transgene
immunotherapeutics

Immuno-oncology R&D Day

Modulating
the tumor micro-environment

Changing the tumor's physical properties

Breaking immune tolerance

Improving homing of effector T-cells

June 22, 2017
Paris

Disclaimer

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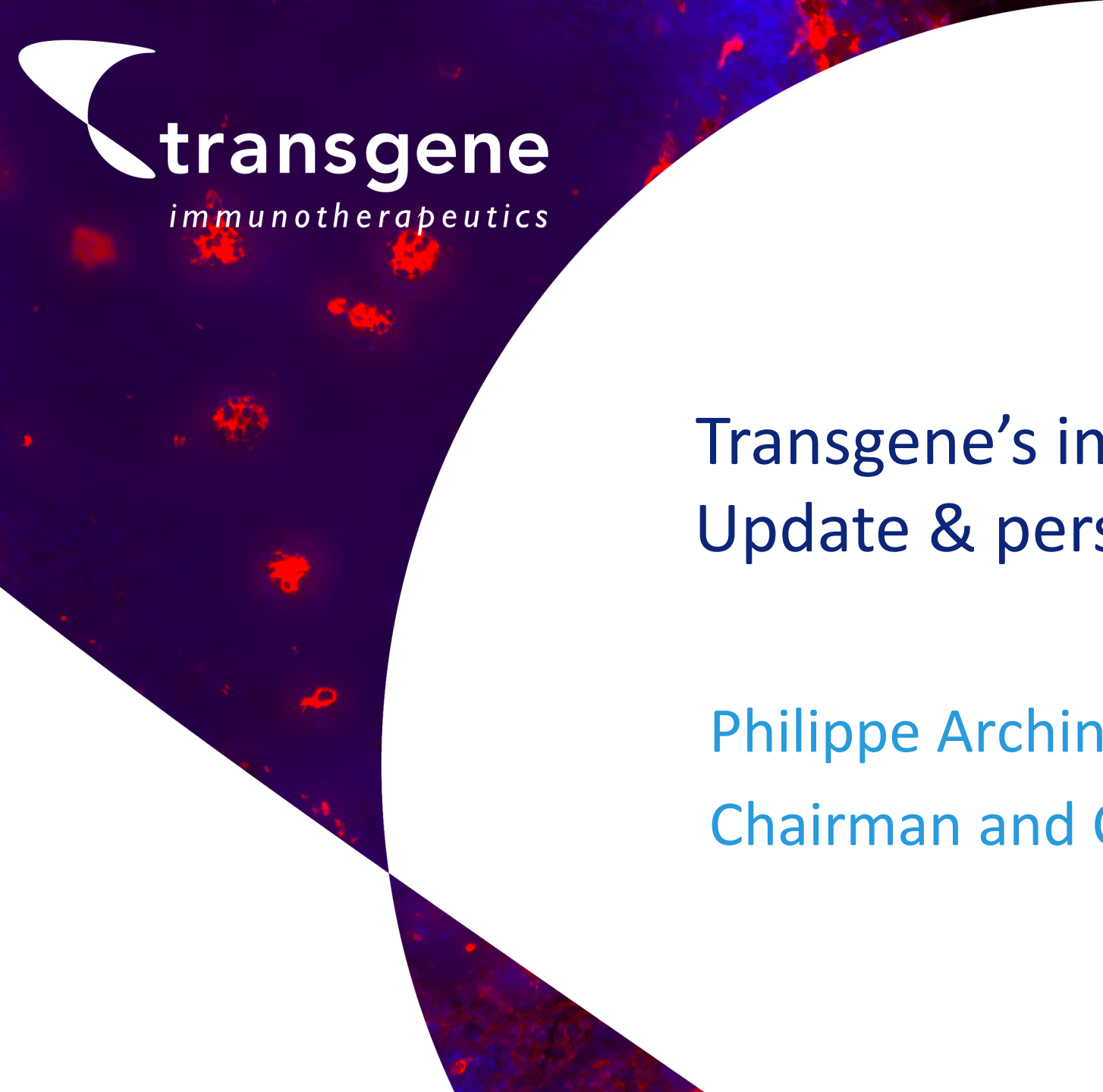

Transgene's immuno-oncology strategy: Update & perspective

Philippe Archinard, PhD

Chairman and CEO, Transgene

Purpose of the day is to provide insights on

- Transgene's progress
- Our vision and opportunities in IO* field
- Our next generation of viral-based immunotherapies

** IO: Immuno-Oncology*

Our strategy

Today

Demonstrate the power of our current immunotherapies by focusing on combination trials with the new standard of care (ICIs)

Tomorrow

Change the cancer combination paradigm by developing multifunctional oncolytic viruses

Today's agenda

2:00 ➔ ~ 4:00 pm

Update and perspective on Transgene's immuno-oncology strategy
Philippe Archinard, PhD, Chairman and CEO, Transgene

Immunotherapy combinations, a game-changer in lung cancer therapy
Karen Kelly, MD, Associate Director for Clinical Research

Novel immuno-oncology approaches in liver cancer
Olivier Rosmorduc, MD, Head of hepato-gastroenterology

Transgene's clinical development strategy in the evolving immuno-oncology landscape
Maud Brandely, MD, PhD, Chief Medical Officer, Transgene

Break

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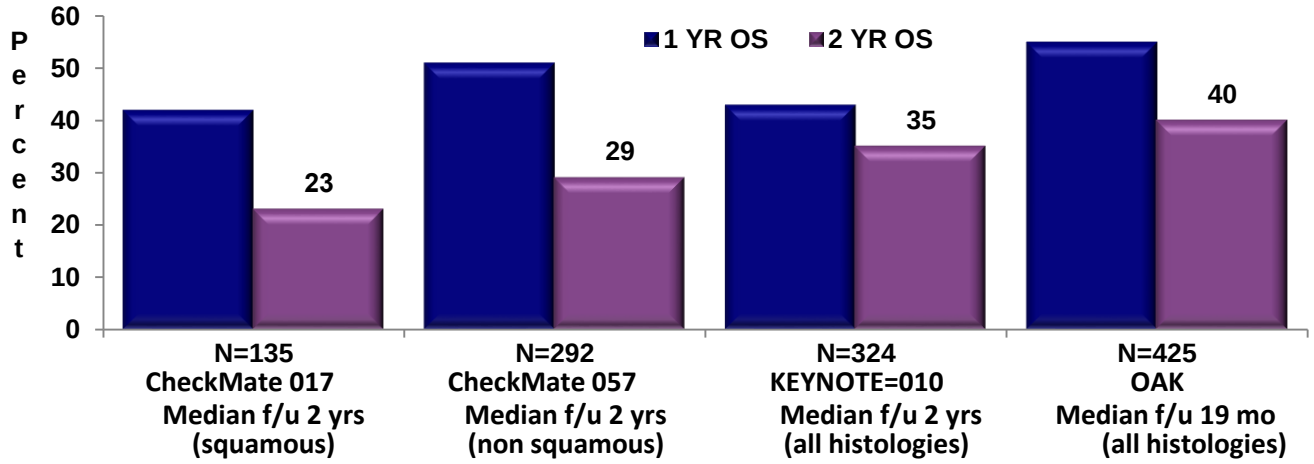
UCDAVIS
COMPREHENSIVE
CANCER CENTER

Immunotherapy combinations, a game-changer in lung cancer therapy

Karen Kelly, MD
Professor of Medicine
Associate Director for Clinical Research
Jennifer Rene Harmon Tegley and Elizabeth Erica Harmon
Endowed Chair in Cancer Clinical Research
UC Davis Comprehensive Cancer Center

Current Status of Immunotherapy
in Non-Small Cell Lung Cancer

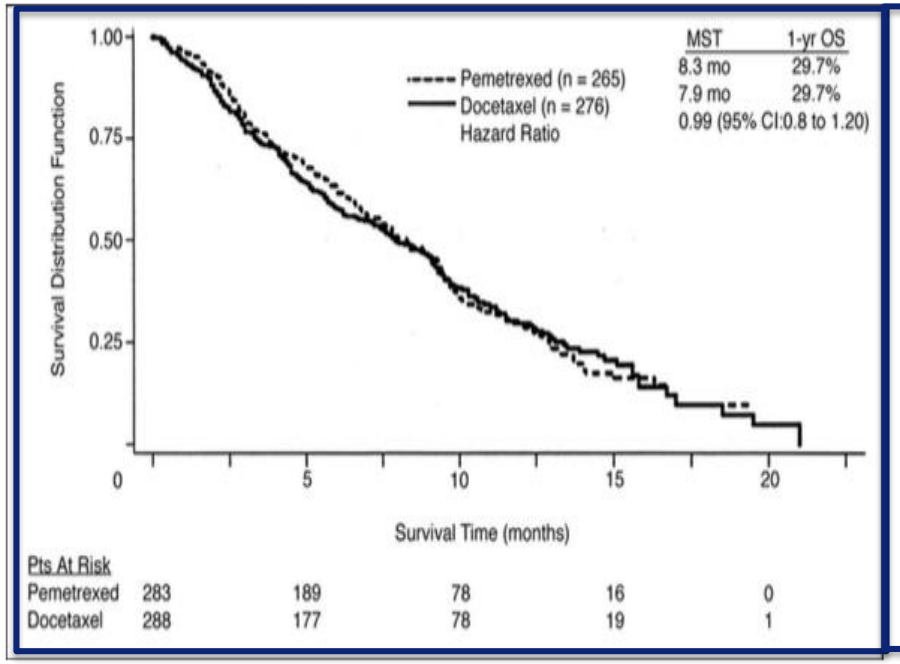
- PD-1/PD-L1 inhibitors are the standard of care for <u>previously treated</u> patients with a platinum doublet



- Phase I trials of Nivolumab and Pembrolizumab report similar 3 YR OS rates at 18% and 19% respectively
  (*Brahmer, JR et al. AACR 2017; Leighl NB et al. ASCO 2017,# 9011)*
- Nivolumab phase I trial reported a 5 YR OS rate of 16%
  (*Brahmer, JR et al. AACR 2017)*
- PD-L1 expression level is not required for treatment but efficacy is enhanced with higher expression levels

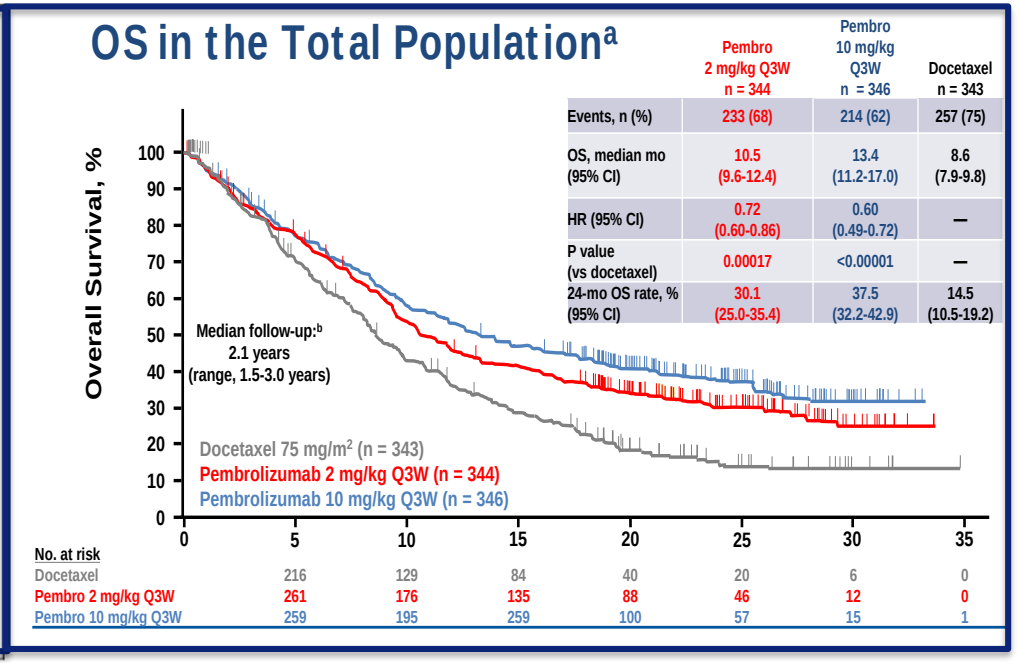
Current Status of Immunotherapy
in Non-Small Cell Lung Cancer

Pemetrexed Vs Docetaxel



Hanna, N et JCO 2004

Pembrolizumab Vs Docetaxel

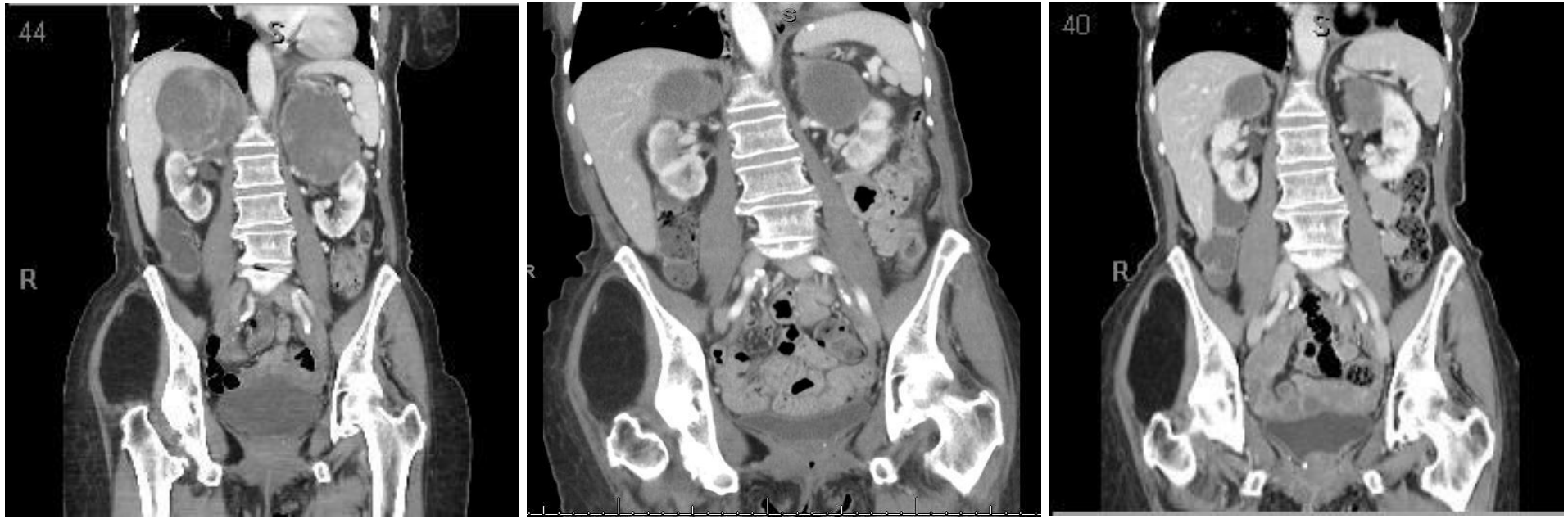


Herbst, RS et al WCLC 2016 #6769

Case Presentation

- 81 YO AA female diagnosed with metastatic squamous cell carcinoma.
- After 2 cycles of gemcitabine/carboplatin, CT scan showed PD with adrenal and brain metastases.
- Patient received SBRT and was then started on nivolumab.

November 2015 | April 2016 | September 2016

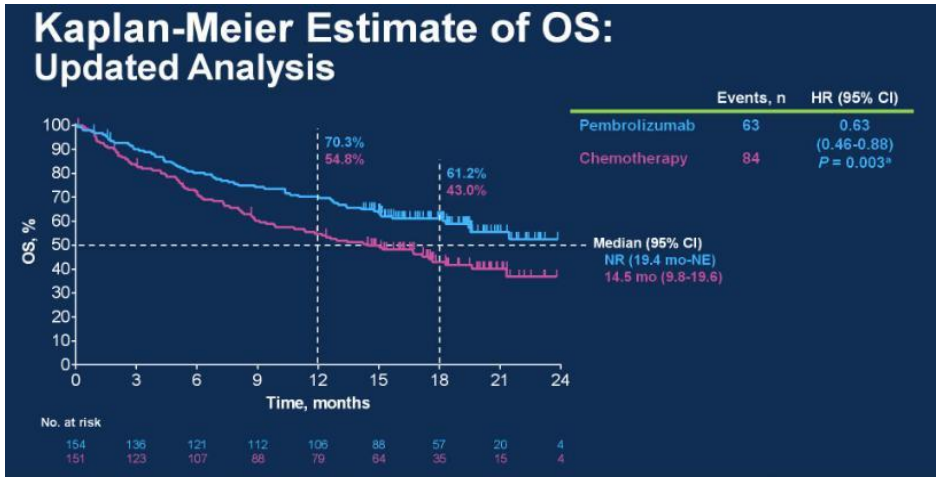


Patient continues on nivolumab as of June 15, 2017

Current Status of Immunotherapy
in Non-Small Cell Lung Cancer

- Pembrolizumab is superior to platinum based chemotherapy in patients whose tumors have ≥50% PD-L1 expression.
  (Brahmer, JR et al. ASCO 2017 #9000)

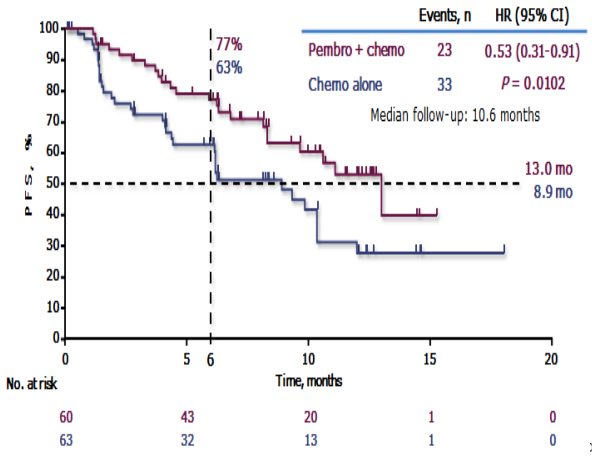
- Pembrolizumab + Pemetrexed and Carboplatin was recently FDA approved based on a randomized phase II trial (KEYNOTE-021).
  (Langer C et al. Lancet Oncology 2017)



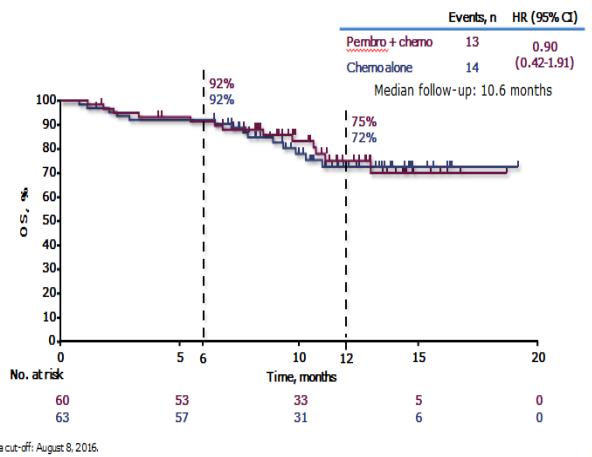
ASCO 2017

PFS remained longer with median fu of 14.5 mos (HR 0.49, 95% CI 0.29-0.83, *P* = 0.0035; ORR was 56.7% vs 30.2% (*P* = 0.0016)

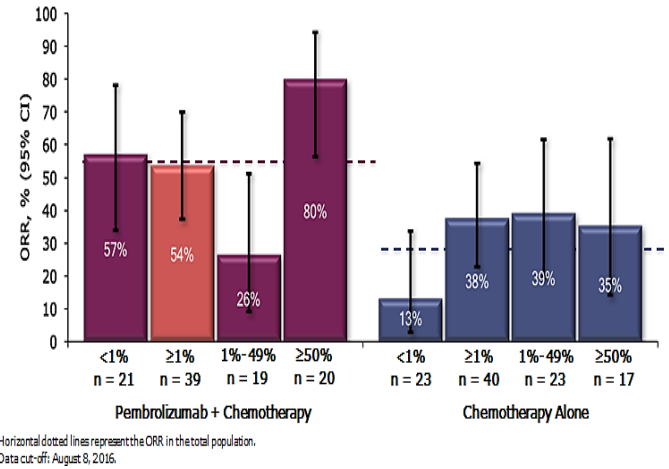
KEYNOTE-021: PFS



KEYNOTE-021: OS



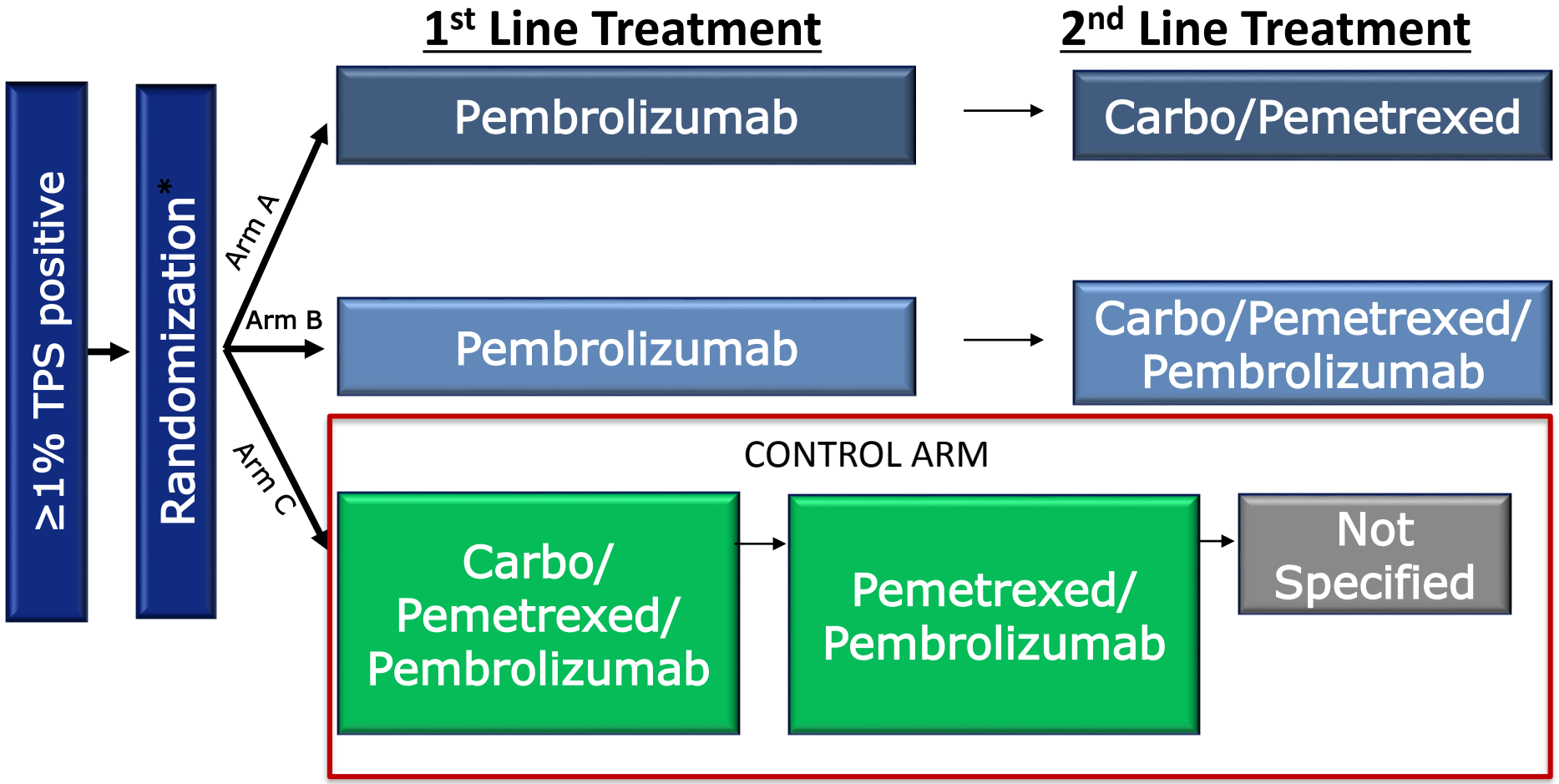
KEYNOTE-021: ORR by PD-L1



Phase III Trials of Chemotherapy + PD-1/PD-L1 Inhibitors

Trial	Histology	Agent	PD-L1 Status
KEYNOTE-189	Nonsquamous	Pemetrexed/carboplatin ± Pembrolizumab (200 mg flat dosing q 3 wk)	Any PD-L1 status
KEYNOTE-407	Squamous	Paclitaxel or nab-paclitaxel and carboplatin ± Pembrolizumab	Any PD-L1 status
Impower 130 Phase III	Nonsquamous	nab-paclitaxel and carboplatin ± Atezolizumab	Any PD-L1 status
Impower 131 Phase III	Squamous	Paclitaxel or nab-paclitaxel and carboplatin ± Atezolizumab	Any PD-L1 status
Impower 132	Nonsquamous	Pemetrexed and carboplatin or cisplatin ± Atezolizumab	Any PD-L1 status
Impower 150	Nonsquamous	Paclitaxel/carboplatin with or without bevacizumab ± Atezolizumab	Any PD-L1 status

INSIGNA | SWOG/ECOG Advanced Non-squamous Trial
with Pembrolizumab



* Stratify on ≥50% versus < 50%

- Dual Objective: OS in ≥50% and >1% TPS
  - Arm C (control) versus Arm A
  - Arm C (control) versus Arm B

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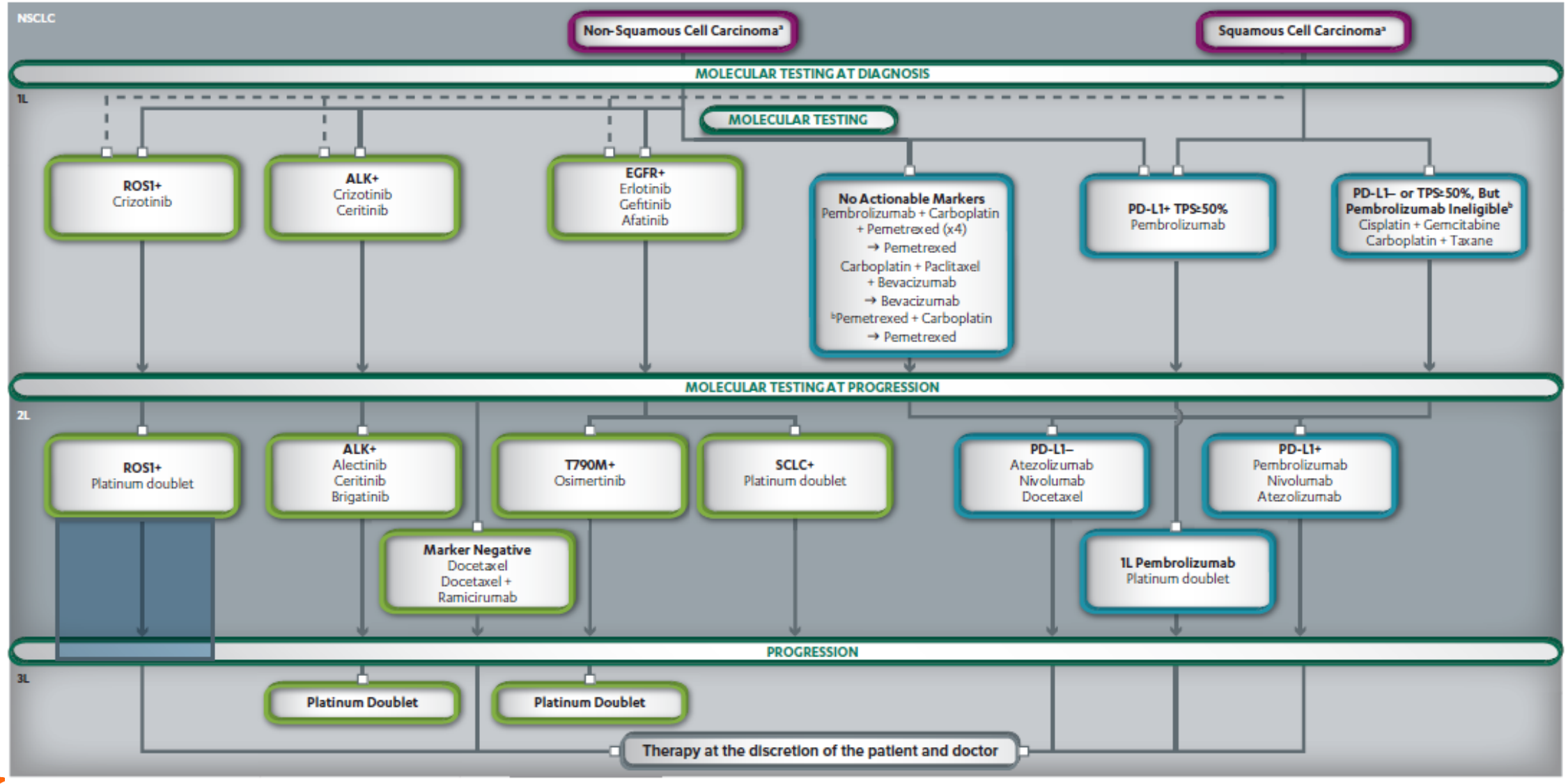
NSCLC | Treatment Algorithm Summer 2017



TPS=Tumor proportion score
[a]Clinical trials should be the first consideration for all patients at all stages
[b]Chemotherapy alone may be the most suitable option for patients with certain comorbidites (eg, autoimmune disease)

→ Followed by maintenance therapy ▪▪▪ Molecular testing may be suitable based on the patient's history

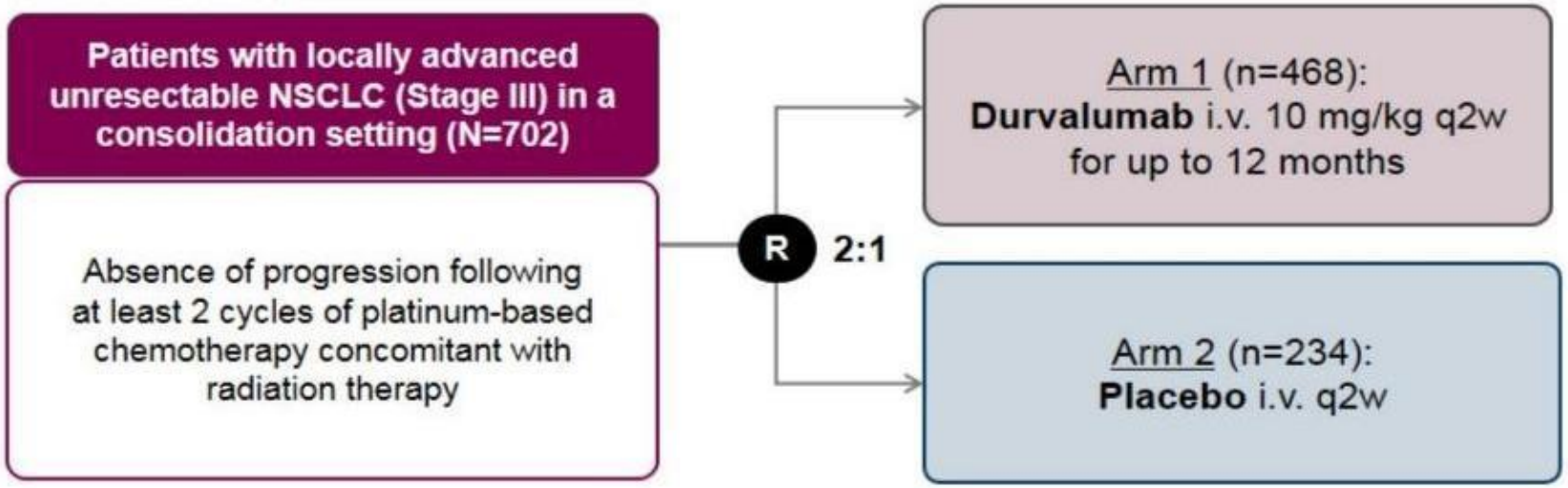
NSCLC | Current Status of Immunotherapy

IMFINZI™ (durvalumab) significantly reduces the risk of disease worsening or death in the Phase III PACIFIC trial for Stage III unresectable lung cancer

Press release

PUBLISHED
15 May 2017

- Phase 3, randomized, double-blind, placebo-controlled, multicenter, global study (28 countries)[1-3]



Primary endpoints[3]
- PFS, OS

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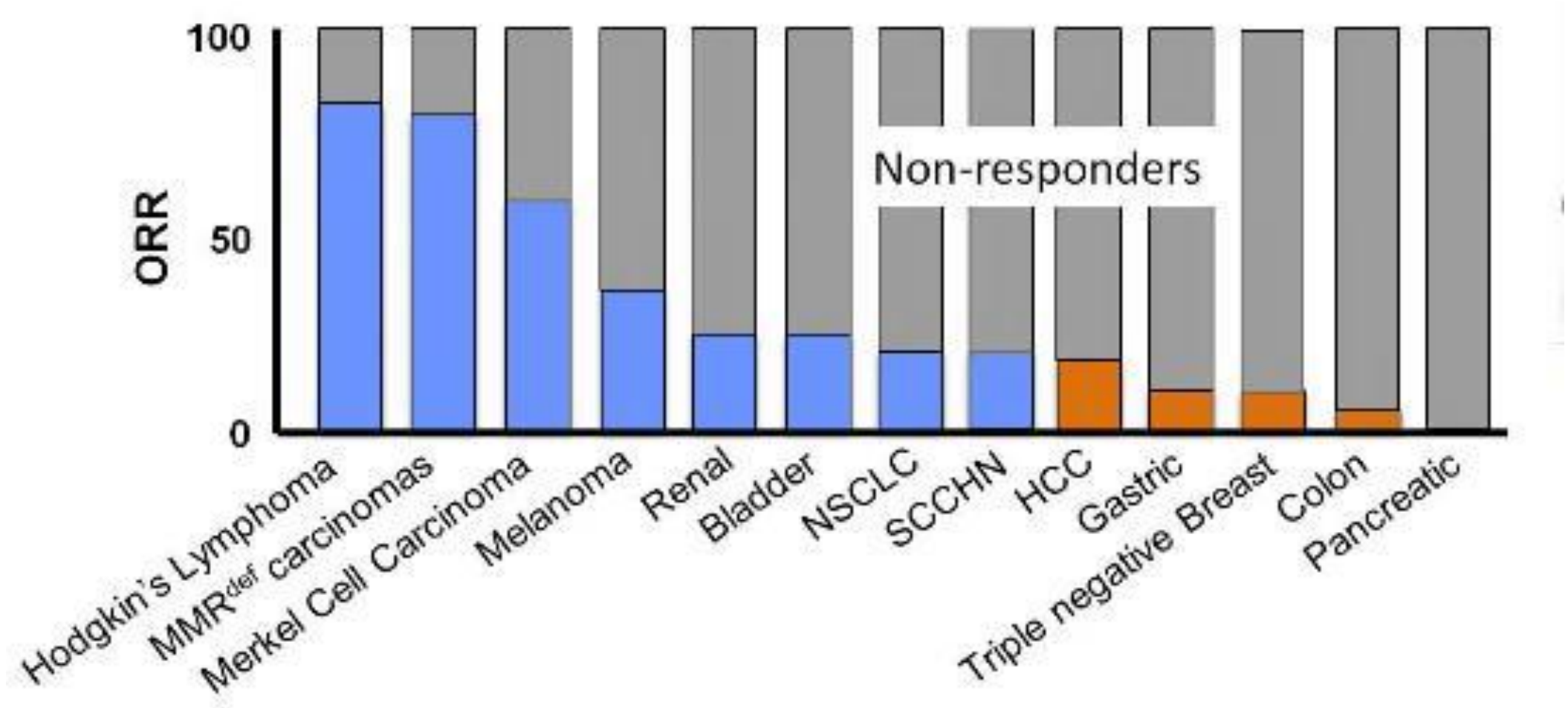
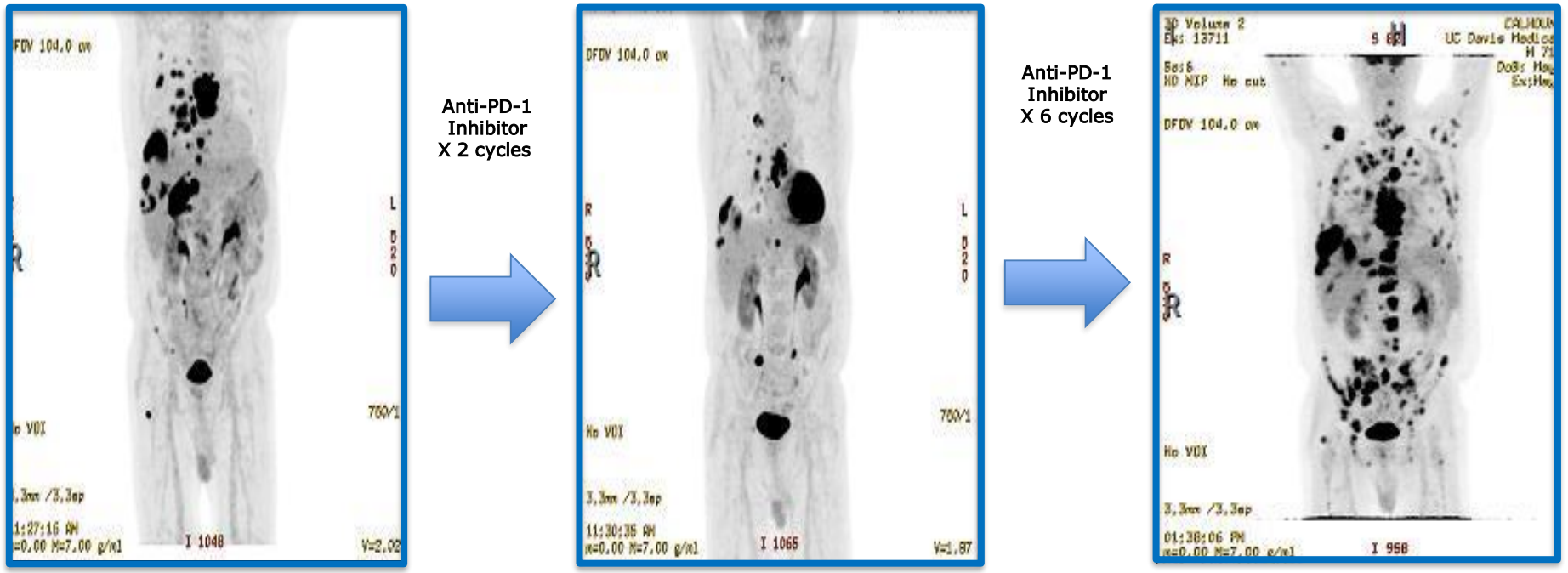
Problem:
Non-responders Represents a Large Group of NSCLC Patients



FDA approved drugs

Problem:
Anti-PD-1/PD-L1 Resistance



90% PD-L1 expression

?

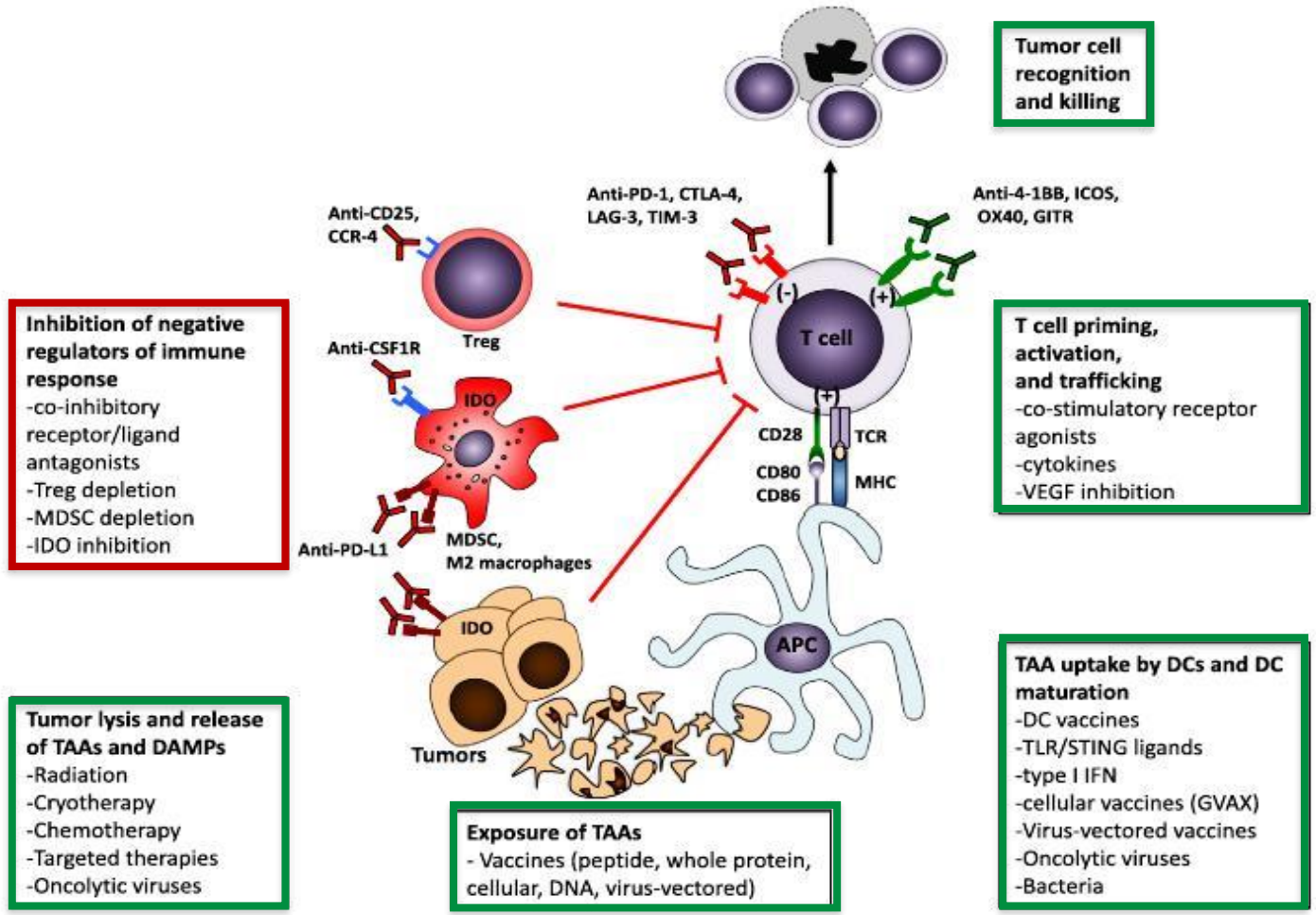
Quickly Moving to Immune Combinations

Drugs that target immune evasion

- Blockade of negative immune regulators
- Blockade of tolerogenic enzymes

Drugs that stimulate the immune process

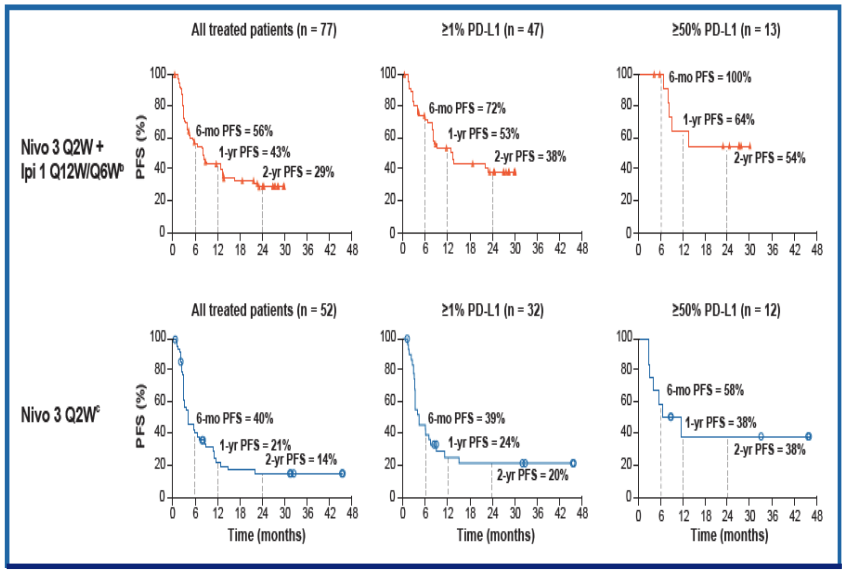
- Agonist of costimulatory receptors
- Enhancers of antigen presentation (vaccines)
- Exogeneous recombinant cytokines
- Oncolytic viruses
- Cell therapies



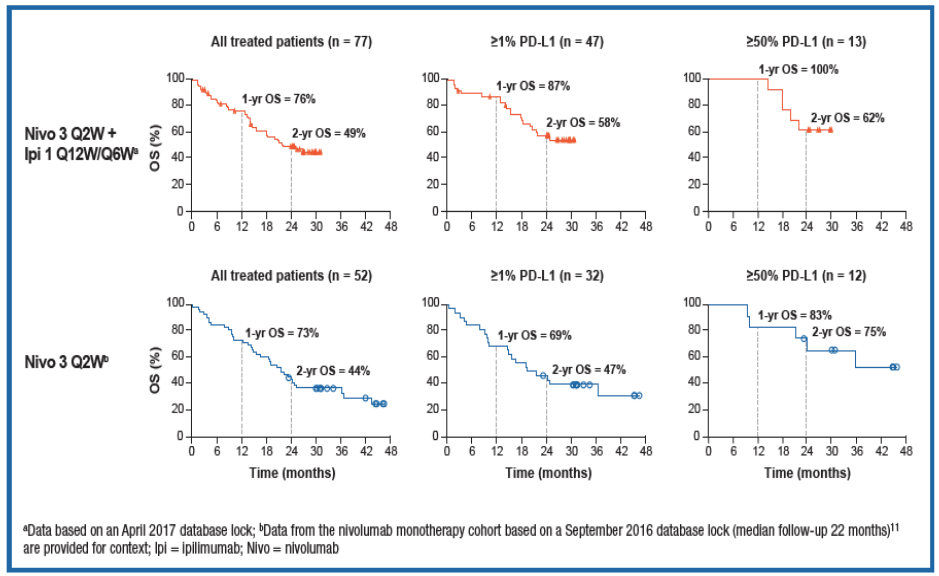
Zamarin D et al. Pharmacol Ther, 150:23-32, 2015.

ASCO 2017 | Nivolumab + Ipilimumab Update

PFS in all treated patients and by PD-L1 expression



OS in all treated patients and by PD-L1 expression



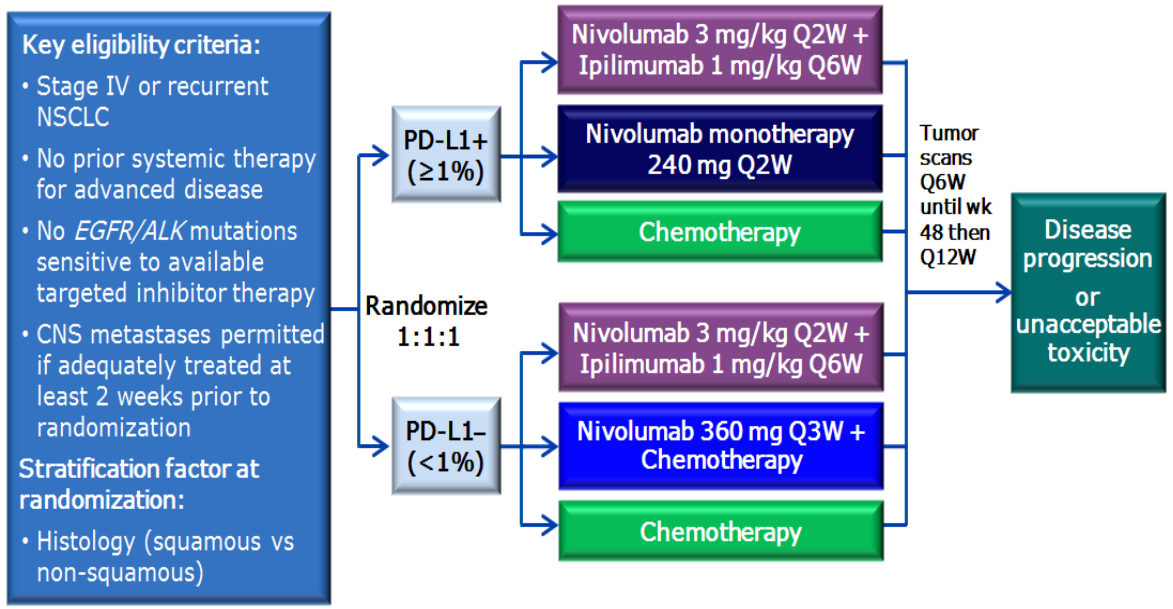
[a]Data based on an April 2017 database lock; [b]Data from the nivolumab monotherapy cohort based on a September 2016 database lock (median follow-up 22 months)[11] are provided for context; Ipi = ipilimumab; Nivo = nivolumab

	Nivolumab 3 Q2W + Ipilimumab 1 Q12W/Q6W (n=77)		Nivolumab 3 Q2W (n=52)	
	Any grade, %	Grade 3-4, %	Any grade, %	Grade 3-4, %
TRAEs	79	36	73	19
Select TRAEs	68	23	69	15
TRAEs leading to discontinuation	18	8	12	12

Goldman JW et al. ASCO 2017 #9093

Randomized Phase III Trials
of Dual Immune Checkpoint Inhibitors

CheckMate-227



Primary endpoints: OS, PFS

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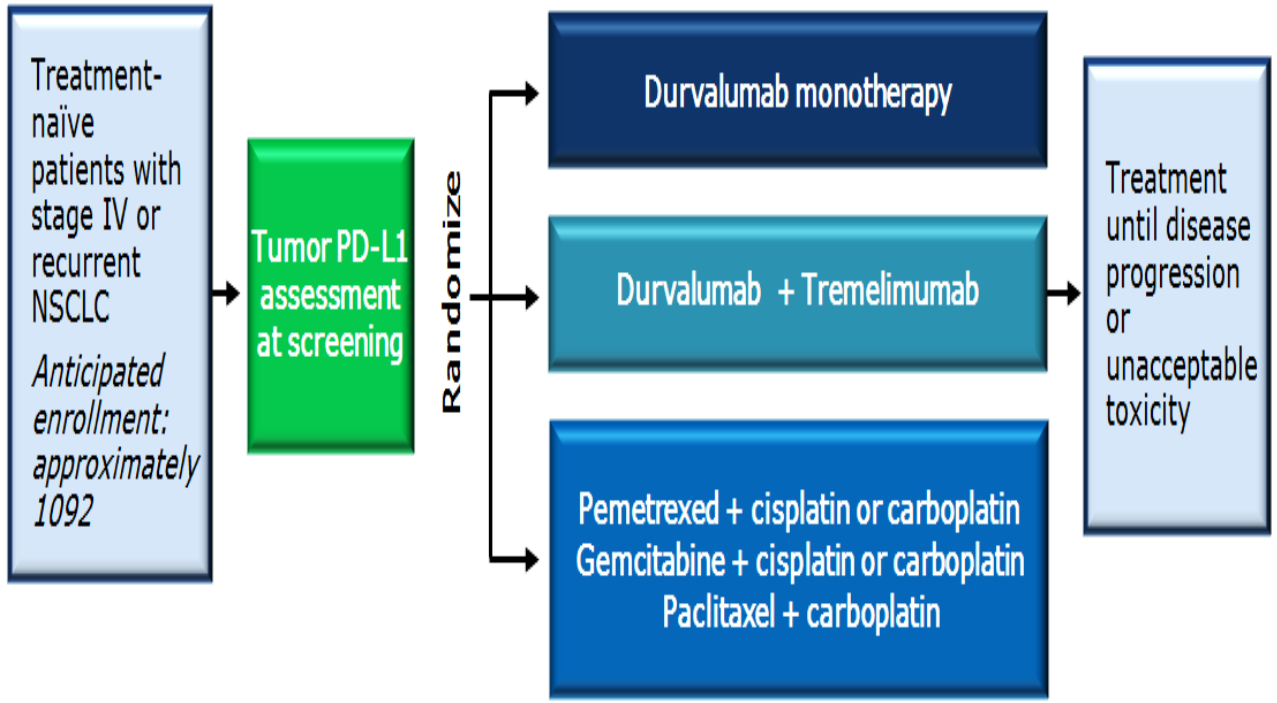
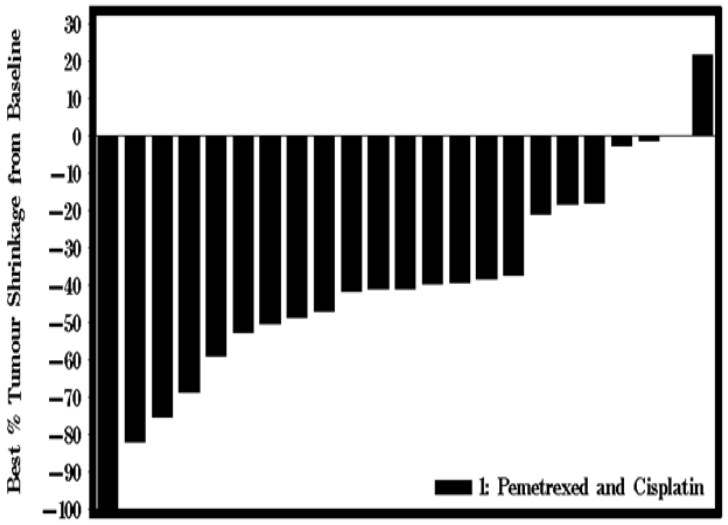


Primary endpoints: OS and PFS

Pemetrexed /Cisplatin+Durvalumab +/- Tremelimumab in Patients with Advanced Non-Squamous NSCLC: A CCTG Phase IB Study IND.226 Cohort 1



Response rate for all treated patients:
16/26 = 61.5% (95% CI: 40.6,79.8%);
CR=0; PR=16; SD= 7; PD=2 (N=25)

	All causality (N=26)		Related to Pem/Cis		Related to D ± T	
	All	≥ G3	All	≥ G3	All	≥ G3
Febrile Neutropenia	1 (4%)	1 (4%)	1 (4%)	1 (4%)	-	-
Mucositis	4 (15%)	-	4 (15%)	-	1 (4%)	-
Vomiting	16 (62%)	2 (8%)	15 (58%)	2 (8%)	6 (23%)	-
Diarrhea	9 (35%)	3 (12%)	4 (15%)	1 (4%)	4 (15%)	1 (4%)
Rash	9 (35%)	1 (4%)	7 (27%)	1 (4%)	4 (15%)	1 (4%)
Fatigue	26 (100%)	3 (12%)	20 (77%)	2 (8%)	13 (50%)	-
Dyspnea	18 (69%)	2 (8%)	2 (8%)	-	3 (12%)	-
Pneumonitis	2 (8%)	1 (4%)	1 (4%)	1 (4%)	2 (8%)	1 (4%) DLT
Hyperthyroid	2 (8%)	-	-	-	2 (8%)	-
Hypothyroid	4 (15%)	-	-	-	3 (12%)	-

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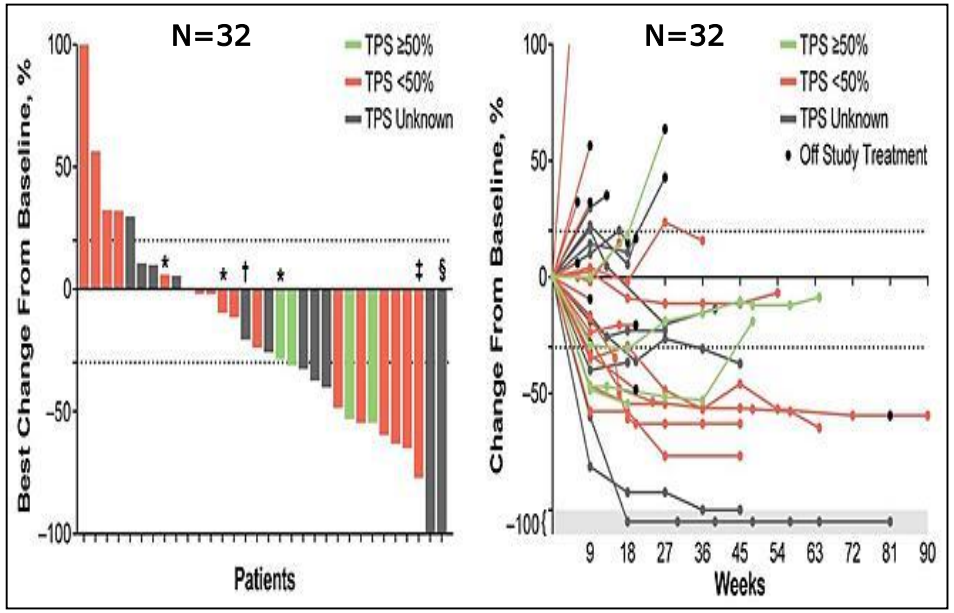
Juergens D et al, WCLC 2016, abstr #5522 (MA09.03)

ASCO 2017 | ECHO-202/KEYNOTE-037 Study – NSCLC Cohort

Epacadostat plus Pembrolizumab

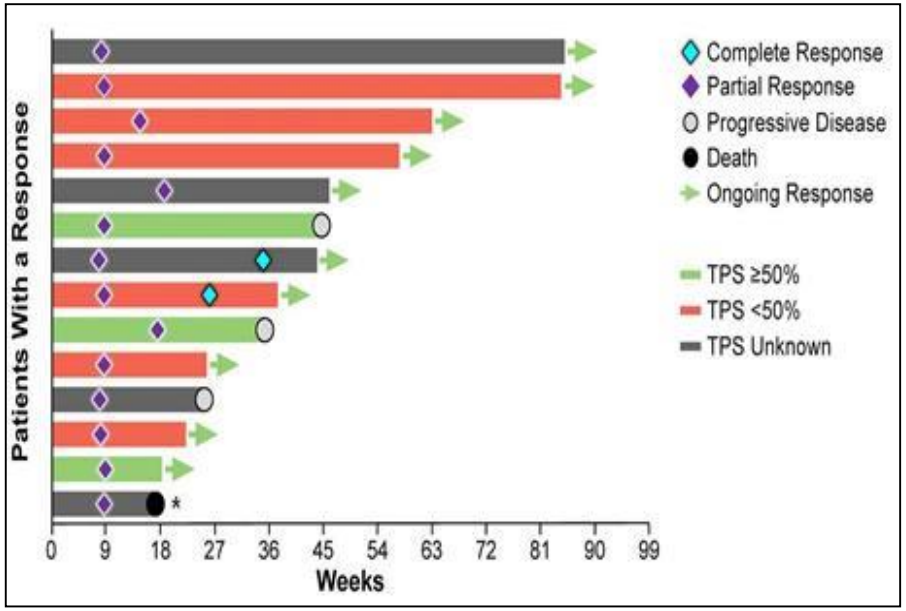
Percentage Change in Target Lesions

ORR=14/36 (39%) 2 CRs (6%) 12 PRs (33%)
DCR=23/36 (64%) BY RECIST



Time to and Duration of Response (RECIST)

10/14 responses were ongoing
Median (range) duration of response
26.9+ (8.9 to 76.6+) weeks

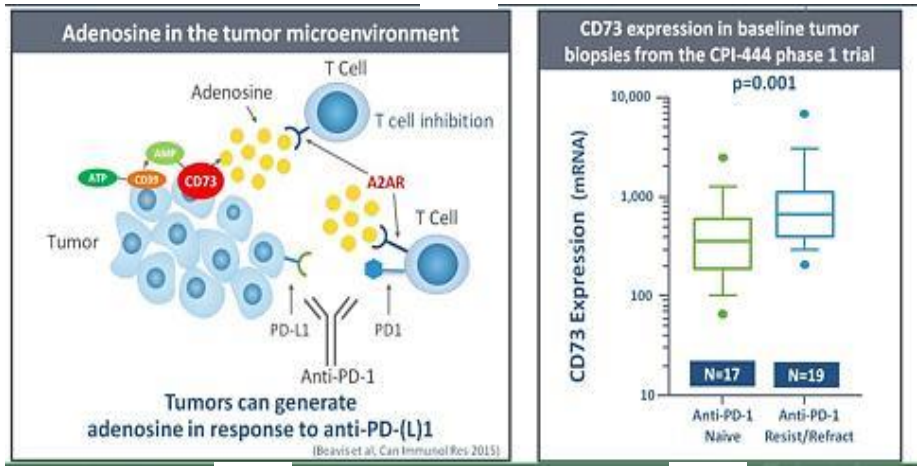


Phase III registration trial ongoing in melanoma

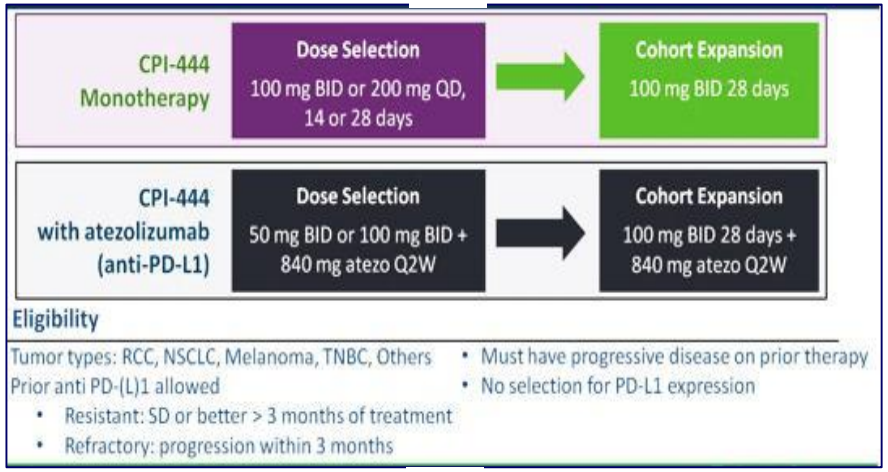
Gangadhar TC, et al. ASCO 2017, abstr #9014

ASCO 2017 | CPI-444 + Atezolizumab

Adenosine Suppresses Immunity and is a Potential Mechanism of Resistance to Anti-PD-(L)1 Therapy

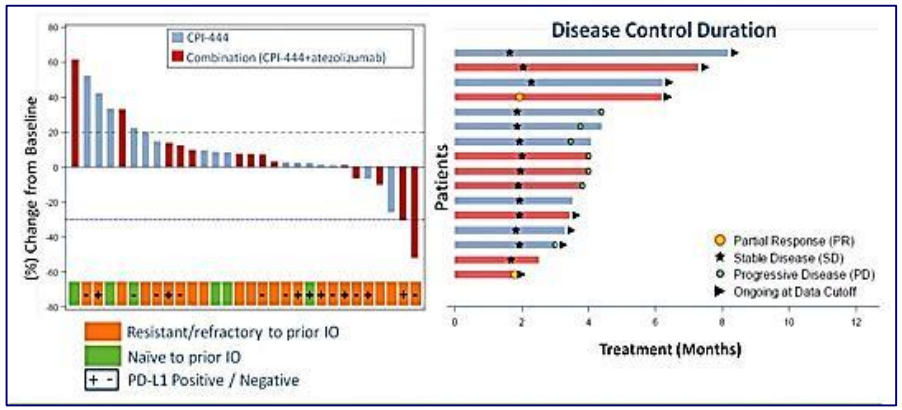


Adenosine A2a Receptor Antagonist ± Atezolizumab

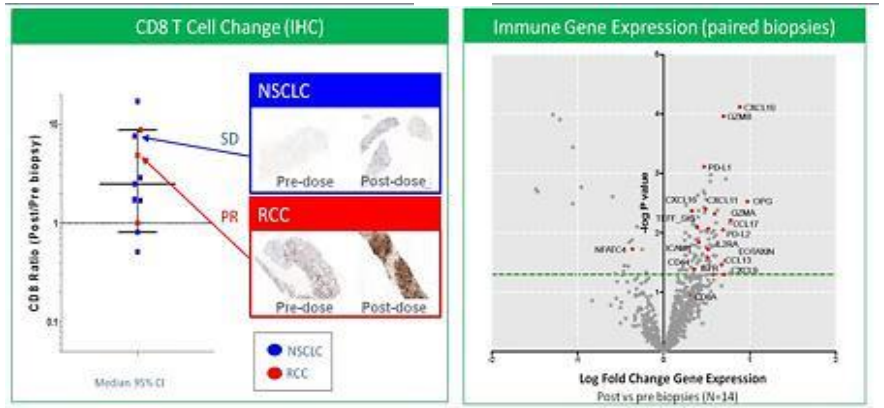


Disease Control in NSCLC

Partial responses can be seen in anti-PD-1 progressors



CPI-444 Induces CD8 T Cell Infiltration and Th1 Gene Expression in Tumor Tissues

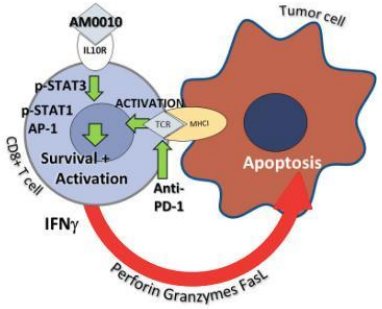


Fong L, et al. ASCO 2017, abstr #3004

ASCO 2017 | AM0010 (PEG-IL10) + Anti-PD-1

AM0010 (PEG-IL-10) Increases & Activates Tumor Infiltrating CD8+ T cells

- Low levels of IL-10 are anti-inflammatory - high levels expand activated CD8 T cells
- Tumor antigen recognition by CD8+ T cells (TCR) induces PD-1 and the IL-10 receptor on CD8+ T cells
  - IL-10 activates CD8+ T cells ("Cytotoxic License")
- PEG-IL-10 induces cytotoxicity, proliferation and survival of CD8+ T cells and the persistence of antigen activated intratumoral CD8+ T cells



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AM0010
10-20 mg/kg SQ daily
+
Anti-PD-1 (pembrolizumab or nivolumab)

PD-L1 (22C3 IHC) (n=22)	<1% (n=10)	1-49% (n=3)	>50% (n=4)	Not available (5)
PR, n (%)	3 (30%)	1 (33%)	3 (75%)	1 (20%)
SD, n (%)	7 (70%)	1 (33%)	1 (25%)	3 (60%)
PD, n (%)	0 (0%)	1 (33%)	0 (0%)	1 (20%)

8/22 (34%)

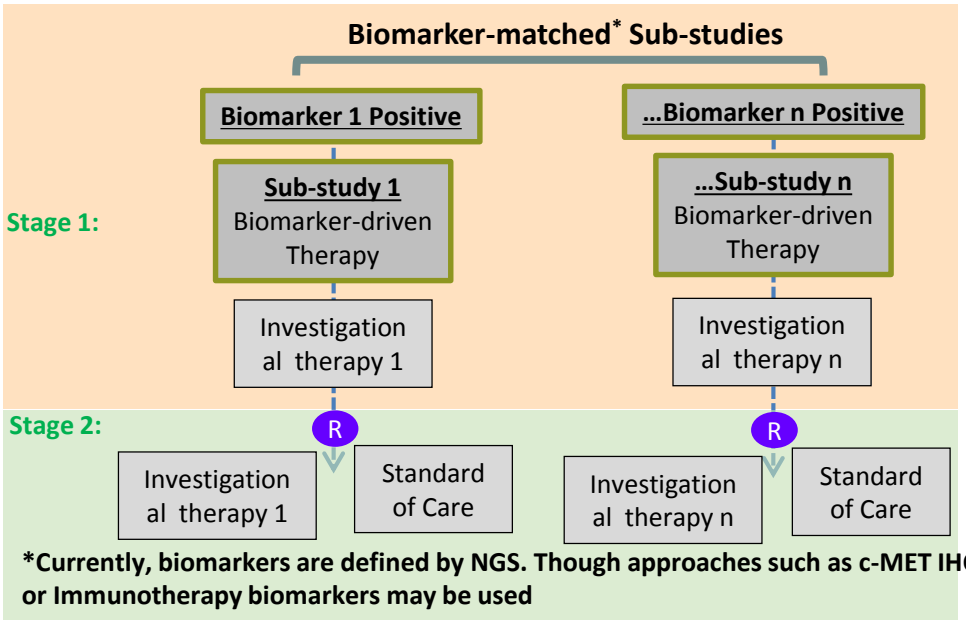
AM0010 plus anti-PD1 increased serum Th1 cytokines (IL-18, IFNγ), the number and proliferation of PD1+ Lag3+ activated CD8+ T cells and a de-novo oligoclonal expansion of T cell clones in the blood while decreasing TGFβ.

