Tumor Immunology in colorectal cancers

From basic biology to clinical practice

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INSERM team 15 « Integrative Cancer Immunology »

Disclosures

- ✓ No conflict of interest

Collaborative Research Agreement (grant):

. BioMerieux, HalioDx

Participation to Scientific Advisory Boards & Meetings:

. BMS, Roche, Janssen, Merck

Consultant:

. Sanofi

Patents: * methods for prognostic evaluation of cancer

** INSERM patents #05292200.2 (2005), 2010, 2011*
"Method for prognostic evaluation of colorectal cancer and other cancers"

From bench to bedside

After years of controversy,…..

Immunotherapies have become the hot new thing in cancer drug development

2013

checkpoint inhibitors

. Ac anti- CTLA-4
. Ac anti- PD-1
. Ac anti- PD-L1

FDA
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Melanoma approved

Lung cancer (NSCLC) approved

Renal cancer

Bladder cancer

Head and neck

Hodgkin disease

Gastric / oesophagus cancer

Ovarian cancer

Lung cancer (SCLC)

MSI+ colorectal cancers

Merkel cell carcinoma

Mesothelioma

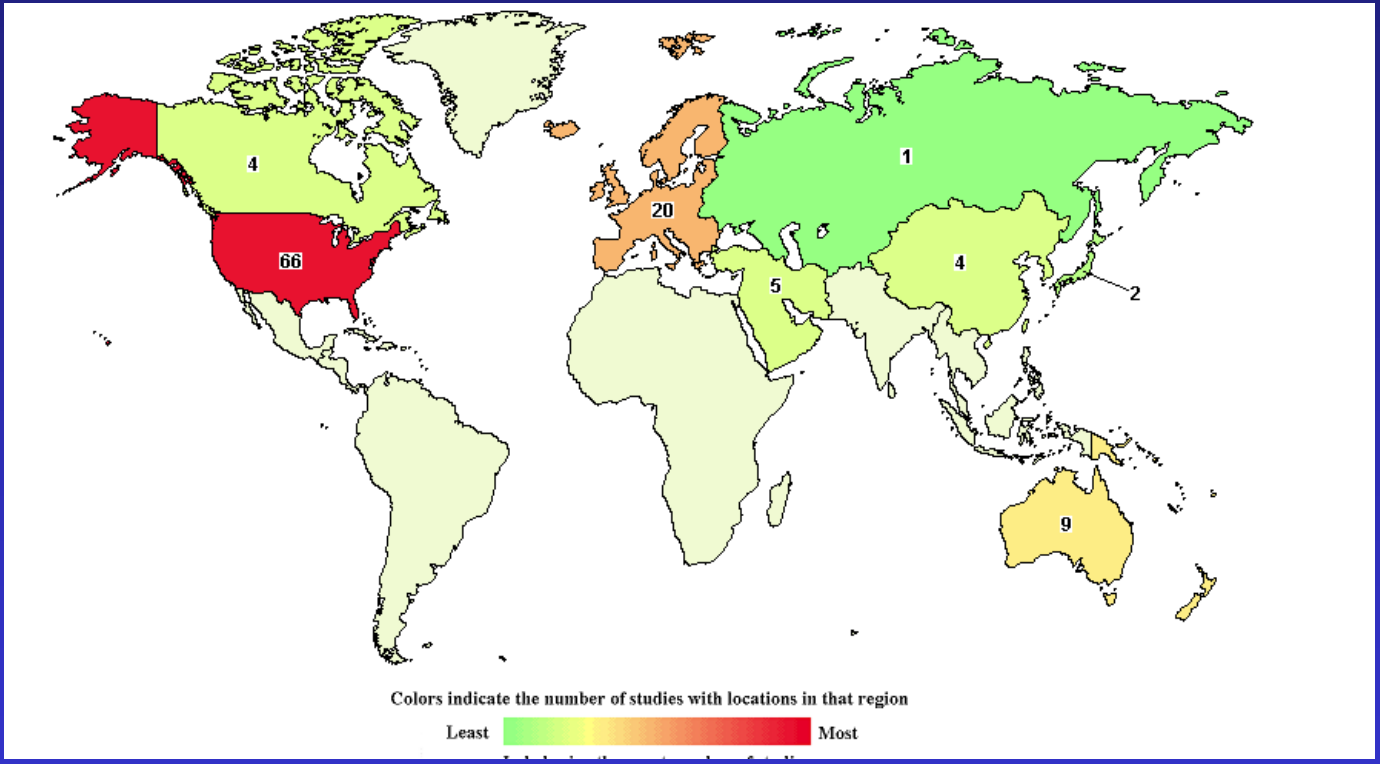
Hepatocarcinoma

Triple negative breast cancer

Clinical Trials with immune checkpoint inhibitors

Juin 2016

Anti-PD-1 ou anti-PD-L1 : 107 open studies



Immunotherapies have become the hot new thing in cancer drug development

June 3-7, 2016
McCormick Place | Chicago, Illinois
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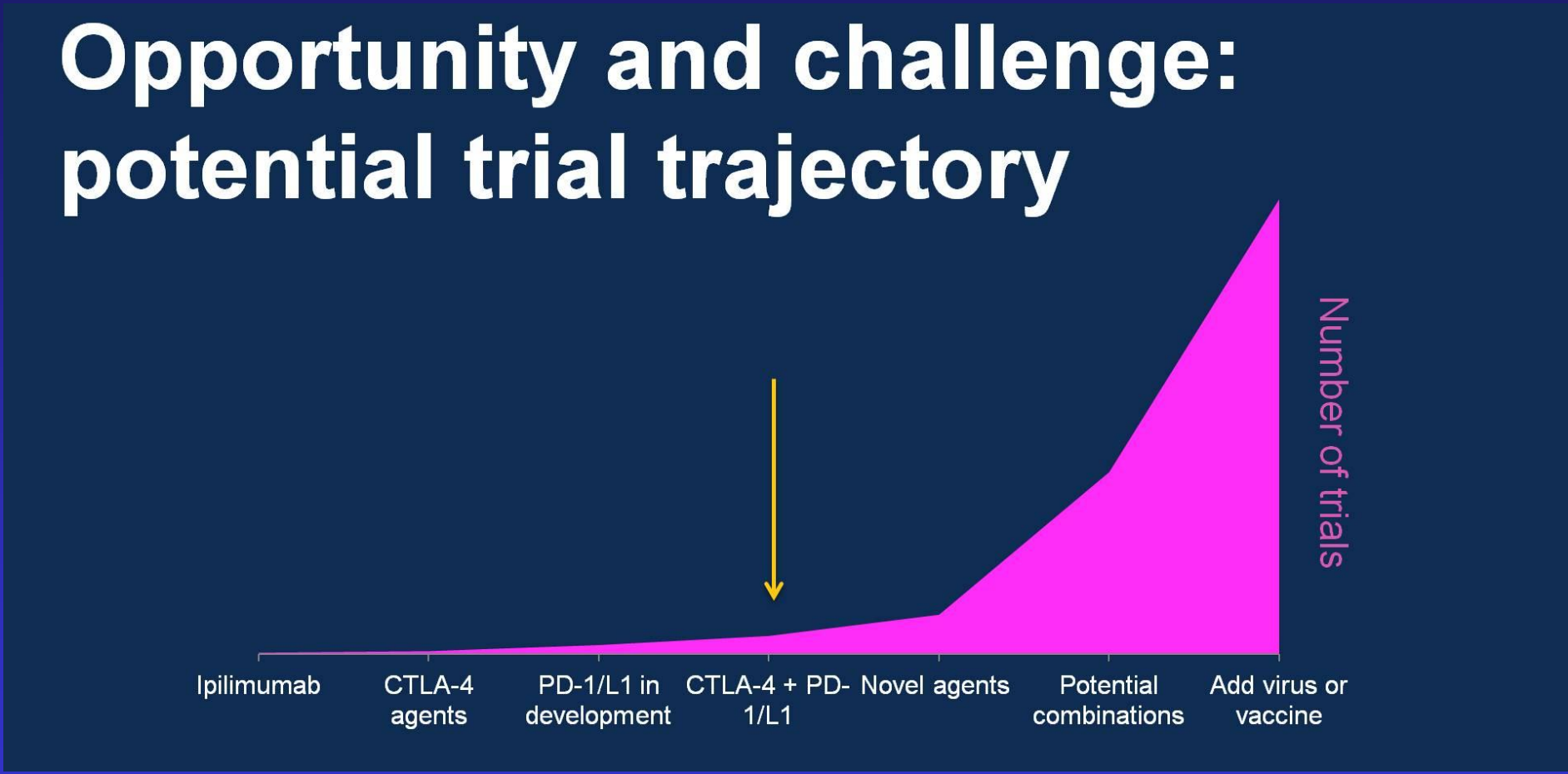
ASCO

