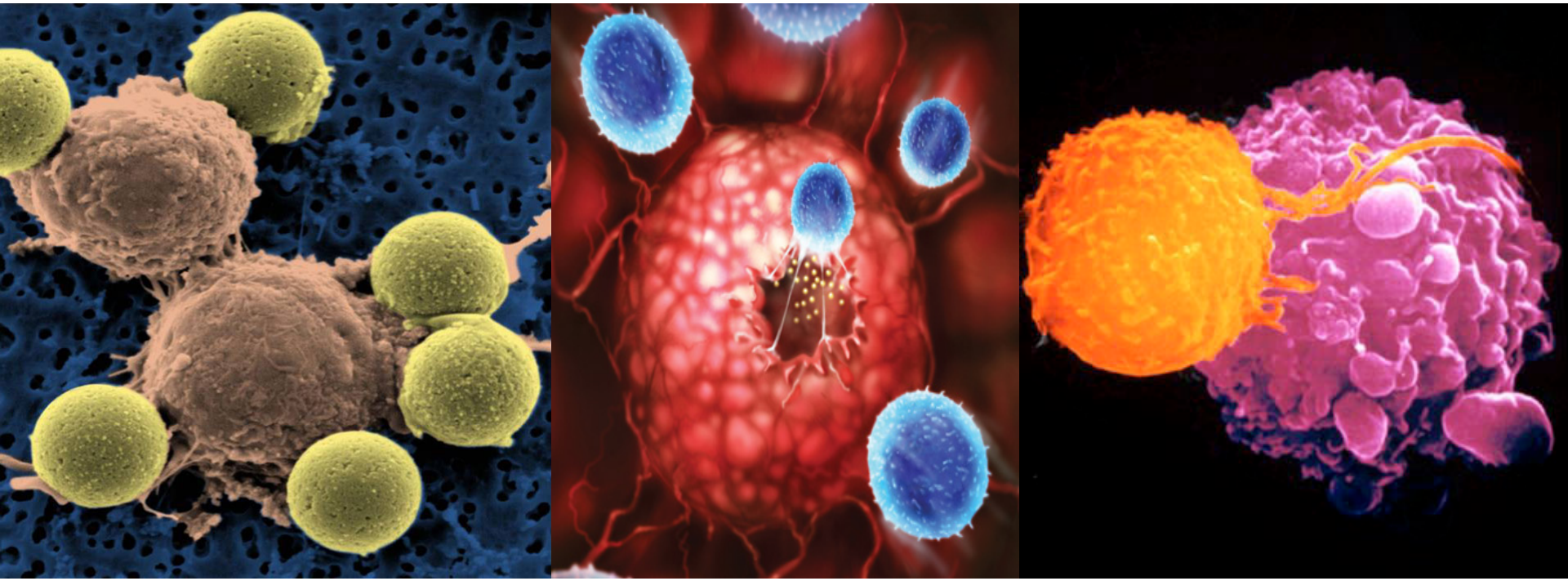
CAN WE AWAKEN THE IMMUNE SYSTEM AGAINST COLON CANCER



DR TOH HAN CHONG

BSc(Lond) MBBChir(Camb) MRCP(UK) FRCP(Edin) FAMS(Spore)

DEPUTY DIRECTOR

NATIONAL CANCER CENTRE SINGAPORE

ASSOCIATE PROFESSOR, DUKE-NUS GRADUATE MEDICAL SCHOOL

What about colorectal cancer?

ClinicalTrials.gov

Try our beta test site

Example: "Heart attack" AND "Los Angeles"

Search for studies: Search

Advanced Search | Help | Studies by Topic | Glossary

IMPORTANT: Listing of a study on this site does not reflect endorsement by the National Institutes of Health. Talk with a trusted healthcare professional before volunteering for a study. Read more...

Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

Home > Find Studies > Search Results

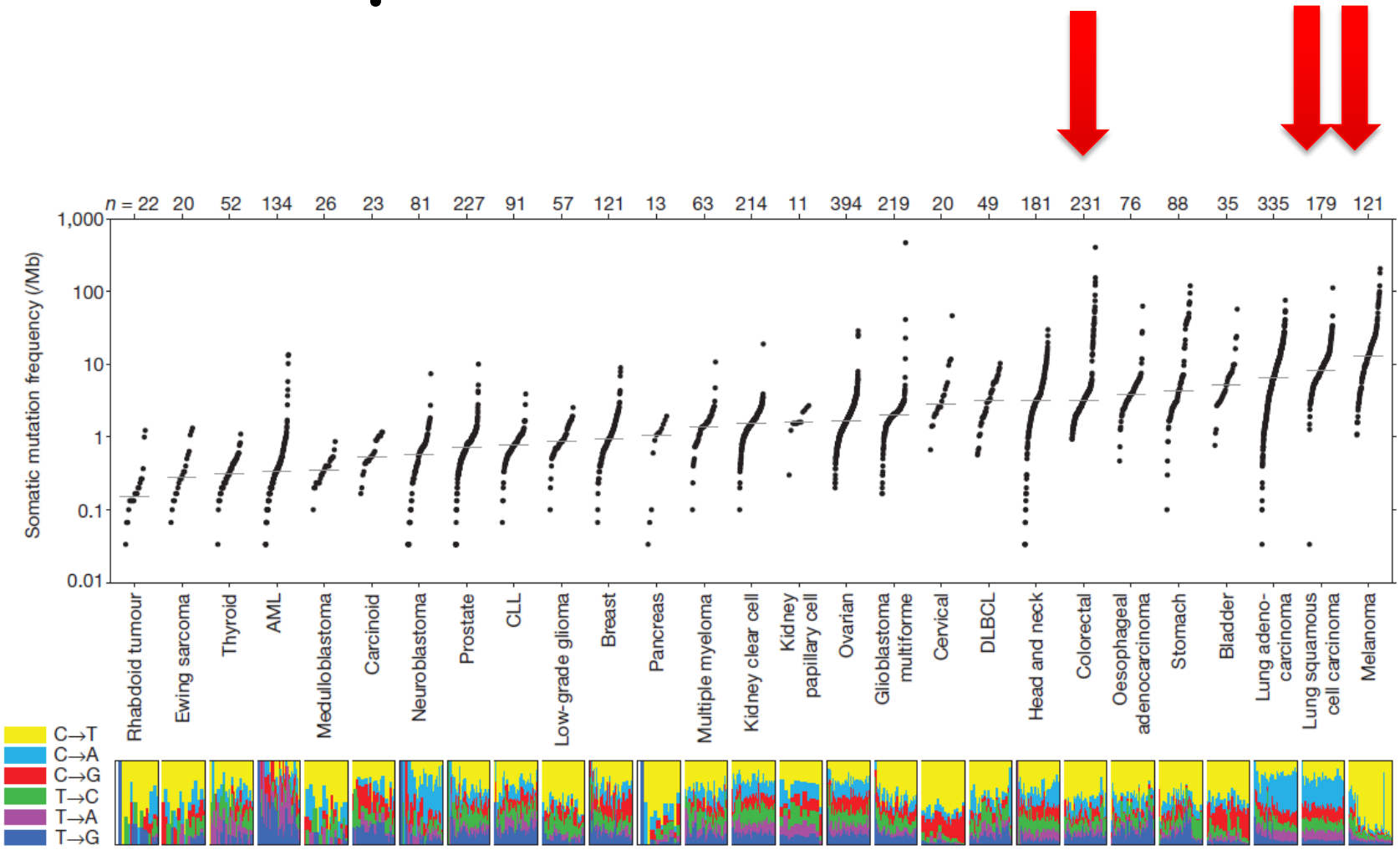
Text Size

94 studies found for: colorectal and immunotherapy

Modify this search | How to Use Search Results

34 pembrolizumab
25 nivolumab
11 atezolizumab

Mutational burden may be important in patient selection



Lawrence et al, Nature 2013

CRC subtypes by gene expression:
distinct immune orientations of the CRC molecular subtypes pave the way for tailored immunotherapies

characterized by overexpression of genes specific to cytotoxic lymphocytes

CRC

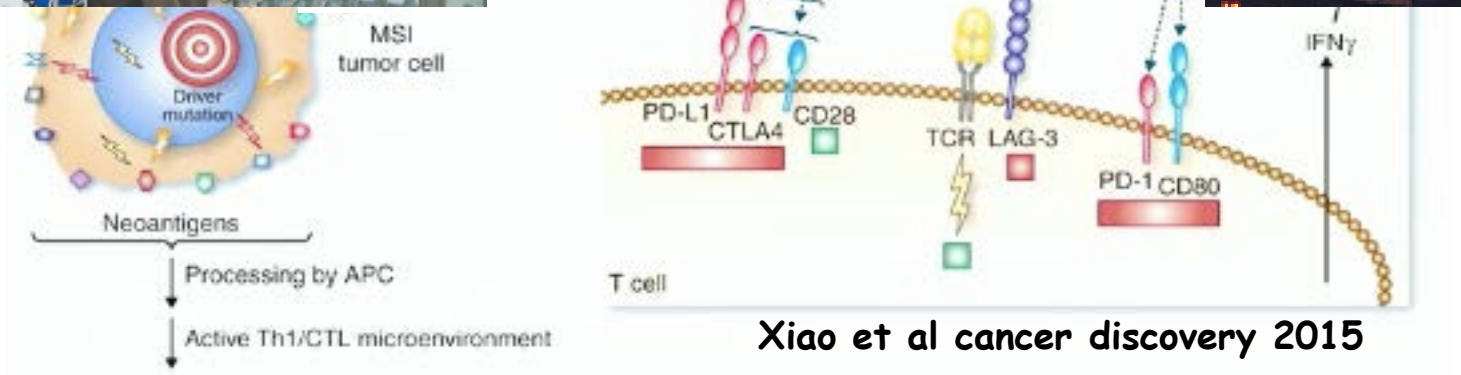
expresses markers of lymphocytes and of cells of monocytic origin

CMS1 (14%) Microsatellite instability immune	CSM2 (37%) canonical	CSM3 (13%) metabolic	CSM4 (23%) mesenchymal
Microsatelite unstable Hypermutated Strong immune activation	Epithelial Marked WNT and MYC signal activation	Epithelial and evident metabolic dysregulation	prominent transforming growth Factor-activation, stromal invasion and angiogenesis

exhibit low immune and inflammatory signatures.