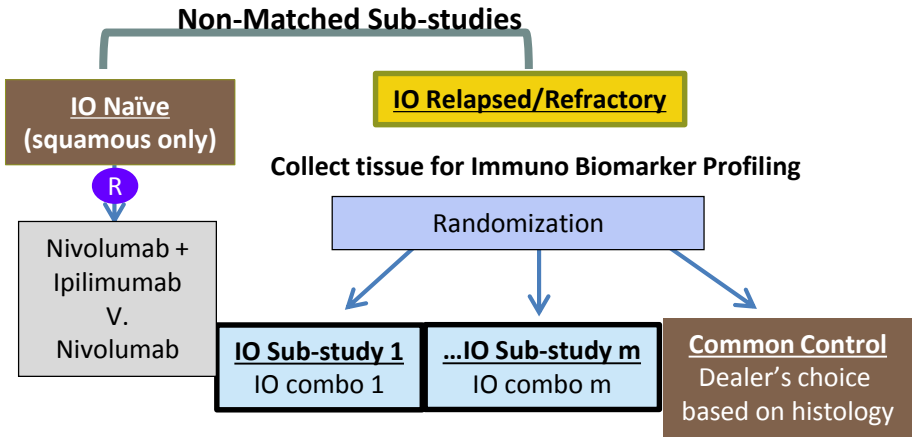
Wong DJL et al. ASCO 2017, abstr #9091

S1400 Lung-MAP Redesign

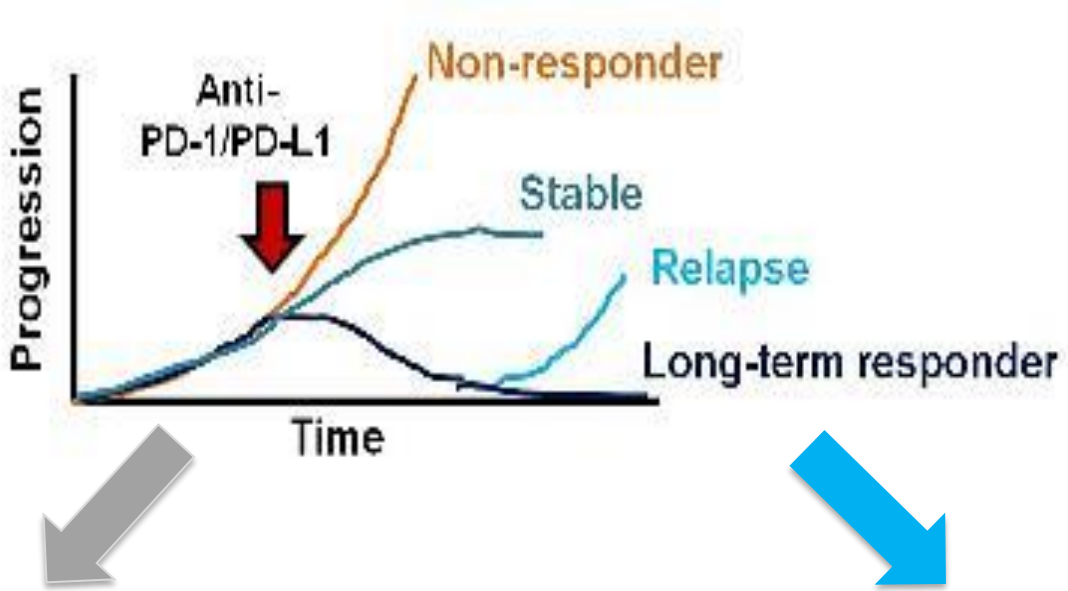
Focusing on IO failures

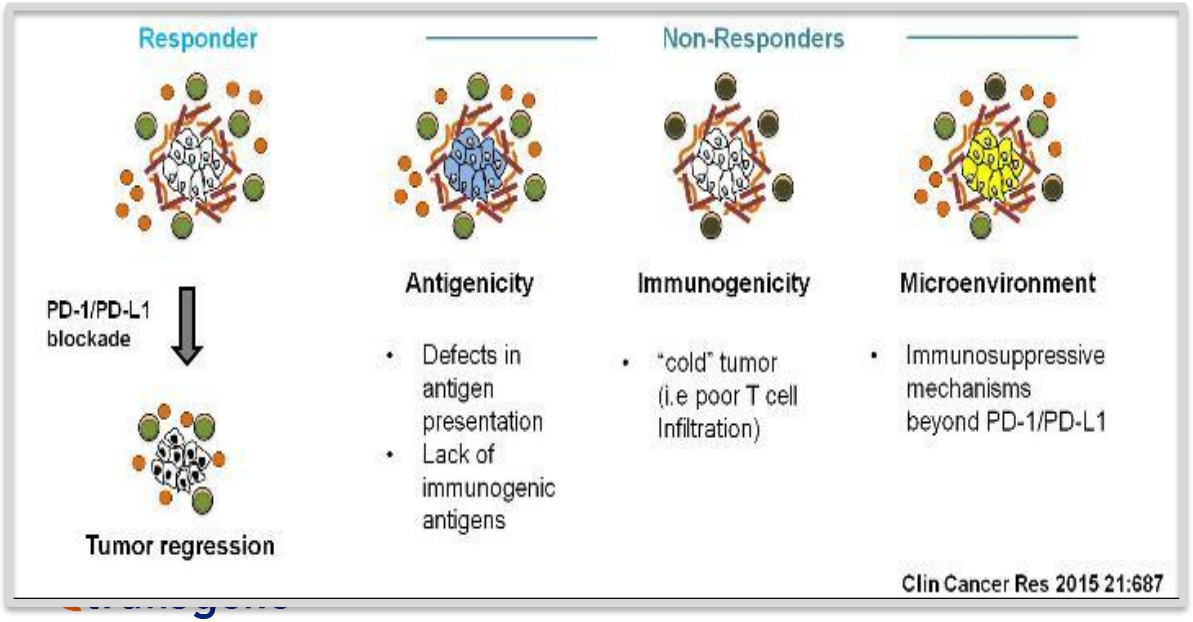
Previously-treated Stage IV or Recurrent Non-Small Cell Lung Cancer (all histology) Immunotherapy or Chemotherapy Relapsed/Refractory Patients

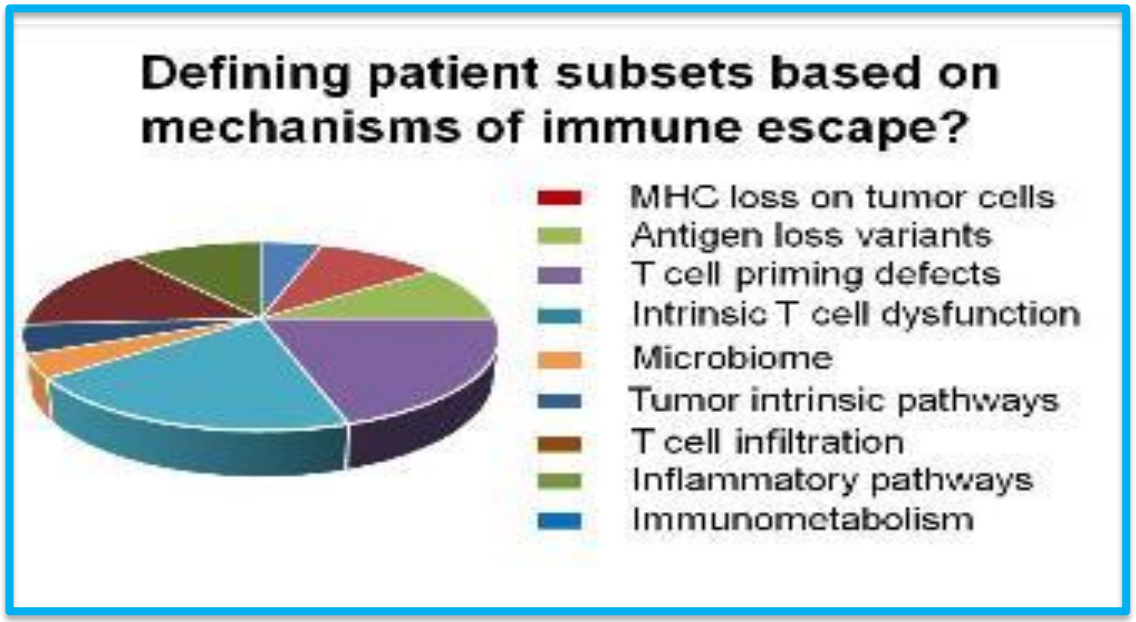




Defining IO subsets







Rationale Combinations

Drug X + **PD-1/PD-L1 antibody**

Which targets to select?
How to demonstrate improved activity?
What biomarkers to follow for response and to understand resistance?

Tumor and Immune Predictive Biomarkers

Tumor Antigens

- Biomarkers indicative of hypermutation & neo-antigens may predict response to IO treatment

Examples:

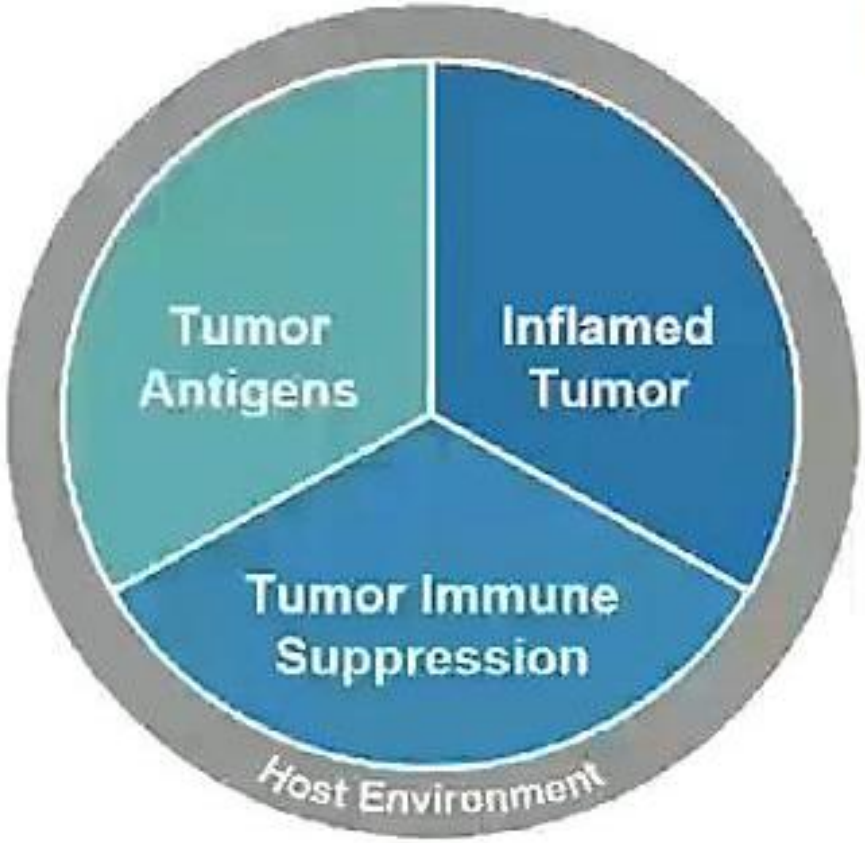
– TMB, MSI-High, Neo-Antigens

Inflamed Tumor Microenvironment

- Biomarkers (intra- or peri-tumoral) indicative of an inflamed phenotype may predict response to IO treatment

Examples:

– PD-L1, Inflammatory Signatures



Tumor Immune Suppression

- Biomarkers that identify tumor immune system evasion beyond PD-1/CTLA-4 to inform new IO targets and rational combinations

Examples:

– Tregs, MDSCs, IDO, LAG-3

Host Environment

- Biomarkers which characterize the host environment, beyond tumor microenvironment, may predict response to IO treatment

Examples:

– Microbiome, Germline Genetics

IDO = indoleamine-2,3 dioxygenase, LAG-3 = lymphocyte activation gene-3, MDSCs = myeloid-derived suppressor cells, MSI-High = microsatellite instability high; TMB = tumor mutational burden. Adapted from Blank C.U. et al., *Science* 2016;352:658–660.

ASCO 2017 | Tumor Antigens

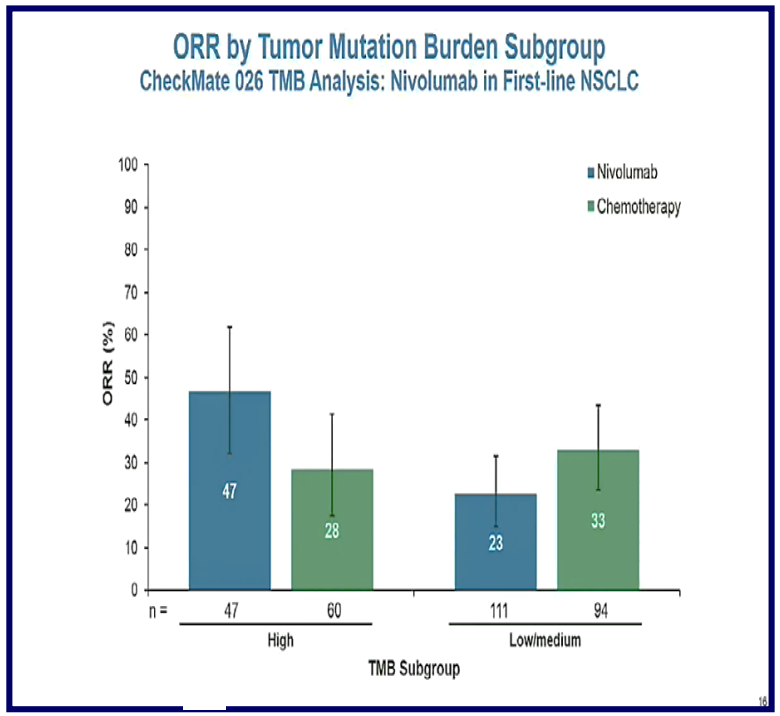
Tumor Antigens

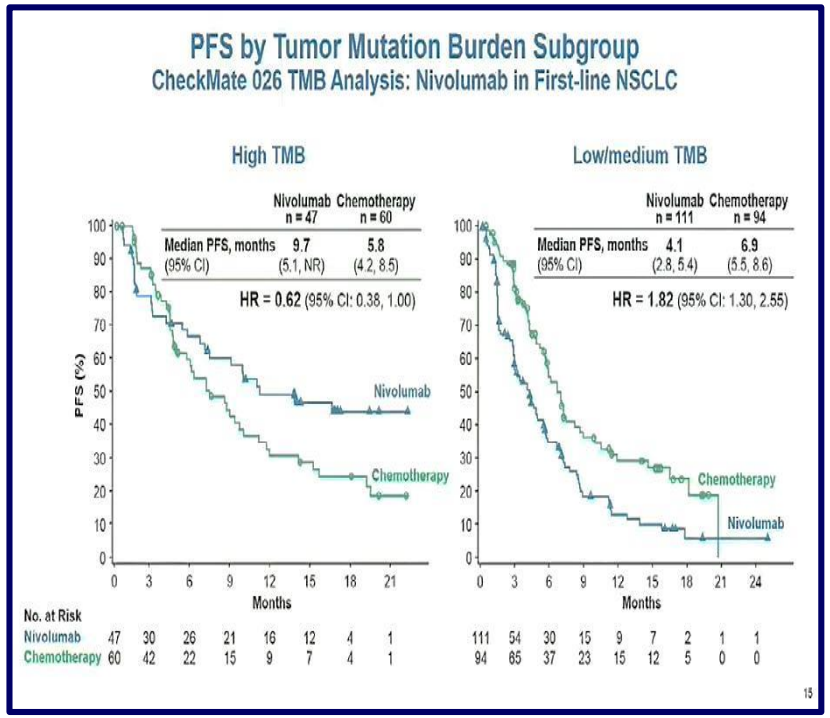
- Biomarkers indicative of hypermutation & neo-antigens may predict response to IO treatment

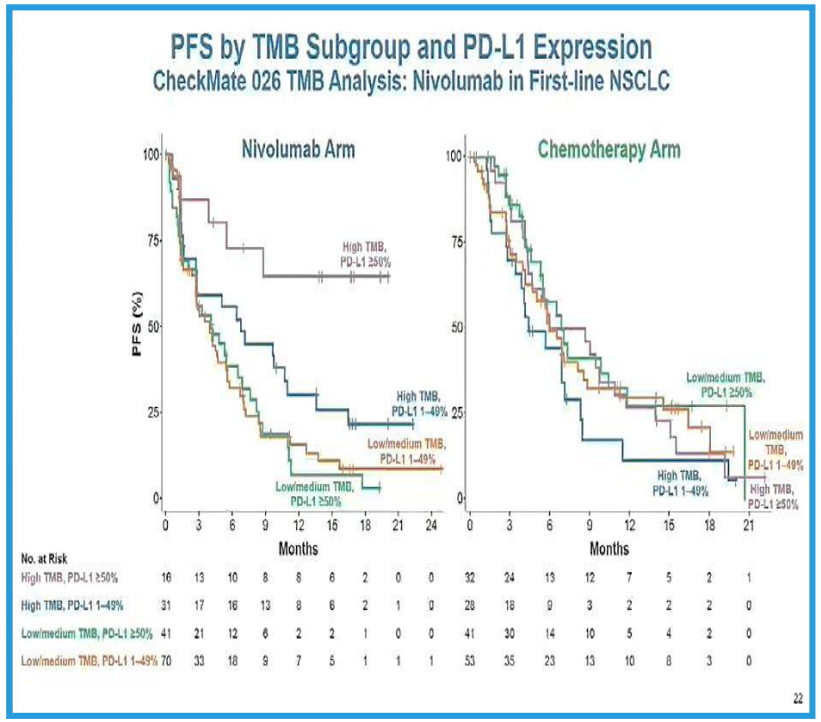
Examples:

– TMB, MSI-High, Neo-Antigens

Tumor mutational burden is a potential predictive marker of efficacy to immune checkpoint inhibitors.







Peters S et al. AACR 2017

ASCO 2017 | Tumor Antigens

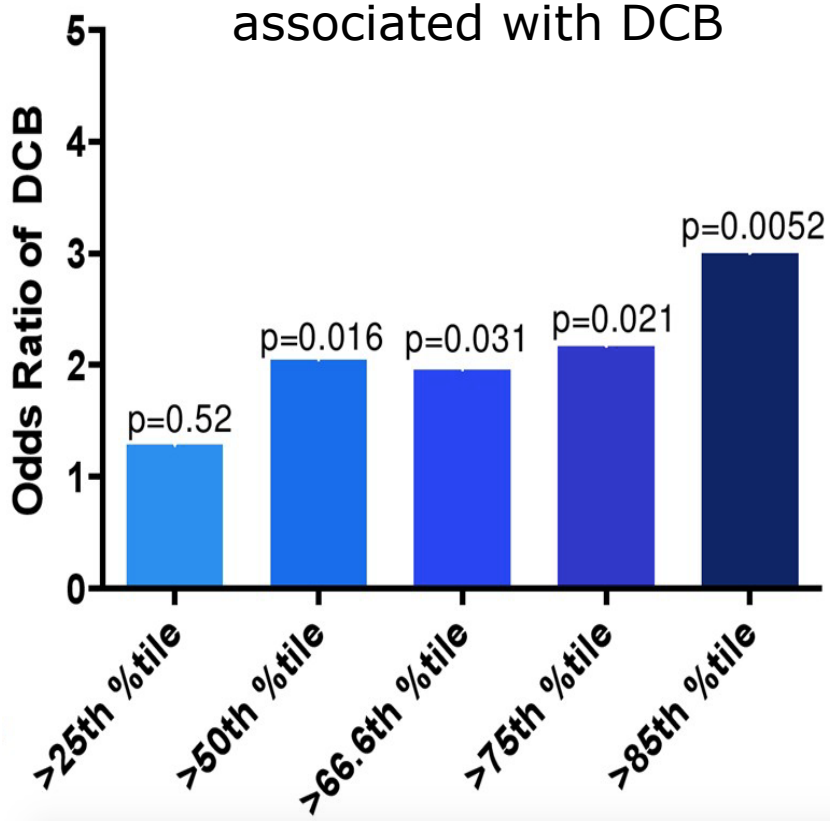
Tumor Antigens

- Biomarkers indicative of hypermutation & neo-antigens may predict response to IO treatment

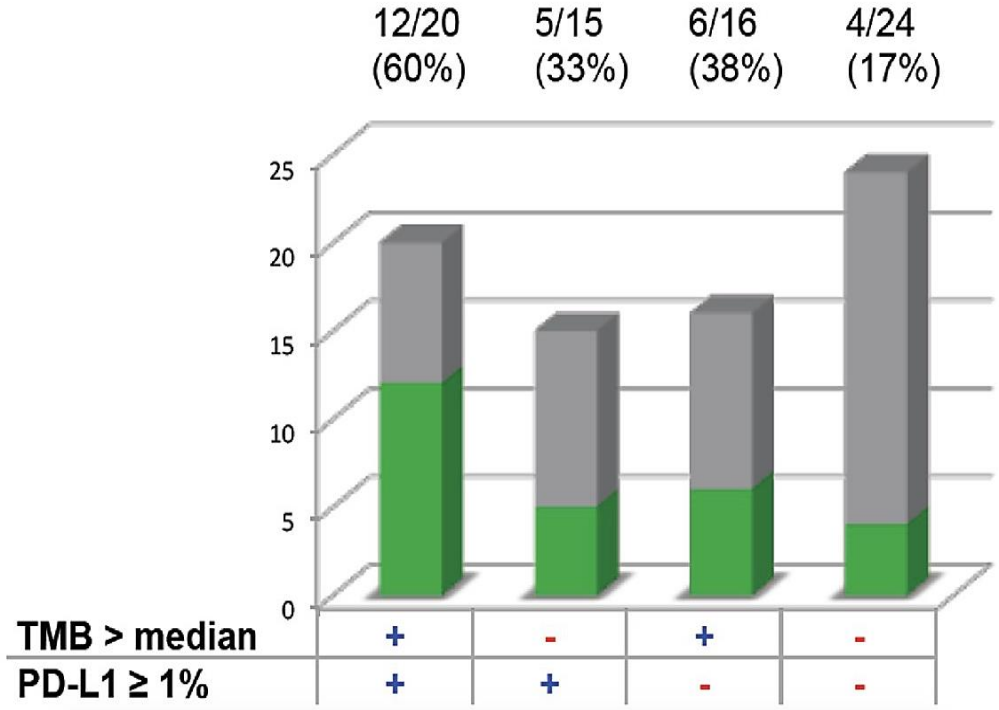
Examples:

– TMB, MSI-High, Neo-Antigens

Higher TMB percentile associated with DCB



TMB and PDL1 associated with increased DCB



Compared to all 197 NSCLCs profiled by NGS, alterations in *STK11* and *EGFR* were enriched in no DCB (p = 0.0008, p = 0.02).

Hellman, M ASCO 2017 #9015

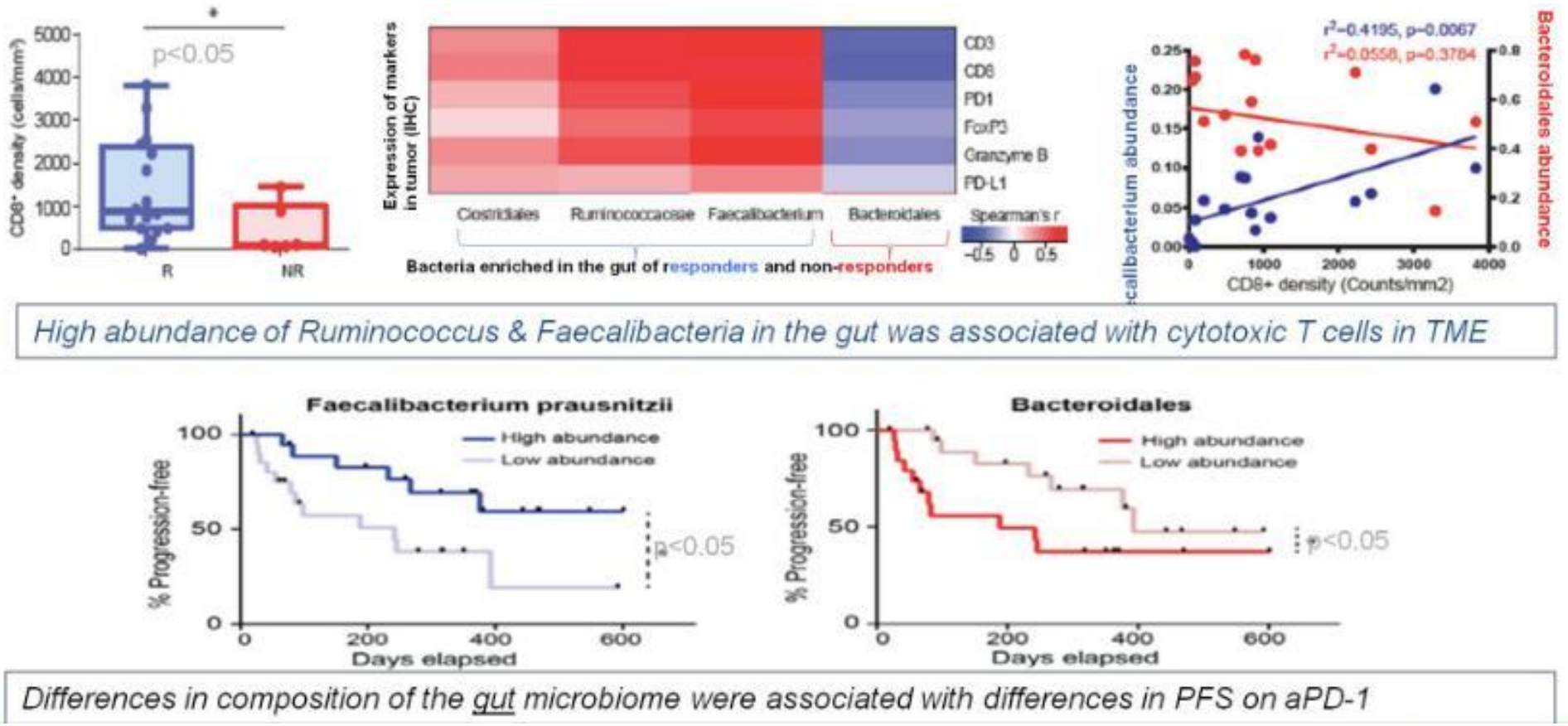
ASCO 2017 | Gut Microbiome

Host Environment

- Biomarkers which characterize the host environment, beyond tumor microenvironment, may predict response to IO treatment

Examples:

– Microbiome, Germline Genetics



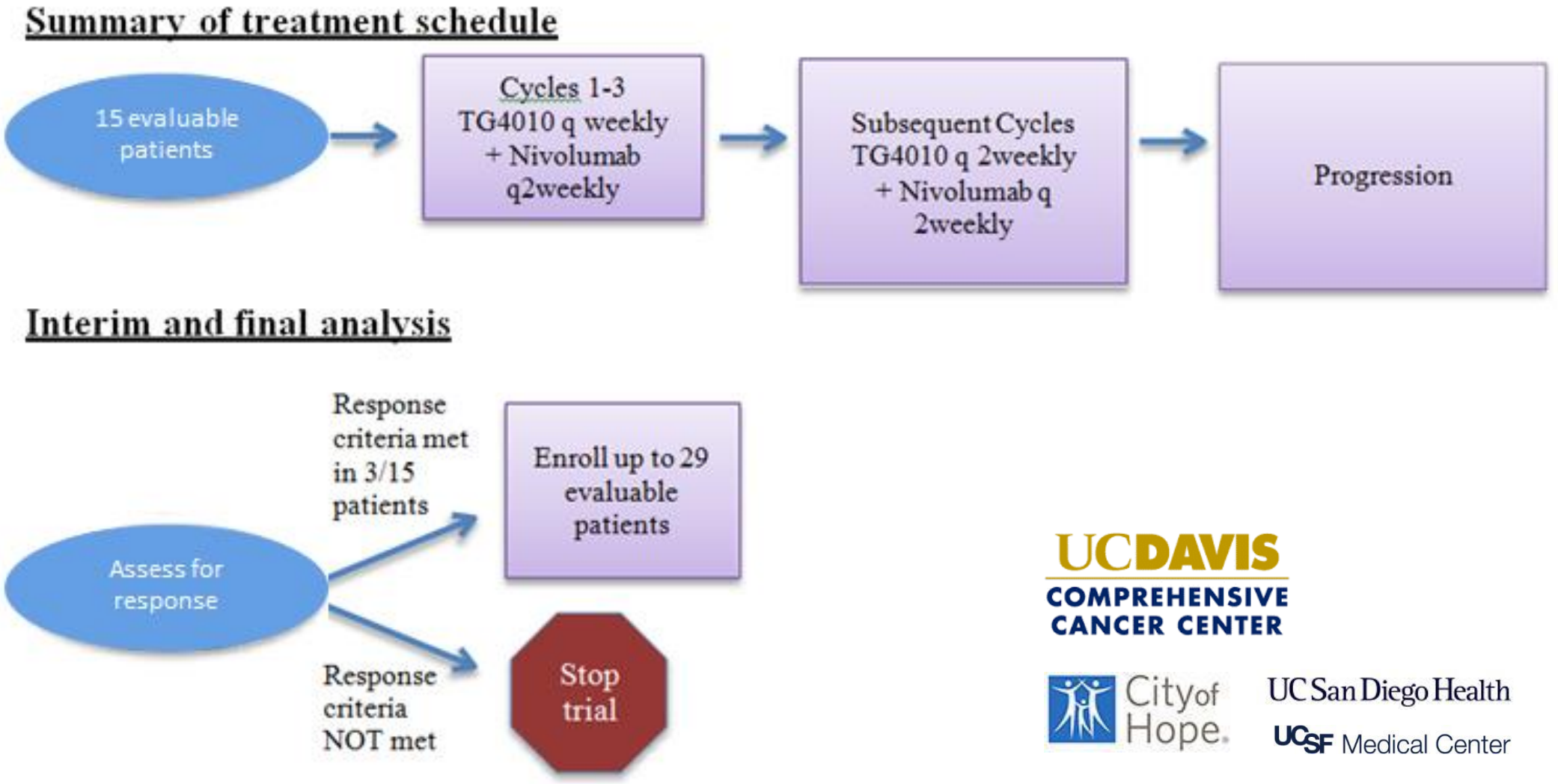
Mechanisms may be due to differences in the metabolites produced

Wargo JA et al. ASCO 2017 #3008

Study Schema

TG4010 + nivolumab

UCDCC#263: Phase II Trial of TG4010 plus Nivolumab in Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC) who have Progressed after One Line of Systemic Therapy. UC San Diego, City of Hope, UCSF



UC DAVIS COMPREHENSIVE CANCER CENTER

City of Hope

UC San Diego Health

UCSF Medical Center

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Study Schema

TG4010 + nivolumab

UCDCC#263: Phase II Trial of TG4010 plus Nivolumab in Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC) who have Progressed after One Line of Systemic Therapy. UC San Diego, City of Hope, UCSF

Tissue

- IHC to assess tumor infiltrating immune cells (CD8, CD4, FoxP3) and expression of other markers with potential prognostic and/or predictive value on efficacy outcomes including MUC-1 and PD-L1 as well as new biomarkers.
- qRT-PCR evaluation of gene signatures in the tumor microenvironment including: cytokines, T-cell activation markers, immunosuppressive enzymes and molecules (IDO, arginase, CTLA4, PD-1/PD-L1), macrophage polarization, etc.
- RNAseq for identification of tumor neo-antigens
- Flow Cytometry quantification, immunophenotyping, and activation / functional assessment of tumor infiltrating immune cells including myeloid-derived suppressor cells (MDSC), regulatory T (Treg) cells, T/B/NK cell immunophenotyping and activated T cells

Stool

- Microbiome composition analysis

Blood

- Flow cytometry assessment of Natural Killer (NK) cells and Triple Positive Activated Lymphocytes (TrPAL) levels in order to analyze their value as a predictive biomarker of TG4010 activity
- Flow Cytometry quantification, immunophenotyping, and activation / functional assessment of tumor infiltrating immune cells including myeloid-derived suppressor cells (MDSC), regulatory T (Treg) cells, T/B/NK cell immunophenotyping and activated T cells
- Evaluation of MUC-1, MVA, known Tumor Associated Antigens (TAA) and neo- antigens specific T-cell responses using a HLA-A*02:01 restricted tetramers
- Evaluation of MUC-1 and MVA specific humoral responses
- qRT-PCR evaluation of gene signatures in circulating cells including: cytokines, T- cell activation markers, immunosuppressive enzymes and molecules (IDO, arginase, CTLA4, PD-1/PD-L1), macrophage polarization, etc.
- Peripheral blood cytokine / chemokine profiling

Summary

Immune checkpoint inhibitors represent a new class of agents that has dramatically changed the treatment paradigm for advanced NSCLC.

Future advances must capitalize on:

- therapeutic approaches that target immune evasion and/or stimulate the immune process,
- integrating tumor, host and immune biology to provide precision and personalized immunotherapy for lung cancer patients to achieve long term benefit.

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immunotherapeutics

HÔPITAUX UNIVERSITAIRES PITIÉ SALPÊTRIÈRE CHARLES FOIX

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Novel immuno-oncology approaches in liver cancer

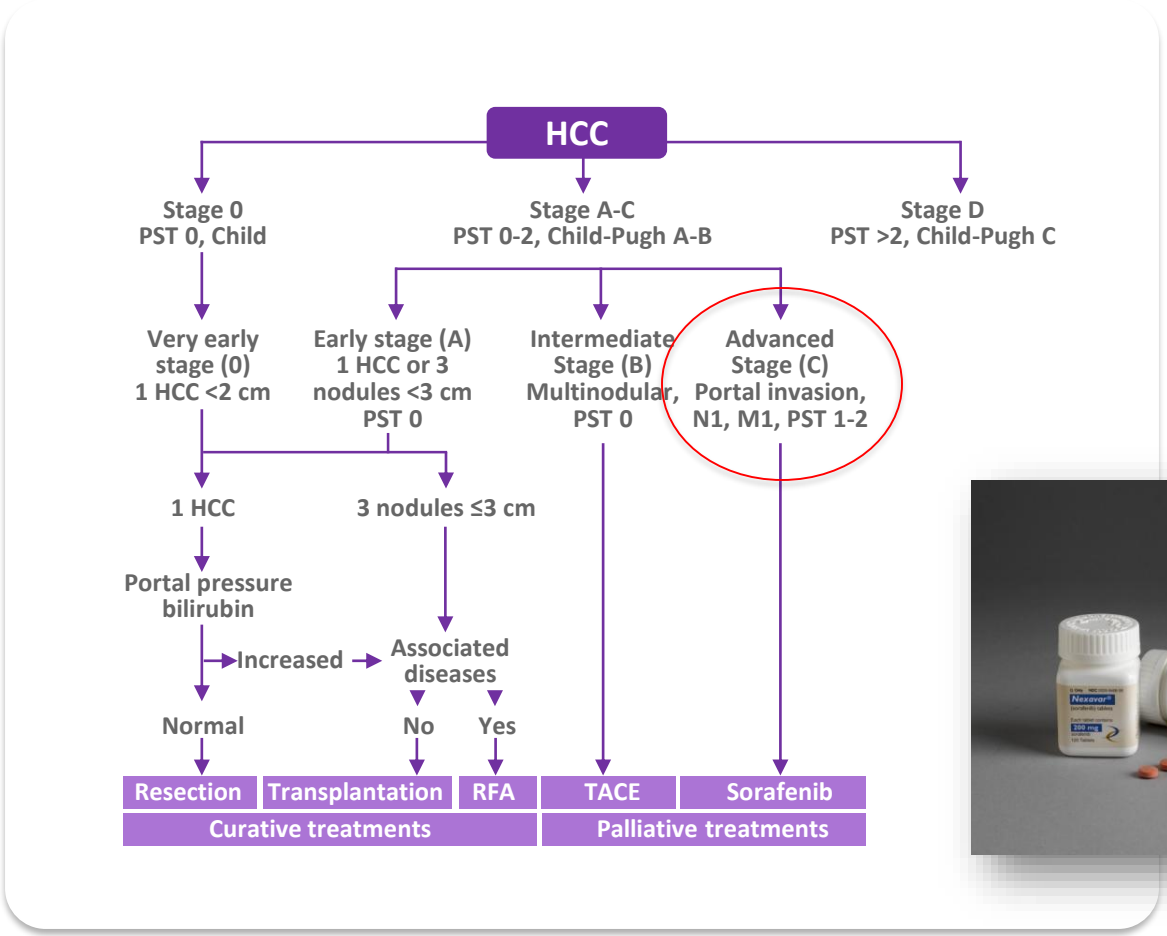
Pr Olivier Rosmorduc

Department of Hepatology and Gastroenterology

Pitié-Salpétrière Hospital, Paris

BCLC Staging from outcome prediction to treatment assignment

Advanced HCC



Bruix J, Hepatology 2011

Pivotal clinical trials using targeted therapies in HCC

Drugs	Targets	Indication	Biomarkers	Status
Sorafenib	BRAF,VEGFR,PDGFR	1st line	none	Approved
Sunitinib	VEGFR,KIT,PDGFR	1st line	none	Negative
Brivanib	FGFR,VEGFR	1st, 2nd line	none	Negative
Linifanib	VEGFR,PDGFR	1st line	none	Negative
Sorafenib + Erlotinib	EGFR/BRAF/VEGFR/ PDGFR	1st line	none	Negative
Everolimus	mTOR	2nd line	none	Negative
Ramucirumab	VEGFR	2nd line	none	Negative
Tivantinib	Met	2nd line	Met-Expression	Negative
Lenvatinib	VEGFR, FGFR	1st line	none	Positive
Regorafenib	BRAF, VEGFR, TIE2	2nd line	none	Positive

Adapted from Villanueva, J Hepatol 2013; Bruix Lancet 2017 and ASCO 2017

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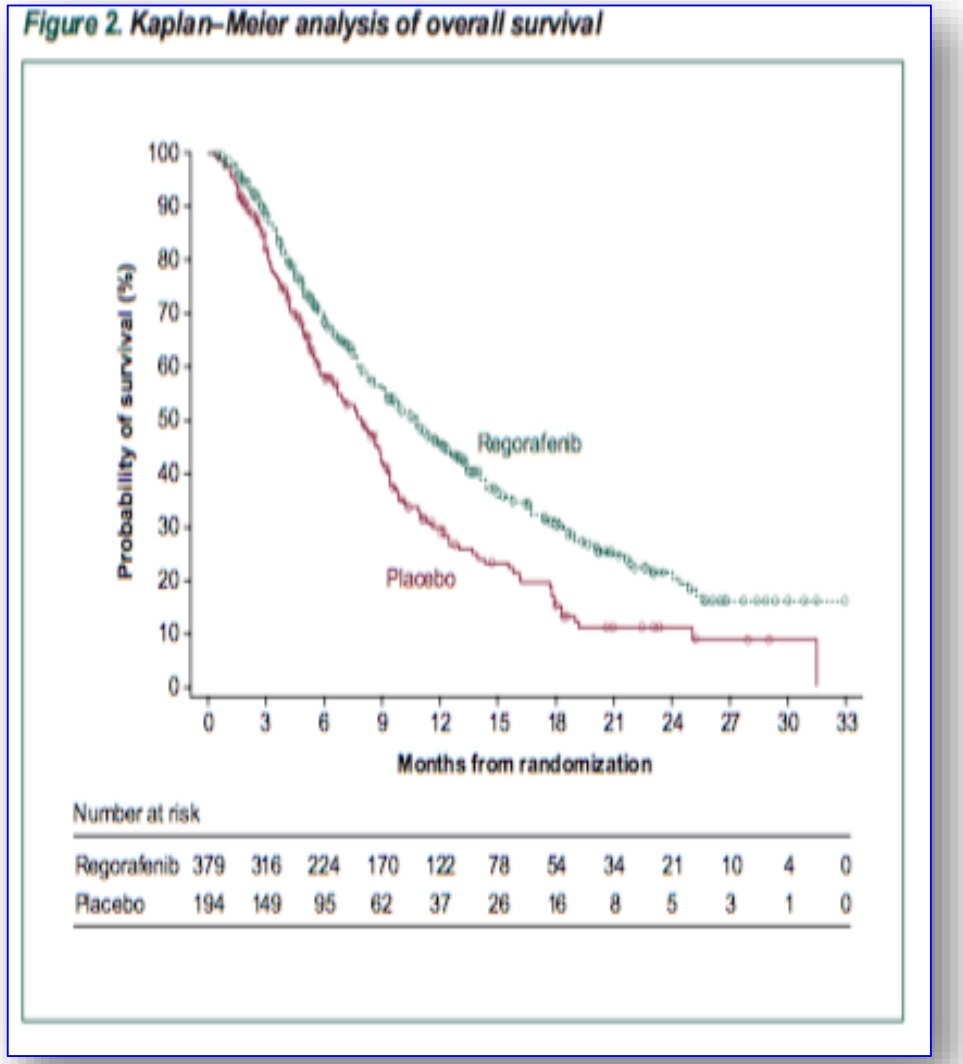
RESORCE Trial | Regorafenib vs placebo in 2nd line
after sorafenib failure



Overall Survival

10.6 mo *vs* 7.8 mo

PFS

3.1 mo *vs* 1.5 mo

Response rate

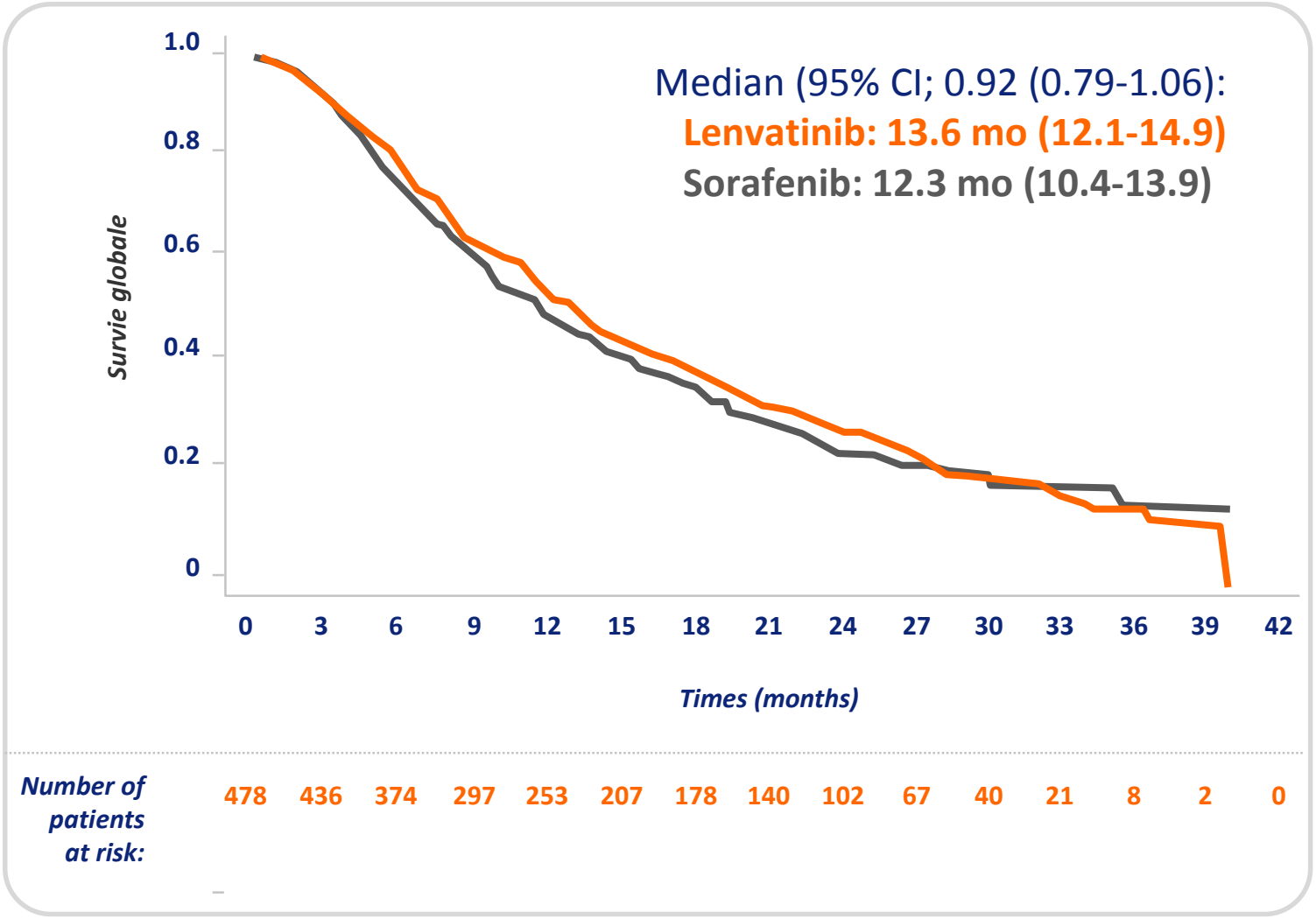
(mRECIST)

11 % *vs* 4 %

Bruix, The Lancet 2017

REFLECT Trial | Lenvatinib vs sorafenib

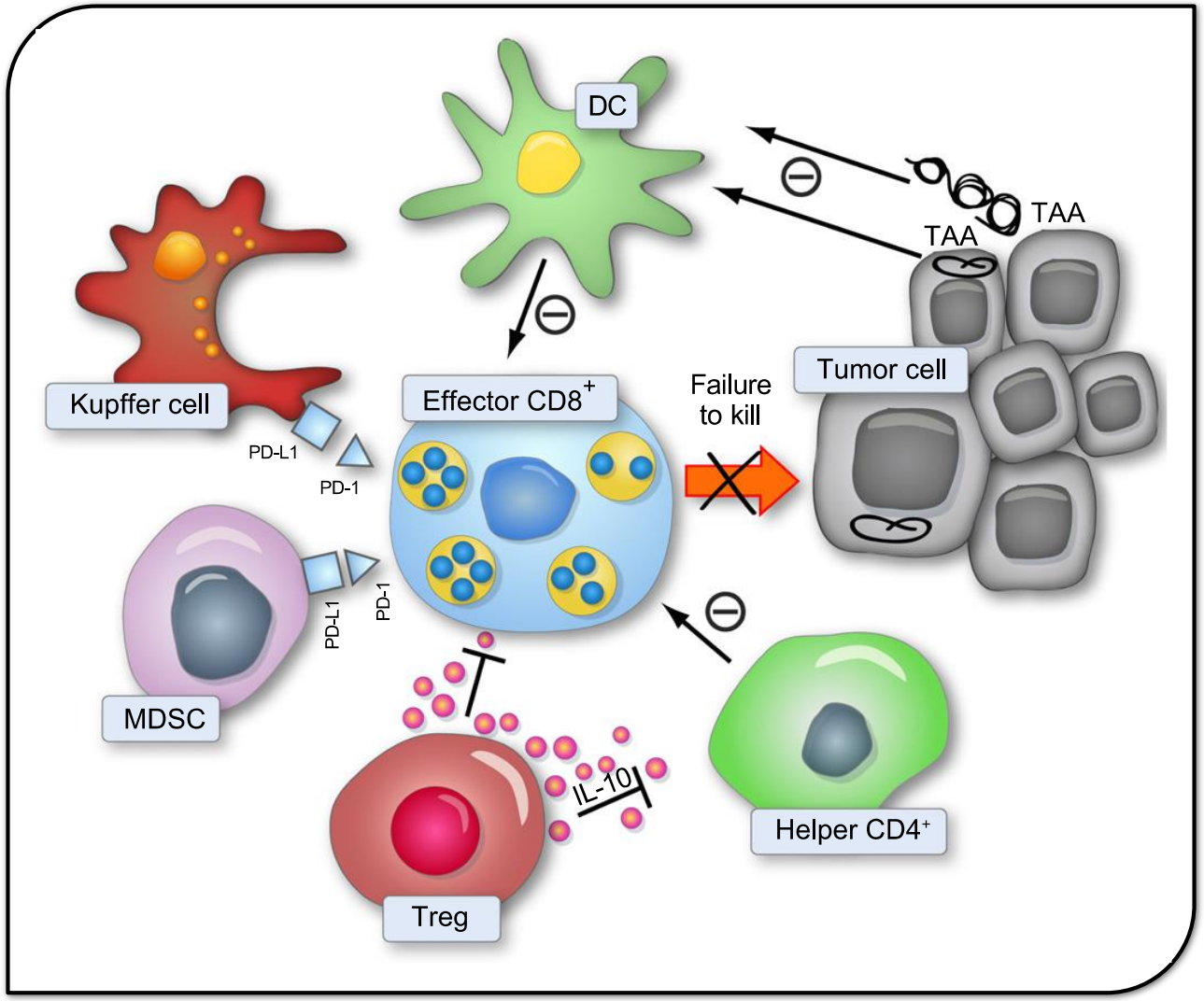
in 1nd line for advanced HCC



Chen Ann Li, ASCO 2017

Tolerogenic environment

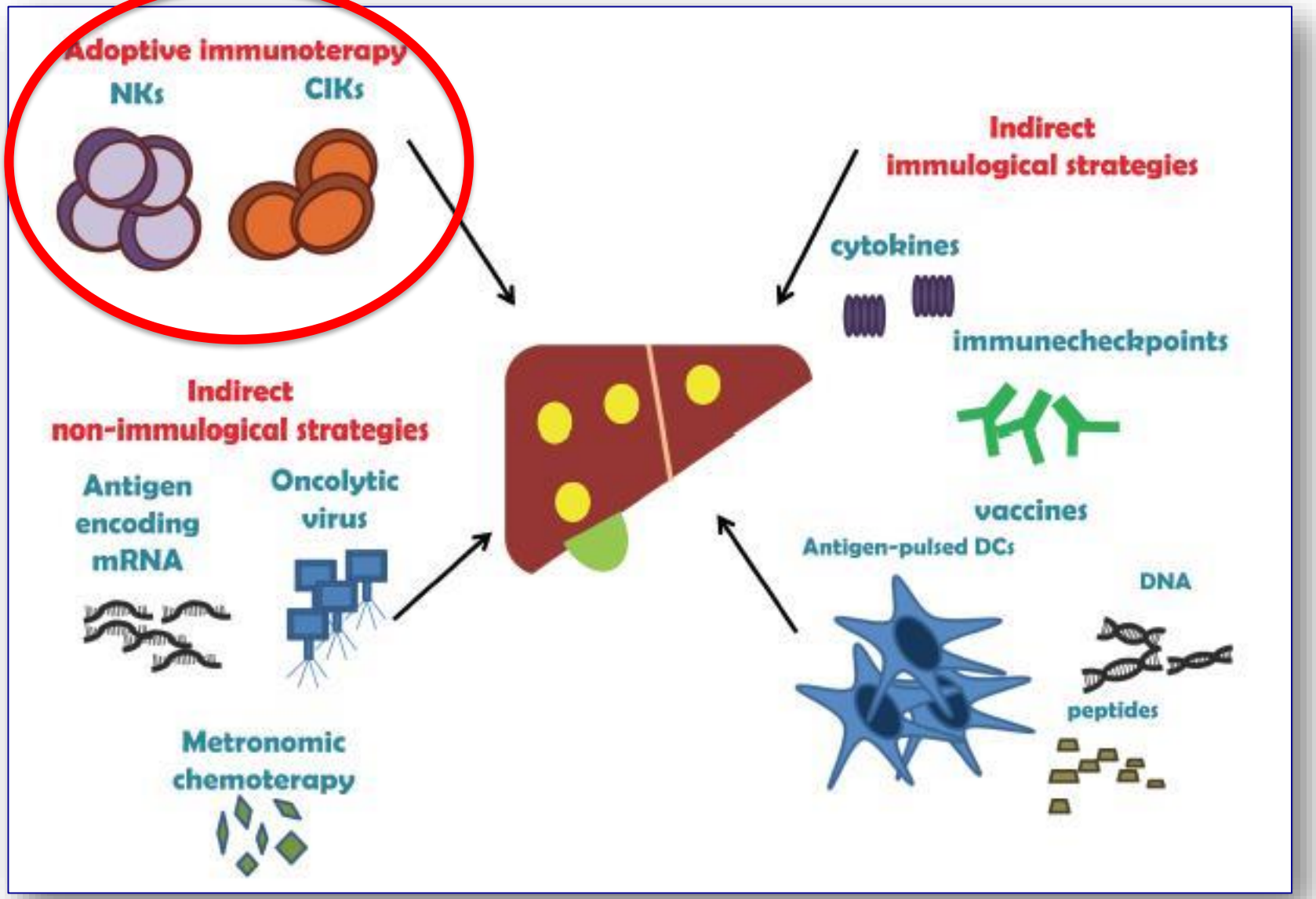
and immuno suppressive mechanisms in HCC



- Suppression of both CD4+ and CD8+ T cells by Tregs
- Negative regulation by PD-1/PD-L1 pathway
- Myeloid-derived suppressor cells (MDSCs)
- Impairment of TAA processing and presentation
- Lack of CD4+ T cell responses

E.Breous, J Hepatol 2013

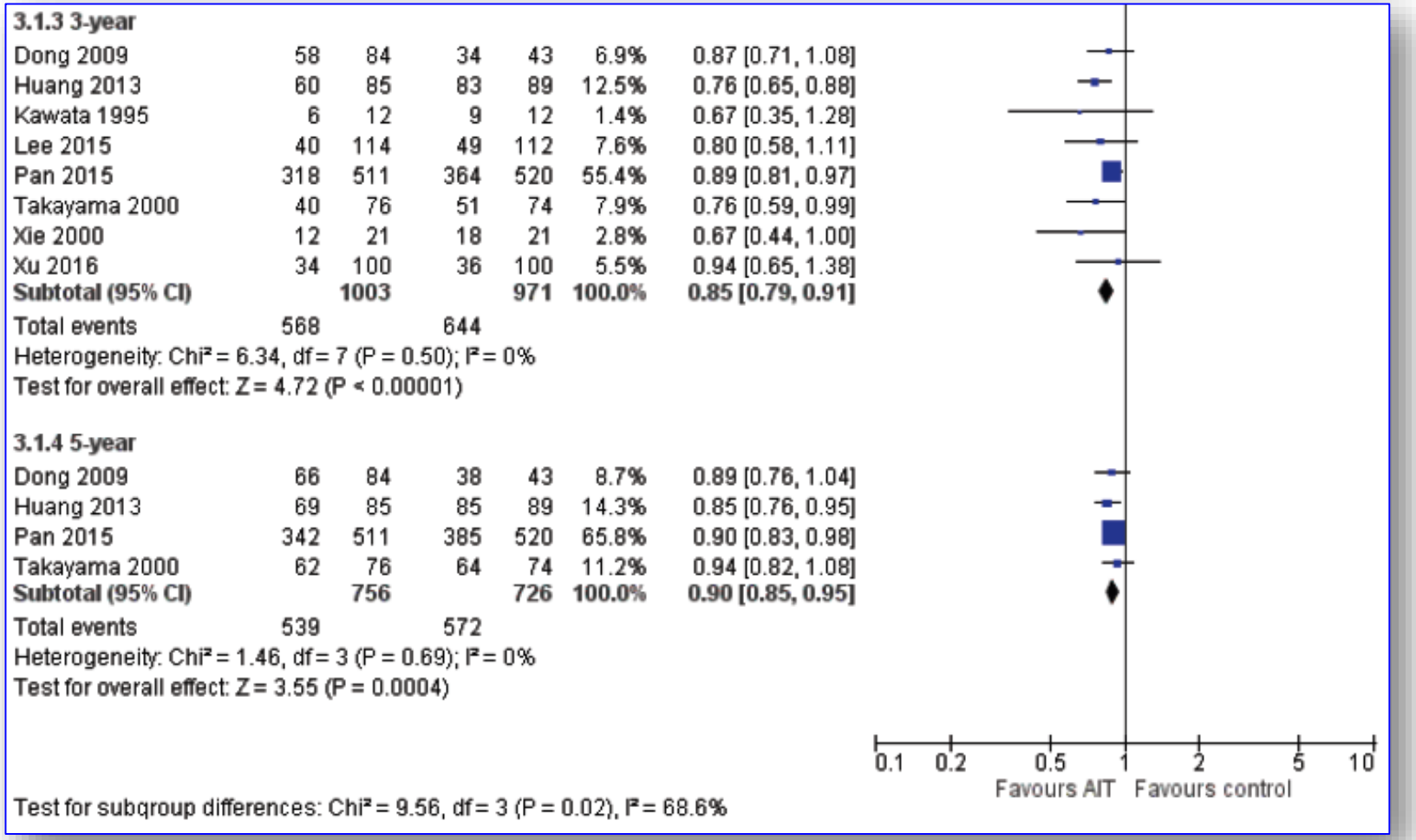
Toward immunotherapy in advanced HCC ?



