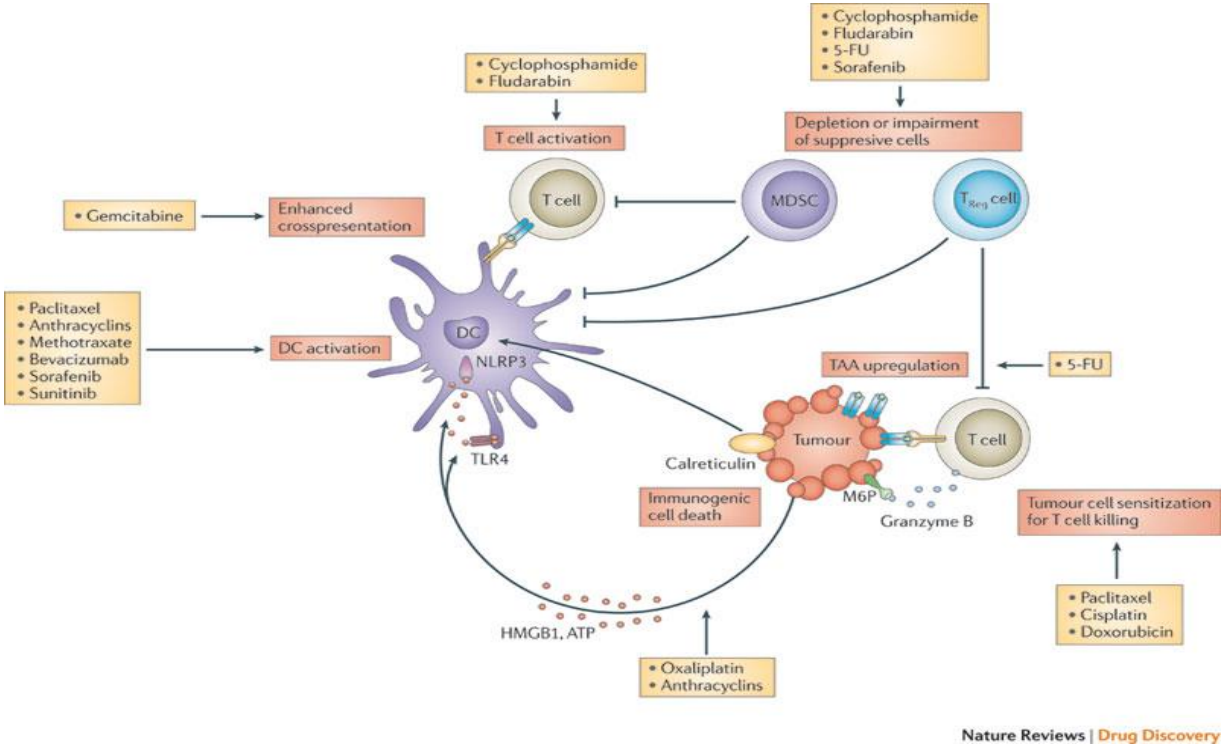
Nivolumab + Ipilimumab in 1st line of NSCLC
Response Rate by PD-L1 Expression Level



PD-L1 expression

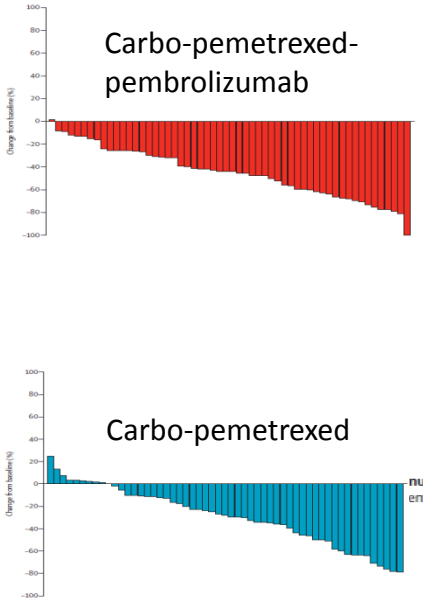
Chemotherapy Impact on Antitumor Immune Response

