SESSION II:
Validation of Biomarkers Identification and Analysis

Society for Immunotherapy of Cancer

Co-Chairs:

Bernard A. Fox, Earle A. Chiles Research Institute
Sacha Gnjatic, Icahn School of Medicine at Mt Sinai

Earle A. Chiles Research Institute

Society for Immunotherapy of Cancer

Identification, Validation & Analysis:

In 2018: Critical Elements for Developing Combination Immunotherapy

Earle A. Chiles Research Institute

REVIEW Open Access

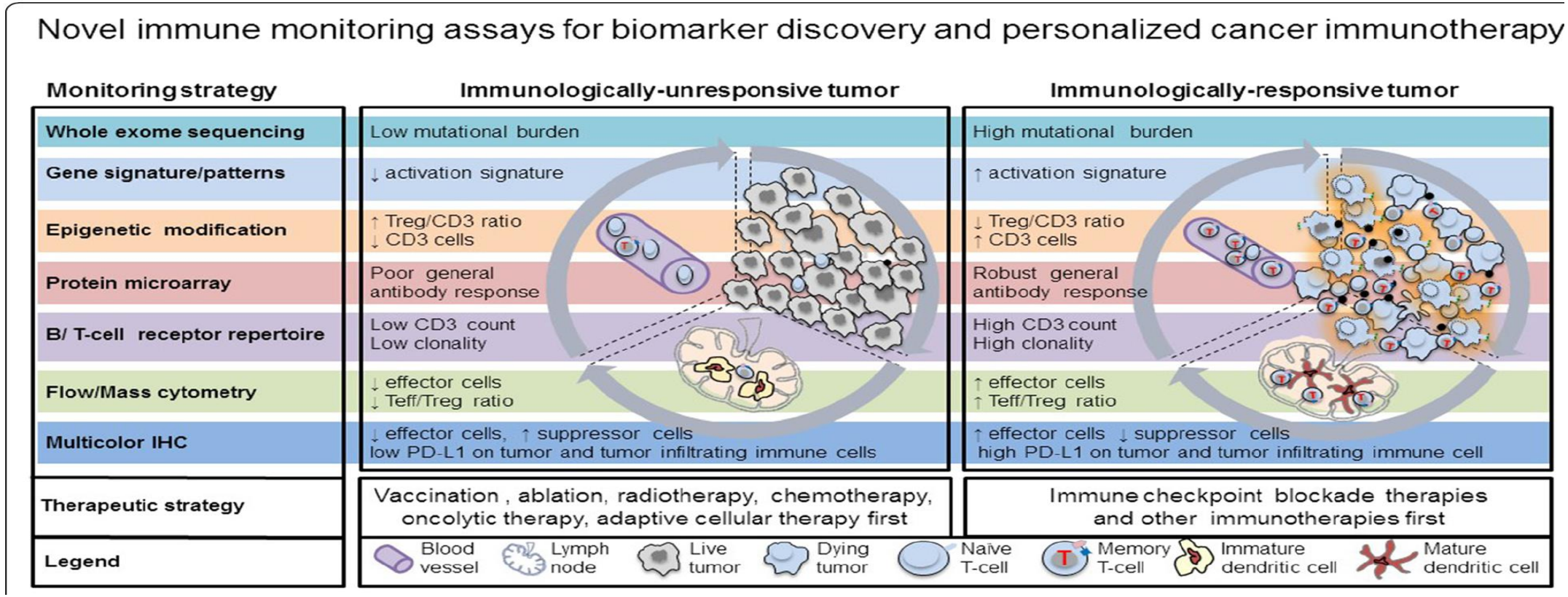
Novel technologies and emerging biomarkers for personalized cancer immunotherapy

Journal for ImmunoTherapy of Cancer

Yuan *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:3
DOI 10.1186/s40425-016-0107-3

Jianda Yuan[1*], Priti S. Hegde[2], Raphael Clynes[3], Periklis G. Foukas[4,5], Alexandre Harari[4], Thomas O. Kleen[6], Pia Kvistborg[7], Cristina Maccalli[8], Holden T. Maecker[9], David B. Page[10], Harlan Robins[11], Wenru Song[12], Edward C. Stack[13], Ena Wang[14], Theresa L. Whiteside[15], Yingdong Zhao[16], Heinz Zwierzina[17], Lisa H. Butterfield[18] and Bernard A. Fox[10*]

SITC Immune Biomarkers Task Force



SITC Needs?