Longo, Oncotarget 2017

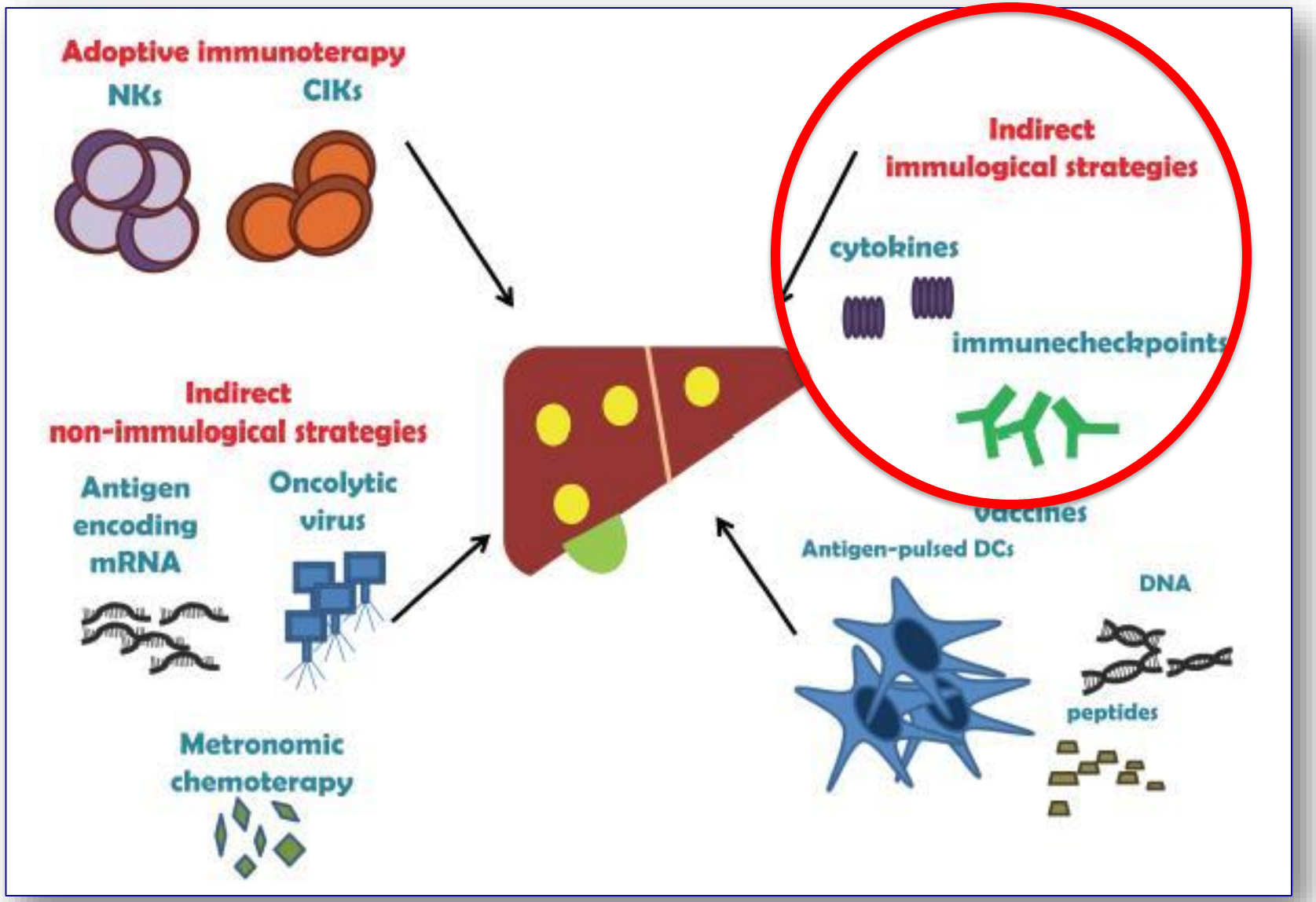
Lower recurrence after curative treatment

and adoptive immunotherapy



Yuan, Oncotarget 2017

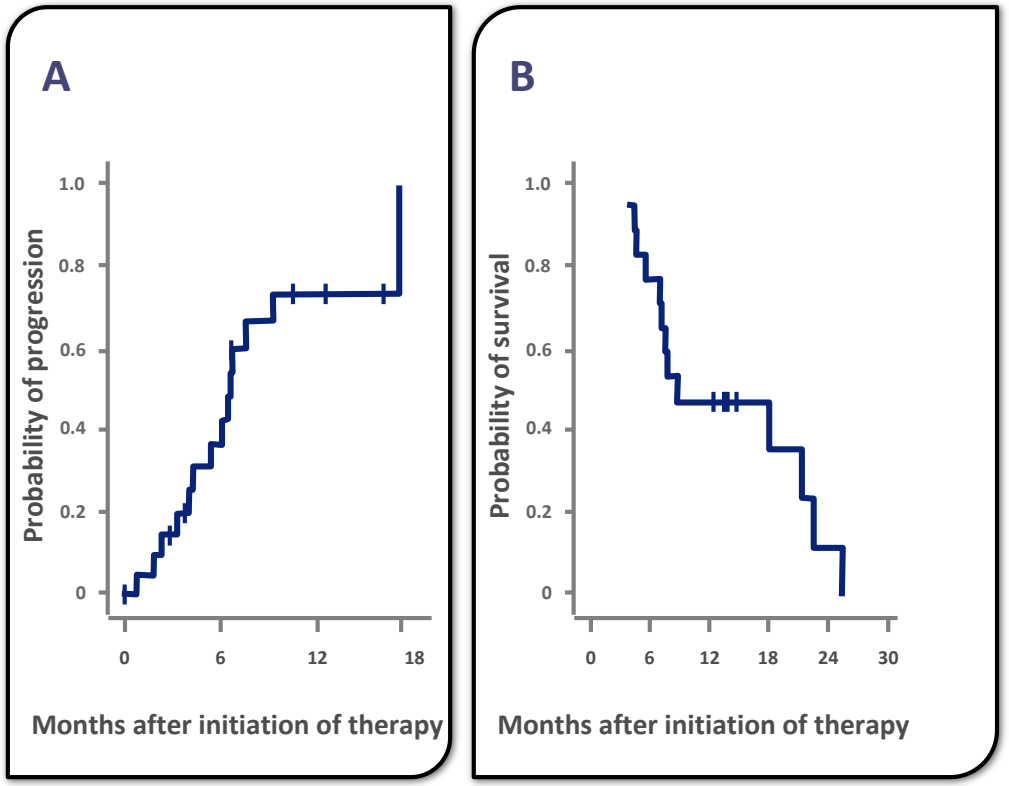
Toward immunotherapy in advanced HCC?



Proof-of-concept

Efficacy of tremelimumab in advanced HCC

Clinical features
21 patients
57 % Child A / 43 % Child B
28 % PT / 9 % EHM
BCLC A/B/C : 14/28/57%
1st line : 57%



RR: 17 % (RECIST)
Median OS 8,2 mo
Acceptable toxicity

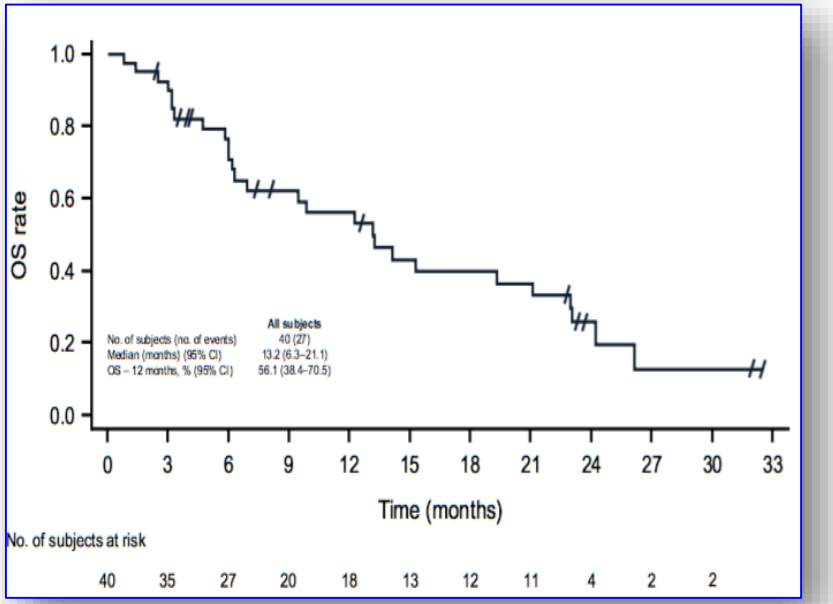
B. Sangro, J Hepatol 2013

Phase ½ using Durvalumab (anti-PD-L1)

in 2nd line after failure of sorafenib in advanced HCC

Anti-tumoral activity	N = 40
RR (PR + CR)	**10%**
Disease control rate (CR + PR + SD) > 24 s	**32,5 %**

OS et DFS	N = 40
OS at 12 mo	**56 %**
DFS at 12 mo	**21 %**

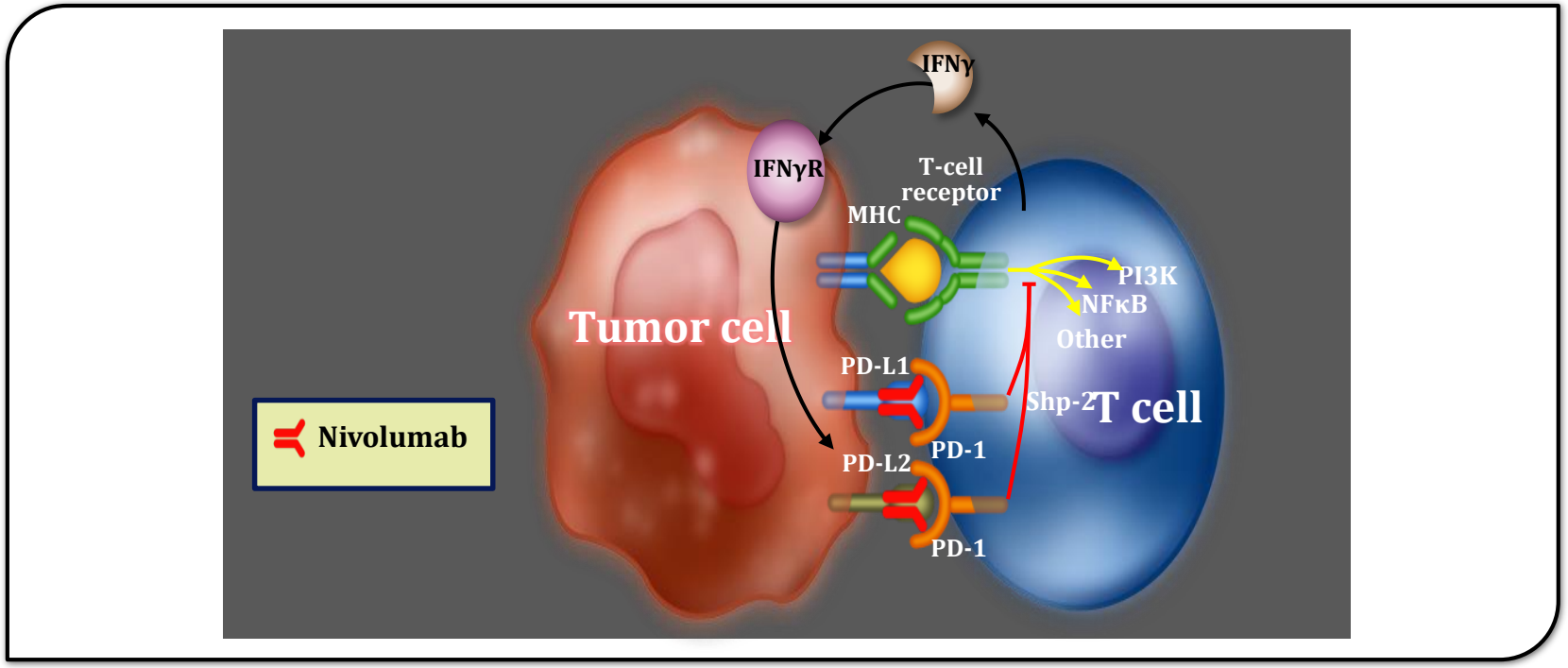


Median OS: 13,2 mo

Toxicity grade ¾: 20 %

Wainberg Z, Poster 4071, ASCO 2017

Targeting PD-1/PDL-1 in HCC?



PD1/anti PDL1 inhibitors

- ***Nivolumab***
- ***Pembrozilumab***

Hayden, Nature 2012
J.Grosso, Cancer Immunity 201

Checkmate 040 | Safety: Dose-Expansion Phase

Patients, n (%)	Uninfected (n = 113)		HCV Infected (n = 50)		HBV Infected (n = 51)		All Dose Expansion (N = 214)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any treatment-related AE (TRAE)	84 (74)	22 (19)	40 (80)	15 (30)	35 (69)	3 (6)	159 (74)	40 (19)
TRAEs (≥ 5%)								
Fatigue	34 (30)	2 (2)	8 (16)	1 (2)	7 (14)	0	49 (23)	3 (1)
Pruritus	18 (16)	0	14 (28)	1 (2)	13 (25)	0	45 (21)	1 (<1)
Rash	16 (14)	2 (2)	9 (18)	0	8 (16)	0	33 (15)	2 (1)
Diarrhea	19 (17)	2 (2)	5 (10)	0	3 (6)	1 (2)	27 (13)	3 (1)
Nausea	10 (9)	0	6 (12)	0	1 (2)	0	17 (8)	0
Dry mouth	9 (8)	0	2 (4)	0	2 (4)	0	13 (6)	0
Decreased appetite	6 (5)	0	2 (4)	1 (2)	3 (6)	0	11 (5)	1 (<1)
Laboratory TRAEs (≥ 5%)								
AST increase	9 (8)	4 (4)	6 (12)	5 (10)	1 (2)	0	16 (7)	9 (4)
ALT increase	7 (6)	2 (2)	7 (14)	3 (6)	3 (6)	0	17 (8)	5 (2)

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Checkmate 040, A B El-Khoueiry, ASCO GI 2017

Checkmate 040 | Best Overall Response

Sorafenib Experienced (2L)

Patients, n (%)	Investigator Assessment		BICR	
	Dose Escalation (n = 37)	Dose Expansion (n = 145)	Dose Escalation (n = 37)	Dose Expansion (n = 145)
Objective response by RECIST v1.1	6 (16.2)	27 (18.6)	7 (18.9)	21 (14.5)
Complete response	3 (8.1)	3 (2.1)	1 (2.7)	1 (0.7)
Partial response	3 (8.1)	24 (16.6)	6 (16.2)	20 (13.8)
Stable disease	16 (43.2)	66 (45.5)	12 (32.4)	59 (40.7)
Progressive disease	12 (32.4)	46 (31.7)	13 (35.1)	56 (38.6)
Not evaluable	3 (8.1)	6 (4.1)	4 (10.8)	9 (6.2)
Objective response by mRECIST	—	—	8 (21.6)	27 (18.6)

BICR, blinded-independent central review.

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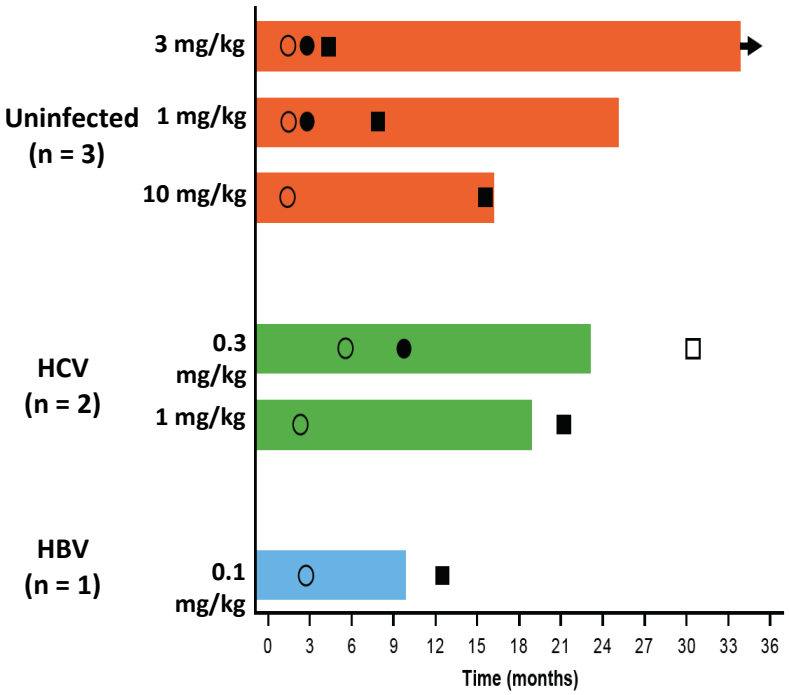
Checkmate 040, A B El-Khoueiry, ASCO GI 2017

Checkmate 040 | Time to Response and Duration of Response

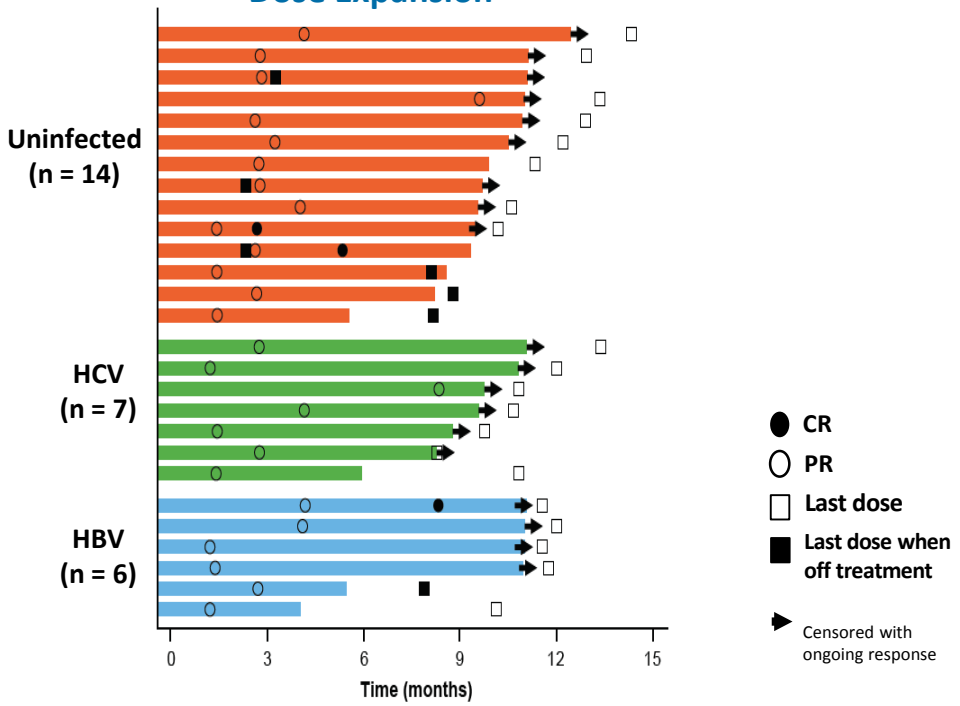
Sorafenib Experienced (2L)

Dose Escalation



TTR, median (range), mo	1.9 (1.4–5.6)
DOR, median (range), mo	17.1 (7.2–32.5+)

Dose Expansion

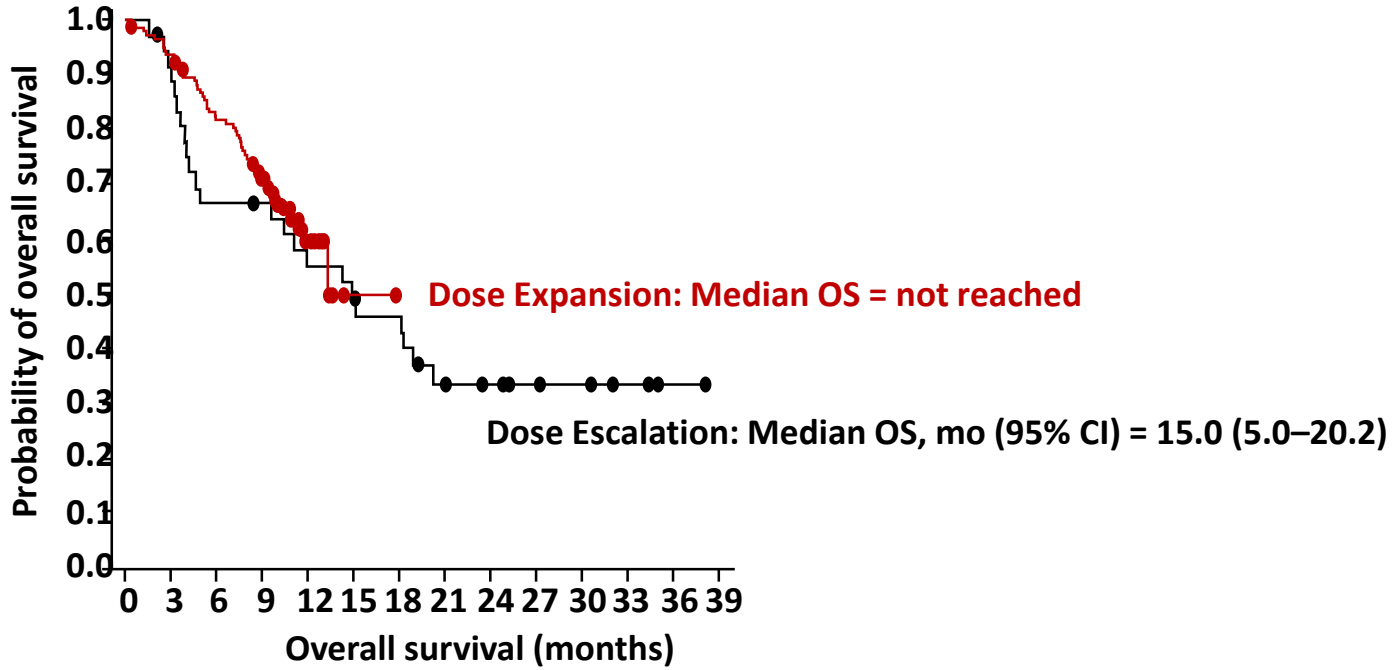


TTR, median (range), mo	2.7 (1.2–9.6)
DOR, median (range), mo	NR (1.4–9.8+)

Checkmate 040, A B El-Khoueiry, ASCO GI 2017

Checkmate 040 |Overall Survival

Sorafenib Experienced (2L)



OS Rate, % (95% CI)	Dose Escalation (n = 37)	Dose Expansion (n = 145)
6 months	67 (49–80)	82 (74–87)
9 months	67 (49–80)	71 (63–78)[a]
12 months	58 (40–72)	NC
18 months	46 (29–62)	NC

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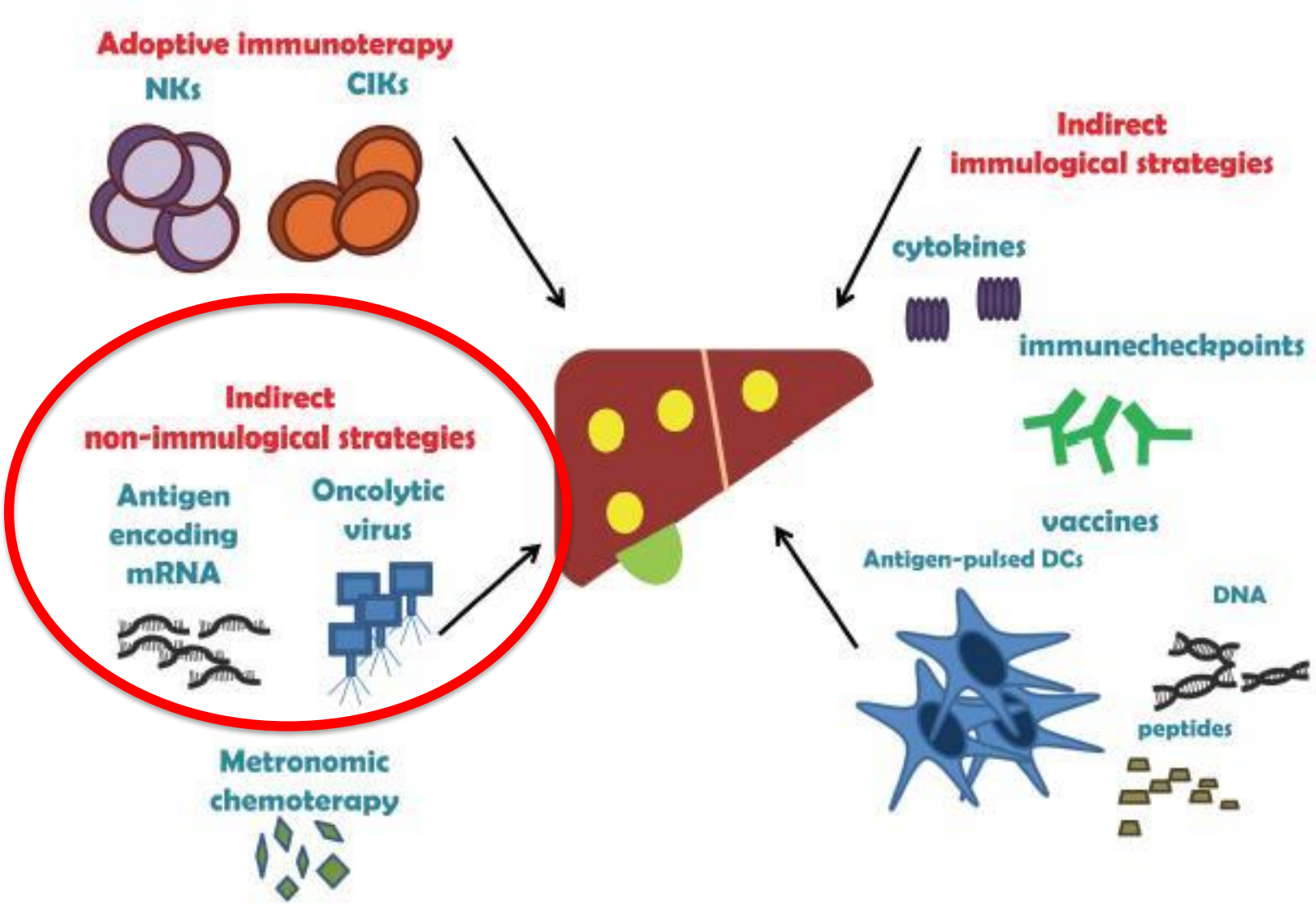
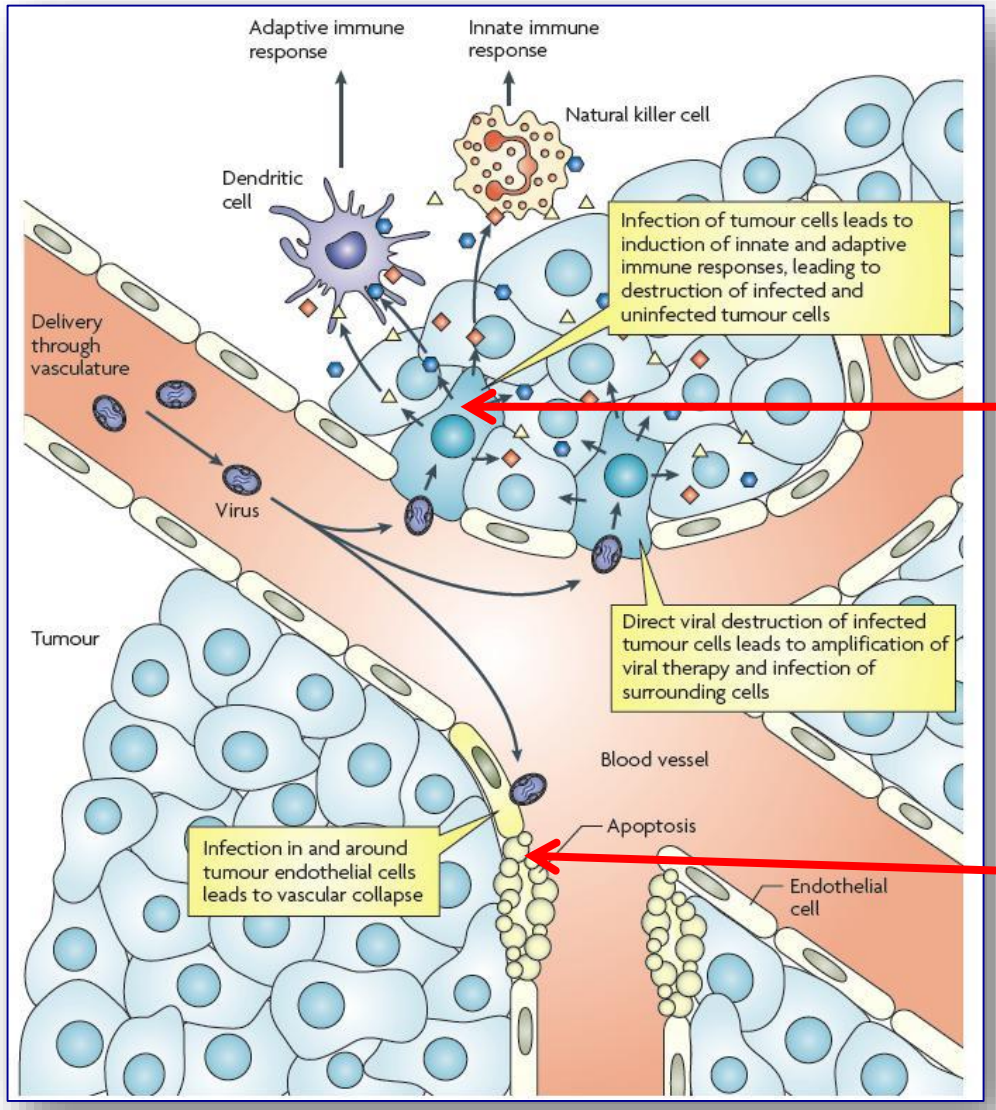
Checkmate 040, A B El-Khoueiry, ASCO GI 2017

Toward oncolytic virotherapy in advanced HCC?



Pexa-Vec |Mechanisms of the anti-tumoral effect



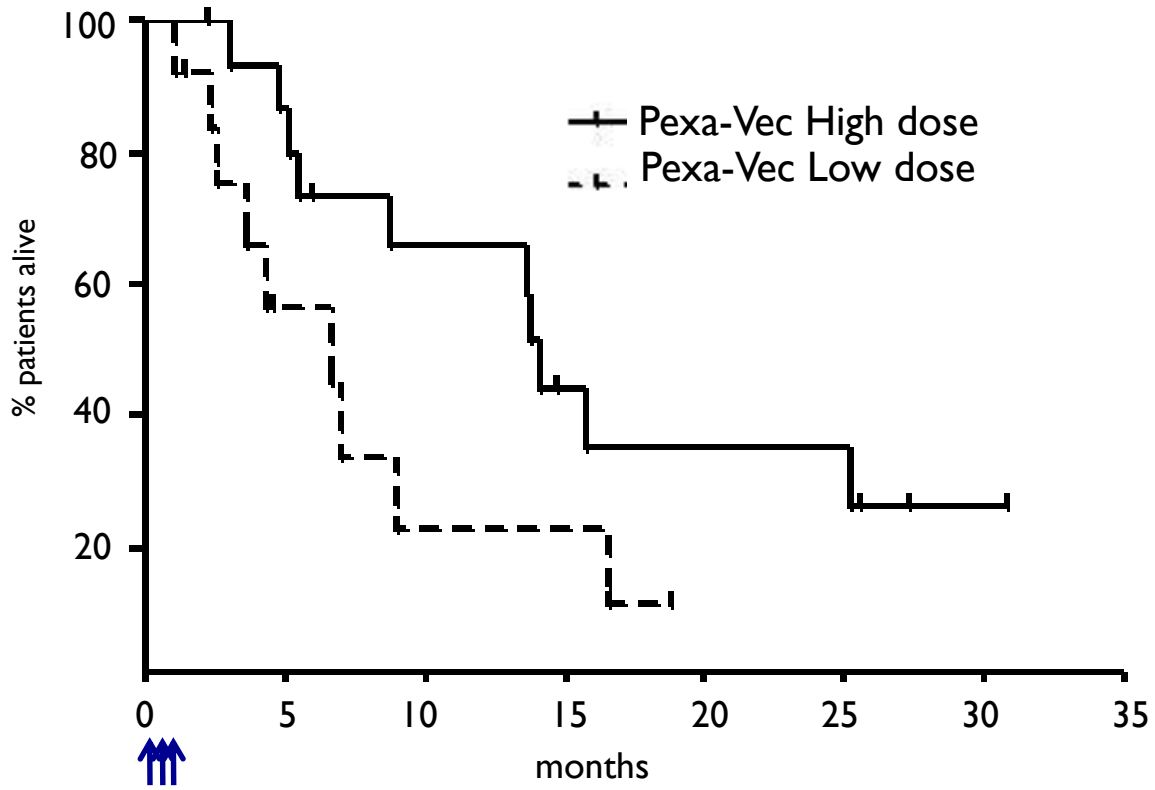
1. Oncolysis

2. Activation of Immune response

3. Vessel destruction

Kirn DH, et al. Nature Reviews, Cancer. 2009

Pexa-Vec | High vs. low dose Pexa-Vec
in predominantly first-line HCC



Overall Survival

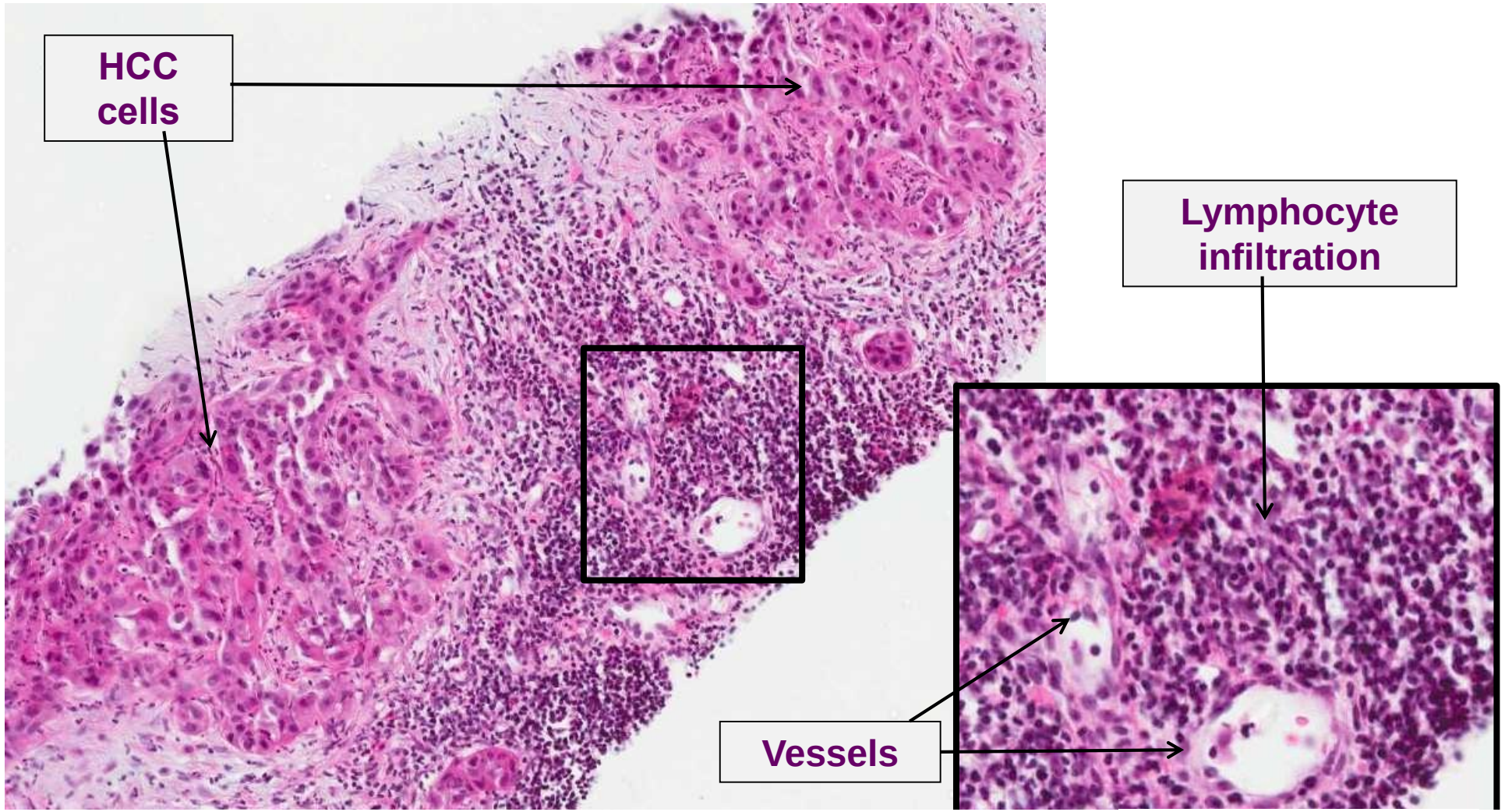
14.1 vs. 6.7 mos.
HR = 0.39, n = 29
p = 0.020

Pexa-Vec IT Injections into tumors on days 1, 15, 29

Heo *et al*, *Nature Medicine* 2013

Pexa-Vec | Long-term effect on vascularized tumor

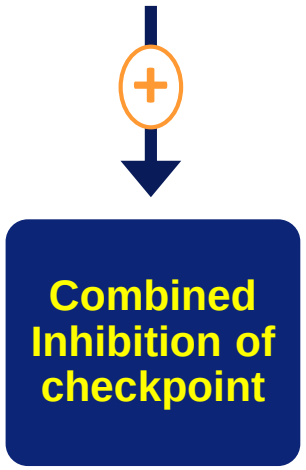
and intense lymphocyte infiltration



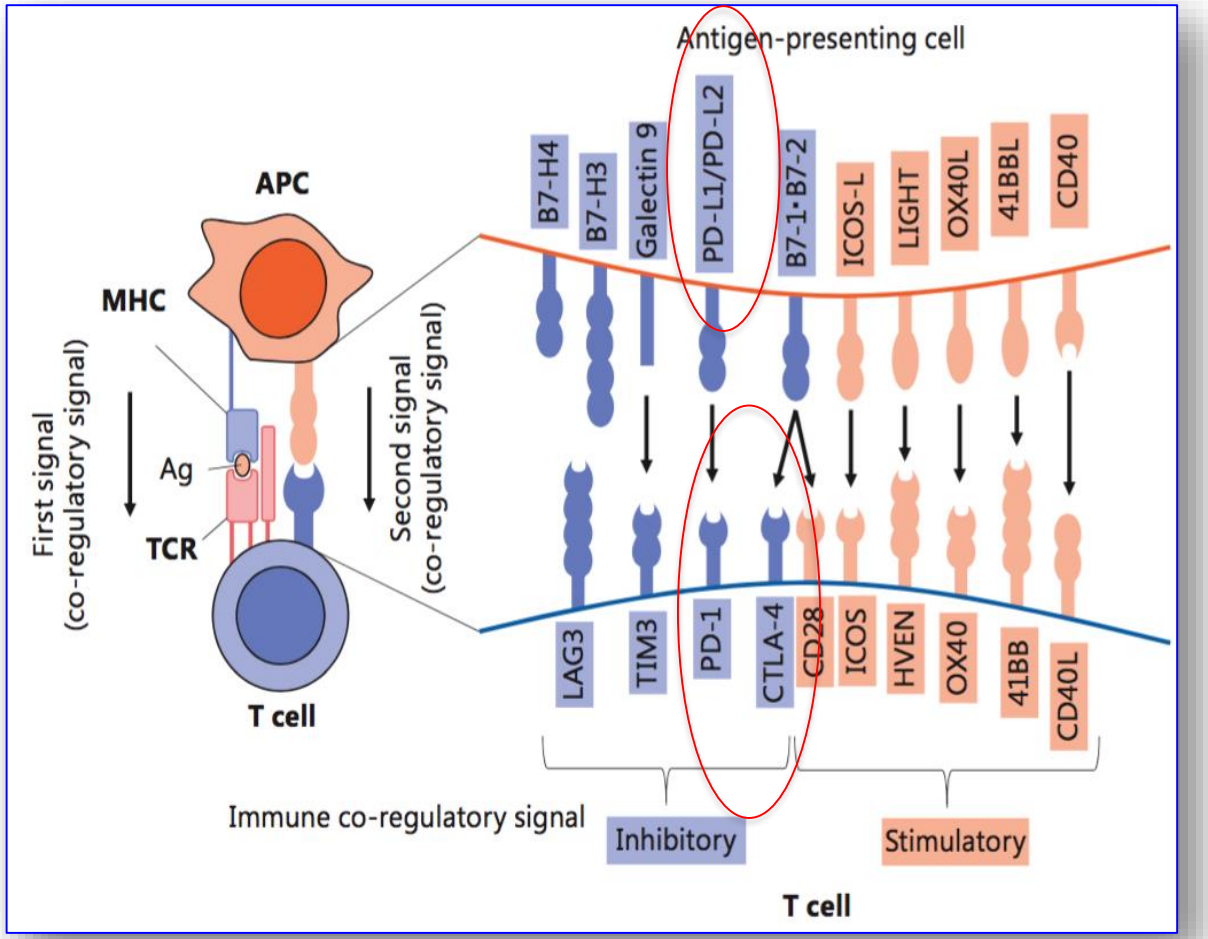
Breitbach, Nature Medicine, 2013

Immune Checkpoint inhibition

(anti-PD1/anti-PDL1/anti-CTL4)



Toward combined immunotherapies?



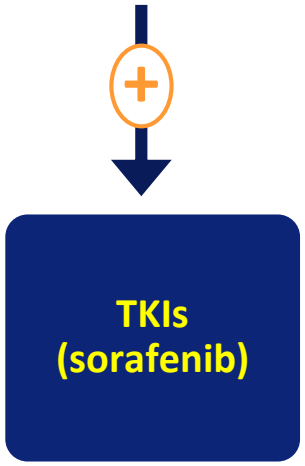
Ipililumab + nivolumab
- Recruitment closed

tremelilumab + durvalumab
- ORR: 15 %; DCR (16): 57,5 %
- Activity in noninfected pts
- 60% AEs, 20% grade ≥3

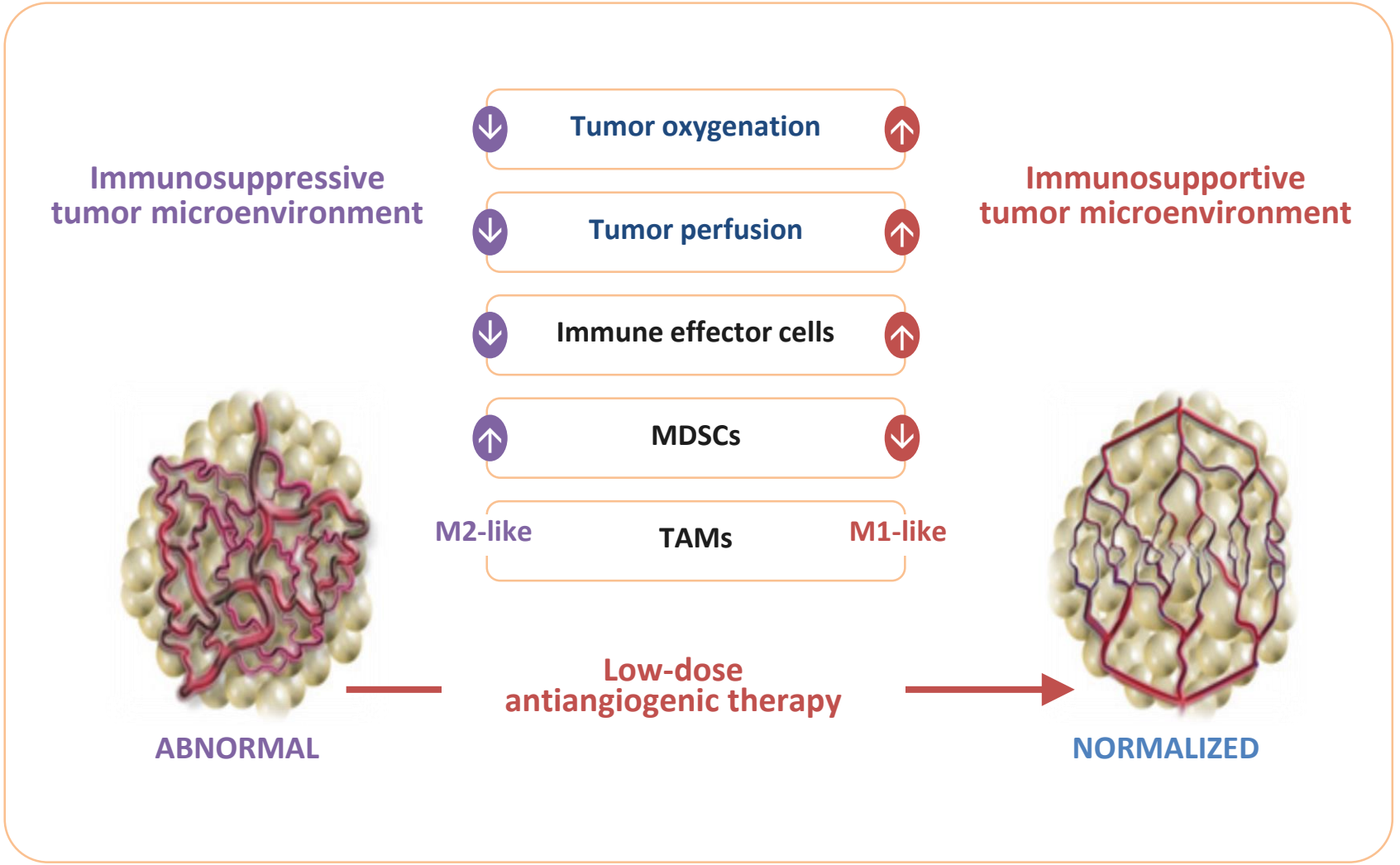
Drake. Ann Oncol 2012
Sharma, Nat Rev Cancer 2013
Kate Kelley LBA Abstract 4073 ASCO 2017

Immune Checkpoint inhibition

(anti-PD1/anti-PDL1/anti-CTL4)



Reprogramming the microenvironement using anti-angiogenic molecules



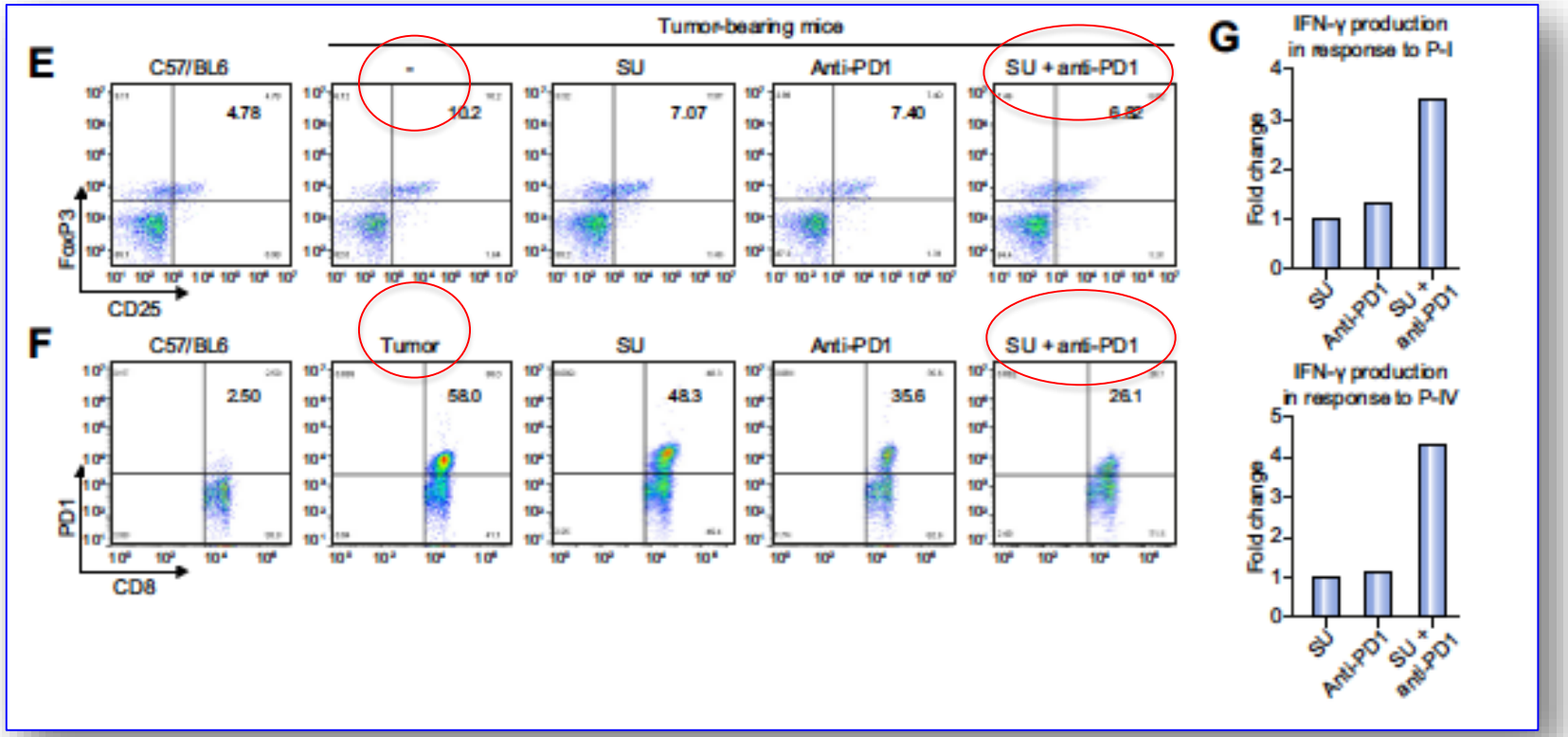
Huang Y, Cancer Res 2013 - Huang Y, PNAS, 2012

