GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

Saint Paul-Nice 2019

Dans les 15 ans, quelles évolutions attendre en oncologie thoracique ?

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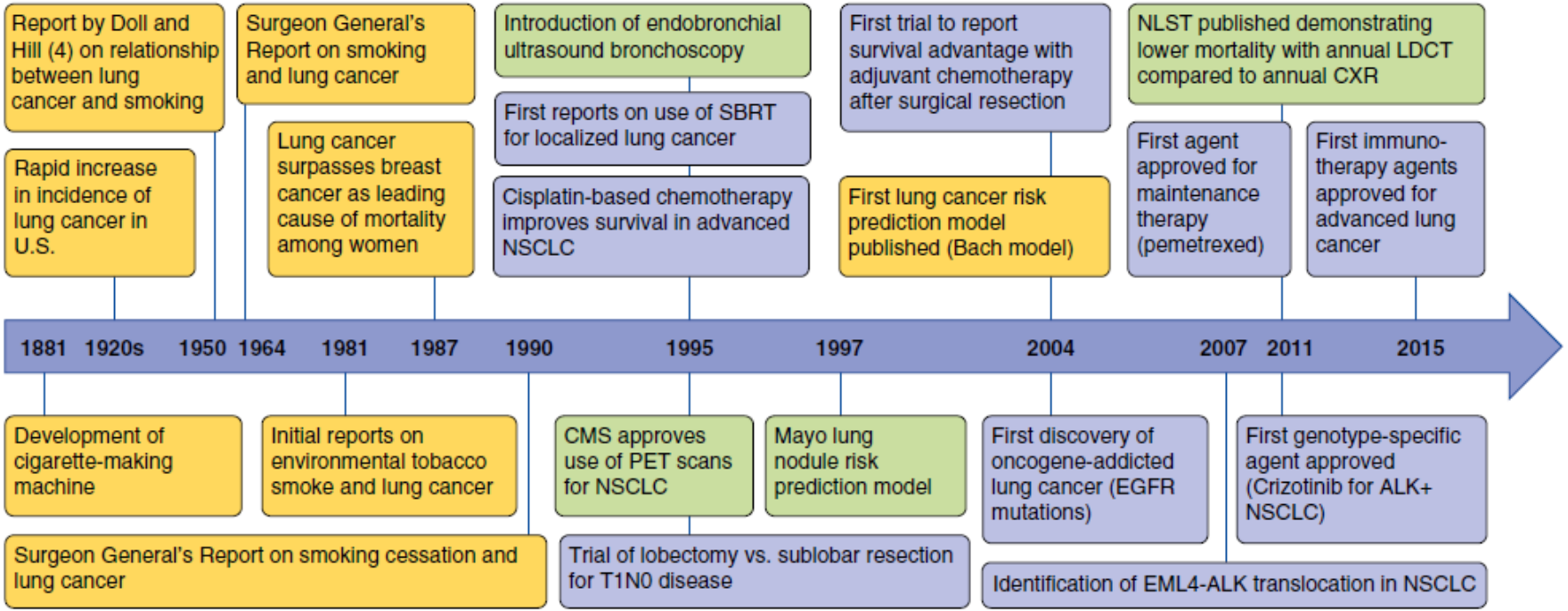
Disclosures

- **No personal financial disclosures**

- **Sponsored Research at Gustave Roussy Cancer Center**
  Abbvie, Amgen, AstraZeneca, Biogen, Blueprint Medicines, BMS, Celgene, Eli Lilly, GSK, Ignyta, IPSEN, Merck KGaA, MSD, Nektar, Onxeo, Pfizer, Pharma Mar, Sanofi, Spectrum Pharmaceuticals, Takeda, Tiziana Pharma.

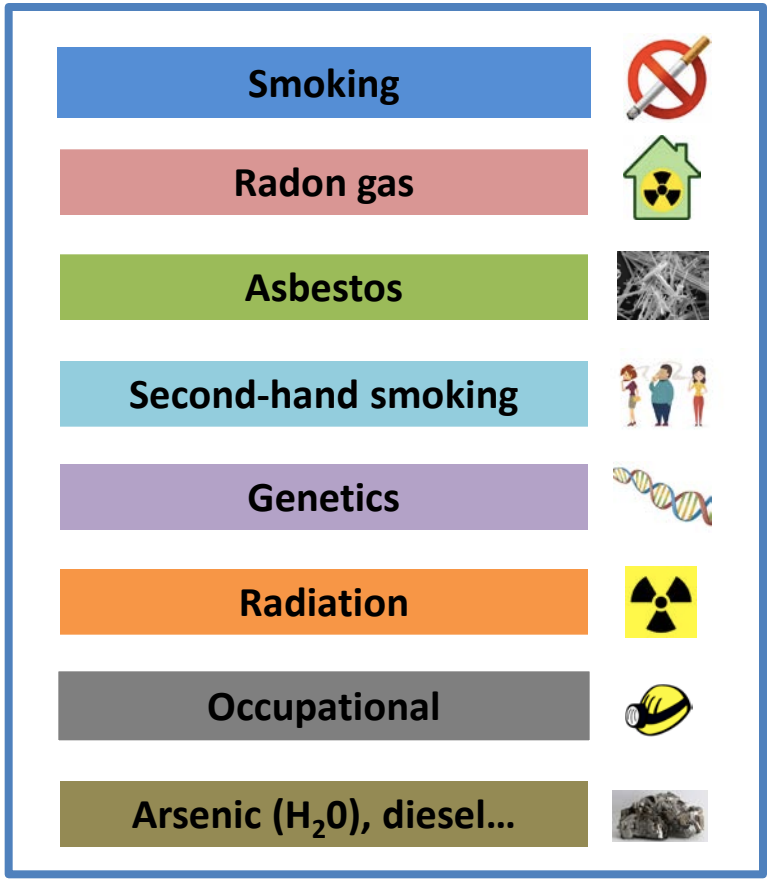
- **Investigator or co-investigator of trials**
  Nerviano, GSK, Pfizer, Roche-Genentech, Lilly, OSE Pharma, MSD, Celgene, Stemcentrx, Ignyta, Abbvie, Loxo Oncology, AstraZeneca, Blueprint Medicines.


Development of cigarette-making machine
Report by Doll and Hill (4) on relationship between lung cancer and smoking
Rapid increase in incidence of lung cancer in U.S.
Surgeon General's Report on smoking and lung cancer
Lung cancer surpasses breast cancer as leading cause of mortality among women
Initial reports on environmental tobacco smoke and lung cancer
Surgeon General's Report on smoking cessation and lung cancer
Introduction of endobronchial ultrasound bronchoscopy
First reports on use of SBRT for localized lung cancer
Cisplatin-based chemotherapy improves survival in advanced NSCLC
CMS approves use of PET scans for NSCLC
Trial of lobectomy vs. sublobar resection for T1N0 disease
Mayo lung nodule risk prediction model
First trial to report survival advantage with adjuvant chemotherapy after surgical resection
First lung cancer risk prediction model published (Bach model)
First discovery of oncogene-addicted lung cancer (EGFR mutations)
Identification of EML4-ALK translocation in NSCLC
NLST published demonstrating lower mortality with annual LDCT compared to annual CXR
First agent approved for maintenance therapy (pemetrexed)
First genotype-specific agent approved (Crizotinib for ALK+ NSCLC)
First immuno-therapy agents approved for advanced lung cancer
1881
1920s
1950
1964
1981
1987
1990
1995
1997
2004
2007
2011
2015

In 15 years

- **Carcinogenesis**

Lung cancer risk factors



- **Group 1 Carcinogen** by *International Agency of Research on Cancer (IARC, WHO)*

- **<u>Smoking</u>** ≈ 80- 90% cases

(RR x 5-10)

- **<u>Radon gas</u>** ≈ 10% cases

✓ *1st risk factor in non-smokers (OMS)*

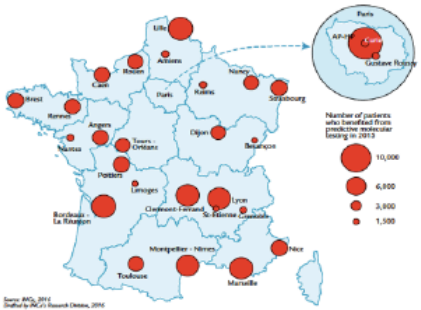
✓ *2nd cause in smokers: synergism*

American Cancer Society 2018, CDC 2018, WHO IARC 2018

METHODS

INSTITUT NATIONAL DU CANCER

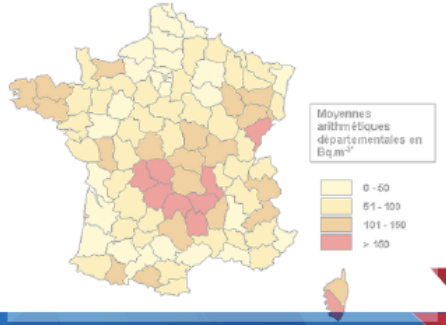
- **National registry**
- **% of driver** molecular alt. by region
- **Period:** 2012-2016



IRSN
INSTITUT DE RADIOPROTECTION ET DE SÛRETÉ NUCLÉAIRE

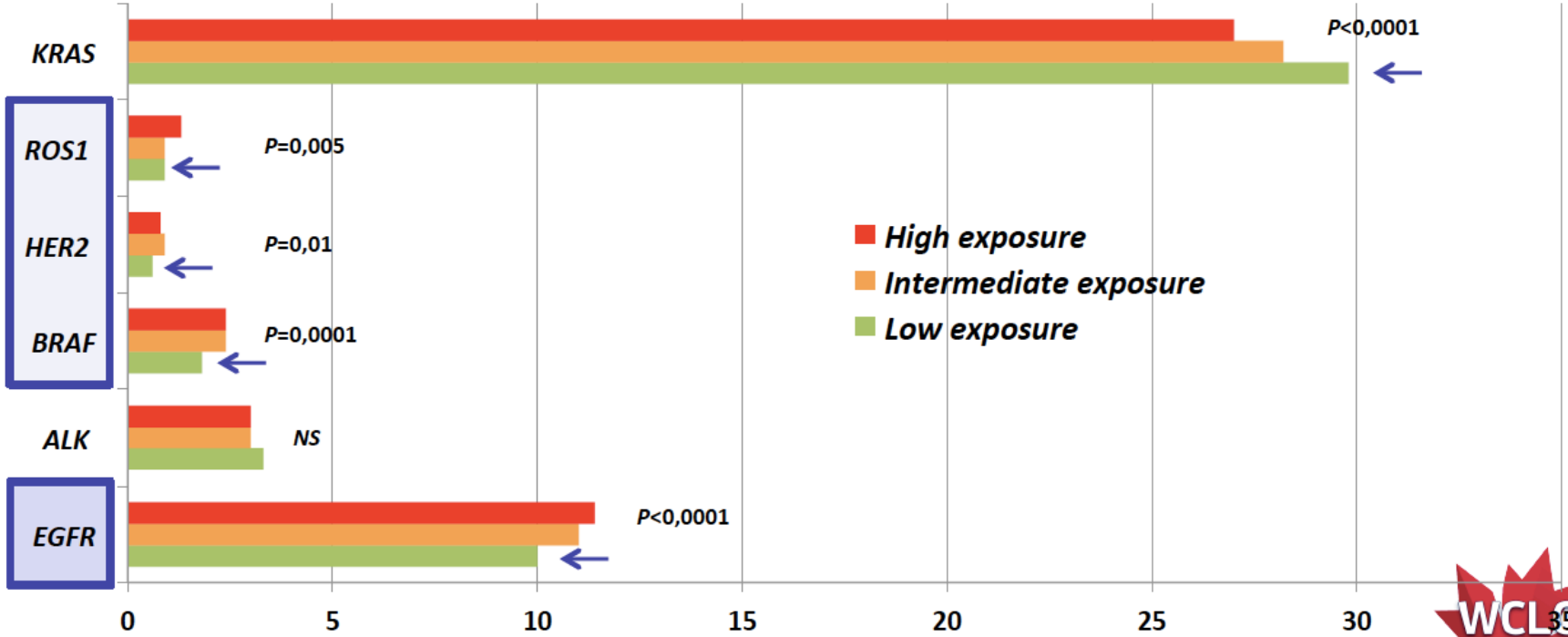
Estimated risk by region in France

High	*Intermediate*	*Low*
Auvergne-Rhône-Alpes	*Bourgogne-Franche-Comté*	*Centre Val-de-Loire*
Bretagne	*Nouvelle Aquitaine*	*Grand Est*
Normandie	*Occitanie*	*Hauts de France*
Pays de la Loire	*Provence-Alpes-Cote-d'Azur*	*Ile de France*



WCLC 2018

Radon France, *by molecular subtype*



Adolescent Vaping and Nicotine Use — U.S.

Lung cancer risk factors

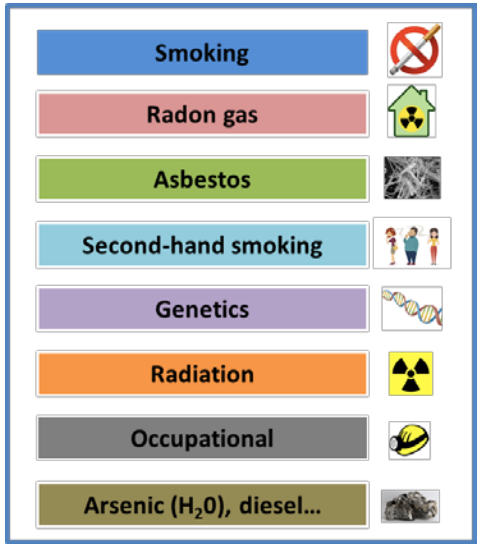


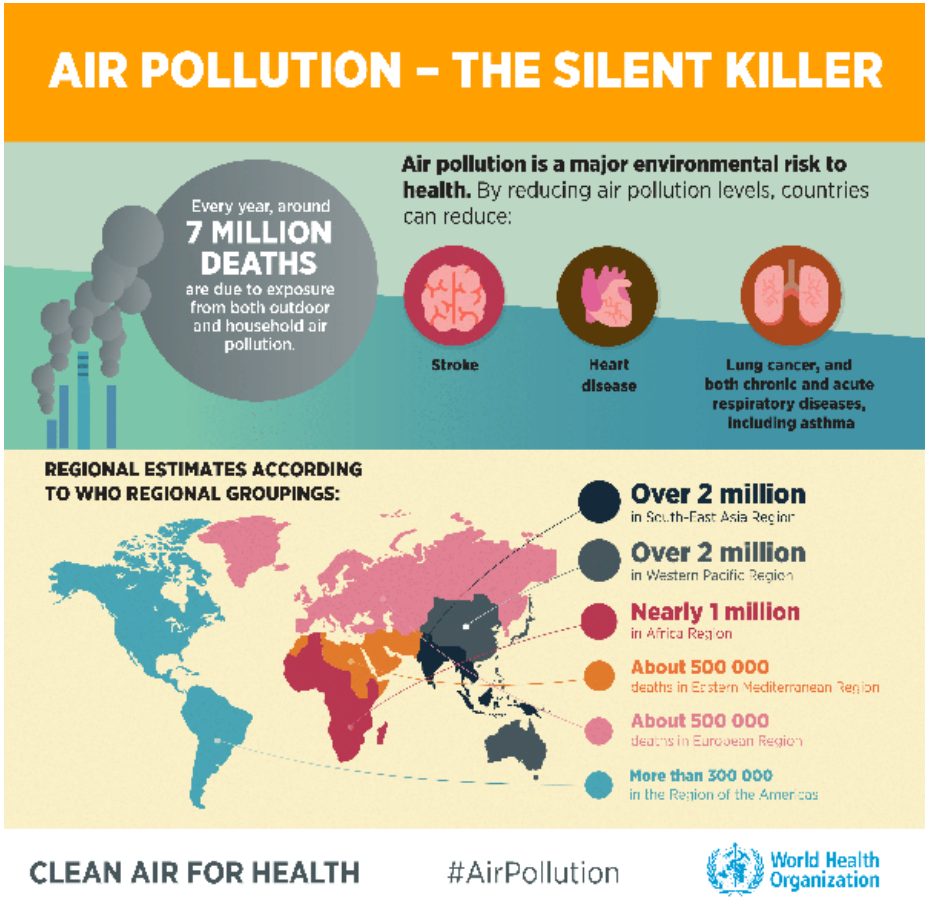
Table 1. Prevalence of Vaping in the Past 30 Days, According to Substance, School Grade, and Year.*

Substance and School Grade	Prevalence in 2017 (95% CI)	Prevalence in 2018 (95% CI)	Change from 2017 to 2018 (95% CI)
	percent		*percentage points*
Vaped nicotine			
12th grade	11.0 (9.2–13.0)	20.9 (17.7–24.6)	10.0 (6.5–13.4)
10th grade	8.2 (6.6–10.2)	16.1 (14.0–18.6)	7.9 (5.6–10.2)
8th grade	3.5 (2.9–4.2)	6.1 (5.1–7.4)	2.6 (1.4–3.8)
Vaped flavoring			
12th grade	9.7 (8.4–11.0)	13.5 (11.8–15.4)	3.8 (1.8–5.9)
10th grade	9.2 (7.7–10.8)	13.1 (11.5–15.0)	3.9 (1.8–6.1)
8th grade	5.3 (4.5–6.3)	8.1 (6.8–9.6)	2.8 (1.2–4.3)
Vaped nicotine or flavoring†			
12th grade	15.2 (13.3–17.4)	25.0 (21.6–28.7)	9.8 (6.1–13.4)
10th grade	12.0 (10.2–14.1)	20.3 (17.9–22.9)	8.3 (5.6–11.0)
8th grade	6.3 (5.4–7.3)	9.7 (8.2–11.4)	3.4 (1.7–5.1)

Risk of Lung Cancer?
New mutational spectrum?

American Cancer Society 2018, CDC 2018, WHO IARC 2018
Miech, NEJM 2019

Our major challenge



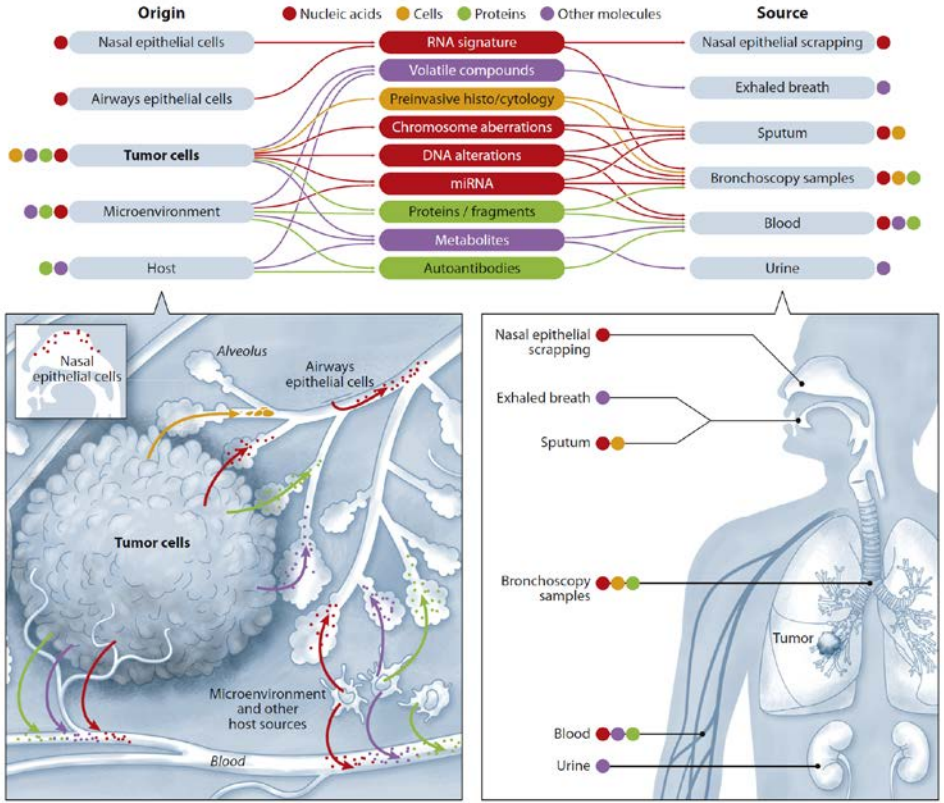
What will be the mutational spectrum of these cancers?

http://www.euro.who.int/en/health-topics/environment-and-health/air-quality/news/news/2018/5/over-half-a-million-premature-deaths-annually-in-the-european-region-attributable-to-household-and-ambient-air-pollution/infographic-air-pollution-the-silent-killer

In 15 years

- **Carcinogenesis**
- **Screening**

Biomarker candidates for screening



- **Management of indeterminate pumonary nodules**

- **Risk assessment**
  - **Risk factors**
  - **Personalized**

Seijo, JTO 2019

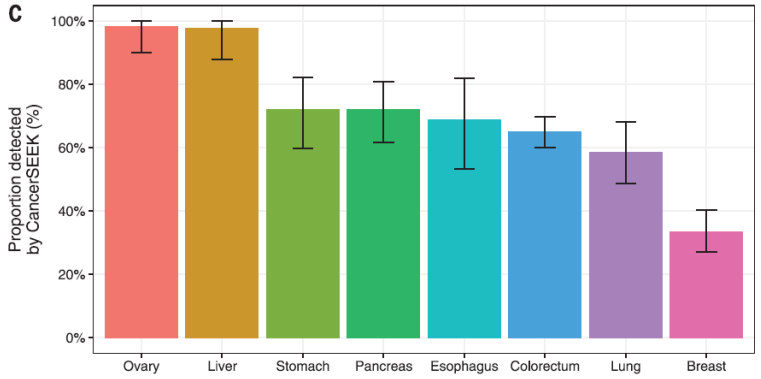
Multi-analyte blood test for screening

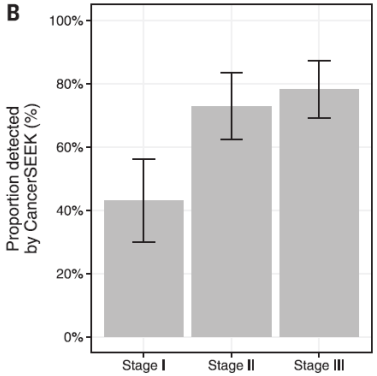
AFP
Angiopoietin-2
AXL
CA-125
CA 15-3
CA19-9
CD44
CEA
CYFRA 21-1
DKK1
Endoglin
FGF2
Follistatin
Galectin-3
G-CSF
GDF15
HE4
HGF
IL-6
IL-8
Kallikrein-6
Leptin
LRG-1
Mesothelin
Midkine
Myeloperoxidase
NSE
OPG
OPN
PAR
Prolactin
sEGFR
sFas
SHBG
sHER2/sEGFR2/sErbB2
sPECAM-1
TGFa
Thrombospondin-2
TIMP-1
TIMP-2
Vitronectin

41 proteins

NRAS	TP53
NRAS	TP53
CTNNB1	TP53
CTNNB1	TP53
PIK3CA	TP53
PIK3CA	TP53
PIK3CA	TP53
PIK3CA	TP53
FBXW7	TP53
FBXW7	TP53
FBXW7	TP53
FBXW7	TP53
APC	TP53
APC	TP53
EGFR	TP53
BRAF	TP53
CDKN2A	TP53
CDKN2A	TP53
PTEN	TP53
PTEN	TP53
PTEN	TP53
PTEN	TP53
FGFR2	TP53
HRAS	TP53
KRAS	TP53
KRAS	TP53
KRAS	TP53
AKT1	TP53
TP53	TP53
TP53	PPP2R1A
	GNAS

16 genes





1005 patients with stage I to III pan-cancer and 812 cancer-free controls.