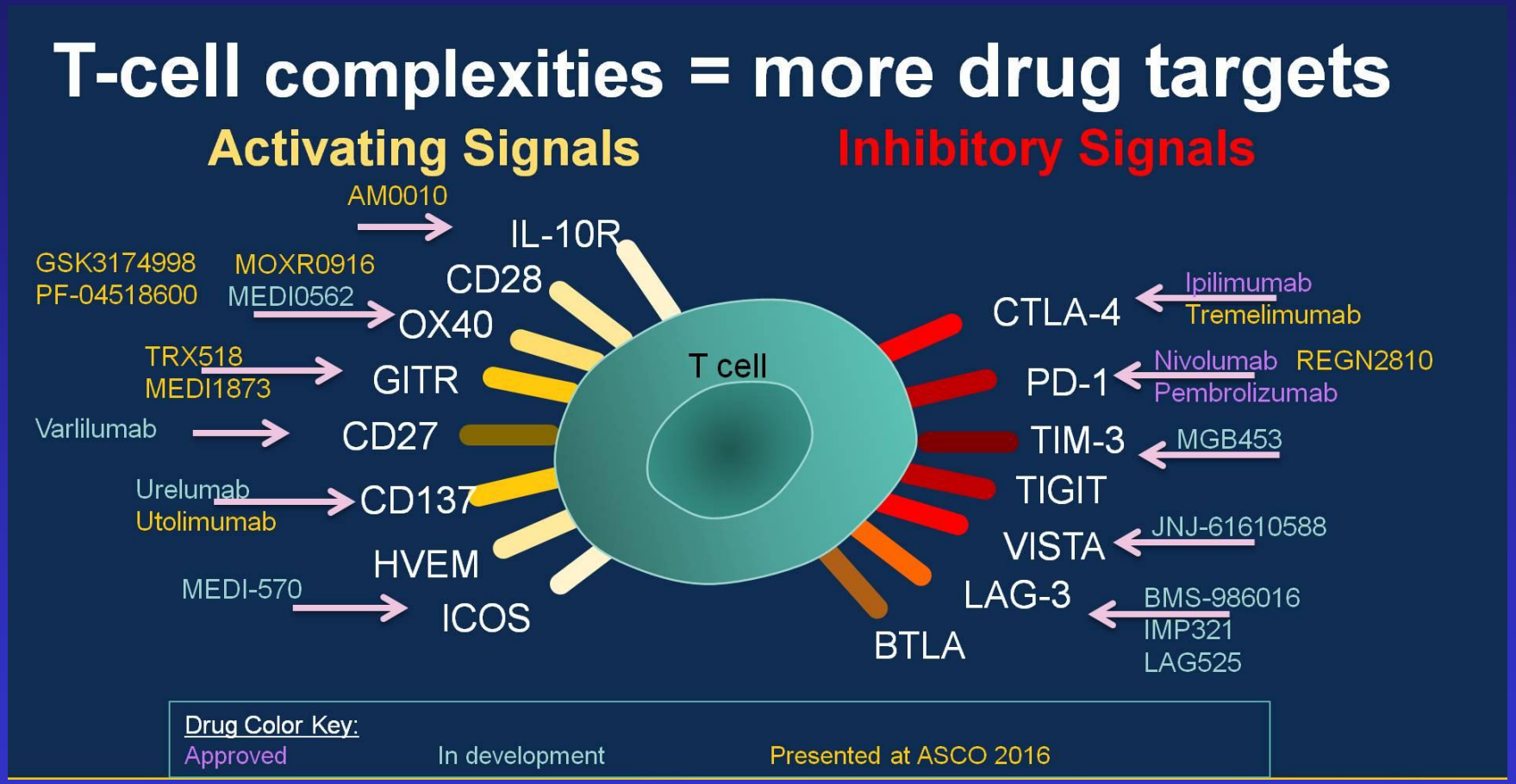
Ac anti-PD-1 (BMS)

From bench to bedside



Presented By J. Chaft at 2016 ASCO Annual Meeting

From bench to bedside



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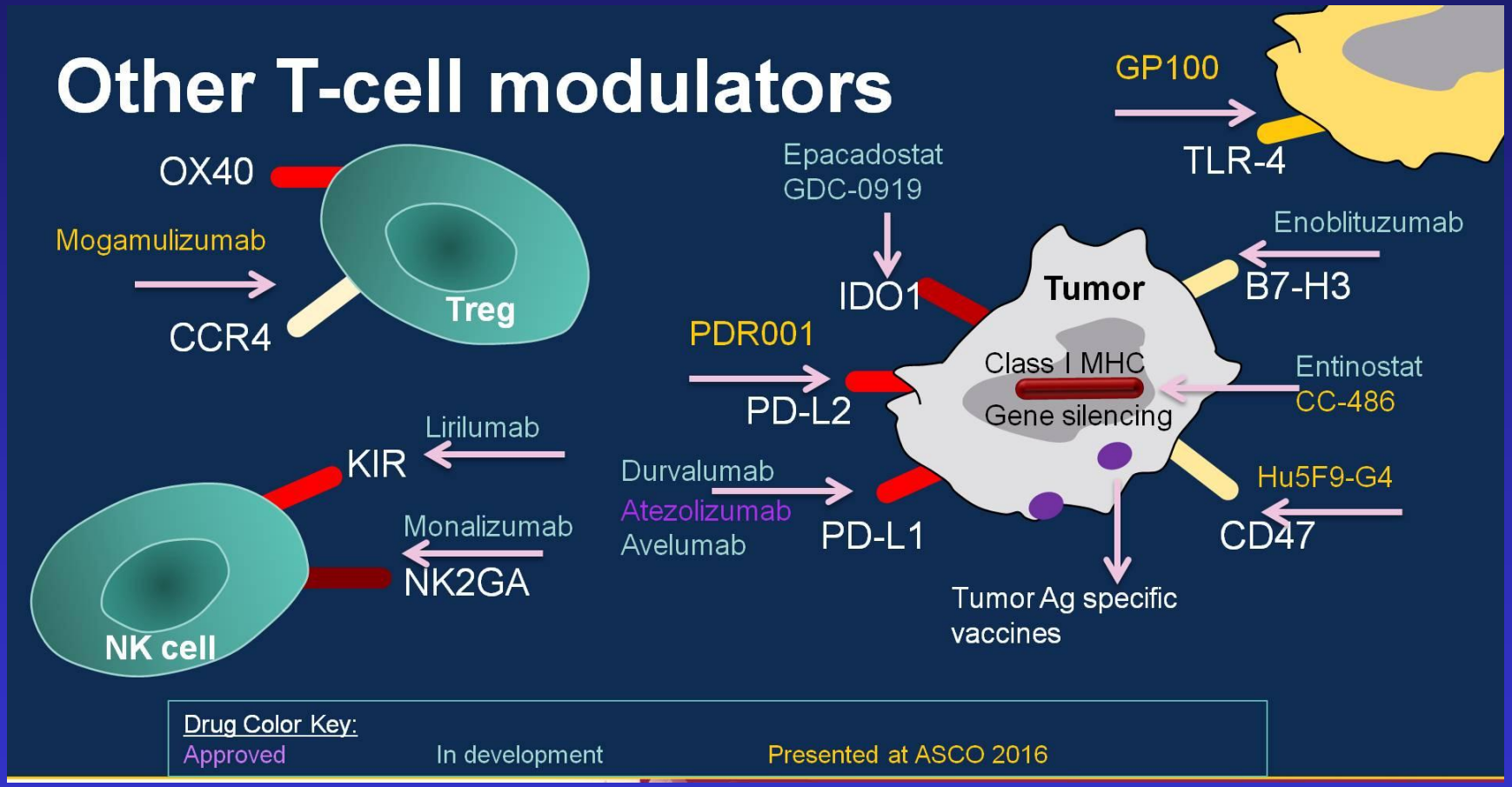
From bench to bedside



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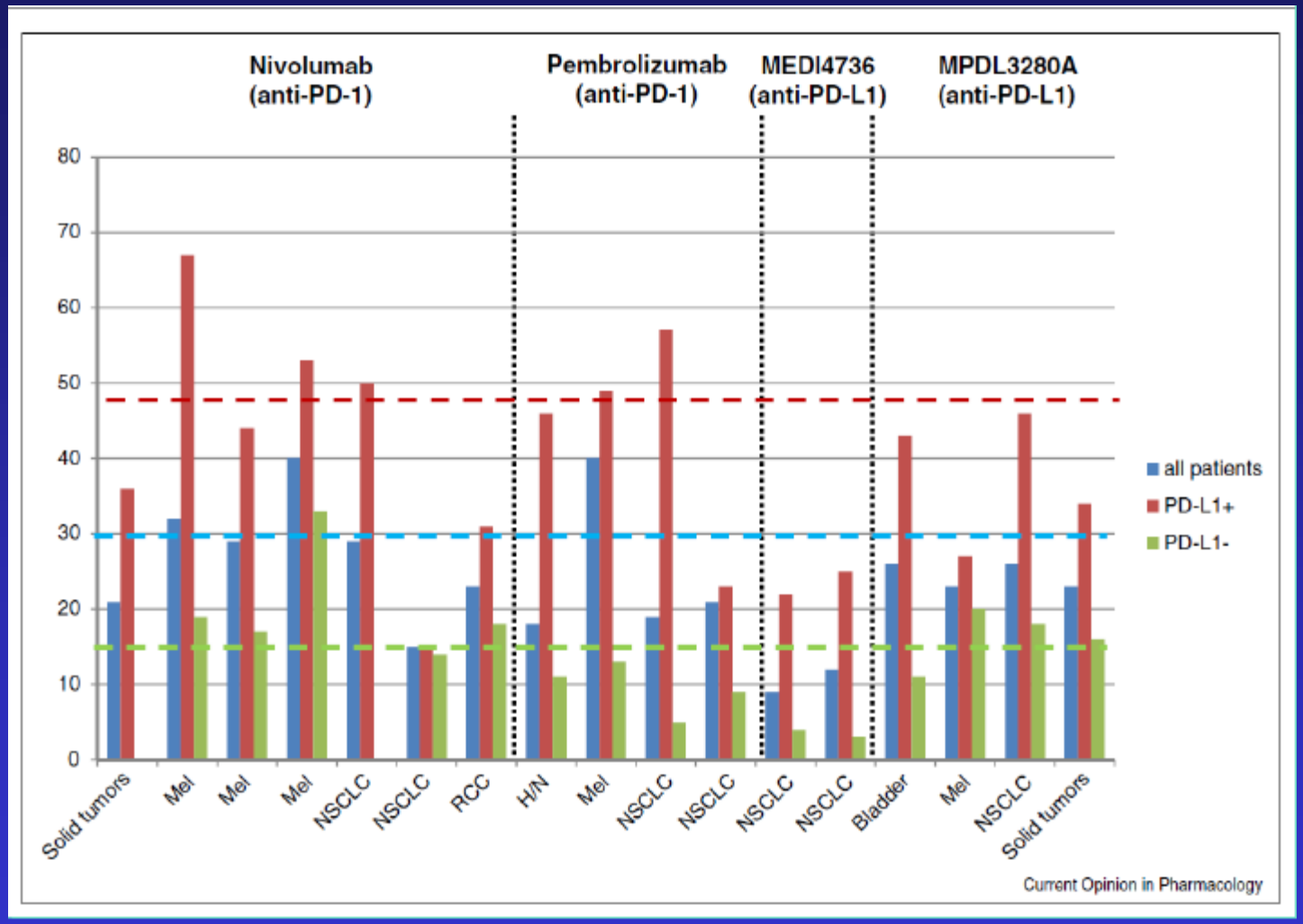
Objective response to anti-PD-1/PD-L1 therapy