E Becht et al CCR 2016

Immune microenvironment of MSI colorectal cancer



Xiao et al cancer discovery 2015

- Single agent anti PDL-1 works
- Can do better with combinations with IDO, LAG3, CTLA-4
  Ultimately finding tools to better select patients

CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 1 of 10)

Patient appropriate for intensive therapy[2]

Initial Therapy

- **FOLFOX ± bevacizumab**
  or
  CAPEOX ± bevacizumab
  or
  FOLFOX + (cetuximab or panitumumab)[3-5]
  (KRAS/NRAS WT and left-sided tumors only)
  → **Progression** → See COL-C 2 of 10
- **or**
  FOLFIRI[6] ± bevacizumab
  or
  FOLFIRI[6] + (cetuximab or panitumumab)[3-5]
  (KRAS/NRAS WT and left-sided tumors only)
  → **Progression** → See COL-C 3 of 10
- **or**
  FOLFOXIRI[6] ± bevacizumab
  → **Progression** → See COL-C 4 of 10
- **or**
  5-FU/leucovorin (infusional preferred) ± bevacizumab[7]
  or
  Capecitabine ± bevacizumab[7]
  → **Progression** → See COL-C 5 of 10

Patient not appropriate for intensive therapy[2]

- **Infusional 5-FU + leucovorin ± bevacizumab**
  or
  Capecitabine ± bevacizumab
  or
  (Cetuximab or panitumumab)[3-5]
  (category 2B) (KRAS/NRAS WT and left-sided tumors only
  or
  (Nivolumab or pembrolizumab) (dMMR/MSI-H only)[3]

  → **Improvement in functional status** → **Consider initial therapy as above[8]**

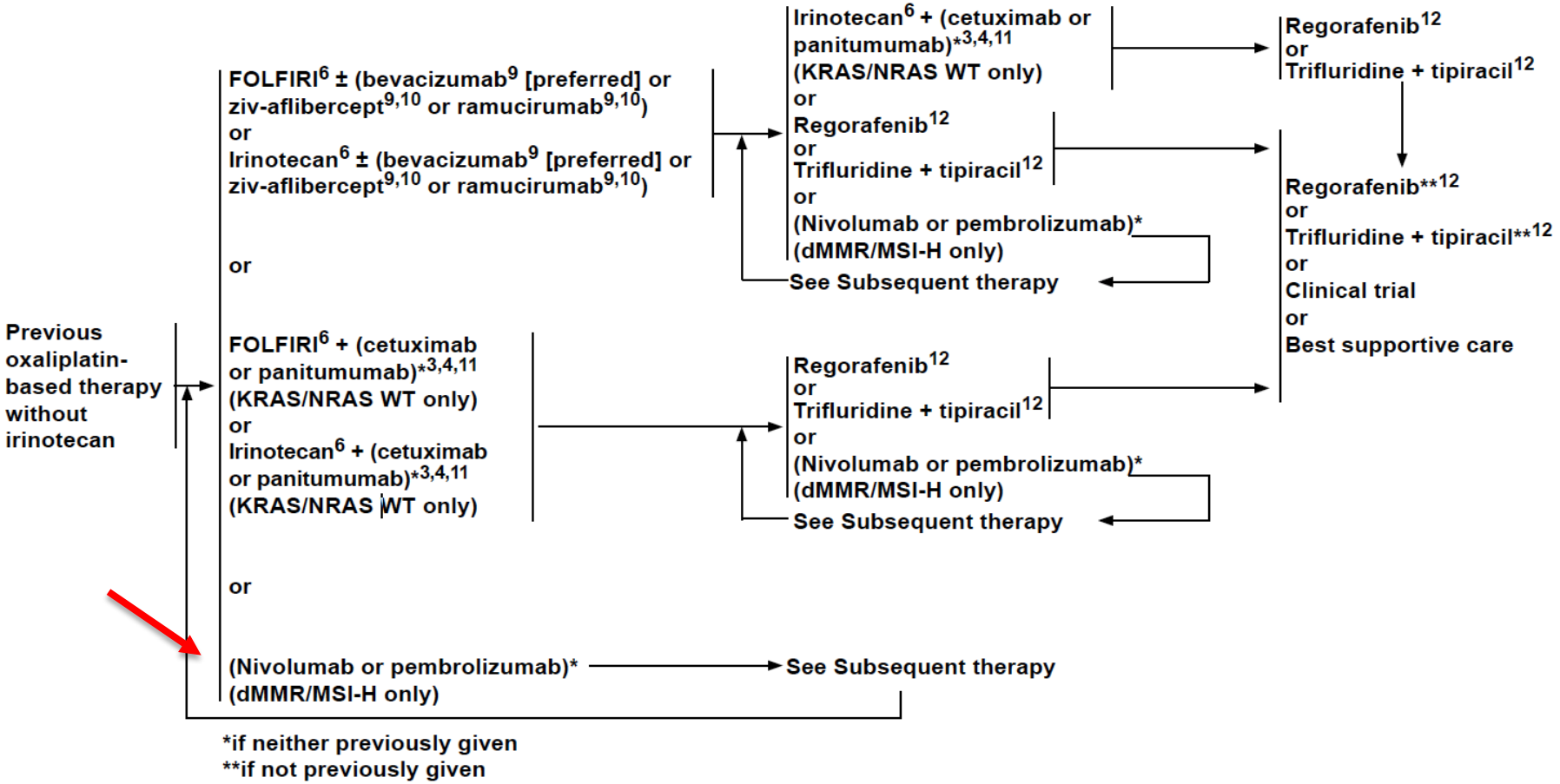
  → **No improvement in functional status** → **Best supportive care**
  See NCCN Guidelines for Palliative Care

See footnotes COL-C 6 of 10

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 2 of 10)

Subsequent Therapy

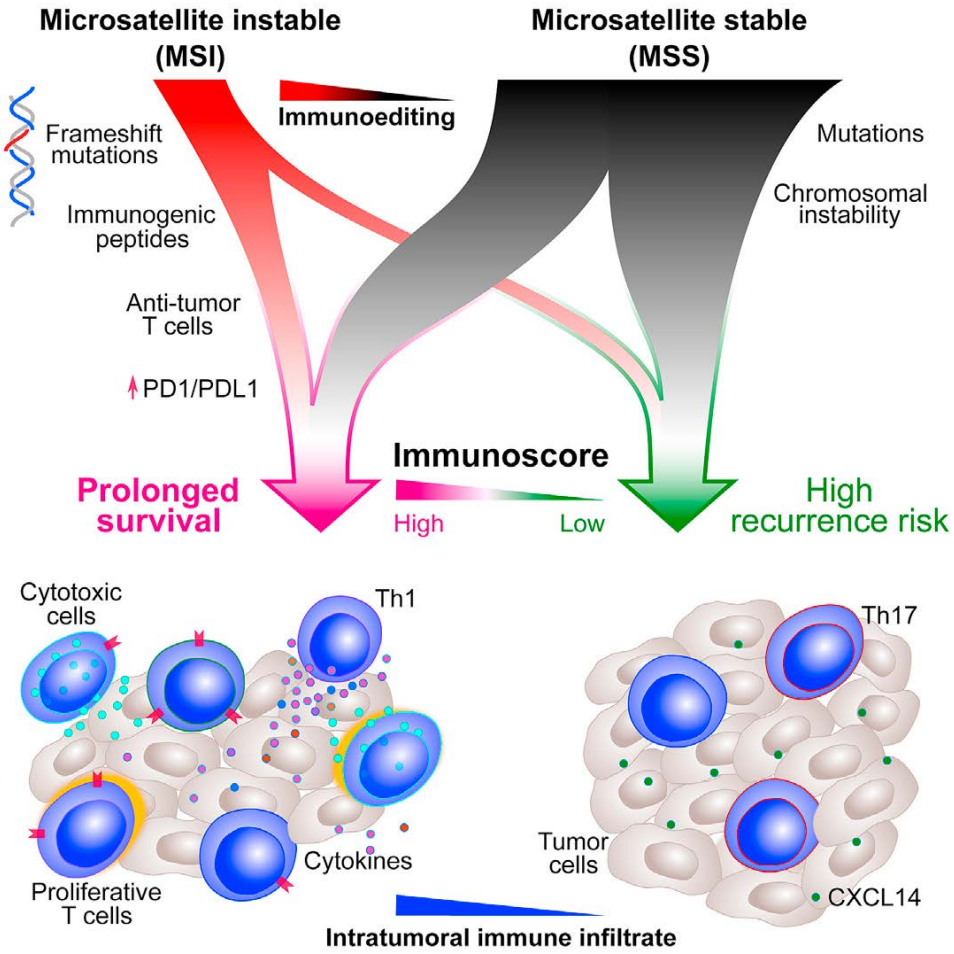


*if neither previously given
**if not previously given

See footnotes COL-C 6 of 10

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Integrative Analyses of Colorectal Cancer Show Immunoscore is a Stronger Predictor of Patient Survival than Microsatellite Instability

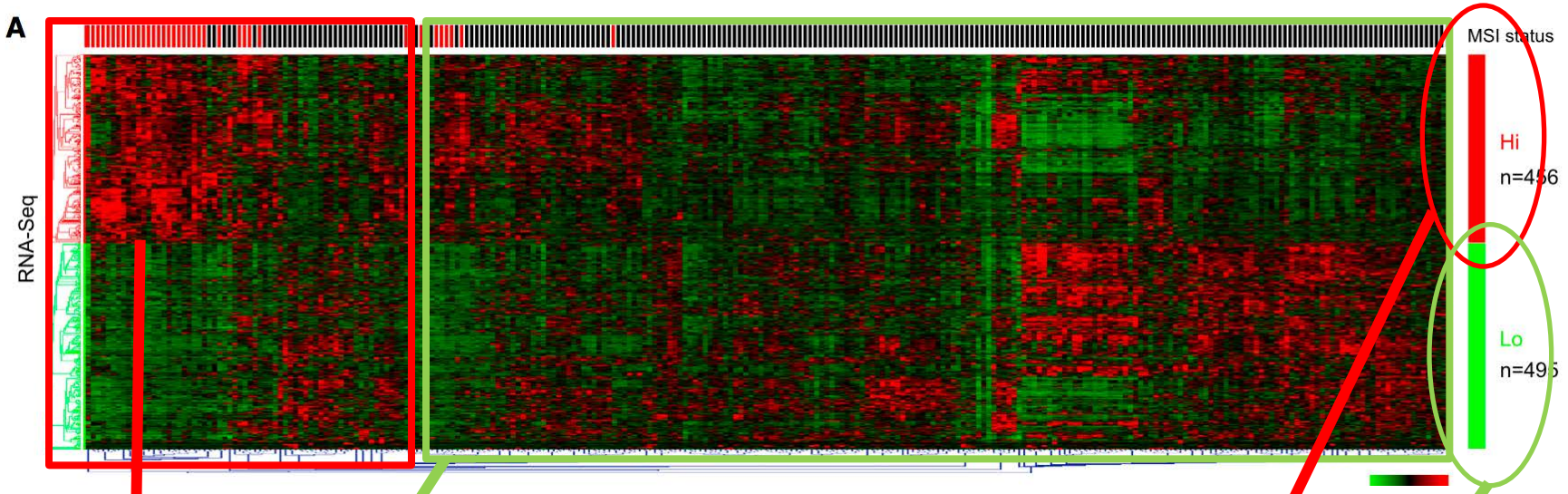


MSI tumours:

- **More responsive to anti-PD1 treatments**
- **Increased numbers of mutations and neoantigens**
- **Dense immune infiltration**
- **High amounts of immune checkpoint molecules**