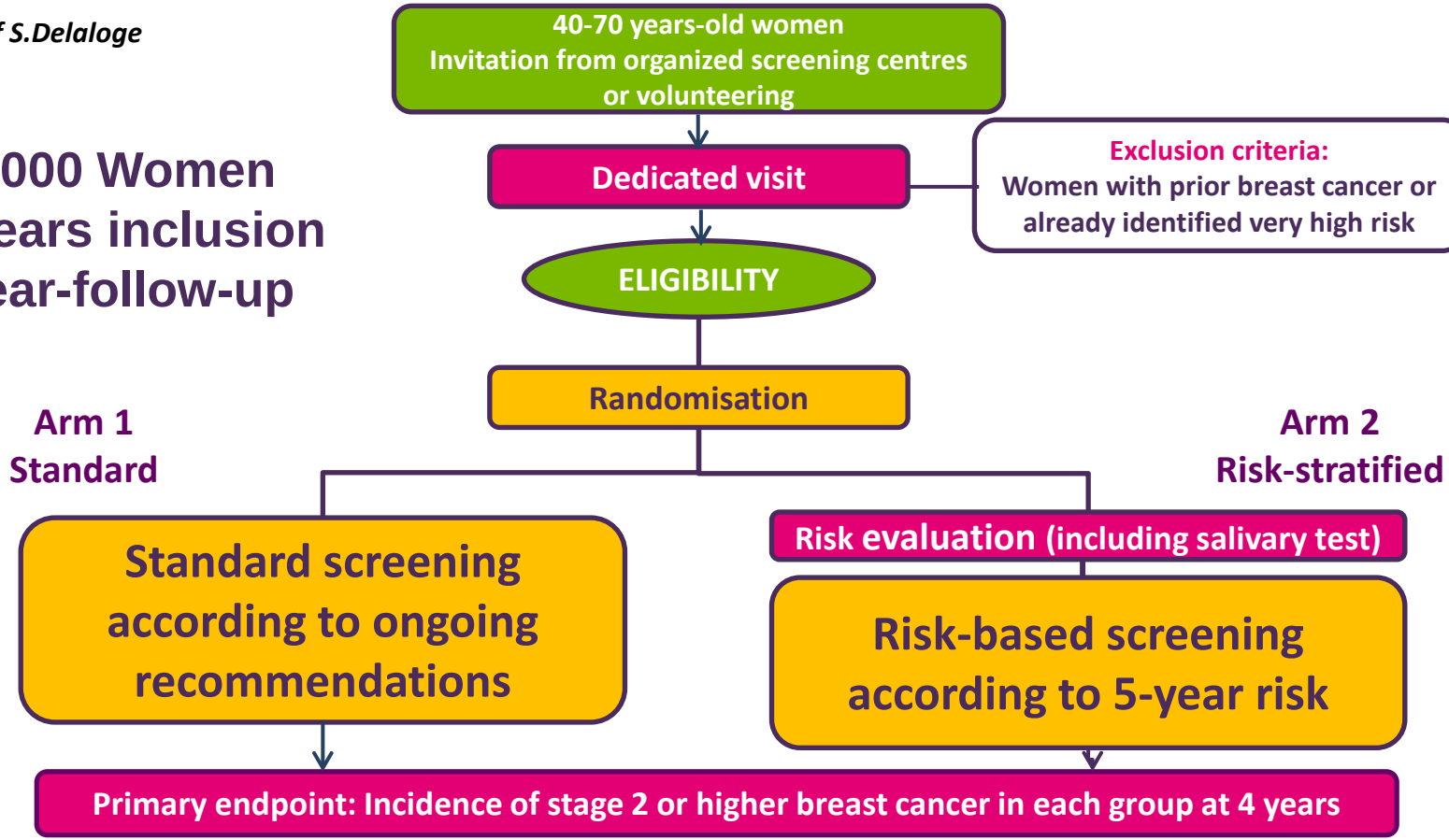
Specificity higher than 99%
Sensitivity 33% for breast cancer to 98% for ovarian cancer, 59% lung cancer (n= 104).

Cohen, Science 2018

MyPeBS –Study scheme

Courtesy of S.Delaloge

85,000 Women
2.5 years inclusion
4 year-follow-up



Past, present and future of NSCLC

Screening

2004 **2019** **2034**

Low Dose CT
Based on smoking status

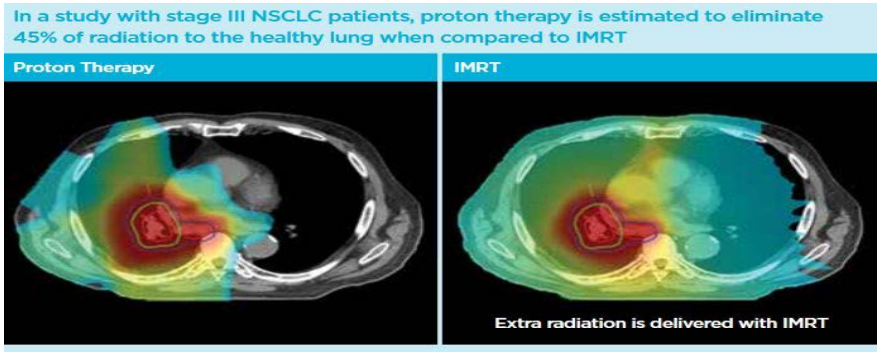
Low Dose CT
Based on smoking status
And other risk factors
And personalized

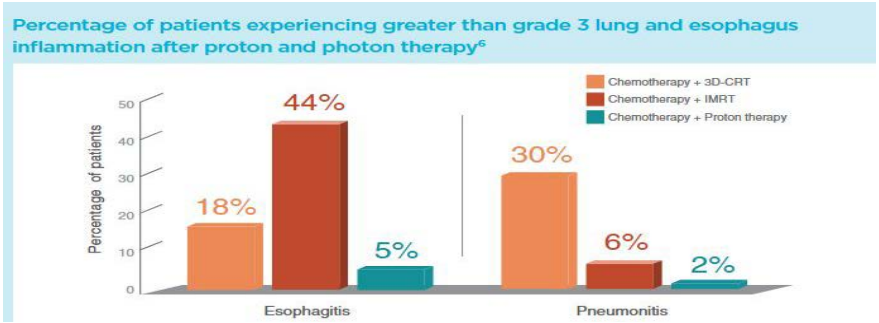
In 15 years

- **Carcinogenesis**
- **Screening**
- **Local treatment**

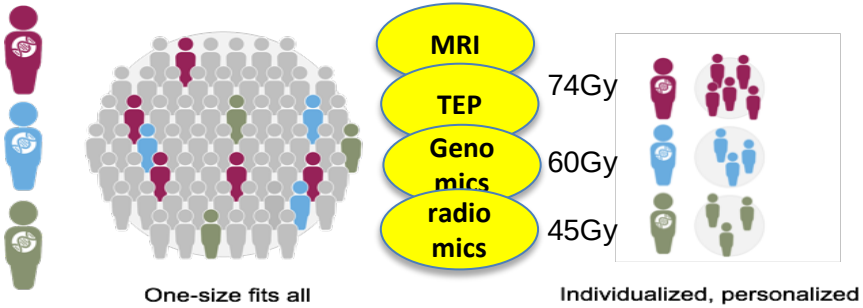
Radiotherapy in 15 years

Proton therapy?

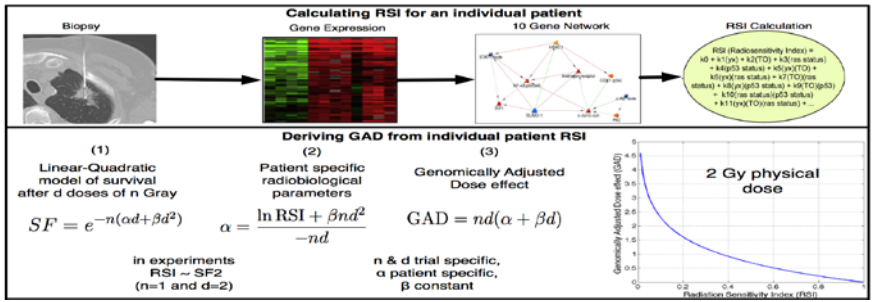




Tumor biology and XRT dose?



Genome-based model for adjusting radiotherapy dose (GARD)

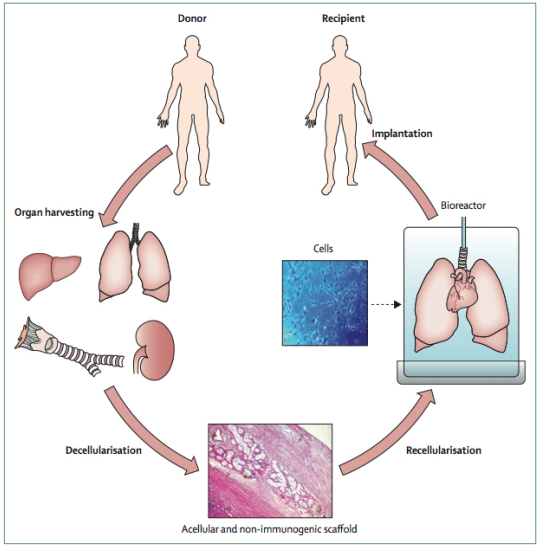


Sejpal Cancer 2011, Scott et al., Lancet Oncol 2017

Surgery in 15 years

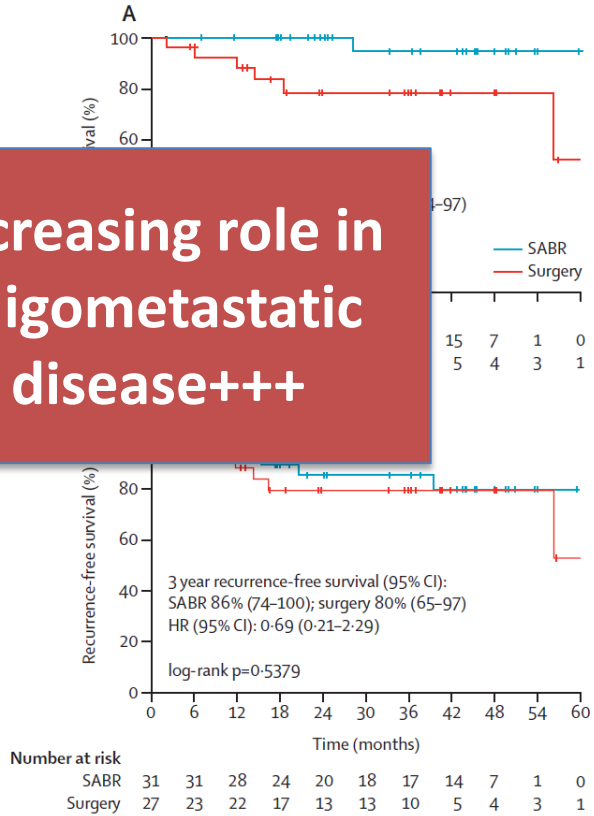
Robotic Surgery

Engineered whole organs and complex tissues



Ricciardi et al, J Thorac Dis 2018, Badylak et al, Lancet 2012

Surgery vs. SABR ?



Increasing role in oligometastatic disease+++

Pooled analysis ROSEL & STARS studies

Phase II study

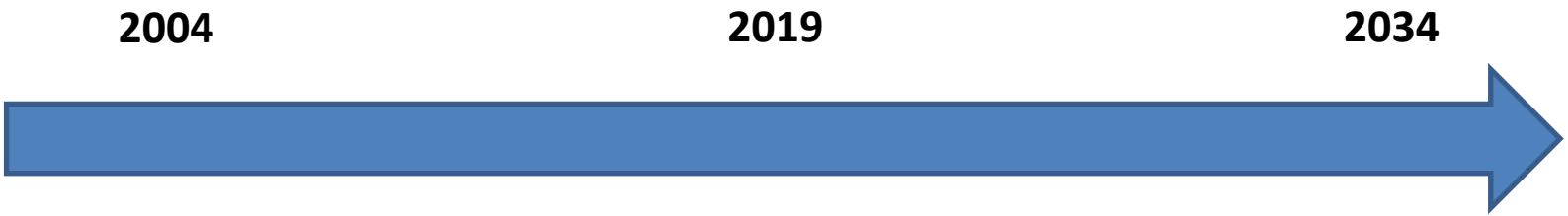
SABR followed by surgery at 10 weeks

Characteristic	All Patients Undergoing Surgery[a] (n = 36)
Pathologic complete response[b]	21 (60)
Pathologic N stage[c]	
ypN0	32 (91)
ypN1	1 (3)
ypN2	2 (6)
Pathologic tumor size, mean (SD), cm	1.8 (1.0)
No. of mediastinal lymph nodes sampled, median (range)	6 (0-16)
Mediastinal lymph nodes, mean (SD), % positive	3.5 (17.0)
Time from start of SABR to surgery, mean (SD), mo	2.9 (0.4)

Chang Lancet Oncol 2015, Palma JAMA Oncol

Past, present and future of NSCLC

Resectable NSCLC



Past, present and future of NSCLC

Resectable NSCLC

2004	2019	2034
Surgery	Surgery SABR	SABR Surgery
Peri-op Chemo *Based on stage*	~~De-escalation ERCC1~~	Peri-op Chemo *Based on stage*
Peri-op RT *Based on stage*		Post-op RT *Based on stage*

Breast cancer adjuvant chemo history

The New England Journal of Medicine

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Volume 332 APRIL 6, 1995 Number 14

ADJUVANT CYCLOPHOSPHAMIDE, METHOTREXATE, AND FLUOROURACIL IN NODE-POSITIVE BREAST CANCER

The Results of 20 Years of Follow-up

GIANNI BONADONNA, M.D., PINUCCIA VALAGUSSA, B.S., ANGELA MOLITERNI, M.D., MILVIA ZAMBETTI, M.D., AND CRISTINA BRAMBILLA, M.D.

1976 adjuvant chemo

Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-ye an overview of the randomised trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)*

Tamoxifen and Chemotherapy for Lymp Node-Negative, Estrogen Receptor-Positive Breast Cancer

*Bernard Fisher, James Dignam, Norman Wolmark, Arthur DeCillis, Birol Emir, D. Lawrence Wickerham, John Bryant, Nikolay V. Dimitrov, Neil Abramson, James N. Atkins, Henry Shibata, I Richard G. Margolese**

End of 90s: all benefit!

2000s: only few really drive an absolute benefit

Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial

Kathy S Albain, William E Barlow, Steven Shak, Gabriel N Hortobagyi, Robert B Livingston, I-Tien Yeh, Peter Ravdin, Roberto Bugarini, Frederick L Baehner, Nancy E Davidson, George W Sledge, Eric P Winer, Clifford Hudis, James N Ingle, Edith A Perez, Kathleen I Pritchard, Lois Shepherd, Julie R Gralow, Carl Yoshizawa, D Craig Allred, C Kent Osborne, Daniel F Hayes, for The Breast Cancer Intergroup of North America

Courtesy of S.Delaloge

Bonadonna NEJM 1976, Fisher J Clin Oncol 1997, EBCTCG Lancet 2005, Albain Lancet Oncol 2009

Breast cancer adjuvant chemo history

TNBC and HER2+

1. Cancer subtypes drive primary trt choices

Effects of cher
early breast ca
an overview o

Tamoxifen and Chemotherapy for Lymp
Node-Negative, Estrogen Receptor-Positive
Breast Cancer

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)*

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End of 90s: all benefit!

Luminal cancer

1976 adjuvant chemo

A ROLE FOR TKI?

Courtesy of S.Delaloge

Bonadonna NEJM 1976, Fisher J Clin Oncol 1997, EBCTCG Lancet 2005, Albain Lancet Oncol 2009

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End of 90s: all benefit!

Luminal cancer

1976 adjuvant ch

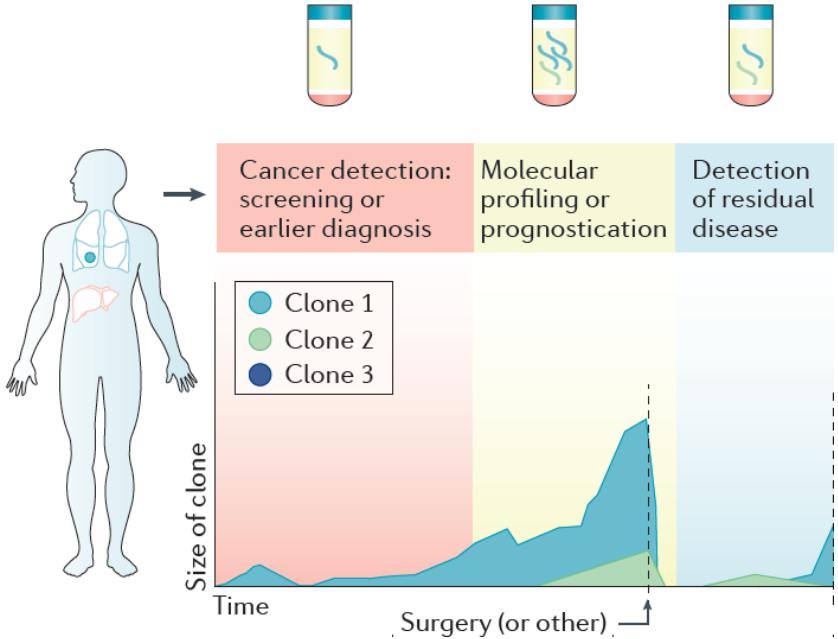
2. Additional Prognostic tools and biomarkers refine trt choices
https://breast.predict.nhs.uk/,
OncotypeDX™, Mammaprint ®, EpClin® e

A LUNG ONCOTYPEDX?

Courtesy of S.Delaloge

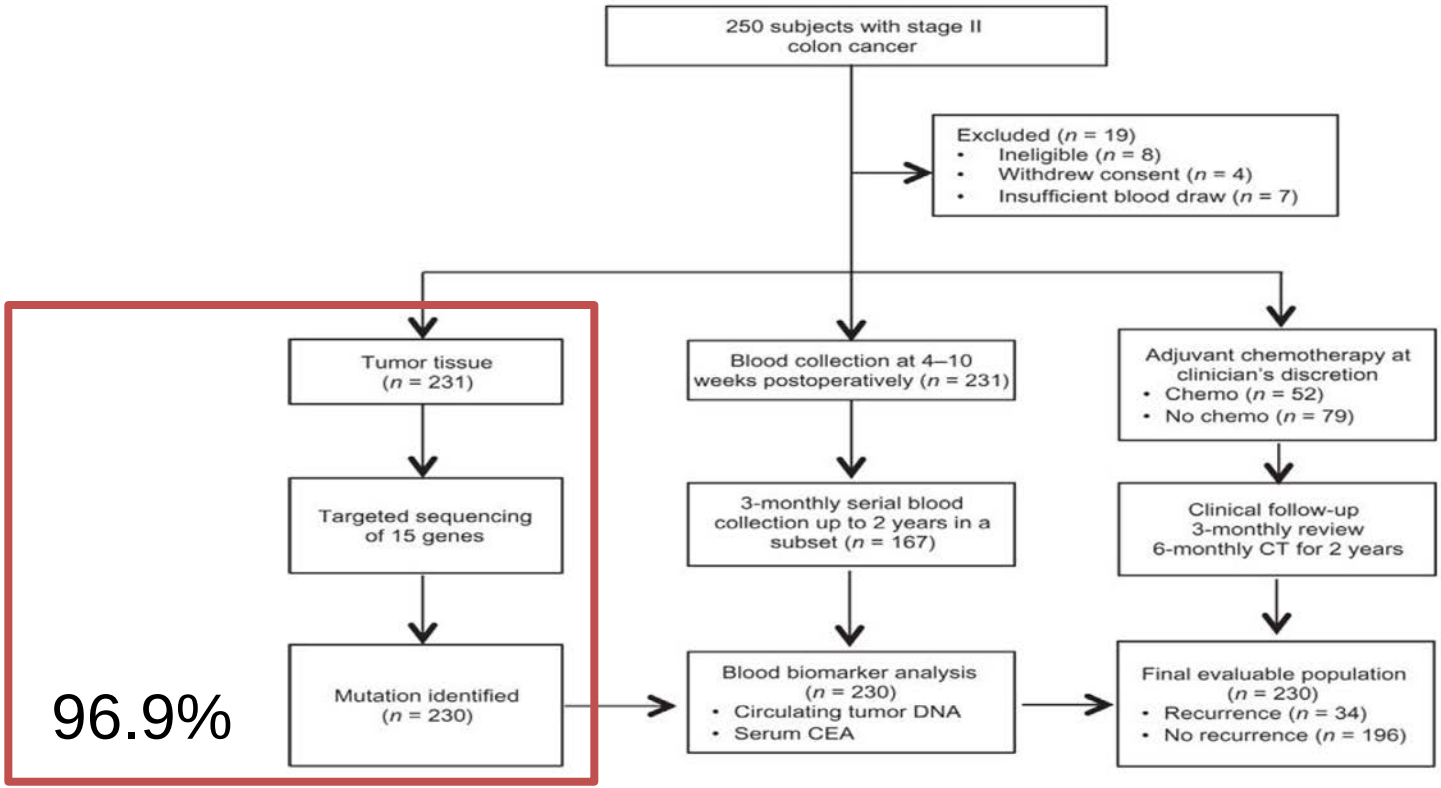
Bonadonna NEJM 1976, Fisher J Clin Oncol 1997, EBCTCG Lancet 2005, Albain Lancet Oncol 2009

Minimal disease



Wan Nat Rev Cancer 2017

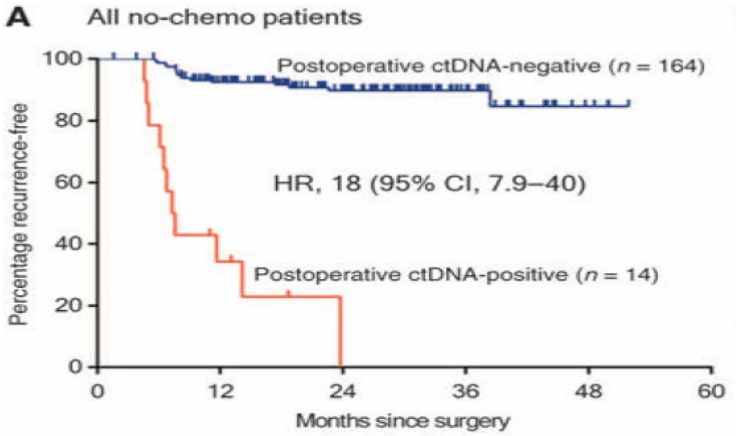
cfDNA in resected stage II colorectal cancer