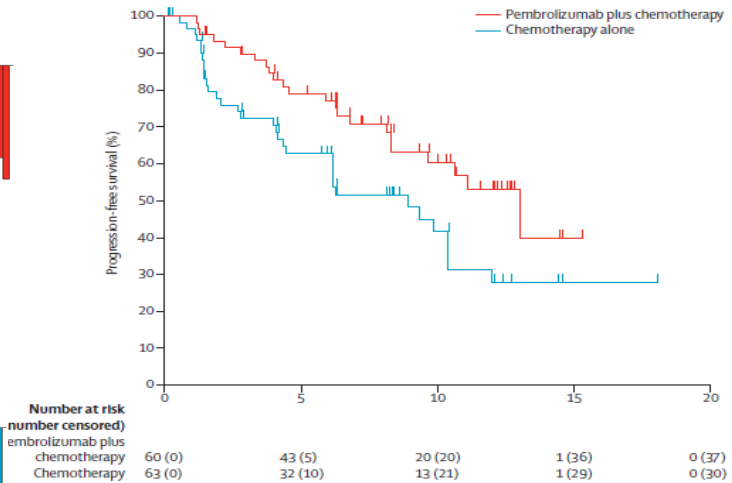




1. Hodge JW. Semin Oncol 2012;39:323–39. 2. Drake CG. Ann Oncol 2012;23(suppl 8):viii41–viii46.3. Ménard C, et al. Cancer Immunol Immunother 2008;57:1579–87. 4. Hannani D, et al. Cancer J 2011;17:351–8.
5. Ribas A at al. Curr Opin Immunol. 2013:25:291–6. 6. Zitvogel, Nat Rev Clin Oncol 2011

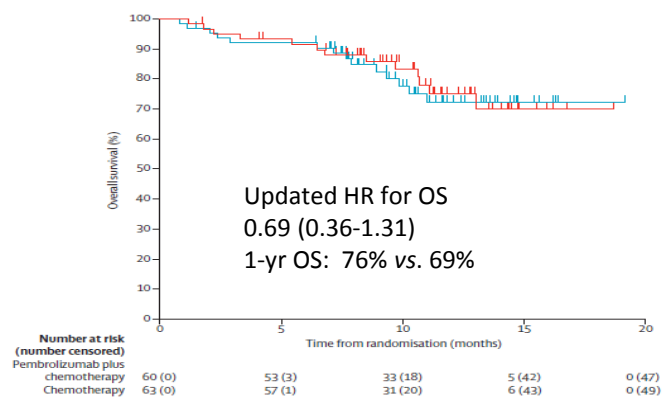
Keynote 021 : cohort G
Carboplatine-pemetrexed ± pembrolizumab





PFS

	Carbo-pem-pembro	Carbo-pem	
N	60	63	
ORR	**55%**	**29%**	*p=0.016*
PD-L1<1%	57%	13%	
PD-L1≥1%	54%	38%	
PD-L1 1-49%	26%	39%	
PD-L1≥50%	80%	35%	
PFS, months	**13**	**8.9**	HR 0.53 (0.31-0.91), *p=0.0102*
1 year OS	75%	72%	