Mlecnik *et al*. 2016 *Immunity*

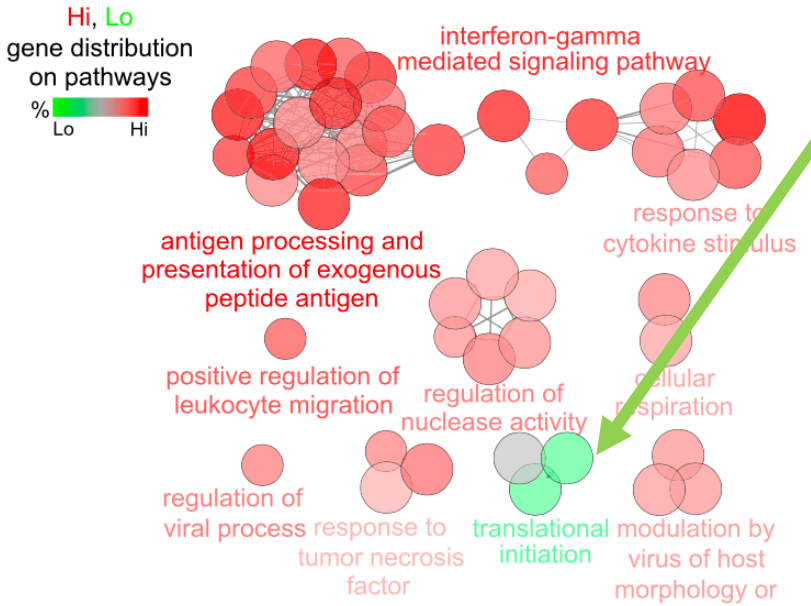
MSI, and a subgroup of MSS, patients have high intratumoural immune gene expression



MSI and subgroup of MSS

Few MSI and most of the MSS

Pathway analysis

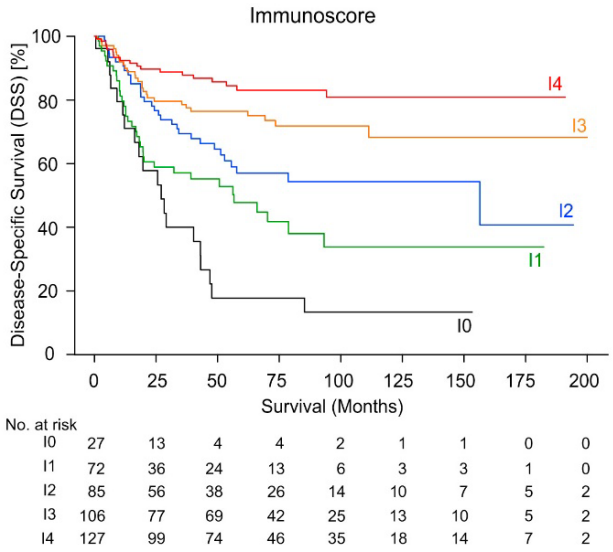


Mlecnik *et al*. 2016 *Immunity*

Immunoscore, but not MSI and Tumour-Staging Parameters, is Significant in Multivariate Analysis for DSS, DFS and OS

Disease-Specific Survival

F



Mlecnik *et al*. 2016 *Immunity*

FINDING CHEMO

5FU — **REDUCES MDSC, INCREASES IFN-gamma producing CD8+ T cells**

OXALIPLATIN — **INCREASES HLA CLASS 1, ENHANCES TUMOUR ANTIGEN CROSS PRESENTATION, SELECTIVELY KILLS MDSC**

BEVACIZUMAB — **MULTIPLE POSITIVE EFFECTS ON ADAPTIVE**

IANCING

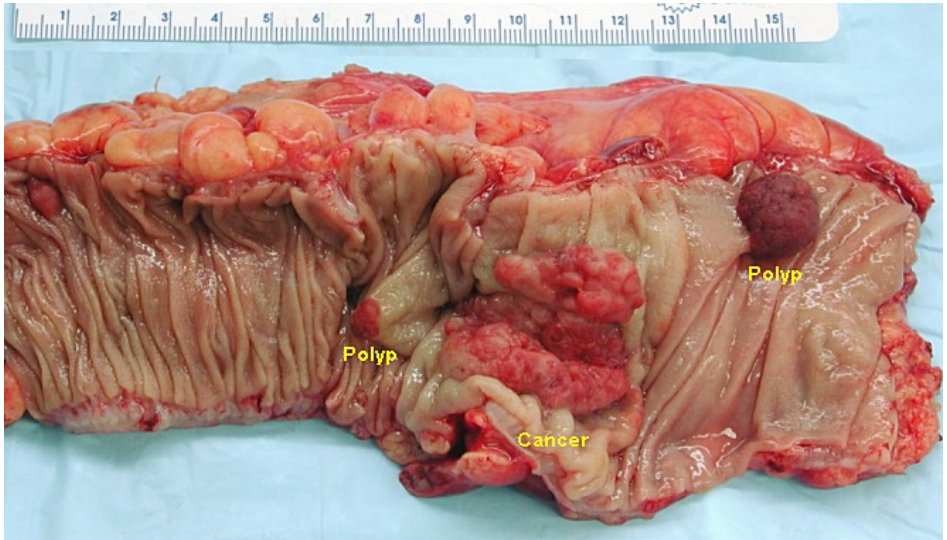
TRASTUZU

Clin Cancer Res 2009;15(24) December 15, 2009

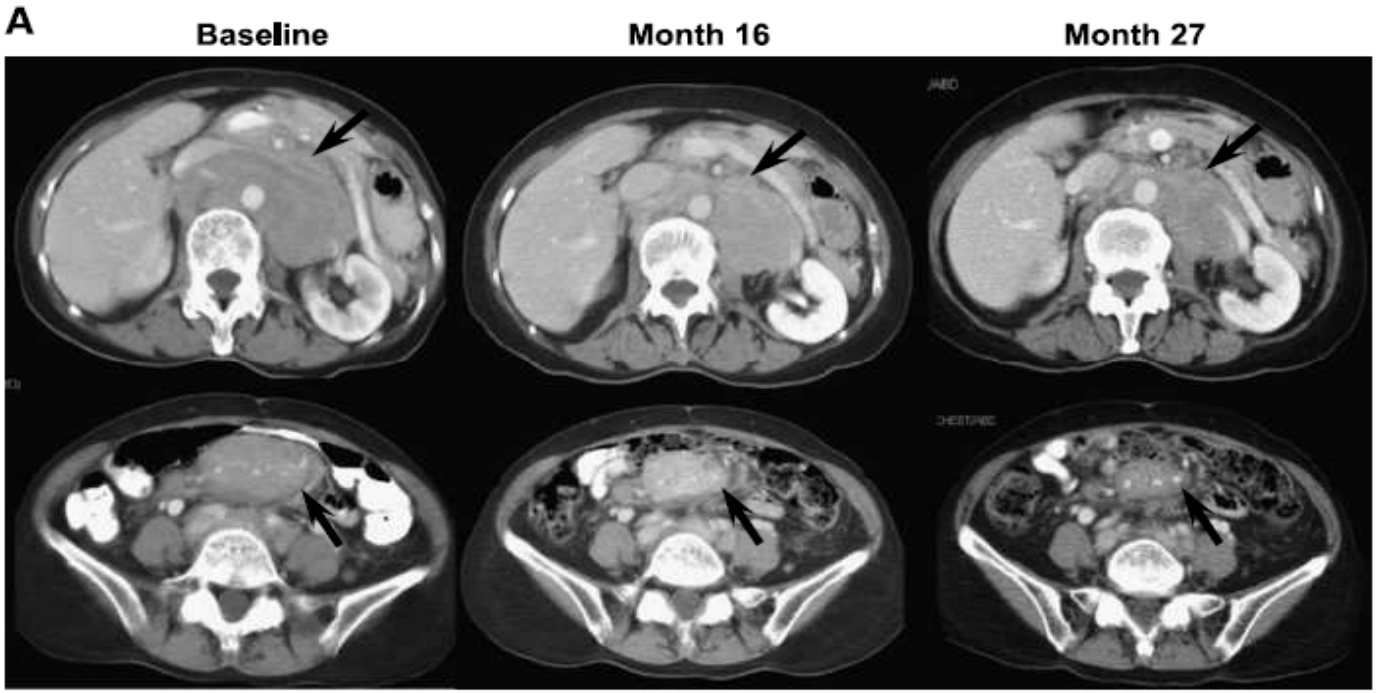
Cancer Therapy: Clinical

Clinical Benefit of Allogeneic Melanoma Cell Lysate–Pulsed Autologous Dendritic Cell Vaccine in MAGE-Positive Colorectal Cancer Patients

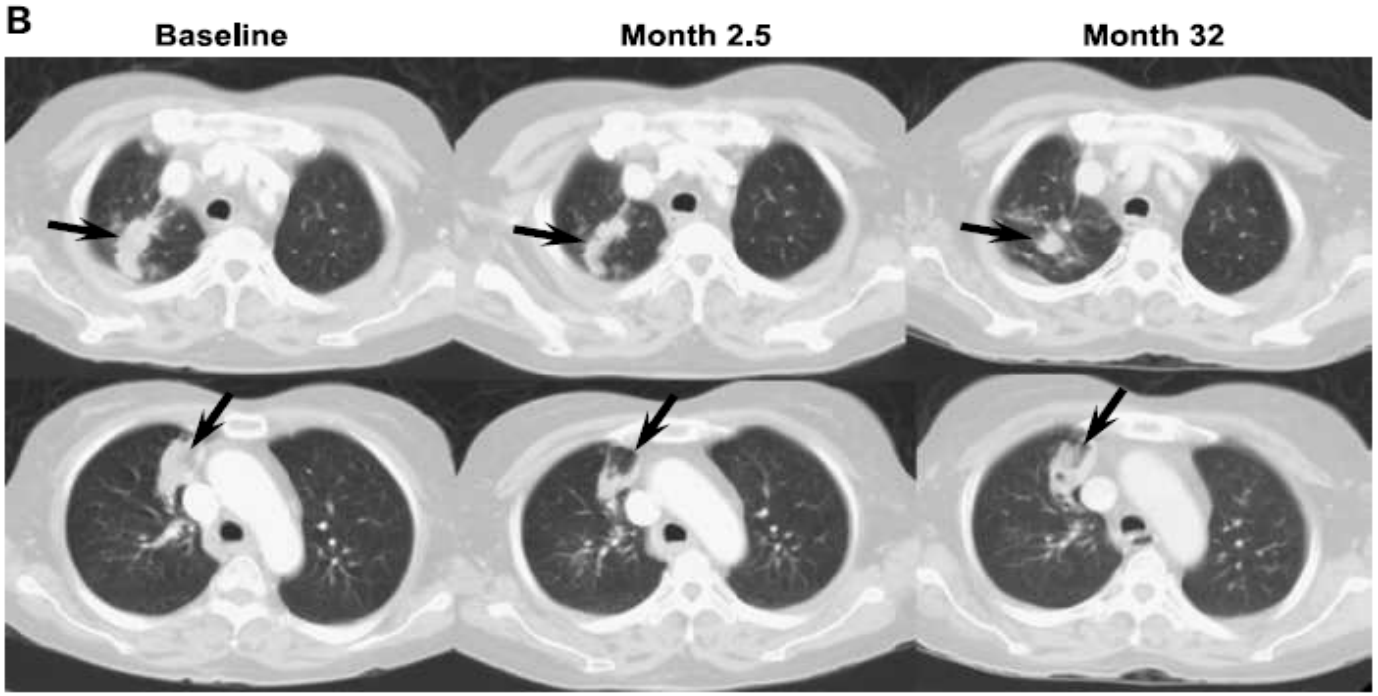
Han Chong Toh,[1] Who-Whong Wang,[1] Whay Kuang Chia,[1] Pia Kvistborg,[2] Li Sun,[3] Kelly Teo,[1] Yee Peng Phoon,[1] Yatanar Soe,[1] Sze Huey Tan,[1] Siew Wan Hee,[1] Kian Fong Foo,[1] Simon Ong,[1] Wen Hsin Koo,[1] Mai-Britt Zocca,[2] and Mogens H. Claesson[4]