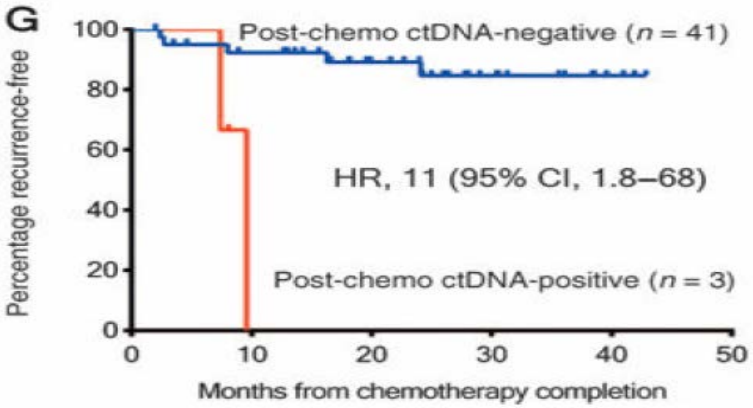


Tie J, Sci. Transl. Med. 2016

cfDNA in resected stage II colorectal cancer

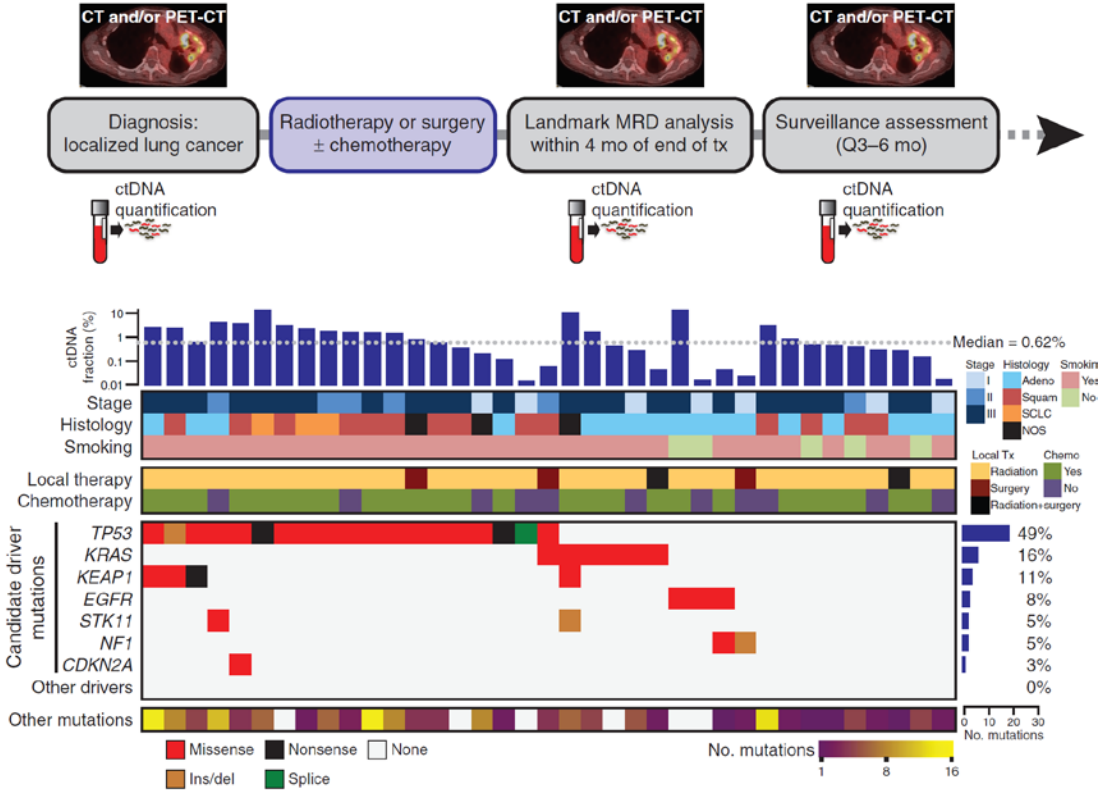
- 1046 plasma from 230 patients
- ctDNA detected in 14 patients (7.9%)



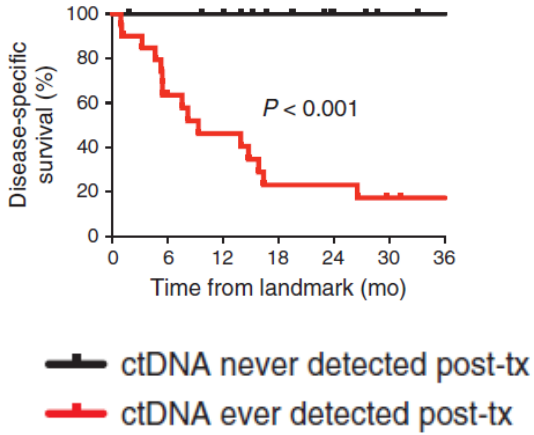


Tie J, Sci. Transl. Med. 2016

Minimal Residual Disease

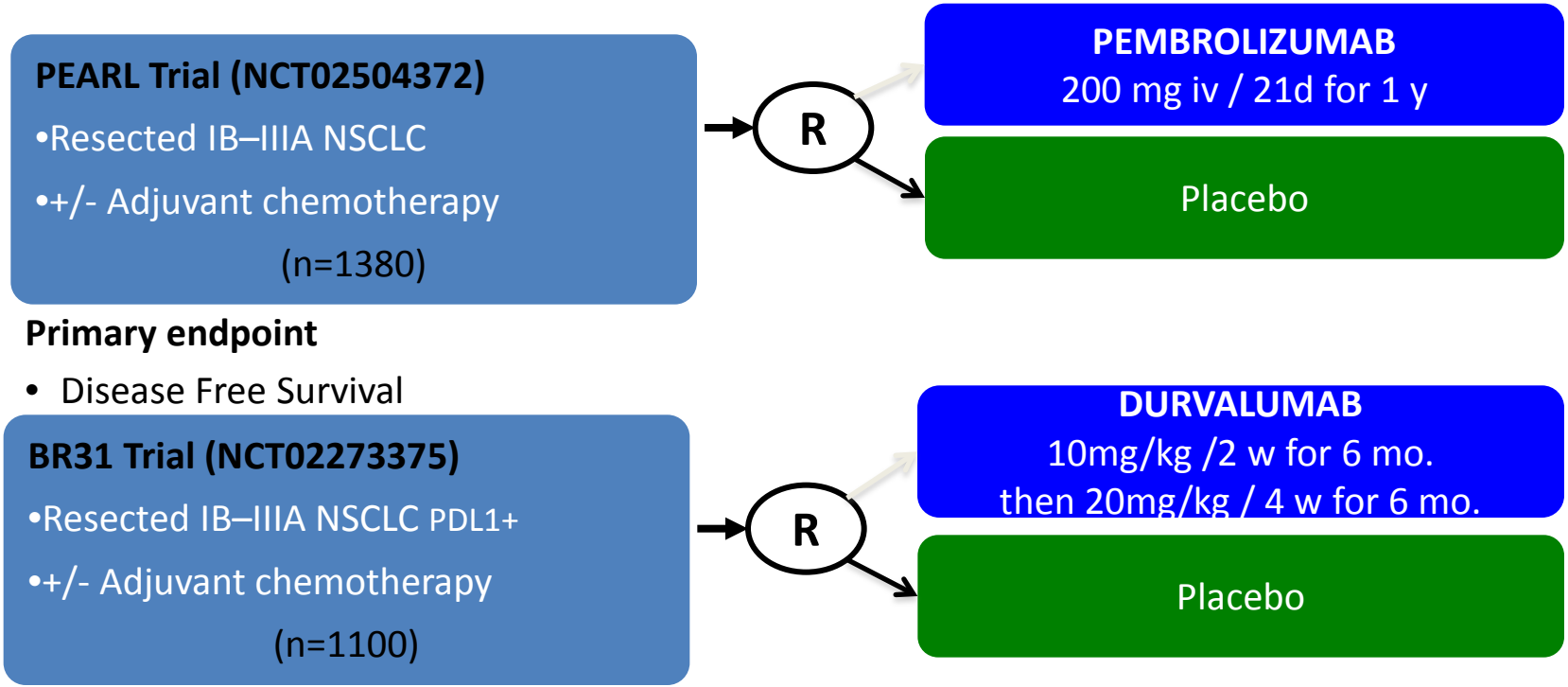


40 pts
Follow up : 20 ctDNA+
ctDNA before scan PD : 72%
Median : 5.2 months before



Chaudhury Cancer Discovery 2017

Adjuvant immunotherapy trials in NSCLC



Past, present and future of NSCLC

Resectable NSCLC

2004	2019	2034
Surgery	Surgery SABR	SABR Surgery
Peri-op Chemo *Based on stage*	~~De-escalation ERCC1~~	Peri-op Chemo *Based on stage*	De-escalation ctDNA Peri-op immunoth Pronostic tools	Peri-op Chemo-IO *Based on MRD and pronostic tool*
Peri-op RT *Based on stage*		Post-op RT *Based on stage*		Post-op RT *Based on stage*

In 15 years

- Carcinogenesis
- Screening
- Local treatment
- Stage III

Past, present and future of NSCLC

Stage III NSCLC

2004		2019	2034
Radiotherapy 2D		Radiotherapy 4D	
Surgery		Surgery	
Concomitant Chemo *Based on PS*	~~Cetuximab~~	Concomitant Chemo *Based on PS*	
	~~Boost~~		
		Consolidation IO *Based on PD-L1*	

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Consolidation immunothera

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

July 26th 2018
DURVALUMAB consolidation approved in PDL1+≥≥1% stage III NSCLC

Stage III NSCLC

Concomitant platinum-based RT

WHO PS score 0 or 1

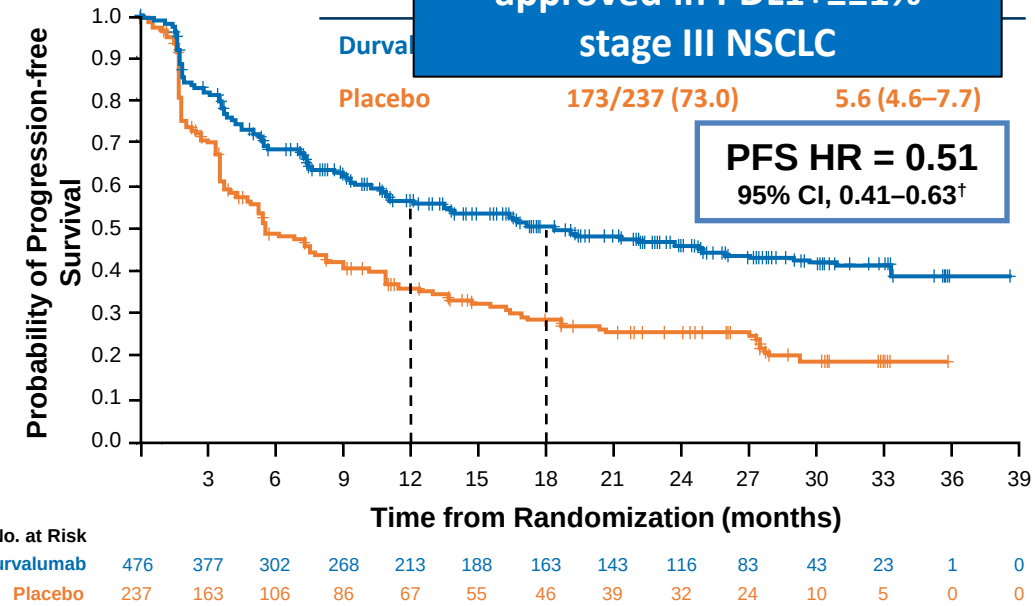
1-42 days post RT

R

Durvalumab
10 mg/kg q2w
1 yr
n = 476

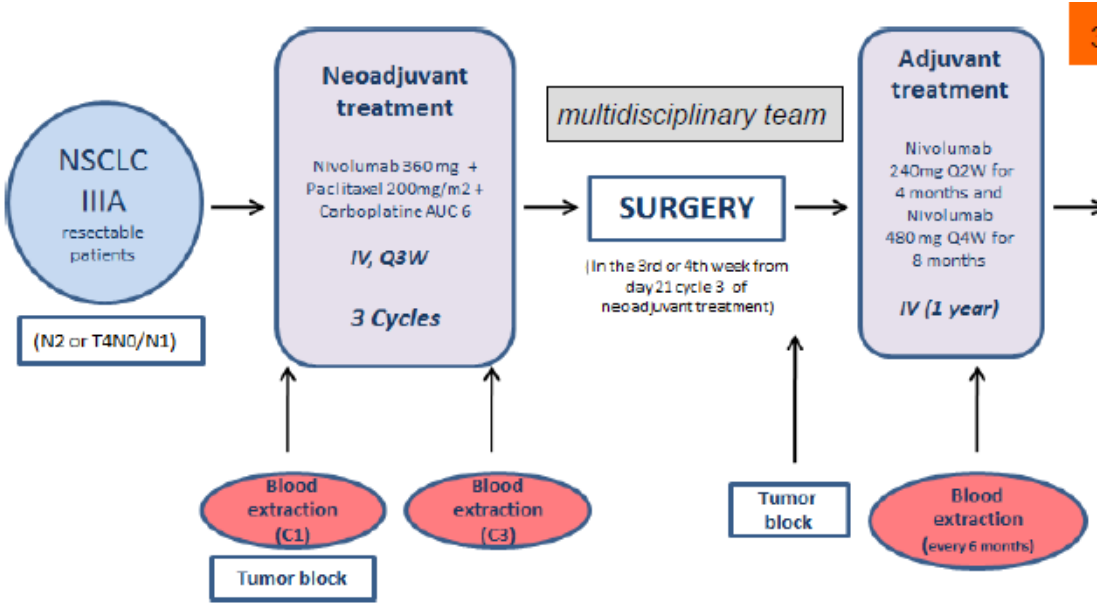
2:1 randomization, stratified by age, sex, and smoking history
N = 713

Placebo
10 mg/kg q2w
1 yr
n = 237



Antonia – WCLC 2018

Induction Chemo-IO
NADIM study



Clinical response

	N	%
Complete response (CR)	3	10.0
Partial response (PR)	18	60.0
Stable disease (SD)	9	30.0
Total	30	100.0

Pathological response

	N	%
Major response[1]	24	80.0
Complete response	18	75.0
Less < 90%	6	20.0
Total	30	100.0

Provencio WCLC 2018

Past, present and future of NSCLC

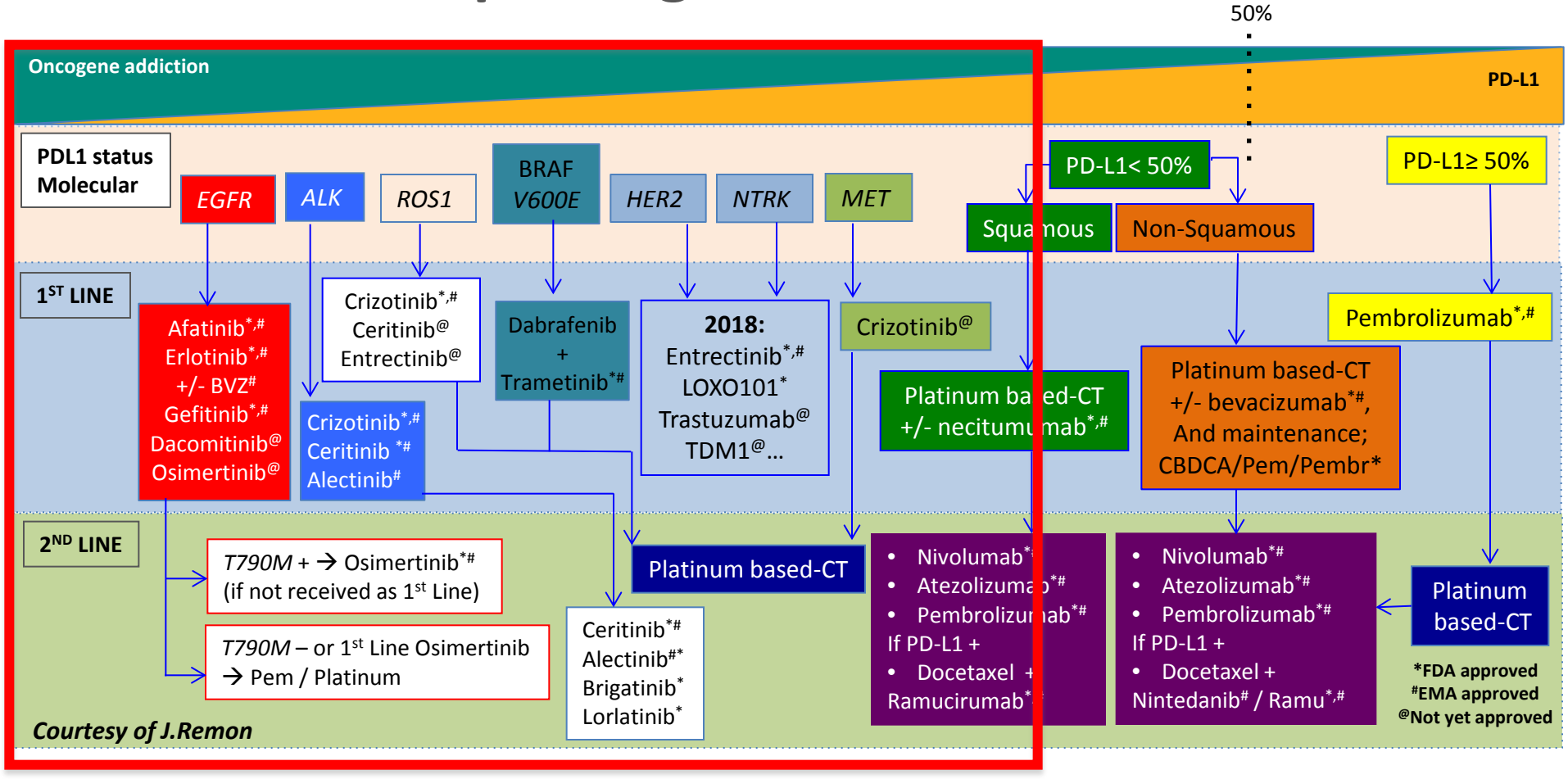
Stage III NSCLC

2004		2019	2034
Radiotherapy 2D		Radiotherapy 4D	Radiotherapy pet uptake driven, proton
Surgery		Surgery	Surgery
Concomitant Chemo *Based on PS*	~~Cetuximab~~ ~~Boost~~	Concomitant Chemo *Based on PS*	Concomitant+ consolidation Chemo *Based on PS and MRD*
		Consolidation IO *Based on PD-L1*	Concomitant IO

In 15 years

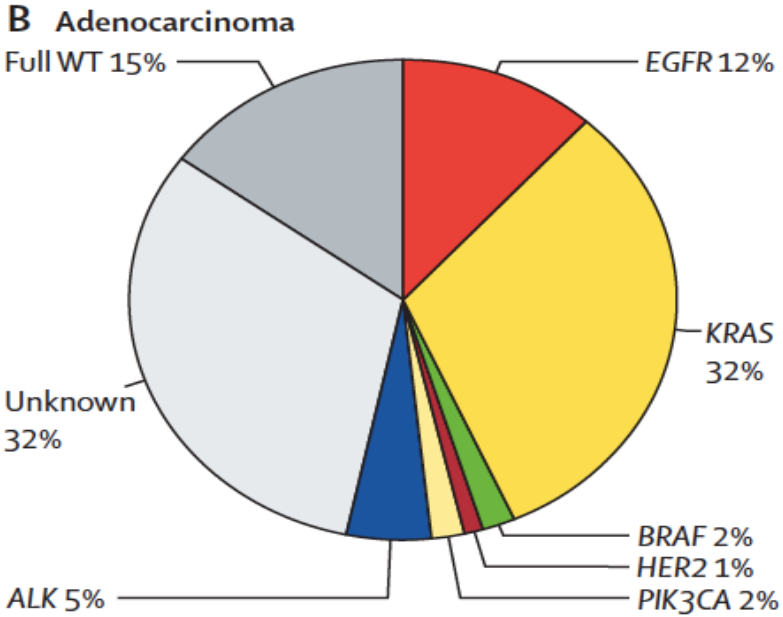
- Carcinogenesis
- Screening
- Local treatment
- Stage III
- Biomarkers

New treatment paradigm in NSCLC



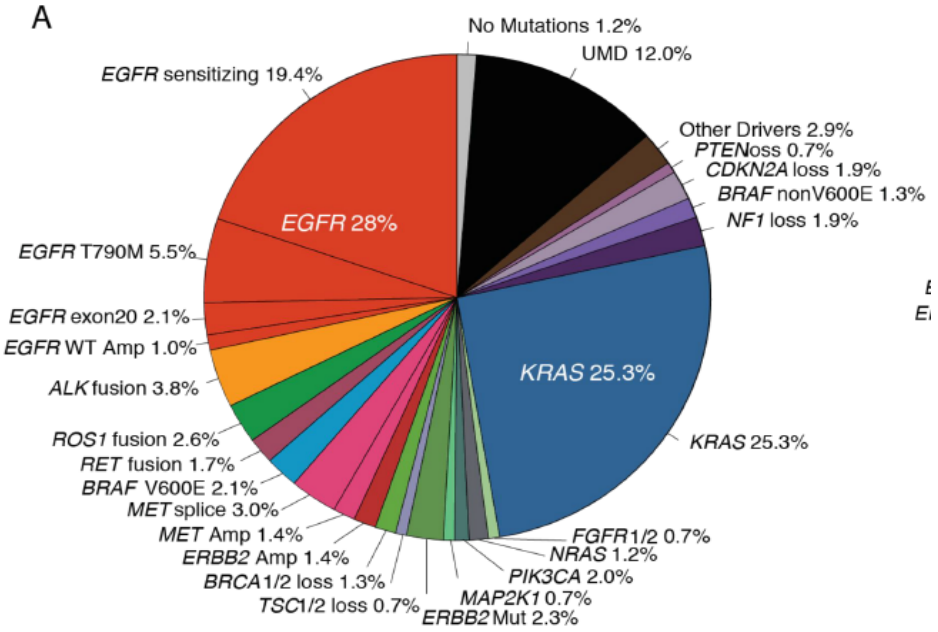
Personalised treatment

N=17,664 (76% ADC). 6 cancer-associated genes



21% Potentially actionable alterations. 11 days

N=860 ADC. ≥ 300 cancer-associated genes



87% Potentially actionable alterations. 28 days

Courtesy of J.Remon

Barlesi – Lancet 2015 * Jordan- Cancer Discovery 2017

MOSCATO trial

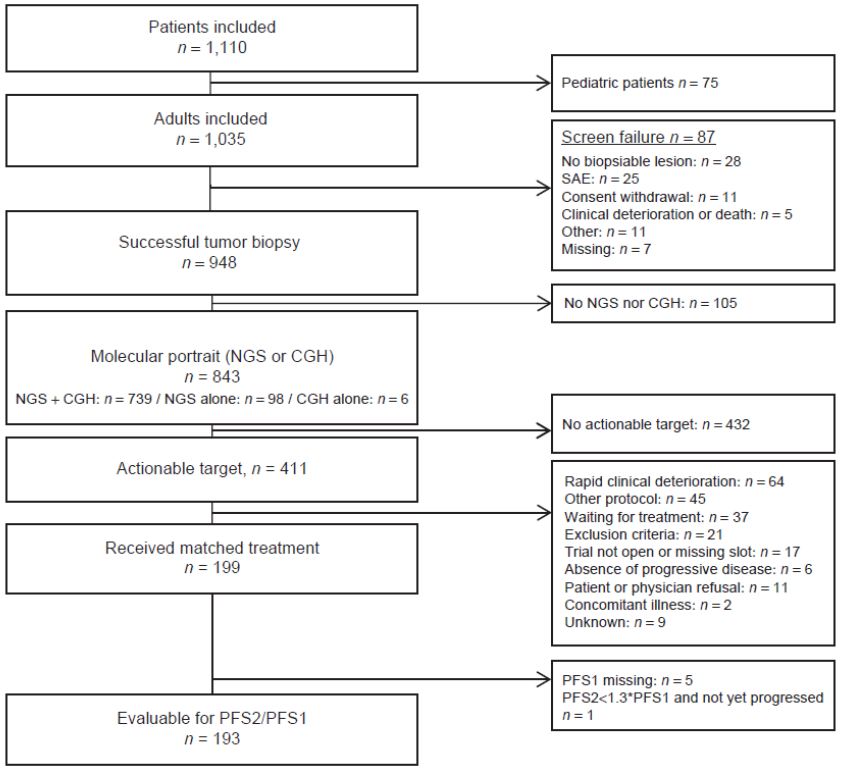
Adults n= 1035

Molecular portrait n=843 (81%)

Actionable target n=411 (40%)

Matched treatment N=199 (19%)

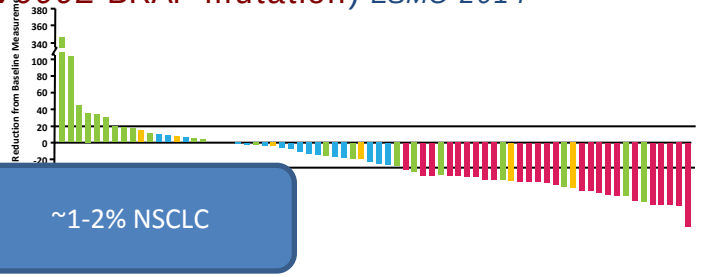
Evaluable PFS2/PFS1 n=193 (19%)