Sunitinib synergizes with anti-PD-1 antibody

to activate anti-tumor-immune response

FoxP3

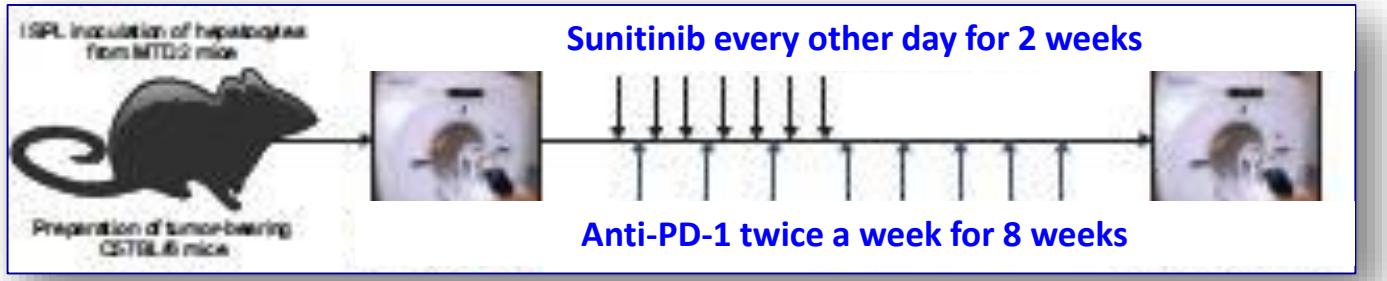
PD-1



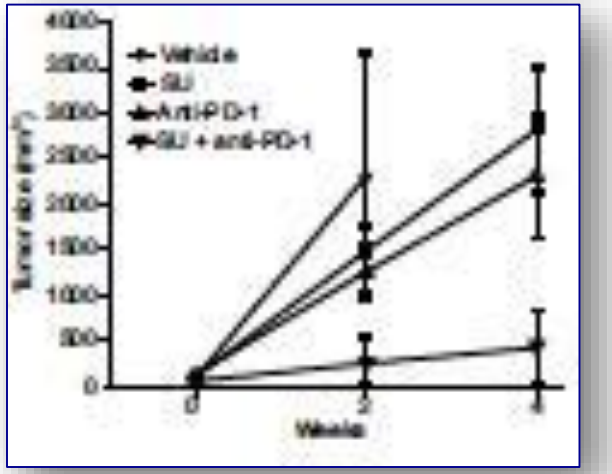
Li, J Hepatol 2017

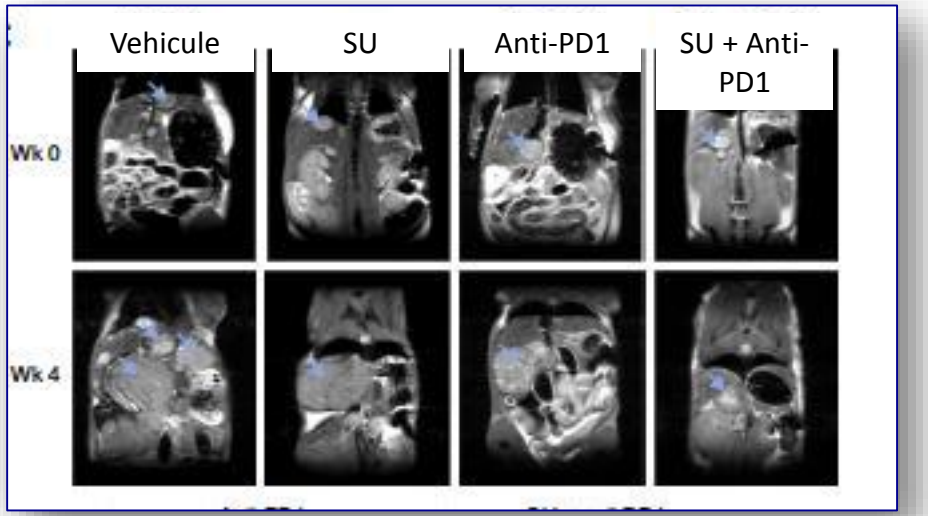
Sunitinib synergizes with anti-PD-1 antibody

to prevent tumor growth



Tumor size

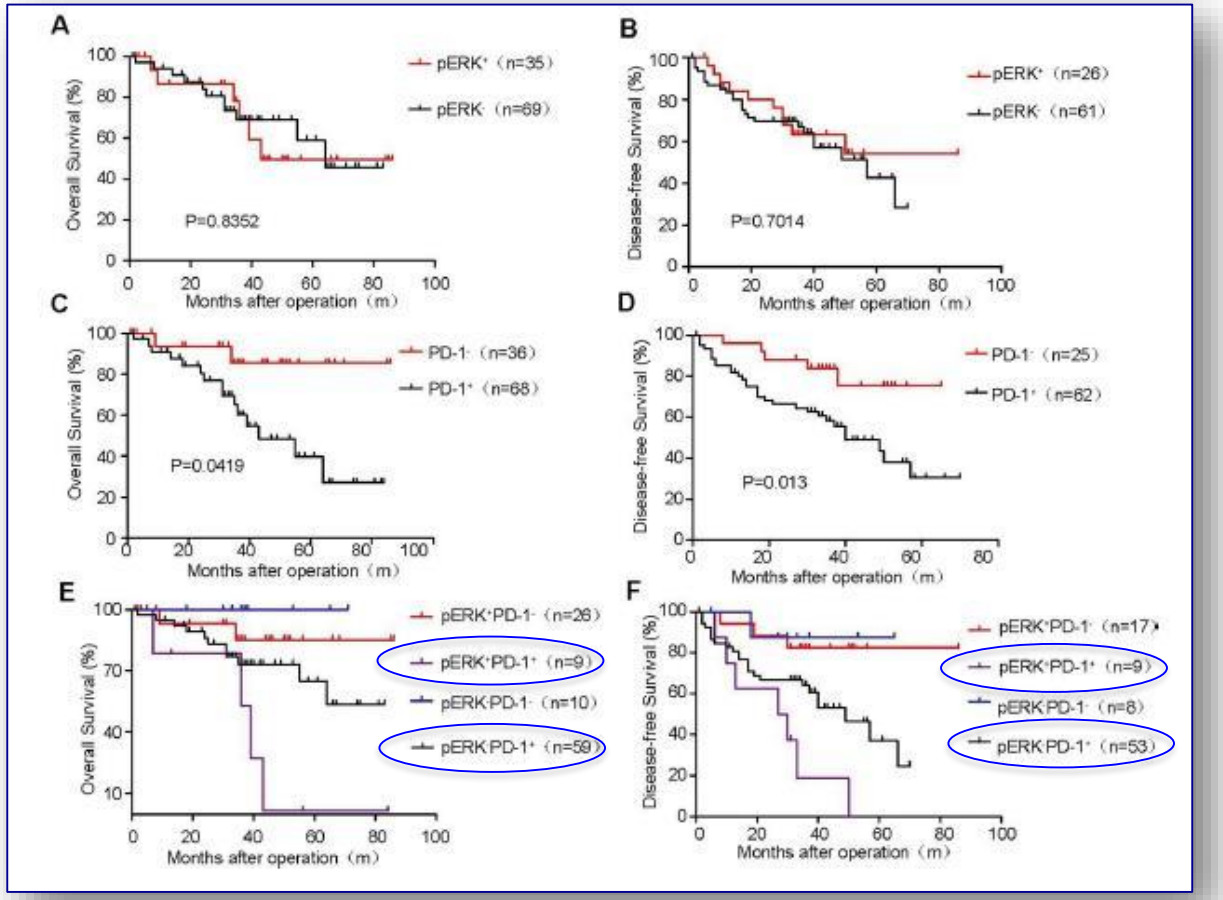




Li, J Hepatol 2017

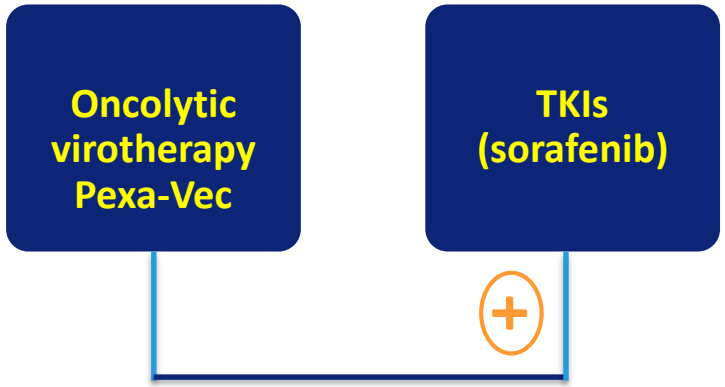
Survival curves (OS and DFS) of post-operative HCC patients

stratified by pERK and PD-1 expression

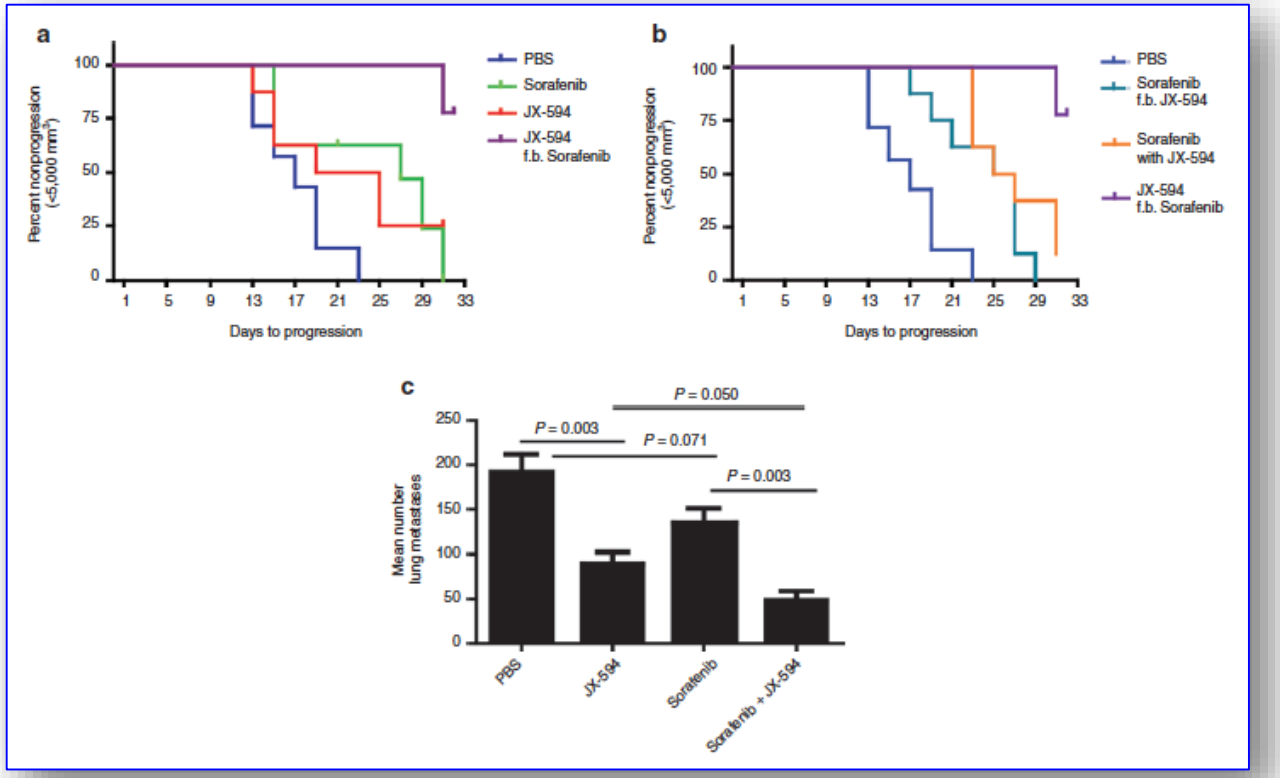


PD-1 +

Chen, Oncotarget 2016


Oncolytic virotherapy Pexa-Vec
TKIs (sorafenib)
+

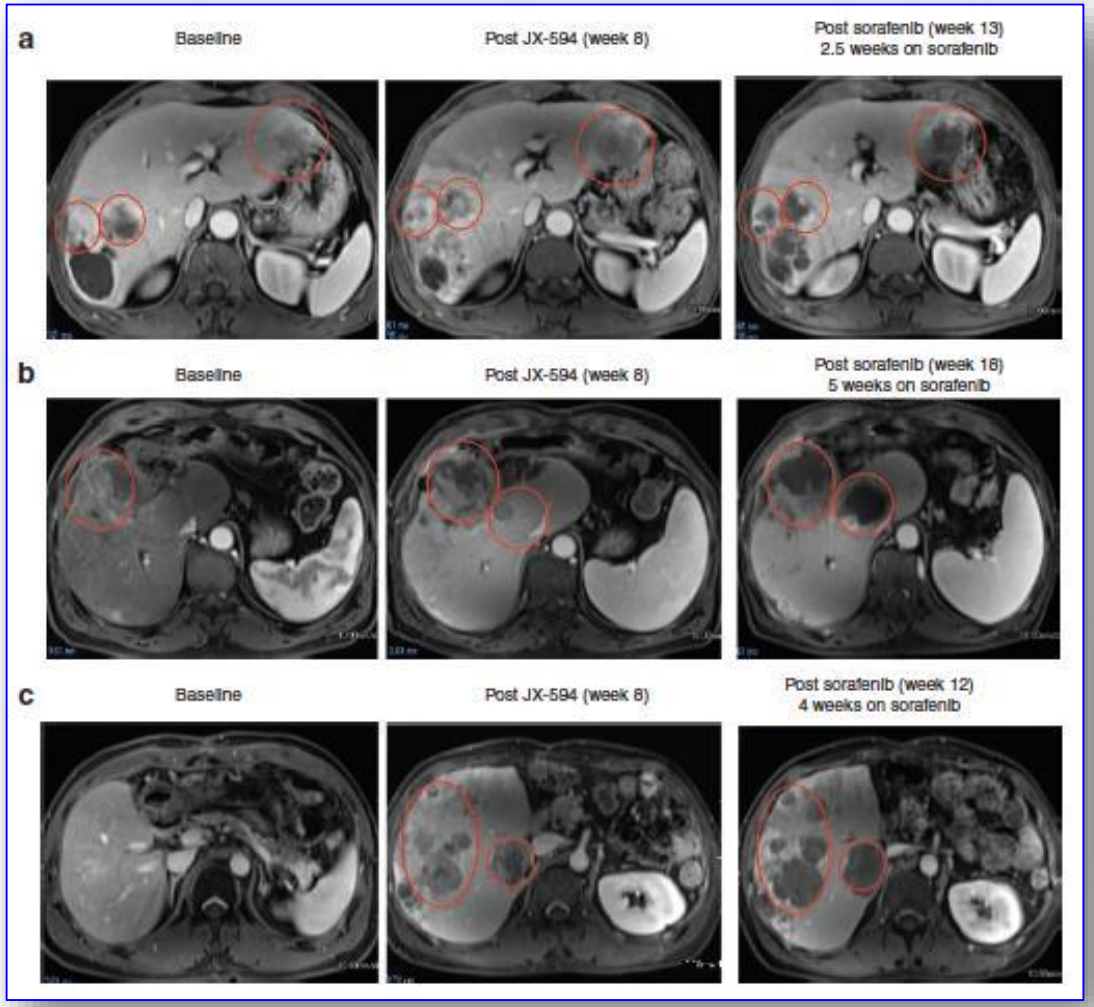
Sequenced therapy of Pexa-Vec followed by sorafenib
in animal model of HCC

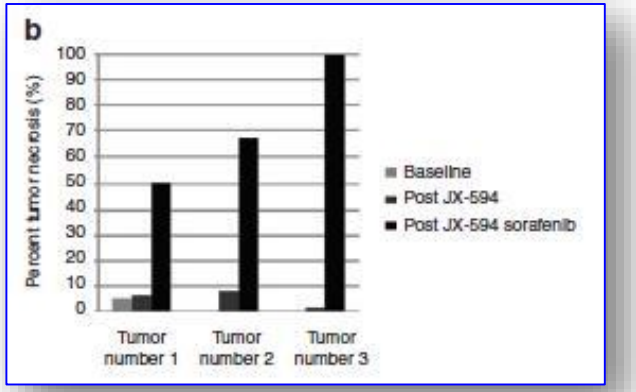


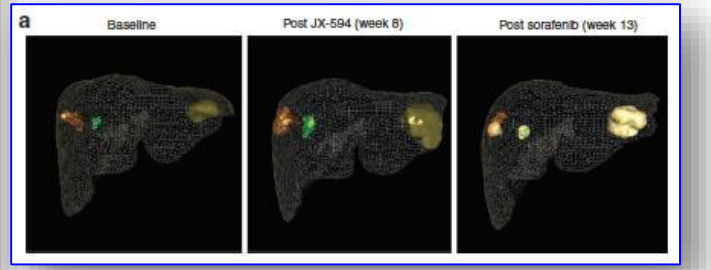
Heo, Molecular Therapy 2011

Sequenced therapy of Pexa-Vec followed by sorafenib

in 3 patients with HCC and failure of Pexa-Vec alone







Heo, Molecular Therapy 2011

Pexa-Vec | First-line Phase 3 in Sorafenib-naïve HCC

N=600
Asia, N. America, Europe

Eligibility Criteria
- Post LCR or metastatic
- BCLC B or C
- No previous systemic therapy
- Histo Dx
- CP A
- ECOG(PS) 0-1
- Measurable and injectable tumors

Randomized 1:1

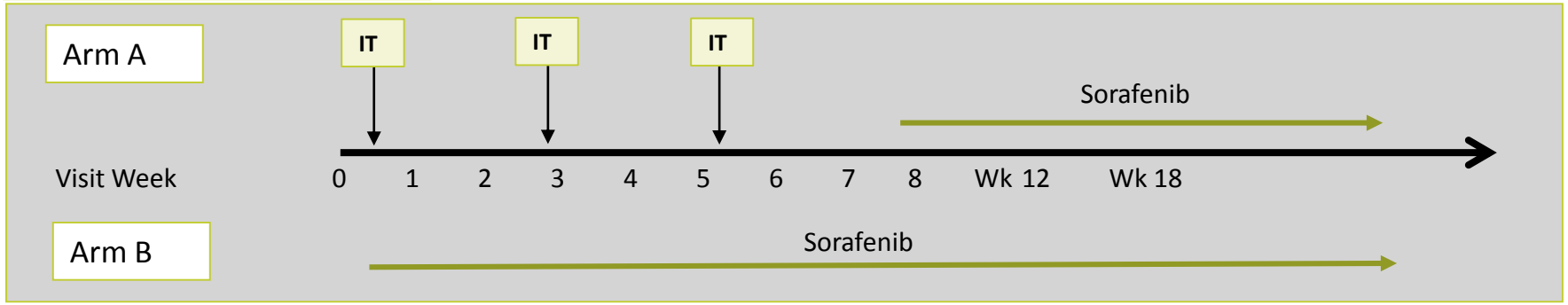
N= 600
HR 0.83*
P.025
Power 86%

Arm A
3 x IT Pexa-Vec10^9 followed by sorafenib 400 mg BID

Arm B
Sorafenib 400 mg BID

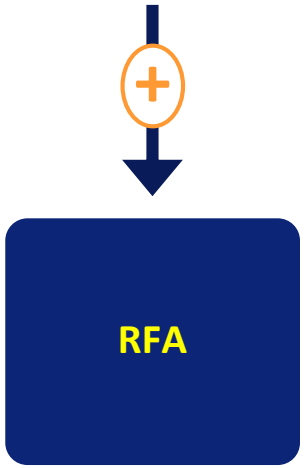
Primary Endpoint
OS

Secondary Endpoints
RR (mRECIST), TTP, TTSP, QOL, safety

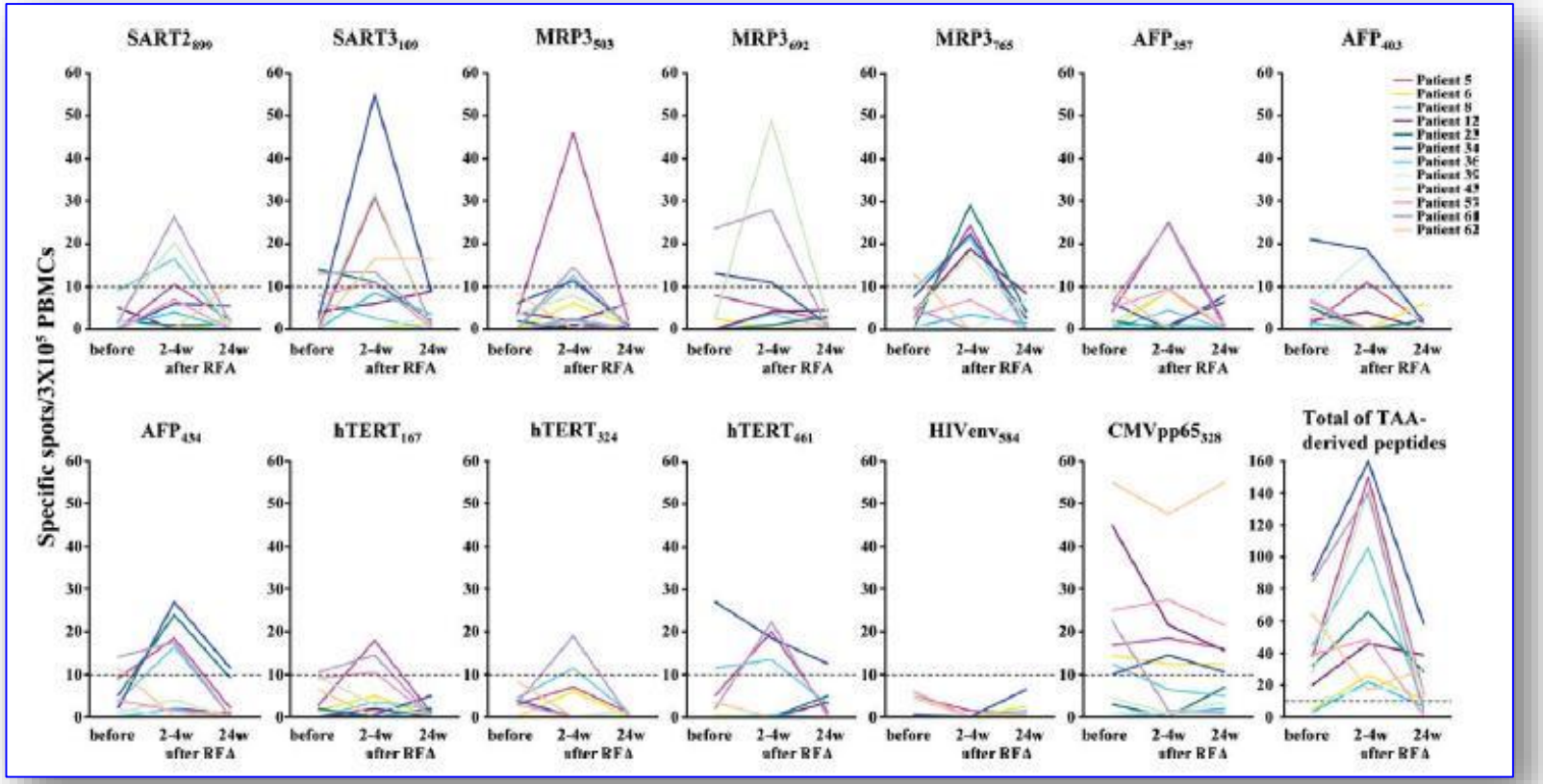


Immune Checkpoint Inhibition

(anti-PD1/anti-PDL1/anti-CTL4)



Enhancement of tumor-associated antigen specific T cell response by RFA of HCC

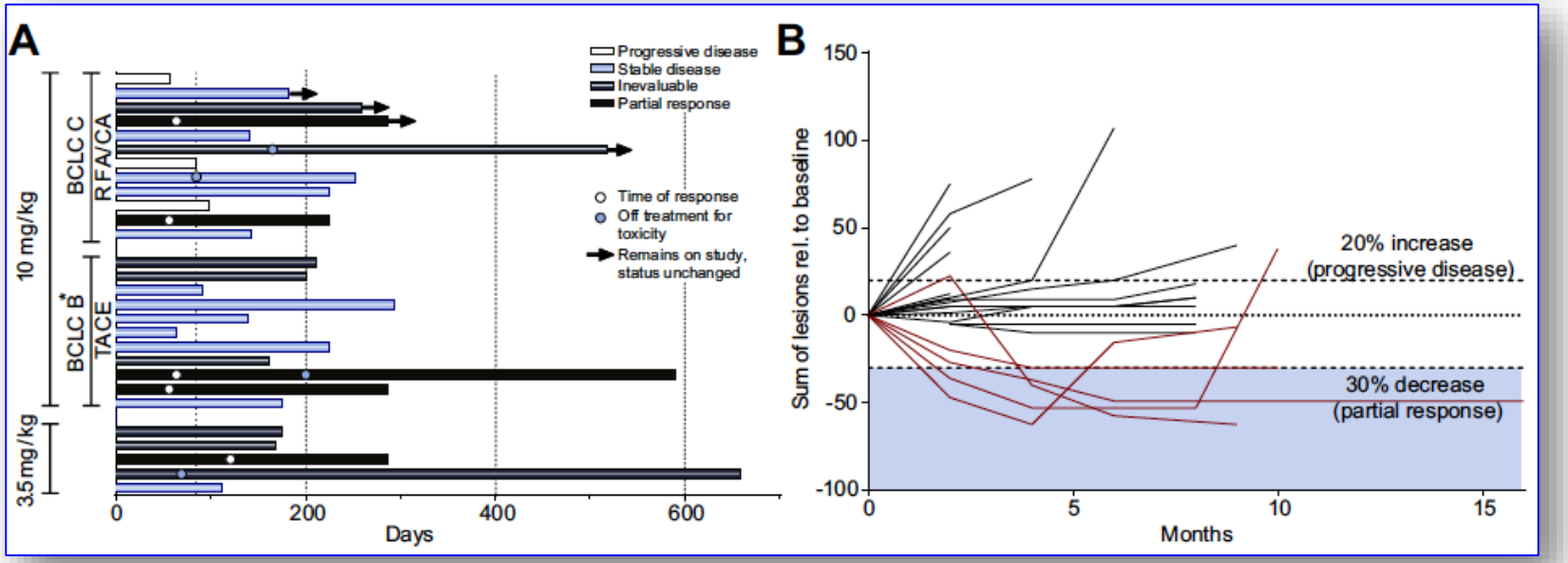


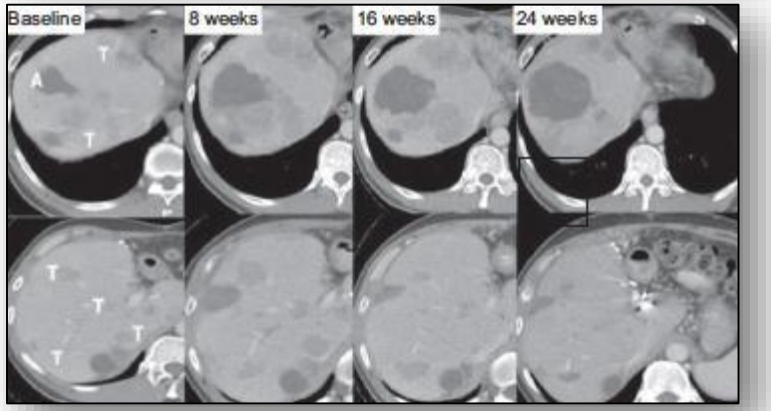
Kinetics of TAA-specific T Cell Response after RFA

Misokushi, Hepatology 2013

Efficacy of tremelilumab combined with ablation

in HCC after sorafenib failure



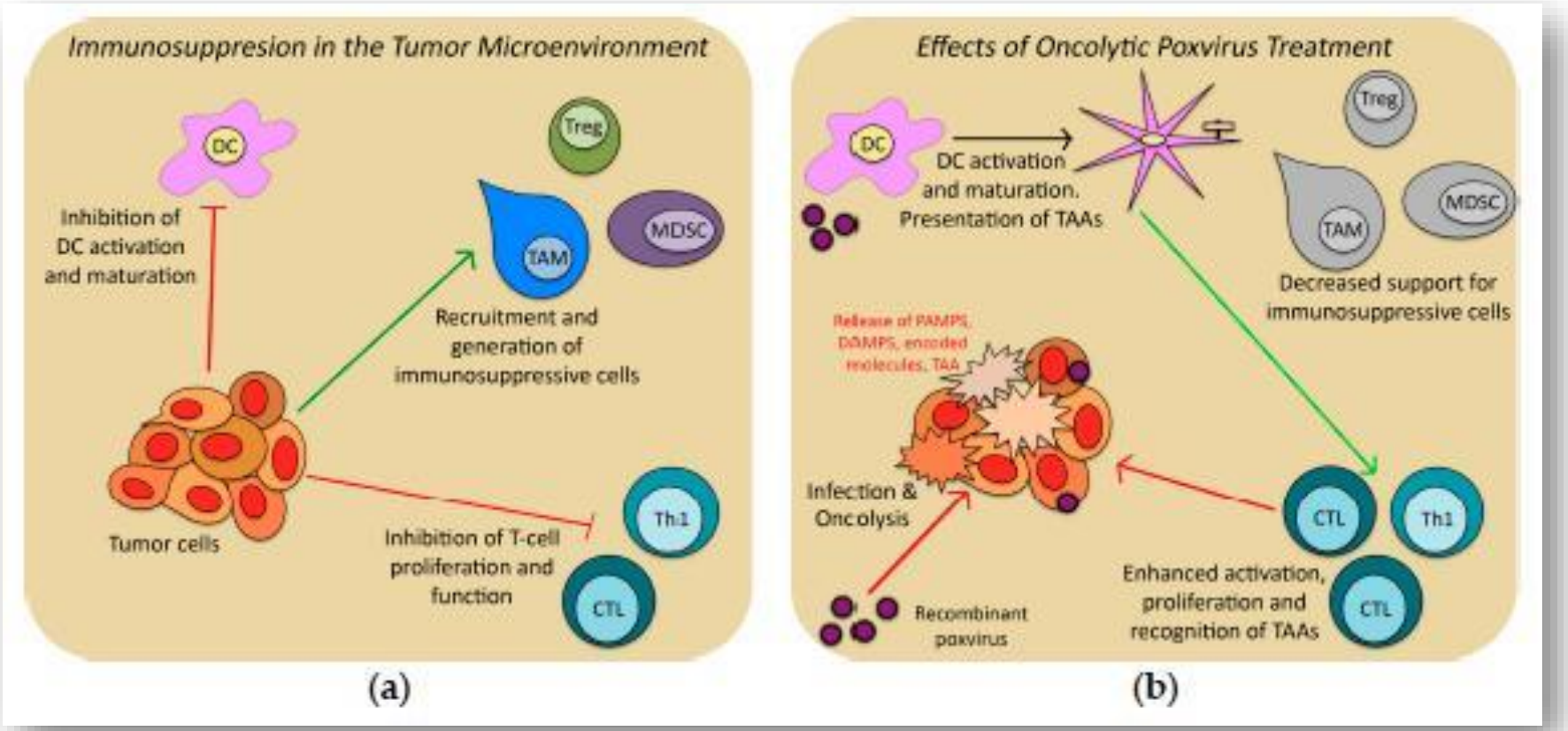


Duffy, J Hepatol 2017

Immune Checkpoint Inhibition

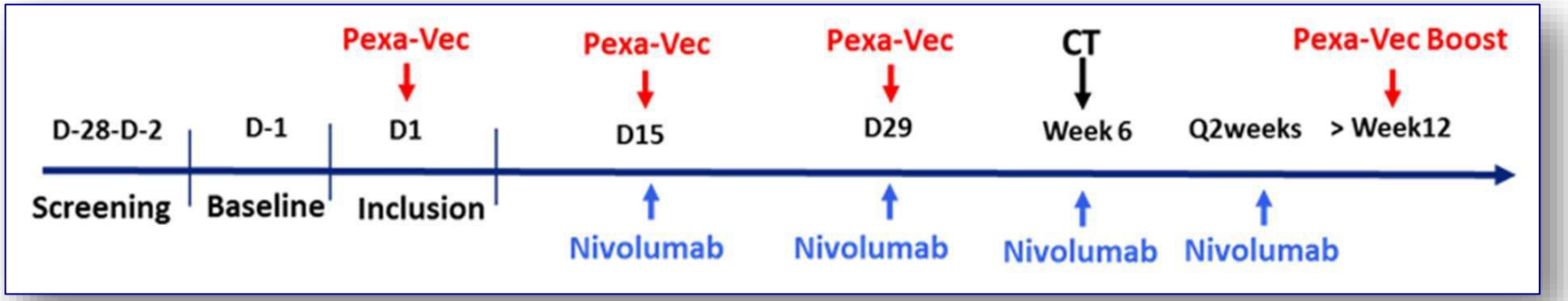
(anti-PD1/anti-PDL1/anti-CTL4)

Oncolytic Vaccinia Virus overcomes the immunosuppressive effect of tumor microenvironement



Sharp; *Biomedicines* 2016

Combination of the oncolytic immunotherapy Pexa-Vec
with nivolumab in HCC (Phase I/IIa)

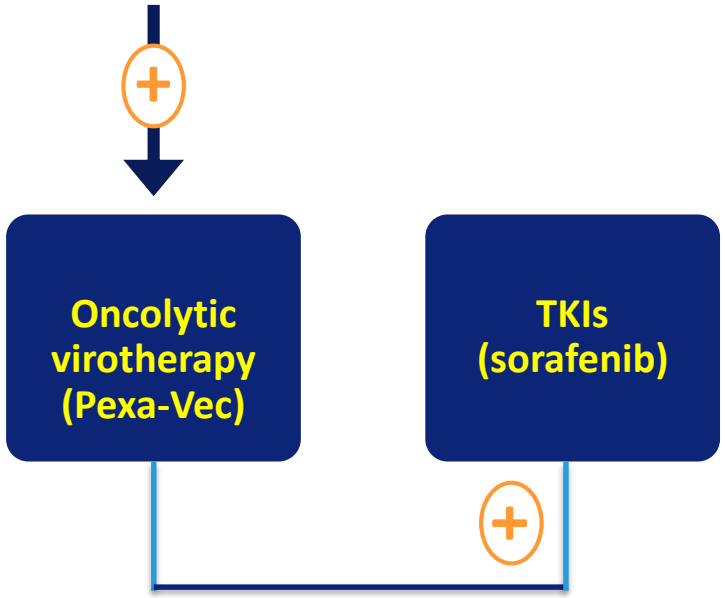


Phase I part: safety and efficacy will be assessed in 6 patients.

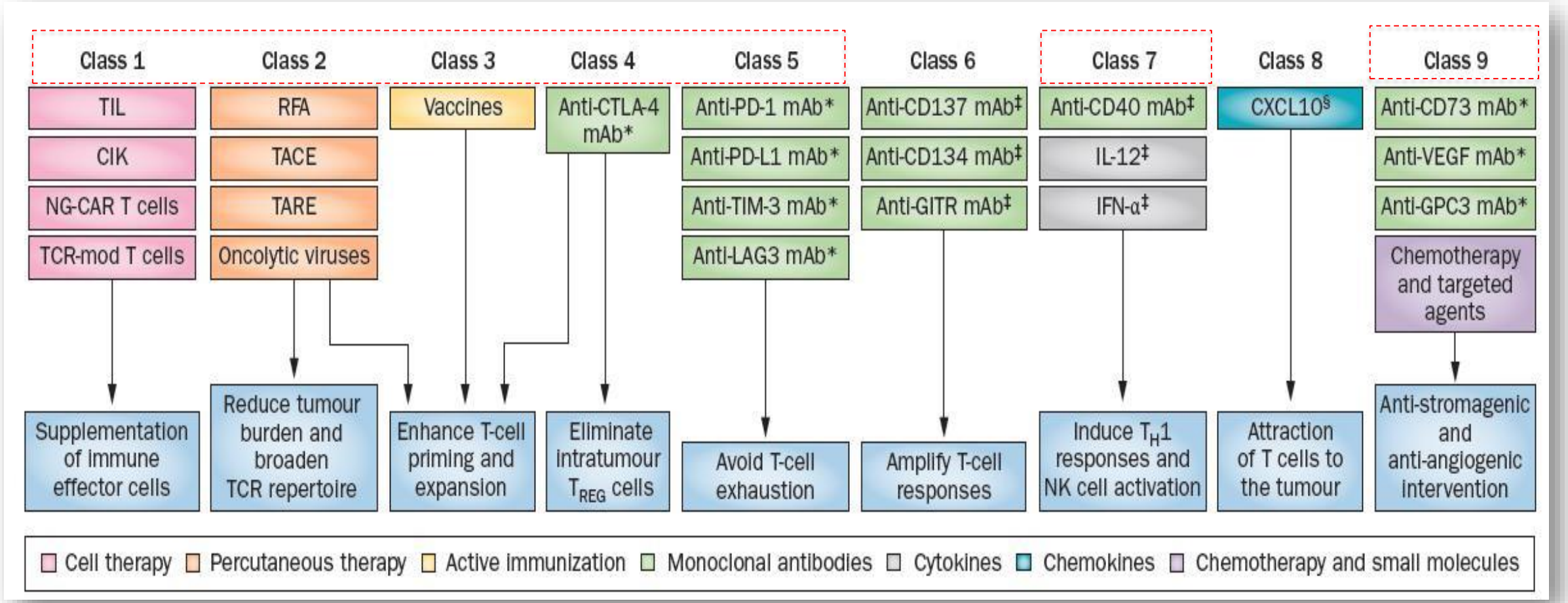
Phase IIa part: further evaluation of safety and efficacy, continuation of enrolment up to 32 patients (29 evaluable).

Immune Checkpoint inhibition (?)

(anti-PD1/anti-PDL1/anti-CTL4)



The future | Combinations of (immuno)-therapies in HCC?



Prieto, Nature Review, Gastroenterology & Hepatology, 2015

Key points

- HCC is an **immunogenic liver lesion** that expresses **tumor-associated antigens and private neo-antigens** arising from specific gene mutations
- **Antitumor immune responses are hampered** by stromal cells and immuno-inhibitory molecules
- **Immunotherapeutic modalities** have been used to treat HCC (i.e. vaccine platforms, adoptive T-cell therapy, cytokines, oncolytic viruses and monoclonal antibodies that target immune checkpoints)
- The abundance of **additive immunosuppressive factors** in the HCC microenvironment calls for a **multitargeted approach (local and systemic)**
- Administration of **monoclonal antibodies, adoptive T-cell therapy or vaccines in combination with oncolytic viruses** are powerful strategies to treat HCC

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Transgene's clinical development strategy in the evolving immuno-oncology landscape

Maud Brandely, MD, PhD

Chief Medical Officer, Transgene

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Transgene set to deliver clinical data

In the next 18 months

Product	Indication	Preclinical / Clinical Phase 1 / 2 / 3
THERAPEUTIC VACCINES		
TG4010	Non-small cell lung cancer – 2nd line	+ nivolumab (ICI) — Bristol-Myers Squibb
	Non-small cell lung cancer – 1st line	+ nivolumab (ICI) + CT — Bristol-Myers Squibb
	Non-small cell lung cancer	Neo-adjuvant *(translational)*
TG4001	HPV positive cancers	+ avelumab (ICI) — MERCK, Pfizer
TG1050	Chronic hepatitis B	+ antiviral
ONCOLYTIC VIRUSES		
Pexa-Vec	Hepatocellular carcinoma – 1st line (PHOCUS)	+ sorafenib — SILLAJEN BioTherapeutics
	Hepatocellular carcinoma – 1st line	+ nivolumab (ICI)
	Other solid tumors	+ ipilimumab (ICI)
	Sarcoma – Breast cancer	+ cyclophosphamide
	Solid tumors	Neo-adjuvant *(translational)*
TG6002	Glioblastoma	

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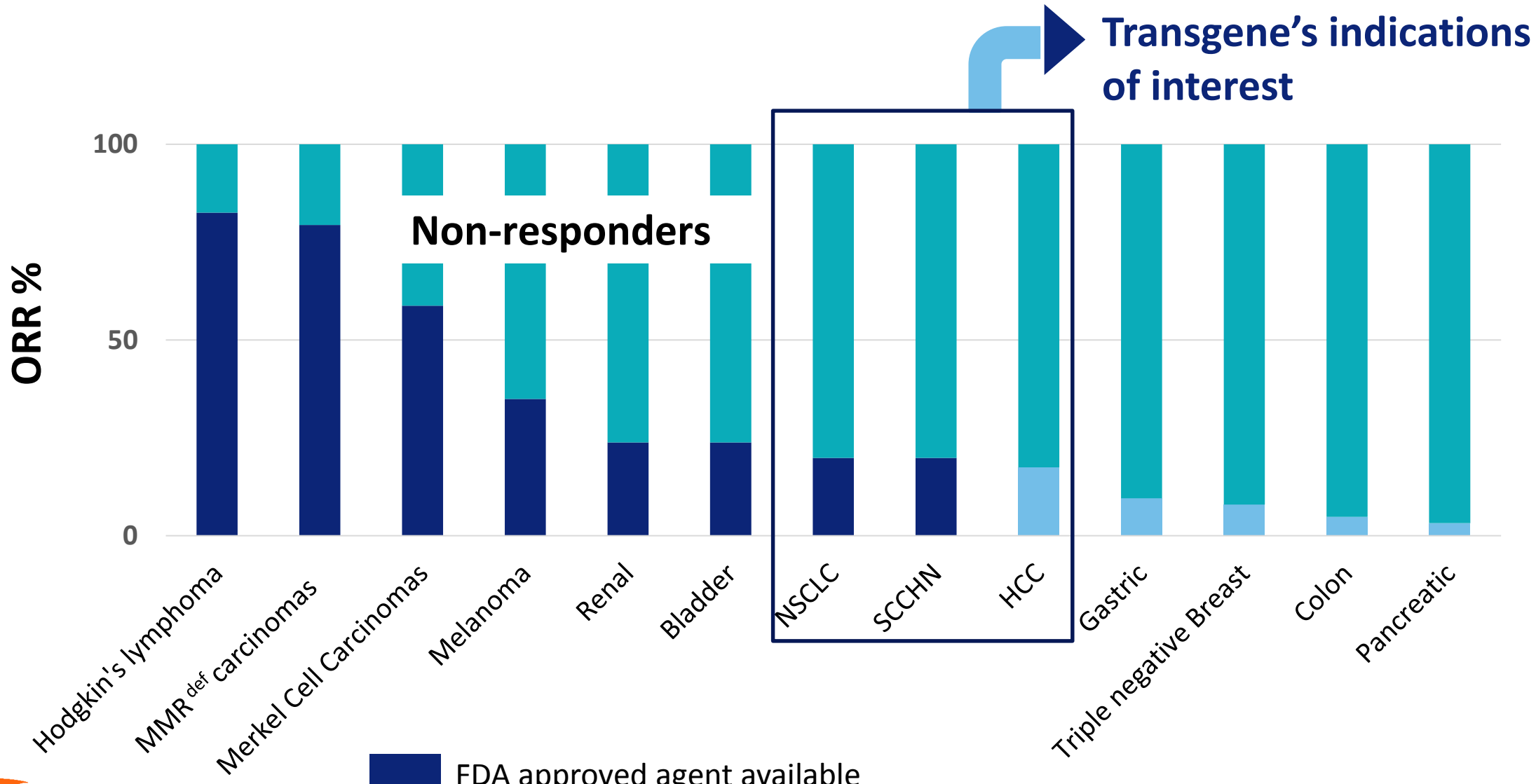
Ongoing | About to start | In preparation

Immune checkpoint blockade of PD-1 / PD-L1 pathway

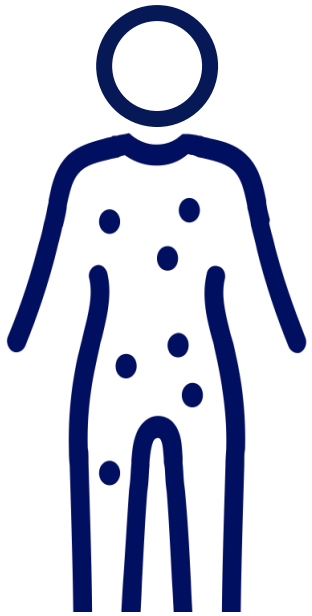


FDA approved agent available

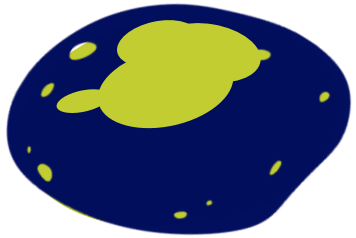
ORR = approximate objective response rate %

Source: from ASCO Annual meeting 2017, by Gregory L. Beatty, MD PhD

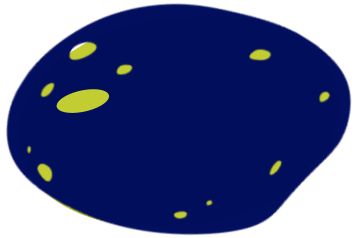
Management of cancer in the anti-PD-1/L1 era



Tumors
sensitive to anti-PD-1/PD-L1



Anti-PD-1 / anti-PD-L1



Bring more effective T cells into tumors

- Change the TME: **Oncolytic viruses**, TLR agonists
- Inhibit negative immune regulators: anti-CTLA4, IDO, TGFb
- Activate immune activators: CD27, CD40, CD137, OX40

Tumors
insensitive to anti-PD-1/PD-L1

Generate T cells

- **Vaccines**
- TCR engineered ACT
- CAR engineered ACT

Source: ASCO Annual meeting 2017,
modified from Ribas, Cancer Discovery 2016

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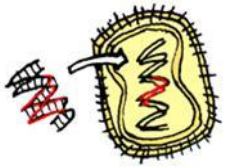
TG4010 Targeting NSCLC



Modified Virus Ankara (MVA)

expressing MUC1 antigen & interleukin 2

TG4010 | Strong clinical data

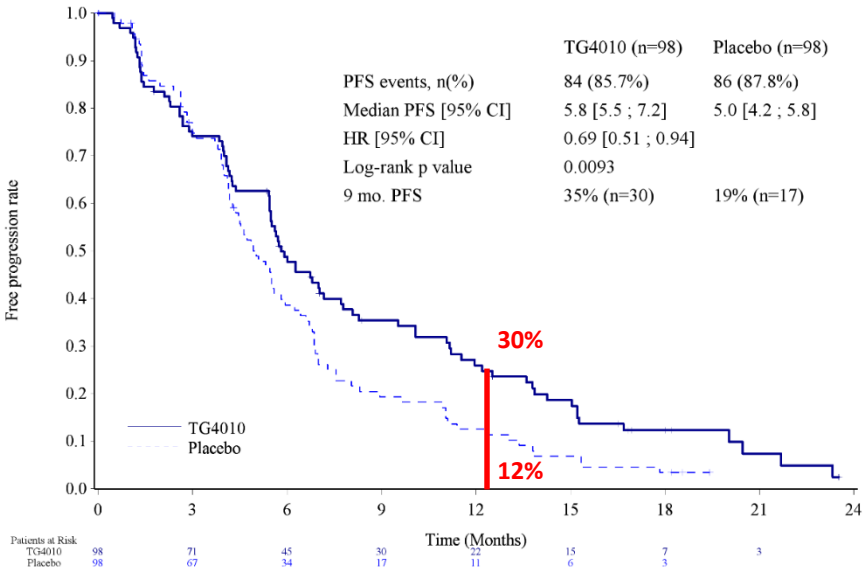
Well positioned for further development in NSCLC

THE LANCET Oncology

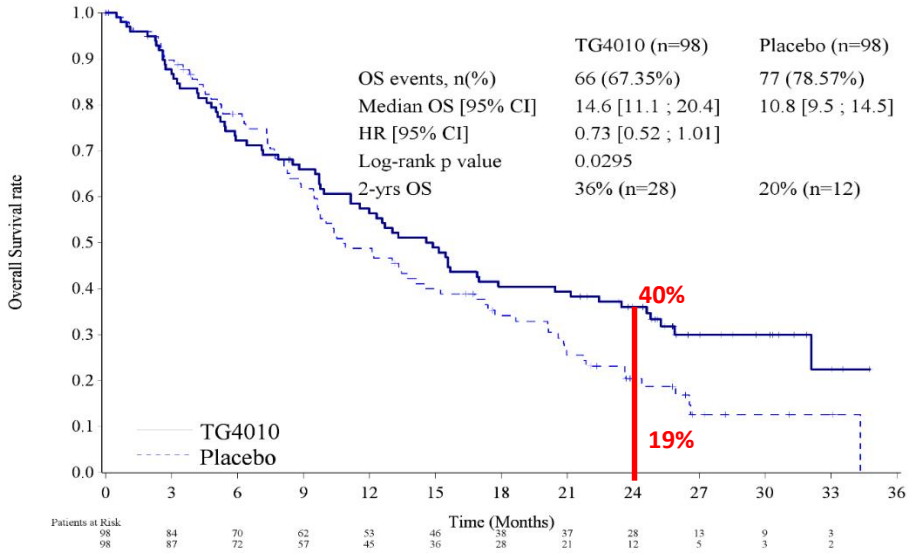
SUCCESSFUL PHASE 2B TRIAL (RANDOMIZED, PLACEBO-CONTROLLED, 222 PATIENTS)

TG4010 in combination with chemotherapy for 1st line NSCLC

Progression-free survival (months)



Overall survival (months)



- ✓ **Significant improvements in PFS and OS** in patients with non-squamous tumors
- ✓ **Clinical efficacy in both PD-L1 negative and PD-L1 positive patients**

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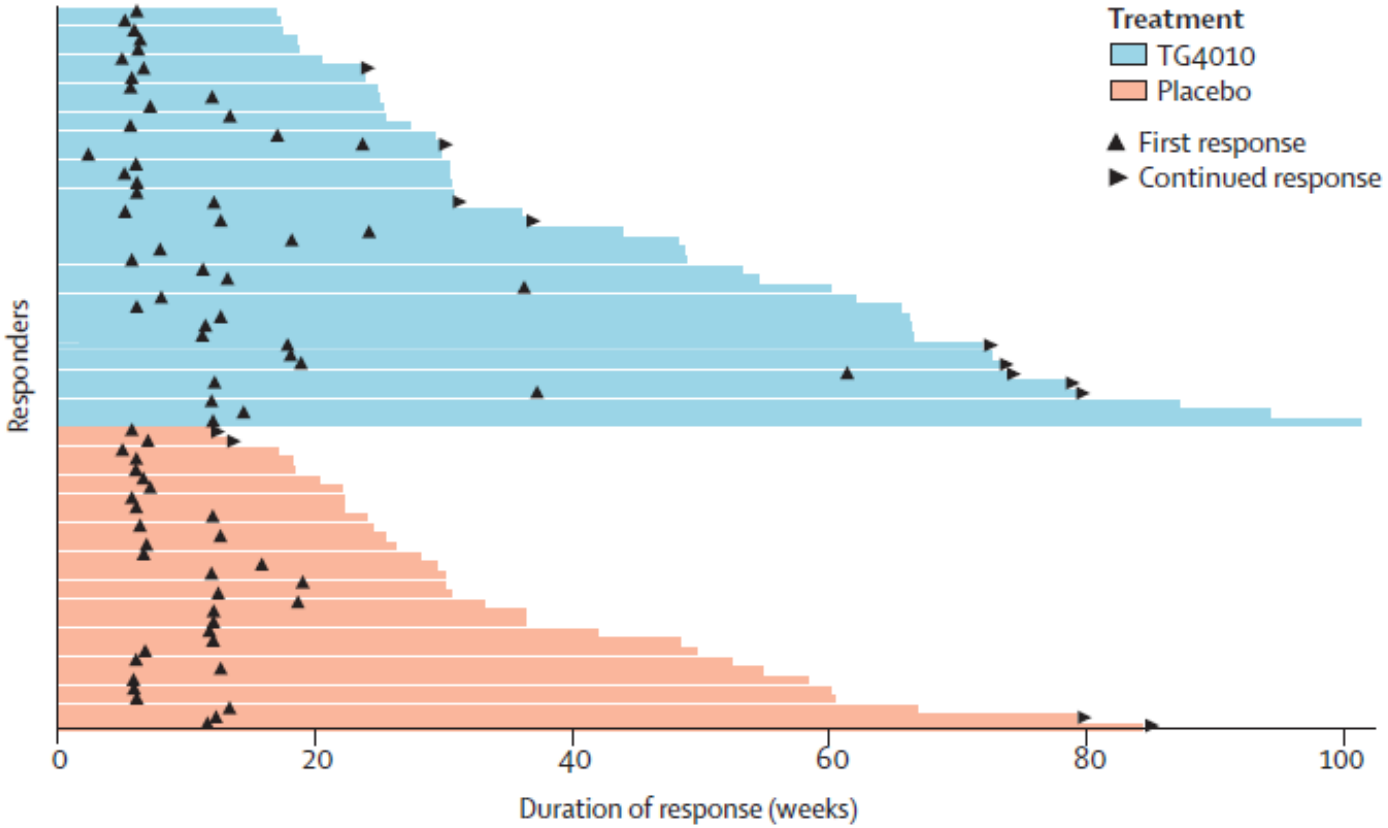
Source: The Lancet Oncology, Dec. 2015, Quoix, E. et al.

TG4010 | Strong clinical data

Improved response rate & duration of response



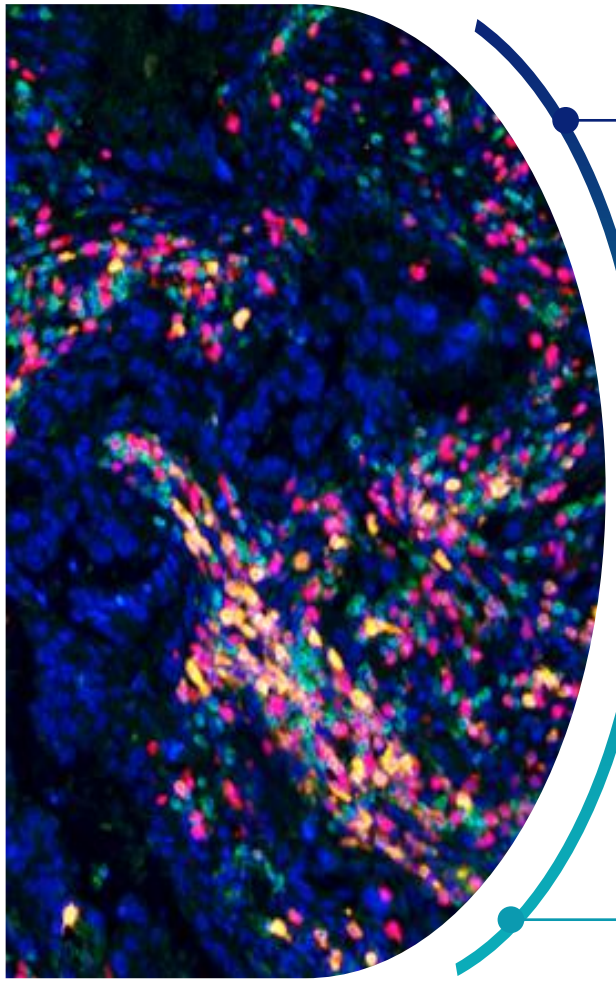
	TG4010	Placebo
Non-squamous (n)	98	98
ORR	**40%**	**28%**
Median duration of response (wks)	**41**	**18**

- ✓ **Improved response rate & duration of response**
- ✓ **Good safety profile**

Source: The Lancet Oncology, Dec. 2015, Quoix, E. et al.