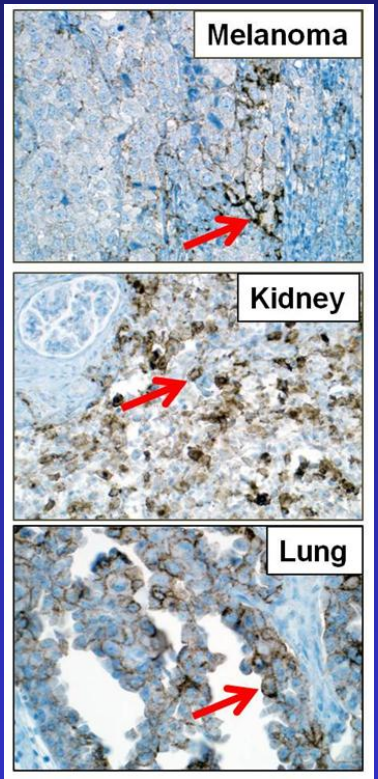
(Sunshine J et al , Curr Op Pharmacol 2015)

Biomarkers to predict the response to ICI

New regulatory terminology: "companion" vs. "complementary" diagnostic

- **Companion diagnostic**: "provides information that is *essential* for the safe and effective use of a corresponding drug or biological product"
  - Example: PD-L1 IHC 22C3 for pembrolizumab in NSCLC
- **Complementary diagnostic**: *not required*, but aids risk/benefit assessment for drug use in individual patients
  - Examples: PD-L1 IHC 28-8 for nivolumab in NSCLC and melanoma, PD-L1 IHC SP142 for atezolizumab in bladder cancer

PD-L1



Adapted from Suzanne Topalian at 2016 ASCO Annual Meeting

The immune infiltrate as a biomarker

LETTER

PD-1 blockade induces responses by inhibiting adaptive immune resistance

Paul C. Tumeh[1,2], Christina L. Harview[3], Jennifer H. Yearley[3], I. Peter Shintaku[3], Emma J. M. Taylor[3], Lidia Robert[3], Bartosz Chmielowski[2,3], Marko Spasic[3], Gina Henry[3], Velcu Ciobanu[3], Alisha N. West[3], Manuel Carmona[3], Christine Kivork[3], Elizabeth Seja[3], Grace Cherry[3], Antonio J. Gutierrez[3], Tristan R. Grogan[3], Christine Mateus[4], Gorana Tomasic[4], John A. Glaspy[1,2], Ryan O. Emerson[5], Harlan Robins[5,6], Robert H. Pierce[5], David A. Elashoff[7,8], Caroline Robert[4] & Antoni Ribas[1,2]

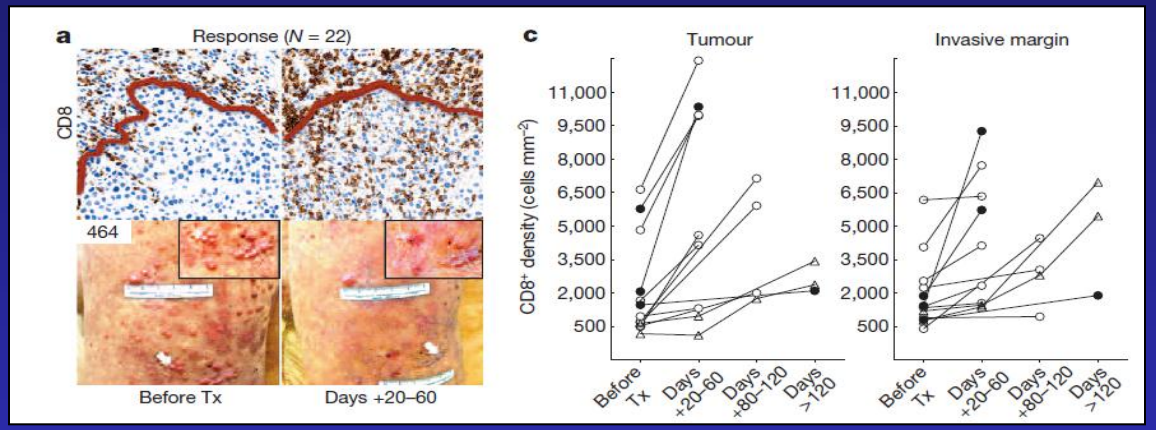
(Tumeh PC et al. *Nature* 2014)

CD8

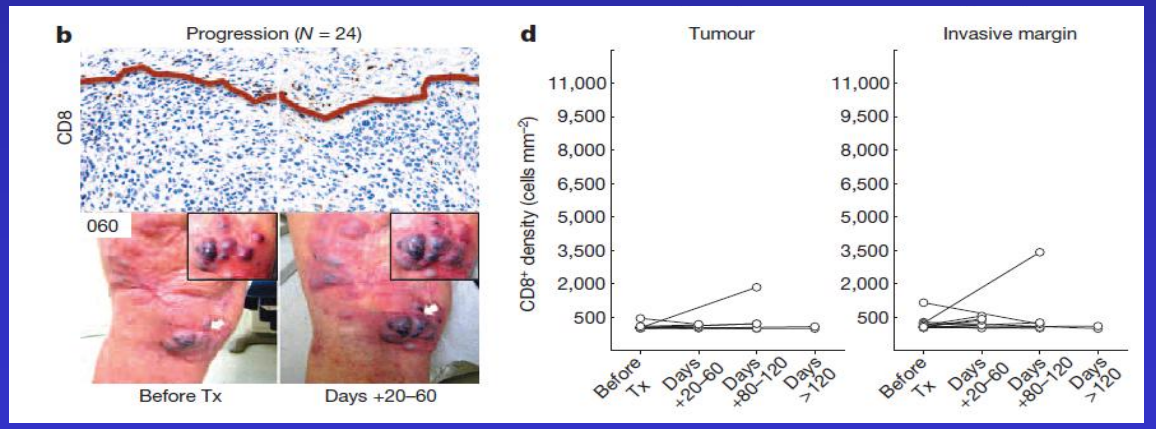
tumor

invasive margin

response



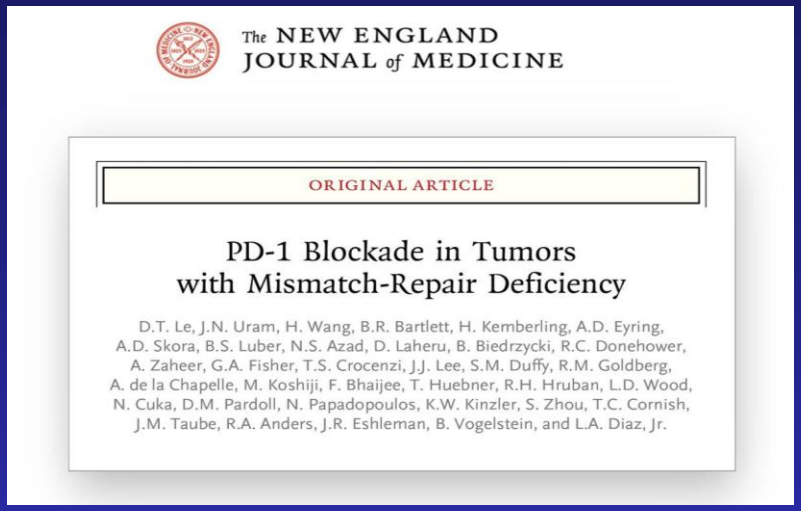
progression



before

after

CRC and ICI



The NEW ENGLAND JOURNAL of MEDICINE

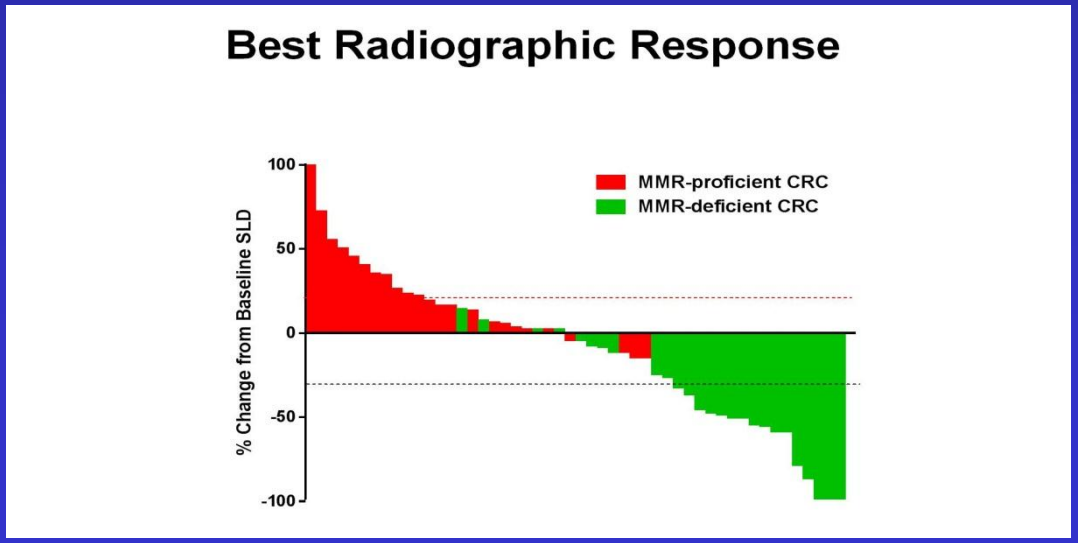
ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

	MMR-deficient CRC	MMR-proficient CRC
Type of Response-no (%)	n=28	n=25
Complete Response	3 (11)	0 (0)
Partial Response	13 (46)	0 (0)
Stable Disease (Week 12)	9 (32)	4 (16)
Progressive Disease	1 (4)	11 (44)
Not Evaluable[1]	2 (7)	10 (40)
Objective Response Rate (%)	16 (57)	0 (0)
95% CI	39 - 73	0 -13
Disease Control Rate (%)	25 (89)	4 (16)
95% CI	73 - 96	6 - 35
Median Follow Up (mos)	9.3	6