Massard - Cancer Dis. 2017

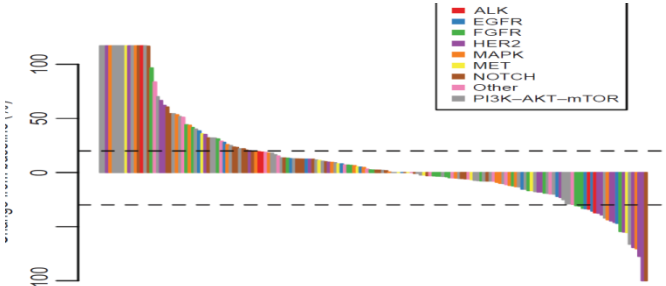
I want de-addiction

B-RAF inhibitor in NSCLC
(*V600E* BRAF mutation) *ESMO 2014*

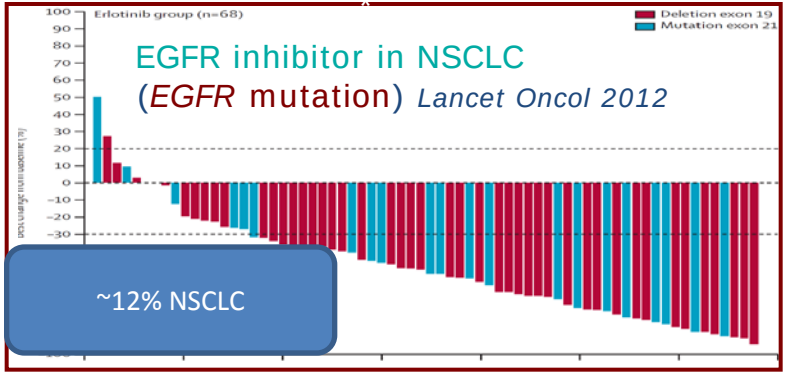


~1-2% NSCLC

MOSCATO *Cancer Dis 2017*

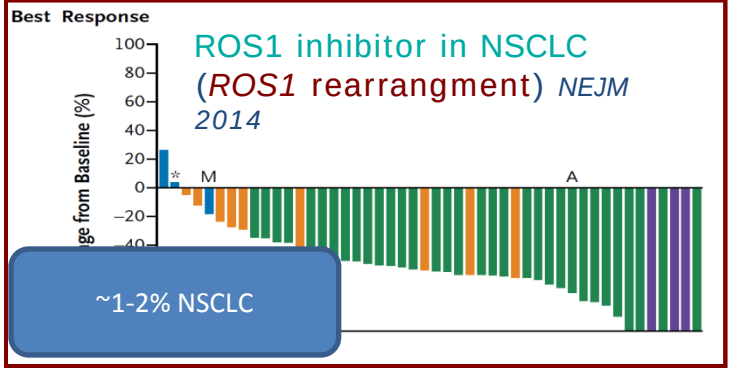


EGFR inhibitor in NSCLC
(*EGFR* mutation) *Lancet Oncol 2012*



~12% NSCLC

ROS1 inhibitor in NSCLC
(*ROS1* rearrangment) *NEJM 2014*

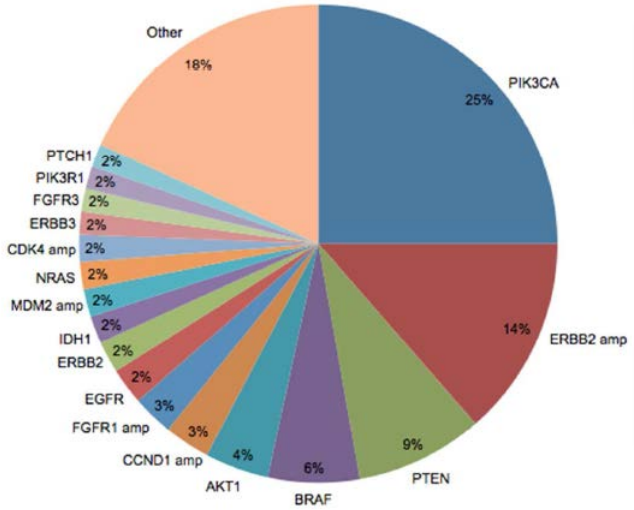


~1-2% NSCLC

Most of the targets are 'SOFT'

Oncology use and Perception of NGS

146 physicians pertaining to 1932 patients diagnosed with one of 49 cancer types



Treatment altered: 21%

13% gene-matched trial
Median time enrol ~5 mo.

By physician

Treatment NOT altered

Physicians reported actionable alterations in 55%

Experts reported alterations in 45%

Physician and expert assessment (OncoKB.org) about actionable alteration differ suggesting that utility and physicians ability to interpret data merits further improvement

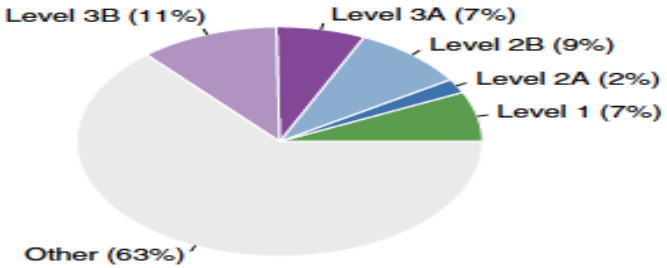
Schram – Ann Oncol 2017

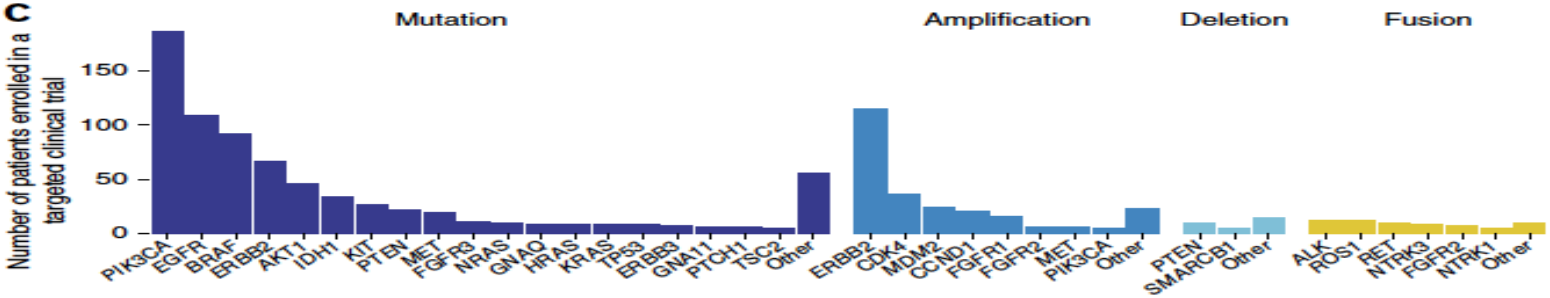
Courtesy of Jordi Remon

MSK-IMPACT

10,945 patients (1,563 NSCLC)
(2014-2016)

Level 1	FDA-recognized biomarker for an FDA-approved drug in the same indication
Level 2A	Standard of care biomarker for an FDA-approved drug in the same indication
Level 2B	Standard of care biomarker for an FDA-approved drug in another indication
Level 3A	Compelling clinical evidence supporting the biomarker as being predictive of drug response in the same indication
Level 3B	Compelling clinical evidence supporting the biomarker as being predictive of drug response in another indication





37% targetable alterations and 11% of patients were enrolled on genomically matched clinical trials

Courtesy of J.Remon

Zehir- Nature Medicine 2017

Past, present and future of NSCLC

Biomakers in NSCLC

Discovery activating mutations

NGS ~10s genes

PDL1

TMB

NGS 100s genes With pathways

DNA REPAIR

EPIGENETIC

Immune phenotype

…

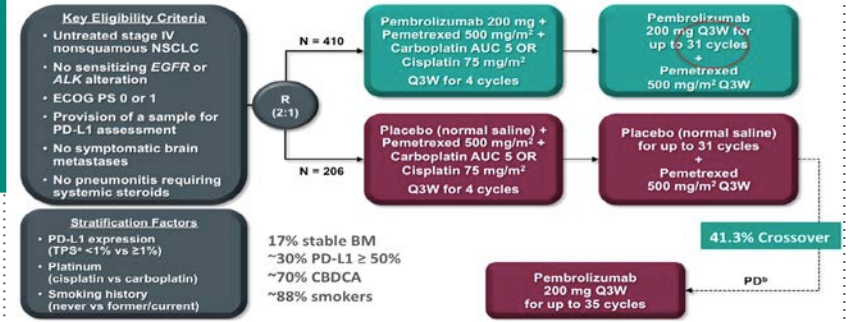
In 15 years

- Carcinogenesis
- Screening
- Local treatment
- Stage III
- Biomarkers
- Stage IV

- Chemotherapy

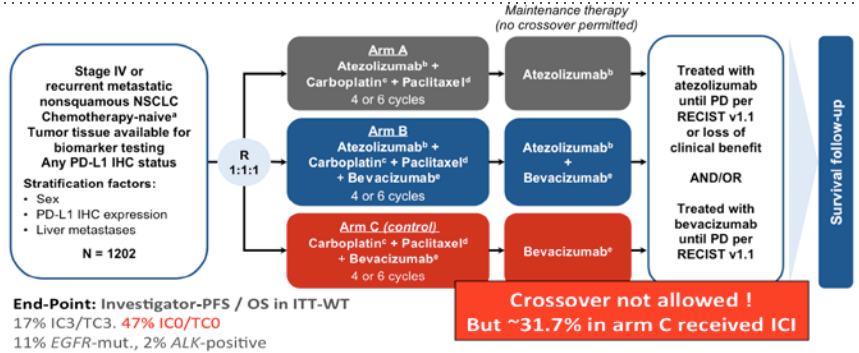
IO + Chemotherapy in Non-Squamous

KEYNOTE 189



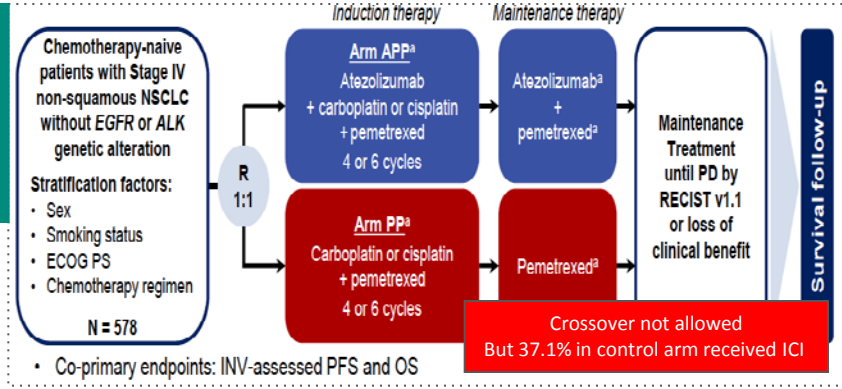
Gandhi – NEJM 2018

IMPOWER 150

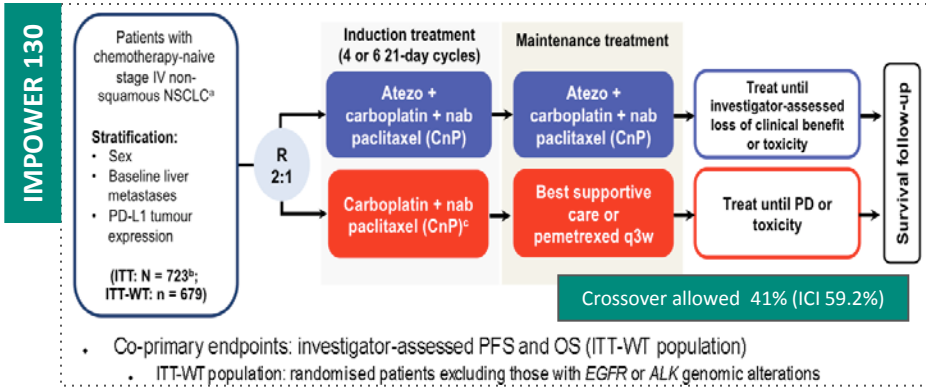


Socinski – ASCO 2018 * Socinski – NEJM 2018

IMPOWER 132



IMPOWER 130



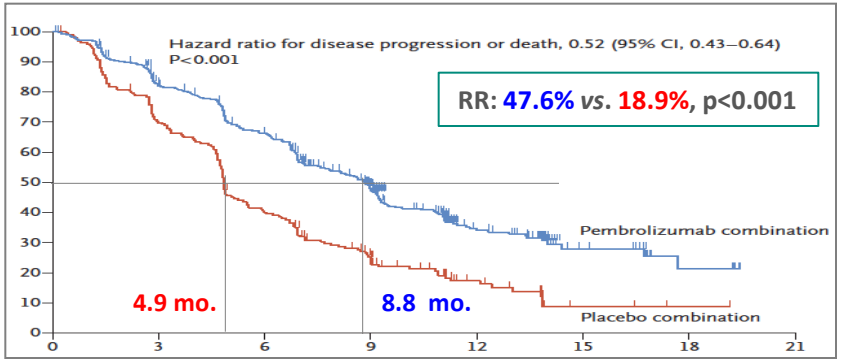
Papadimitakoupolou – WCLC 2018

Cappuzzo – ESMO 2018

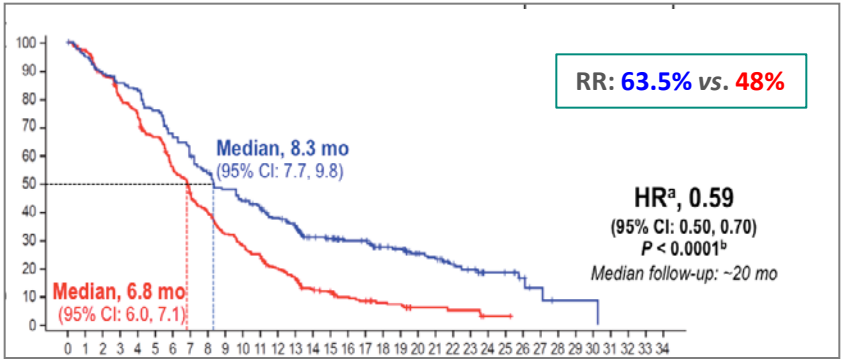
Courtesy of J.Remon

IO + Chemotherapy in Non-Squamous: PFS

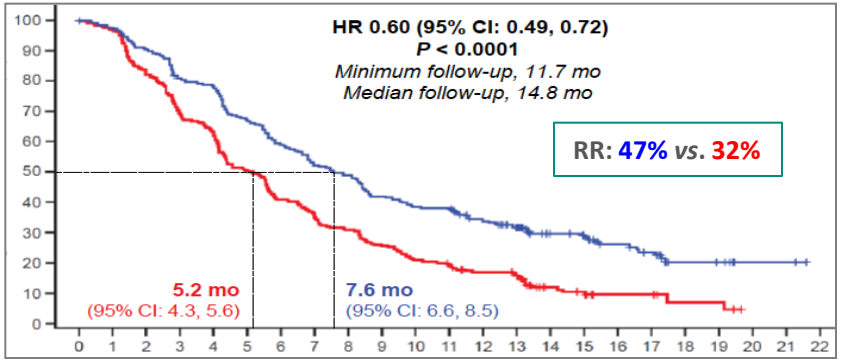
KEYNOTE 189 Platinum/Pem +/- Pembrolizumab



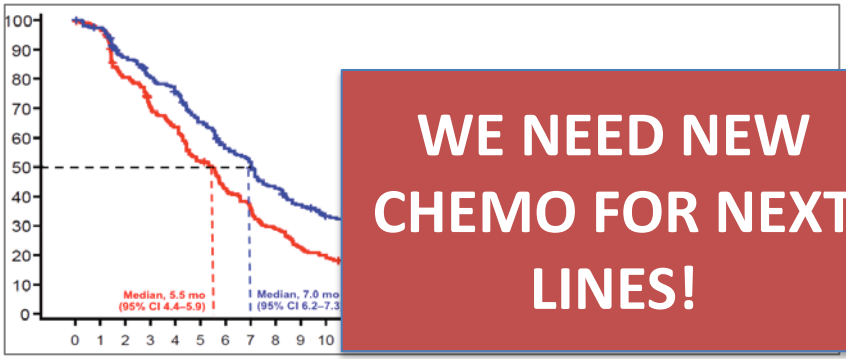
IMPOWER 150 CBDCA/Taxol/BVZ +/- Atezolizumab (B *vs.* C)



IMPOWER 132 Platinum/Pem +/- Atezolizumab



IMPOWER 130 CBDCA/nab-Paclitaxel +/- Atezolizumab



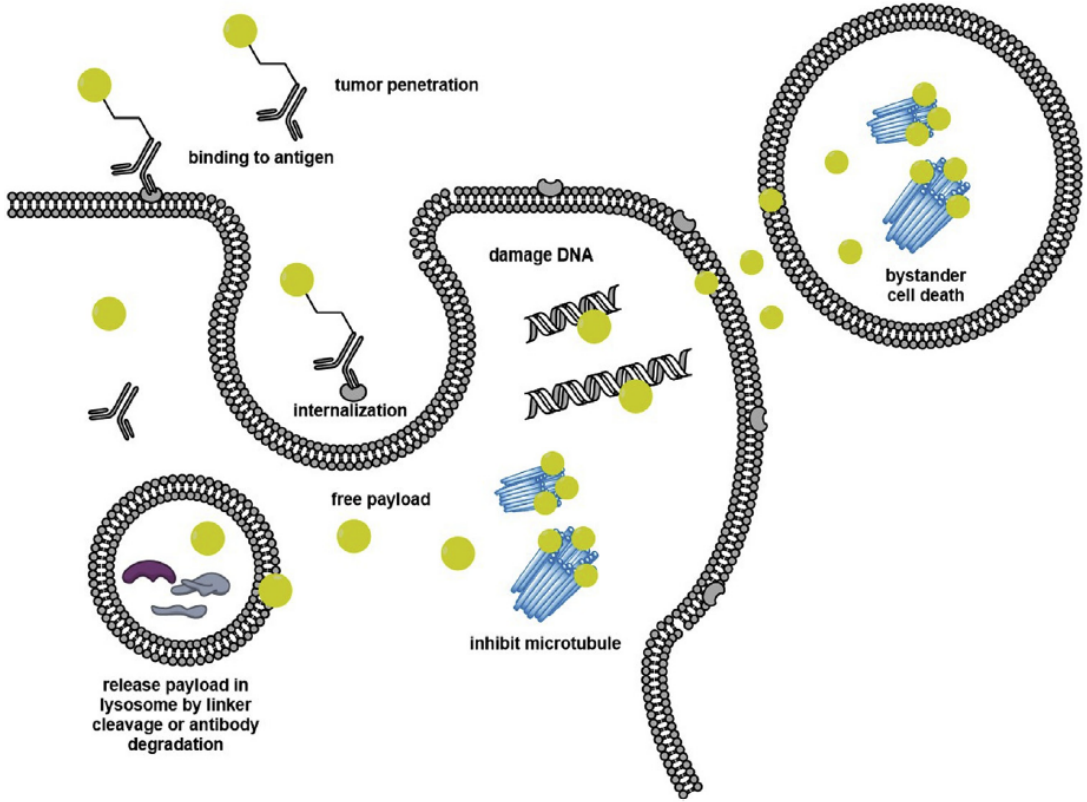
WE NEED NEW CHEMO FOR NEXT LINES!

Courtesy of J.Remon

Gandhi – NEJM 2018 * Papadimitakoupolou – WCLC 2018

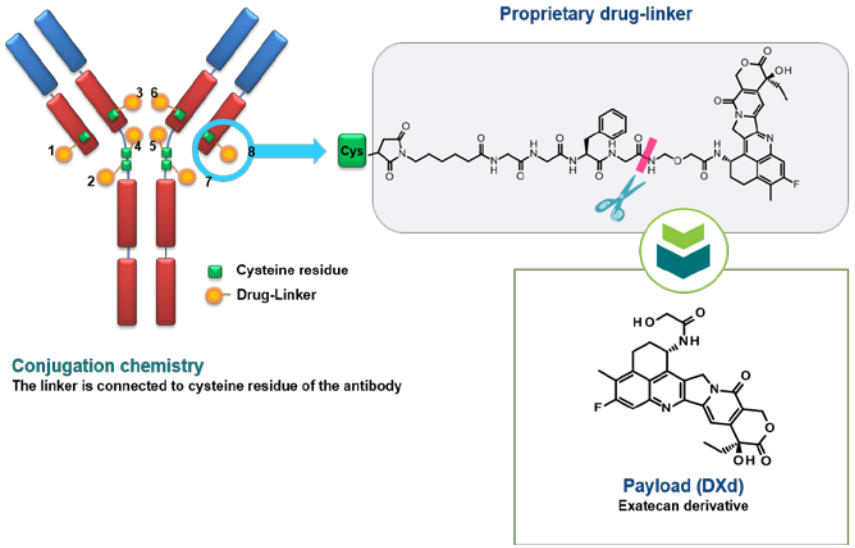
Socinski – NEJM 2018 * Cappuzzo – ESMO 2018

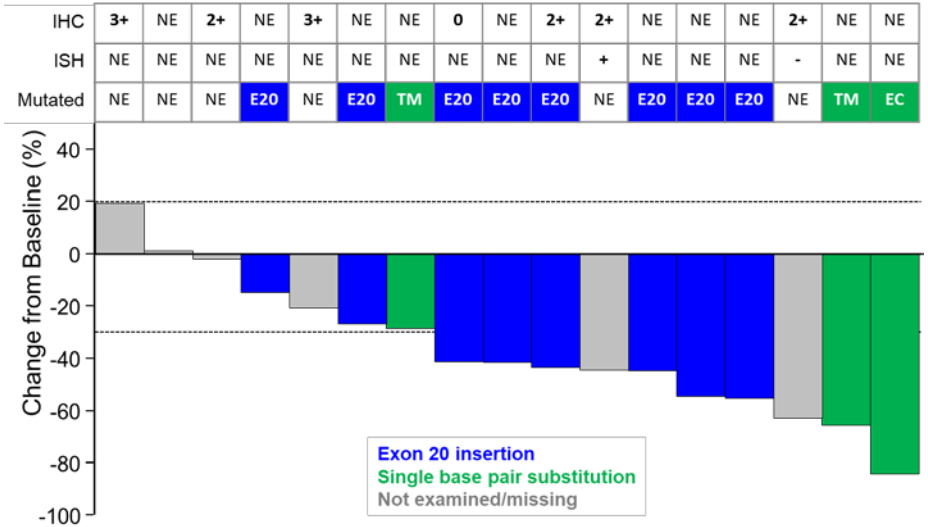
ADC - Antibody drug conjugates



Xie, JTO 2019

Anti-HER2 : DS-8201a





	Confirmed[a] ORR, % (n/N)	DOR, median (range), months	TTR, median (range), months	PFS, median (range), months
HER2-expressing or HER2-mut. NSCLC - N = 18	58.8% (10/17)	9.9 (0.0+, 11.5)	1.4 (1.0, 4.2)	14.1 (0.9, 14.1)
HER2-mutated NSCLC n = 11	72.7% (8/11)	11.5 (0.03+, 11.5)	1.4 (1.0, 4.2)	14.1 (4.0+, 14.1)

Tsurutani, WCLC 18

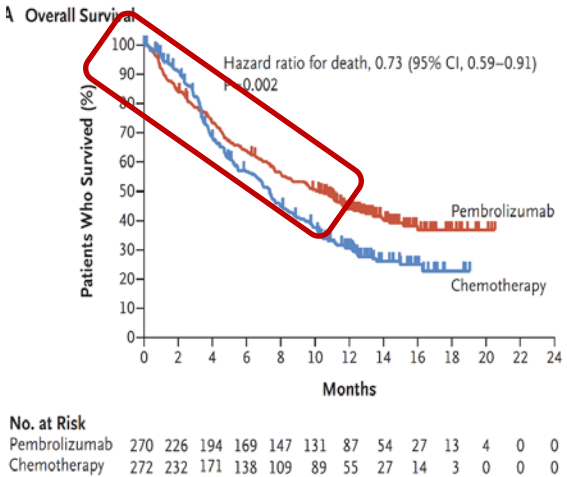
In 15 years

- Carcinogenesis
- Screening
- Local treatment
- Stage III
- Biomarkers
- Stage IV

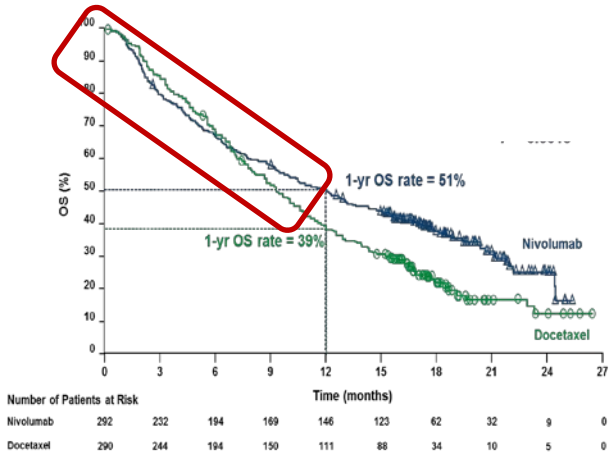
- Chemotherapy
- Immunotherapy

Common Pattern?