Patient 1

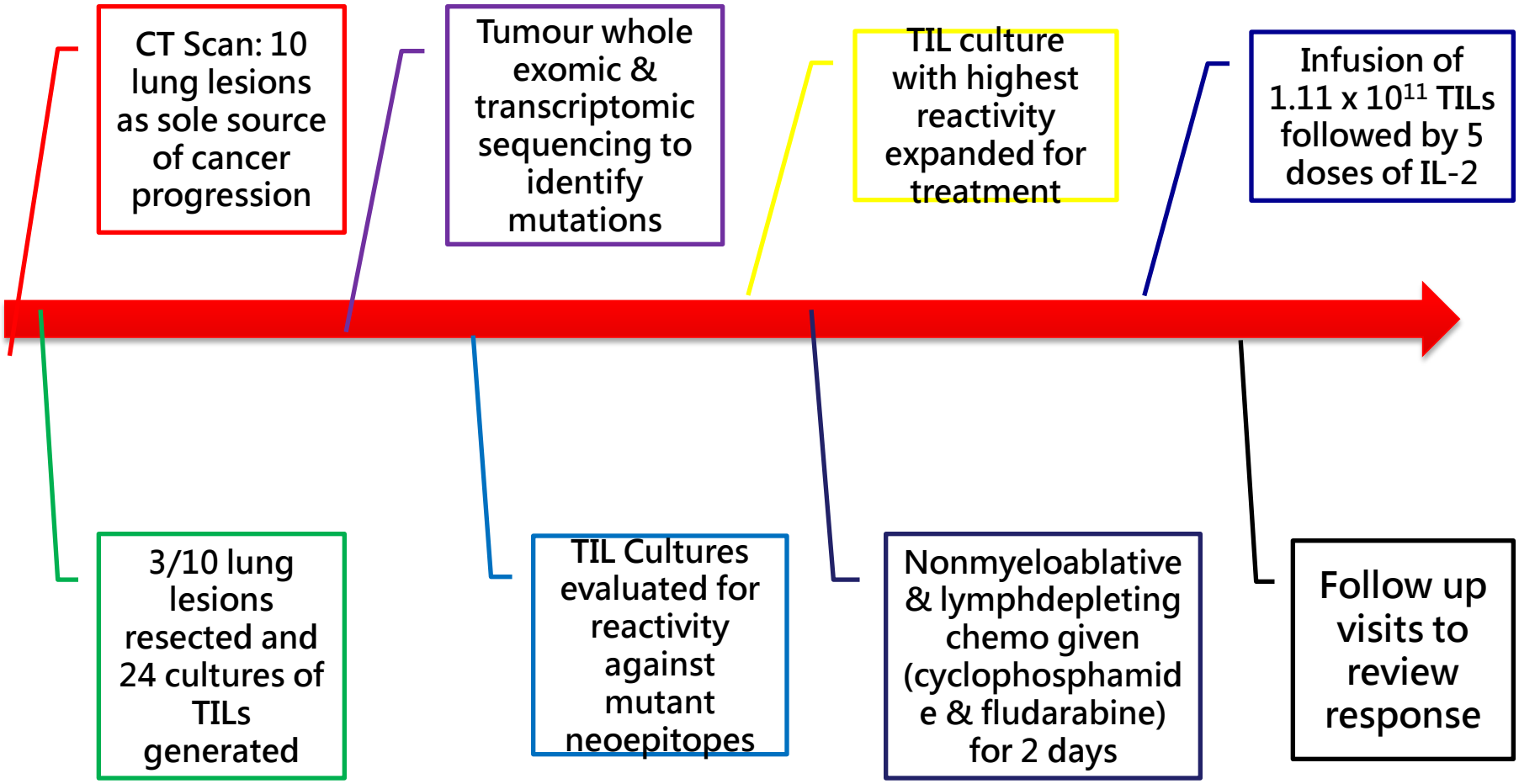


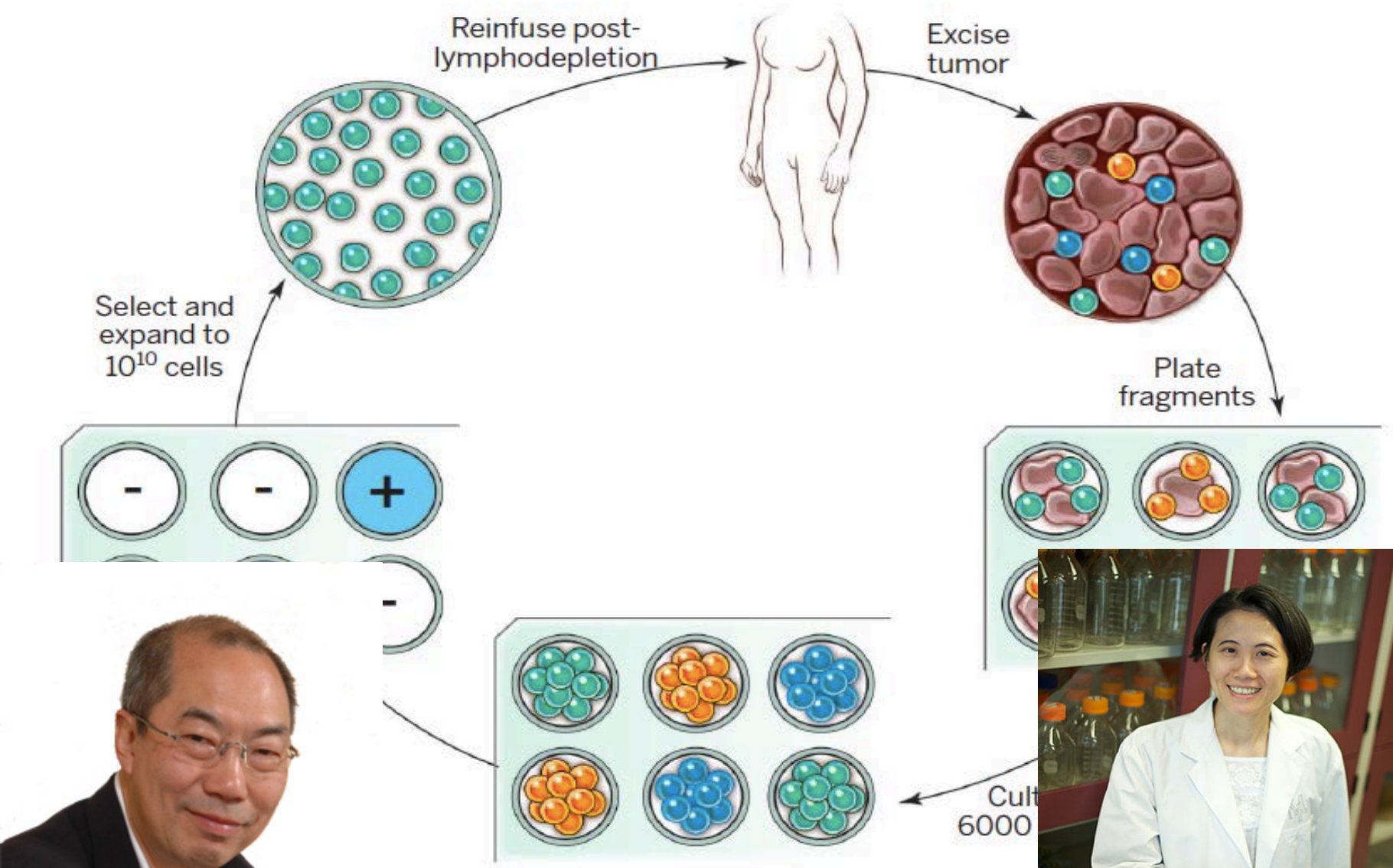
Patient 9



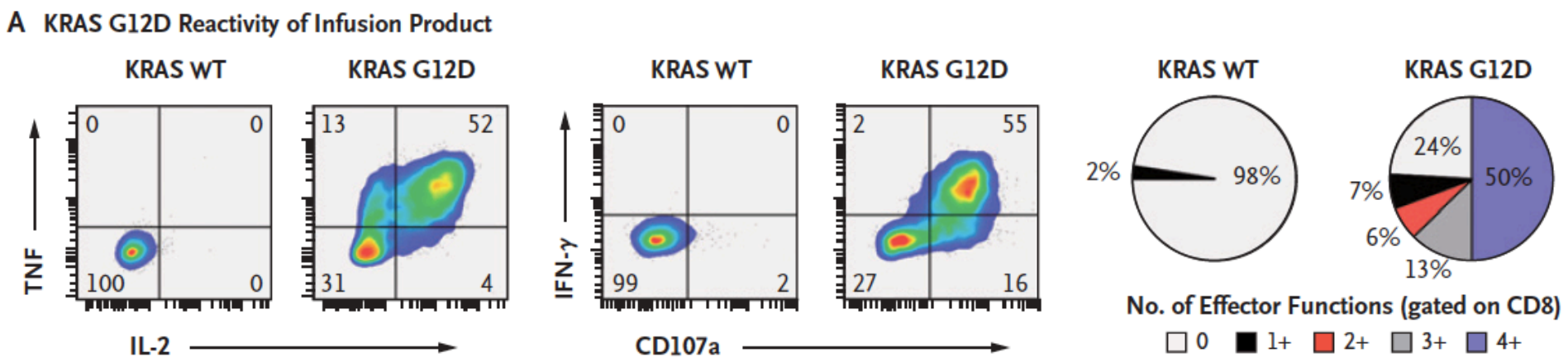
Adoptive T-Cell Transfer Therapy in Metastatic Colon Cancer

50-Year old woman with KRAS-mutant metastatic colon cancer




Reinfuse post-lymphodepletion
Excise tumor
Select and expand to 10^{10} cells
Plate fragments
-
-
+
-
Cult
6000