TG4010 | Proven mechanism of action

Efficacy driven by T-cell response (CD8+)



Specific CD8+ T cell response to MUC1 epitopes
is associated with **increased survival**

OS improvement during TG4010 treatment is driven
by the development of a **larger CD8+ T cell anti-MUC1 repertory**

Specific CD8+ T cell response to MUC1 after TG4010 administration
is **associated with responses against other lung tumor antigens**

Increased CD8+ response without **increase in inhibitory T reg** frequency

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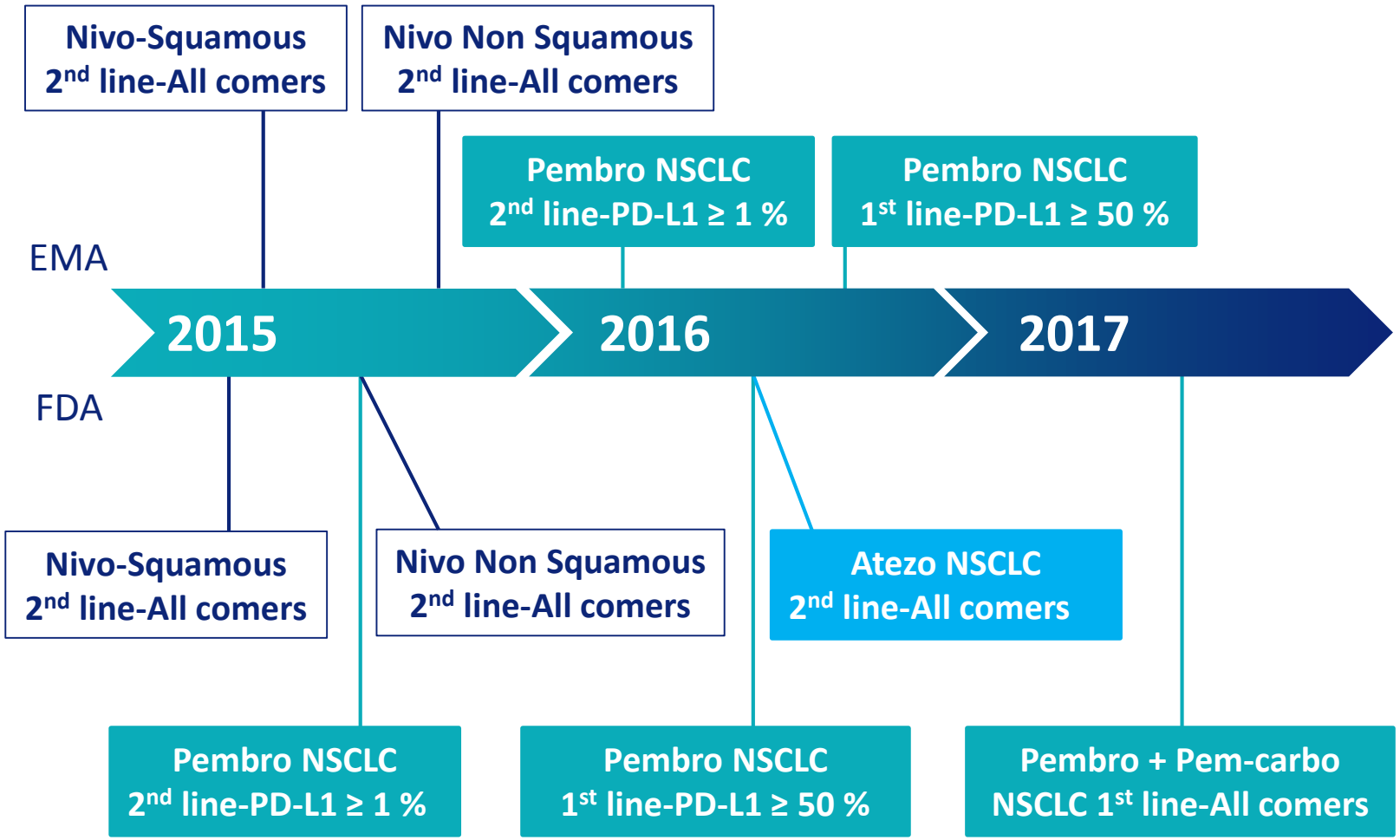
Tosch et al., 2017; Viral based vaccine TG4010 induces broadening of specific immune response and improves outcome in advanced NSCLC; submitted

TG4010 | Anti-PD1/PD-L1 are now SoC in NSCLC

but combinations are needed to deliver better efficacy



RR remain low

Still no cure

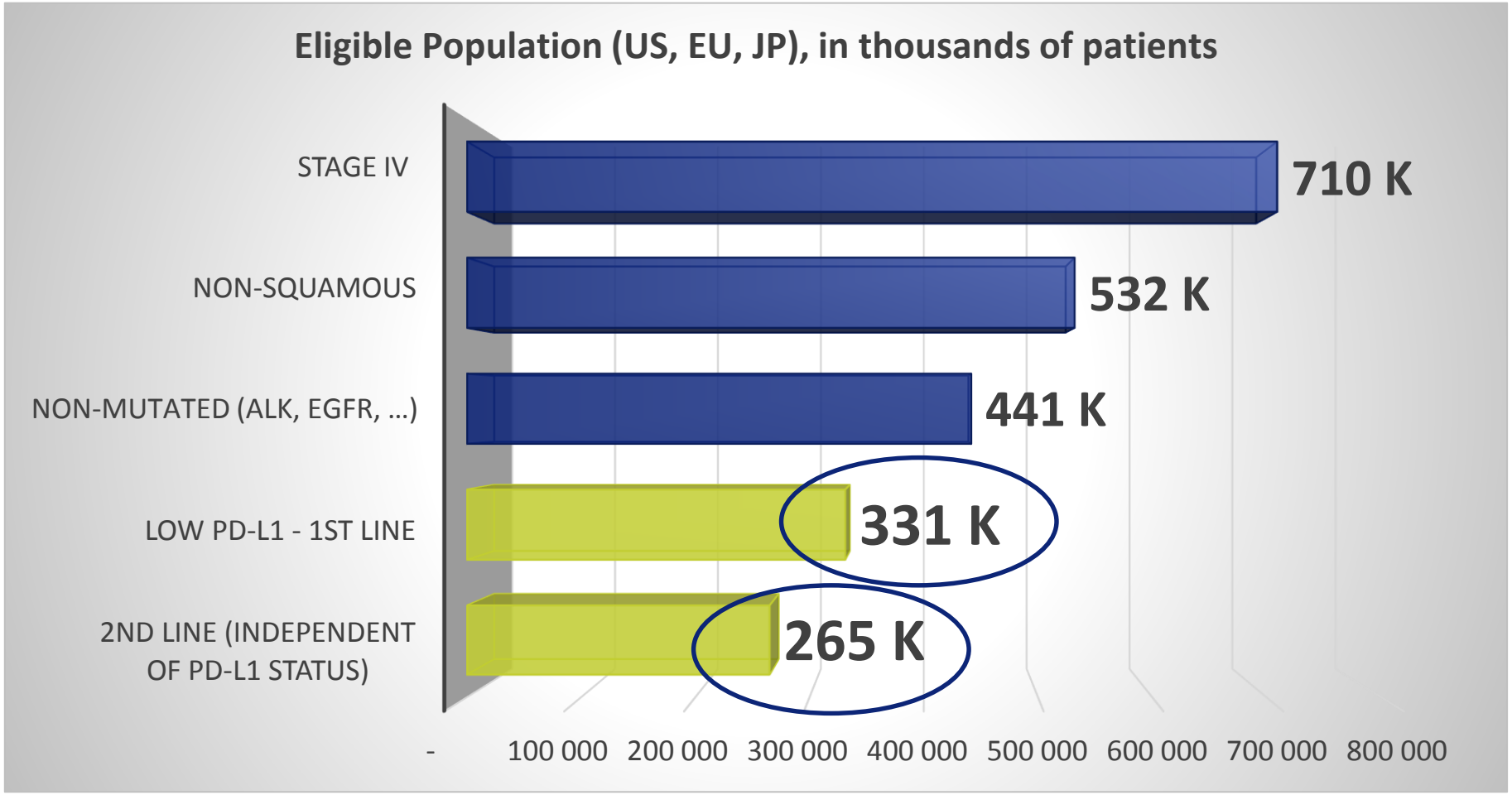
➔ Necessity to improve efficacy of ICIs via combination

TG4010 | Clinical positioning

A very large population in NSCLC, stage IV, non-squamous patients

1L TG4010 positioning

2L TG4010 positioning



TG4010 | Combination with ICIs

Scientific Rationale

TG4010
(Therapeutic vaccine)

- Demonstrated mechanism of action: induction of CD8+ T cell response
- Activity shown in patients with no/low PD-L1 expression(1)

Immune Checkpoints Inhibitors
(ICIs)

- **Block the signal that prevents activated T-cells from attacking cancer cells**

  Enhance the efficacy of anti-tumor T-cell response

Increased response rate, longer duration of response, extended OS

Positive effects of the combination of TG4010 with ICIs have been demonstrated in preclinical tumor models(2)

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(1) *The Lancet Oncology, Dec. 2015, Quoix, E. et al.*

TG4010 | Clinical development plan (non sq. NSCLC)

Generate additional data in combination with ICIs

3 trials to position TG4010 in all settings of advanced NSCLC

➔ Initiate two Phase 2 trials in combination with PD-1 inhibitor and one study to further document MoA

NSCLC - *2nd line*	**TG4010 + PD-1 Inhibitor**	• Multi-center Phase 2 trial in the US • PI: Dr Karen Kelly (UC Davis) • BMS to supply nivolumab
NSCLC - *1st line* patients with no or low level of PD-L1 expression	**TG4010 + chemotherapy + PD-1 Inhibitor**	• Multi-center trial in US and Europe • BMS to supply nivolumab
Resectable NSCLC	**Neo-adjuvant chemotherapy ± TG4010**	• Translational research study in the neoadjuvant setting • PI: Prof. Quoix at University of Strasbourg • FPI expected to be enrolled around the end of 2017

TG4010 | Non-Small Cell Lung Cancer (NSCLC) - 2nd line

Phase 2 in combination with Opdivo® (Nivolumab)

Support of

UC DAVIS COMPREHENSIVE CANCER CENTER

Bristol-Myers Squibb

- Principal Investigator: Dr Karen Kelly
- Collaborative agreement
  - with UC Davis Medical Center (USA)
  - and Bristol-Myers Squibb (supply of nivolumab)
- First patient treated in March 2017
- **First results expected around the end of 2017**

Protocol

- Up to 33 patients
- Multi-center, single-arm, open label study
- Stage IV non-squamous NSCLC who have progressed after one line of systemic therapy

Endpoints

- Primary endpoint: Objective response rate (ORR)
- Secondary endpoints: progression-free survival (PFS), overall survival (OS), duration of response and safety

Participating centers

- UC Davis
- UC San Francisco
- City of Hope
- UC San Diego

TG4010 | Non-Small Cell Lung Cancer (NSCLC) – 1st line

Phase 1/2 in combination with Opdivo® + Chemotherapy (CT)

Support of

Bristol-Myers Squibb

- Collaborative agreement with BMS (supply of nivolumab)
- **First patient expected to be enrolled by the end of 2017**

Study regimen

- TG4010 10^8 PFU weekly for 6 weeks then every 3 weeks by SC route
- Nivolumab 360 mg every 3 weeks by IV route
- Pemetrexed-carboplatin (or cisplatin) every 3 weeks for 4 cycles

Protocol

- Up to 39 patients
- Multi-center, single-arm, open label study
- Stage III B-IV or delayed relapse, tumors with **low or undetectable PD-L1 expression**

Endpoints (Phase 2 part)

- Primary endpoint: Objective response rate (ORR)
- Secondary endpoints: progression-free survival (PFS), overall survival (OS), duration of response and safety

Participating countries

- USA
- Belgium
- Denmark
- France

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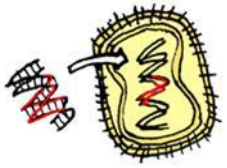
TG4001 targeting HPV-positive head and neck cancer



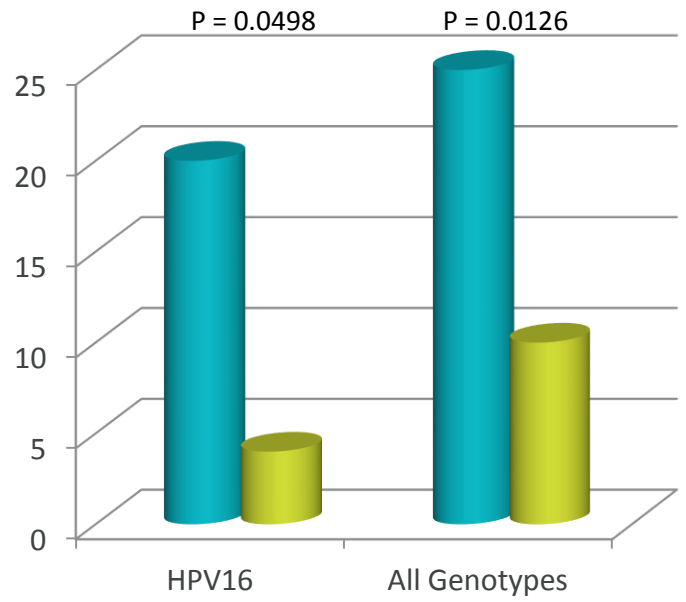
MVA expressing HPV16 E6 & E7 antigens & interleukin 2

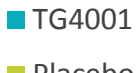
TG4001 | Positive Phase 2b in HPV-associated CIN 2/3

Demonstration of statistically significant curative activity at 6 months

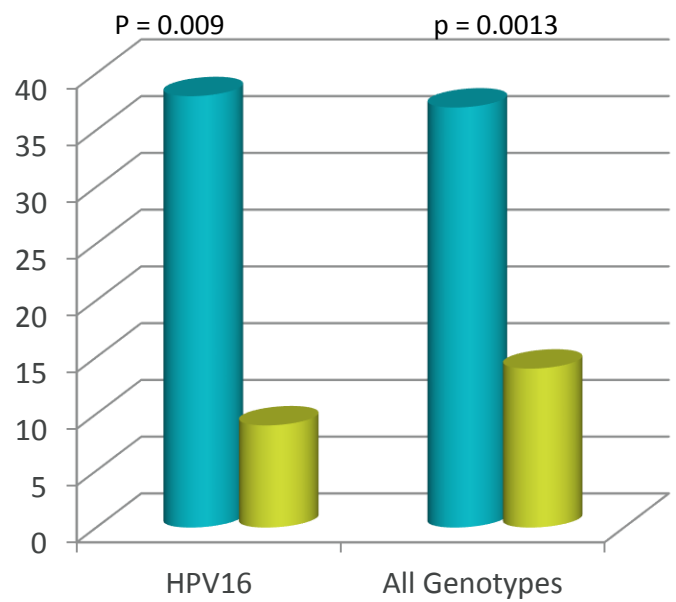
PHASE 2B TRIAL (RANDOMIZED, PLACEBO-CONTROLLED, 206 PATIENTS)
in patients with cervical carcinoma in situ of high grade (2/3)

Resolution (%)





Viral clearance (%)



- ✓ **Single agent TG4001 is active, and able to address HPV-related carcinomas**
- ✓ **Data represent a strong POC of active immunotherapy**
  - TG4001 was 5x superior in HPV16 patients compared to placebo to induce complete disease regression
  - TG4001 showed an efficacy 4 fold superior compared to placebo regarding the viral clearance

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TG4001 | Targeting HPV-positive head & neck cancers (HNSCC)

- ✓ **Efficacy demonstrated** in patients with high grade CIN associated with HPV-16

- ✓ **Clinical experience in more than 300 patients**, demonstrating good safety profile. Injection site reactions were the most common adverse events

- ✓ **Strong rationale for testing TG4001 in advanced stage HPV-positive HNSCC**
  ➔ High unmet medical need

TG4001 | Current treatments for recurrent/metastatic HNSCC

Dismal prognosis

Better therapeutic options needed

~60% of oropharyngeal HNSCC are HPV-positive
Increasing incidence in western countries
→ 25 000 patients

First-line therapy

- For patients with good performance status: historically platinum-based doublet
  (eg. Cisplatin/5-FU or carboplatin/paclitaxel)
  - ORR: 30% to 40%;
    median OS: 6-9 months regardless of specific drug
- For patient with poor performance status: use single agent CT or cetuximab

Second-line therapy

- Nivolumab, pembrolizumab
  - ORR: 16% to 19%; median OS: 7-8 months

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TG4001 | HPV-positive Head & Neck Cancers (HNSCC)

Phase 1/2 in combination with avelumab (Bavencio®)

Support of

Collaborative agreement

- with the alliance of Merck KGaA and Pfizer (supply of avelumab)

Principal Investigator

- Pr Christophe Le Tourneau, Institut Curie

Protocol

- Up to 50 patients (France)
- Multi-center, single-arm, open label trial
- Metastatic or refractory/recurrent HPV-16+ head & neck cancer, after failure of standard therapy

Endpoints (Phase 2 part)

- Primary endpoint: Objective response rate (ORR)
- Secondary endpoints: progression-free survival (PFS), overall survival (OS), duration of response and safety

First patient expected in H2 2017

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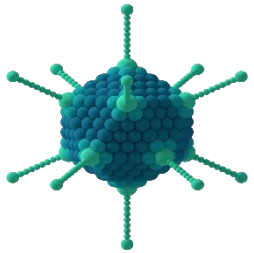
TG1050 targeting chronic hepatitis B



Modified Adenovirus 5
that expresses 3 different HBV
(Hepatitis B Virus) antigens

TG1050 | Current treatments for chronic hepatitis B

Large unmet medical need as cure rate is extremely low

Need to improve clinical outcome:
High risk of developing **cirrhosis** and **hepatocellular carcinoma**

→ 500 000 eligible patients*

Treatment recommendations (EASL 2017 clinical guidelines)

- Long-term administration of entecavir (Baraclude®), tenofovir disoproxil fumarate (Viread®) or tenofovir alafenamide (Vemlidy®) as monotherapy
  - High level of viral suppression ~98 %
  - Low level of functional cure (HBsAg loss) < 3 % per year
- PegIFNα for 48 weeks in highly selected patients
  - Moderate level of viral suppression ~50 %
  - Low level of functional cure < 9% per year

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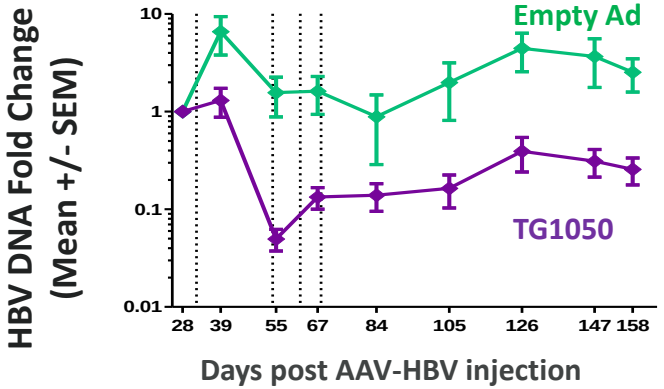
** Sources: Decision Resources: expert opinions, Company estimates, USA, Europe, Japan, 2020*

TG1050 | Strong pre-clinical data

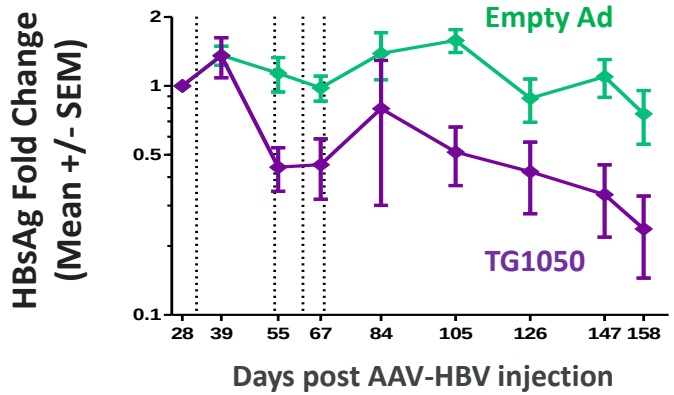
Sustained anti-viral effects in HBV mouse models (AAV)

- Only viral-based therapeutic vaccine that integrates the 3 relevant HBV antigens (polymerase, core, HBsAg)
- Demonstrated immunogenicity & functionality
  - Similar to those of spontaneous resolvers
    i.e. robust and broad CD8 T-cell responses
  - **Capacity of HBV-specific T cells induced by TG1050 to recognize epitopes all HBV genotypes**
  - Capacity to induce **functional T-cells in tolerant HBV mouse models** (Novel AAV-based model, other)
- Antiviral properties
  - Capacity to control HBsAg and induce HBsAg seroconversion with no detectable liver inflammation in tolerant HBV mouse models
- Ongoing preclinical experiments (direct/indirect antivirals, immuno-modulators,…)

HBV DNA (viral load)
Mean viral load at D28 : 1.4x106 copies/mL



Circulating HBsAg
Mean HBsAg titers at D28 : 20µg/mL



Martin et al., Gut, 2014
Inschauspé et al., EASL, 2015

TG1050 | Phase 1/1b trial

Principal investigator

- Pr Fabien Zoulim,
  Hospices civils, Lyon (France)

Hospices Civils de Lyon

Protocol

- Up to 48 patients
- International, randomized safety and dose-finding study
- Patients currently being treated with standard-of-care antiviral therapy (tenofovir or entecavir)

Participating countries

- Canada, France, Germany

Primary objectives

- ✓ Evaluate safety and tolerability of TG1050 administered in single and multiple doses (3 injections at one week interval)
- ✓ Determine dose and schedule of administration for further development

Secondary endpoints

- ✓ Antiviral activity: HBsAg levels
- ✓ Cellular and humoral immune responses

Phase I/Ib accrual close to completion

First data readout in H2 2017

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immunotherapeutics

A promising portfolio of oncolytic viruses in clinical development

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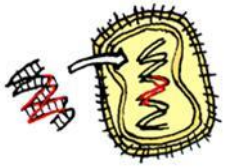
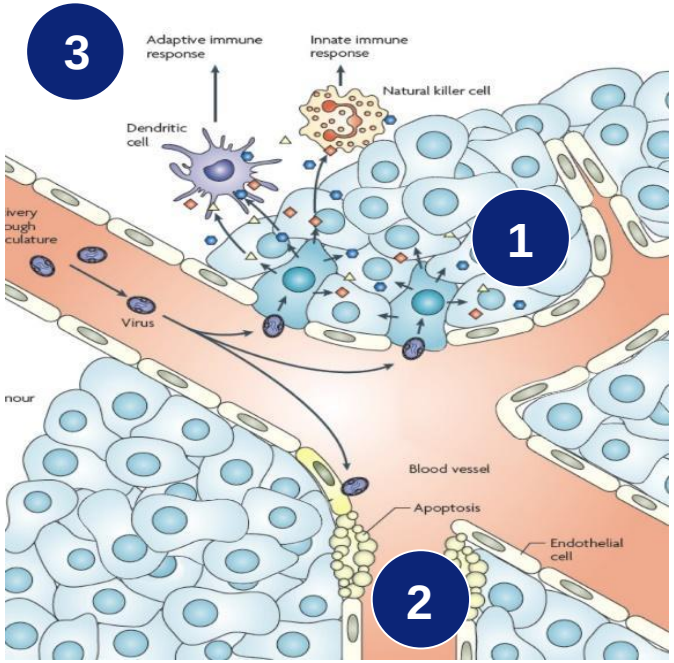
immunotherapeutics

Pexa-Vec in hepatocellular carcinoma (HCC)



Vaccinia Virus expressing GM-CSF

Pexa-Vec | 3 complementary mechanisms of action



1. **Cancer cell oncolysis** *(Kirn D 2009)*: Infection, cell lysis and viral spread

nature REVIEWS CANCER

2. **Tumor vascular shutdown** *(Breitbach C 2013)*: Infection and cell lysis

Cancer Research

3. **Active immunotherapy** *(Kim MK, 2013)*: Tumor-specific immune response stimulation (GM-CSF)

Science Translational Medicine

Kirn DH, et al. *Nature Reviews, Cancer.* 2009

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Pexa-Vec | Large unmet medical need in HCC

Dismal prognosis

Better therapeutic options needed

25,000 eligible patients in Europe

First-line therapy

- Sorafenib is currently the only approved product - modest activity
  - ORR: 2% ; median OS: 10.7 months
- Nivolumab likely to become a new therapeutic option: Promising activity in Phase 2
  - ORR: 14% to 16% ; median OS: 14 to 15 months

Second-line therapy

- Regorafenib
  - ORR: 10%; median OS: 10.6 months

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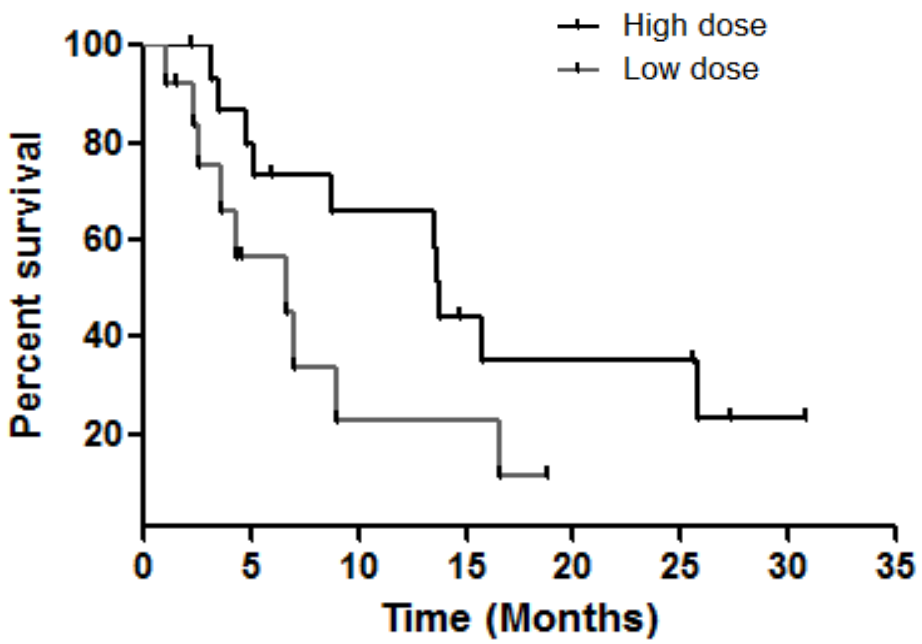
Pexa-Vec | Key Phase 2 clinical trial results

Clinical activity demonstrated in multiple trials

More than 10 trials with >300 patients treated with Pexa-Vec in variety of tumor types, including liver, colorectal and kidney

30-patient dose-finding Phase 2 trial in HCC (80% of patients first-line)

- Proof of concept for MOA: active immunotherapy
- OS results - high dose versus low dose
  - Median OS: 14.1 (high dose) vs. 6.7 months (low dose)
  - Hazard Ratio = 0.39
  - p = 0.020



Nature Medicine, Volume 19, Issue 2, February 2013

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Pexa-Vec | Clinical development plan

Pivotal Phase 3 and three complementary studies

1. Complete the Phase 3 Trial in 1st Line HCC in Combination with Sorafenib

Advanced HCC *1st line*	**Pexa-Vec + sorafenib**

- Multi-center Phase 3 trial in Europe, US, Asia
- Randomized, two arm trial
- Ongoing recruitment – Results expected in 2019

2. Conduct three Phase 2 Trials in combination with ICI and other agents based on supportive preclinical data

Advanced HCC *1st line*	**Pexa-Vec + Opdivo® (nivolumab)**

- Multi-center Phase 2 trial in France, Italy, US
- Sponsor: Transgene
- Open label, single arm trial, FPI expected in coming weeks

Solid tumors	**Pexa-Vec + Yervoy® (ipilimumab)**

- Multi-center Phase 2 trial in France
- Sponsor: Léon Bérard (France)
- 1st patient dosed in February 2017 / 1st results around the end of 2017

Breast cancer STS	**Pexa-Vec + cyclophosphamide**

- Multi-center Phase 2 trial in France
- Sponsor: Bergonié (France), funded by INCA
- 1st patient dosed in April 2017

Pexa-Vec | Ongoing Phase 3 Clinical Trial (PHOCUS trial)

1st line advanced hepatocellular carcinoma

Phase 3 study in combination with sorafenib (Kinase inhibitor)

Design

- Pexa-Vec + sorafenib versus sorafenib (only approved drug for advanced HCC)
- N=600 patients (Europe, North America and Asia), 140 clinical centers
- 1:1 randomized trial

Endpoints

- Primary: overall survival (OS)
- Secondary: safety, time to progression, progression-free survival, overall response rate and disease control rate

Conducted by

SILLAJEN BioTherapeutics

✓ **Orphan drug** designation granted
✓ **SPA** with FDA

- First patient enrolled in January 2016
- Recruitment ongoing
- 1st patient recently treated in Europe
- **First results expected in 2019**

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Pexa-Vec | Phase 1/2, combo with nivolumab

Advanced stage HCC - 1st line

Principal Investigator

- Pr Olivier Rosmorduc,
  La Pitié-Salpêtrière, Paris (France)

Protocol

- Up to 36 patients
- Multi-center, open label trial
- Patients with advanced-stage HCC, treatment naive

Participating countries

- France, Italy, US

Study regimen

- Pexa-Vec: 3 intratumoral injections, 10^9 pfu, q2w +/- boosts
- Nivolumab: IV, 240mg, q2w until progression, start at D15

Endpoints (Phase 2 part)

- Primary endpoint: Objective response rate (ORR)
- Secondary endpoints: progression-free survival (PFS), overall survival (OS), duration of response and safety
- Exploratory endpoints: extended translational program (PDL1 …) including biopsy during treatment

- **FPI Expected in coming weeks**

Pexa-Vec | Phase 1/2, combo with ipilimumab (Yervoy®)

Solid tumors

Principal Investigator

- Dr A. Marabelle,
  Gustave Roussy (France)
- Sponsor: Centre Léon Bérard (France)

Protocol

- Up to 60 patients
- Multi-center, open label trial
- Injectable solid tumors
  (focus on sarcomas and breast cancer in Phase 2)

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

Study regimen

- Pexa-Vec: 4 intratumoral injections, 10^9 pfu, q2w +/- boost
- Ipilimumab: 3 intratumoral low dose (10 mg) injections, starting at Day 15 +/- boost

Endpoints (Phase 2 part)

- Primary endpoint: Objective response rate (ORR)
- Secondary endpoints: progression-free survival (PFS), overall survival (OS), duration of response and safety
- Exploratory endpoints: extended translational program (PDL1 …) including biopsy during treatment

- **First results expected around the end of 2017**

Transgene | Optimizing immunotherapy

COMBINATION STRATEGY	**Combining of our immunotherapies with ICIs has a strong rational to improve the efficacy of ICIs in difficult-to-treat solid tumors (NSCLC, HCC, HNSCC)**
CLINICAL DATA	**Clinical data to support this combination approach will be delivered in the next 18 months**

Increased efficacy
↑ ORR, ↑OS

Good safety profile

transgene

We would like to thank patients, clinicians and support personnel

for their commitment to the fight against severe diseases

UC DAVIS COMPREHENSIVE CANCER CENTER

HÔPITAUX UNIVERSITAIRES PITIÉ SALPÊTRIÈRE CHARLES FOIX

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

FUDAN UNIVERSITY 1905

Hospices Civils de Lyon

institut Curie

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

City of Hope

UNIVERSITY OF LEEDS

INSTITUT BERGONIÉ UNICANCER Centre Régional de Lutte Contre le Cancer de Bordeaux et du Sud-Ouest

Les Hôpitaux Universitaires de STRASBOURG

UKE HAMBURG

UC San Diego Health

UCSF Medical Center

MHH Medizinische Hochschule Hannover

JG|U JOHANNES GUTENBERG UNIVERSITÄT MAINZ

CHUM Centre hospitalier de l'Université de Montréal

UNIVERSITÄTS KLINIKUM FREIBURG

CALGARY DIVISION OF GASTROENTEROLOGY & HEPATOLOGY

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Today's agenda

4:15 ➔ ~ 6:00 pm

Modulating the tumor micro-environment with viral-based therapeutics

Christian Ottensmeier, MD, PhD, Director

Engineering viruses to create the next generation of immunotherapy

Eric Quéméneur, PharmD, PhD, Executive VP, Chief Scientific Officer

Effective translational research, the benefits of academic collaboration

Eliane Piaggio, PhD, Head of the translational research in immunotherapy team

Closing remarks

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immunotherapeutics

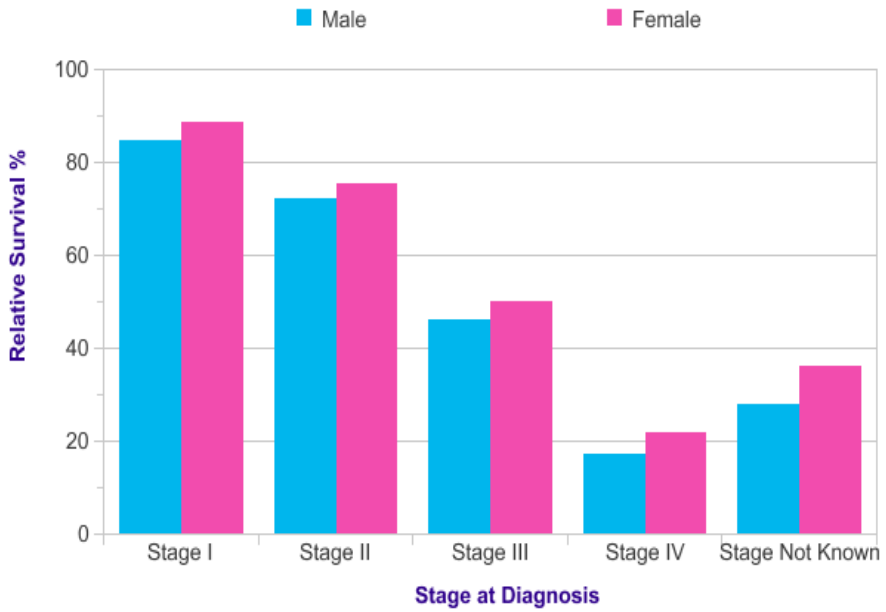
UNIVERSITY OF Southampton

Immune modulators and immuno-oncology
Where do we stand
and where should we go next?

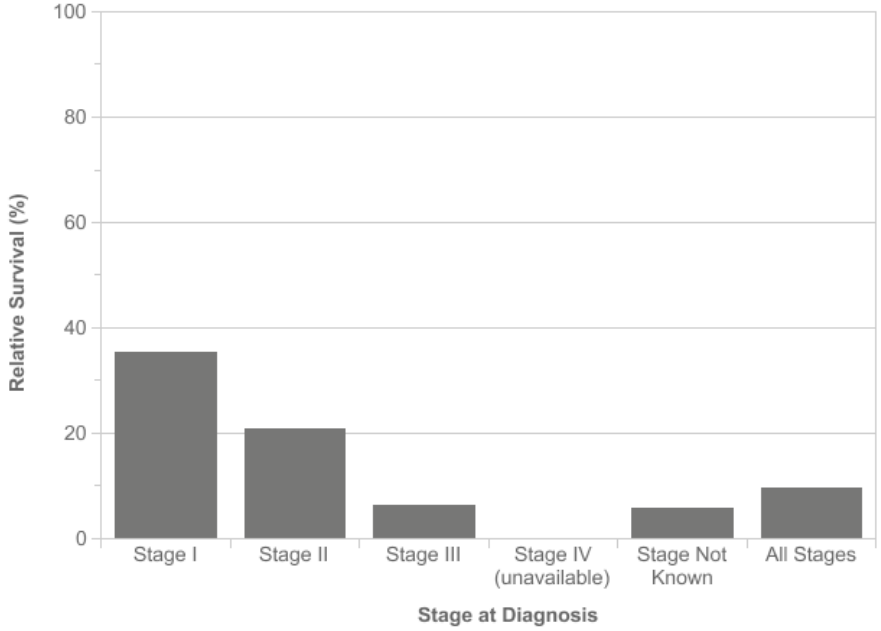
Christian Ottensmeier, MD, PhD
Director, ECMC

After stagnating progress for many years…

One-Year Relative Survival (%) by Stage.



Five-Year Relative Survival (%) by Stage, Adults 15-99.



Prepared by Cancer Research UK
Original data sources:
Survival estimates were provided on request by the Cancer Research UK Cancer Survival Group at the London School of Hygiene and Tropical Medicine.
http://www.lshtm.ac.uk/eph/ncde/cancersurvival/

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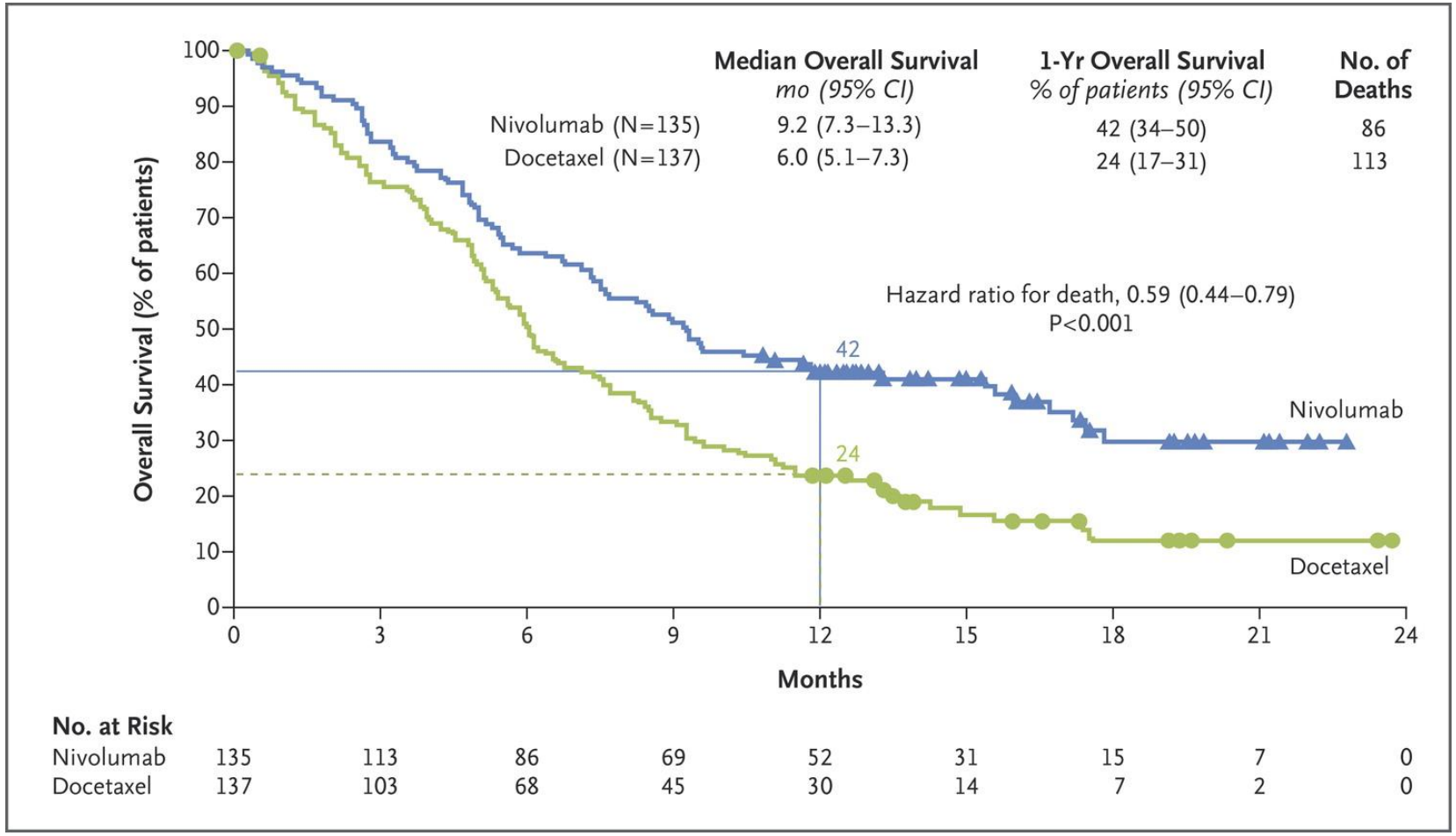
CANCER RESEARCH UK

…clinically relevant progress with immunotherapy

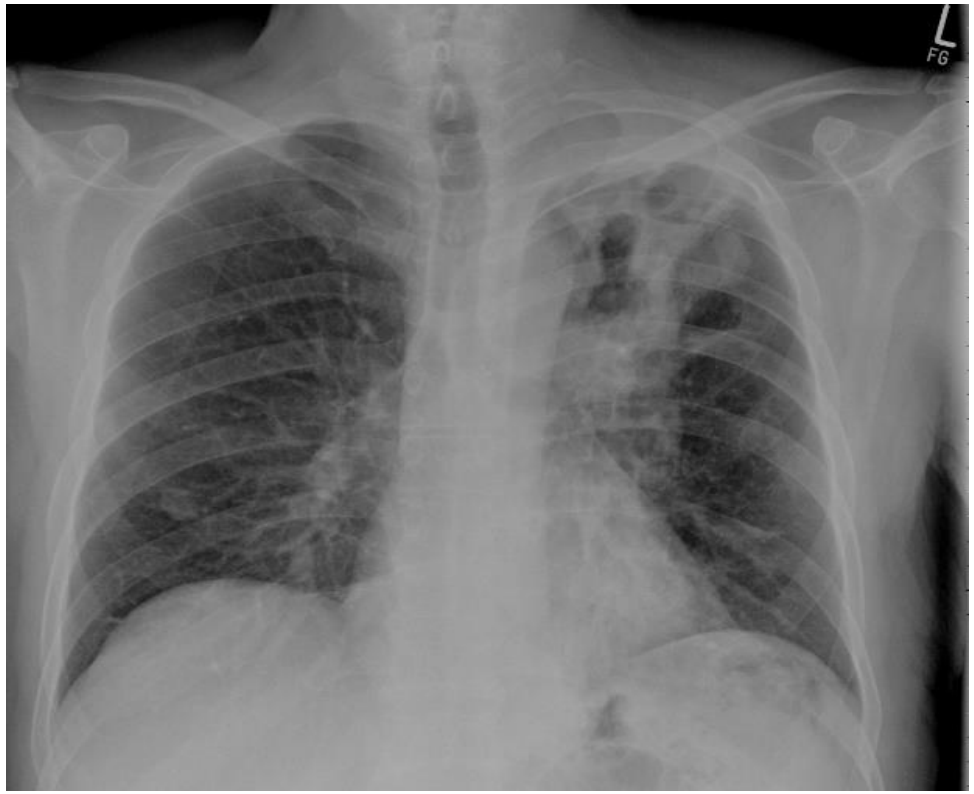


Brahmer J et al. N Engl J Med2015;373:123-135.

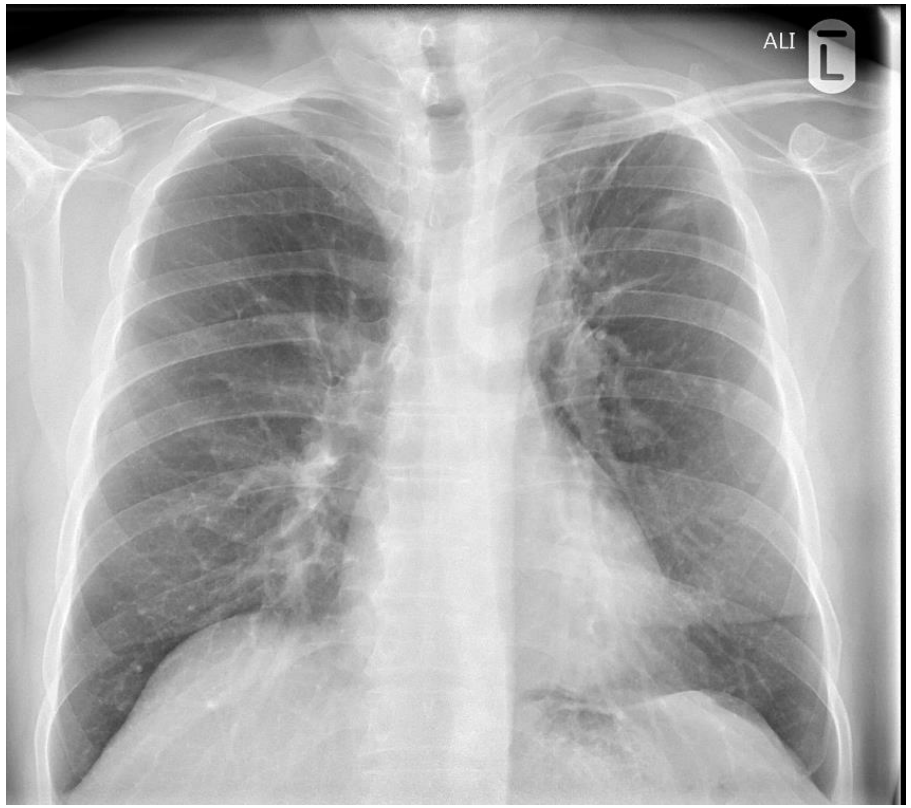
Check point inhibitor treatment

Large volume cancer gets better

Metastatic non-small cell lung cancer, adenocarcinoma



1st June 2016
PS=1
Weight loss, intractable cough



18th of Nov 2016
PS=0
Appetite normal, back to gym

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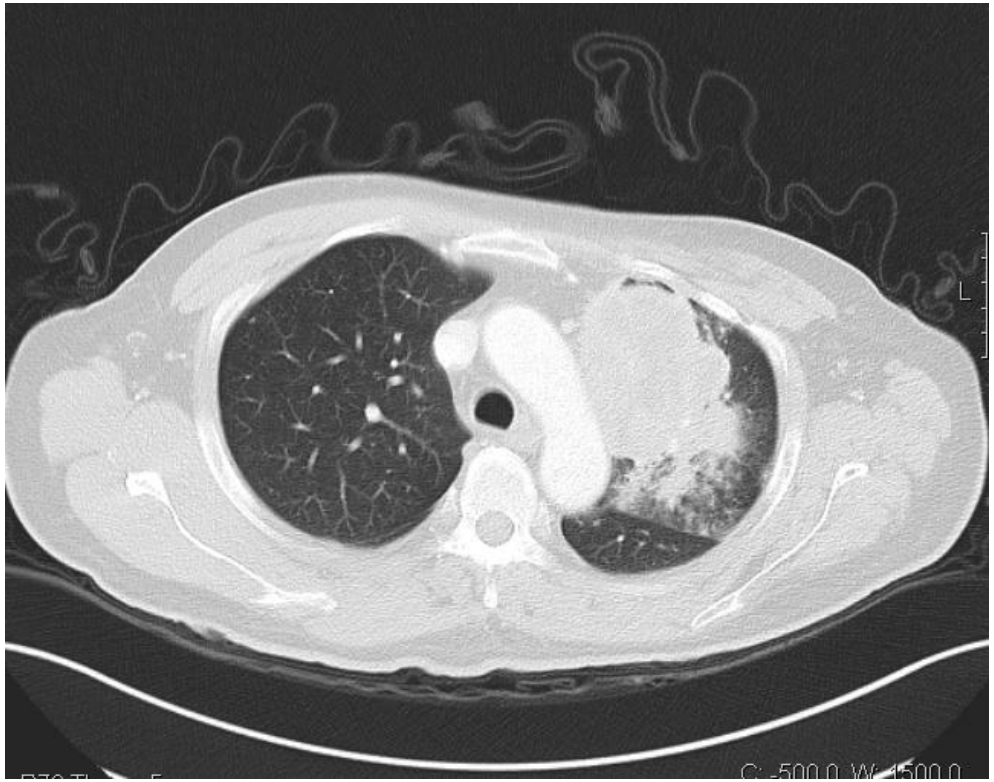
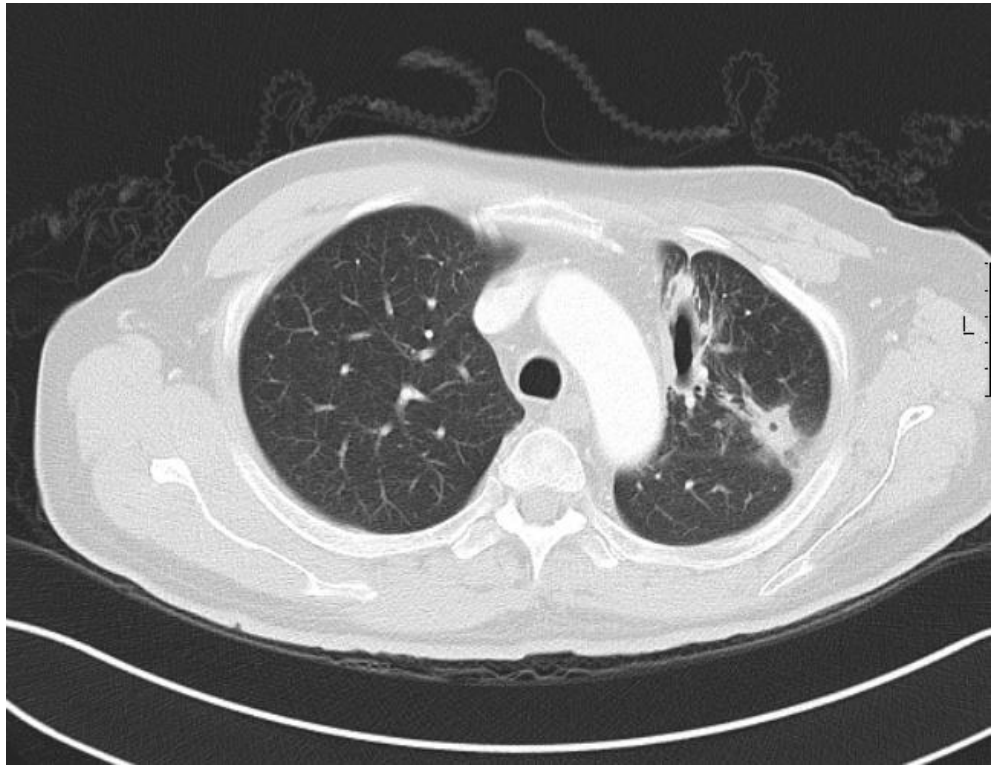
Check point inhibitor treatment

Large volume cancer gets better

Metastatic non-small cell lung cancer, adenocarcinoma, PDL1 >80%



15th April 2016
PS=1
Weight loss, intractable cough



11th of July 2016
PS=0
Appetite normal, no cough

We are in a time of unprecedented change:

Clinical perspective:

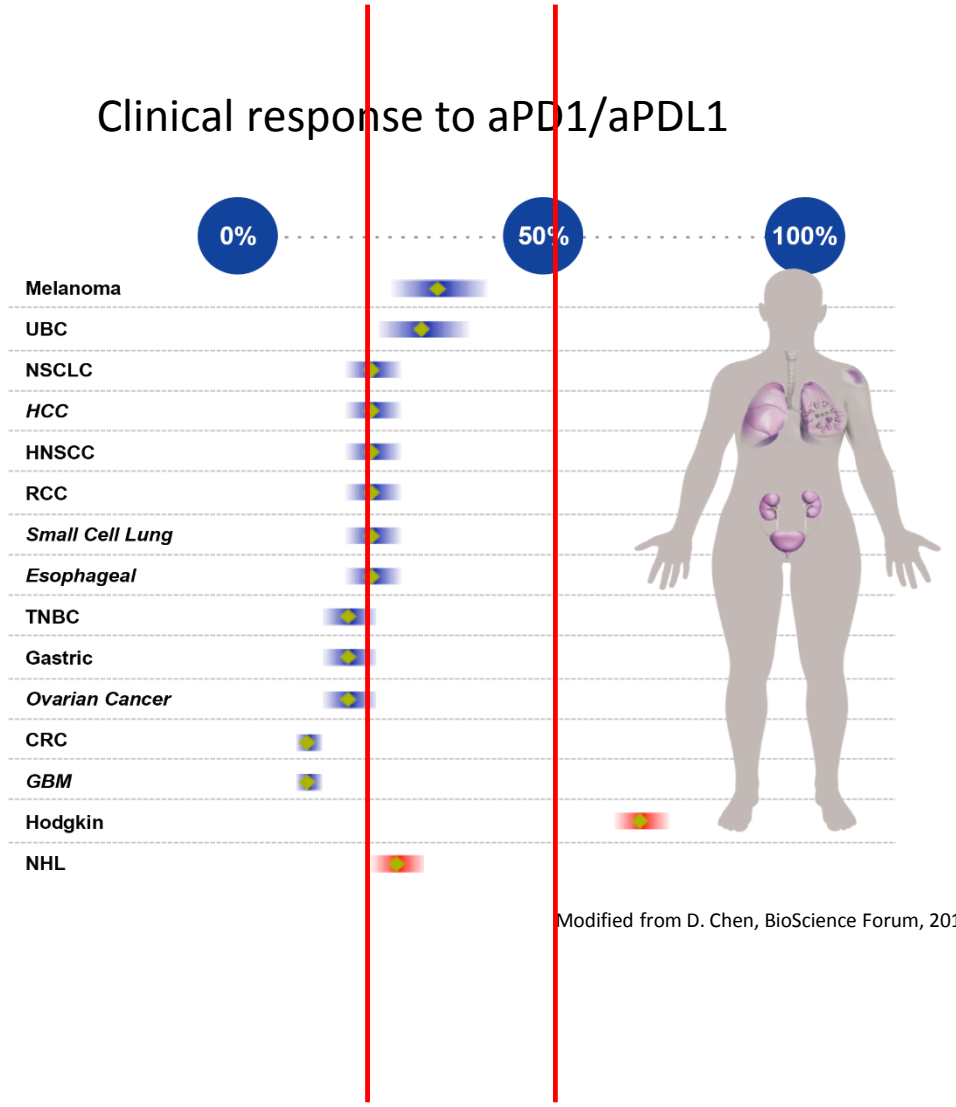
» Immunotherapy has become a standard treatment
» Stunning clinical benefit in responders

Current reference standard:

» PD1/PDL1 inhibition
» single agent efficacy ~25% in many (solid) cancers
» In combination ~50% in melanoma

Predictive tools are currently poor

» Blood based markers of limited value
» The immune events happen in the cancer tissue



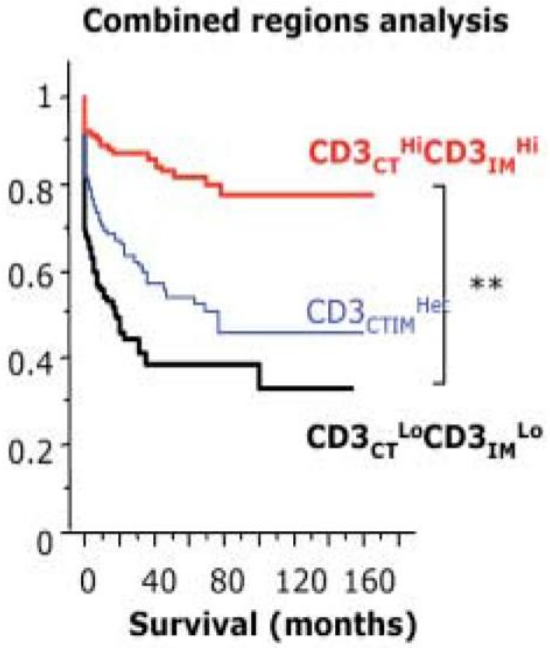
Modified from D. Chen, BioScience Forum, 2015

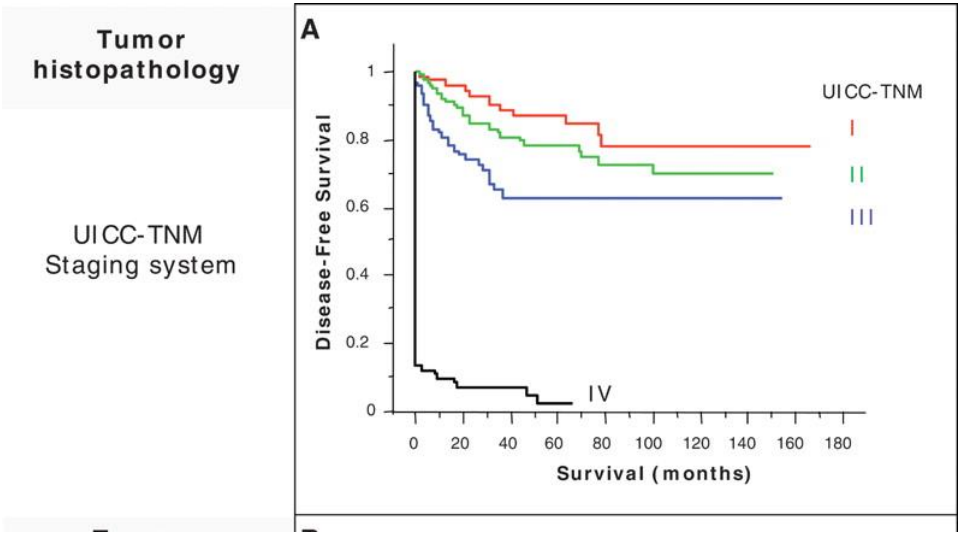
Good for the patient: the immune system is trying

Science
AAAS

Type, Density, and Location of Immune Cells Within Human Colorectal Tumors Predict Clinical Outcome

Jérôme Galon,[1*†] Anne Costes,[1] Fatima Sanchez-Cabo,[2] Amos Kirilovsky,[1] Bernhard Mlecnik,[2] Christine Lagorce-Pagès,[3] Marie Tosolini,[1] Matthieu Camus,[1] Anne Berger,[4] Philippe Wind,[4] Franck Zinzindohoué,[5] Patrick Bruneval,[6] Paul-Henri Cugnenc,[5] Zlatko Trajanoski,[2] Wolf-Herman Fridman,[1,7] Franck Pagès[1,7†]





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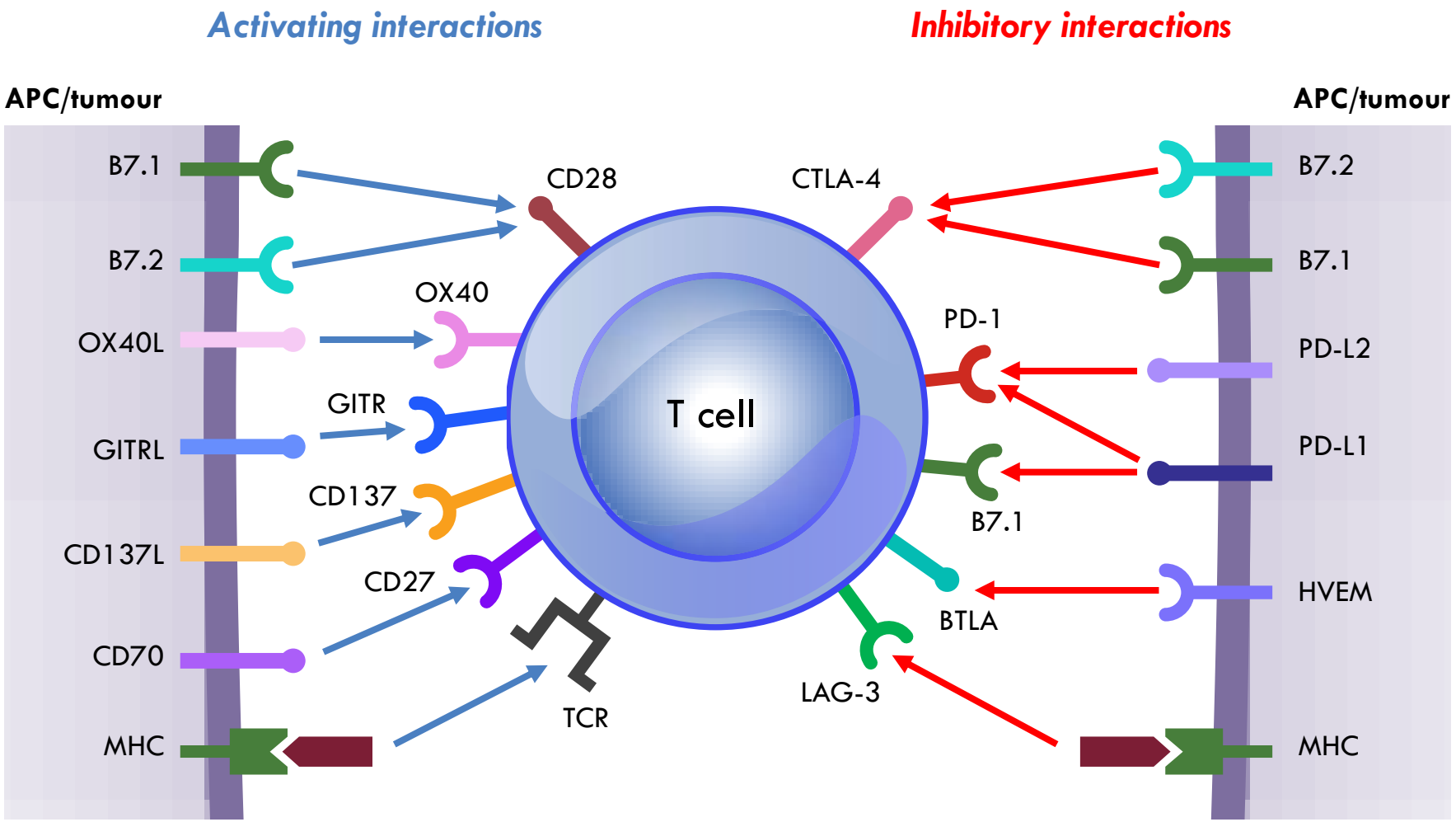
Switching T cells on and off: multiple players



Pardoll DM. Nat Rev Cancer 2012

Combinatorial testing:

- Currently 6 inhibitory targets/ligand pairs N=6
  - (For aPD1/PDL1 alone now about 10 agents)
- Currently 4 activatory targets/ligand pairs N=4
- Combination with
  - Radiotherapy N=1
  - Vaccines N=2
  - TKI N=1
  - Chemo N=2

- **Total variables:** **N=16**

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So many combinations and no way to choose

- 16 variables, assume a 3 drug combo

  = 16 X 15 X 14 = 3360 options *

  Assume 50% obvious nonsense: 1680 trials:

- At **500** patients per trial and a cost of **£50 million** per trial

  = **840.000** patients

  = **£84.000** million trial cost = **£84** billion

  Assume 20 trials per annum

  = **64** years

  Gulp!!!

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* n!/(n-r)!
n= number of options, r = elements in combo

Too many options!

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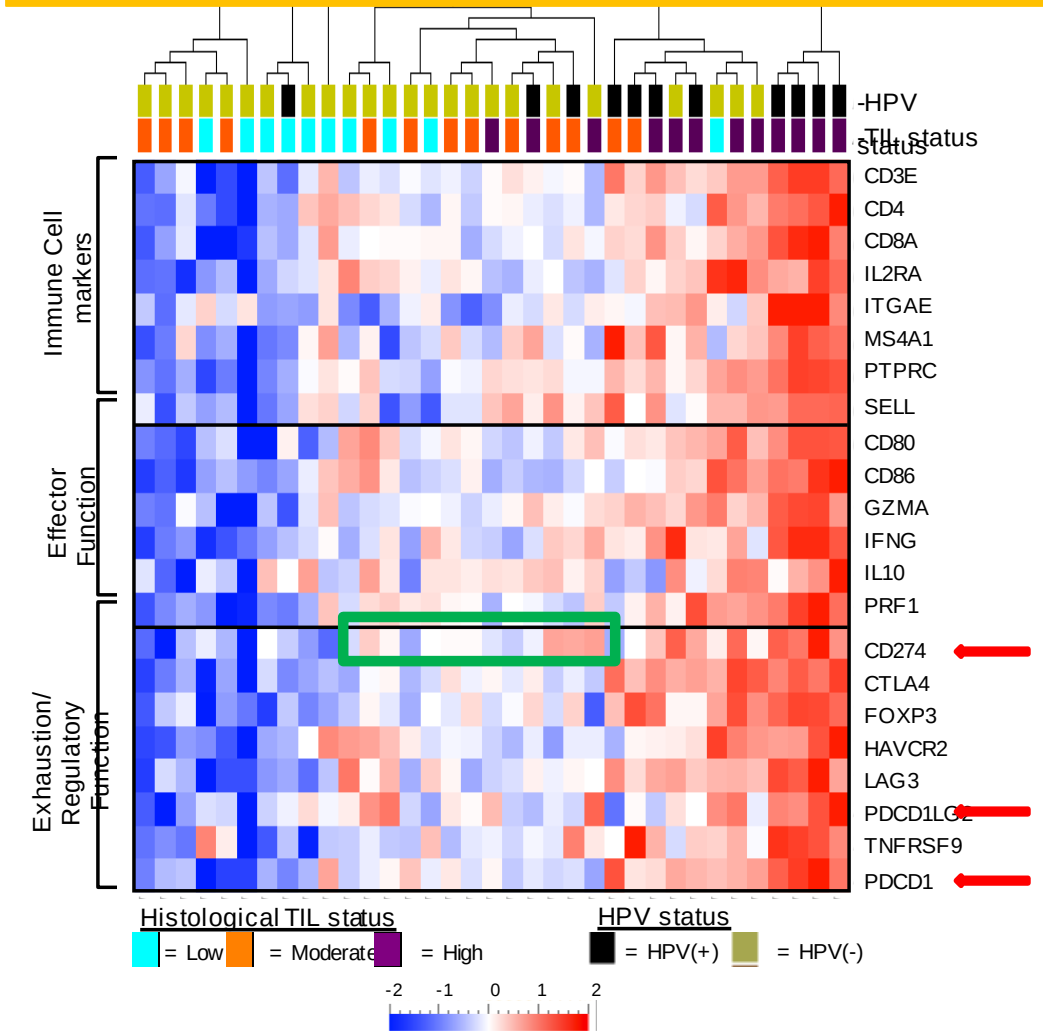
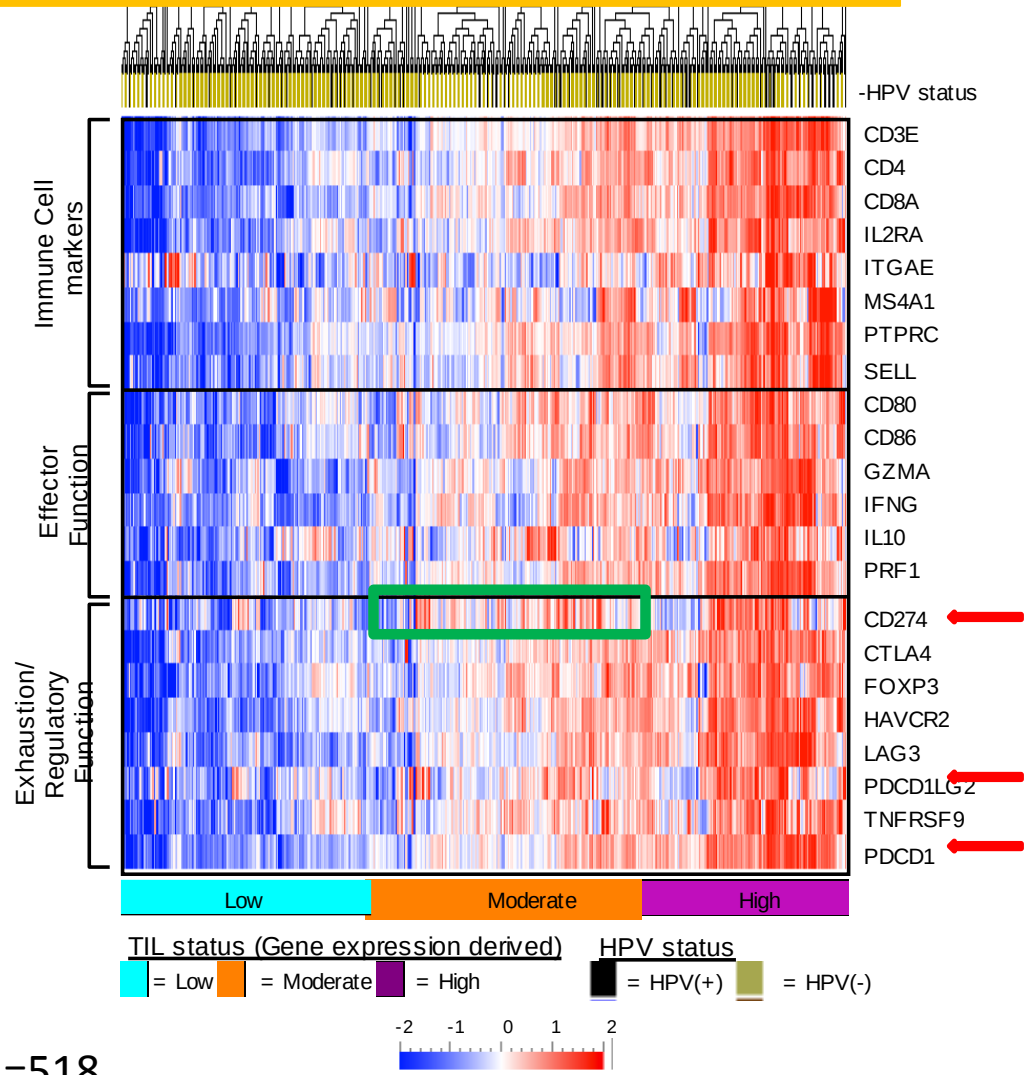
Immune engagement can be read out!