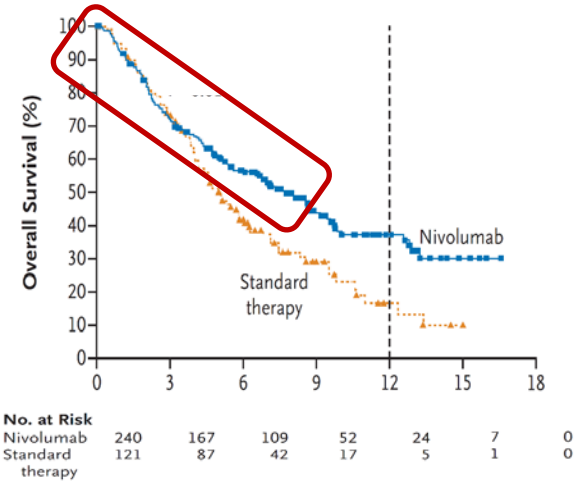
UROTHELIAL
KEYNOTE-045



LUNG
CHECKMATE-057



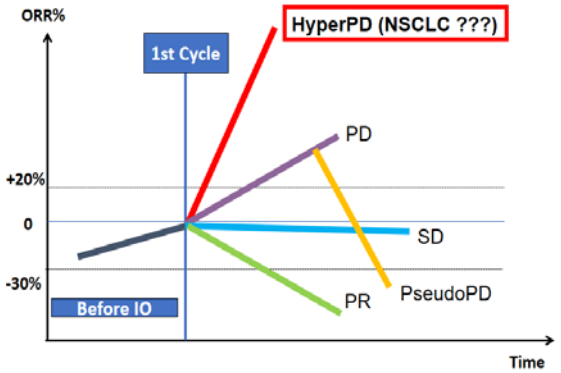
H&N
CHECKMATE-141

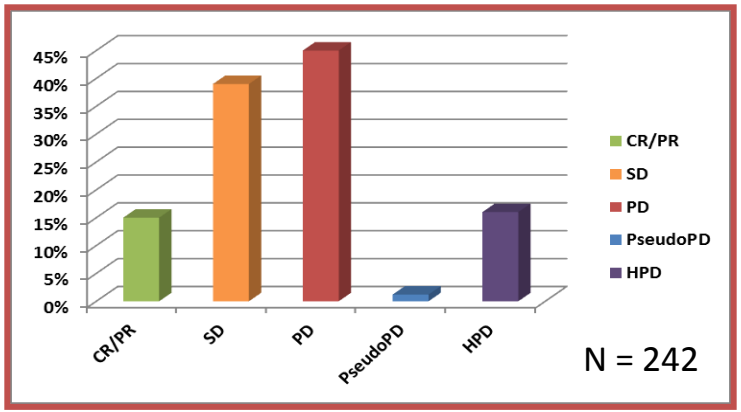


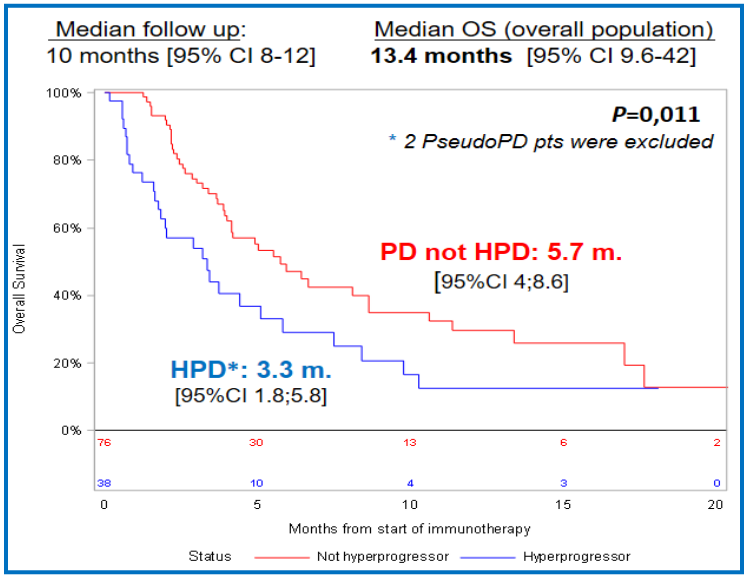
Curves cross, suggesting a deleterious effect in a subgroup of patients

Bellmunt J, et al. *N Engl J Med.* 2017;376(11):1015-1026; Ferris R, Gillison ML. *N Engl J Med.* 2017;376(6):596; Borghaei H, et al. *N Engl J Med.* 2015;373(17):1627-1639.

Hyperprogressive Disease in Lung Cancer







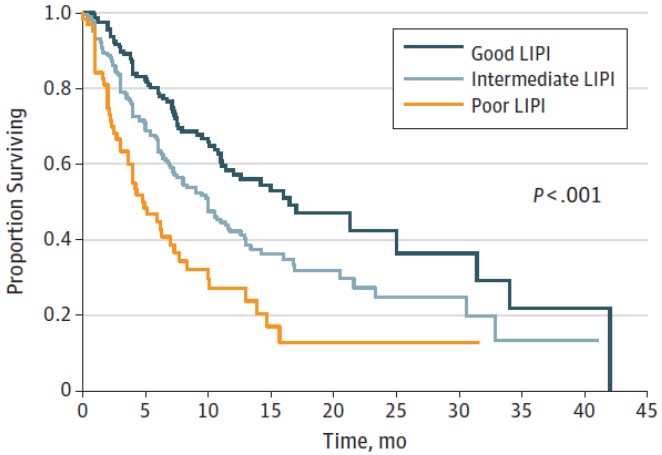
HPD:
16% of NSCLC
26% of H&N
25% of bladder

Ferrara R, et al. ESMO 2017. Abstract 1306PD; Saâda-Bouzid E, et al. *Ann Oncol.* 2017;28(7):1605-1611; Champiat S, et al. *Clin Cancer Res.* 2017;23(8):1920-1928.

LUNG IMMUNE PROGNOSTIC INDEX (LIPI) SCORE

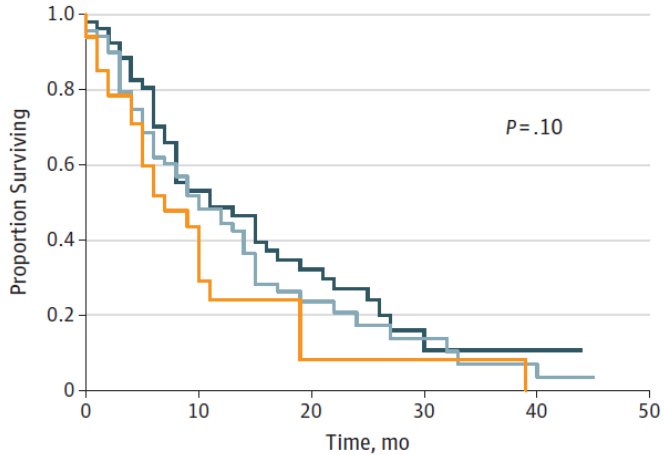
$$dNLR = \frac{Neutrophils}{Leukocytes - Neutrophils} \geq 3 \quad \& \quad LDH \geq ULN$$

A OS in the immunotherapy pooled cohort



No. at risk										
Good LIPI	162	118	69	34	12	7	5	3	3	0
Intermediate LIPI	206	125	72	28	15	9	5	2	1	0
Poor LIPI	63	29	13	5	2	1	1	0	0	0

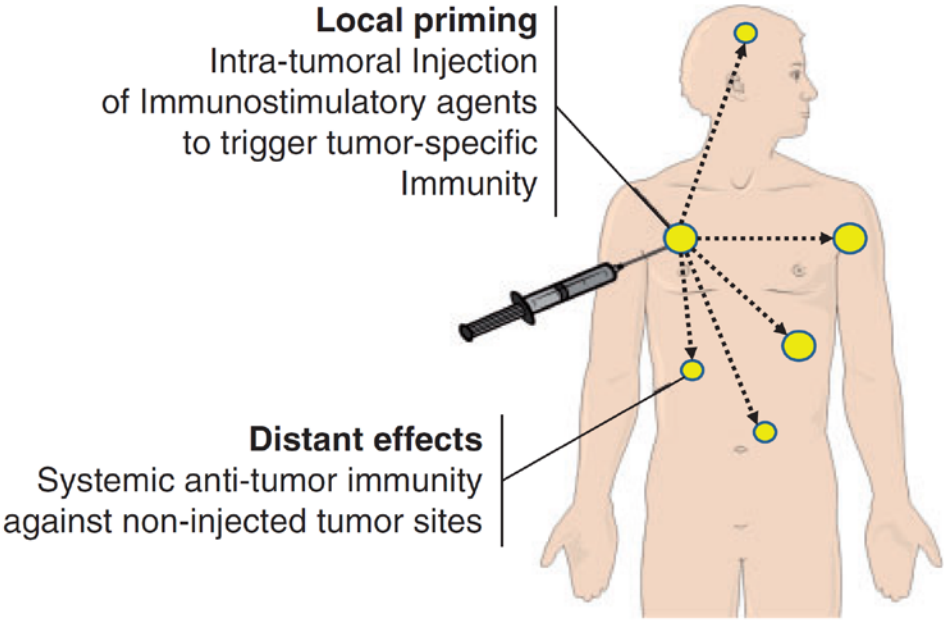
C OS in the chemotherapy cohort



No. at risk						
Good LIPI	53	24	13	3	2	0
Intermediate LIPI	70	30	9	4	2	0
Poor LIPI	34	9	1	1	0	0

Mezquita L, et al. JAMA Oncol 2018;4:351–7.

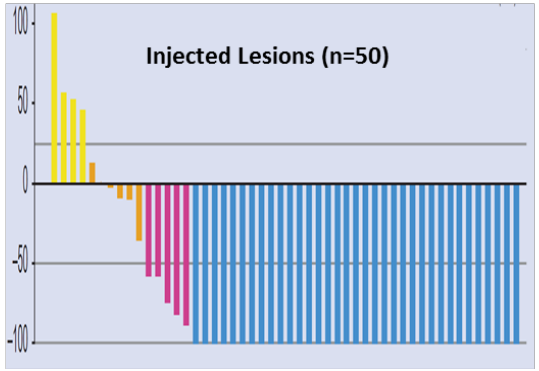
Human Intra-Tumoral Immuno-Therapy (HIT-IT)



Marabelle, A. et al. (2017). Ann. Oncol. 28, xii33-xii43.

Courtesy of A.Marabelle

IT T-VEC + IV pembrolizumab in Melanoma



ORR = 57% (irRC)

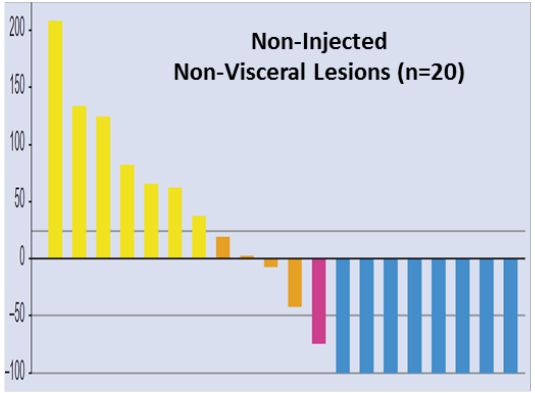
ORR pembro alone ~ 33%

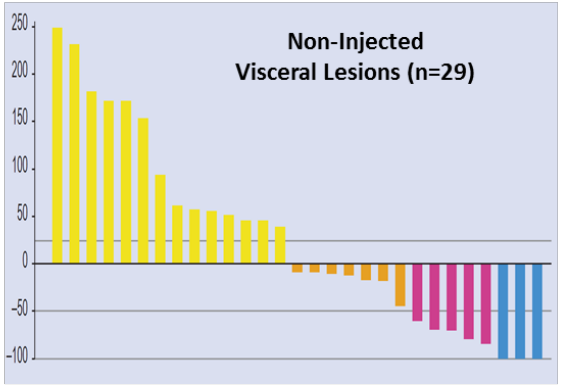
CR rate = 24% (irRC)

CR rate pembro alone ~ 6% (RECIST)

PFS at 9 month = 71%

PFS at 9 months pembro alone ~40%

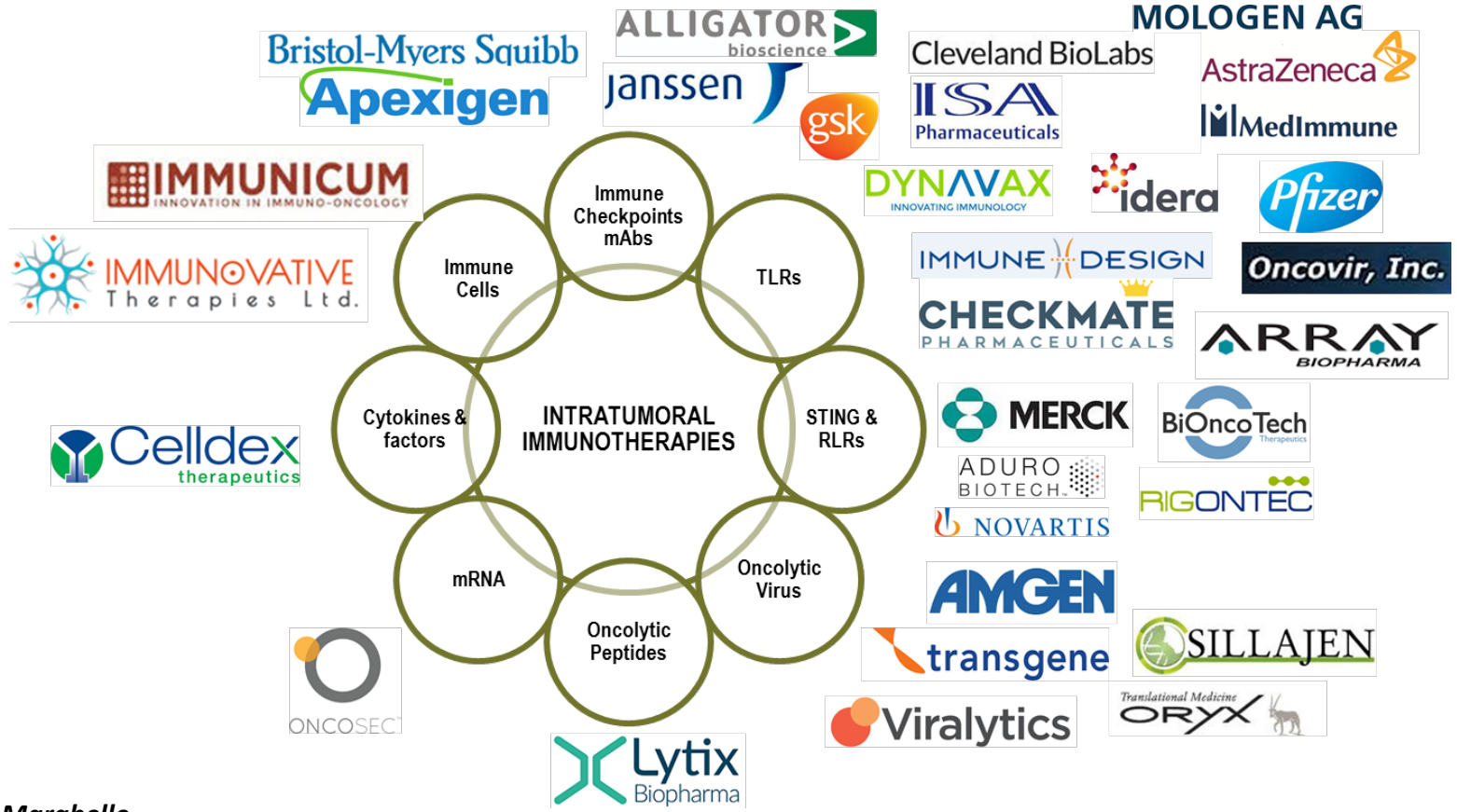




Courtesy of A.Marabelle

G.Long, ASCO 2016

Human Intra-Tumoral Immuno-Therapy (HIT-IT) in 2019



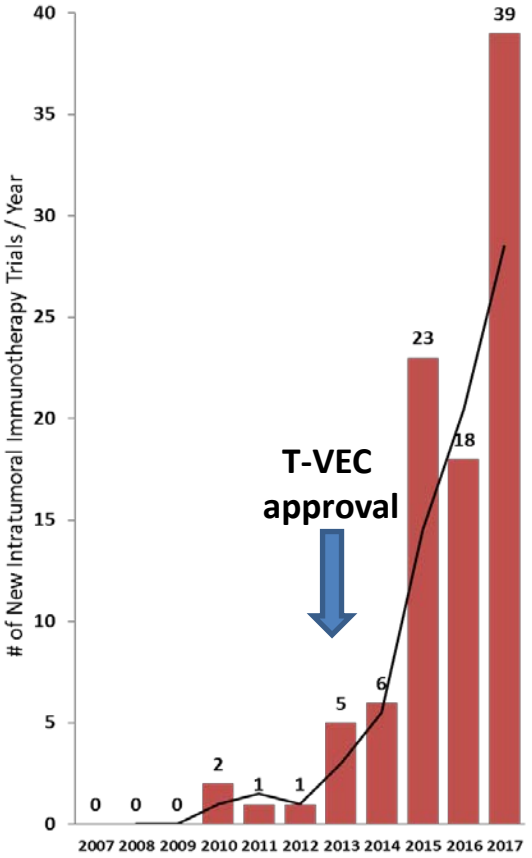
Courtesy of A.Marabelle

HIT-IT: Usual Skepticism

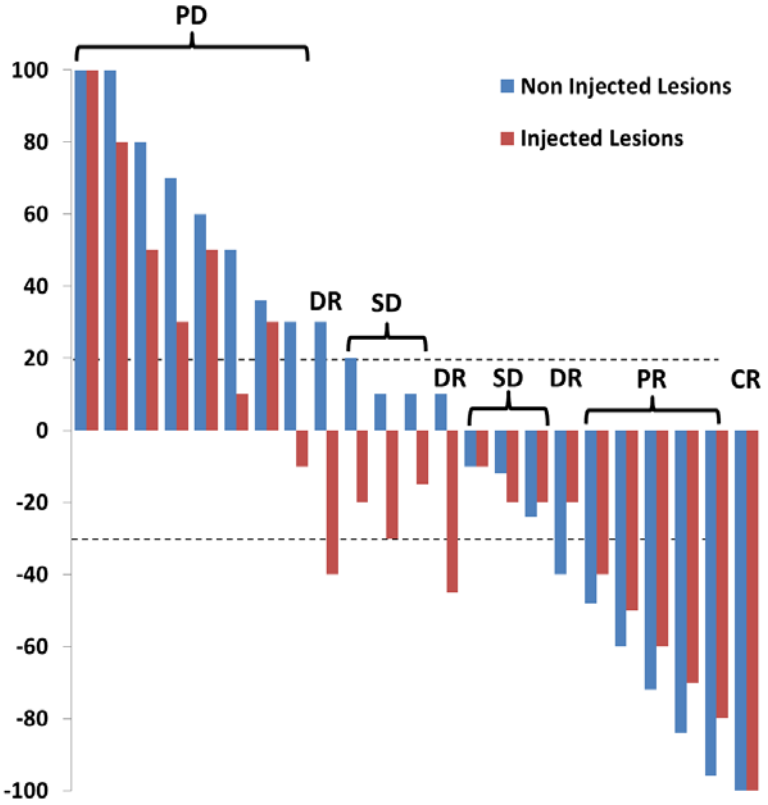
- Feasibility
- Acceptability
- Implementation
- Ability to register an intratumoral drug

Courtesy of A.Marabelle

Number of New Intratumoral Immunotherapy Trials / Year (clinicaltrials.gov)