Rosenberg



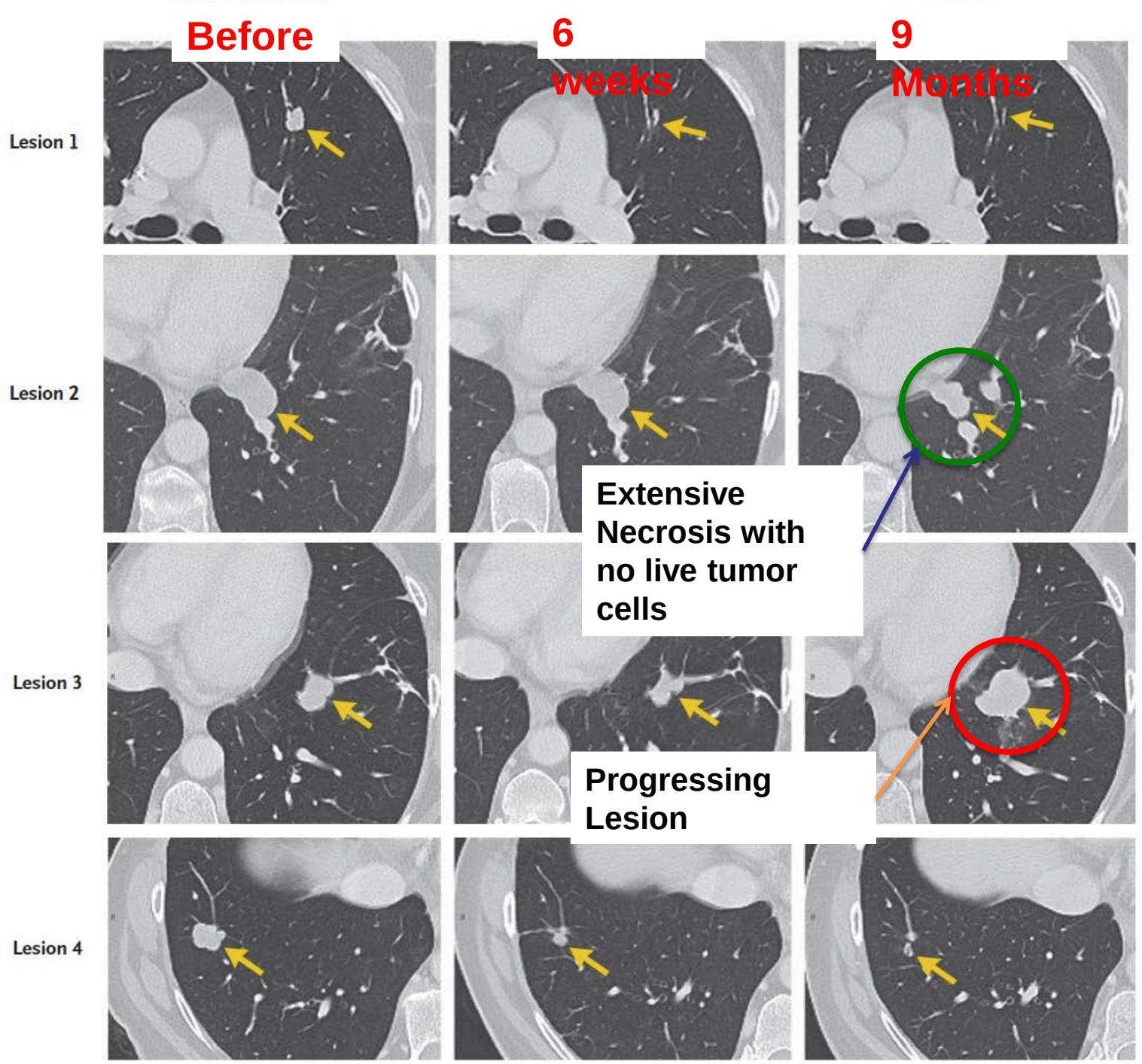
- TILs found to specifically recognize mutant KRAS G12D

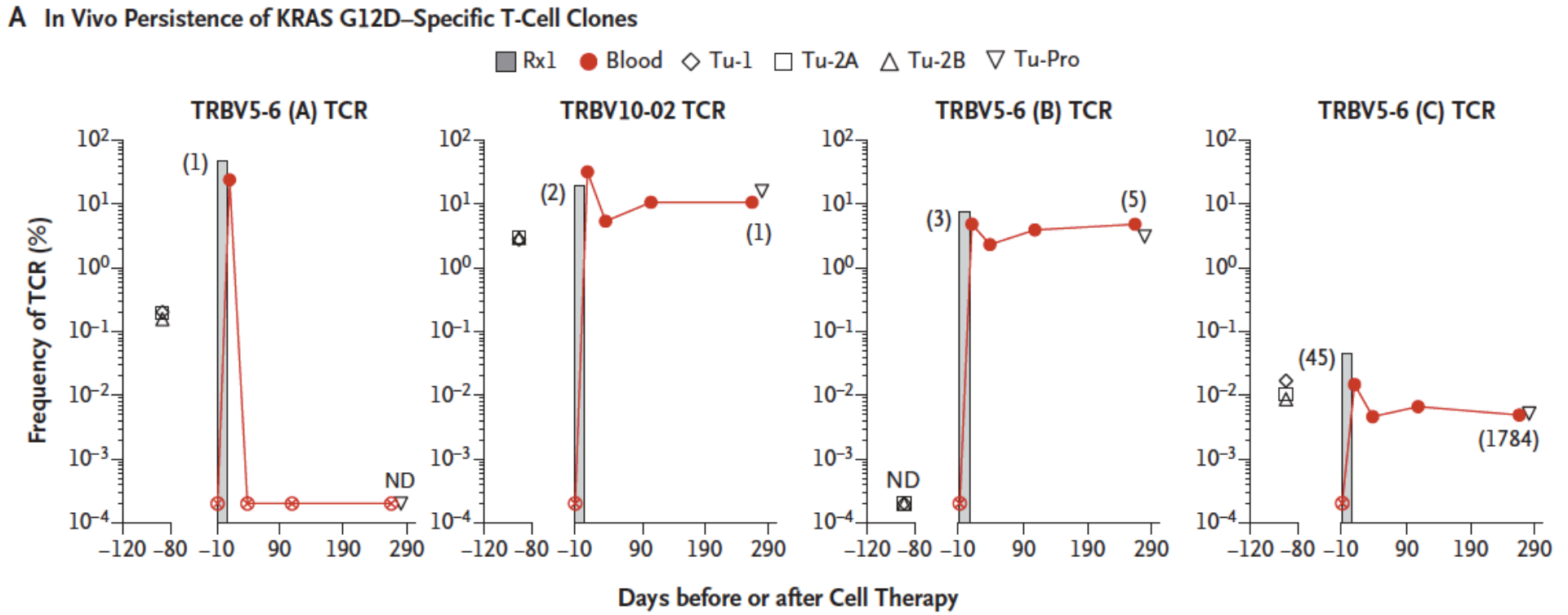
- Culture with highest frequency of G12D reactive CD8+ T cells expanded for treatment

- T-cells in infusion product produced multiple effector cytokines (IFN-y, TNF, IL-2) and showed cytolytic potential

Eric Tran et al. NEJM 2016

CT Scan showing 4/10 lung lesions 6W and 9M post-TILs infusion. Other lesions (not shown here) either completely regressed after 9M or removed for sampling with VATS

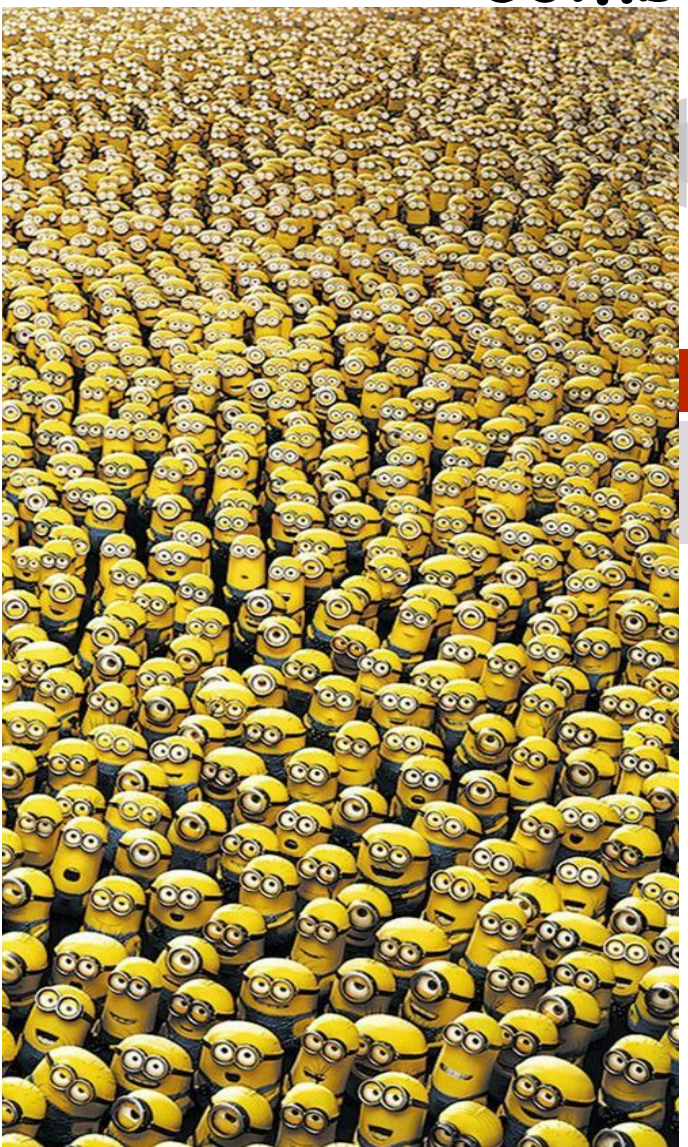




- ¾ T-cell clonotypes persisted in peripheral blood after 9 months
- No enrichment of T-cell clones in progressing tumor relative to blood
- Progressing tumor still expressed KRAS G12D mutation but lost heterozygosity at chromosome 6 which encoded the HLA-C*08:02 allele

Eric Tran et al. NEJM 2016

How can we best treat the other 95% of CRC tumours that are MSS: combination approaches

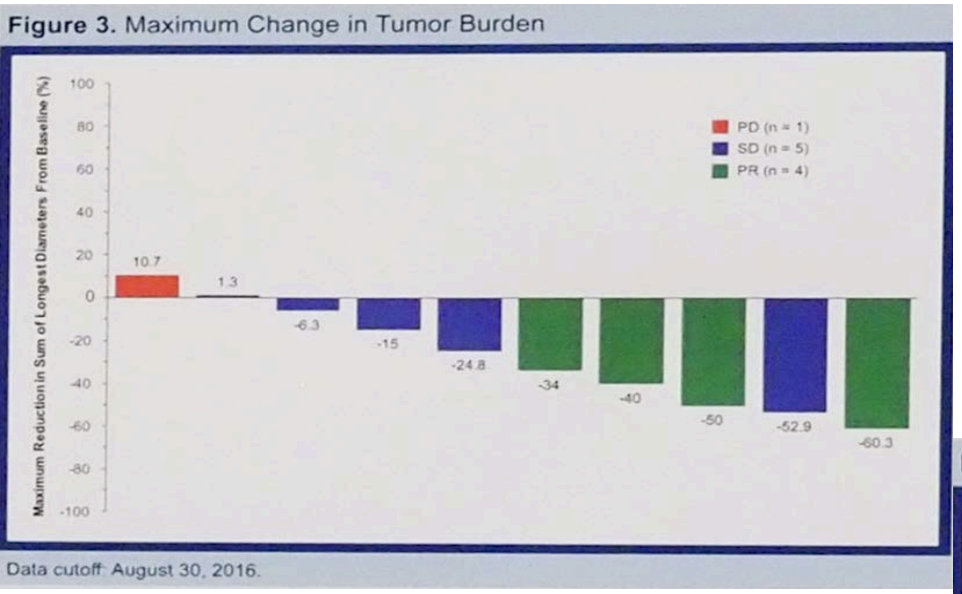


Can we **convert non-inflamed tumors** to become **inflamed?**

IMMUNE EXCLUDED	IMMUNE DESERT
CD8+ T cells accumulated but not efficiently infiltrated	CD8+ T cells absent from tumor and periphery
Bring T cells in contact with cancer cells	Increase number of antigen-specific T cells or increase antigen presentation