Key diagnostic information is right there



HNSCC, N=35



HNSCC, N=518

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The prediction

The transcriptome contains valuable information about key genes

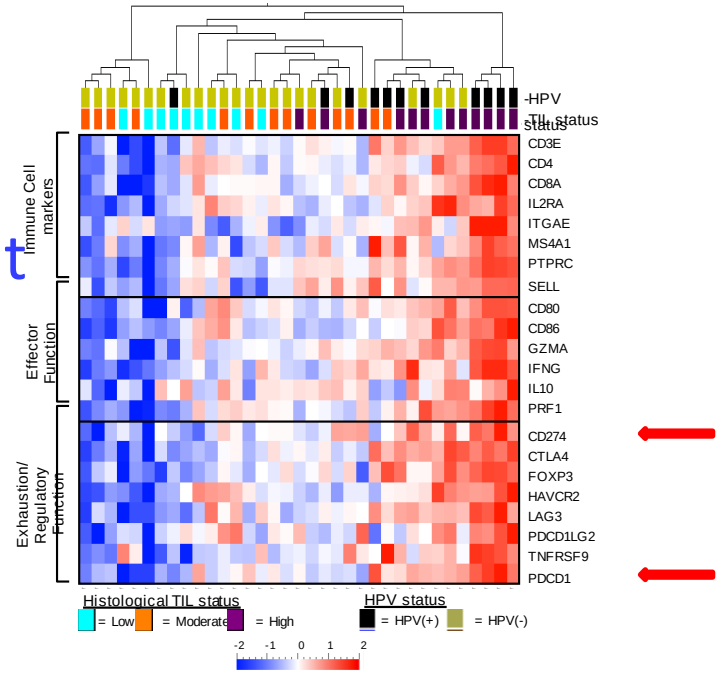
These patients will **relapse early**

- And not respond to aPD1 treatment

These patients will **relapse late**

or not at all

- And respond to aPD1 treatment



We should know this for our patients

The prediction

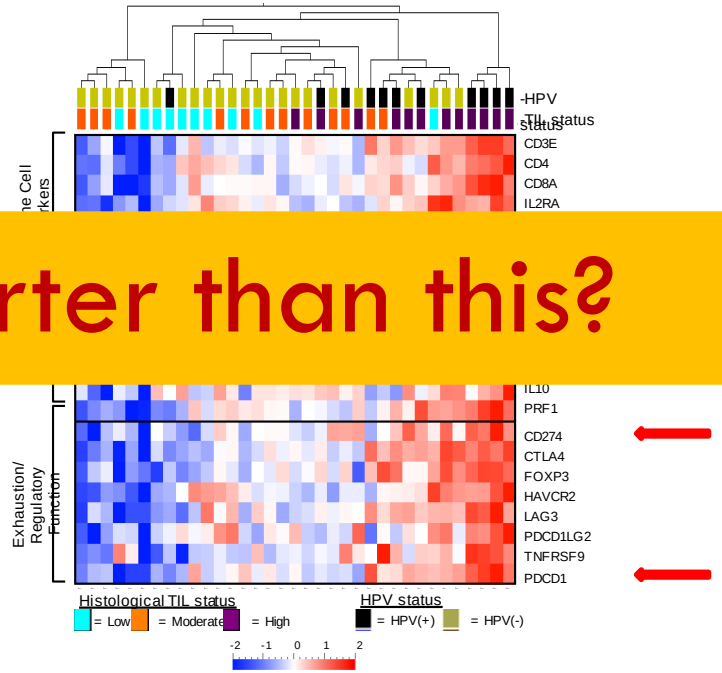
The transcriptome contains valuable information about key genes

These patients will **relapse early**

Can we be smarter than this?

or not at all

- And respond to aPD1 treatment

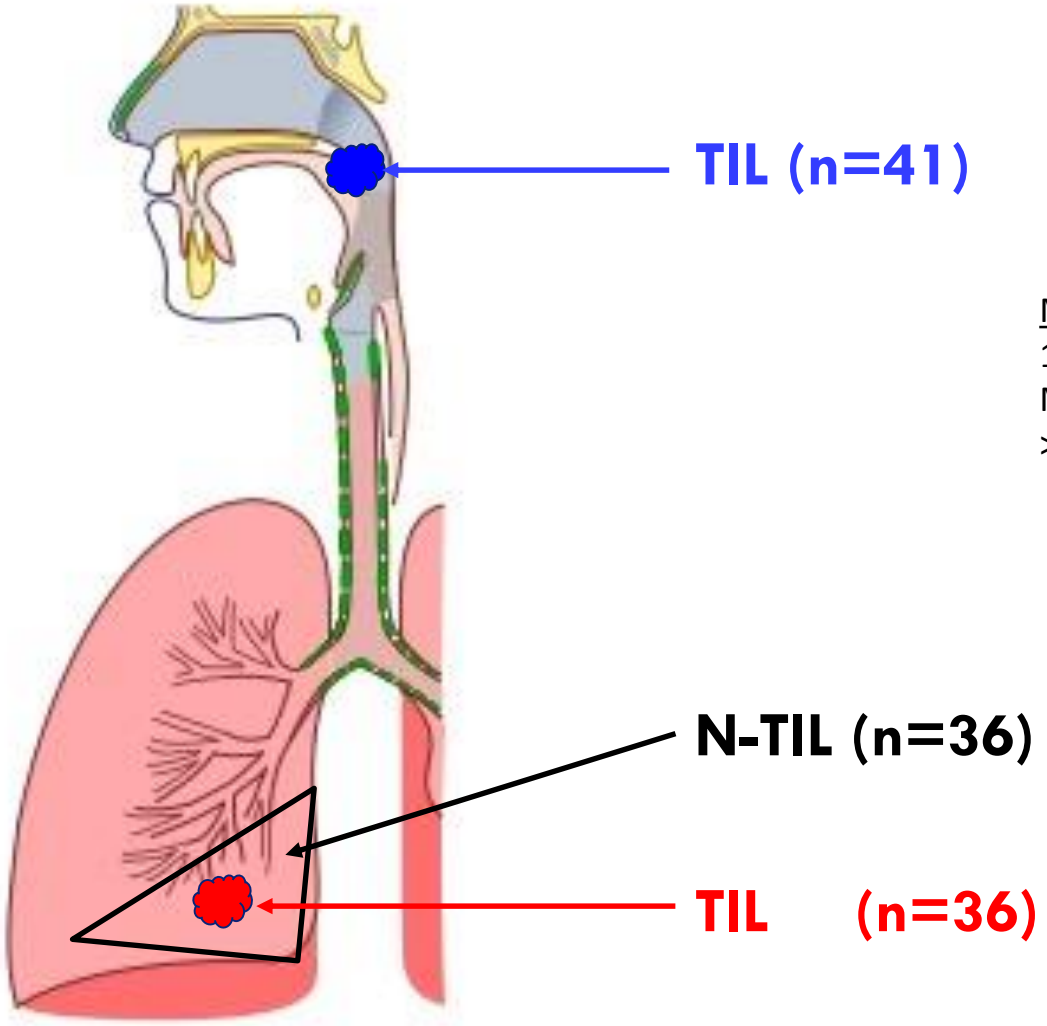


We should know this for our patients

CD8 TIL evaluation in lung cancer and HNSCC

HNSCC

Oral cavity, oropharynx



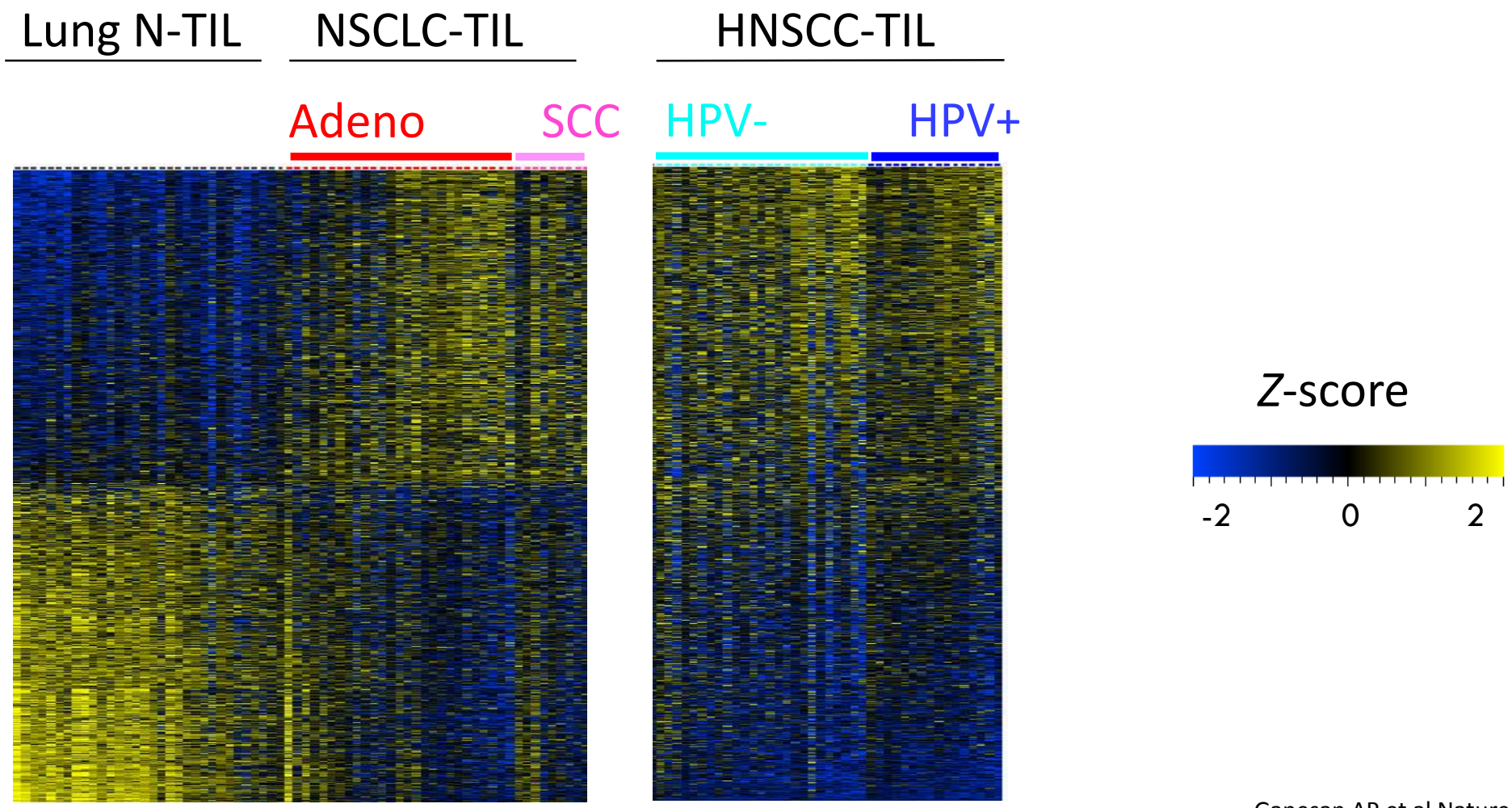
NSCLC

Methods
1000 -10000 CD8 T cells
Micro-scaled RNA-Seq assay[1,2]
>100 CD8 transcriptomes

[1] Seumois G N.Immunol; 2014
[2] Engel I, N.Immunol 2016

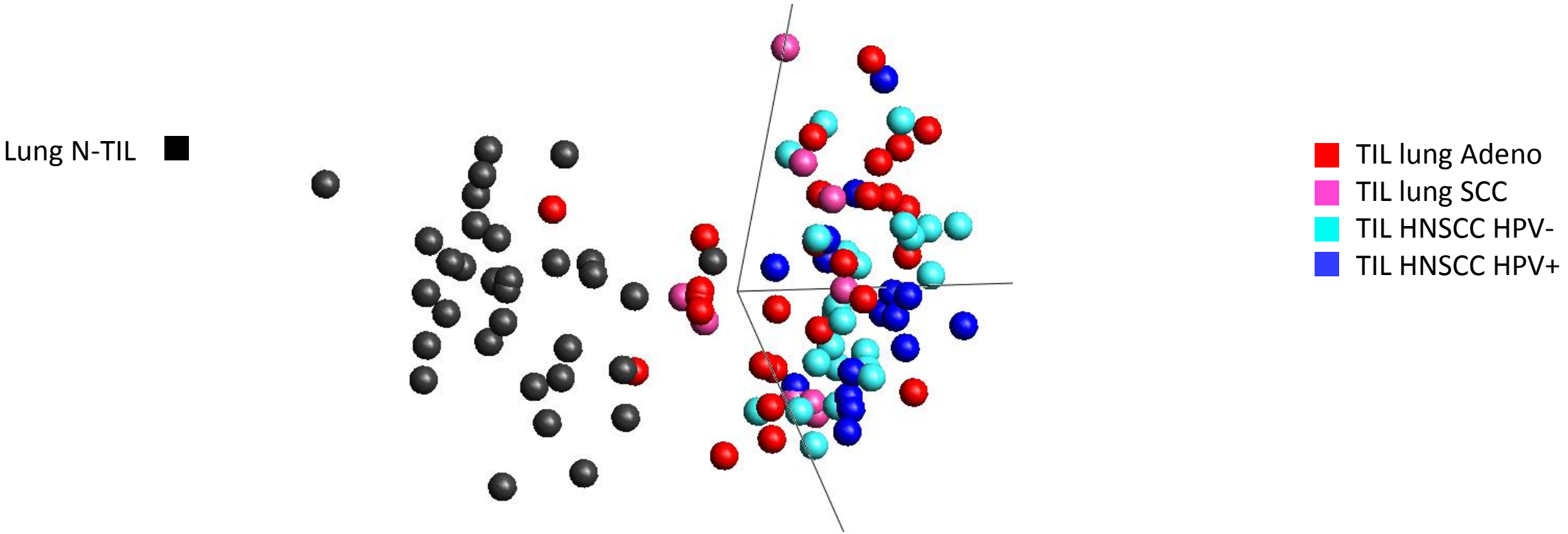
Ganesan, Nat Immunology in press

A defining transcriptional profile of CD8 TILs



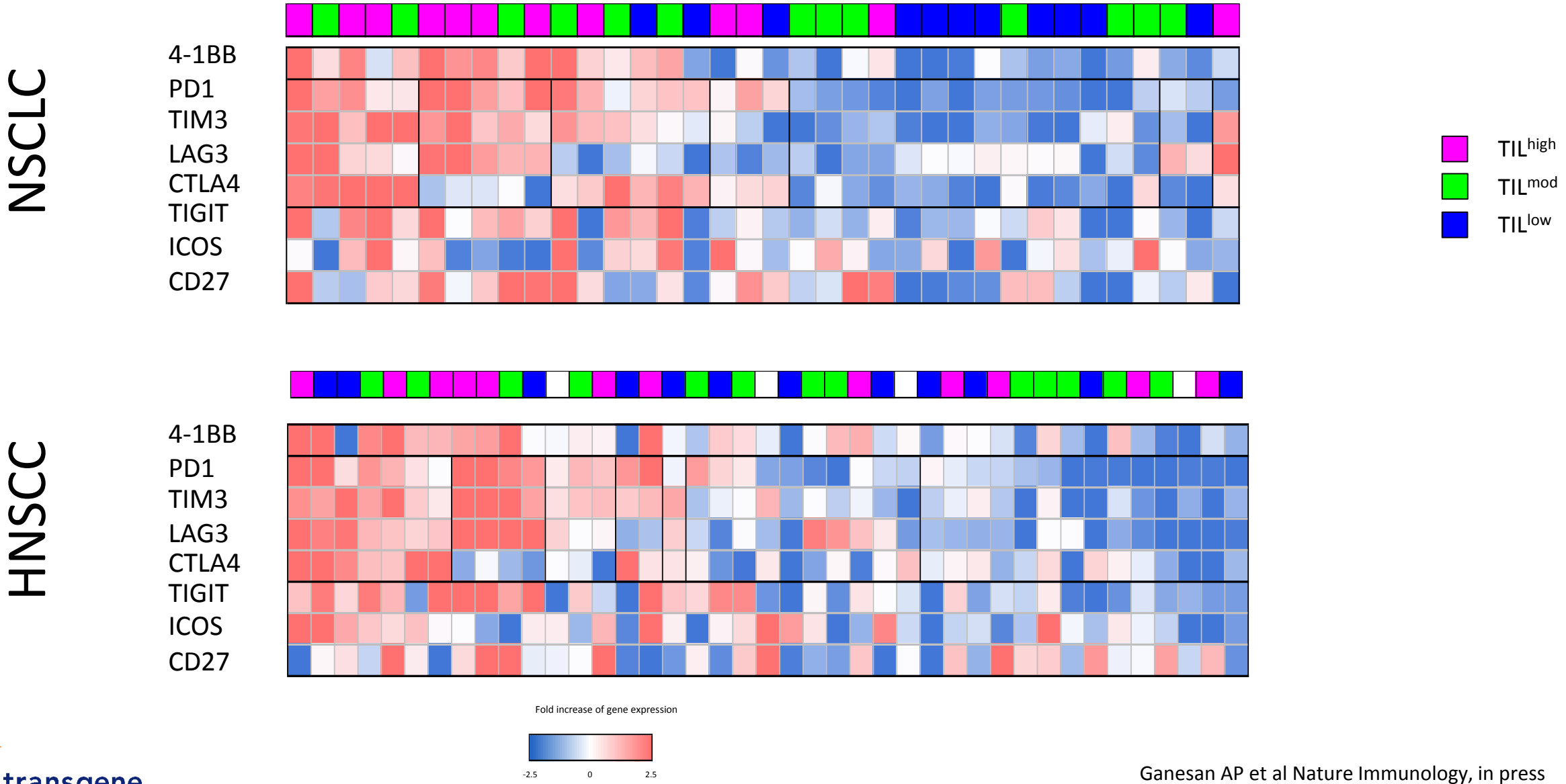
Ganesan AP et al Nature Immunology, in press

Core signature conserved across tumor subtypes



Ganesan AP et al Nature Immunology, in press

Key genes are co-expressed



Ganesan AP et al Nature Immunology, in press

We have learned:

T cells in cancer look similar between cancer types

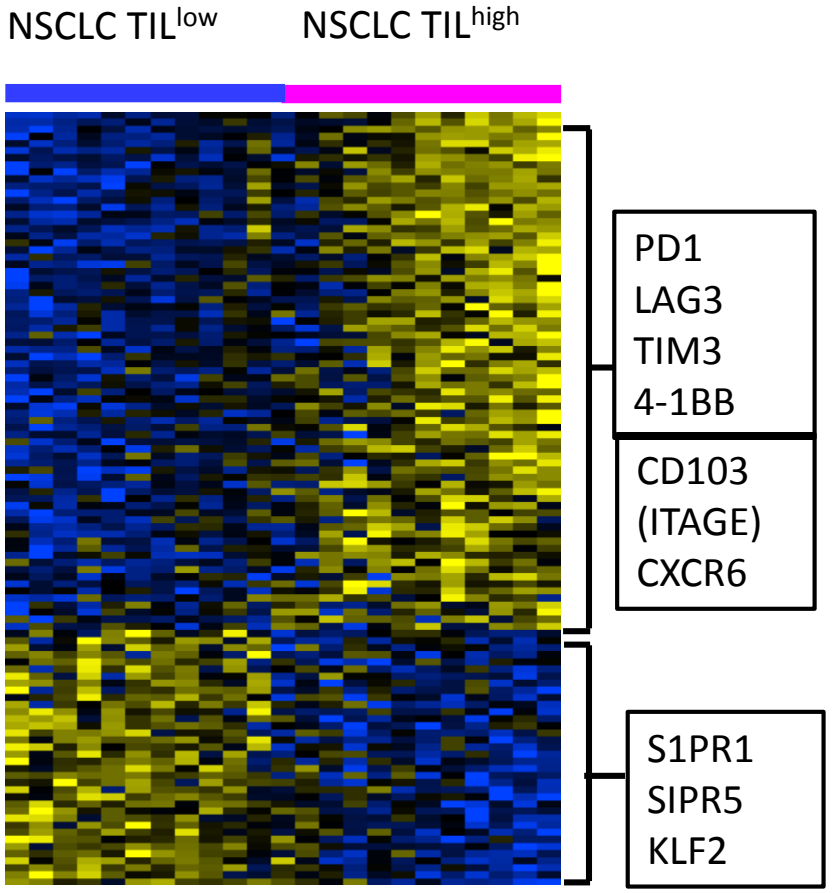
- This means that we can use the same treatments in different cancers

T cells between patients look very different

- That means we will need to use different treatments for different patients

Information is readily accessible by examining the immune cells!

TIL-HIGH VS LOW



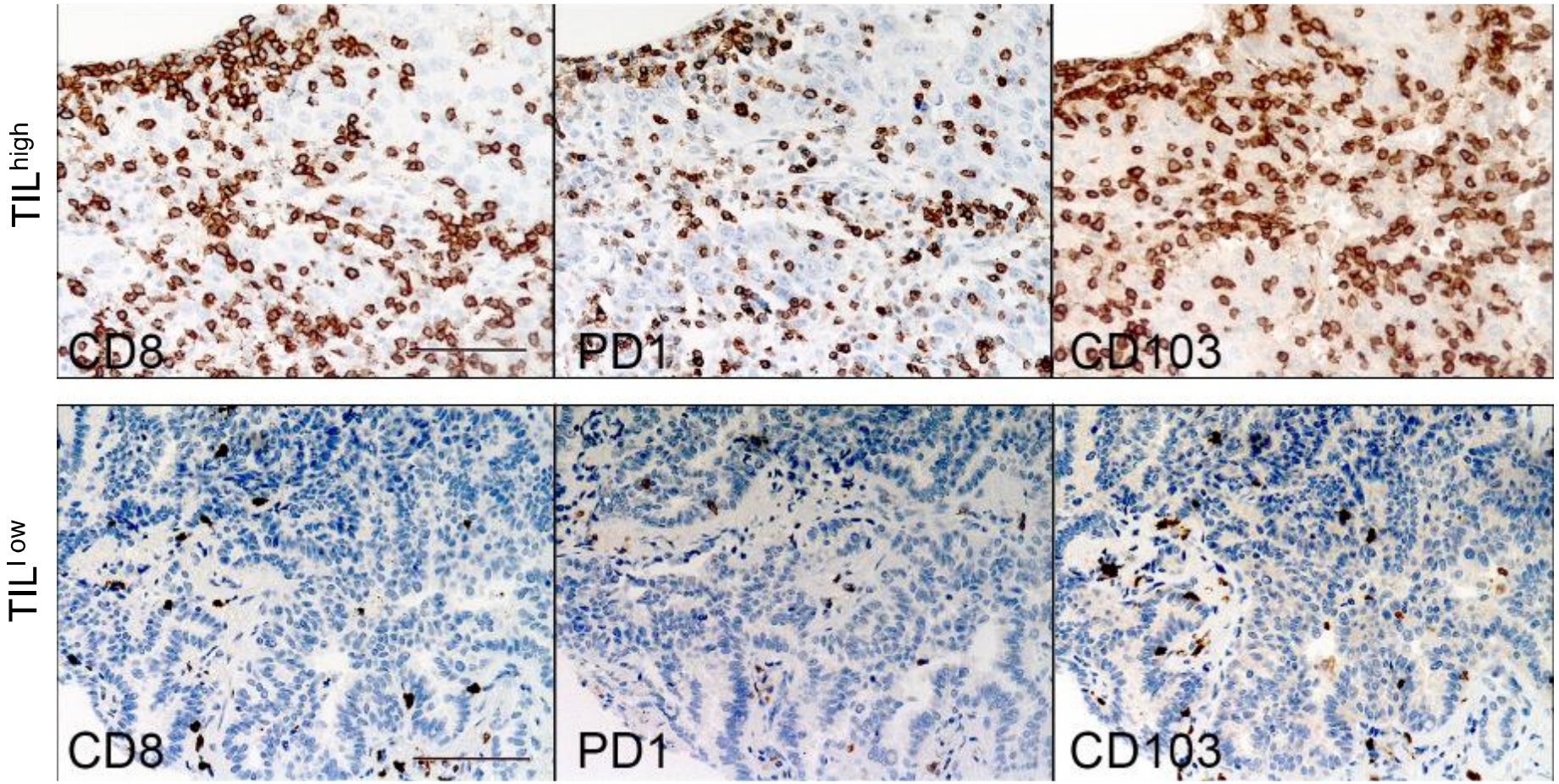
>150 differentially expressed genes

Key differences TIL low vs TIL high

- TCR engagement
- TRM signature
  - Gain of CD103
    - (binds E-cadherin on epithelium)
  - Loss of KLF2
  - Loss of S1PR1

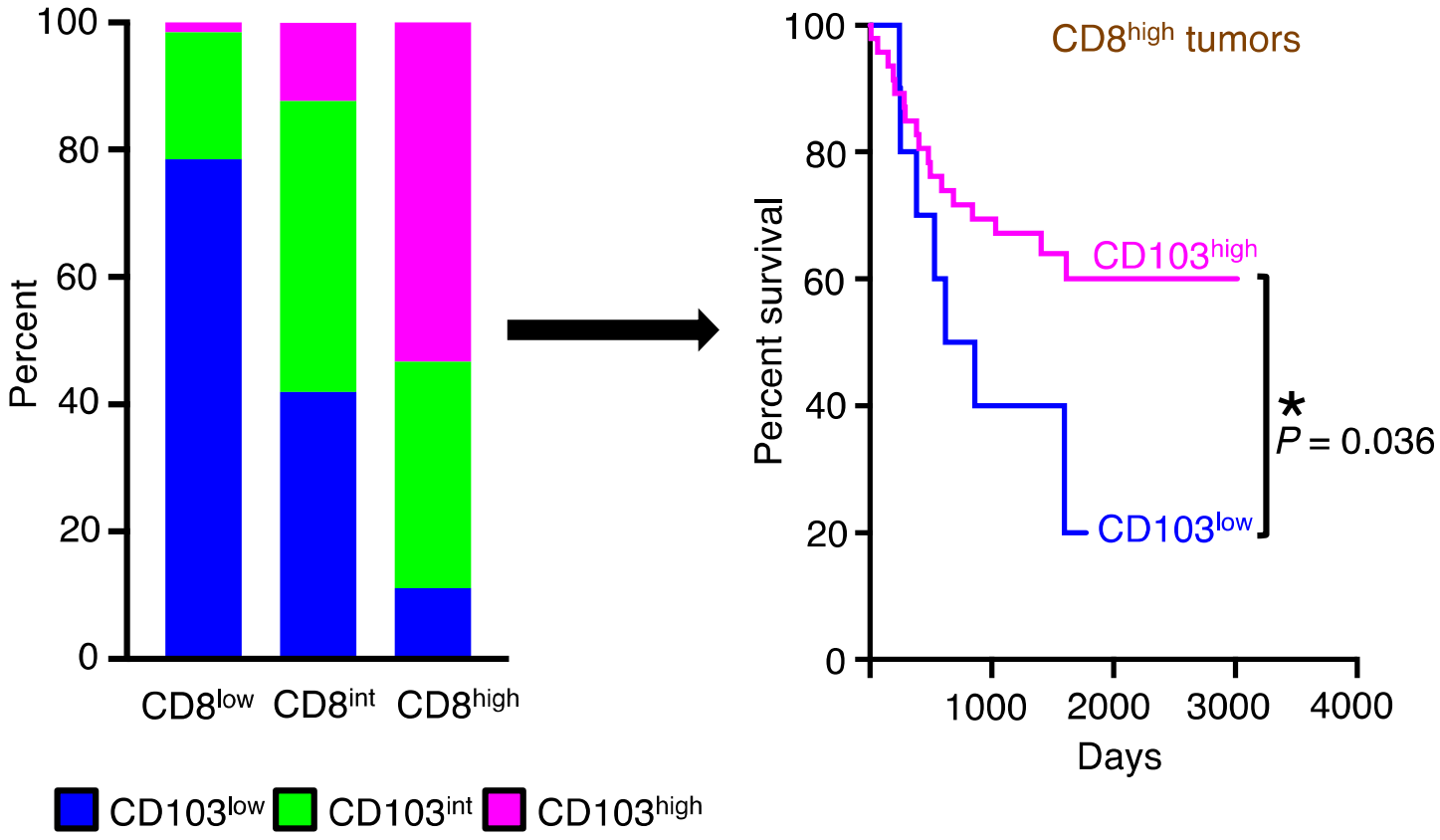
Ganesan AP et al Nature Immunology, in press

TIL: CD8 and CD103+ density correlate



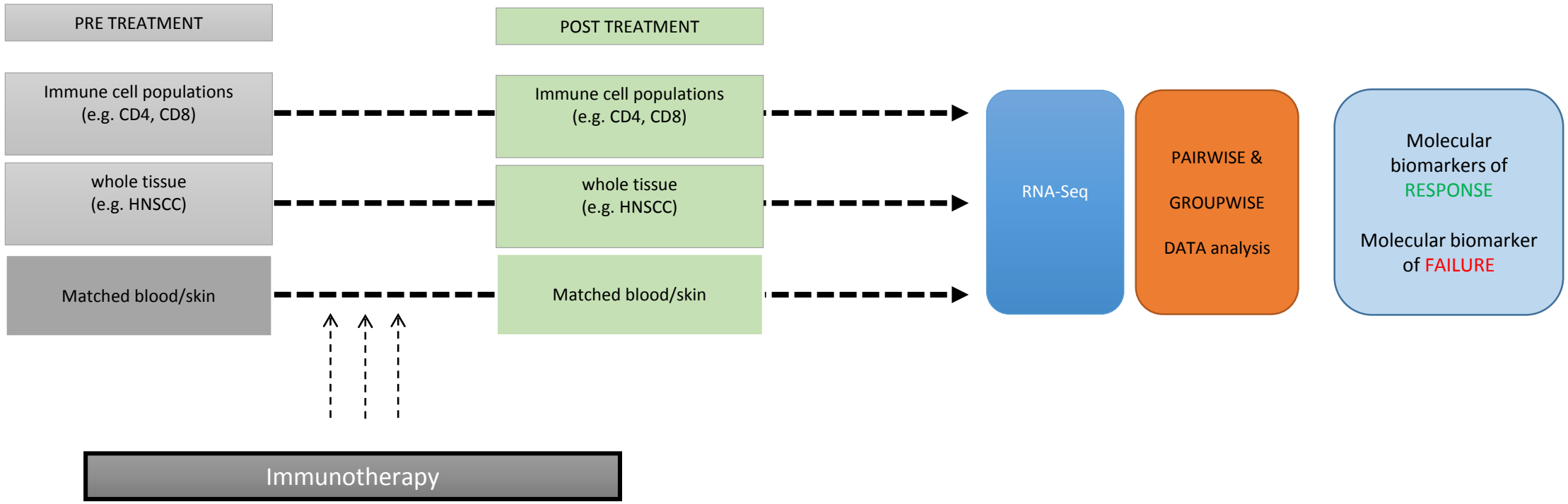
Ganesan AP et al (accepted Nature Immunology)

CD103/TRM: better predictor of survival than CD8

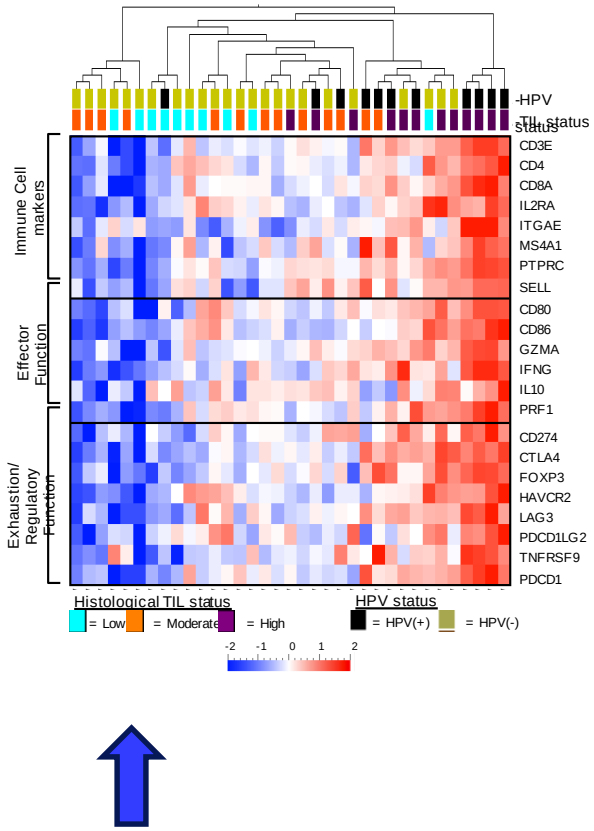


Ganesan AP et al Nature Immunology, in press

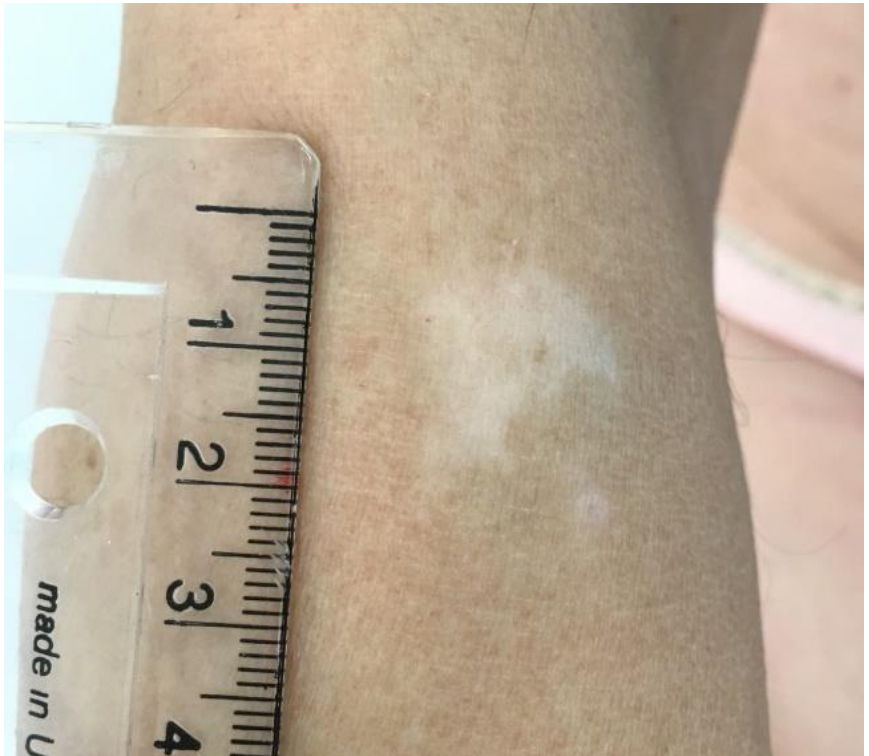
Biomarker driven trials: can we induce TRM?

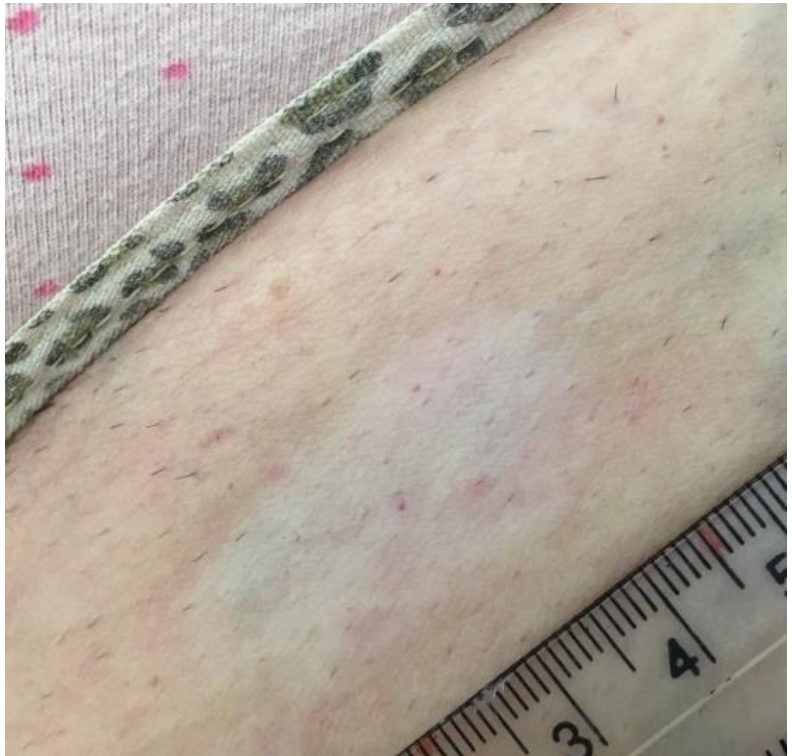


Can we turn immune cold tumours hot?



- Preclinically: vaccination achieves this
- Clinically: viral therapy achieves this
  - In this case intralesional injection of TVEC





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What are appealing targets for vaccine?

Shared antigens: HPV16 E6 and E7

- No central tolerance
- ‘Foreign’ targets
- Known immunogenicity

Well documented TAAs: MUC1

- Strong clinical data

Patient specific antigens

- Derived from mutations
- Unique to each patient
  - = no expected toxicity

Mutanome targeting - feasibility experiment

Patient with NSCLC

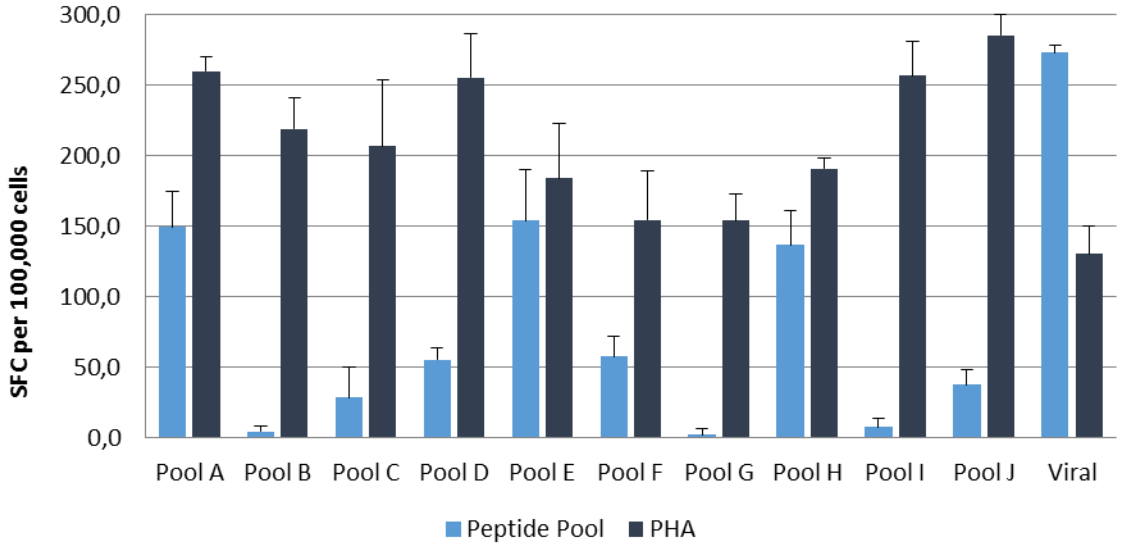
- **Exome before and after chemo**
- **Validate in RNAseq**
  - Finn Cilius, Copenhagen
  - Bjoern Peters, La Jolla
- **29 mutations (0.1%)**
  - 19 shared
- **Peptides tested against PBMC**
  - Bjoern Peters, Schoenberger, La Jolla
  - Short IL2 culture, own method
- **Vaccine made**
  - Trangene, France
  - Testing in HLA A2 mice ongoing
  - Clinically not quick enough

	Variant		Chr	Position	Reference		Alternate (Alt)		Frequency		Effect	Impact	Gene
	ID	Type			Seq	Protein	Seq	Protein	Tumour_Alt	RNA_Alt			
1	82441	snp	chr1	230819343	T	Leu	C	Ser	0.26	0.5	Missense	Moderate	COG2
	63092	snp	chr1	230819343	T	Leu	C	Ser	0.34	0.37	Missense	Moderate	COG2
2	149259	snp	chr11	33308043	T	Val	C	Ala	0.36	0.28	Missense	Moderate	HIPK3
	117923	snp	chr11	33308043	T	Val	C	Ala	0.3	0.29	Missense	Moderate	HIPK3
3	152937	snp	chr11	47198391	G	Pro	C	Arg	0.29	0.19	Missense	Moderate	ARFGAP2
	120874	snp	chr11	47198391	G	Pro	C	Arg	0.34	0.42	Missense	Moderate	ARFGAP2
4	221447	snp	chr12	89891065	C	Arg	T	Lys	0.53	0.48	Missense	Moderate	POC1B
5*	221447	snp	chr12	89891065	C	Arg	T	Lys	0.53	0.48	Missense	Moderate	POC1B
	173774	snp	chr12	89891065	C	Arg	T	Lys	0.49	0.35	Missense	Moderate	POC1B
6	364840	snp	chr16	67208095	C	Pro	T	Leu	0.31	0.38	Missense	Moderate	NOL3
7*	364840	snp	chr16	67208095	C	Pro	T	Leu	0.31	0.38	Missense	Moderate	NOL3
	280999	snp	chr16	67208095	C	Pro	T	Leu	0.35	0.42	Missense	Moderate	NOL3
8	398915	snp	chr17	37566375	G	Pro	T	Gln	0.36	0.45	Missense	Moderate	MED1
	305562	snp	chr17	37566375	G	Pro	T	Gln	0.31	0.34	Missense	Moderate	MED1
9	448386	snp	chr19	1912926	C	Leu	G	Val	0.28	0.69	Missense	Moderate	ADAT3
	341992	snp	chr19	1912926	C	Leu	G	Val	0.48	0.87	Missense	Moderate	ADAT3
10	464252	del	chr19	10597378	TG	Val	T	fs	0.48	0.74	Frameshift	High	KEAP1
	351328	del	chr19	10597378	TG	Val	T	fs	0.44	0.35	Frameshift	High	KEAP1
11	482538	snp	chr19	21713480	C	Pro	A	Thr	0.43	0.77	Missense	Moderate	ZNF429
12*	482538	snp	chr19	21713480	C	Pro	A	Thr	0.43	0.77	Missense	Moderate	ZNF429
	362061	snp	chr19	21713480	C	Pro	A	Thr	0.44	0.81	Missense	Moderate	ZNF429
13	505745	snp	chr19	49950714	C	Met	T	Ile	0.26	0.12	Missense	Moderate	PIH1D1
	378240	snp	chr19	49950714	C	Met	T	Ile	0.24	0.16	Missense	Moderate	PIH1D1
14	506321	snp	chr19	50357709	C	Ser	T	Leu	0.67	0.61	Missense	Moderate	PTOV1
	378646	snp	chr19	50357709	C	Ser	T	Leu	0.38	0.53	Missense	Moderate	PTOV1
15	647609	snp	chr22	38610488	C	Ser	T	Leu	0.31	0.22	Missense	Moderate	MAFF
16*	647609	snp	chr22	38610488	C	Ser	T	Leu	0.31	0.22	Missense	Moderate	MAFF
17*	647609	snp	chr22	38610488	C	Ser	T	Leu	0.31	0.22	Missense	Moderate	MAFF
	491038	snp	chr22	38610488	C	Ser	T	Leu	0.26	0.32	Missense	Moderate	MAFF
18	652346	snp	chr22	45923798	G	Met	T	Ile	0.16	0.27	Missense	Moderate	FBLN1
	495245	snp	chr22	45923798	G	Met	T	Ile	0.2	0.2	Missense	Moderate	FBLN1
19	1036381	snp	chrX	54049260	C	Glu	G	Gln	0.55	0.96	Missense	Moderate	PHF8
	811979	snp	chrX	54049260	C	Glu	G	Gln	0.75	0.84	Missense	Moderate	PHF8
20	572009	snp	chr2	201757010	G	Arg	T	Leu	0.19	0.24	Missense	Moderate	NIF3L1
21	704363	snp	chr3	174814651	G	Asp	A	Asn	0.2	0.25	Missense	Moderate	NAALADL2
22	848795	snp	chr6	127765276	C	Arg	T	Gln	0.39	0.67	Missense	Moderate	KIAA0408
23	1004854	snp	chr9	139750198	G	Glu	C	Gln	0.25	0.75	Missense	Moderate	MAMDC4
24	479636	snp	chr21	47545888	G	Arg	A	His	0.4	<0.01	Missense	Moderate	COL6A2
25	728317	snp	chr8	39009041	G	Asp	T	Tyr	0.52	0.5	Missense	Moderate	ADAM32
26	549567	snp	chr4	16597450	C	Gly	A	Val	0.33	0.09	Missense	Moderate	LDB2
27	319278	snp	chr17	74017771	G	Ala	A	Val	0.4	0.52	Missense	Moderate	EVPL
28	706385	snp	chr7	116412043	G	Asp	A	Asn	0.65	0.12	Missense	Moderate	MET
29	804992	snp	chrMT	13004	A	Lys	T	Ile	0.43	0.4	Missense	Moderate	MT-ND5

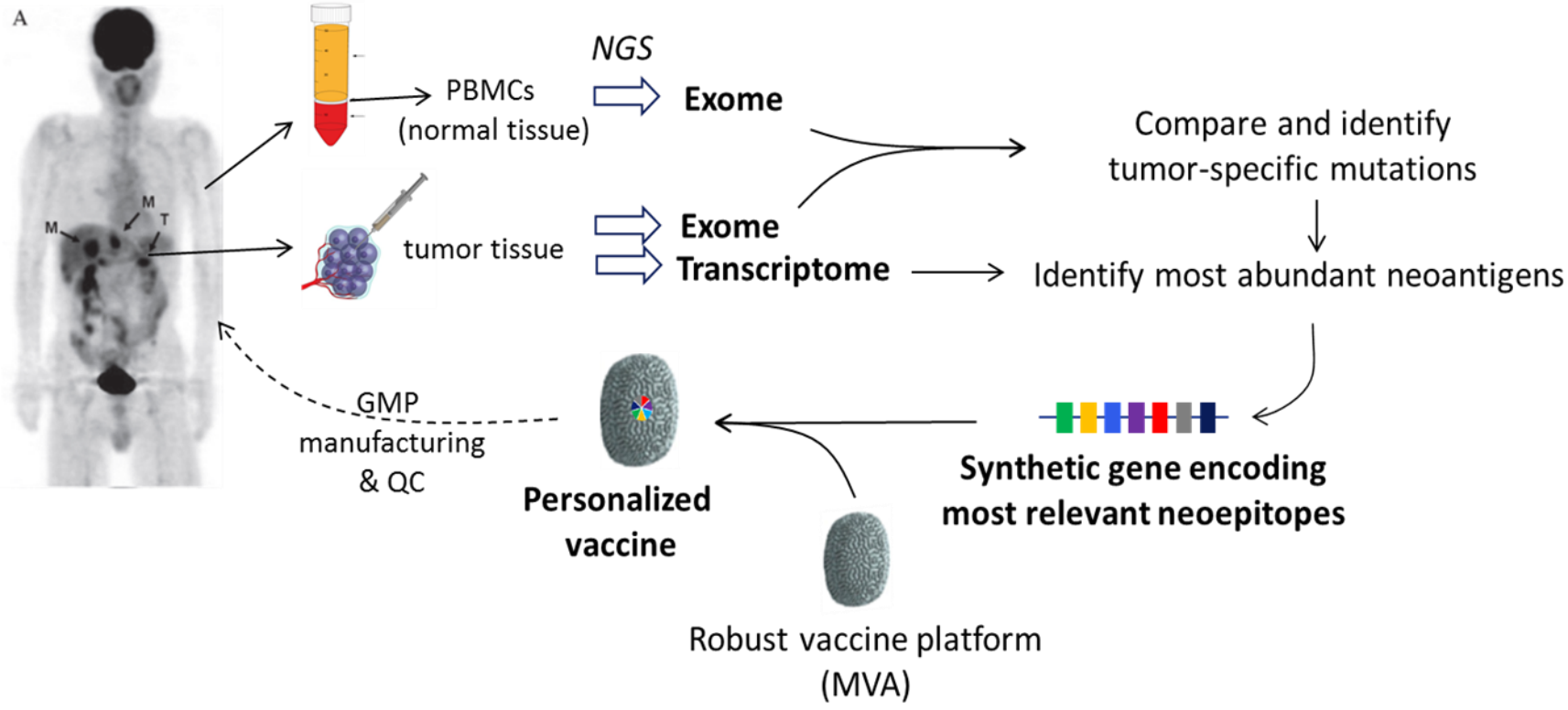
Mutanome targeting - feasibility experiment

	Mean SFC per 100,000 cells	SDEV	runDFR (2x) response
Pool A	**149.7**	25.0	Positive
Pool B	4.7	3.8	Negative
Pool C	**28.7**	21.7	Positive
Pool D	**55.3**	8.9	Positive
Pool E	**154.3**	36.3	Positive
Pool F	**58.0**	13.9	Positive
Pool G	2.3	4.2	Negative
Pool H	**136.7**	24.5	Positive
Pool I	7.7	6.4	Negative
Pool J	**37.7**	11.0	Positive
Viral Pool	**273.0**	5.0	Positive
A-PHA	260.0	9.9	Positive
B-PHA	219.3	21.5	Positive
C-PHA	207.0	46.7	Positive
D-PHA	255.3	31.5	Positive
E-PHA	184.0	38.9	Positive
F-PHA	154.7	34.9	Positive
G-PHA	154.3	18.6	Positive
H-PHA	191.0	7.2	Positive
I-PHA	257.0	23.8	Positive
J-PHA	285.7	14.4	Positive
VP-PHA	130.3	20.3	Positive

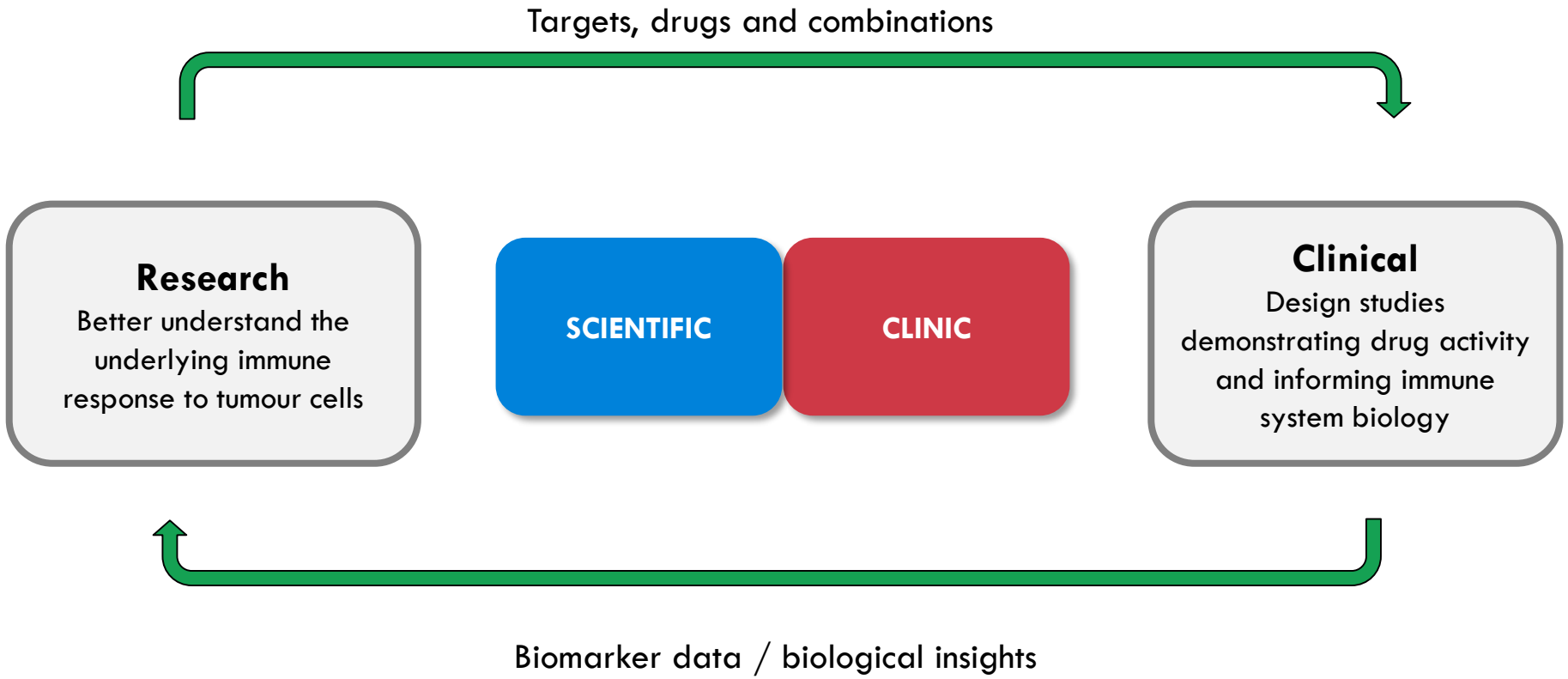
	Pool A	Pool B	Pool C	Pool D	Pool E
Pool F	Pep_1	Pep_2	Pep_3	Pep_4	Pep_5
Pool G	Pep_6	Pep_7	Pep_8	Pep_9	Pep_10
Pool H	Pep_11	Pep_12	Pep_13	Pep_14	Pep_15
Pool I	Pep_16	Pep_17	Pep_18	Pep_19	Pep_20
Pool J	Pep_21	Pep_22	Pep_23	Pep_24	Pep_25

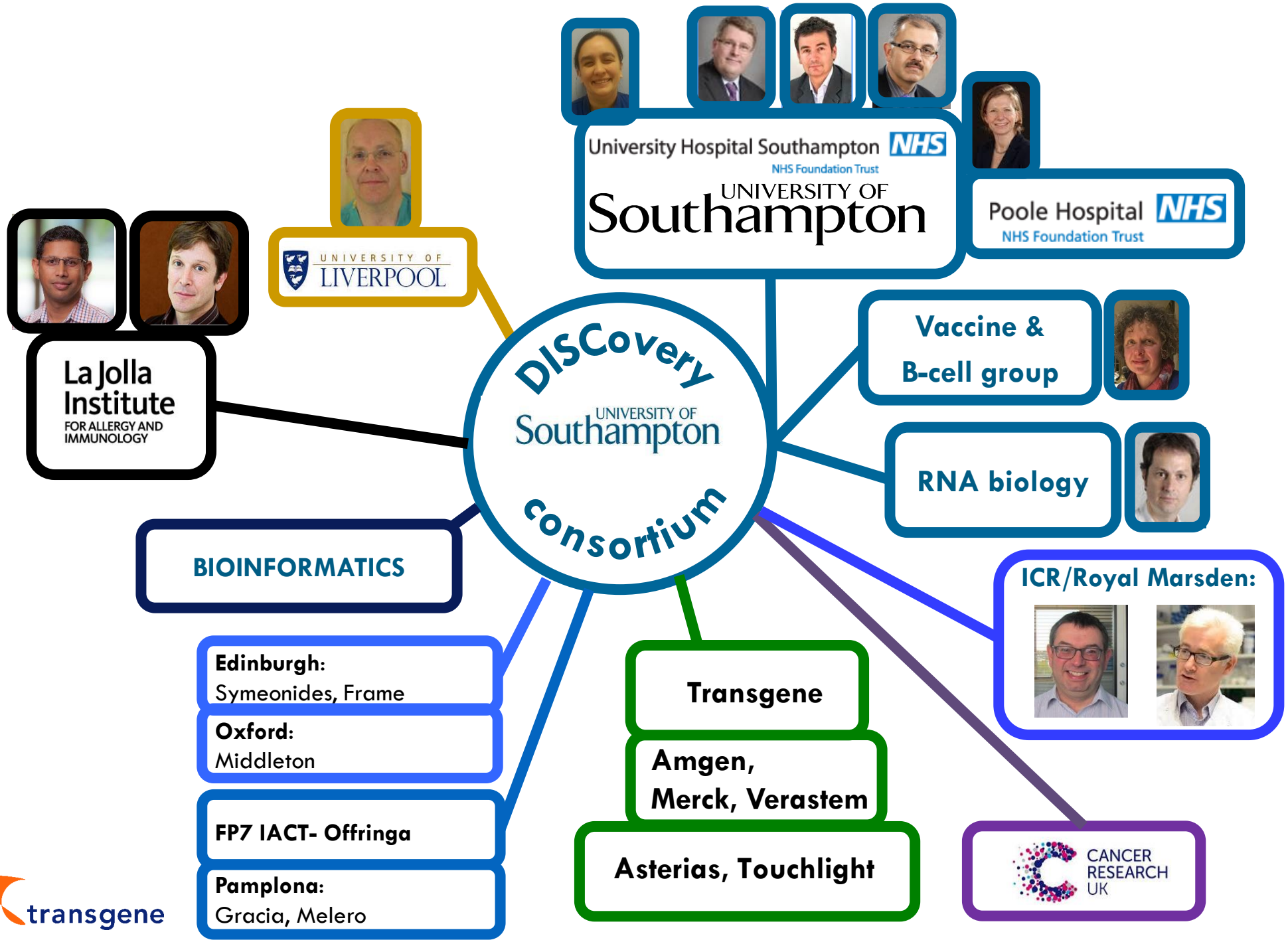


Mutanome targeting – how best to target with vaccination



Summary


Targets, drugs and combinations
Research
Better understand the underlying immune response to tumour cells
SCIENTIFIC
CLINIC
Clinical
Design studies demonstrating drug activity and informing immune system biology
Biomarker data / biological insights



Special mentions:

Preethi Ganesan
Gregory Seumois
Divya Singh
Vijayanand lab

Ben Johnson
Serena Chee

Oliver Wood
James Clarke

Emma King
Aimen Alzetani

Gareth Thomas

transgene

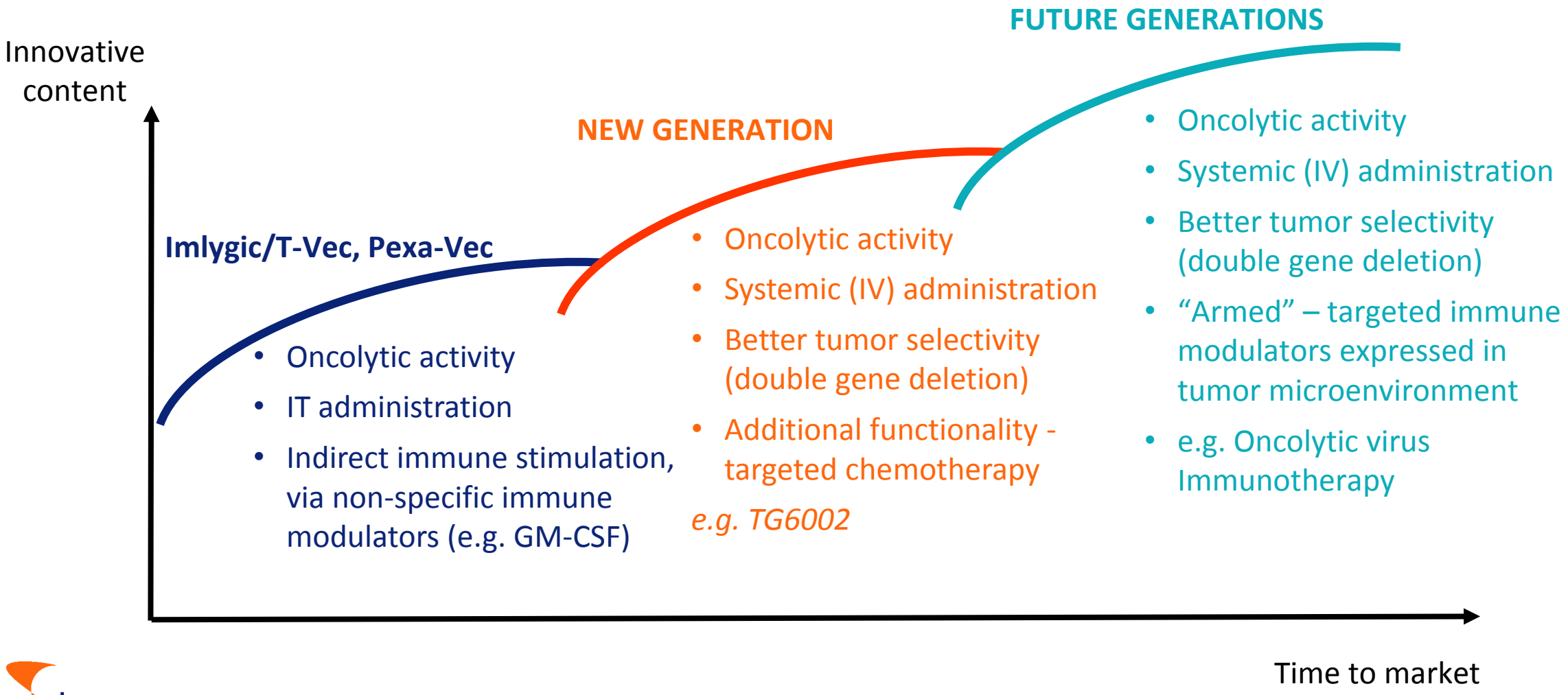
Engineering viruses to create the next generation of immunotherapy

Eric Quéméneur, PharmD, PhD

Executive VP, Chief Scientific Officer, Transgene

transgene

Oncolytic viruses | Transgene's roadmap for success



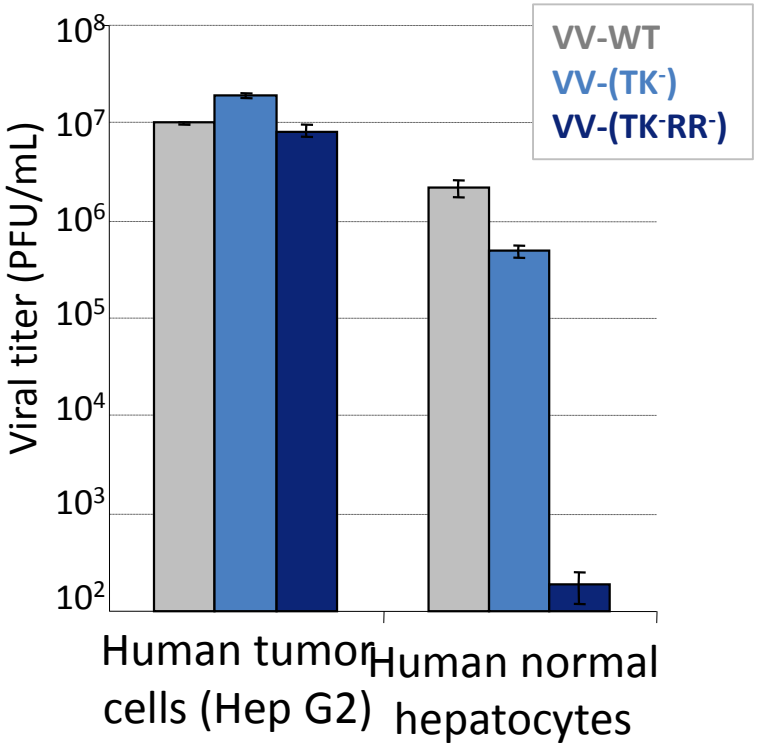
Oncolytic virus | Features of an ideal oncolytic virus

✓	**TUMOR SELECTIVE**	Replication only in tumor cells
✓	**ANTITUMOR IMMUNITY**	Should induce immunogenic cell death and specific immune response
✓	**NO NEUTRALIZATION**	Should not be prone to vector neutralization
✓	**SAFE, IV**	Must be safe, even after systemic delivery (intravenous adm.)
✓	**LARGE CAPACITY**	Must have sufficiently large genome capacity to accommodate multiple transgenes
✓	**NO NUCLEUS INTEGRATION**	Should not integrate into host DNA, and/or be mutagenic

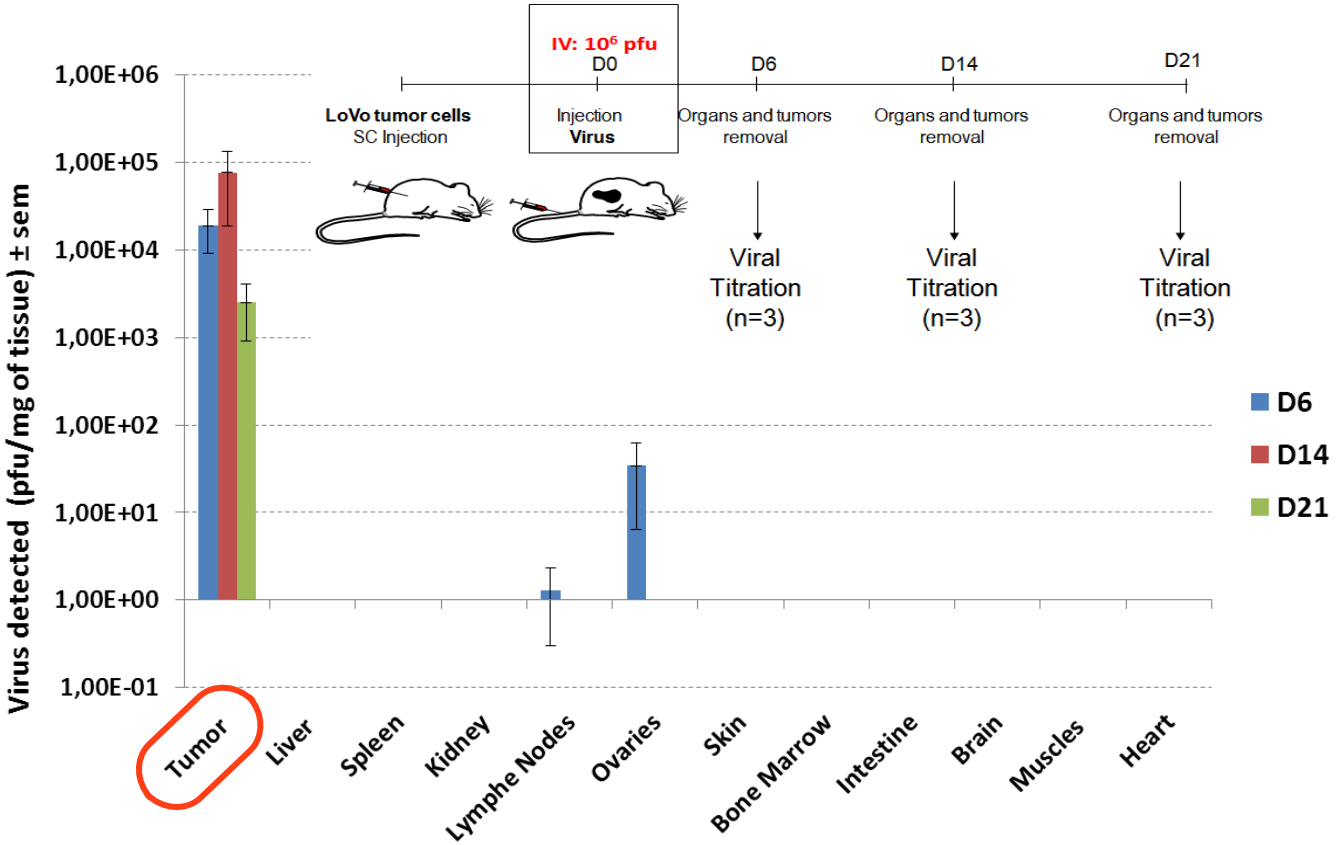
VACCINIA VIRUS MATCHES THESE IDEAL FEATURES

Our patented proprietary backbone ($VV_{COP}^{TK\text{-}RR\text{-}}$) displays an optimal safety profile and therapeutic index

in vitro replication assay



Biodistribution *in CRC tumor-bearing mice*



PK/PD data also available for healthy NHP and tumor-bearing dogs

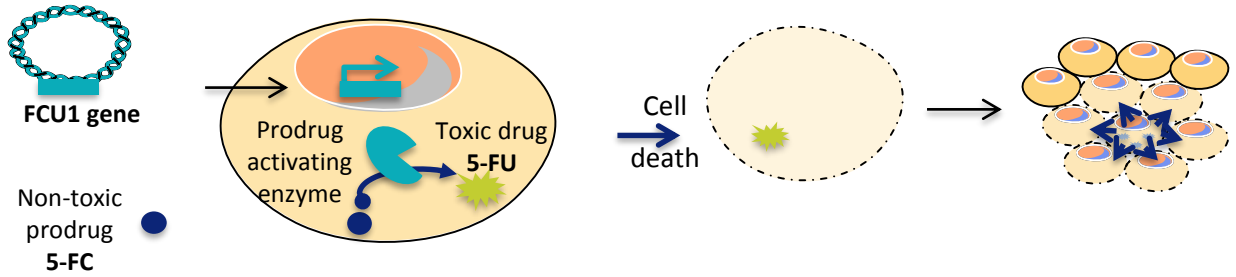
TG6002 | First product from our new generation platform

Improved backbone and advanced therapeutic payload

Superior oncolytic properties with local production of chemotherapy

- Proprietary backbone
- Double gene deletion TK- RR-

- Viral oncolysis
- Targeted chemotherapy



- Phase 1 trial in **glioblastoma**, open label, dose escalation, IV administration
- PI: **Pr J-Y. Delattre** (Pitié Salpêtrière)
- INCA Grant

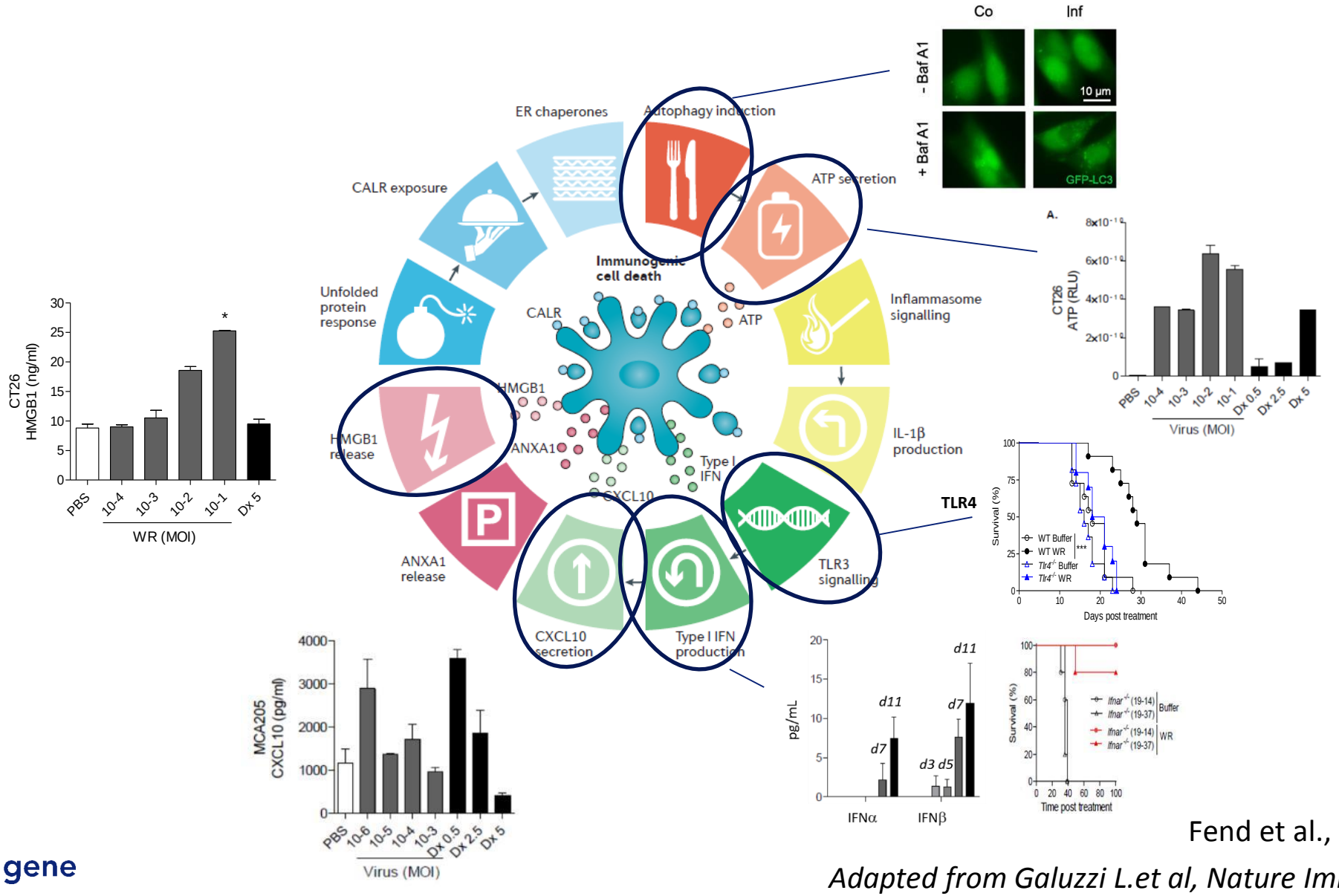
First-in-human trial
FPI in H2 2017

INSTITUT NATIONAL DU CANCER

Development in GI cancers
in active preparation

transgene

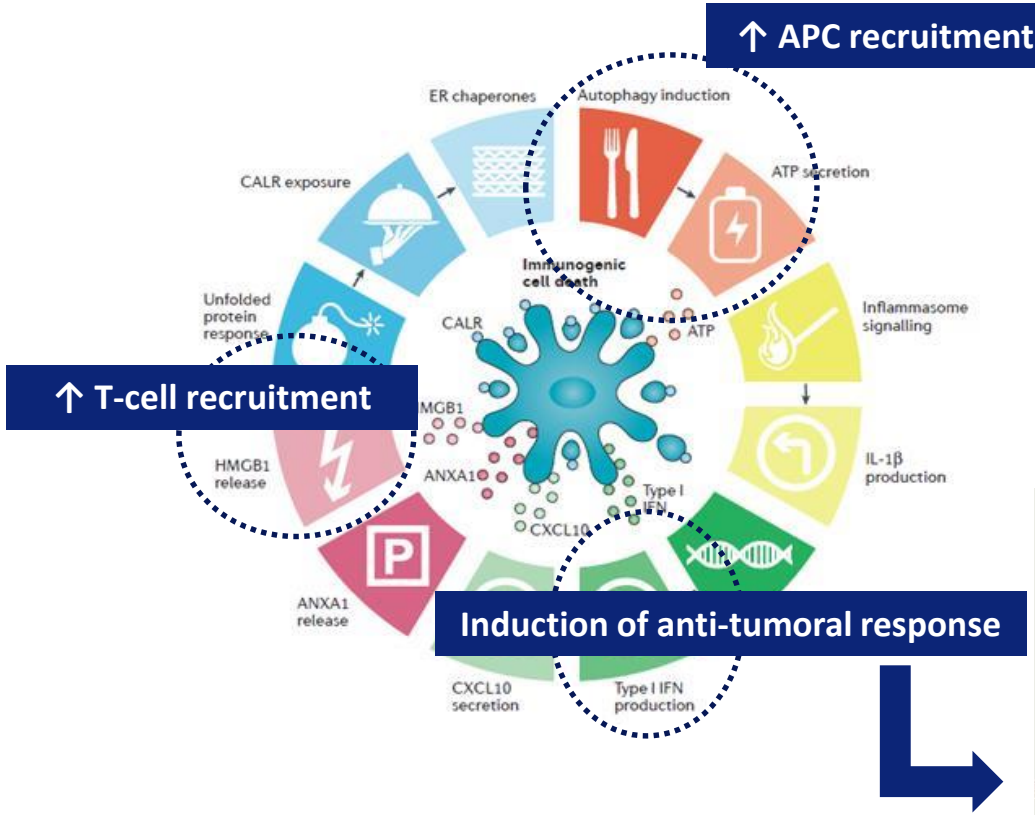
Oncolytic vaccinia viruses | Induce immunogenic cancer cell death and triggers anti-tumor immune response

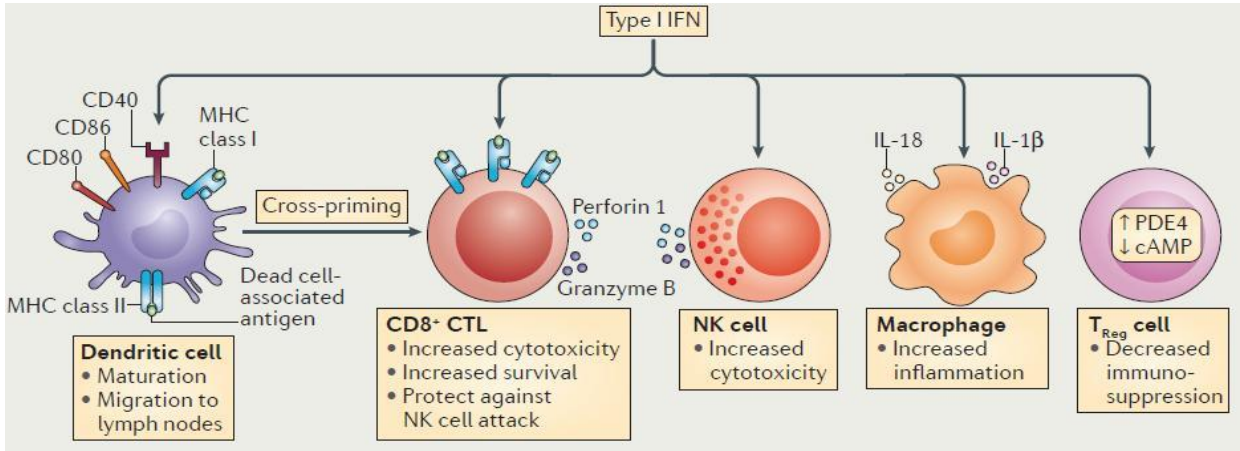


Fend et al., *Cancer Research, 2017*

Adapted from Galuzzi L.et al, Nature Immunol. Reviews, 2016

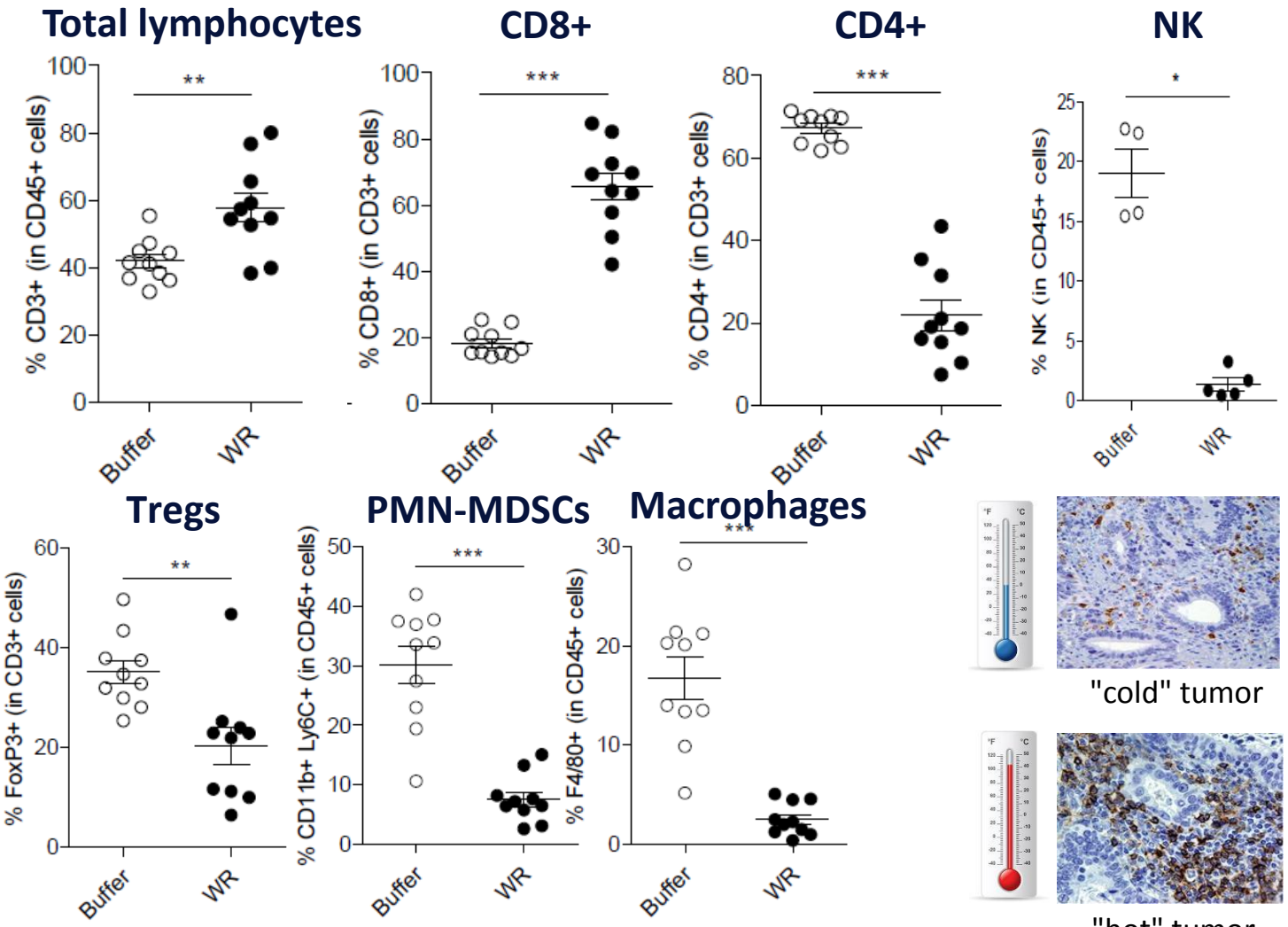
Oncolytic vaccinia viruses | Induce immunogenic cancer cell death and triggers anti-tumor immune response





From Zitvogel et al, Nature Rev Immunol, 2015

OVV | Reprogramming the tumor microenvironment



"cold" tumor

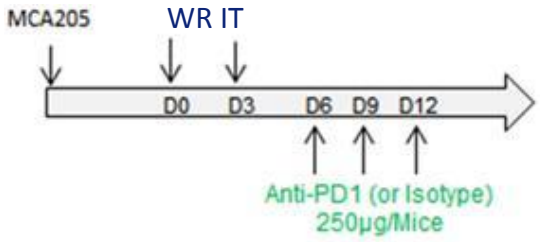
"hot" tumor

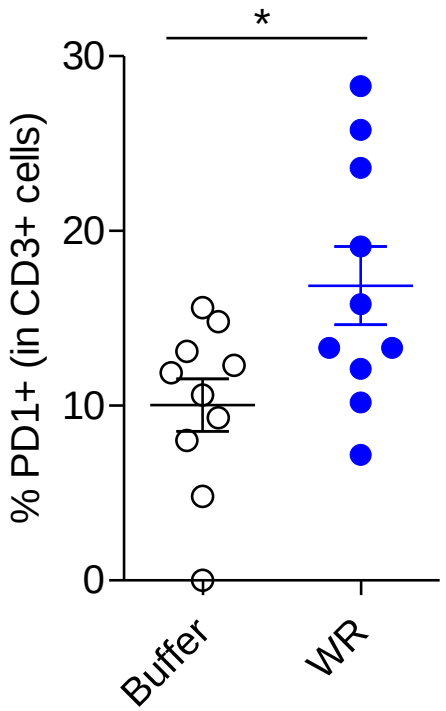
Large infiltration of CD8+ effector T cells, at the expense of CD4+ T cells, and NK cells.

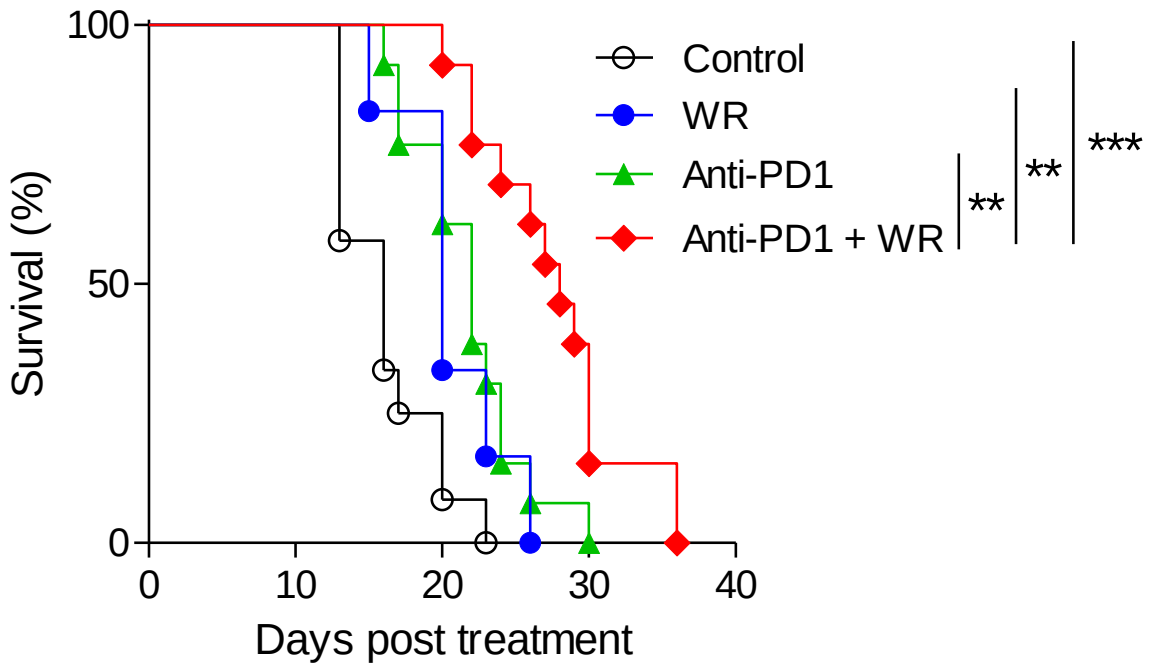
Strong decrease of regulatory components of TME, i.e. CD4+ Foxp3+ T cells, CD11b+Ly6c+, and F4/80+ macrophages.

Fend et al. *Cancer Research, 2017*

OVV | Boost the efficacy of anti-PD1 therapy







A significant part (~18%) of infiltrated lymphocytes are PD1+

Synergy between oVV and anti-PD-1 in a rather aggressive tumor model

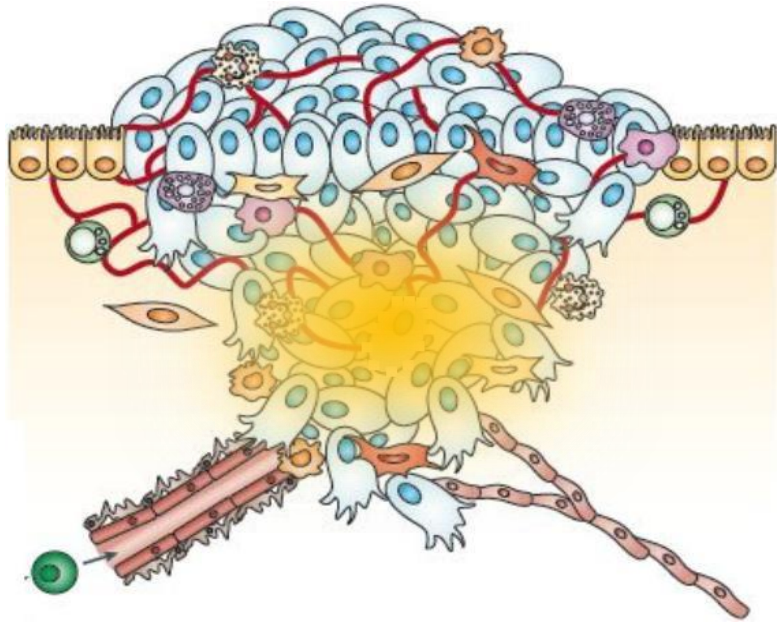
A STRONG RATIONALE FOR COMBO TRIAL WITH ICI

transgene

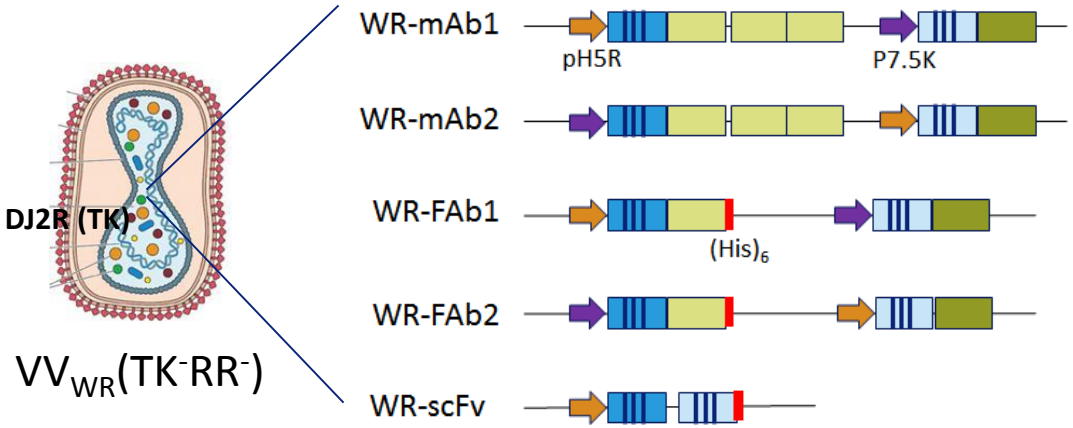
Fend et al. *Cancer Research,* 2017

transgene
immunotherapeutics

Preclinical PoC – Expression of functional antibody in the TME



Immuno-arming of OVV | Proof of concept with anti-PD1



J43 anti-mPD1 variable domains in an anti-CD79b scaffold

Rec-Ab yields

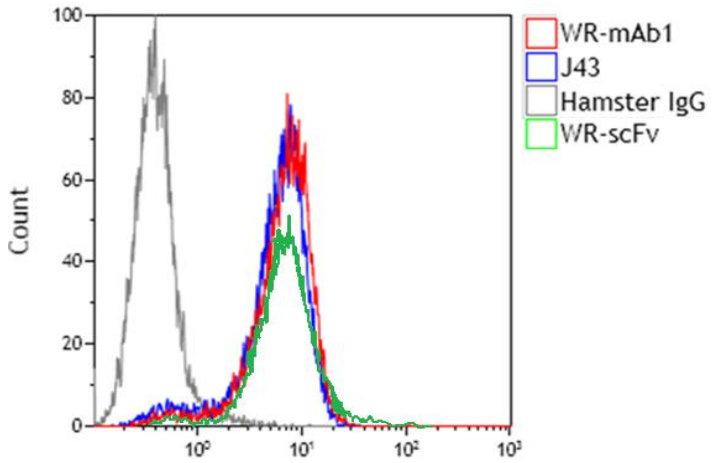
(MCA205, 48 hrs post-infection)

mAb1 : 30 ± 5 µg/mL

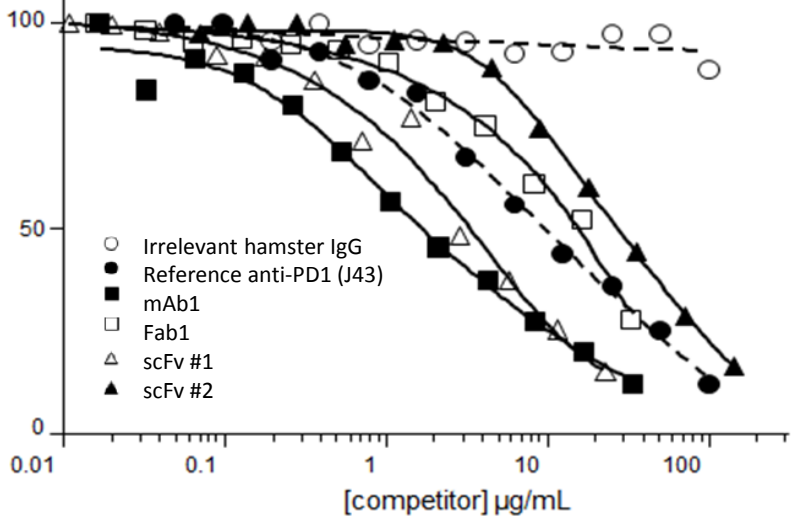
scFv : 150 ± 40 µg/mL

Native-like structure (incl. folding and glycosylation) and activity

Direct binding assay to PD1$^+$ EL4 cells



PDL-1 binding (competition assay)

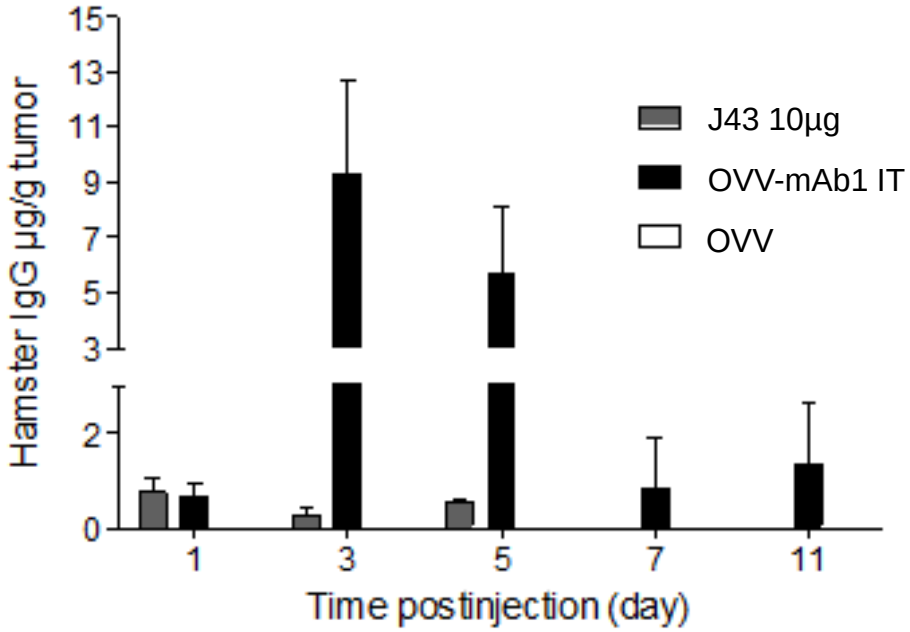


Kleinpeter et al. *OncoImmunology,* 2016

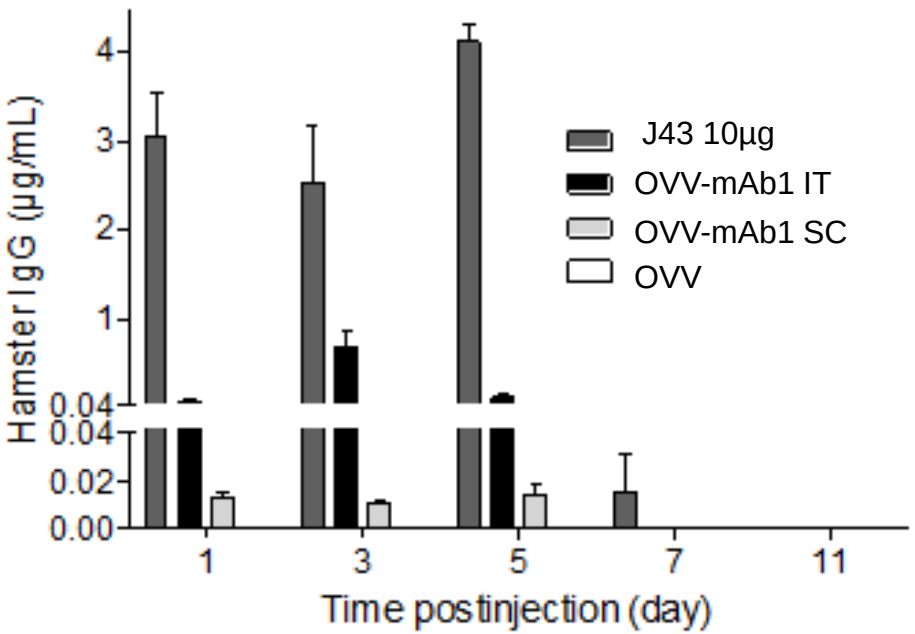
OVV-encoded anti-PD1 mAb | Remarkable PK/PD properties

Preclinical model : MCA205 s.c. in C57BL6 mice
WR-antiPD1 at day 15 post tumor implant

Intratumoral anti-PD1 concentration



Serum anti-PD1 concentration



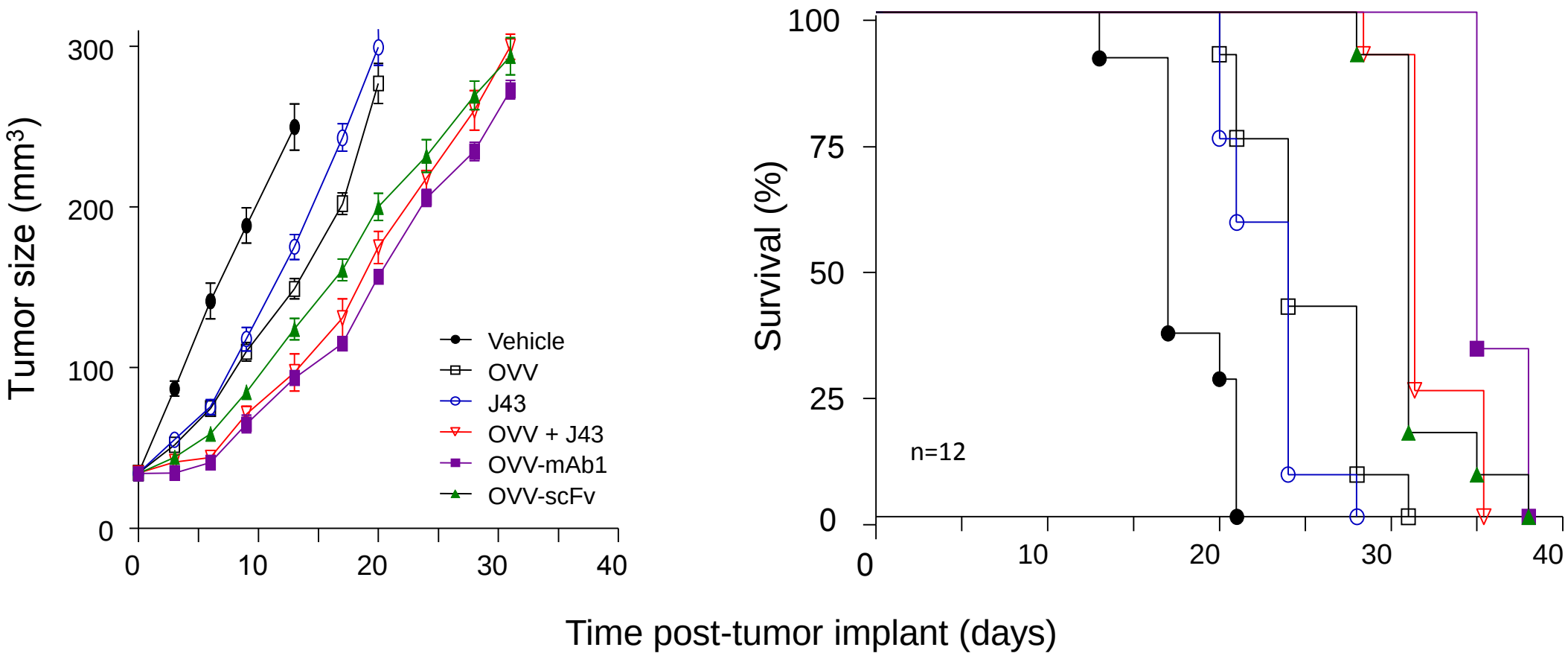
High local concentration in the tumor (T/S ratio ~50 at day 5)
Long lasting action, as compared to reference antibody given by the same route, with continuous production until tumor regression

transgene

Kleinpeter et al. *OncoImmunology,* 2016

OVV-encoded anti-PD1 mAb | More active than the corresponding combination in terms of survival

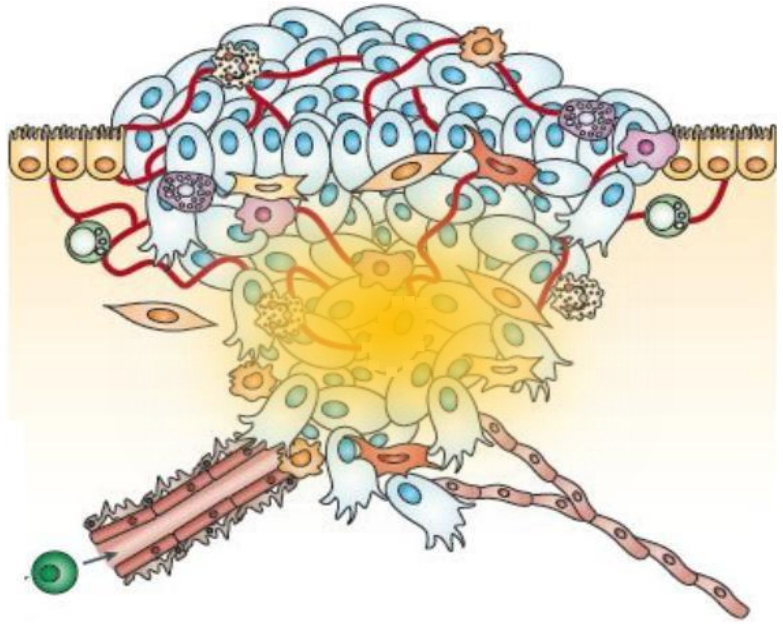
Product activity in a preclinical sarcoma model (MCA205)



Kleinpeter et al. *OncoImmunology*, 2016

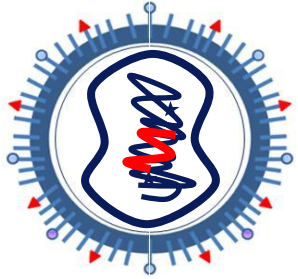
transgene
immunotherapeutics

The future

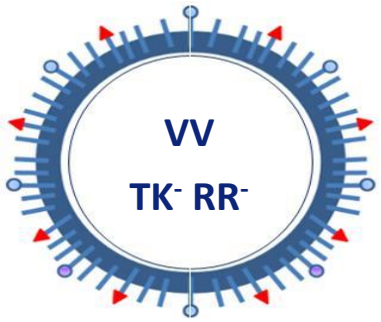


Immuno-armed oncolytic strategy

A multifunctional design



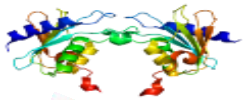
1 Validated backbone



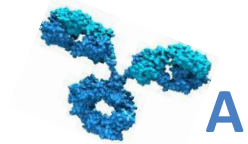
Oncolytic activity
Immunogenic properties
Tumor targeting from the IV route

+

2 Differentiating Targets



Enzyme

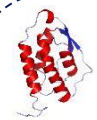


Antibody

Key effectors of the tumor microenvironment
Very effective mechanisms but toxic when administered systemically, and benefiting from local delivery

+

3 Additional Targets



Cytokines / Chemokines

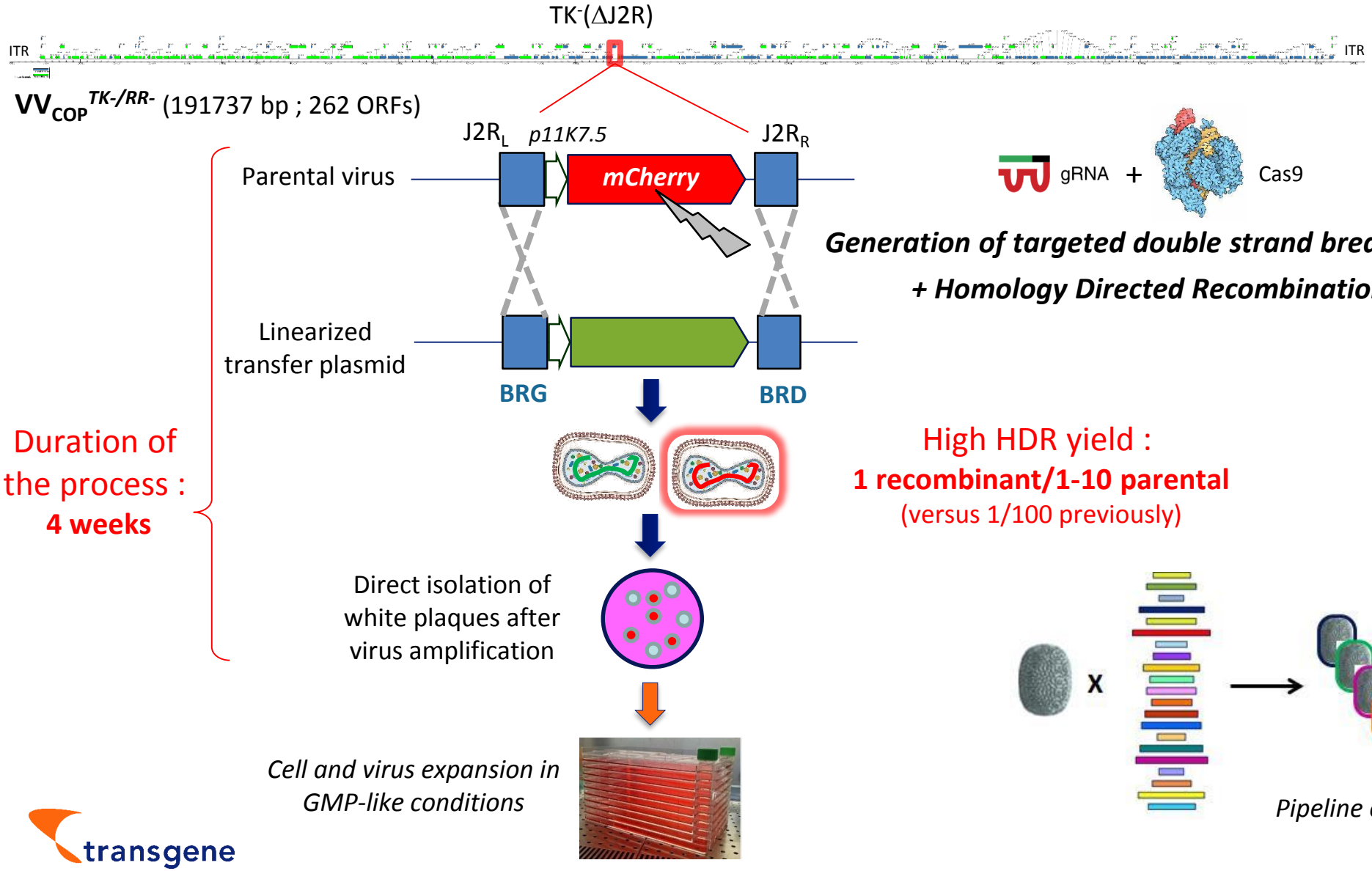
2nd antibody

Receptor ligands

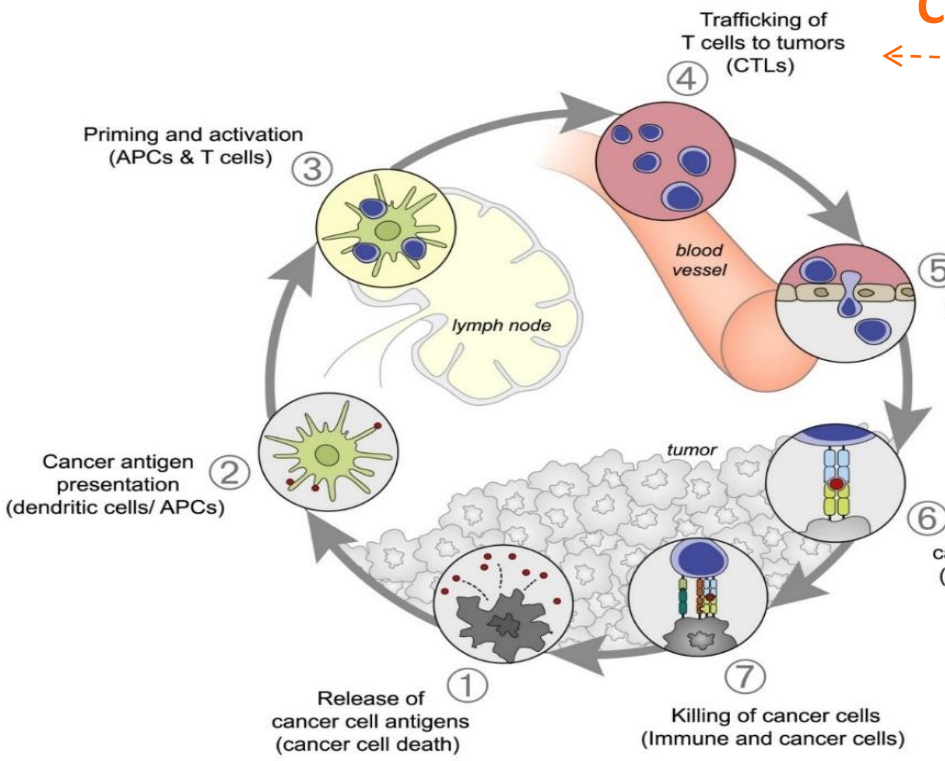
Complementary effectors of the tumor microenvironment,
Might be already commercially available but expensive (e.g. anti-PD1)

Fast and efficient R&D engine

to produce a pipeline of immuno-armed OVVs



Future generation OVs | Engineering and partnering options

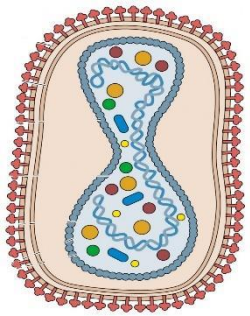


Attract effector cells / express CTL chemo-attractants

BLOOD RELEASE OF CYTOKINES & IMMUNE SIGNALS

Local delivery of stroma-modifying enzymes, vasculature disrupters

DELIVERY OF CHEMOKINES & REMODELING FACTORS



Restore immuno-competence

TARGETED DELIVERY OF mABs & ENZYMES DEGRADING IMMUNO-SUPPRESSIVE METABOLITES

Improve debulking by local delivery of apoptotic inducers, & APC-stimulators

OPTIMIZED ONCOLYTIC AND IMMUNOGENIC FEATURES

Targeting immunosuppressive cells and metabolites in the TME:
> 20 constructs in progress

Lead target	Additional target	
Enzymes 1, Enzyme 2, etc.	→	**Depletion of immuno-suppressive metabolites**
MAb 1, MAb2, etc.	→	**Depletion of Tregs**
Anti-CSF1R	→	**Depletion of M2 macrophages**
Anti PD1	→	**Restore T-cell/tumor interaction**
Chemokines	→	**Favor infiltration of CD8-Tcells and/or DCs**
Cytokines	→	**Proliferation of NK, B, and T cells (not Tregs)** **Induction of memory $CD8^+$-T cells**

Perspectives
We are poised to change the OV therapeutic landscape

- We want to develop our global leadership in the OV field based on our recognized capabilities in molecular engineering
- Our vision is to design innovative products for oncolytic virotherapy and precision oncology
- Our patented proprietary platform, the $VV^{COP}_{TK\text{-}RR\text{-}}$, is an efficient backbone for the development of pipeline immuno-armed oncolytics
  - Strong ability of the platform to induce anti-tumor immunity, suitability for the IV route
  - First clinical trials about to start to confirm safety and efficacy for TG6002, the lead product
  - Demonstrated platform polyvalence in terms of functional arming (enzyme, antibody, cytokine, etc.)
  - Start of a large engineering campaign for OVs targeting the tumor microenvironment with a goal of clinical trials starting from the end of 2018
- Transgene is an ideal partner for either pharmas or biotechs based on its expertise, which spans from virus engineering to clinical development of GMOs

transgene
immunotherapeutics

trans.im
Translational immunotherapy team

SiRIC Institut Curie
Site de Recherche Intégrée sur le Cancer

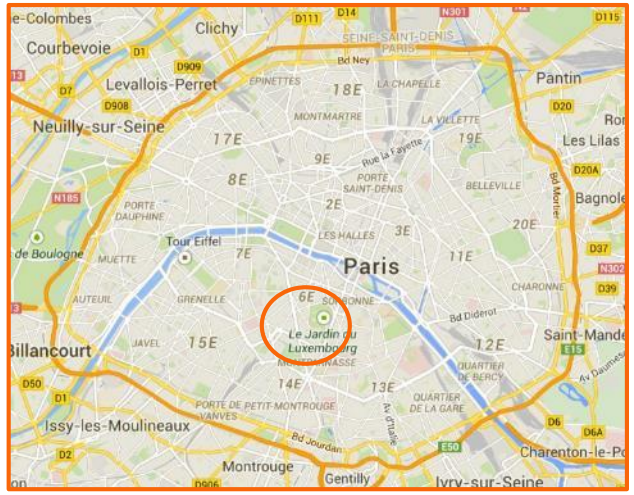
institutCurie

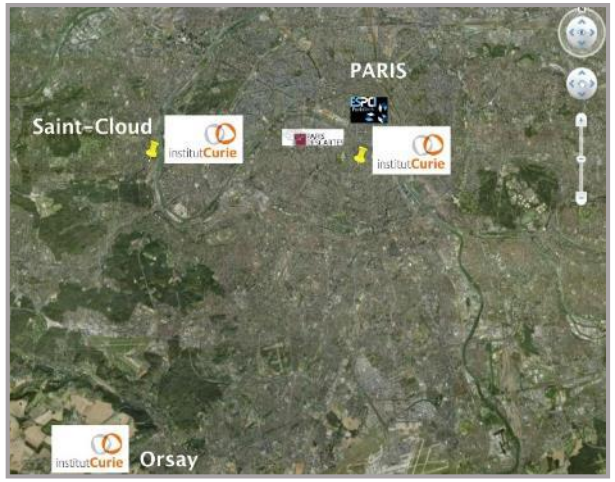
Translational research in cancer immunotherapy: innovation through academic-industrial collaborations

Eliane Piaggio, PhD

Translational Immunotherapy Team
U932 “Immunity and cancer” Unit
Transfer Department

Institut **Curie**



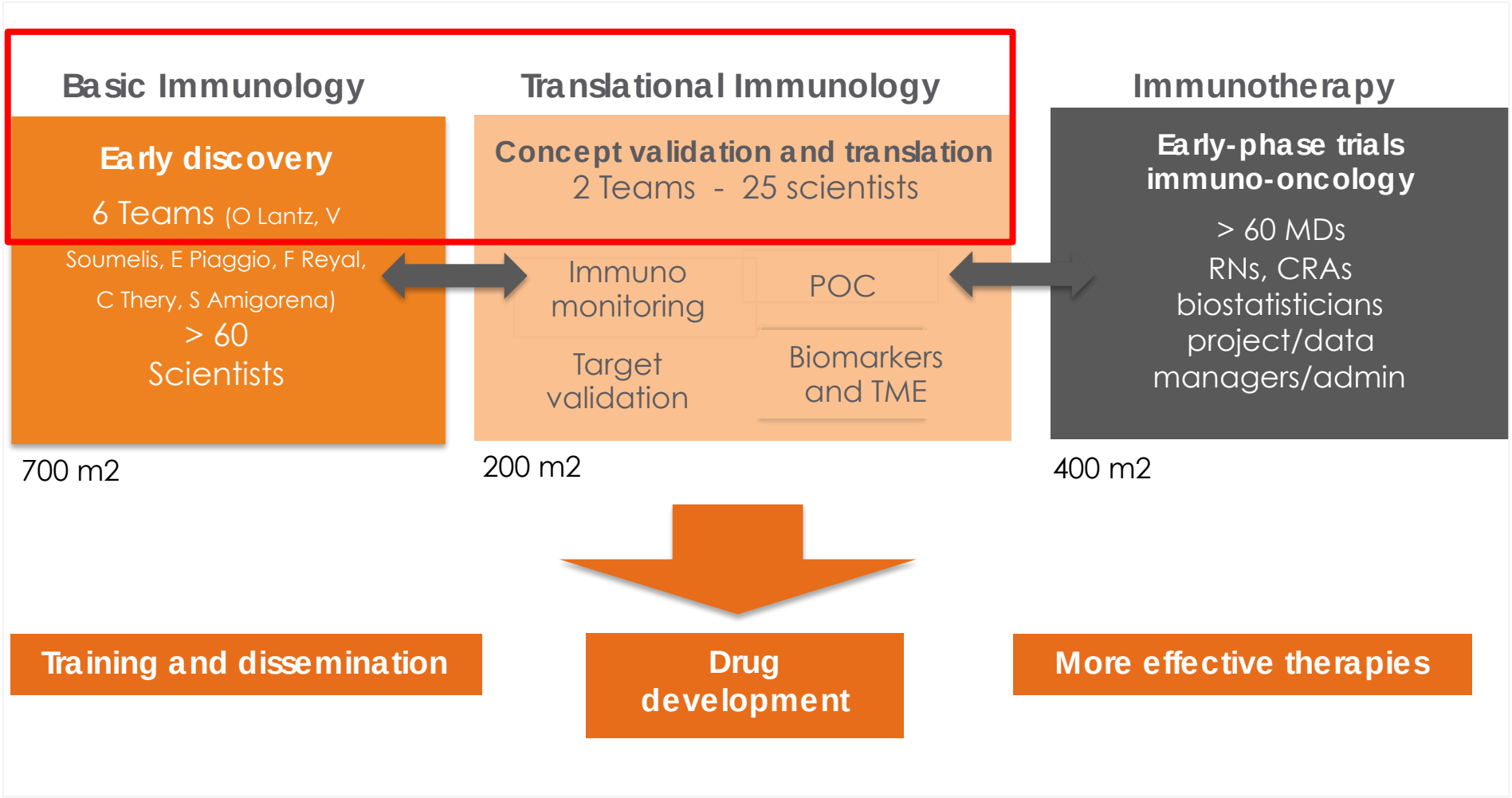


CANCER HOSPITAL

+

RESEARCH CENTER

Center for Cancer Immunotherapy | Overview

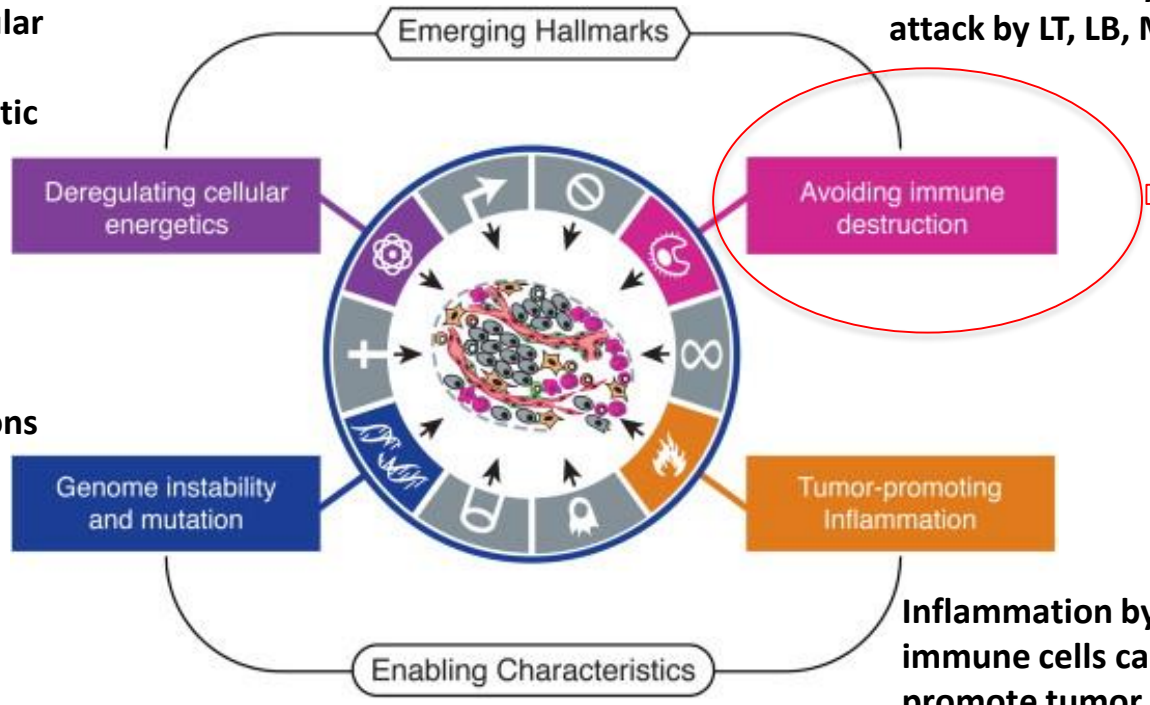


Funding of translational research projects: institutional services, public and private including industrial partnerships

Cancer Immunotherapy | Since when?