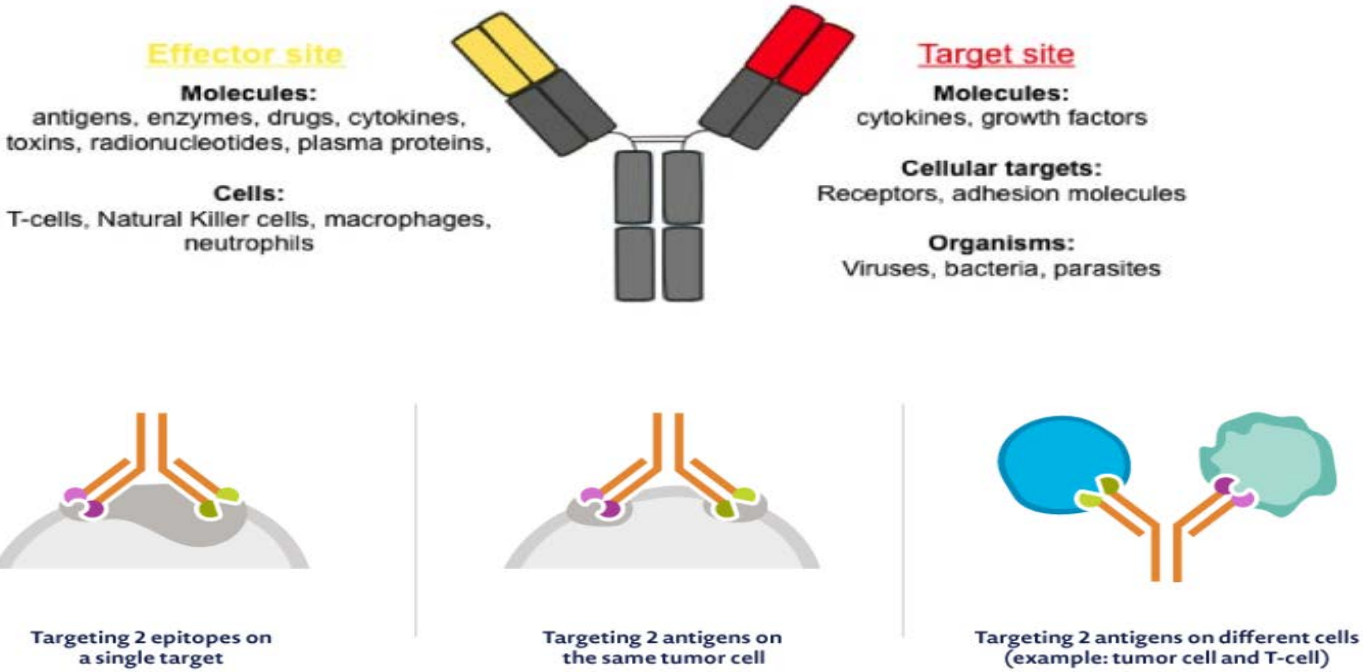
Waterfall Plots for HIT-IT



Marabelle A, et al Ann Oncol. 2018;29:2163–74

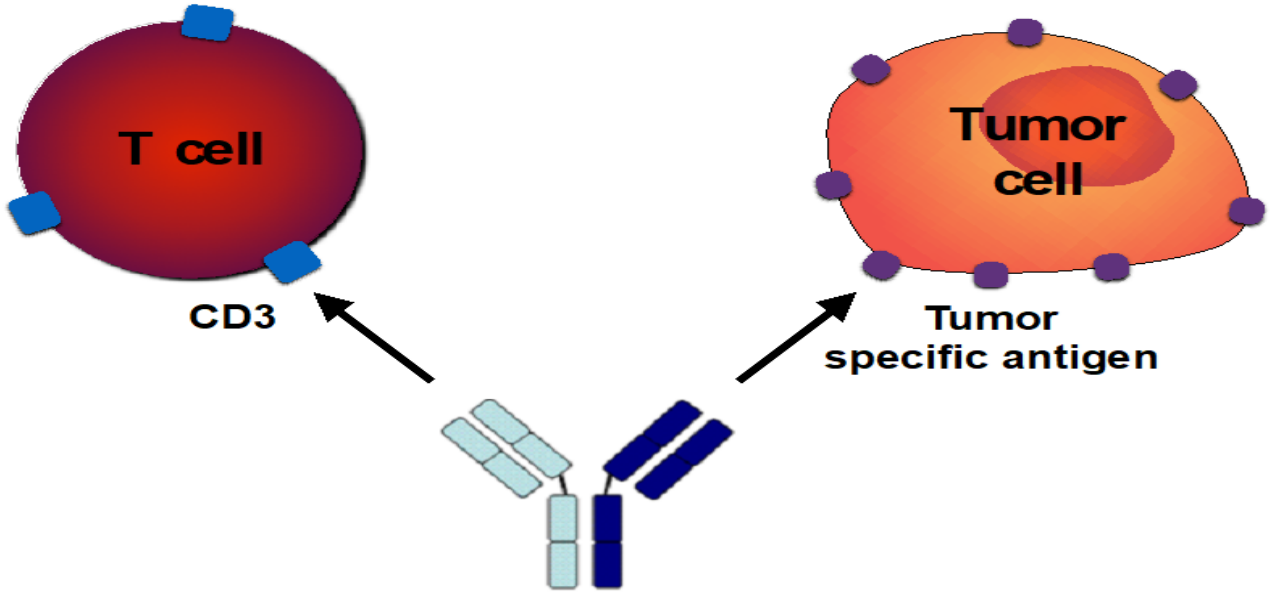
Courtesy of A.Marabelle

Bispecific Antibodies



Courtesy of S.Champiat

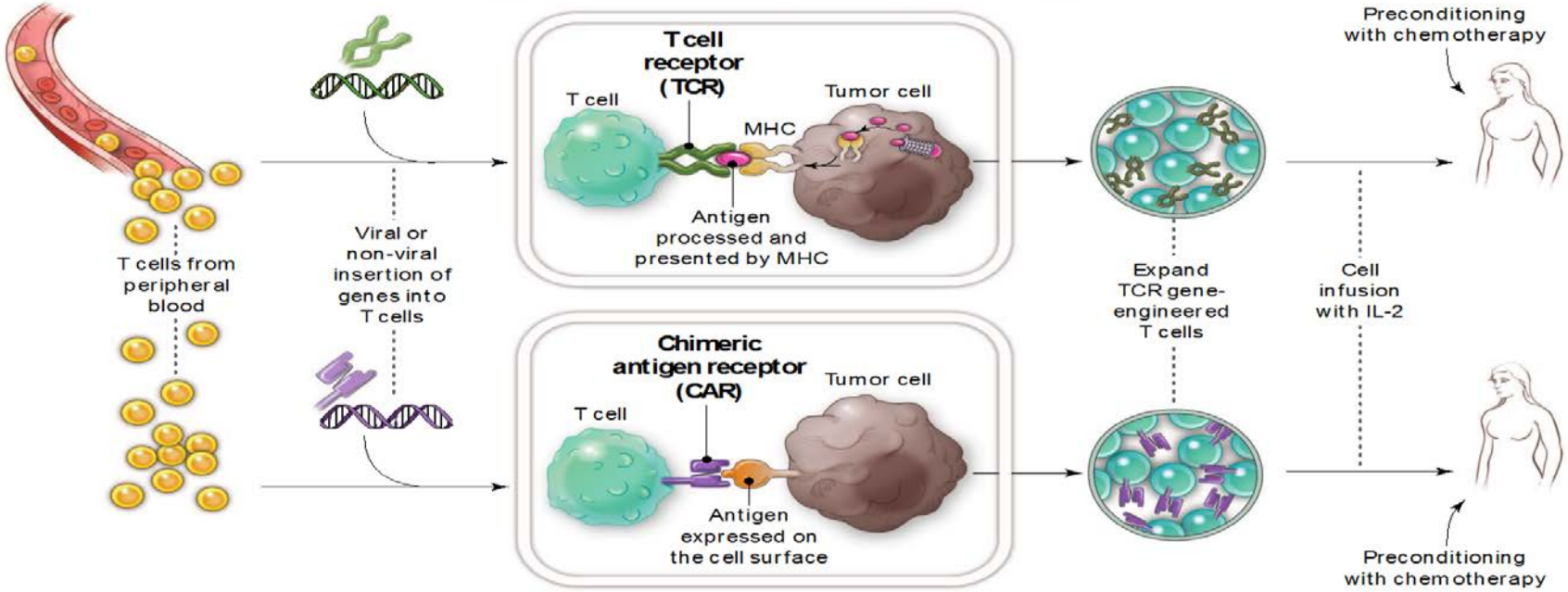
Bispecific T-cell Engaging mAbs



Courtesy of Dr. Marabelle

Courtesy of

Adoptive T-cell therapy



Rosenberg, S. A., & Restifo, N. P. (2015). Adoptive cell transfer as personalized immunotherapy for human cancer. *Science*

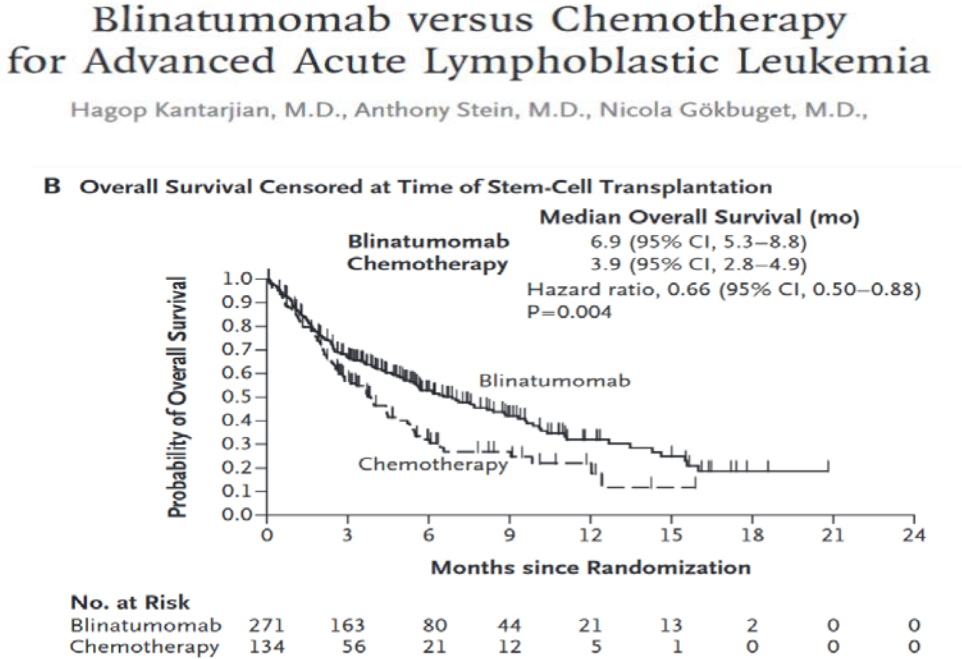
CAR-Ts vs Bispecific Antibodies

CAR-Ts	BISPECIFIC T-CELL ENGAGERS
MHC-I BYPASS	
POTENT ON TARGET ACTIVITY	LIMITED ON TARGET ACTIVITY
HIGH OFF TARGET TOXICITY	
LIMITED (IF ANY) ANTIGEN SPREADING / CLONAL SELECTION	
CAN CROSS THE BBB	DO NOT CROSS THE BBB
COMPLICATED TO IMPLEMENT	EASIER TO IMPLEMENT
VERY EXPENSIVE	CHEAPER

Courtesy of S.Champiat

Blinatumomab: Bispecific T-Cell Engager Antibody

- **Blinatumomab[1]**
  - **Bispecific T-cell engager antibody construct that directs cytotoxic T cells to CD19-positive cells [2]**
  - **CD19: highly specific and expressed in >90% of B-cell lineage cancers[3]**
  - **Blinatumomab was approved in December 2014 by the FDA to treat pts with Ph- precursor B-cell ALL**



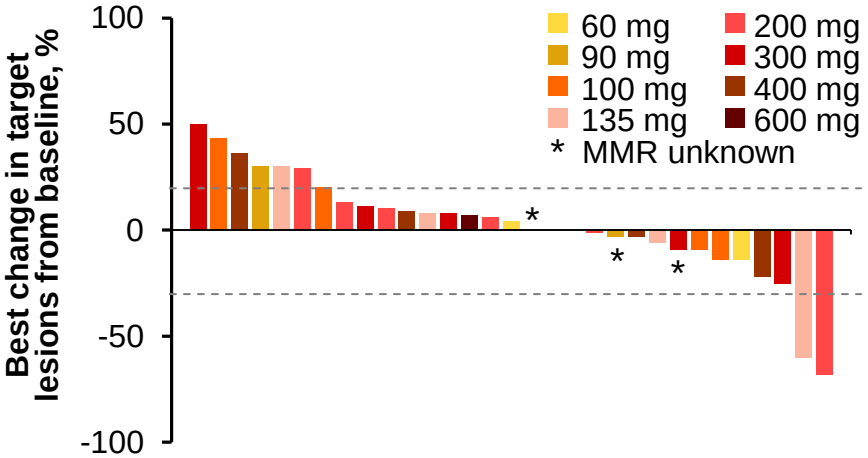
H Kantarjian, NEJM 2017

1. Gökbuget N, et al. ASH 2014. Abstract 379.
2. Bargou R, et al. Science. 2008;321:974-977.
3. Raponi S, et al. Leuk Lymphoma. 2011:52;1098-1107.

Courtesy of S.Champiat

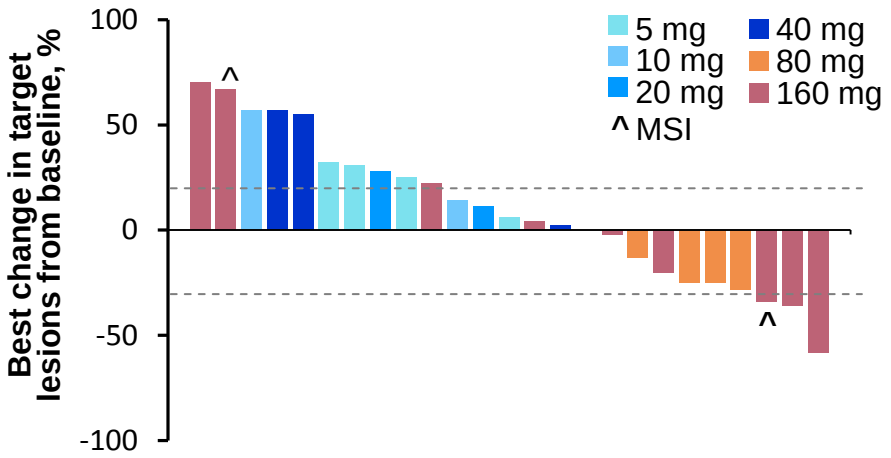
CEA-TCB in mCRC

Study 1: CEA-TCB monotherapy
n = 31, 60-600 mg



No clear correlation between CEA-TCB dose and response

Study 2: CEA-TCB + atezolizumab
n = 25, 5-160 mg



Correlation between CEA-TCB dose and response

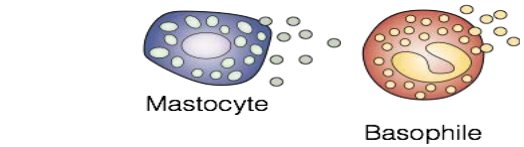
Data reported by investigators, cutoff: March 3, 2017.

[a] Radiological signs of tumor inflammation seen at ≥ 60 mg (safety data cutoff is ≥ 40 mg).

Courtesy of S.Champiat

Réaction à la perfusion

Réaction à la perfusion



Hypersensibilité

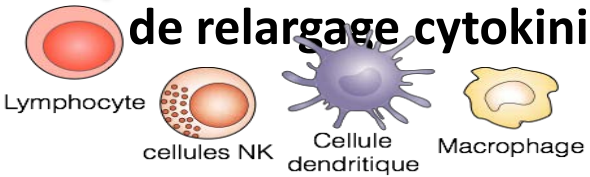
Allergique
IgE médié

À partir de la 2ème perfusion

Non-Allergique
Non IgE médié

Dès la 1ère perfusion

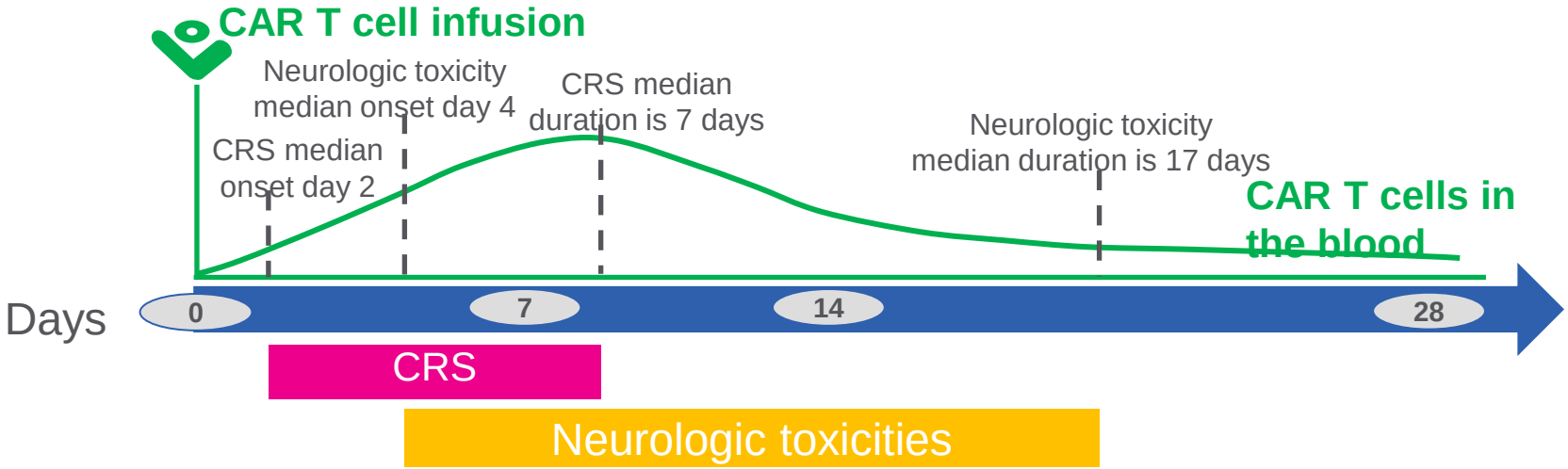
Syndrome de relargage cytokinique



À la 1ère perfusion
Si charge tumorale importante

Courtesy of S.Champiat

Cytokine release syndrome with CAR-Ts
Timing of toxicities



98% of all patients recovered from neurologic adverse reactions
98% of all patients recovered from CRS

Adapted from Lee DW, et al. *Blood*. 2014;124:188-195. 2.

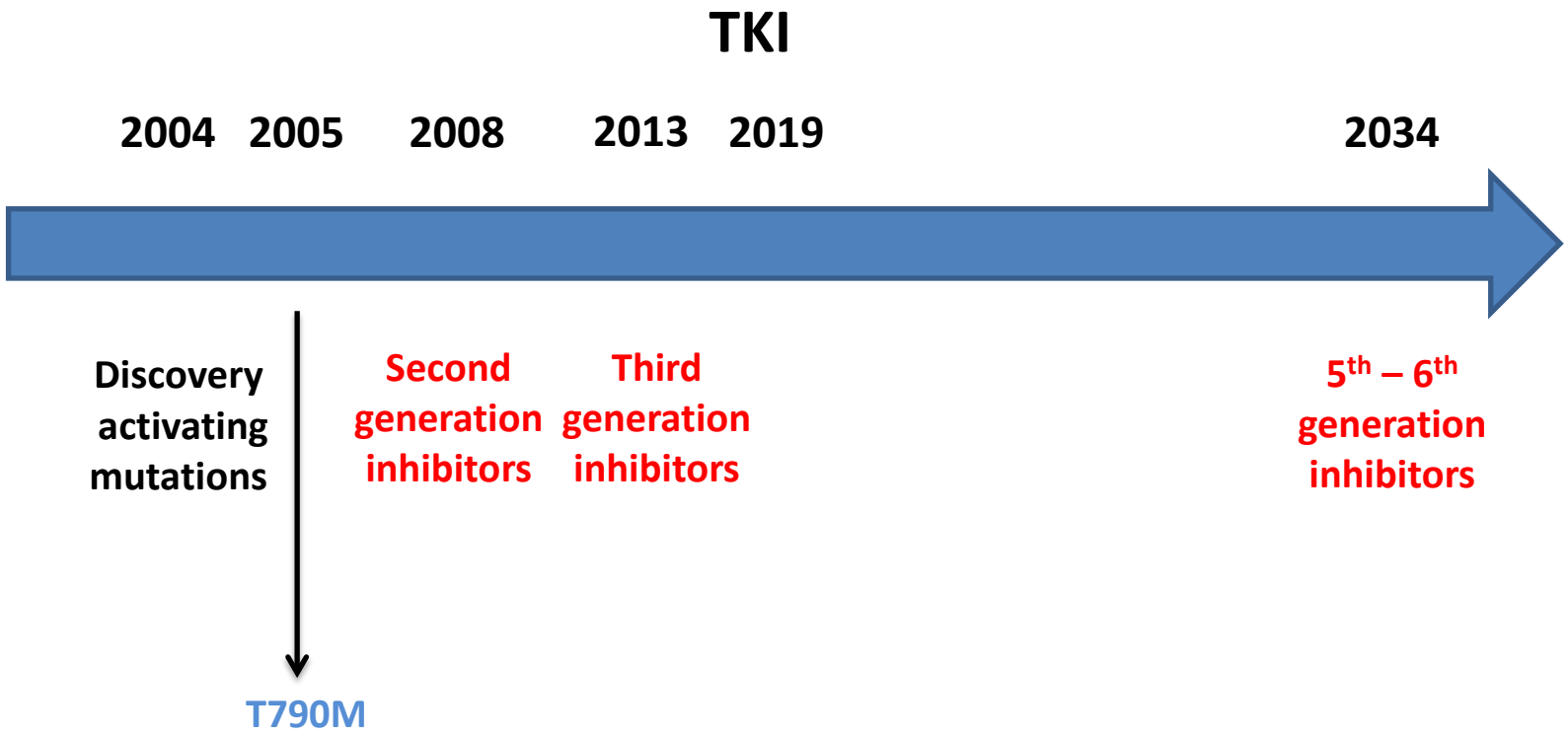
Courtesy of S.Champiat

In 15 years

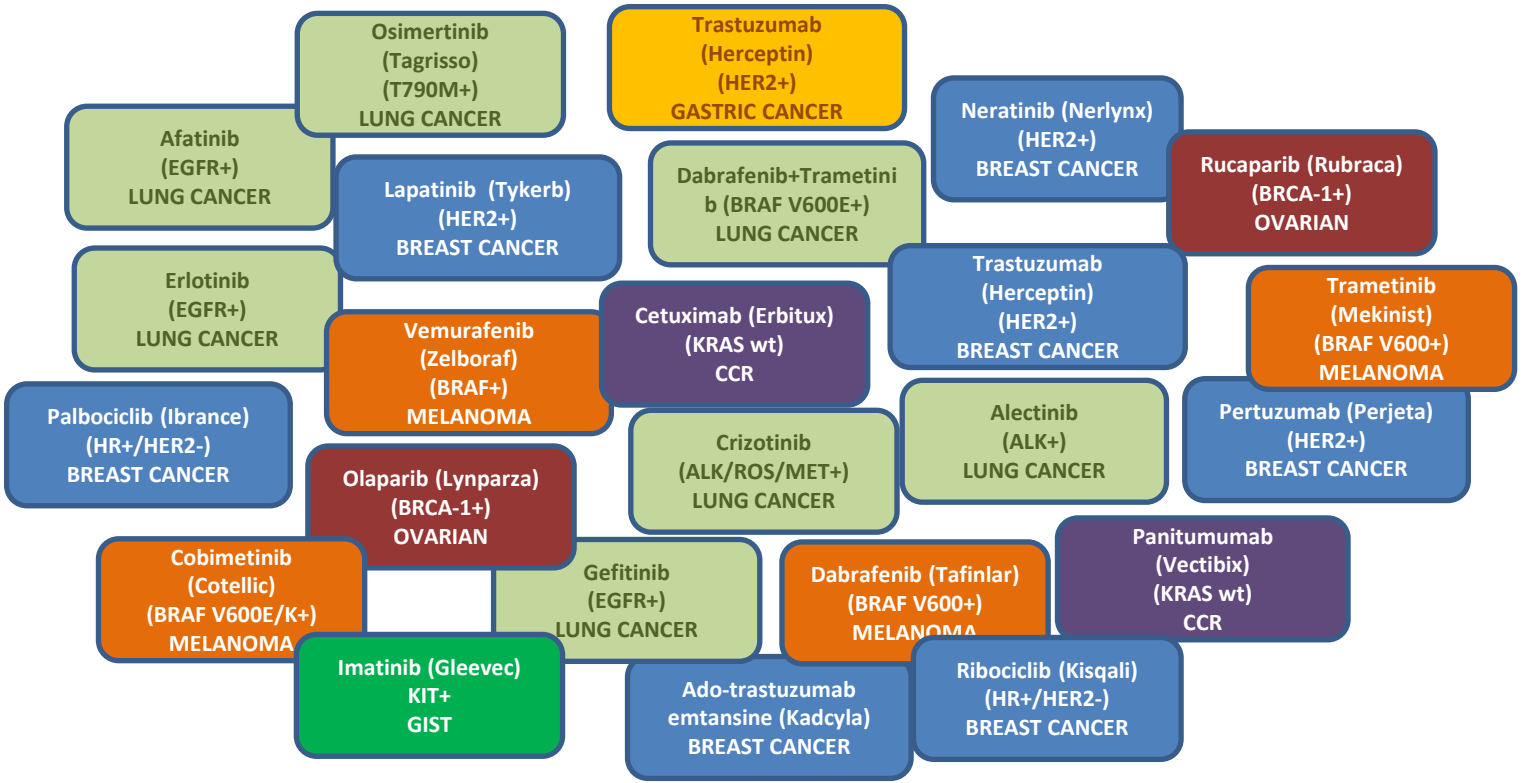
- Carcinogenesis
- Screening
- Local treatment
- Stage III
- Biomarkers
- Stage IV