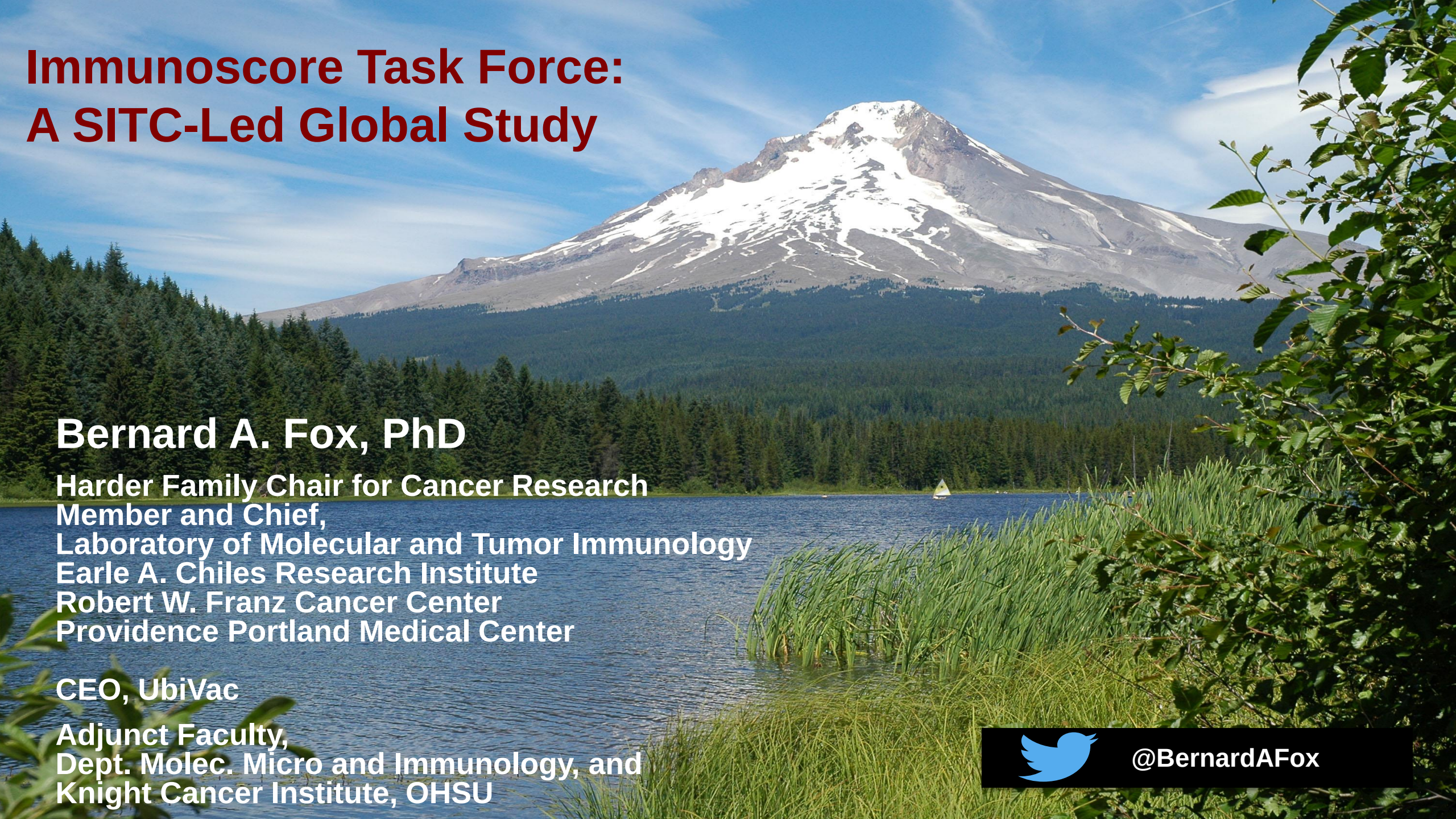
Society for Immunotherapy of Cancer

SITC Needs?

- **YOU!**

Representatives of Working Groups in Immune Responsiveness TaskForce / May 14, 2018

Immunoscore Task Force: A SITC-Led Global Study



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Bernard A. Fox, PhD – COI Disclosures

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Outline

- A brief history of Immune cell infiltrates into cancer
- Describe the immunoscore method
- Review the SITC-Led Immunoscore Study
- Perspective on next steps

Immune cell infiltration: Common feature of many human solid tumors

1863 Virchow (1863) stated that the frequent presence of lymphatic cells in human tumors reflected the origin of cancer at sites of previous chronic inflammation.