[1]Patients were considered not evaluable if they did not undergo a 12 week scan



Presented By Dung Le at 2016 ASCO Annual Meeting

News Release

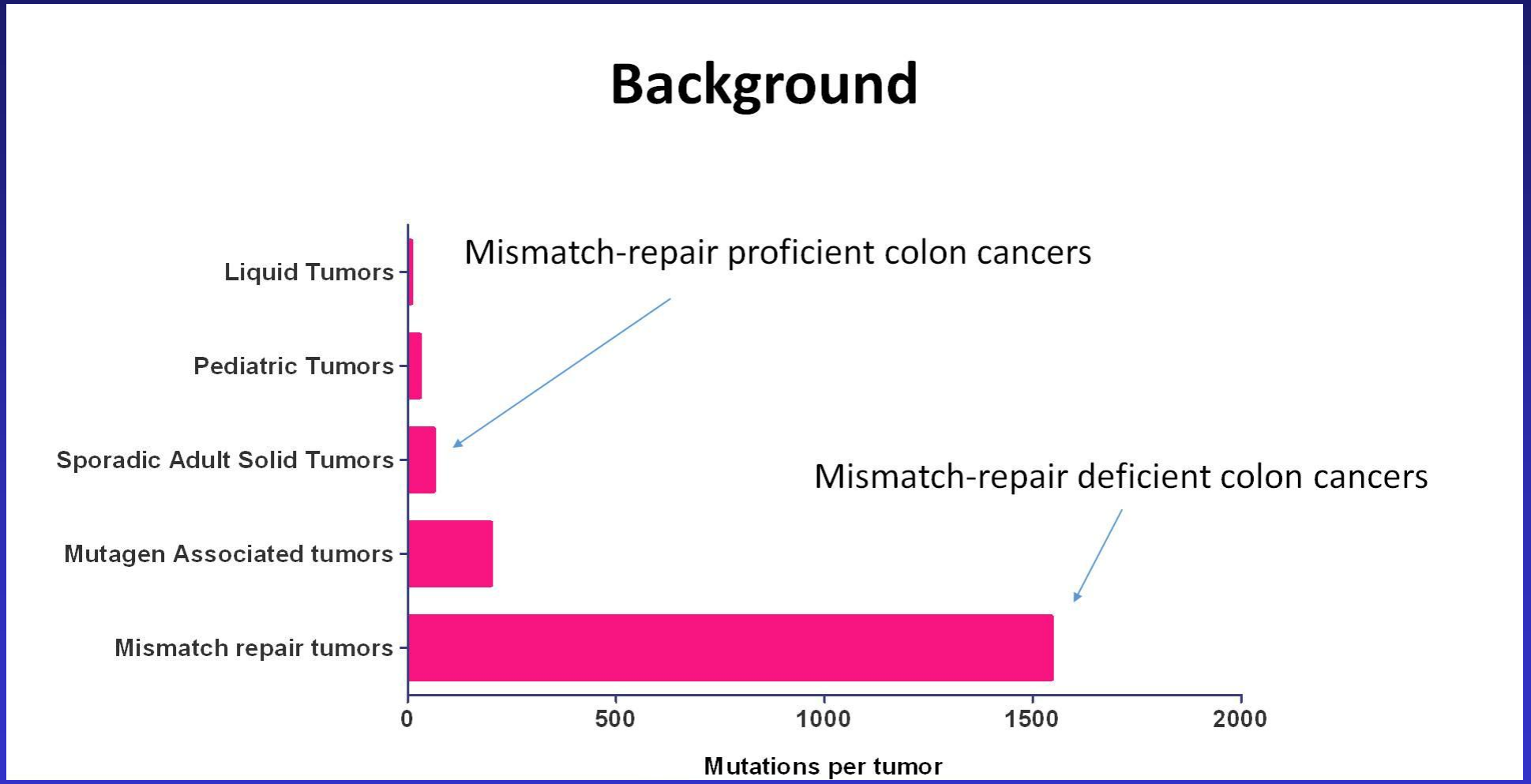
FOR IMMEDIATE RELEASE

Media Contacts:	Pamela Eisele (267) 305-3558	Investor Contacts:	Teri Loxam (908) 740-1986
	Kim Hamilton (908) 740-1863		Justin Holko (908) 740-1879

Merck Receives Breakthrough Therapy Designation from U.S. Food and Drug Administration for KEYTRUDA® (pembrolizumab) in Advanced Colorectal Cancer

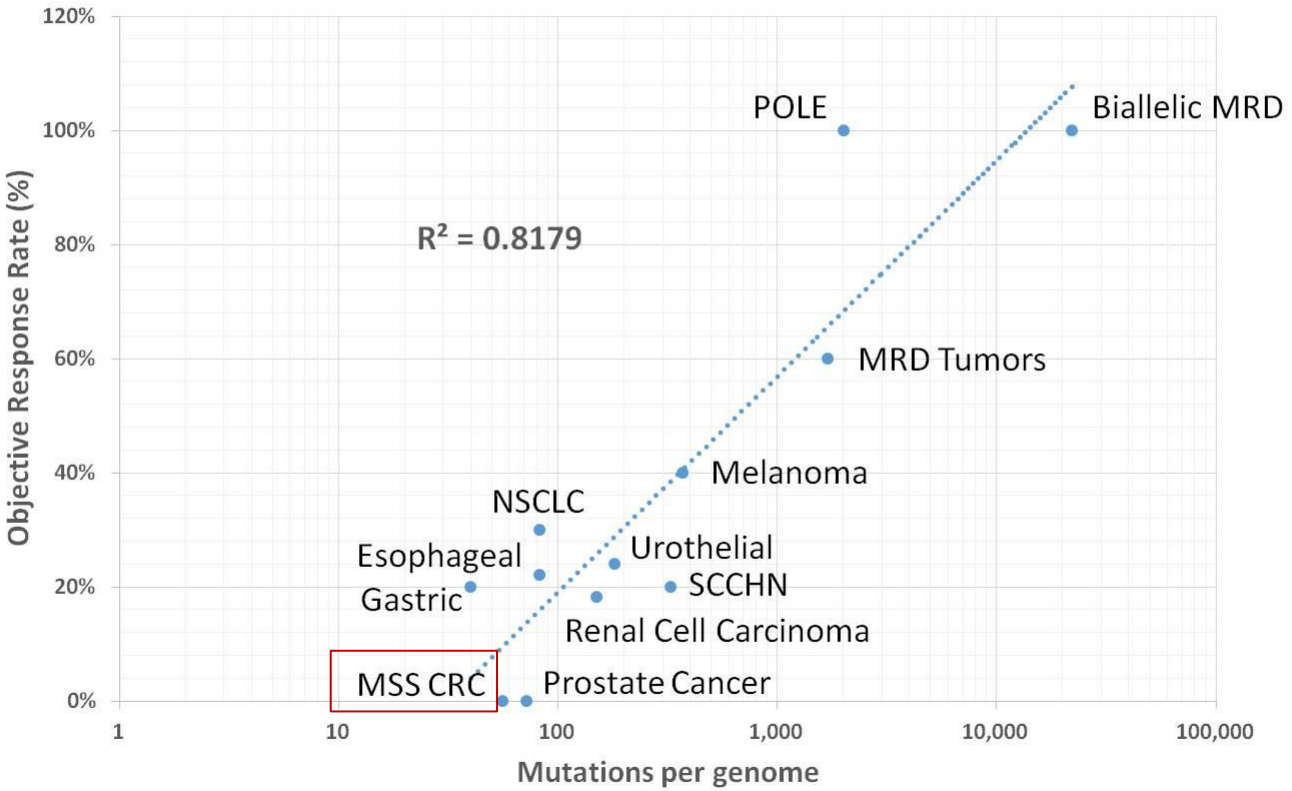
Designation Based on Results in Patients with Metastatic Colorectal Cancer with High Levels of Microsatellite Instability

CRC and ICI


Background
Mismatch-repair proficient colon cancers
Mismatch-repair deficient colon cancers
Liquid Tumors
Pediatric Tumors
Sporadic Adult Solid Tumors
Mutagen Associated tumors
Mismatch repair tumors
0
500
1000
1500
2000
Mutations per tumor

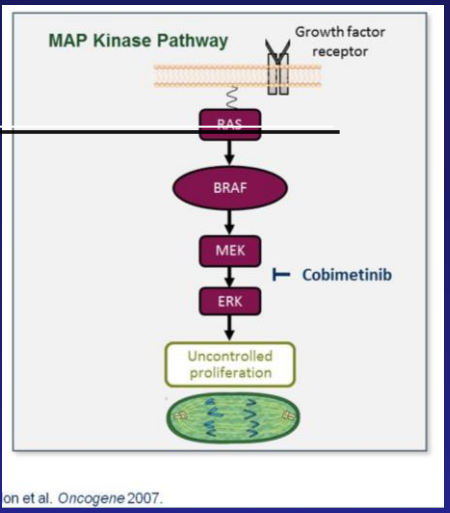
CRC and ICI

Mutation Burden vs. Response to PD-1 Blockade



Presented By Dung Le at 2016 ASCO Annual Meeting

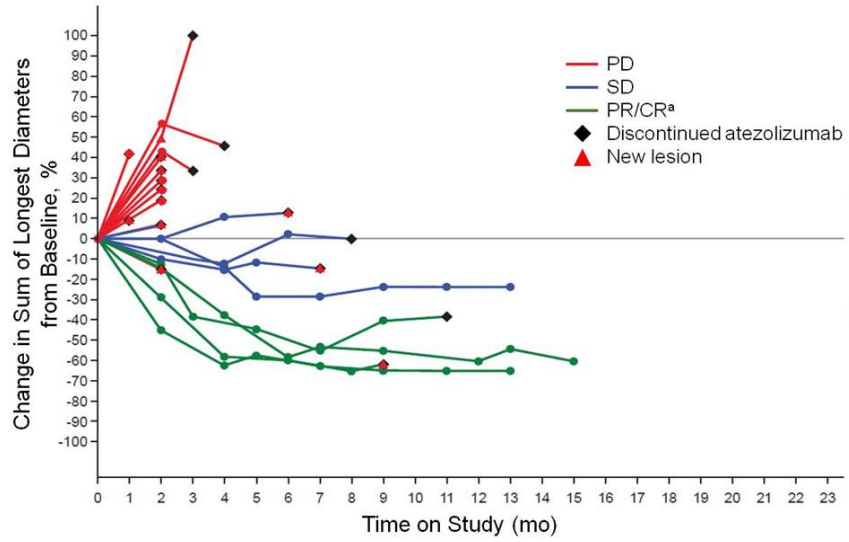
CRC and ICI: potential combinations



on et al. *Oncogene* 2007.