- Chemotherapy
- Immunotherapy
- TKIs

Past, present and future of NSCLC

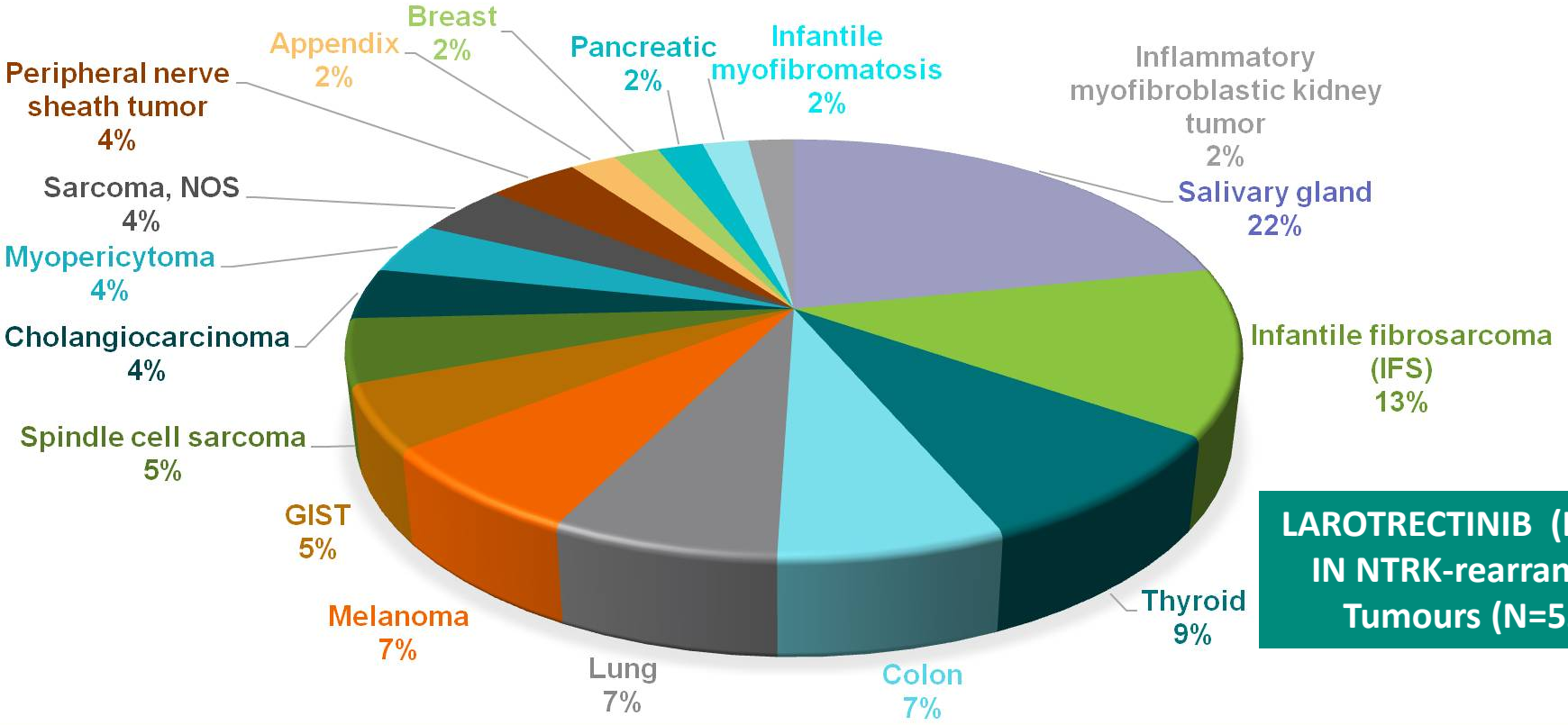


Treating cancer types based on genomic profiles: targeted therapies



Courtesy of Noemi Regart

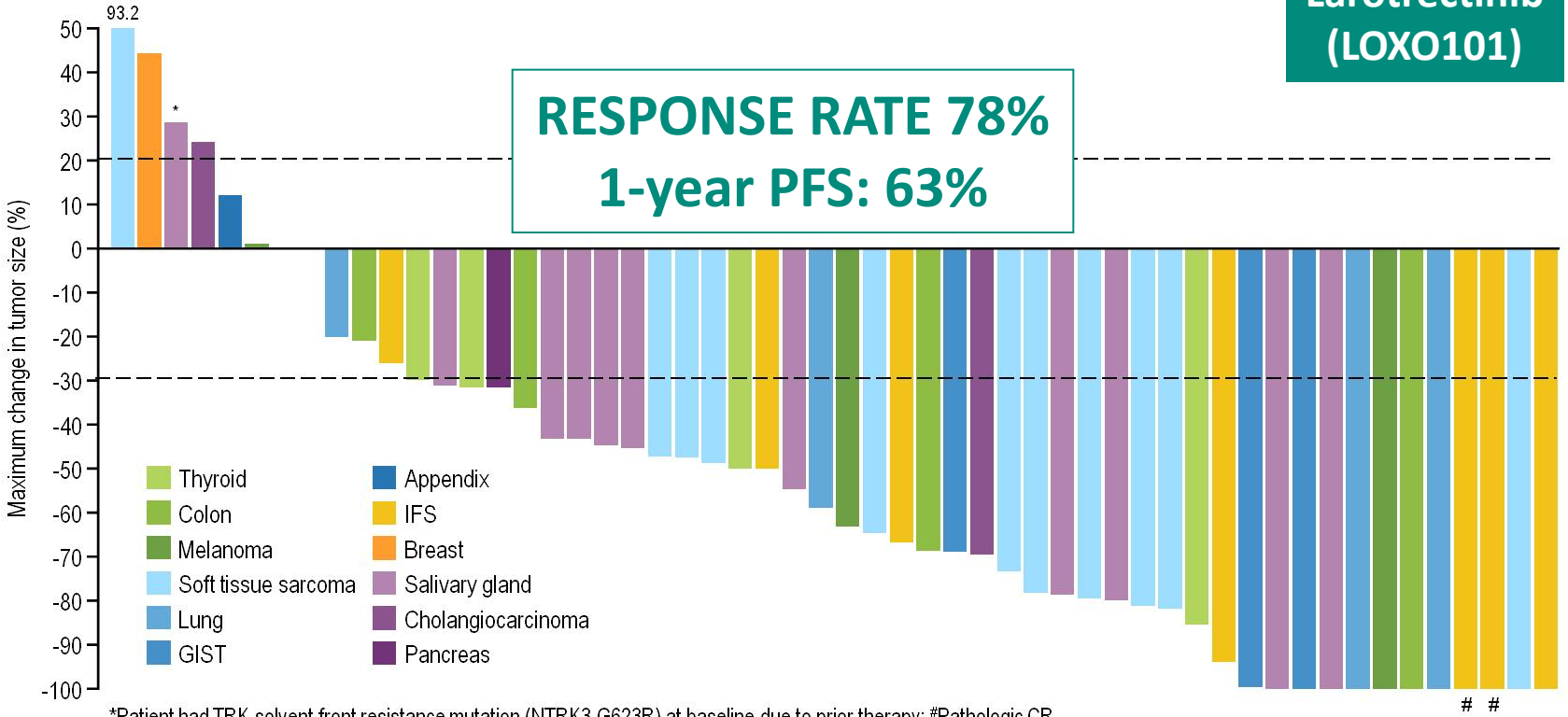
Diversity of cancers treated - 17 unique types



LAROTRECTINIB (LOXO) IN NTRK-rearranged Tumours (N=55)

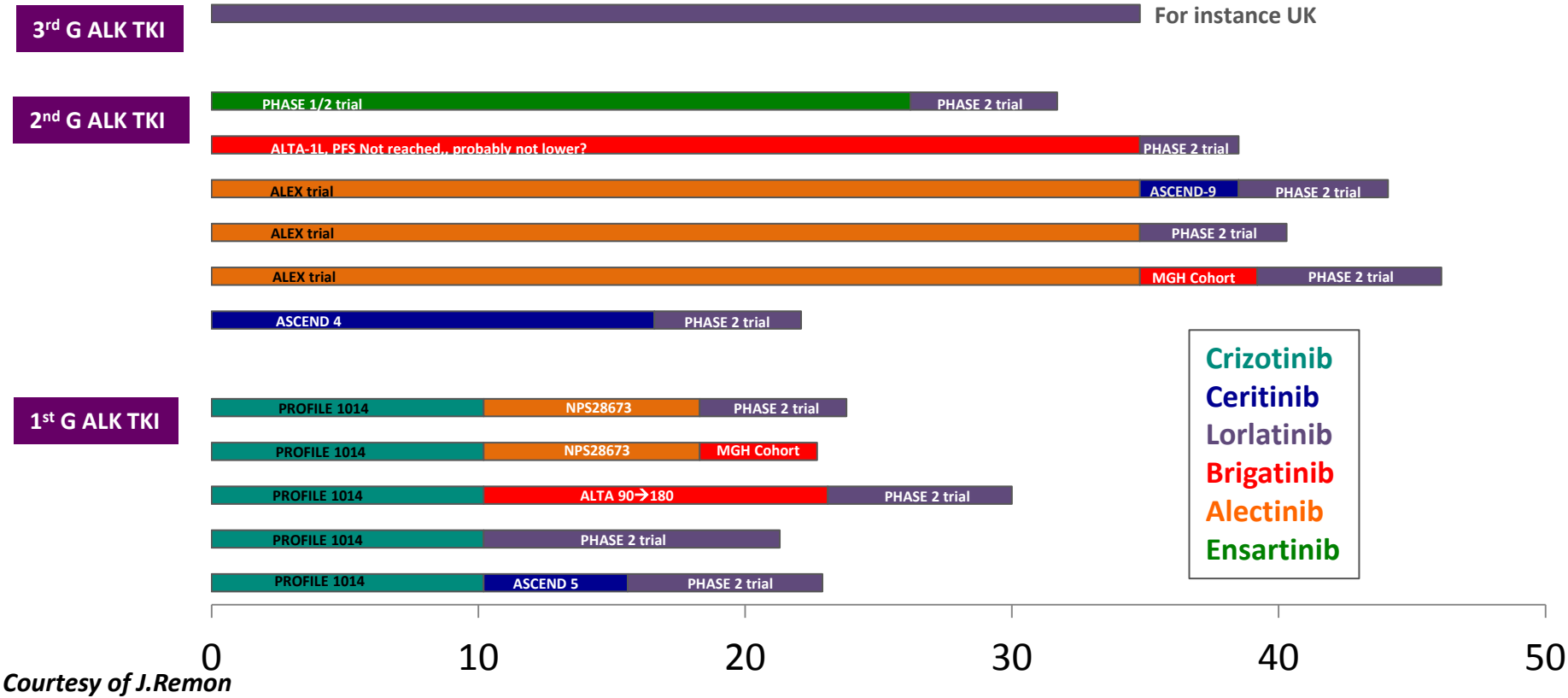
Efficacy regardless of tumor type

Larotrectinib (LOXO101)



*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; #Pathologic CR
Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.

Does really exist a sequence?



Courtesy of J.Remon

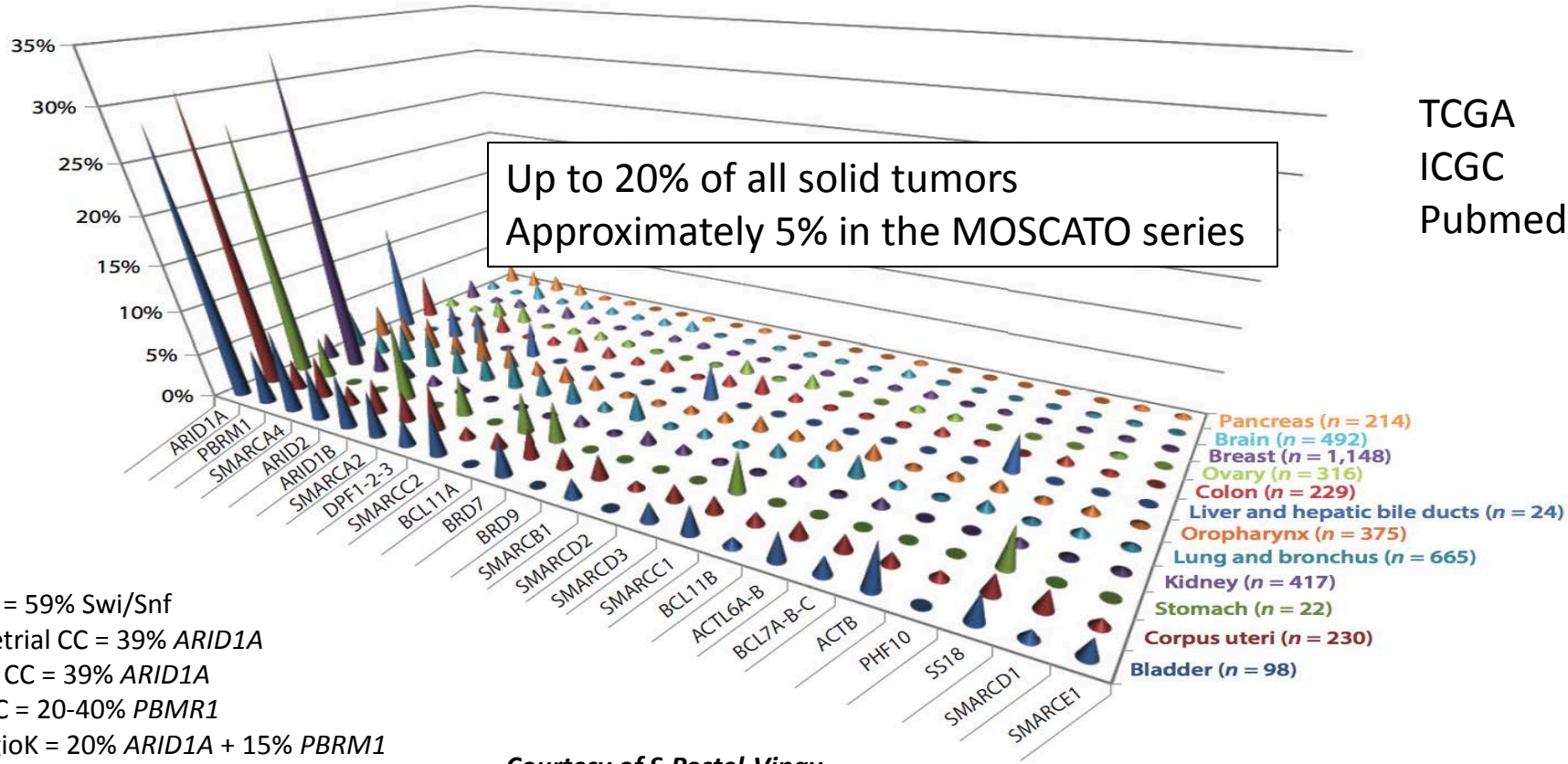
Solomon – NEJM 2014 * Soria – Lancet 2016 * Camidge – ASCO 2018 * Camidge – NEJM 2018 * Lin, JTO 2018 * Besse – ASCO 2018 * Hida, Cancer Sci 2018 * Crino – JCO 2017 * Kim – JCO 2017 * Camidge – JCO 2018 * Shaw – Lancet Oncol 2016 * Gadgeel –JCO 2016 * Camidge – JCO 2018 * Besse – ASCO 2018

In 15 years

- Carcinogenesis
- Screening
- Local treatment
- Stage III
- Biomarkers
- Stage IV

- Chemotherapy
- Immunotherapy
- TKIs
- Next big ones

Swi/Snf mutations in cancer



Up to 20% of all solid tumors
Approximately 5% in the MOSCATO series

TCGA
ICGC
Pubmed

Bladder = 59% Swi/Snf
Endometrial CC = 39% *ARID1A*
Ovarian CC = 39% *ARID1A*
Renal CC = 20-40% *PBMR1*
CholangioK = 20% *ARID1A* + 15% *PBRM1*
Lung = 20% Swi/Snf

Courtesy of S.Postel-Vinay

Masliah-Planchon et al, Ann Rev Pathol 2015

SWI/SNF genetic dependencies

SWI/SNF deficiency	Dependency (SL/EA)	Reference
SMARCB1	EZH2	Kia, 2008; Wilson, 2010; Knutson, 2013
	HDAC	Muscat, 2016
SMARCA4	SMARCA2	Hoffman, 2014; Oike, 2013; Wilson, 2014
	MAX	Romero, 2013
	EZH2	Kim, 2015
	PARP	Smith-Roe, 2015
ARID1A	ARID1B	Helming, 2014
	PI3K/AKT	Zhang, 2016
	PARP	Shen, 2015
	Dasatinib	Miller, 2016
	ATR	Williamson, 2016
	EZH2	Bitler, 2015; Kim, 2015
PBRM1	EZH2	Kim, 2015
SSX–SS18 (fusion)	ATR	Jones, EORTC–NCI–AACR 2016

SWI/SNF
Polycomb
Histone modifiers
TF / super–enhancers
DNA repair
Oncogenic signalling

Morel, …, Postel–Vinay; Ann Oncol 2017

Courtesy of S.Postel-Vinay

Clinical evaluation

DNA repair

PARP inhibitors, …

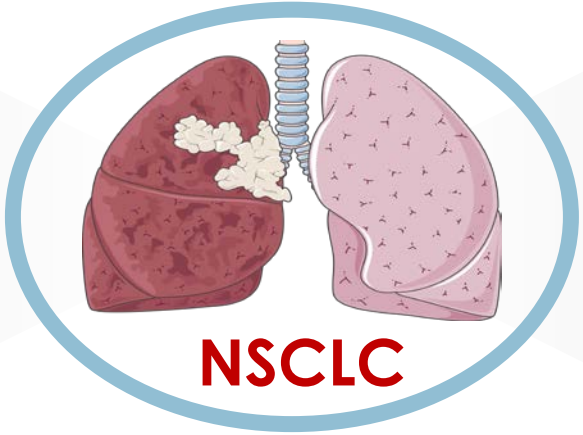
Leading cause of cancer-related death

>15% survival after 5-years

DDR gene	Expression level
ERCC1	Low 22-66%
BRCA1	Low 30%
BRCA2	Low 35%
MSH2	Low 18-38%

Biomarker of response to platinum and PARPi

(Olaussen et al. NEJM 2006)
(Postel-Vinay et al. Oncogene 2013)



NSCLC

New standard treatment

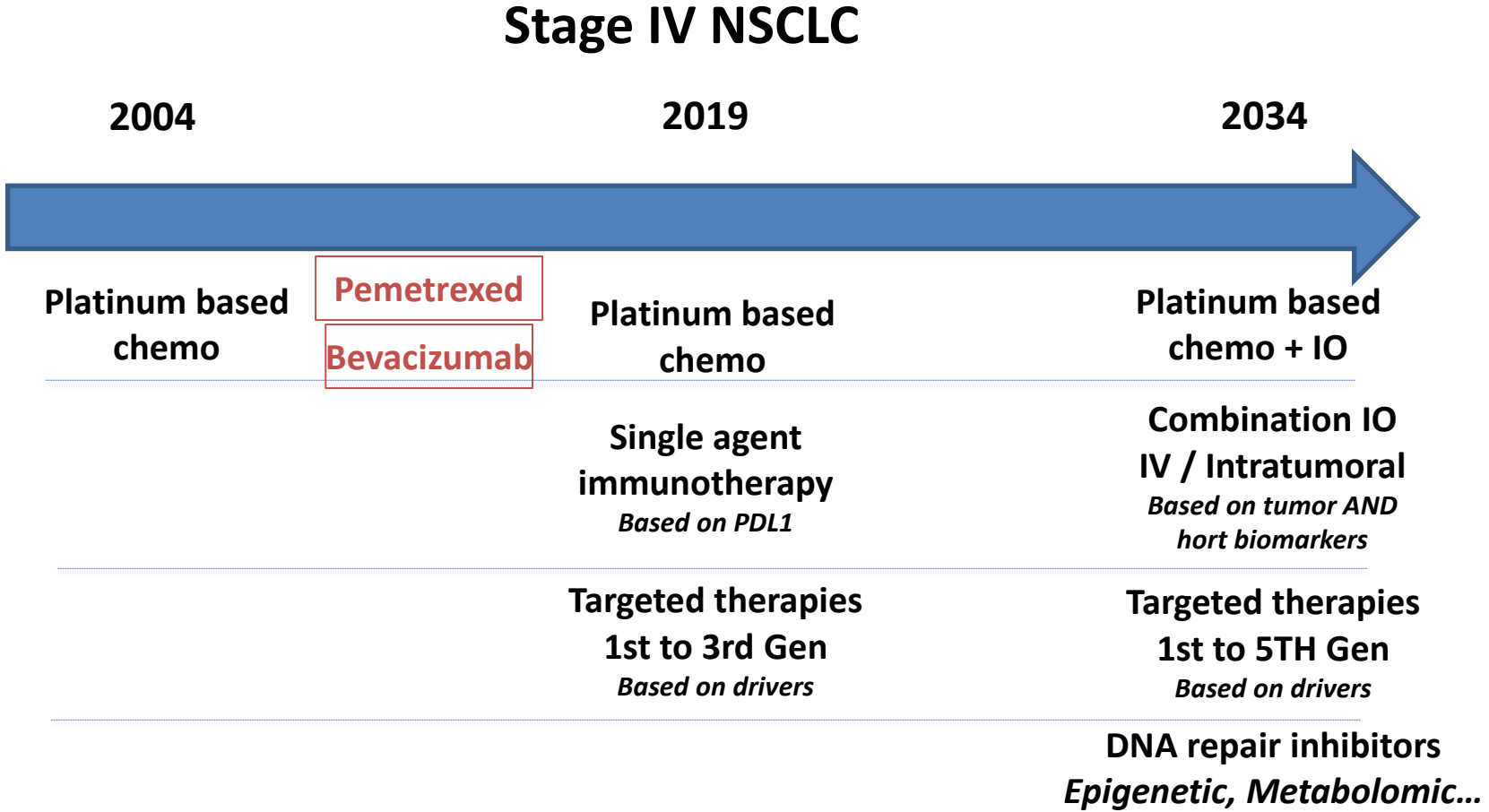
Anti-PD-1 +
Platinum-based therapy
70% survival at 1 year

(Gandhi et al. NEJM 2018)

DDR defects influence the immune response?

Courtesy of S.Postel-Vinay

Past, present and future of NSCLC



In 15 years

- Carcinogenesis
- Screening
- Local treatment
- Stage III
- Biomarkers
- Stage IV

- Connected tools

Past, present and future of NSCLC

Iphones

2004 2019 2034

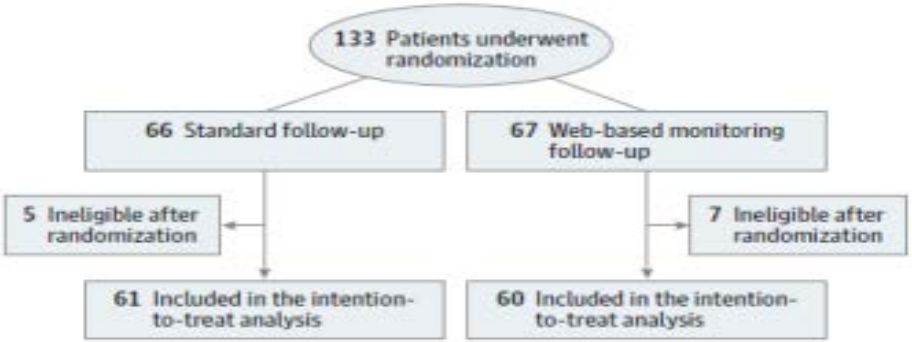
First iPhone in which year?