Virchow R: *Die Krankhaften Geschwülste*. 1863.

1872 Waldeyer et al. (1872) suggested that a local disturbance of connective tissue was an essential prelude to tumor growth.

Waldeyer HGW: Die Entwicklung der Karzinome. Virchows Arch Path Anat 1872, 55:67.

1907 Handley described that a “round cell infiltrate” indicated a regressive process in melanoma.

Handley WS. *The Lancet* 1907, 169:927–933.

1908 Wade et al. (1908) described a regressing transplanted canine sarcoma as “the tumor being borne away on a lymphocyte tide” .

Wade H:. *J Path Bact* 1908, 12:384.

Immune cell infiltration: Common feature of many human solid tumors

1912	De Fano concluded from a study on murine tumor grafts that a peritumoral infiltration of lymphocytes and plasma cells was an expression of a defensive mechanism akin to immunity [5].
	De Fano C. Fifth Sci Rep Imrp Cancer Res Fund 1912.
1920's	MacCarty et al. weak associations of local immune response with improved prognosis
	*MacCarty WC, Mahle AE: J Lab Clin Med 1921, **6**:473.*
1920-1970s	Strong affirmation in over 30 publications.
	*Underwood JC: Br. J. Cancer 1974, **30**:538–548.*
1980-1990s	Positive correlation between density of immune infiltrate and prognosis /melanoma/ head and neck cancer/ breast cancer/ ovarian cancer/ colorectal/ mycosis fungoides.

Breakthrough: Digital Imaging and Objective Assessment

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†]

The role of the adaptive immune response in controlling the growth and recurrence of human tumors has been controversial. We characterized the tumor-infiltrating immune cells in large cohorts of human colorectal cancers by gene expression profiling and in situ immunohistochemical staining. Collectively, the immunological data (the type, density, and location of immune cells within the tumor samples) were found to be a better predictor of patient survival than the histopathological methods currently used to stage colorectal cancer. The results were validated in two additional patient populations. These data support the hypothesis that the adaptive immune response influences the behavior of human tumors. In situ analysis of tumor-infiltrating immune cells may therefore be a valuable prognostic tool in the treatment of colorectal cancer and possibly other malignancies.