Colorectal cancers (MSS)

PD-L1 and MEK Inhibition: A Rational Combination



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

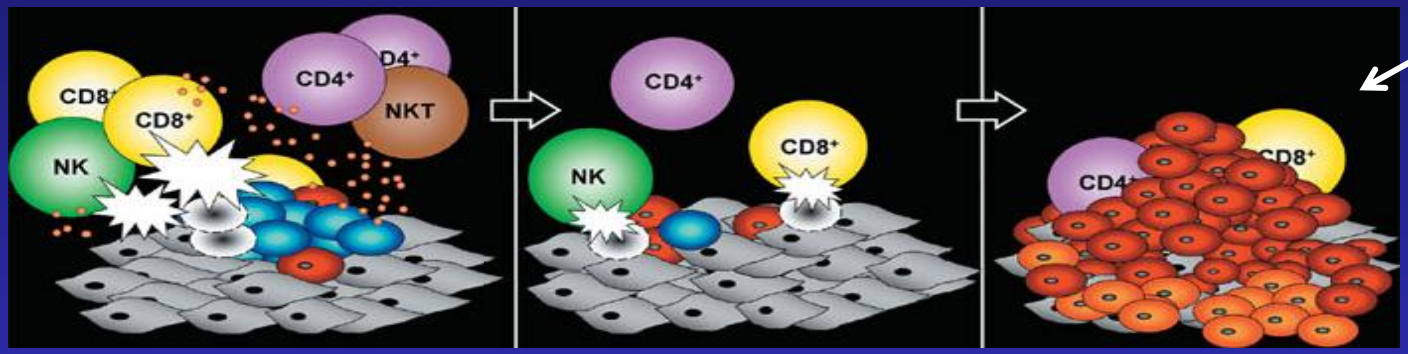
[a]Confirmed per RECIST v1.1. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease. Efficacy-evaluable patients. 2 patients missing or unevaluable are not included. Data cut-off February 12, 2016.

Rational: intratumoral T-cell accumulation and MHC I upregulation

Adapted from Johanna Bendell at 2016 ASCO Annual Meeting

The concept of immunosurveillance

The tumor process



(Dunn et al.
Nature Immunol. 2002)

Elimination Equilibrium Escape

-> The exhausted T cells are not completely disconnected
can be turned on ++

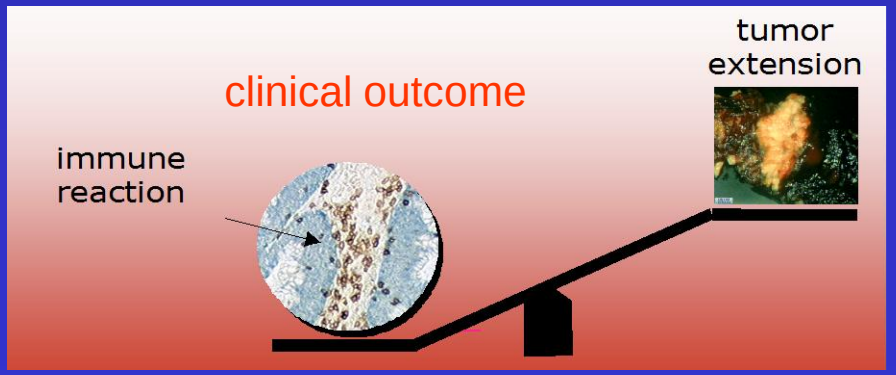
change of paradigm

-> combination of large scale analyses (Integrative Cancer Immunology)

cohorts of colorectal cancer patients (> 600 patients)

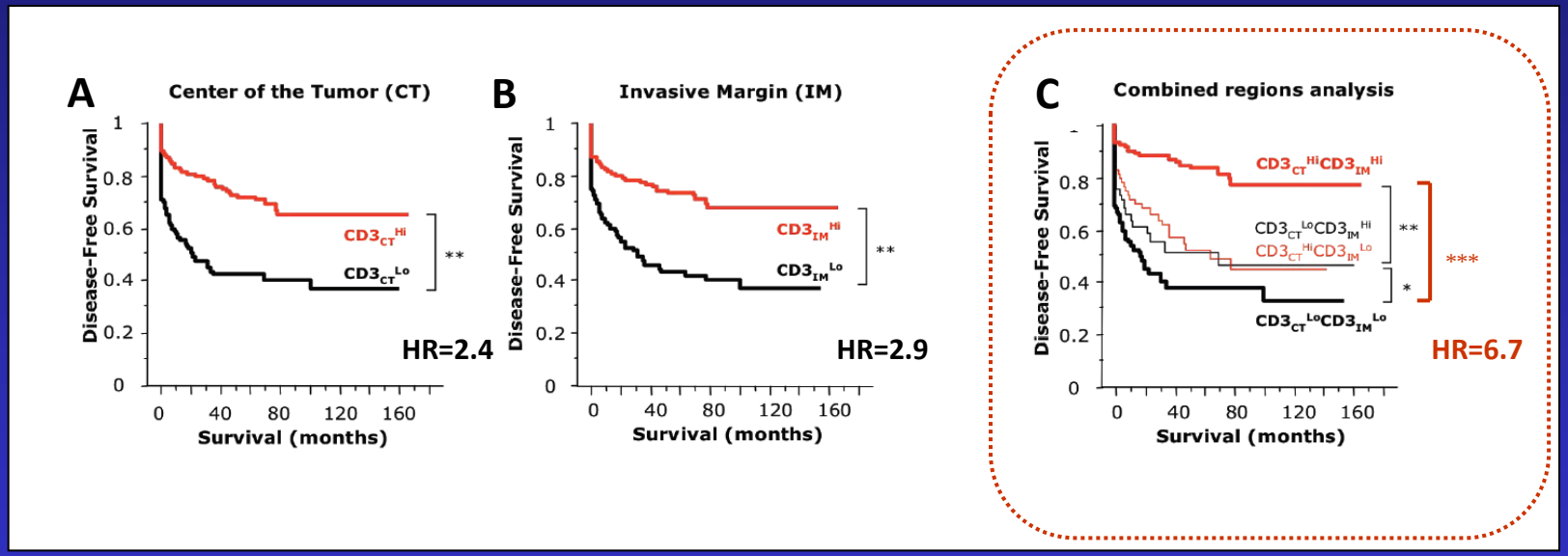
(Pagès F et al. *New England J Med, 2005)*
(Galon J et al, Science 2006)
(Pagès F et al, J Clin Oncol 2009)
(Mlecnik B et al, J Clin Oncol 2011)
(Fridman H et al, Nat Rev Immunol 2012)
(Bindea G et al, Immunity 2013)
(Anitei G et al, Clin Cancer Res 2014)
(Bindea G et al, Science Transla Med 2016)
(Mlecnik B et al, Immunity in press)

Cytotoxic T lymphocytes (CD8) & memory T lymphocytes (CD45RO)
in the tumor and the invasive margin have a major influence
on clinical outcome



Results

Each tumor region is informative



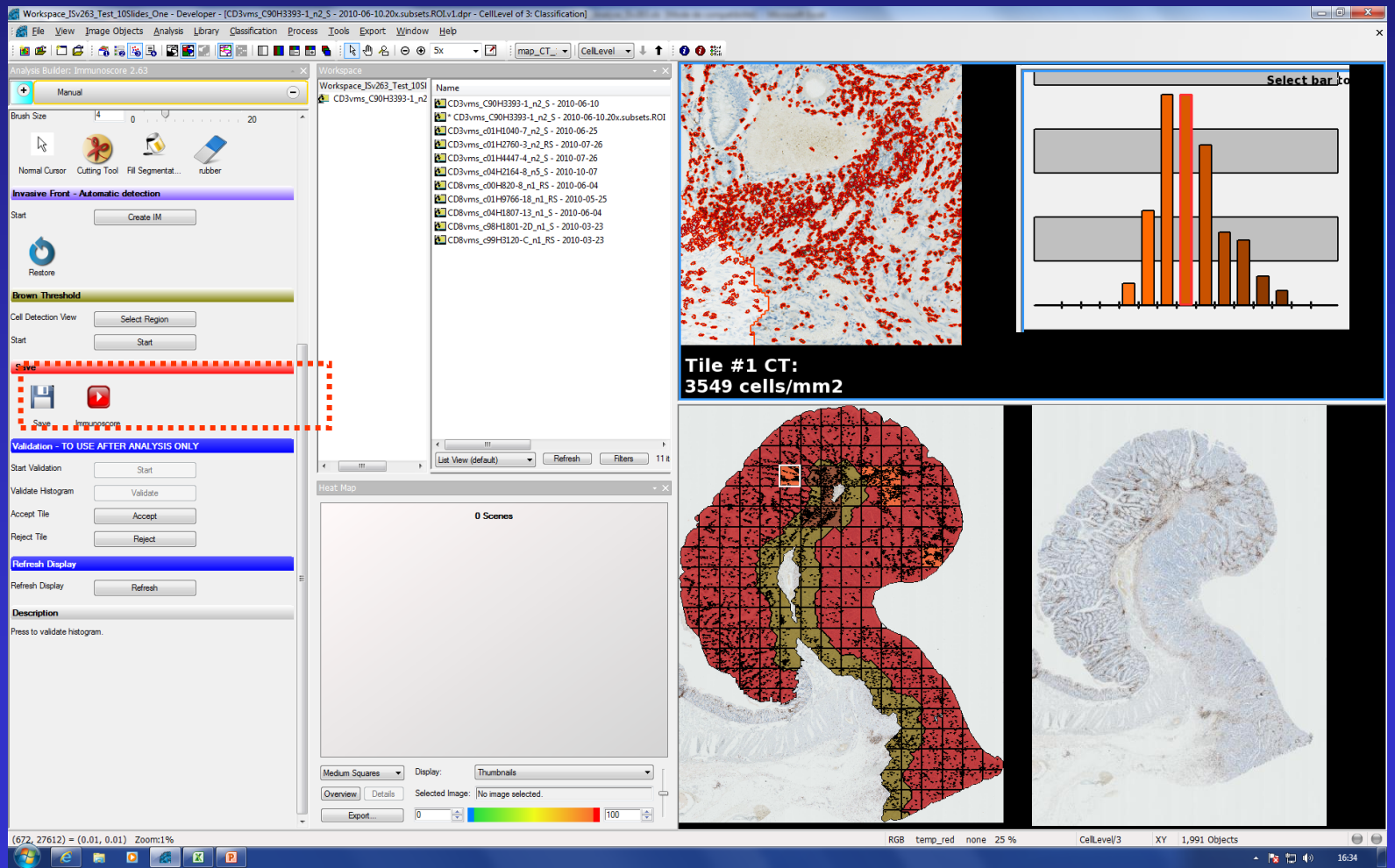
Combining the tumor regions increase the accuracy for prognosis