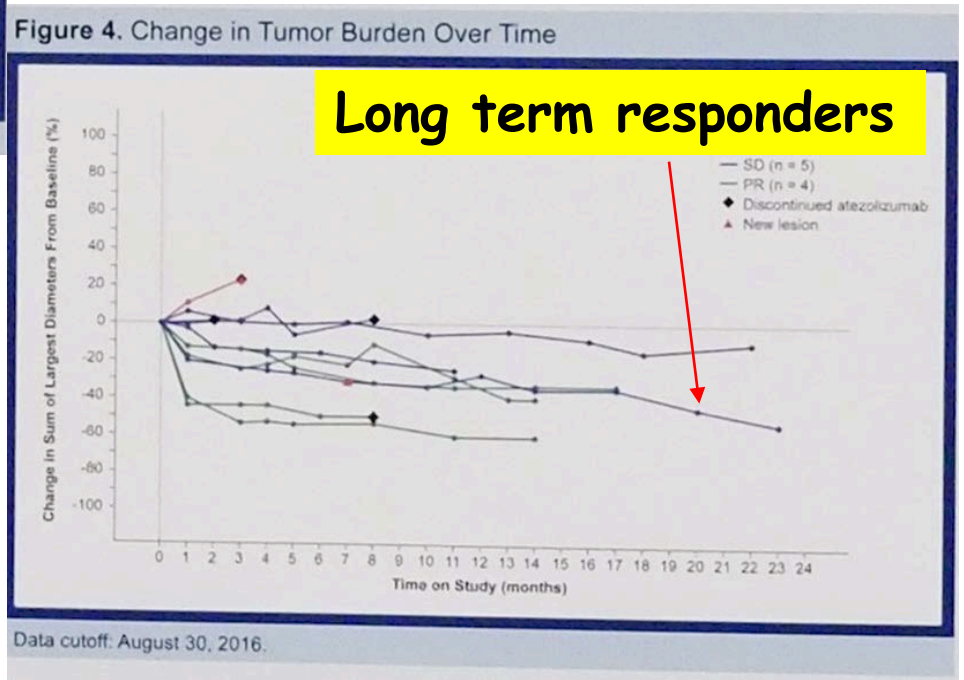
Phase Ib: Atezolizumab and bevacizumab in MSI-H metastatic CRC

(Bevacizumab has a role in lymphocyte tracking and immune regulation)



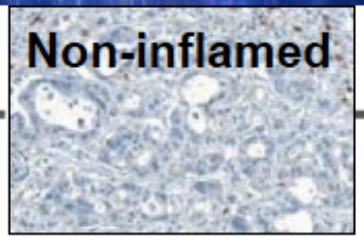
- N= 10
- 40% had 2 lines of therapy
- 70% prior bevacizumab
- Confirmed Lynch Syndrome in 30%

- ORR= 40%
- CR= 0%
- PR= 40%
- SD= 50%
- DCR= 90%



Hochester H et al. ASCO 2016

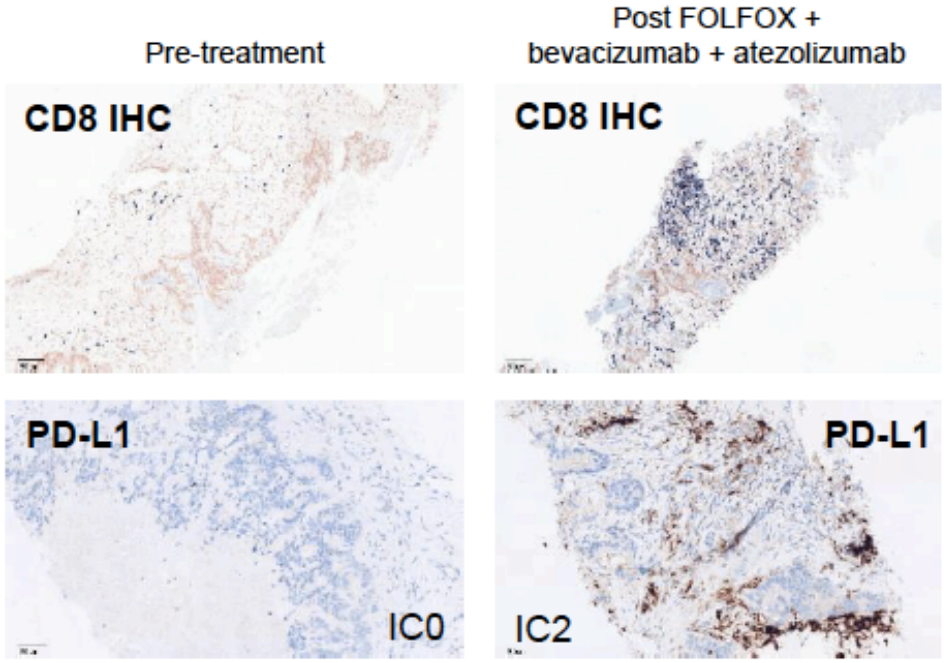
Emerging clinical data on the ability to convert "non-inflamed" to "inflamed" tumors with chemotherapy and/or targeted therapies



Chemotherapy combinations with atezolizumab in NSCLC

PD-L1 IHC level	ORR % (n/total)
TC3 or IC3	84% (5/6)
TC2 or IC2	27% (3/11)
TC1 or IC1	29% (2/7)
TC0 or IC0	57% (8/14)

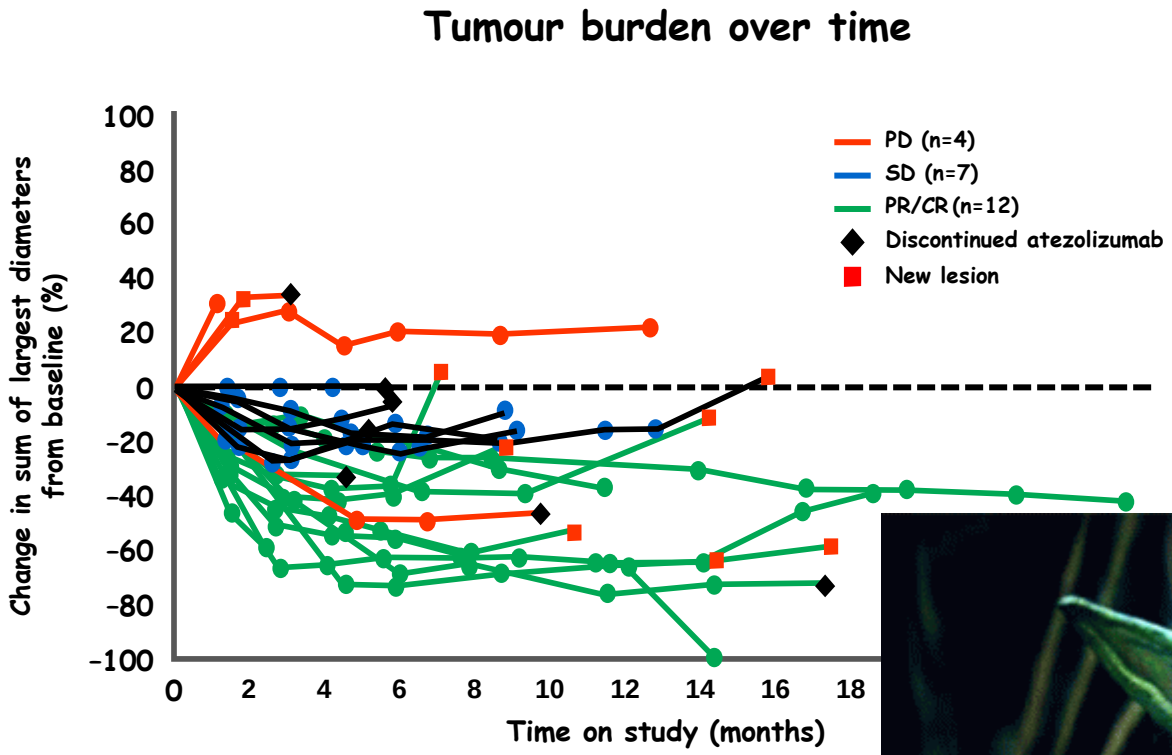
Chemotherapy combinations with atezolizumab in CRC



Giaccone et. al. ECC 2015
Chen CRI EATI CIMT AACR 2015

U Colorado (PI Eckhardt)

Atezolizumab plus Bevacizumab and/or FOLFOX in mCRC: phase Ib



Patient number	ORR	mPFS	DOR
23	52%	14.1 months	11.4 months

- 3/9 patients treated beyond 15 months continue to be on treatment
- No unexpected toxicities

Nivolumab ± Ipilimumab in Treatment of Patients With Metastatic Colorectal Cancer With or Without High Microsatellite Instability: CheckMate 142 Interim Results

(Q2W)

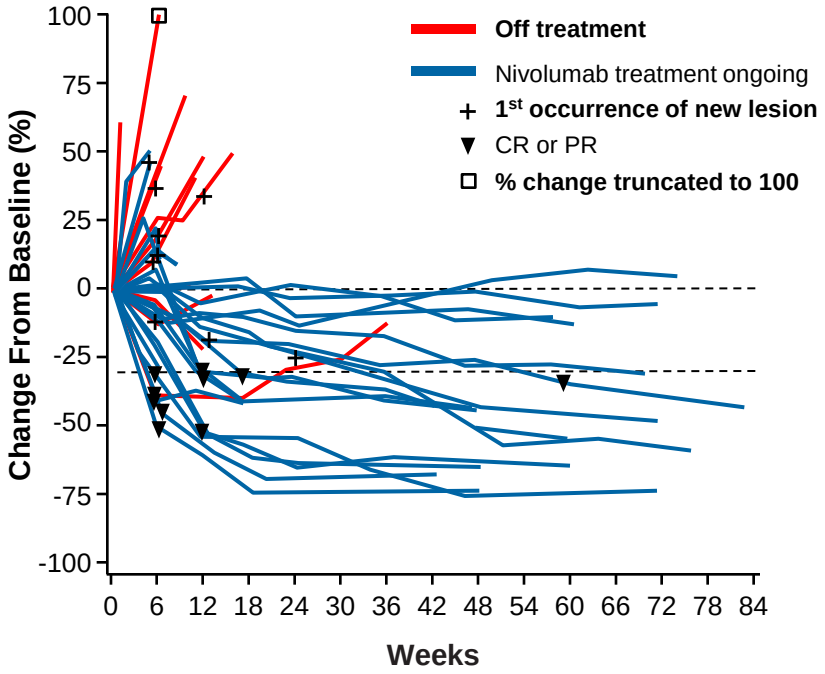
- Primary end point : ORR
- 40% RAS wild type
- 50% > = 3 lines of therapy

Overman M et al. ASCO 2016.