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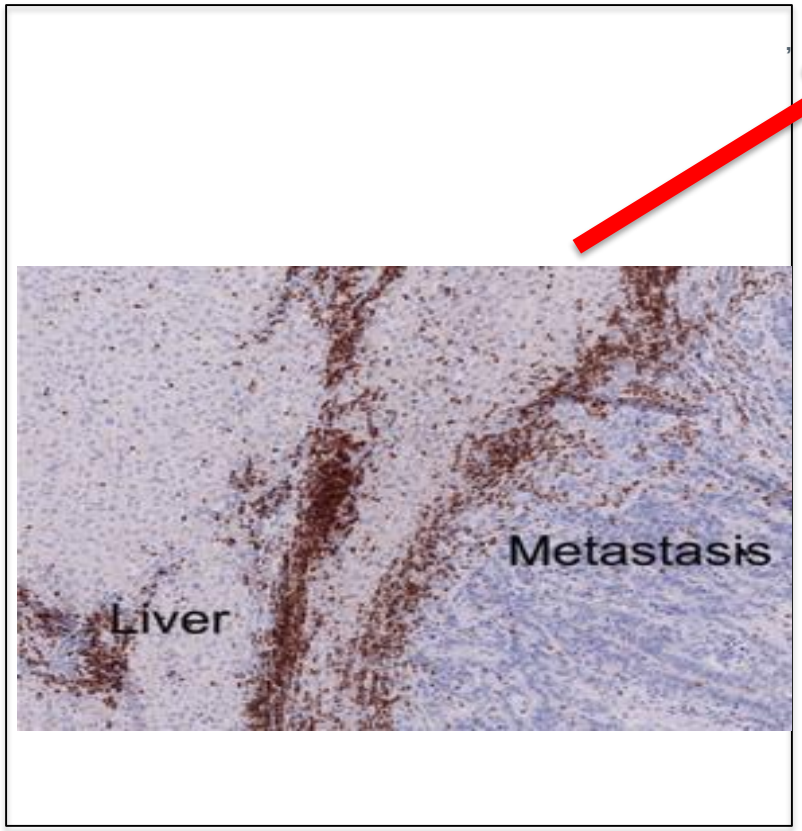
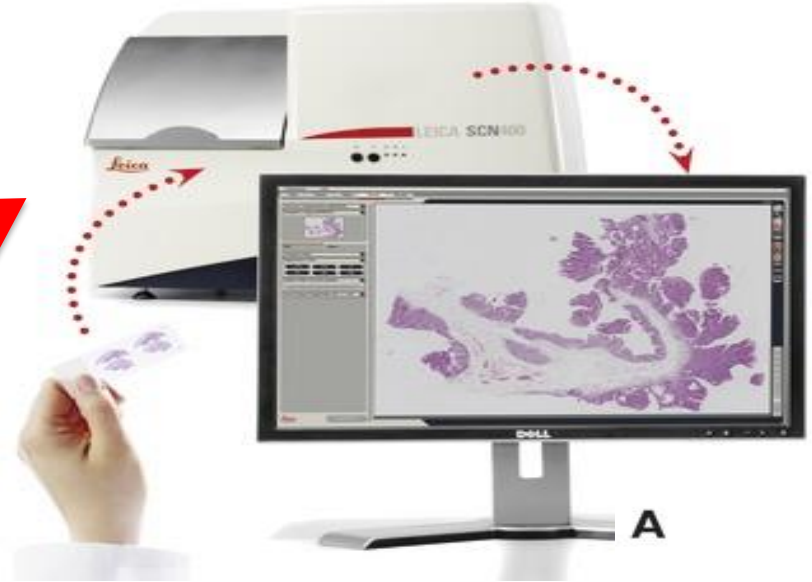
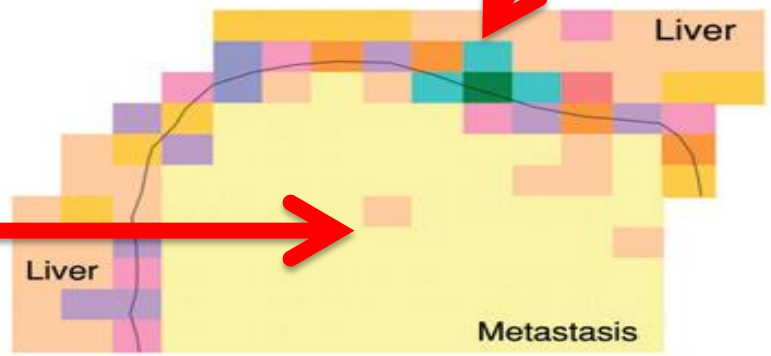
Digital imaging and objective assessment of immune infiltrates