From bench to bedside

. The Tumor is divided in tiles (500-700 /tumor)

. Histogram to check the intensity of the stained cells detected

. A map for the immune cell densities is created



From bench to bedside

To translate into the clinic

Immunomonitoring Plateform

to determine the immune densities on tissue sections in a routine setting (whole slide analysis)

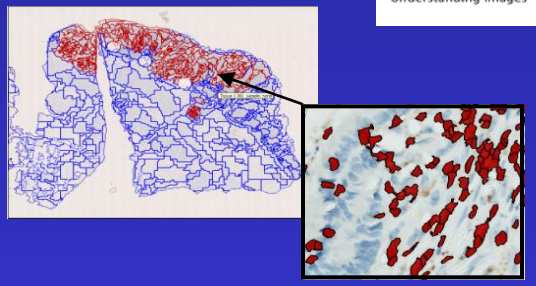
Immunohisto. Automate

High resolution Scanner

virtual microscopy

Whole slide image analysis software

DEFINIENS Understanding Images



INSTITUT NATIONAL DU CANCER

Cancéropôle Île-de-France

From bench to bedside

June 3-7, 2016
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The Immunoscore as a New Possible Approach for the Classification of Cancer

sitc

World Immunotherapy Council inaugural meeting (Feb 2012)

The NEW ENGLAND JOURNAL of MEDICINE

Pagès F, et al. ***N Engl J Med***. 2005

Science AAAS

Galon J et al. ***Science*** 2006

Support (moral) from the World Immunotherapy Council (WIC), and support from societies including, EATI, BDA, CCIC, CIC, CRI, CIMT, CSCO, TIBT, DTIWP, ESCII, NIBIT, JACI, NCV-network, PIVAC, ATTACK, TVACT…

Worldwide Immunoscore consortium (PI: J Galon) (coPI: F Pagès)

(21 Centers, 15 countries: >3000 patients)

Assay harmonization

Immunoscore meetings :

- Feb 2012, Italy
- Dec 2012, Italy
- Nov 2013, SITC, USA
- Dec 2013, Italy
- Jan 2014, Qatar
- Jul 2014, Paris, France
- Nov 2014, SITC, USA
- Nov 2015, SITC, USA
- Dec 2015, Italy

June 3-7, 2016
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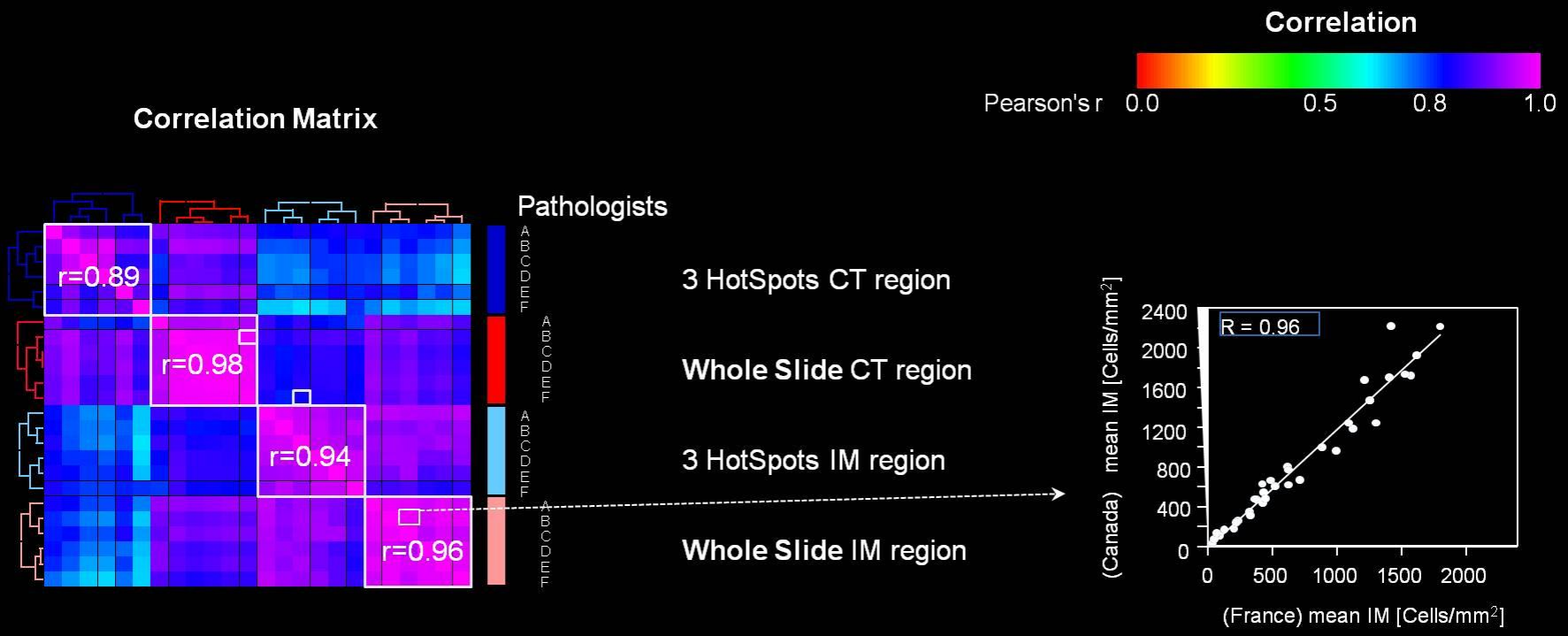
High reproducibility of Immunoscore



- ✓ Whole slide quantification shows the best correlation and reproducibility
- ✓ Immunoscore is **quantitative, reproducible and robust**

Patient population and clinical characteristics

Cohorts

	TS: Training set	IVS: Internal Validation	EVS: External Validation
Age :	68.3 (±12.6)	68.3 (±12.2)	68.2 (±32.7)
Male :	346 (49.4%)	339 (53.3%)	497 (51.3%)
Female :	354 (50.6%)	297 (46.7%)	472 (48.7%)
T1 :	37 (5.3%)	34 (5.3%)	32 (3.3%)
T2 :	109 (15.6%)	97 (15.3%)	153 (15.8%)
T3 :	452 (64.6%)	427 (67.1%)	635 (65.5%)
T4 :	102 (14.6%	78 (12.3%)	149 (15.4%)
N0 :	508 (73.4%)	482 (76.3%)	608 (64.1%)
N1 :	124 (17.9%)	107 (16.9%)	223 (23.5%)
N2 :	60 (8.7%)	43 (6.8%)	117 (12.3%)
# tot LN :	22.1 (±15.2)	21.8 (±16.9)	16.4 (±11.8)
Proximal :	349 (49.9%)	307 (48.3%)	527 (54.9%)
Distal :	349 (49.9%)	327 (51.5%)	431 (44.9%)
Missing :	2 (0.3%)	1 (0.2%)	2 (0.2%)

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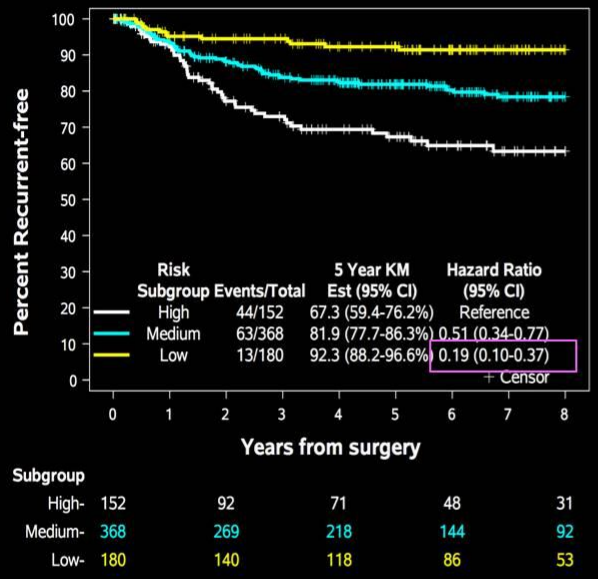
Secondary Objective: Time to recurrence for Immunoscore (High/Int/Low)

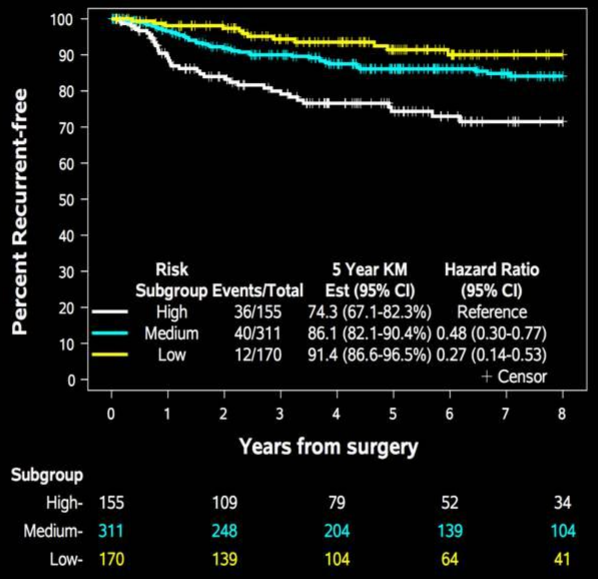
TS



Subgroup					
High-	152	92	71	48	31
Medium-	368	269	218	144	92
Low-	180	140	118	86	53