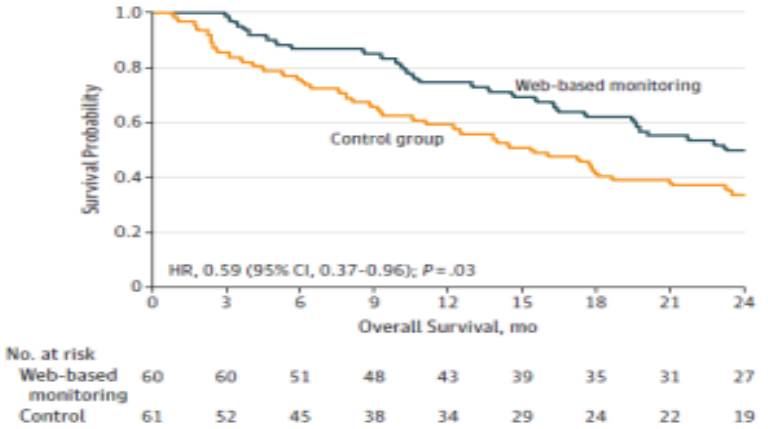
Past, present and future of NSCLC

Iphones

2004 2007 2019 2034

Moovcare





Source	Median OS	12-mo OS, %	24-mo OS, %
Web-based monitoring	22.5 mo	75	50
Control	14.9 mo	56	34

- **13 symptoms, « email alert »**
- **5 centres**
- **Heterogeneous population : NSCLC, SCLC, stage II – IV**
- **Heterogeneous treatments**

Denis F. JAMA 2019

Lots of App…

CUREETY

Un parcours de soin novateur en oncologie pour **améliorer le suivi et les prises en charge des patients ayant un cancer.**

Cureety est une solution intégrée à la chaîne des opérations des services hospitaliers, en tant que **dispositif médical (classe 1) de télésurveillance dédié à l'oncologie.**

Lots of App…

APPLI CHIMIO

Une application pour le suivi des effets secondaires de médicaments contre le cancer

POUR QUOI FAIRE ?

Appli Chimio a été conçue par une équipe de professionnels de santé. L'objectif est de dépister le plus précocement possible les éventuels effets indésirables de votre traitement pour une prise en charge adaptée, rapide et coordonnée.

In 15 years

- Carcinogenesis
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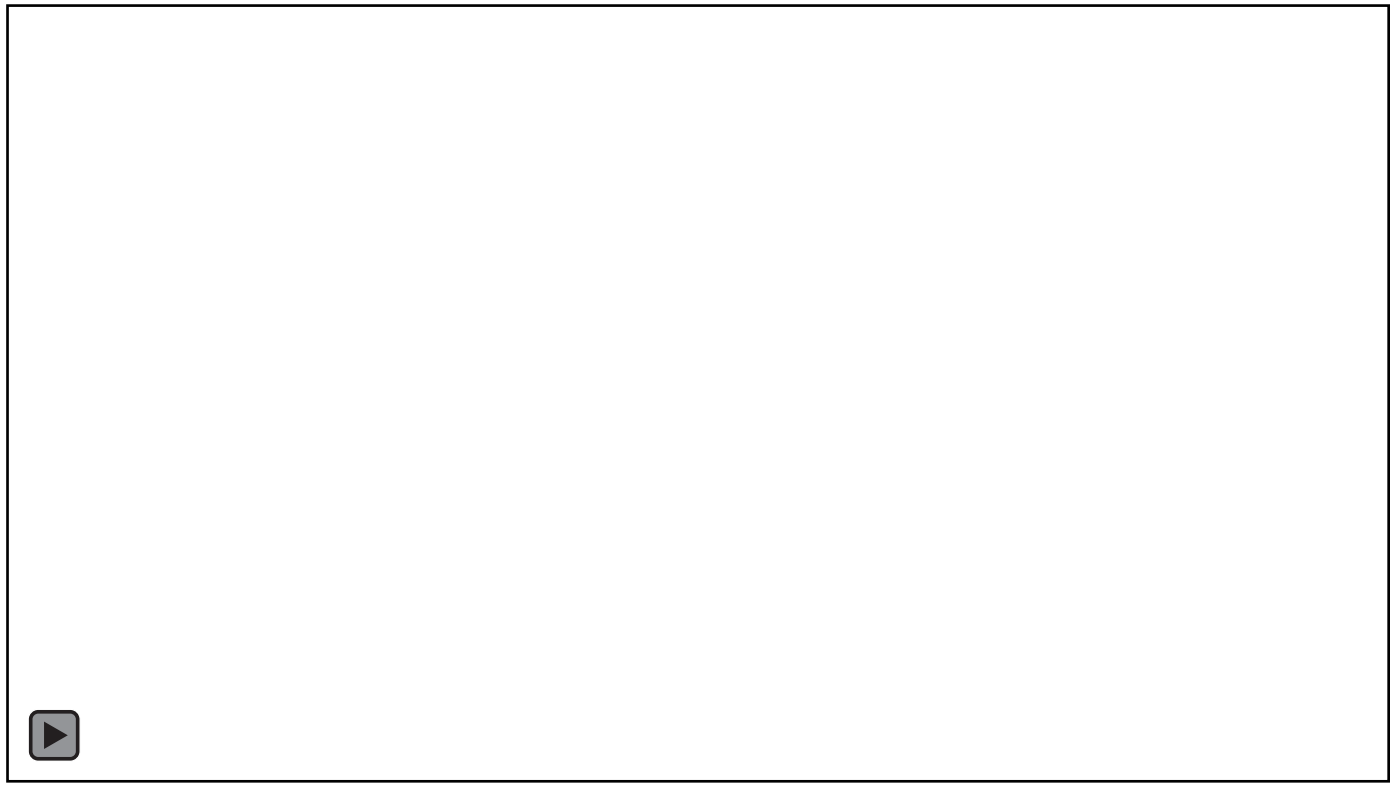
- Stage IV

- Connected tools
- Artificial intelligence

DUPLEX

DUPLEX



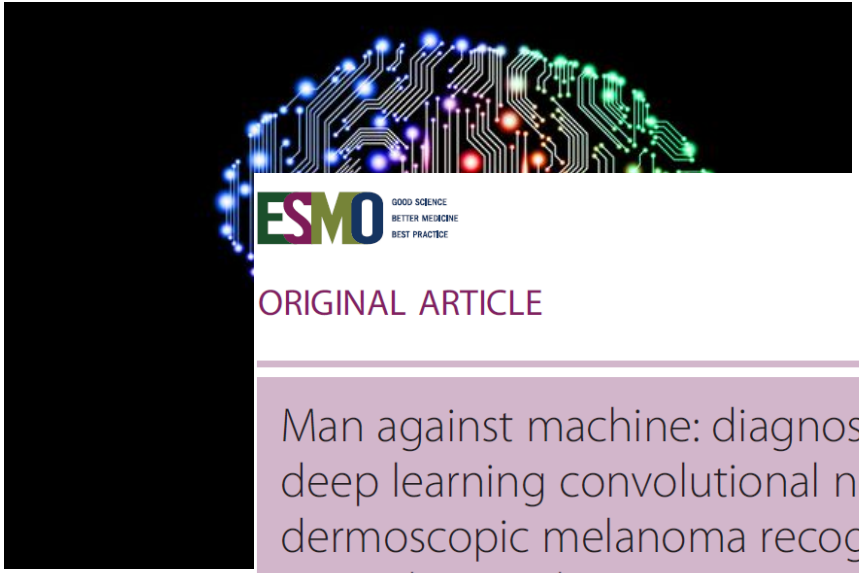
Melanoma screening

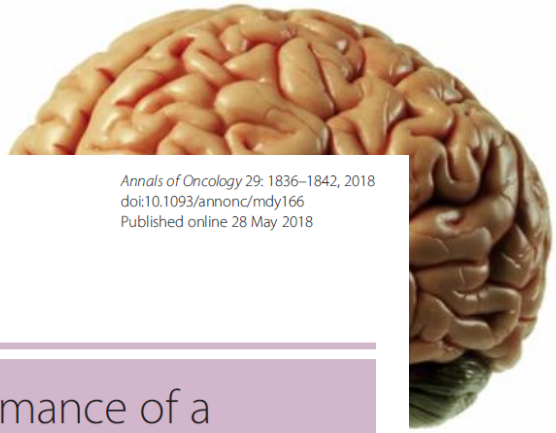
« Prenez chaque année votre peau en photo »

C.Robert,
Dermatologist-Oncologist,
Gustave Roussy

First AI publication in 2017

AI vs. human





ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

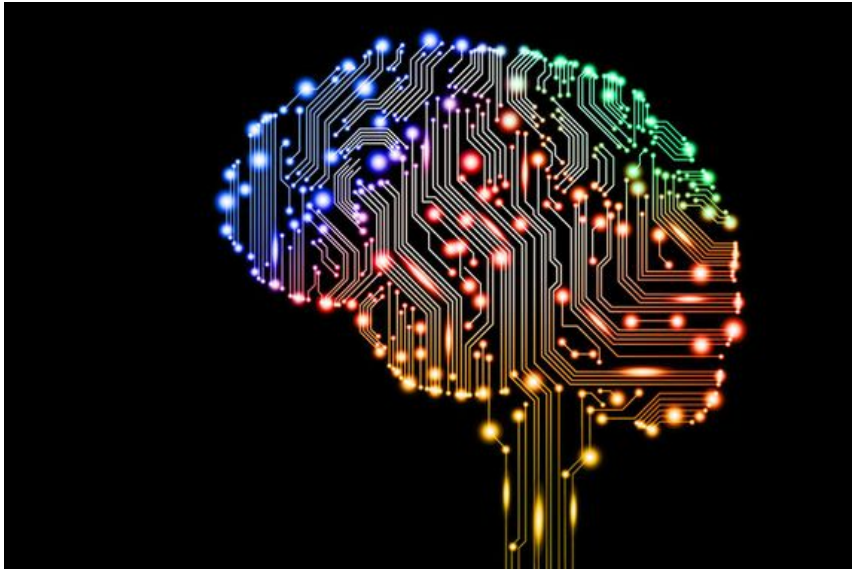
Annals of Oncology 29: 1836–1842, 2018
doi:10.1093/annonc/mdy166
Published online 28 May 2018

ORIGINAL ARTICLE

Man against machine: diagnostic performance of a deep learning convolutional neural network for dermoscopic melanoma recognition in comparison to 58 dermatologists

Haenssle, Ann Oncol 2018

AI and human

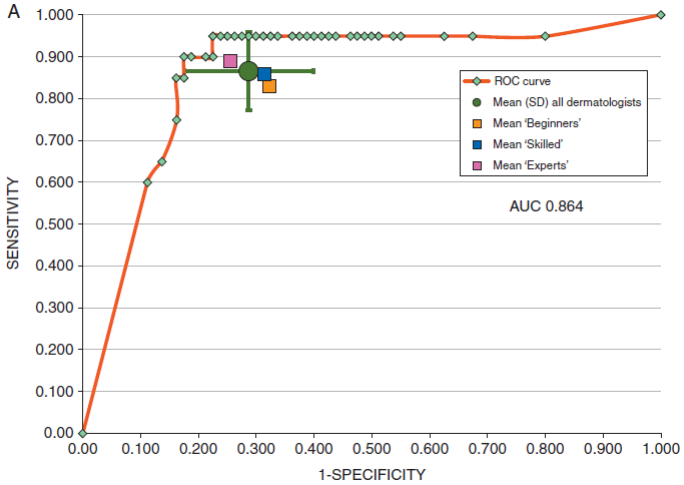


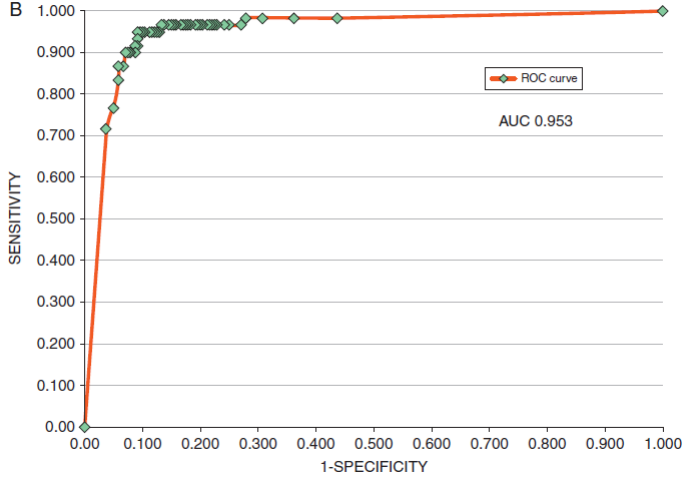
GoogleNet Inception CNN architecture

- 300 images, 20% melanoma
- 100 selected by 2 dermatologists
- 58/172 readers invited answered (International Dermoscopy Society) ranked by expertise level

Haenssle, Ann Oncol 2018

ROC curve to the average sensitivity and specifity to diagnose a melanoma

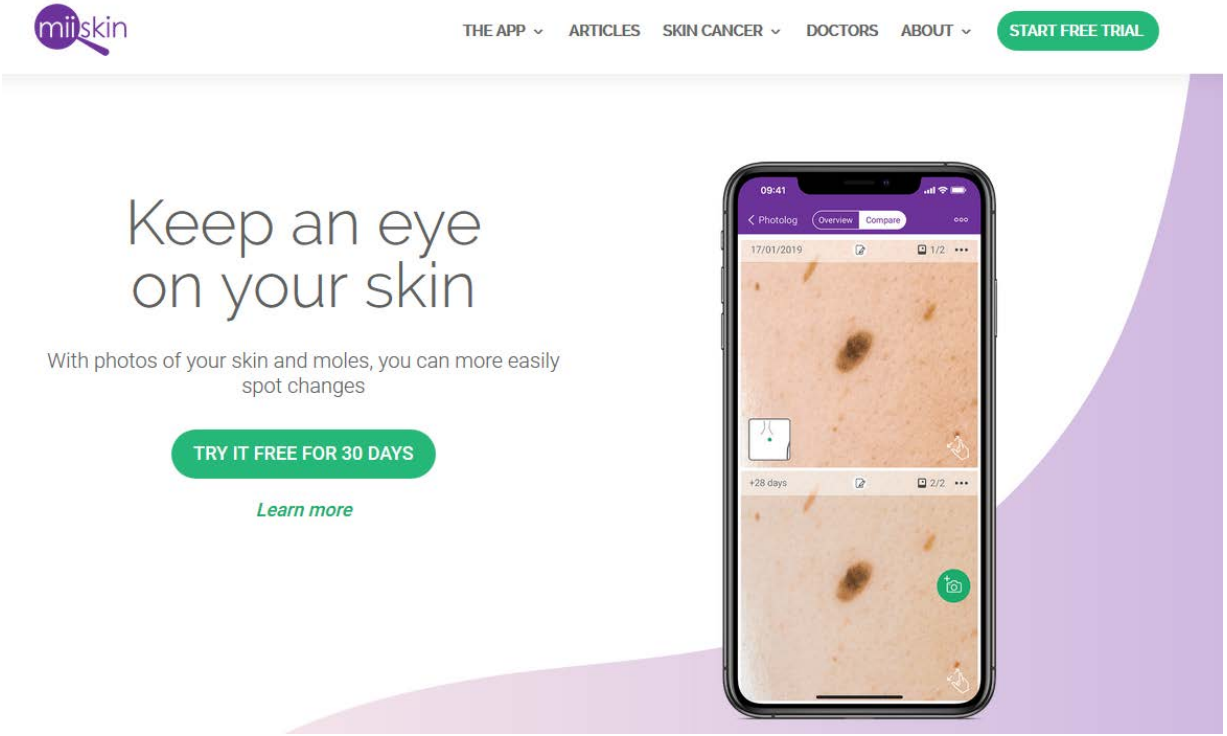




Haenssle, Ann Oncol 2018

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

From Bench to bedside…



In 15 years

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- Connected tools
- Artificial intelligence
- Big data

Get rid of preclinical models?

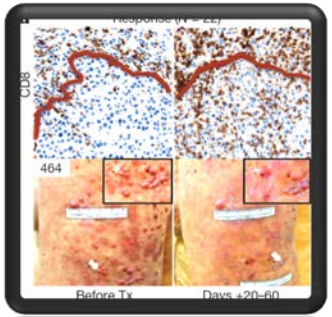
Post-traumatic stress disorder models

Escapable/inescapable electric shocks	Siegmund and Wotjak, 2006
Predator/predator scent exposure	Roth et al., 2011
Single prolonged stress	Souza et al., 2017
Restraint/immobilization	Mitra et al., 2005
Underwater holding	Richter-Levin, 1998
Social defeat	Golden et al., 2011

Musazzi L, Front Pharmacol. 2018

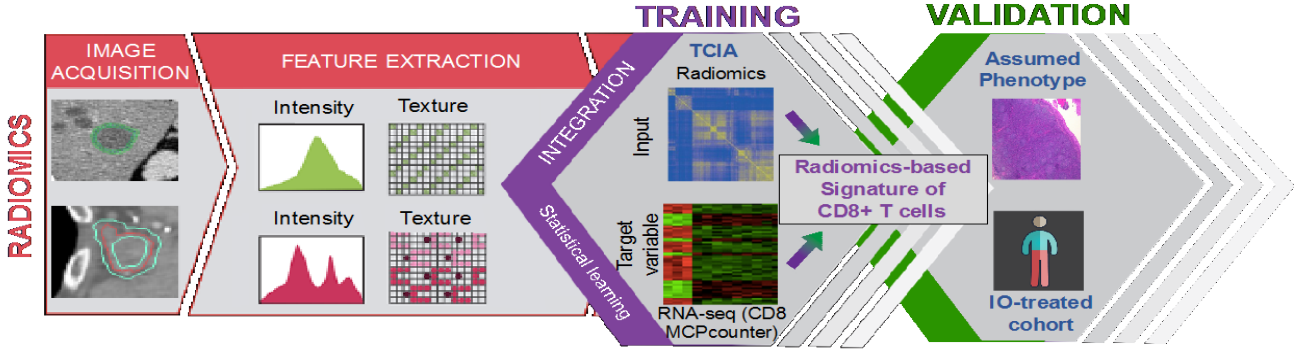
Imaging of inflammation

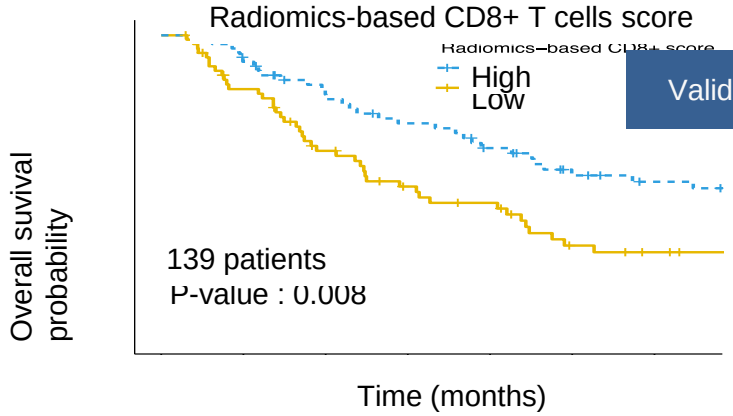
➢ *Determination of an imaging-base signature of tumor immune infiltrate*



Immune inflamed phenotype

Immune-desert





Validation: Phase 1 anti-PD-1/PD-L1

Sun R et al, Lancet Oncol 2018

In 15 years

- Carcinogenesis
- Screening
- Local treatment
- Stage III
- Biomarkers
- Stage IV

- Connected tools
- Artificial intelligence
- Big data
- Different cares

Mieux vivre le cancer

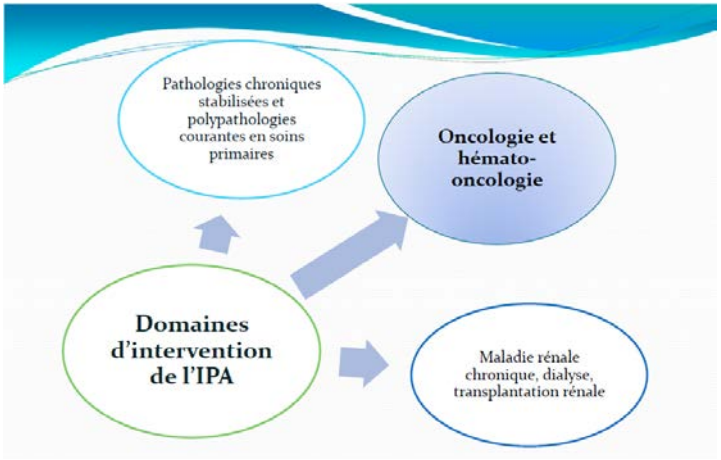
Programme MOLITOR EVASION
KIP HOM **(programme APA connecté)**
Méditation Pleine Conscience **(stage d'initiation en 8 séances)**
YOGA **(cycle en 12 séances)**
ROSE DANSE **(cycle en 10 séances)**
Marche nordique **(cycle de 12 semaines)**
Atelier de QI GONG **(atelier ouvert)**

Cami sport&cancer

Quand le sport devient une thérapie !

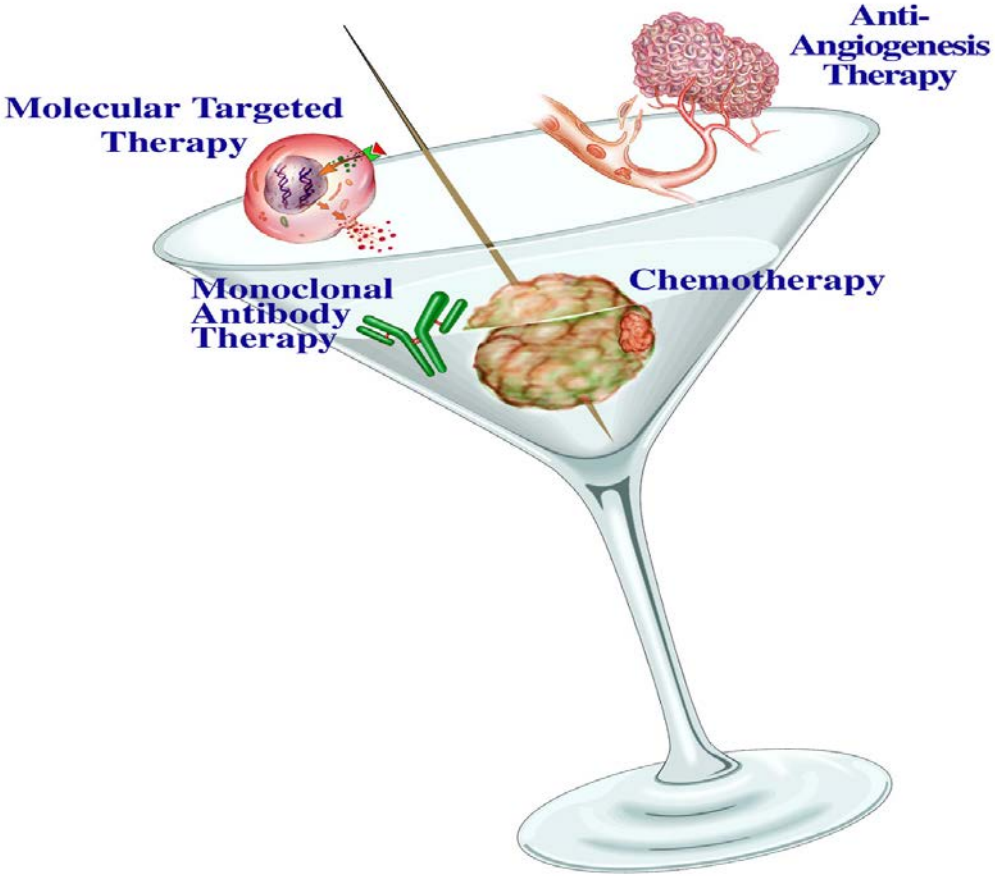
Infirmière de Pratique Avancée

- **Décrets du 18 juillet 2018**
- **<u>Compétences :</u>**
- Evaluation clinique
- Actes techniques
- Surveillance para clinique
- Prescriptions :
  - examens complémentaires,
  - renouvellements ou des adaptations de prescriptions médicales.



Courtesy of Pascal Dielenseger

Le cocktail anti-cancéreux du XXI^{ème} siècle



Roy HERBST

ASCO 2001

Immunotherapy revolution unseen!!

Le cocktail anti-cancéreux du XXI^{ème} siècle

Chemotherapy and ADC

Immunotherapy Hard (CAR-T…) vs. Soft (BITEs, ICI)

TKIs New targets, next gen. drugs

Local treatments everytwhere

Integrated cares (IPA…)

AI everywhere (maybe too much)
Strategy tools
Connected tools…