Nivolumab ± Ipilimumab in Treatment of Patients With Metastatic Colorectal Cancer With High Microsatellite Instability:

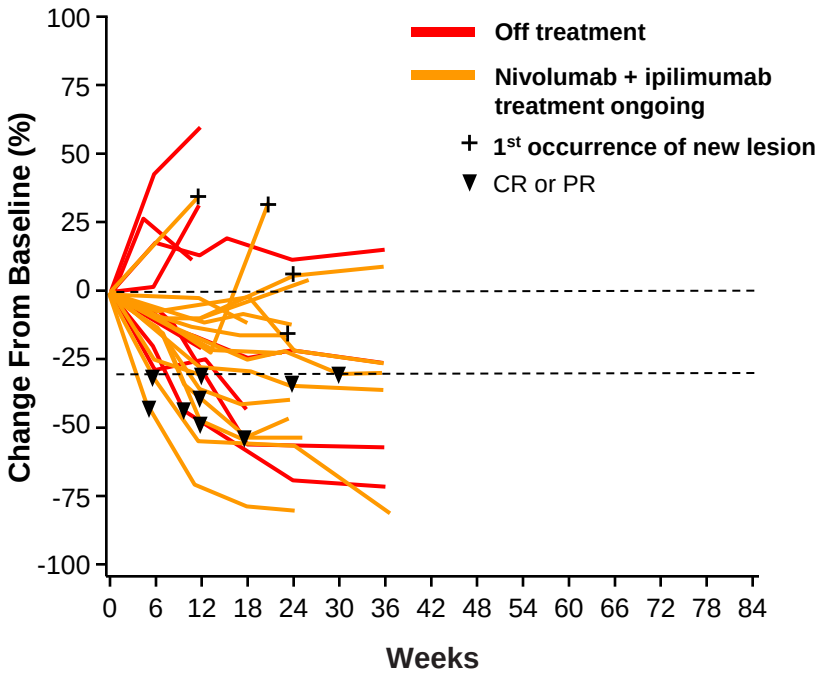
CheckMate 142 Interim Results

Nivolumab 3 mg/kg



ORR = 25.5 %
SD = 29.8%
CR = 0%
Median time to response : 2.12 m
PFS = 5.3 m

Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg

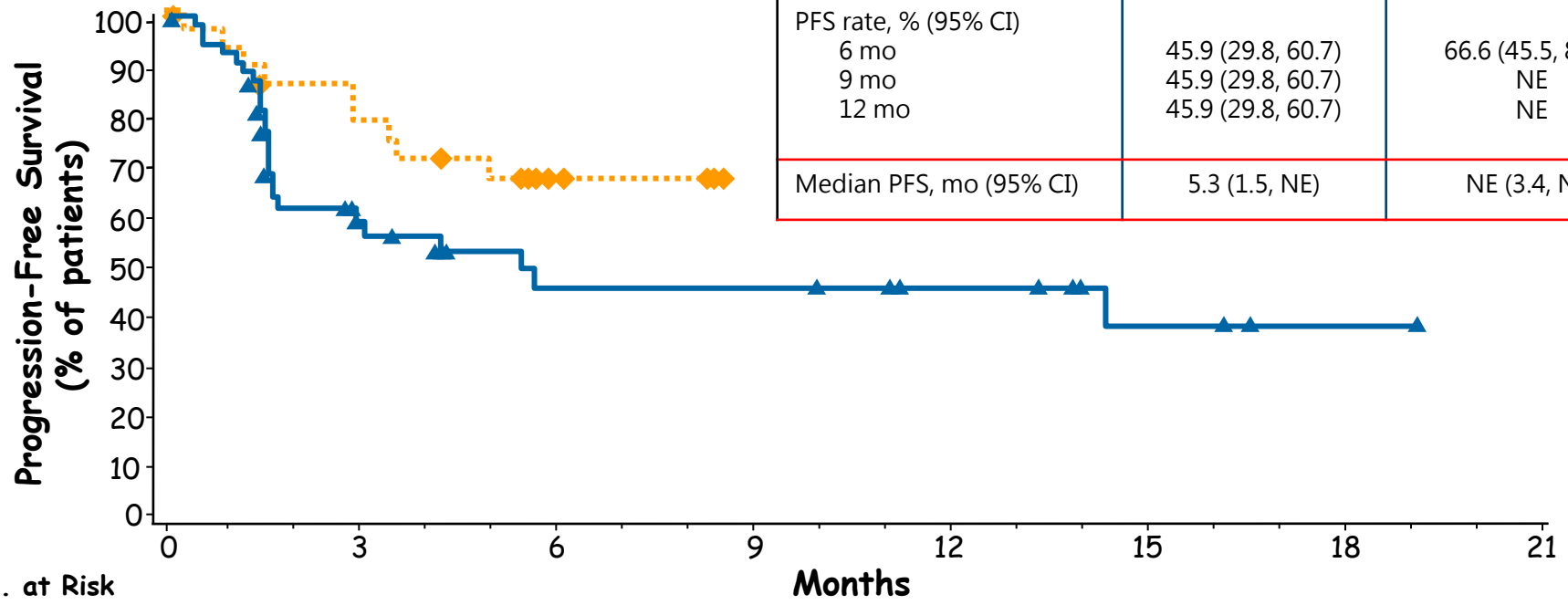


ORR = 33.3 %
SD = 51.9%
CR = 0%
Median time to response : 2.73 m
PFS = not reached

Investigator-Assessed PFS in Patients With MSI-H

Nivolumab ± Ipilimumab in Metastatic CRC

	Nivolumab 3 mg/kg (n = 70)	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n = 30)
PFS rate, % (95% CI)		
6 mo	45.9 (29.8, 60.7)	66.6 (45.5, 81.1)
9 mo	45.9 (29.8, 60.7)	NE
12 mo	45.9 (29.8, 60.7)	NE
Median PFS, mo (95% CI)	5.3 (1.5, NE)	NE (3.4, NE)



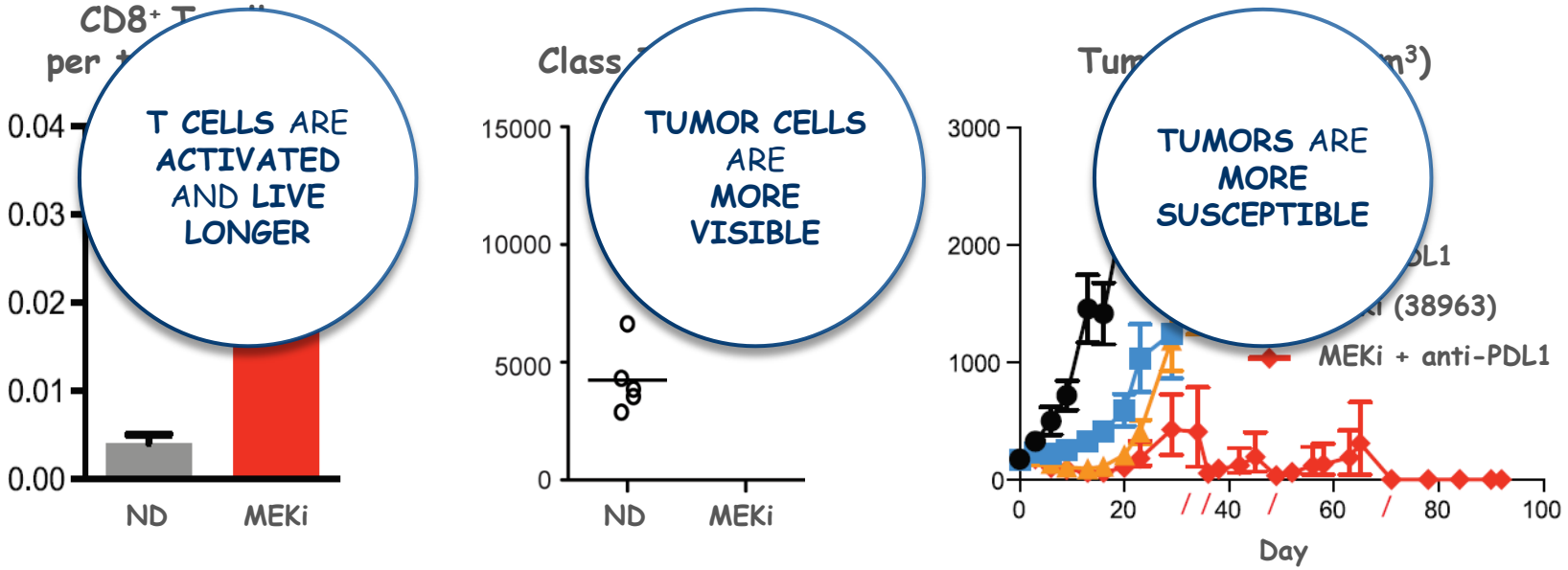
No. at Risk							
Nivolumab	70	19	13	13	9	5	1	0
Nivolumab + Ipilimumab	30	21	7	0	0	0	0	0

NE = not estimable

Data in perspective!

	Pembro Keynote -12	Nivolumab Checkmate 40 MSI-H	Nivo/Ipi Checkmate 40 MSI-H	Nivo/Ipi (3mg) Checkmate 40 MSS
ORR	57%	25.5%	33.3%	10% (1/10)
SD	32%	29.8%	51.9%	
CR	11%	0%	0%	
PFS	NR	5.3m	NR	2.28m
OS	NR	17.1m	NR	11.53m

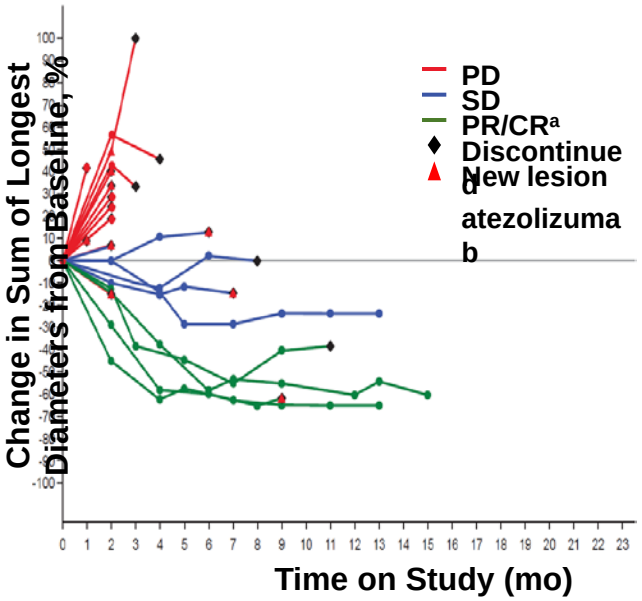
MEK inhibition has a direct effect on T cells and the tumor microenvironment



A more favorable tumor microenvironment from MEK inhibition may help to unlock the full anti-tumor potential of PD-1/ PD-L1 inhibition

PJ Ebert et al. Immunity 2016

Clinical activity and safety of cobimetinib and atezolizumab in colorectal cancer: Phase Ib dose escalation and expansion study



- Median duration of response was not reached (range: 5.4 to 11.1+ mo)
- Responses are ongoing in 2 of 4 responding patients

KRAS mutant chemo refractory cohort
ORR = 20%
PR = 20%
SD 20%
Median time to response 3.7 m
Of the 4 patients who had a PR 3 had pMMR tumor

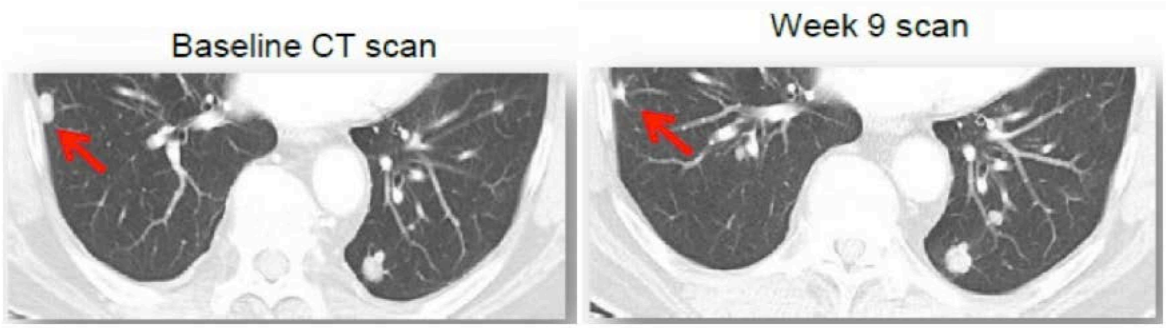
	Median PFS (95% CI)	6-mo PFS (95% CI)	Median OS (95% CI)	6-mo OS (95% CI)
KRAS Mutant CRC Cohort (n = 20)	2.3 mo (1.8, 9.5)	39% (0.16, 0.61)	NE (6.5, NE)	77% (0.57, 0.97)
All CRC patients (N = 23)	2.3 mo (1.8, 9.5)	35% (0.14, 0.56)	NE (6.5, NE)	72% (0.52, 0.93)

Data in perspective!