Updated HR for OS
0.69 (0.36-1.31)
1-yr OS: 76% *vs*. 69%

Langer, ESMO 2016 and Lancet Oncol 2016; Papadimitrakopoulou, ASCO 2017

Approved in US, not approved in NSCLC in EU

Following Steps of Immuno-Oncology in NSCLC
The Second Wave

ARCTIC

CheckMate 017
CheckMate 057
KEYNOTE-010
POPLAR
OAK
Javelin 200

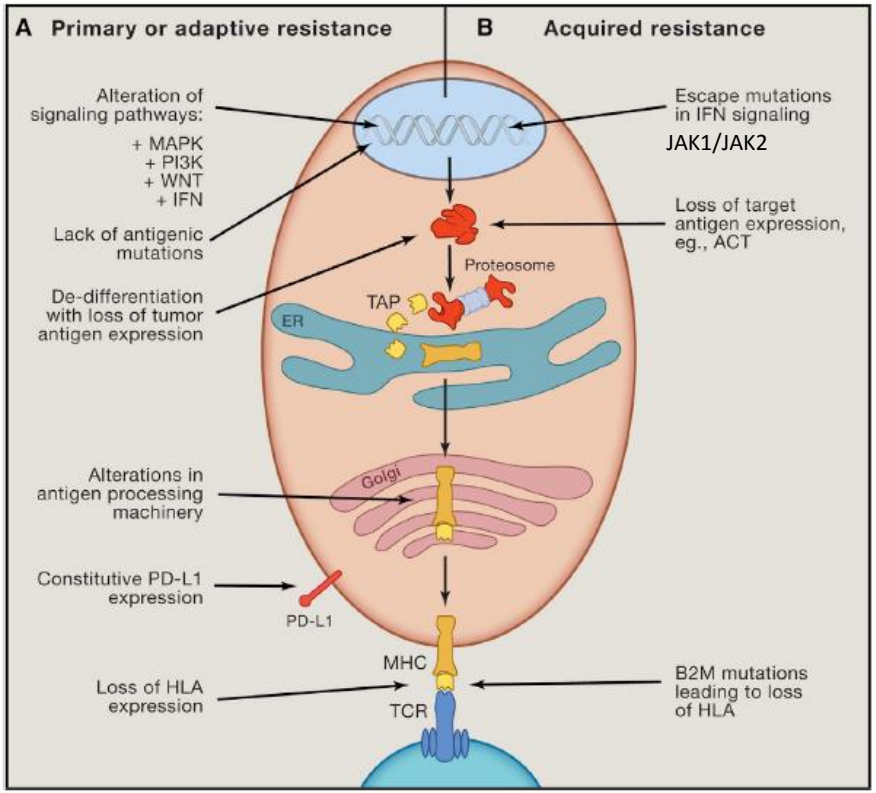
KEYNOTE-024
CheckMate 026
KEYNOTE 189, 042, 407
IMpower 150, 130, 131, 132,110, 111
Checkmate 227
MYSTIC
NEPTUNE
Javelin 100

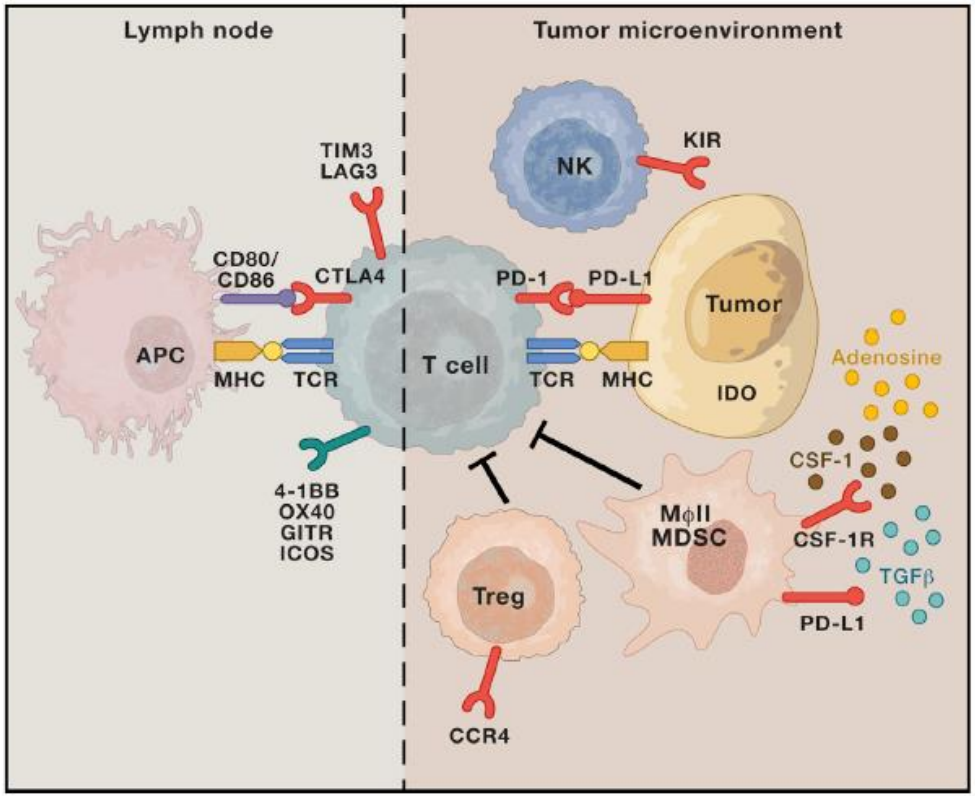
BR31
KEYNOTE-091
ANVIL
PACIFIC
IMpower010