***P*< 0.0001**
HR (0-2)= 0.19
C-index= 0.64

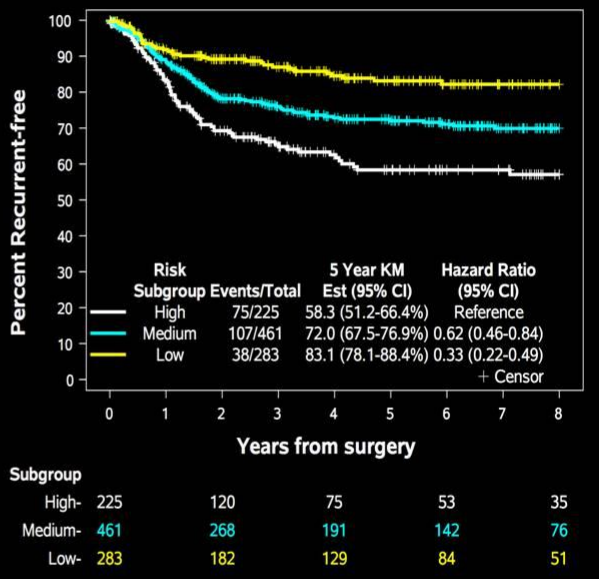
IVS



Subgroup					
High-	155	109	79	52	34
Medium-	311	248	204	139	104
Low-	170	139	104	64	41

***P*= 0.0001**
HR (0-2)= 0.27
C-index= 0.63

EVS



Subgroup					
High-	225	120	75	53	35
Medium-	461	268	191	142	76
Low-	283	182	129	84	51

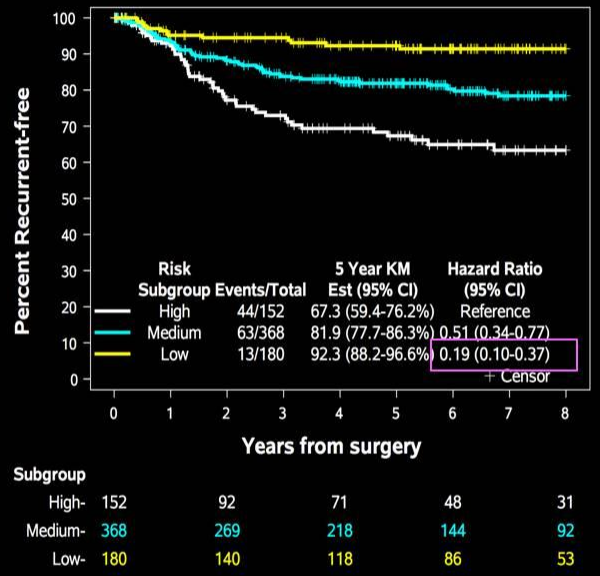
***P*< 0.0001**
HR (0-2)= 0.33
C-index= 0.60

Secondary objective is reached

Immunoscore **3 groups** (**and 5 groups**) predicted time to recurrence on Training Set (TS), and on 2 independent validation sets (IVS and EVS), blinded to clinical outcome.

Secondary Objective: Time to recurrence for Immunoscore (High/Int/Low)

TS



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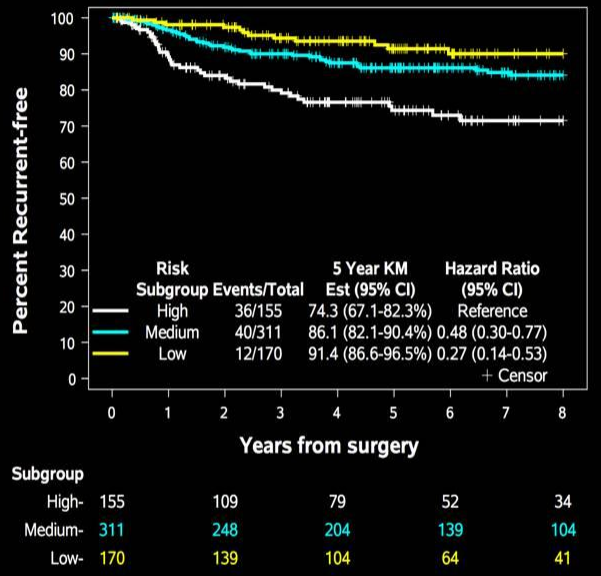
IVS



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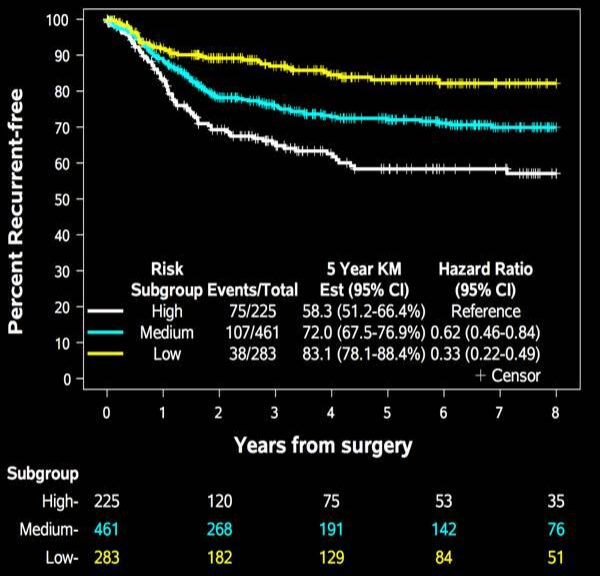
EVS



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Immunoscore **3 groups** (**and 5 groups**) predicted time to recurrence on Training Set (TS), and on 2 independent validation sets (IVS and EVS), blinded to clinical outcome.

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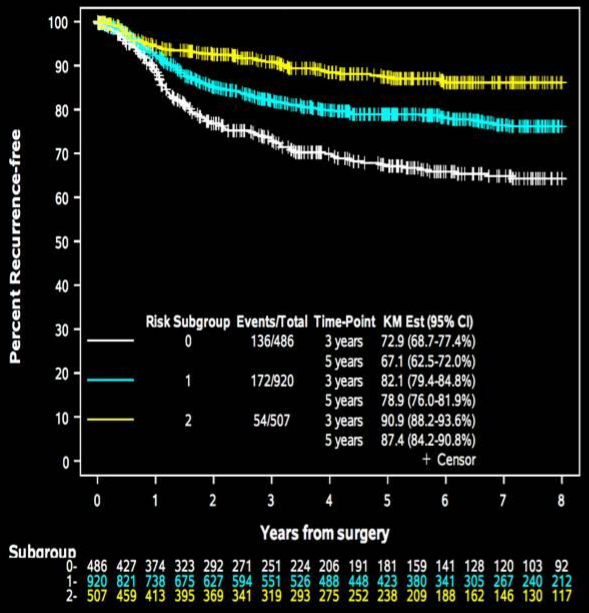
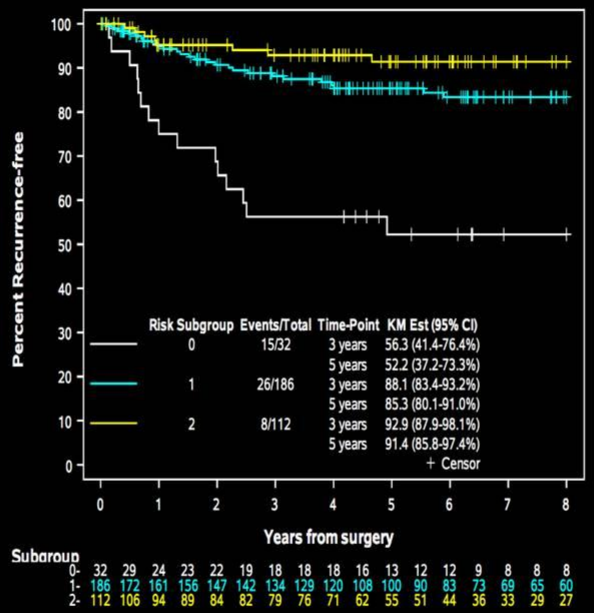
Secondary Objective: Time to recurrence for Immunoscore for each Continent

Europe



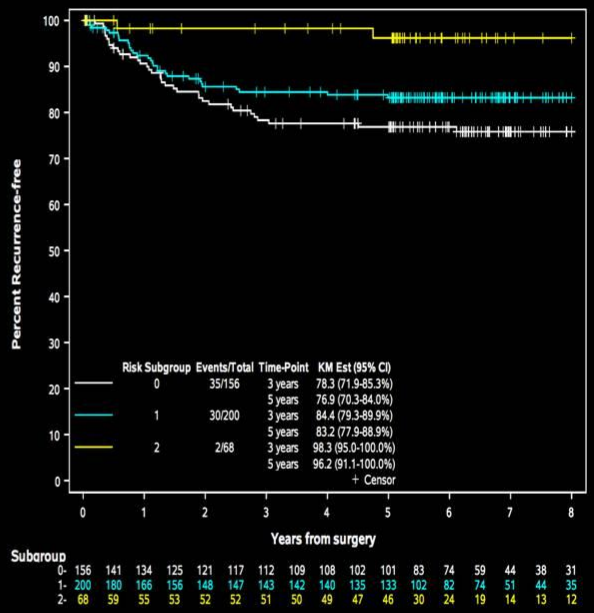
***P*< 0.0001**
HR (0-2) = 0.31 (0.22-0.43)