	Pembro Keynote -12	Nivolumab Checkmate 40 MSI-H	Nivo/Ipi Checkmate 40 MSI-H	Atezo/ cobemetinib pMMR
ORR	57%	25.5%	33.3%	20%
SD	32%	29.8%	51.9%	20%
CR	11%	0%	0%	0%
PFS	NR	5.3m	NR	2.3m
OS	NR	17.1m	NR	NR

Non-randomized phase II study to assess the efficacy of pembrolizumab (Pem) plus radiotherapy (RT) or ablation in mismatch repair proficient (pMMR) metastatic colorectal cancer (mCRC) patients.

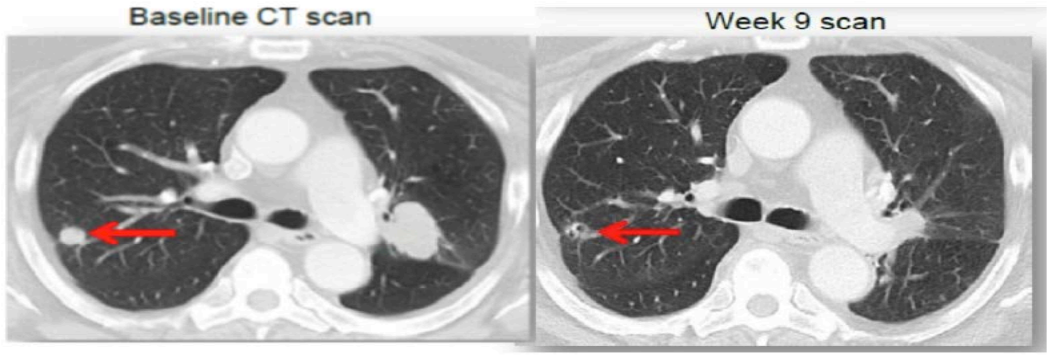
- **One year Objective**: Response rate
- **Key eligibility**: A lesion for which palliative RT or ablation is standard therapy, and another lesion for RECIST
- **Treatment:** RT or ablation within 1 week prior to pembrolizumab 200mg Q3W



Patient 1: RT to the liver

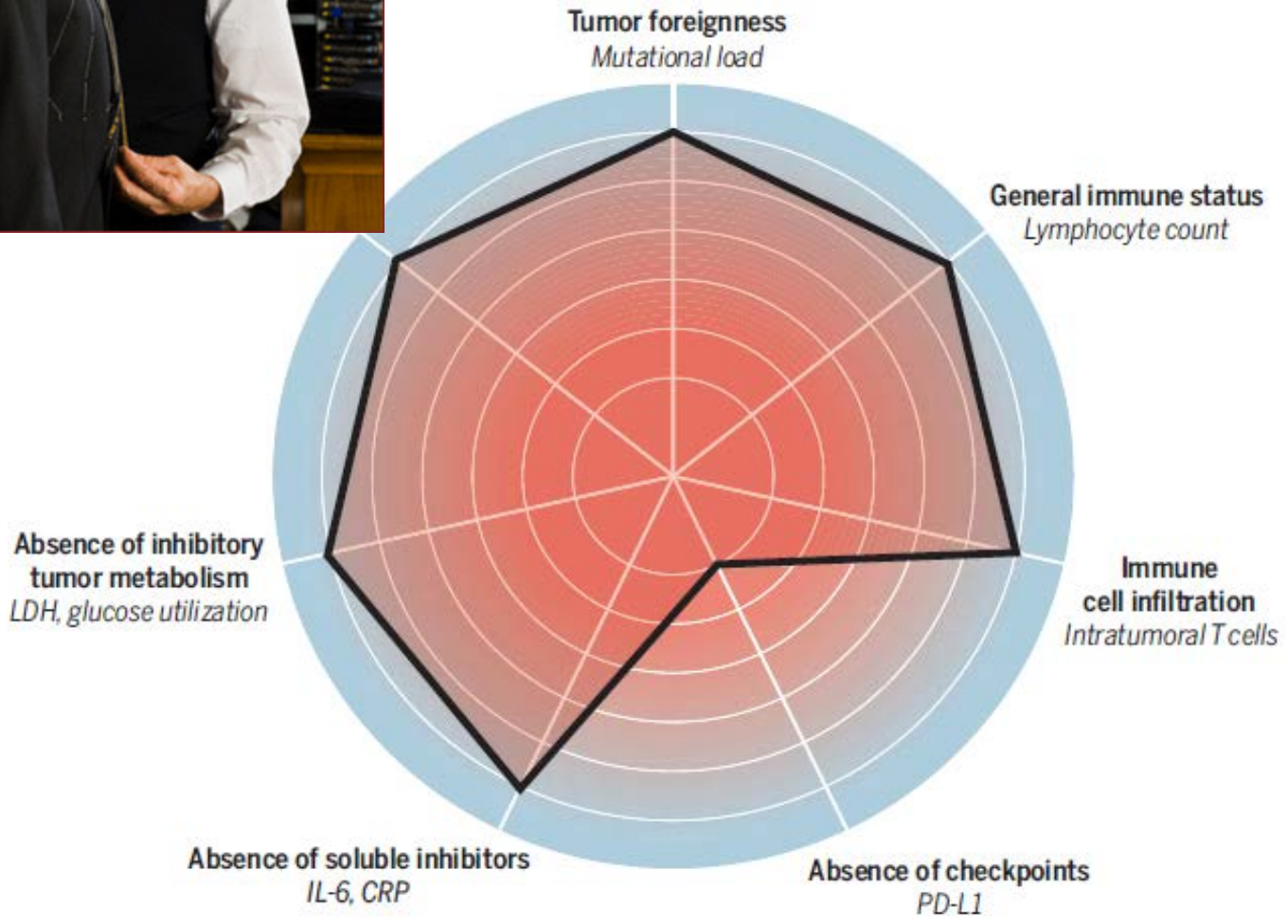
Patient 2: RT to the hilum

- No response in the ablation cohort
- RT cohort: 1 PR (4.5%) and 2 mixed response (9%)
- DOR : 4.1 months
- One patient on treatment beyond 42 weeks



Segal et al. ASCO 2016.

n Cancer Immunogram (? even each cancer lesion) :
ed solution based on immunogram

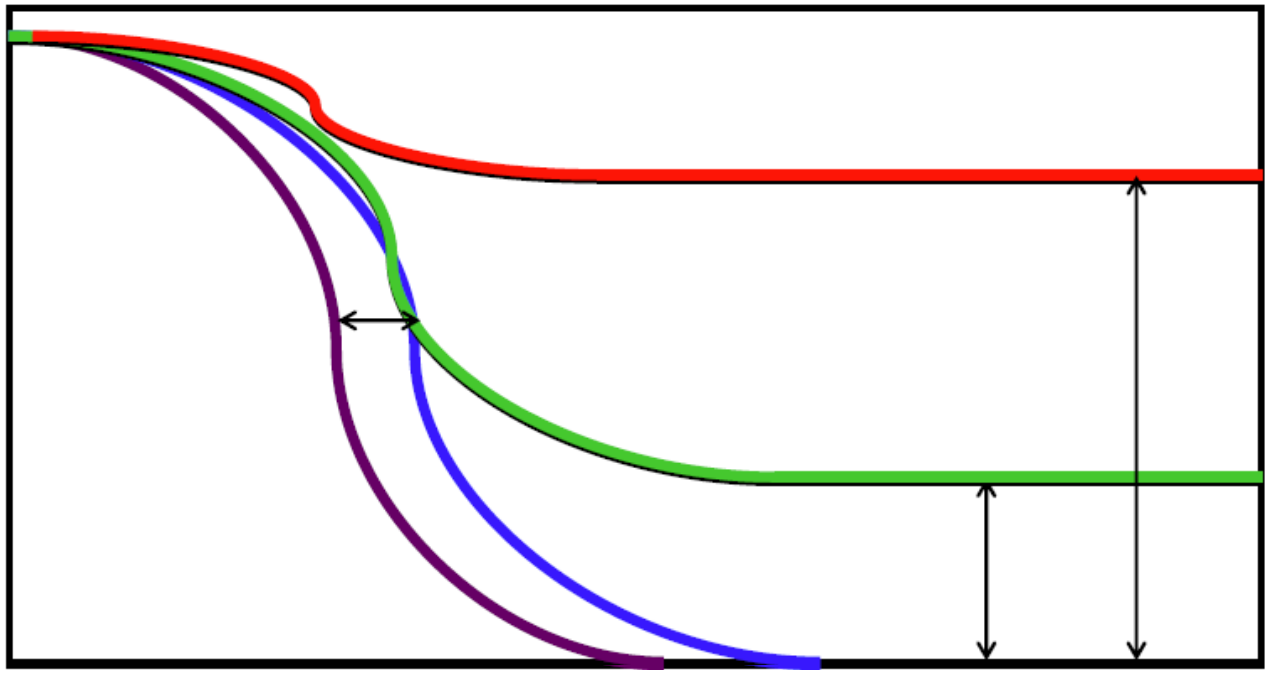


Blank, Haanen, Ribas, Schumacher, Science 2016

Key lessons

- **Key lesson 1:** Good single agent activity of ICP in the dMMR/MSI-H subtype of mCRC
- **Key lesson 2:** Emerging combination strategy to overcome resistance and converting " Cold tumors " to " inflamed tumors"
- **Key Lesson 3:** We are going to have to find biomarkers other than MMR to more broadly select patients for immunotherapy

Is This the Beginning of a Cure for Cancer?



No Treatment

Immune Checkpoint blockade

Standard Treatment

Combination Treatment

Thank You


APGCS
2017
AMGEN