- Many ongoing trials are combination studies
- Many have completed accrual

Ongoing studies
Completed studies

Adapted from M. Boyer, WCLC 2016





Tumor cell intrinsic

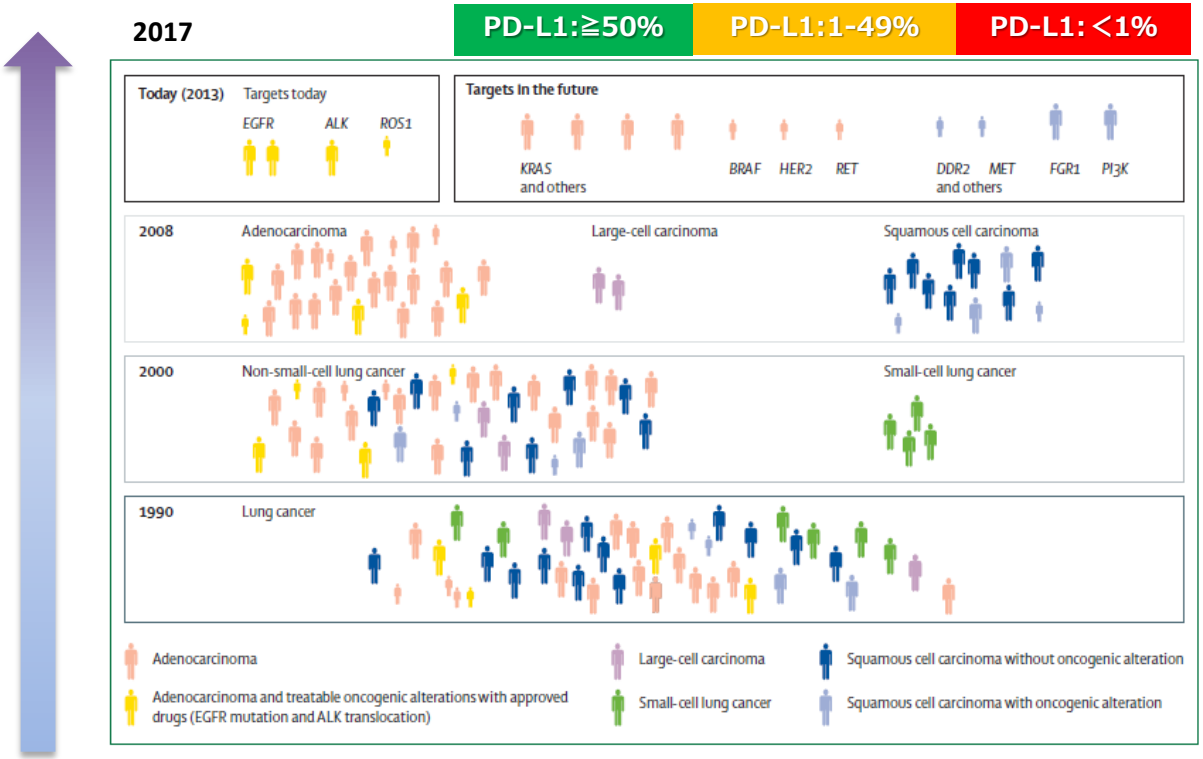
Tumor cell extrinsic (microenvironment)

Sharma, Cell 2017

Cancer pulmonaire non à petites cellules
Quels biomarqueurs en 2017 et au-delà ?

- ≈ 15 à 20% des adénocarcinomes pulmonaires dépendent d'une addiction oncogénique
  - Panel actuel des biomarqueurs permettant d'axer le traitement sur l'inhibition de la voie oncogénique dès la 1ère ligne, mais aussi en 2ème, voire en 3ème ligne
  - Modification de l'histoire naturelle de la maladie mais émergence invariable de résistances
  - Nécessitant des analyses séquentielles de la pérennité ou de la transformation de la voie oncogénique
  - Hétérogénéité tumorale croissante au fil des traitements : nécessité d'élargir le spectre des analyses biologiques moléculaires
- La révolution de l'immunothérapie
  - Expression de PD-L1 par IHC : biomarqueur d'enrichissement imparfait, mais facilement réalisable et validé
  - Recours nécessaire à d'autres biomarqueurs probablement composites
  - Validation prospective et transposition à la pratique clinique difficiles
- L'évolution des techniques de biologie moléculaire
  - Elargit le champ de la biologie moléculaire à partir d'un seul prélèvement et facilite les analyses séquentielles (ADNc)
  - Mais nécessite un recours croissant aux ressources bio-informatiques et aux RCP moléculaires
    - intégrer un volume majeur de données à l'histoire naturelle de la maladie et l'évolution clinique des patients
    - établir la pertinence du recueil de ces données

Evolution of Advanced NSCLC Treatment



Adapted from Reck M, Lancet 2013

Discussion

Avec le soutien du
Groupe Français de
Cytogénomique Oncologique