North-America



***P*< 0.0001**
HR (0-2) = 0.13 (0.05-0.30)

Asia



***P*= 0.027**
HR (0-2) = 0.19 (0.04-0.83)

Immunoscore: High, Int, Low

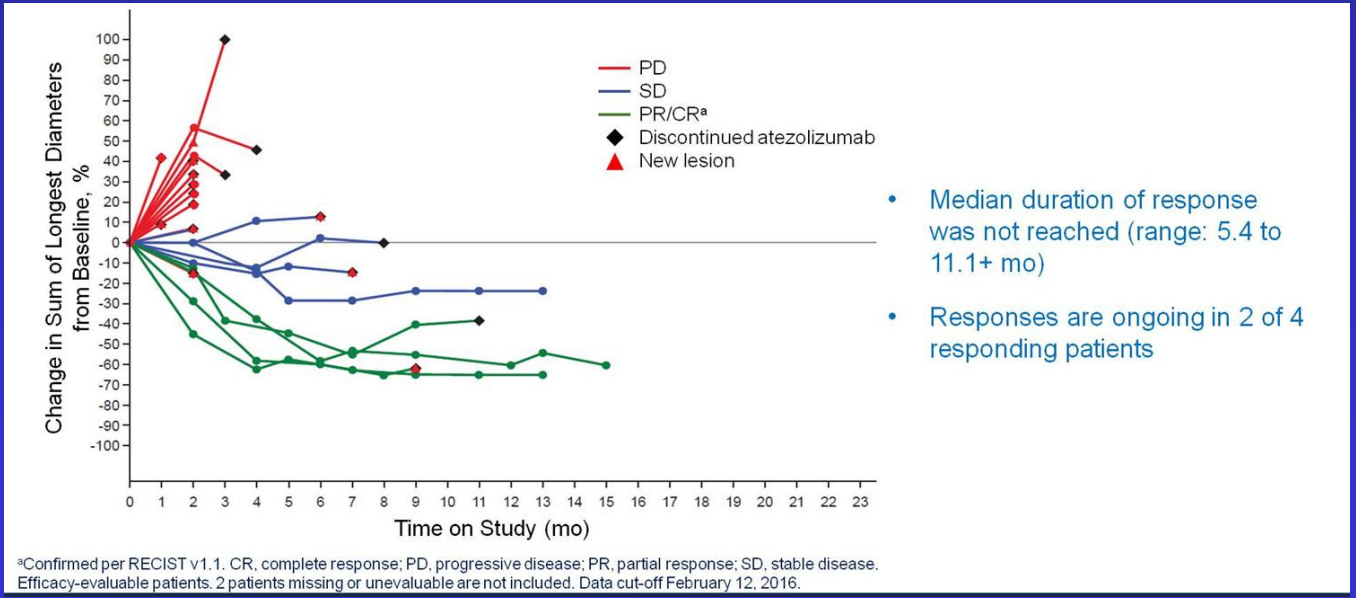
Immunoscore (3 groups) predicted time to recurrence, for each continent (Europe, North-America, Asia).

The immunoscore in clinical practice

. What could be the positioning of the IS in CRC patients ?

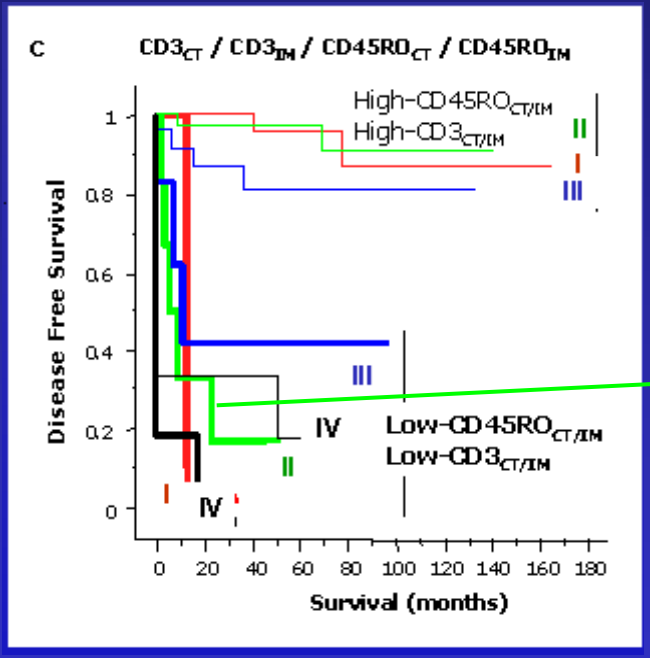
1) Companion or complementary diagnostic in MSS patients

treated with combination therapies (eg. anti-PD-L1 and MEK inhib.) ?



The immunoscore in clinical practice

. What could be the positioning of the IS in CRC patients ?



2) <u>UICC TNM Stage II:</u>

to predict the patients at high risk of relapse

That could benefit for an adjuvant therapy

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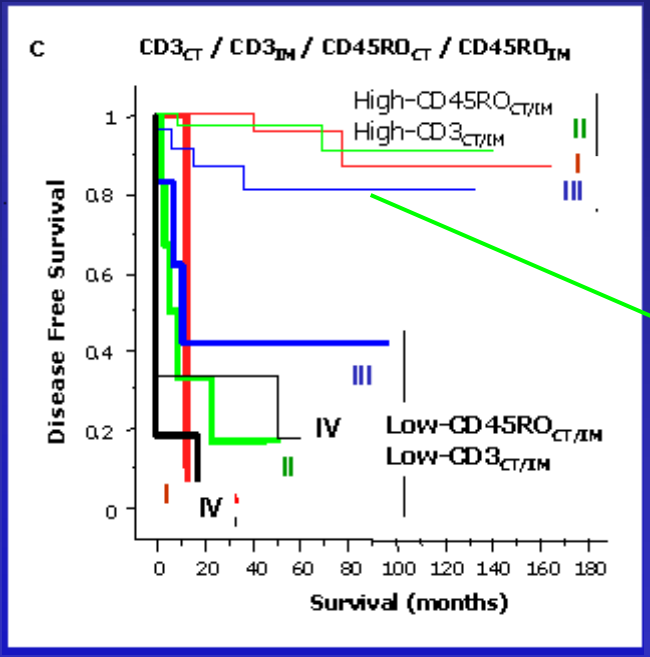
. What could be the positioning of the IS in CRC patients ?



3) <u>UICC TNM Stage III:</u>

to predict the patients at very low risk of relapse

that should not be treated

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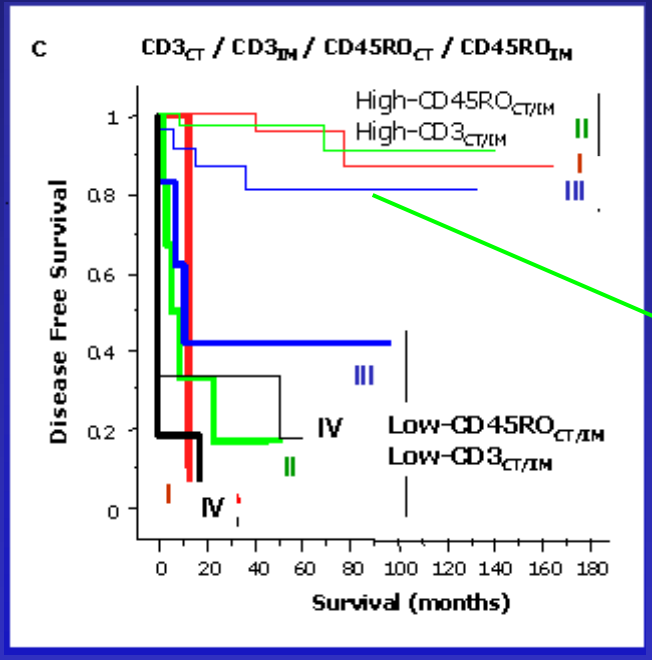
. What could be the positioning of the IS in CRC patients ?

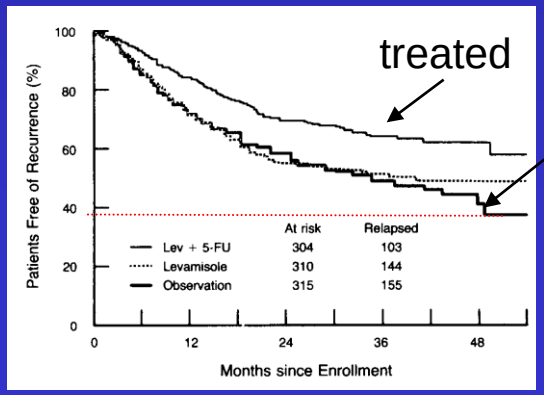


3) <u>UICC TNM Stage III:</u>

to predict the patients at very low risk of relapse

that should not be treated

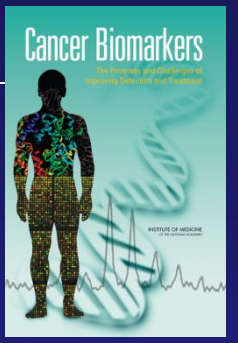
TNM Stage III



-> 30% of stage III patients without adjuvant treatment will not relapse

(Moertel et al. NEJM 1990)

Conclusion



. The immune system is now recognized as a major player in the control of the tumor process

. Immunotherapy has now gain a forefront position in cancer drug development

. There is a need for biomarkers to influence treatment decisions

. The Immunoscore could be one of the first to integrate the clinical practice

Acknowledgments:

- Jérôme GALON
- Hervé Fridman

- Amos KIRILOVSKY (doc)
- Marie TOSOLINI (doc)
- Bernhard MLECNIK, (PDCS)
- Gabriella BINDEA (PDCS)
- Pornpimol CHAROENTONG (doc)
- Stéphanie MAUGER (IE)
- Vanessa SAIDI (TR)
- Tessa FREDRIKSEN (AI)

- Florence MARLIOT, (AI)
- Nacilla HAICHEUR (IE)
- Valerie PONCET (TR)

- Franck ZINZINDOHOUE (PU-PH)
- Anne BERGER (PU-PH)
- Guy ZEITOUN (PH)
- Christine LAGORCE-PAGES (MCU-PH)

- Philippe WIND (PU-PH)

Pr. V. Scripcariu
Dr. Gabriela Anitei
Dr. Anna Maria Todosi