Reprogram cellular metabolism to support neoplastic proliferation

Genetic alterations can drive tumor progression



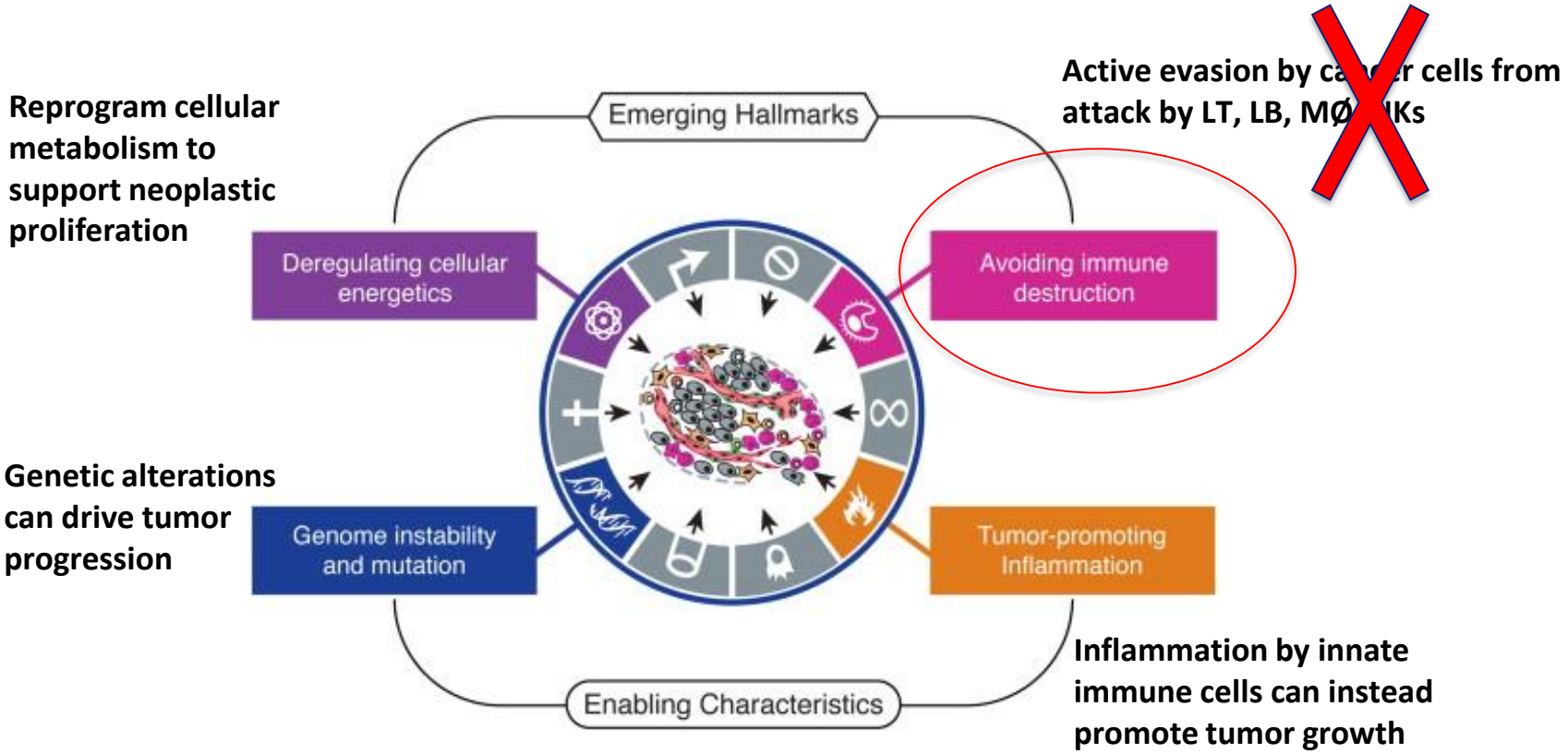
Active evasion by cancer cells from attack by LT, LB, MØ, NKs

Inflammation by innate immune cells can instead promote tumor growth

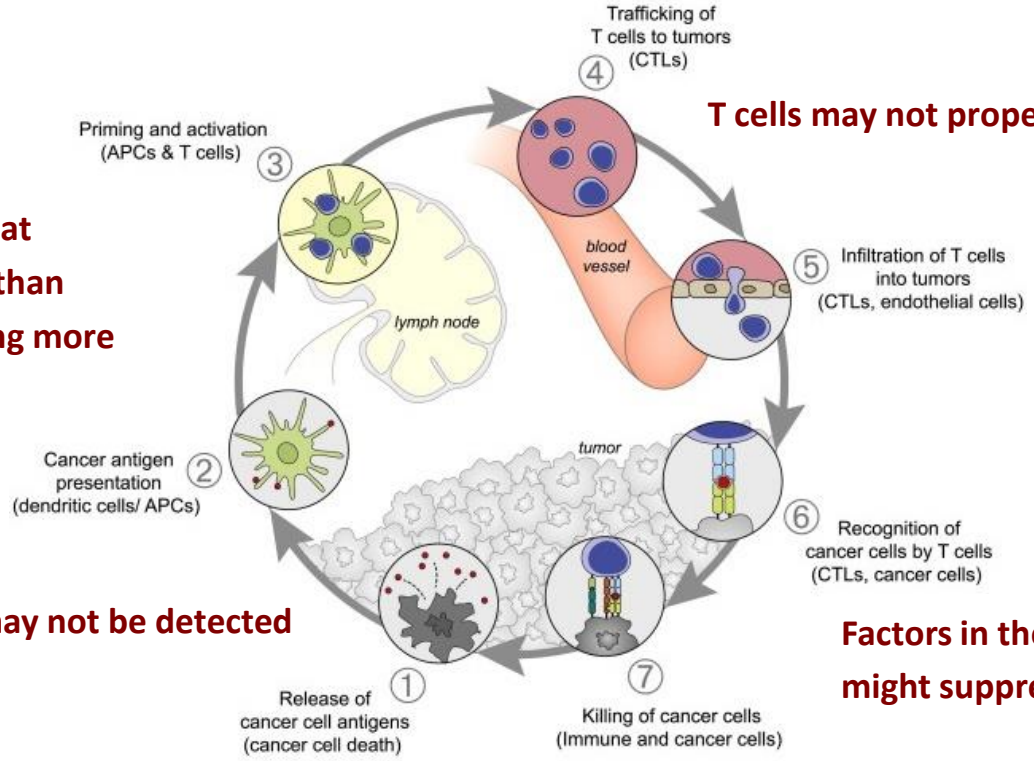
D. Hanahan, R. Weinberg,. ***Cell 2011***

Cancer Immunotherapy | Switching cancer treatment

from targeting the tumor to targeting the immune system



The cancer-immunity cycle | Failures in cancer patients



T cells may not properly home to tumors

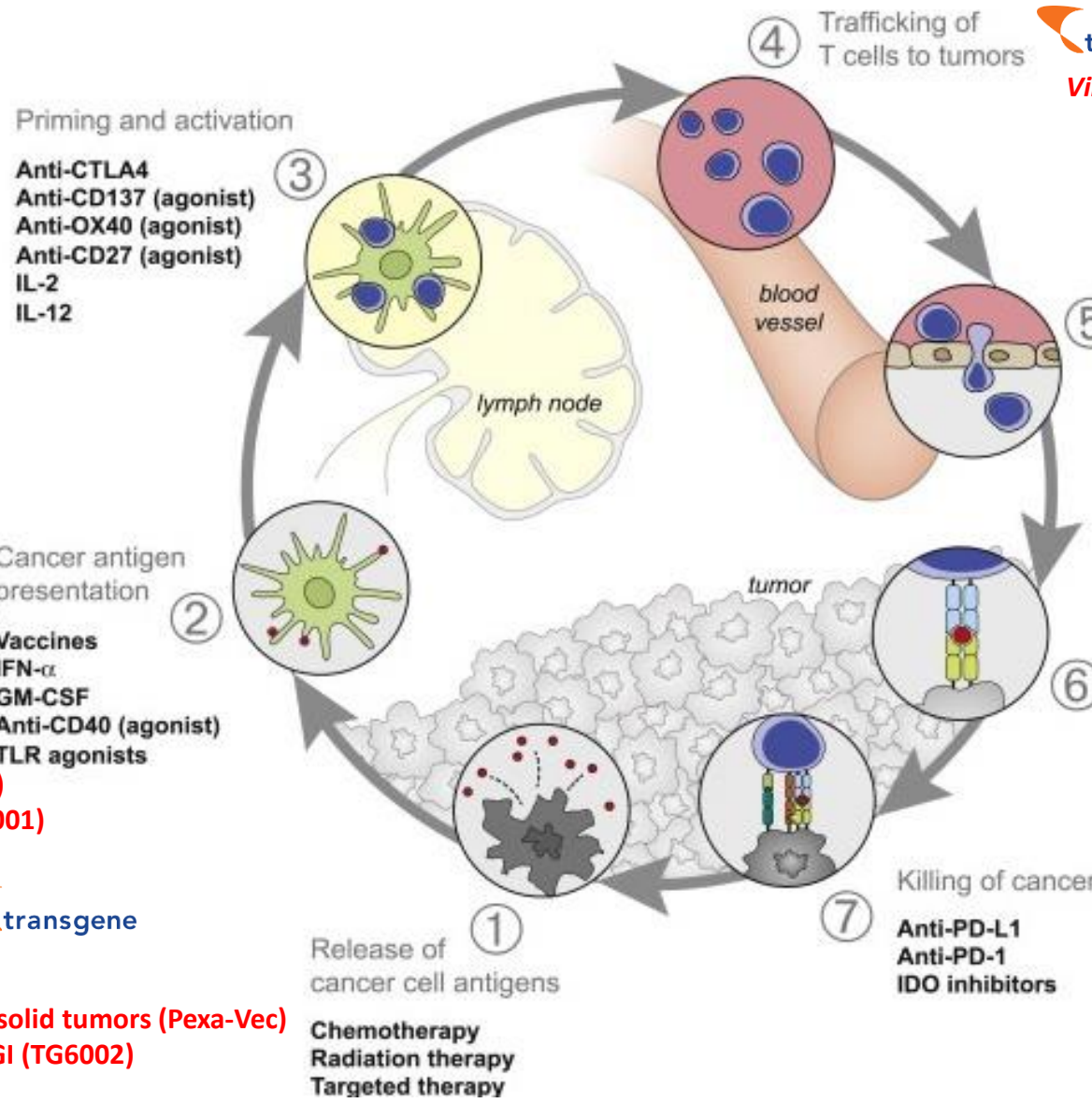
DCs and T cells may treat antigens as self rather than foreign thereby inducing more Tregs than Teffs

Tumor antigens may not be detected

Factors in the tumor microenvironment might suppress the effector cells

Chen DS and I Mellman, 2013

Therapies modulating the cancer-immunity cycle



transgene

Virus + ICIs (TG4010, TG4001, Pexa-Vec)

transgene

Virus + CKs

transgene

Virus + ICIs
Virus + Enzymes

transgene

T cell-genetically engineered by viruses

transgene

Therapeutic vaccines
MVA-MUC1/IL-2-NSCLC (TG4010)
MVA-HPV E6/7/IL-2—H&N (TG4001)
Neo-epitopes

transgene

Oncolytic viruses
VV-GM-CSF– Liver, BCC, solid tumors (Pexa-Vec)
VV-Fcu1-Glioblastoma, GI (TG6002)

transgene

Virus + ICIs (TG4010, TG4001, Pexa-Vec)
Virus + Enzymes

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Chen DS and I Mellman, 2013

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Cancer immunotherapy | Where are we today?

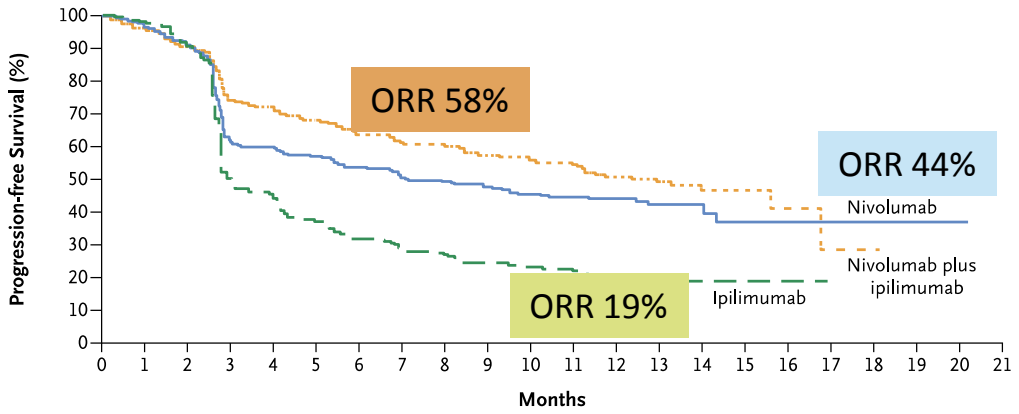
Abs against Immune checkpoints represent an efficient treatment with durable responses.

Novel and promising immunomodulators are under clinical development.

The challenges:

1. **Extend these immunotherapies to other types of tumors.**
2. **10 to 40 % of patients respond to immune checkpoints therapies, so, there is a need to gain knowledge on the mechanism of action, to find biomarkers of response and toxicity.**
3. **Give priorities to test the growing list of available anti-checkpoint Abs in the clinics, as monotherapies or in combinations.**
4. **Put in place personalized immunotherapies.**

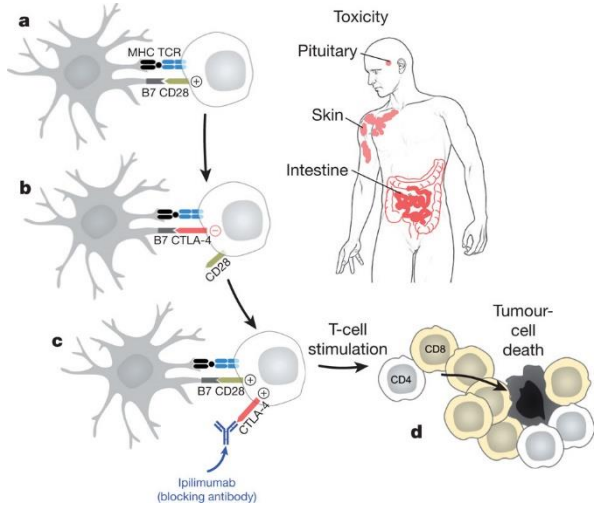
Higher efficacy of combination therapies



From Larkin J. et al. NEJM 2015

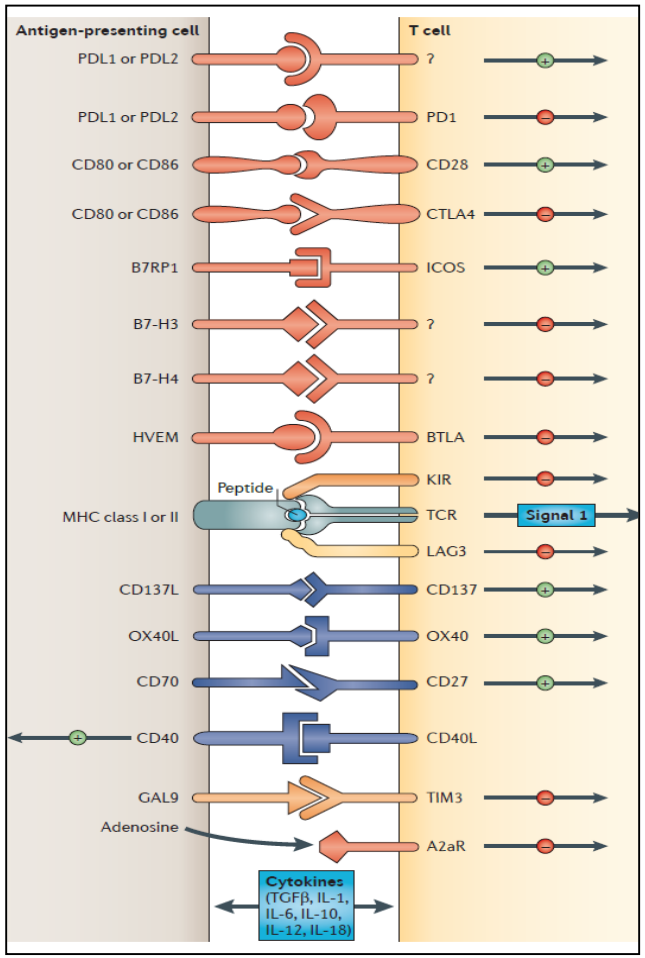
Grade 3-4	Ipilimumab	Nivolumab	Ipi + Nivo
Side effects	**27%**	**16%**	**55%**

Immune side effects: the price to pay

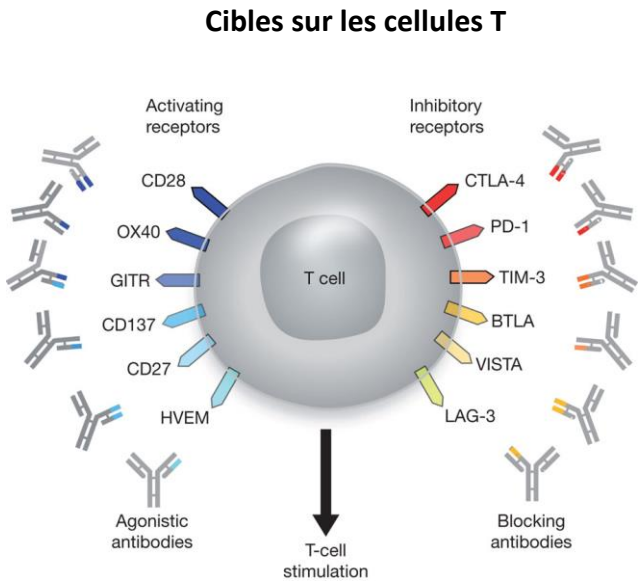


I Mellman Nature (2011)

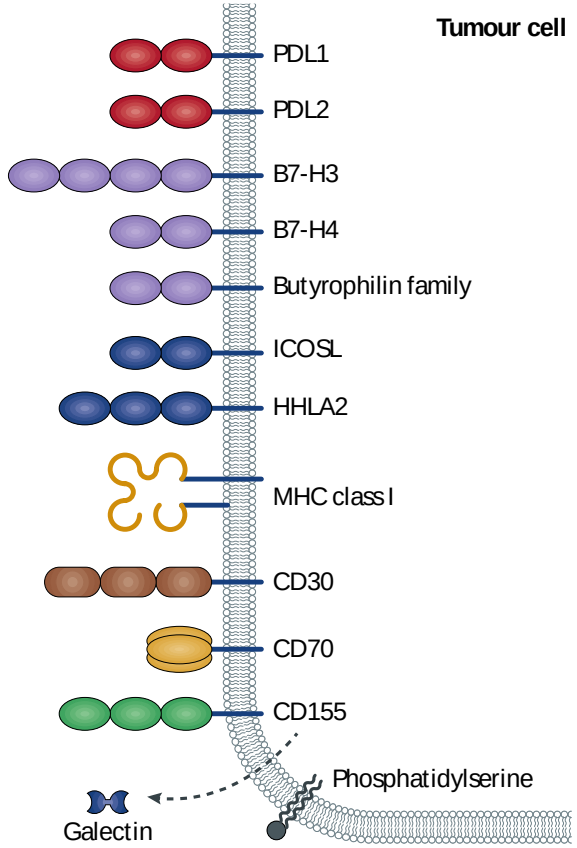
The future | A dynamic list of immunomodulators



Pardoll D., 2012



I Mellman et al. Nature 2011

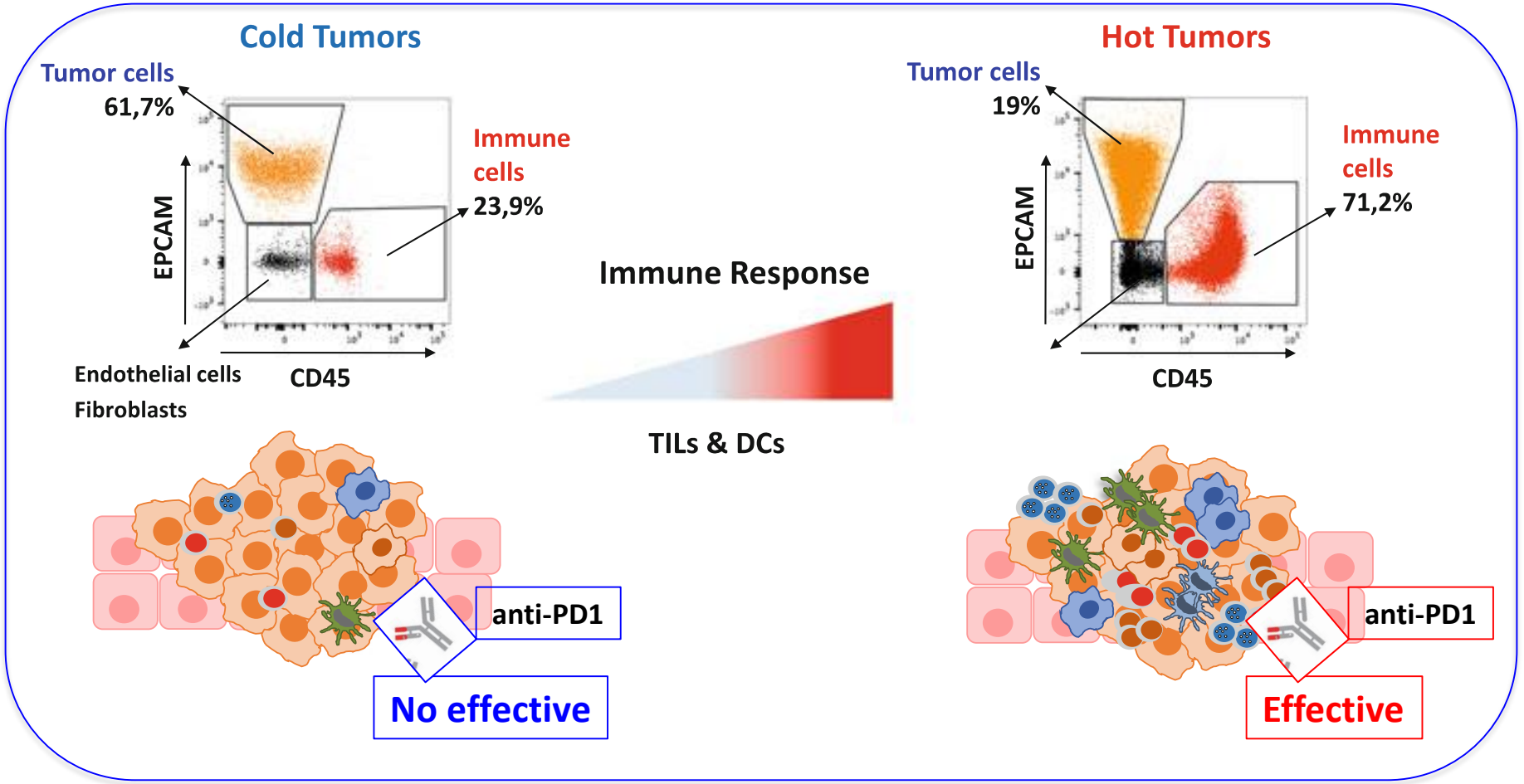


Mahoney K, 2015

New combinations …
Towards personalized immunotherapies

Emerging concepts for rationalized immunotherapies: from individual tumor types to shared tumor features

1- The « cold » versus « hot » tumor theory

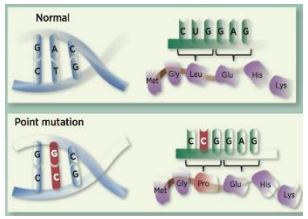


Ramos RN, Piaggio E, Romano E., Handb Exp Pharmacol. 2017

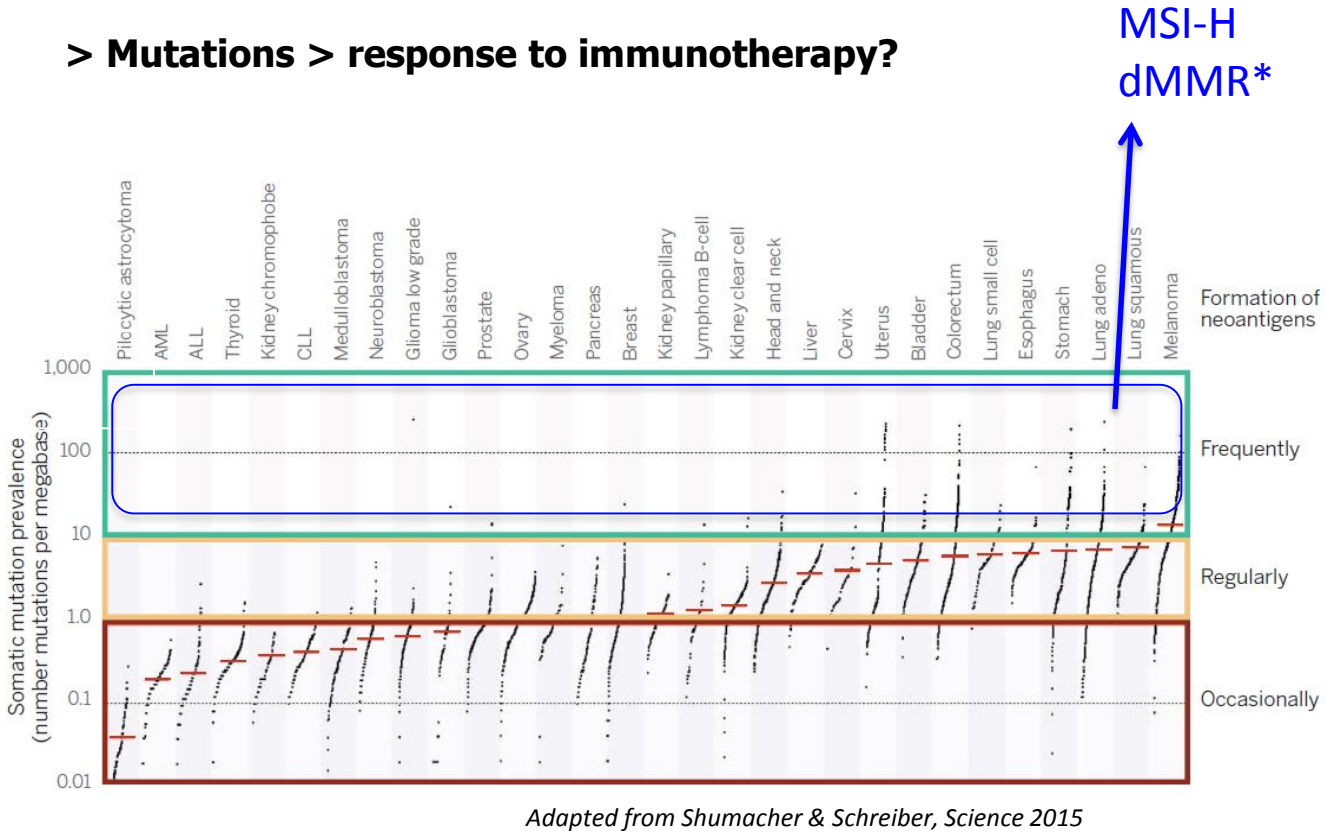
Emerging concepts for rationalized immunotherapies: from individual tumor types to shared tumor features

2- Mutated versus non mutated tumors

Neoepitope formation > Mutations > response to immunotherapy?



Türeci O et al.,
Clin Can Res 2016



Adapted from Shumacher & Schreiber, Science 2015

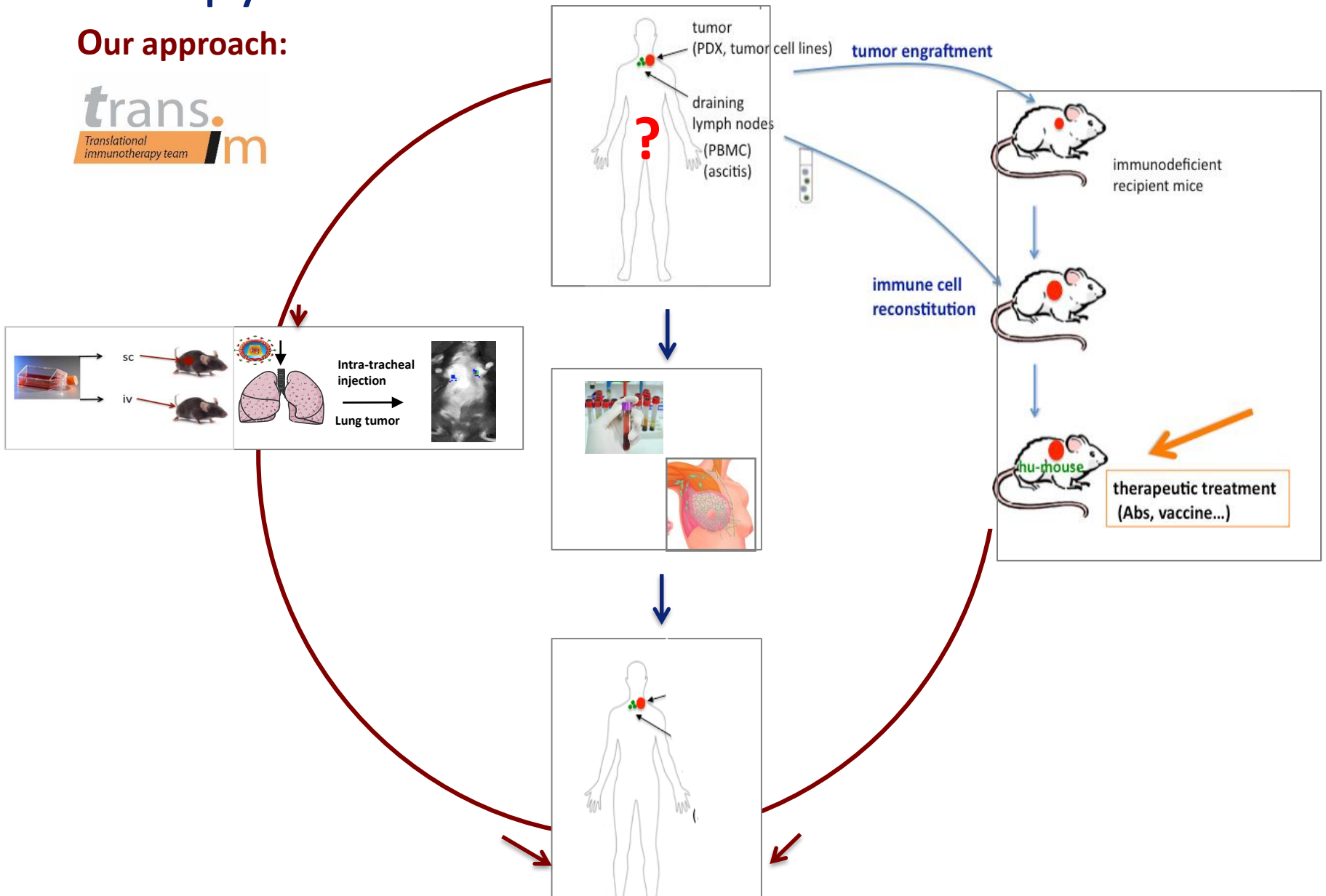
*** FDA's first tissue-agnostic approval (May 2017):**

- **MSI-H: microsatellite instability-high**
- **dMMR: mismatch repair deficient**

Objective | Contribute to the Implementation/Optimization of Immunotherapy at IC

Our approach:

trans.im
Translational immunotherapy team

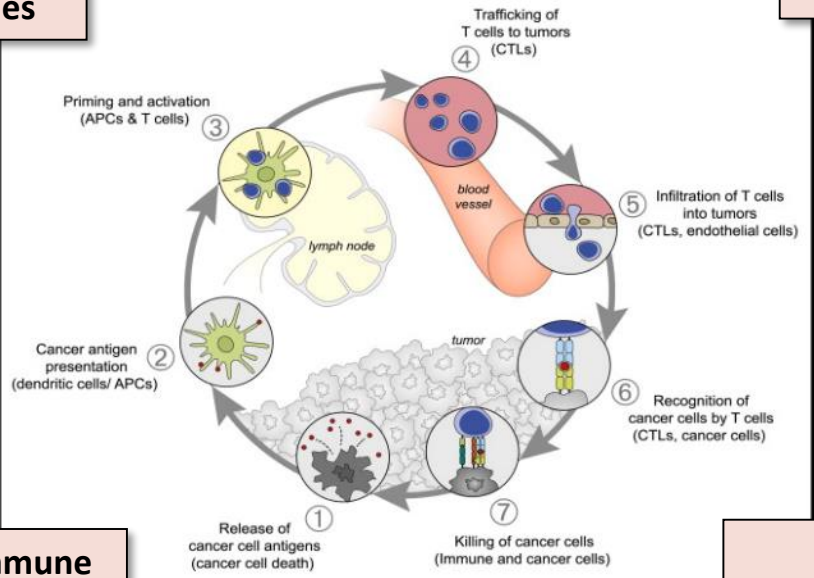


TransIm ongoing translational projects in immunotherapy

Tumor neo-epitopes

Immune profile of tumor-draining lymph nodes

Epigenetic inhibitors,



Dendritic cell development and cancer

IL-2/anti-IL-2 complexes in cancer immunotherapy

Cancer genetics and immune infiltrate

Pre-clinical development of immunotherapies: Syngeneic and humanized mouse models for immunotherapy

- Immunomonitoring/clinical studies

trans.im Translational immunotherapy team

transgene

institutCurie

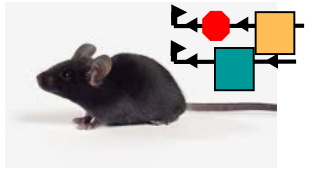
Pre-clinical development of anti-cancer immunotherapies

- Identification of optimal antigen vaccine formulation and/or adjuvant. POC & mechanistic studies

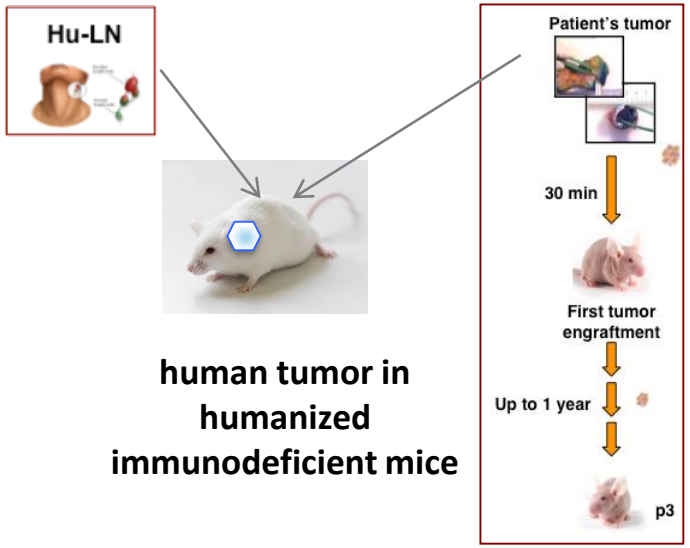
- Test of molecules developed in our Unit or by external collaborators, as monotherapy or in combination with anti-checkpoints Abs.

mouse syngeneic tumor (sc or iv)

mouse syngeneic tumor in HLA-transgenic mice



spontaneous inducible tumor



human tumor in humanized immunodeficient mice

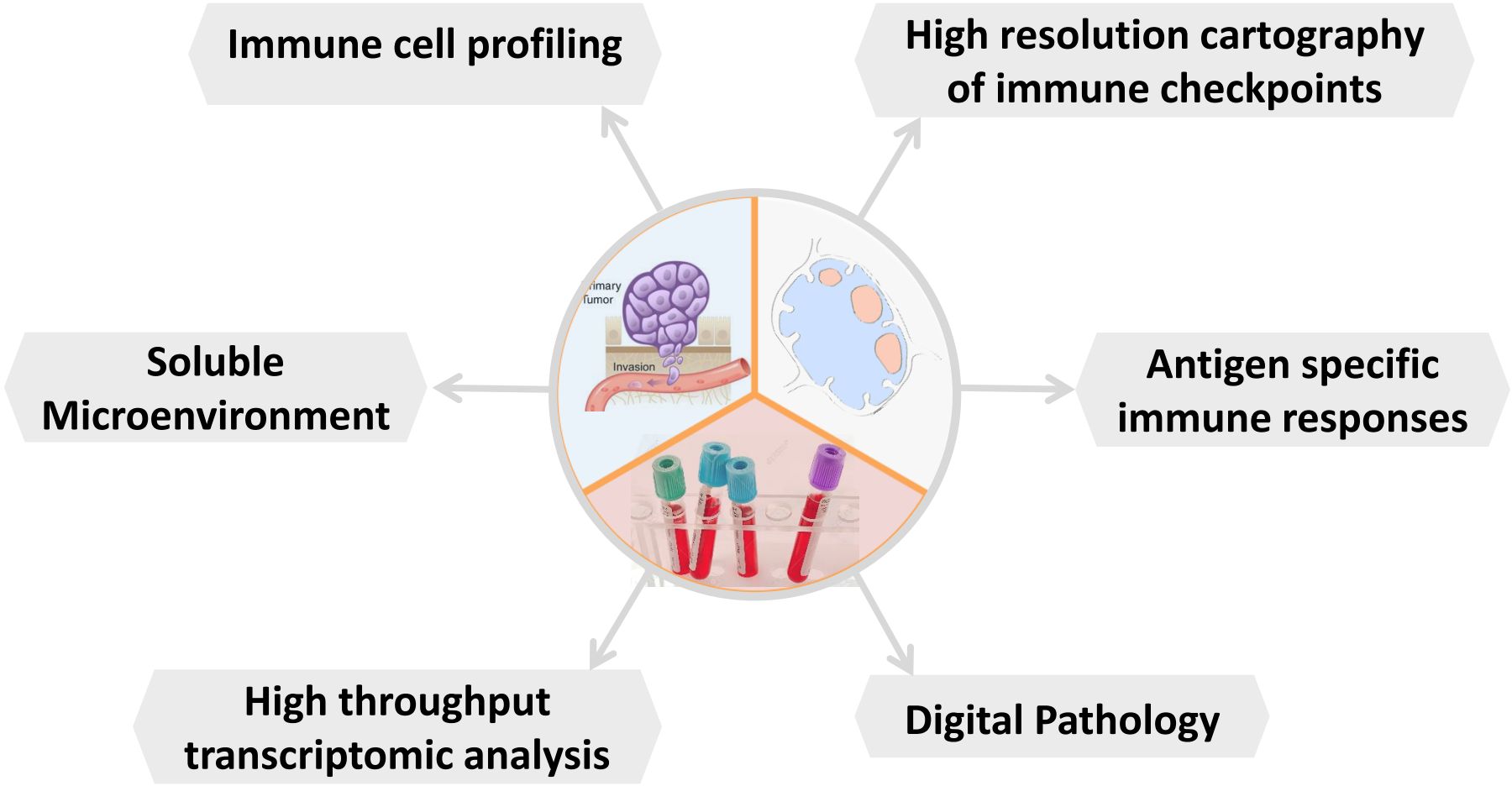
PDX, Platform LIP, I. Curie

- tumor growth

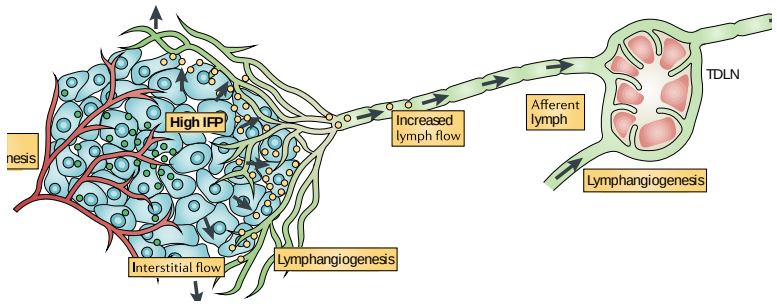
- immunomonitoring (analysis of CD4, CD8 T cell reponses, Ab production, serum cytokines…)

- **RNAseq, IHC, nanostring**

Immunomonitoring at Institut Curie



Study of the immune profile of tumor-draining lymph nodes

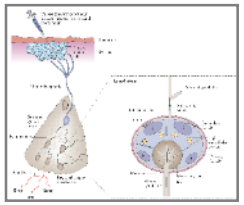


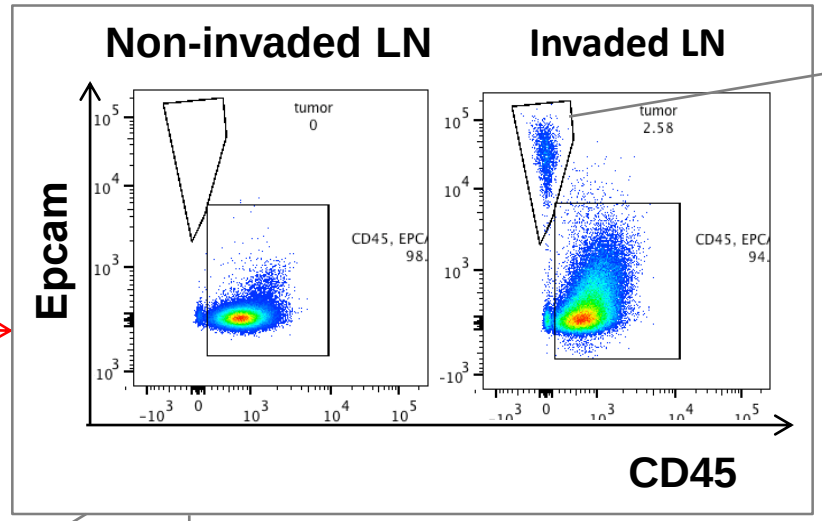
From the clinical standpoint: first site of metastasis, prognostic value.

From the immunologic standpoint, DLNs: sites of immune activation or tolerization?

- **Identification of immunomodulatory mechanisms associated to the presence of the tumor**
- **Discovery of biomarkers**

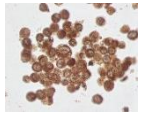
Global approach: Immune profile of tumor-draining lymph nodes



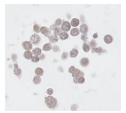


4- Establishment of tumor cell lines:

- **Invasive ductal carcinoma G3**



RO +++



RP1-

- humanized mouse models

1- Fresh staining FACS

T cells
DCs
NK
B
Fibroblasts
Tumor cells
Checkpoint signature

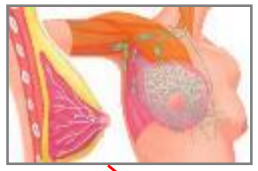
2- Functional assays *in vitro* and *in vivo*

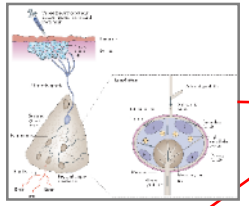
T cells, DCs

3- Creation of a "lymph node collection" at IC

Tumor type
Breast
H&N
Melanoma
Others
Healthy donors

Phenotypic and functional analysis of immune cells in tumor and lymph nodes of breast cancer patients





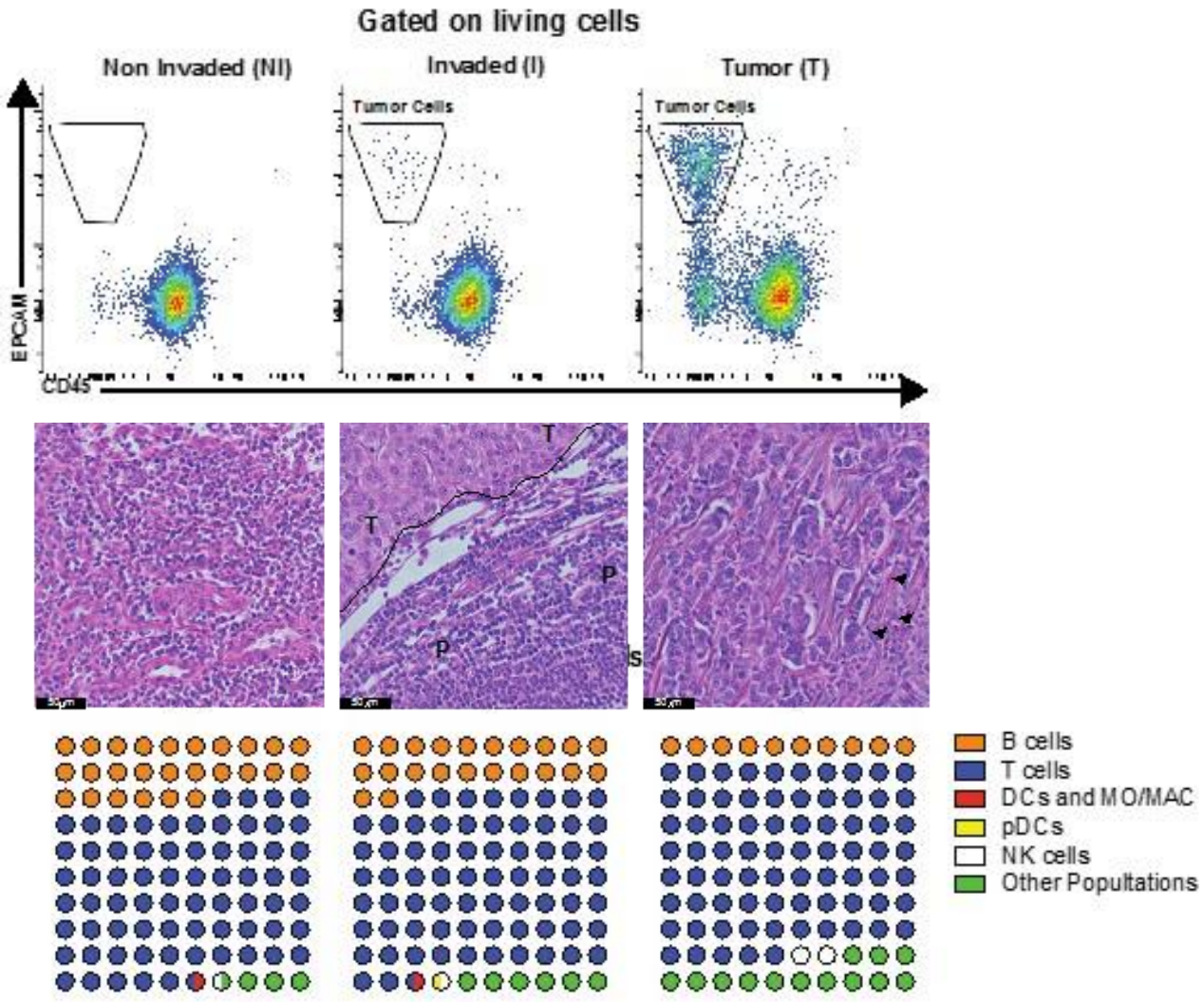
1- FACS and functional tests

T cells

DCs

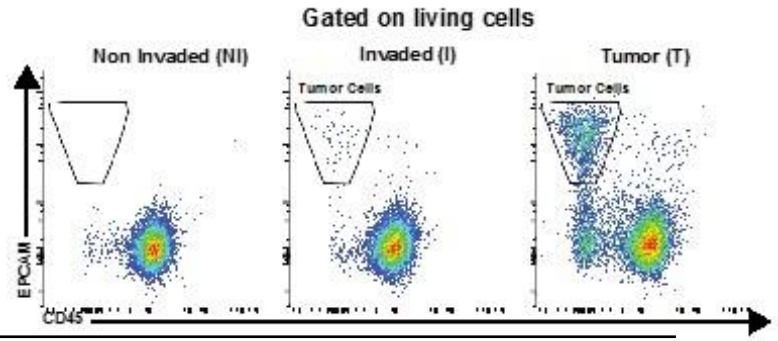
Checkpoint signature

N= 59 luminal B untreated breast cancer patients

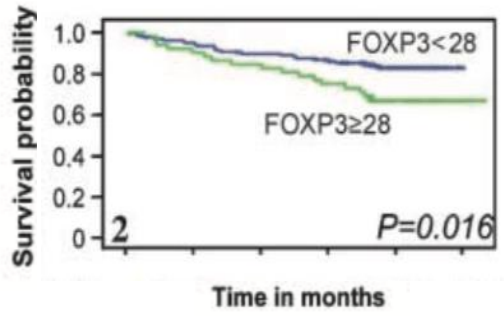


Regulatory T cells and myeloid cells are biomarkers of LN invasion

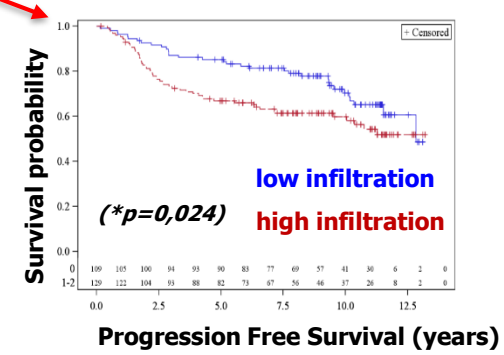
untreated luminal B breast cancer



Eff Tregs Foxp3+	**3.3 ±0.2**	**4.8 ±0.6**	**13.2 ±3.2**
CD14+ cells	**0.04 ±0.006**	**0.11 ±0.02**	**3.02 ±0.6**



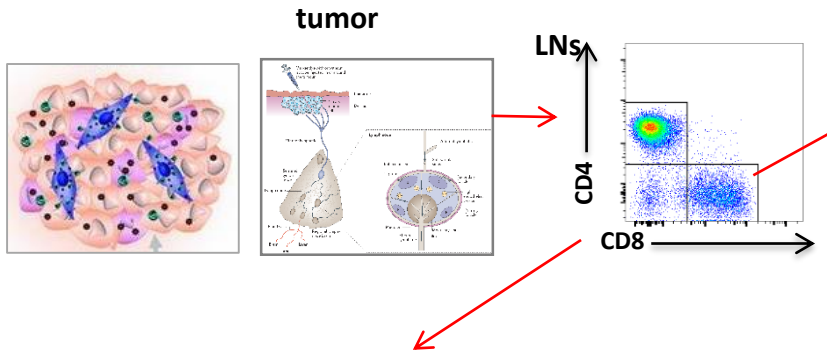
Gobert M, et al., Can. Res. 2009



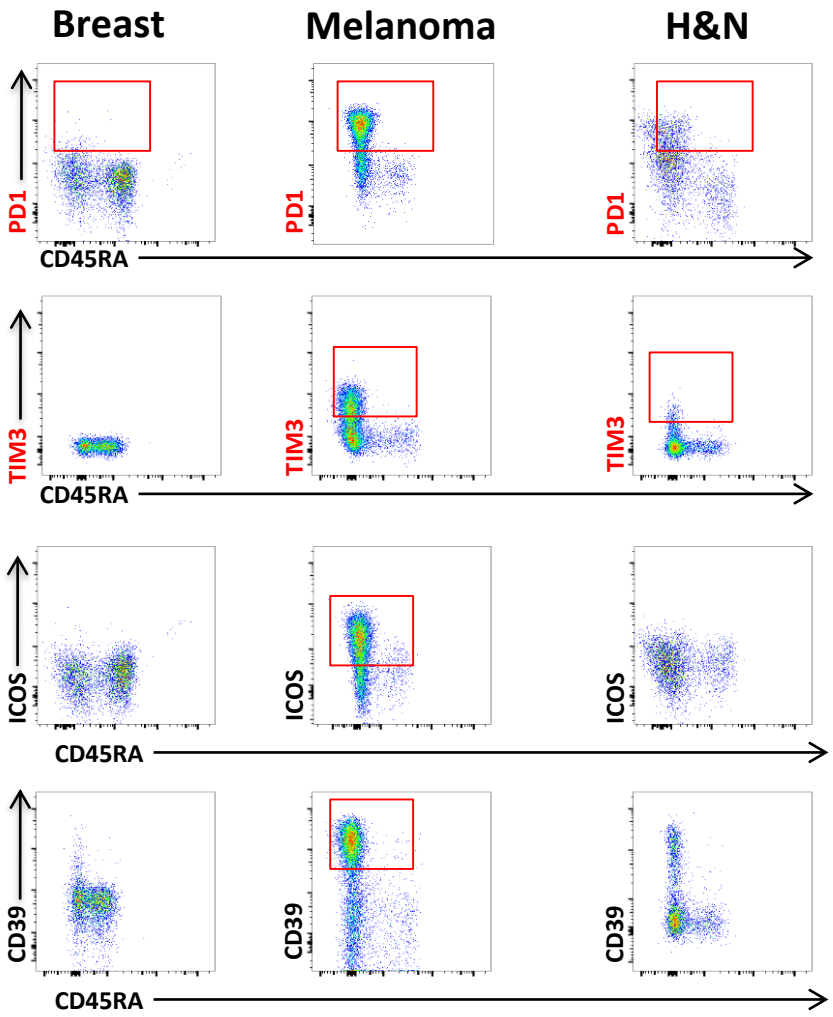
Ramos RN, Thesis 2015

- **Identification of specific targets on Tregs and myeloid cells for immunomodulation using scRNAseq and phage display**

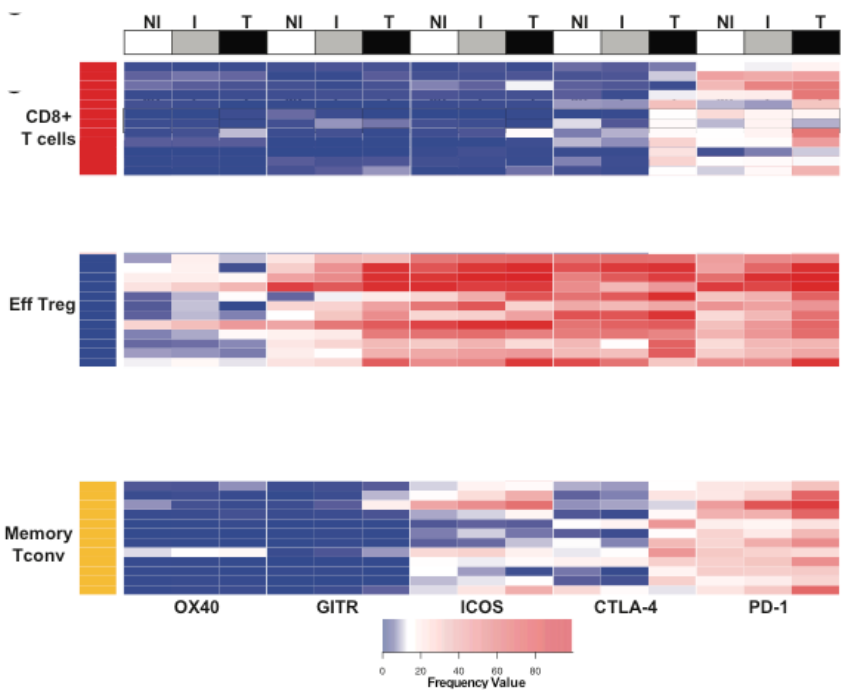
Towards personalized medicine



Facs analysis on CD8+ T cells from lymph nodes



Facs analysis T cells from tumor and lymph nodes

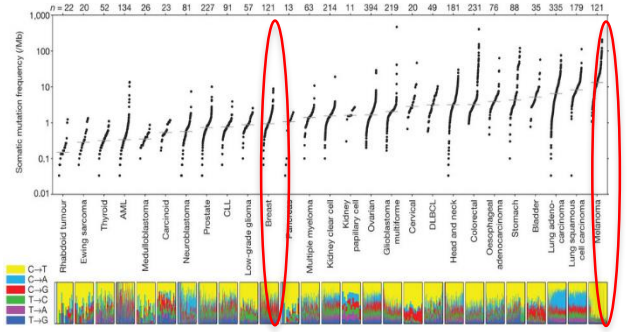


- **T cells from different tumors and different locations express unique immune-CKPT patterns**

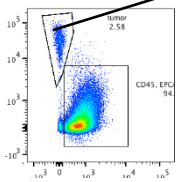
Identification of T cells specific to mutated tumor-epitopes in LNs

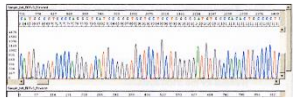
- **Neoepitopes, originating from tumor mutations: safe and potent vaccine immunogens.**

Breast/melanoma patients → **LNs, Blood, Tumor** → **WES+ RNAseq + *In silico* prediction of mutated MHCI epitopes** → **synthetic peptides and MHC dextramers**

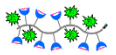


Lawrence MS, Nature 2013

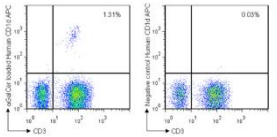


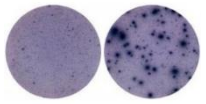


AAGIGILTV
LLGRNSFEV



study of frequency and functionality of the neo-epitope-T cell response (LNs, TILS, blood)





➢ **Prioritization of immunogenic tumor mutated epitopes for "personalized NeoAntigen tumor vaccines"**

Concluding remarks

Our mission at Institut Curie:
support therapeutic innovation for better patient care

Institut Curie:
cutting edge research capability associated to clinical programs

- Ex: TG4001 (collaboration Institut Curie / Transgene)
  - ➔ State of the art immunomonitoring integrated with clinical operations

- Potential to develop additional translational programs in cancer vaccines and oncolytic viruses

transgene
immunotherapeutics

Closing remarks

2017 - A year of significant progress

TG4010	1st line: • Collaboration agreement ✓ • 1st patient of the Phase 2 trial 2nd line: • 1st patient treated ✓ • First readout around the end of 2017
TG4001	First patient treated (H2 2017)
TG1050	First results (H2 2017) Combination preclinical results
Pexa-Vec	Phase 3, HCC, 1st line: 1st patient treated in Europe (Q2 2017) ✓ Phase 2, HCC, 1st line: 1st patient treated (Q2 2017) Phase 1, solid tumors: • 1st patient treated ✓ • First results around the end of 2017
TG6002	First patient treated in the Phase 1 trial (Q2 2017)

Key takeaways

Transgene on track to deliver significant clinical results

Viral-based immunotherapies - potential to revolutionize IO

Our next generations multifunctional OVs have the potential to change the IO combination paradigm

Thanks for your attention