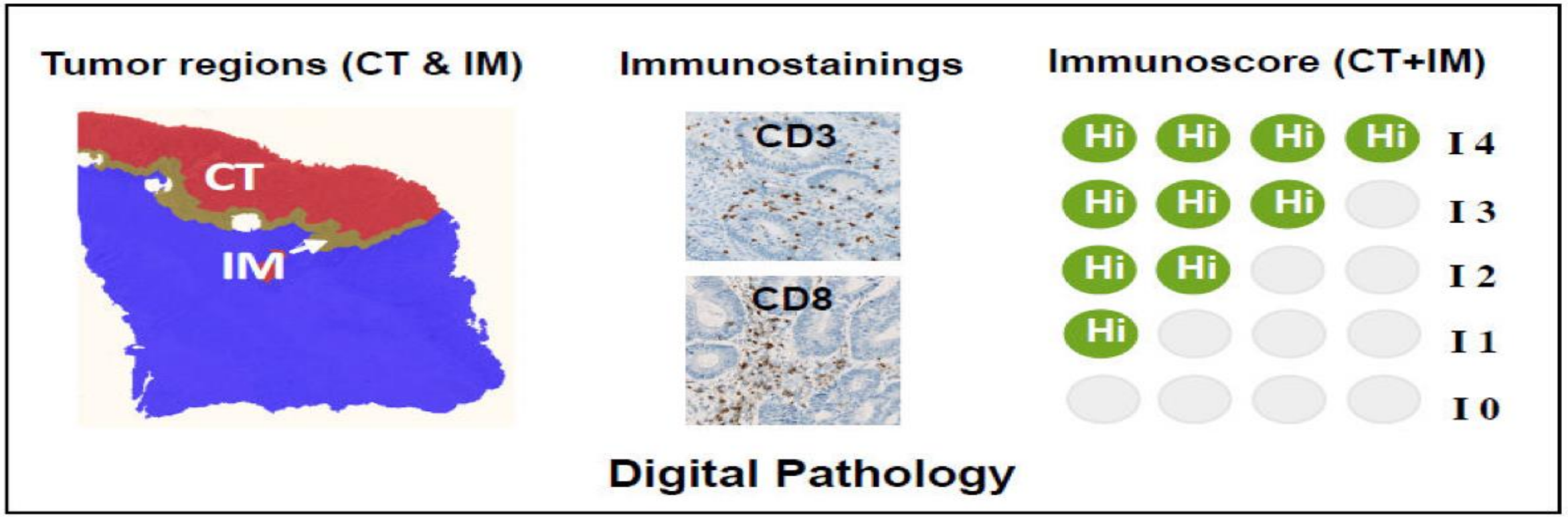
Invasive Margin

Tumor



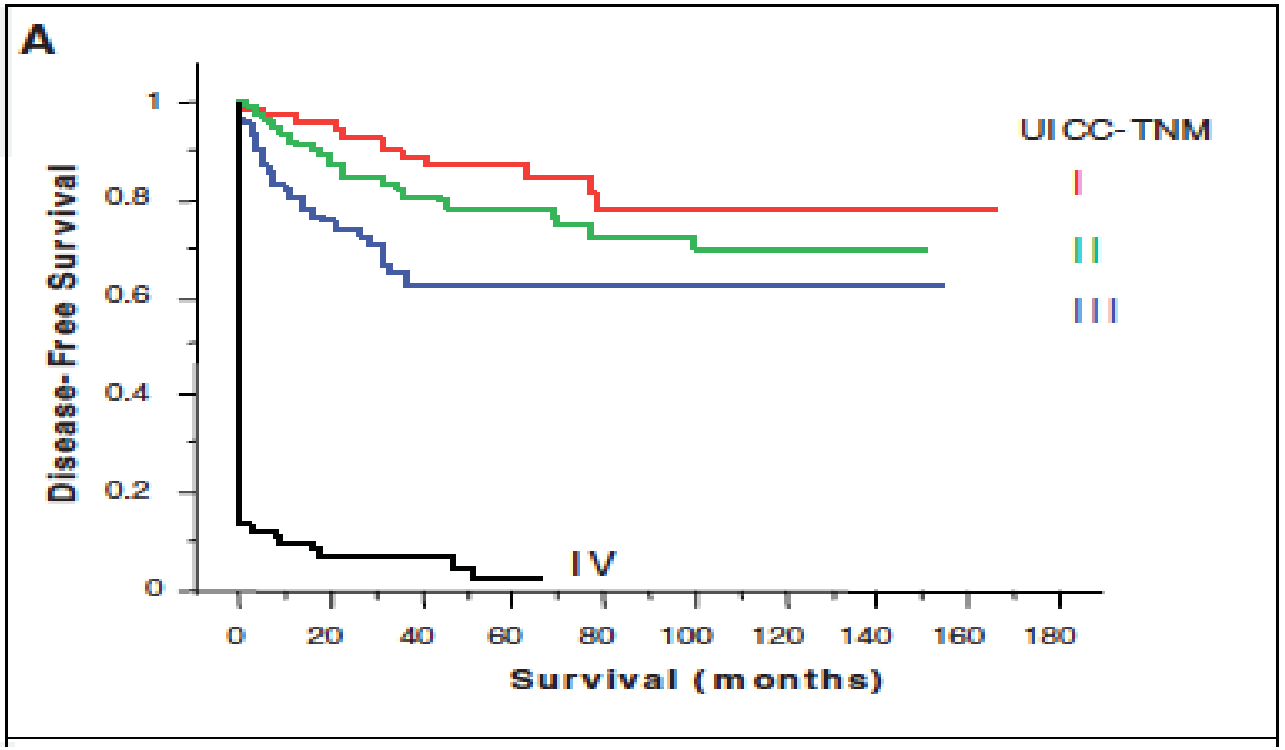
Halama N, et al. Can Res 71:5670 2011

Immunoscore Definition:



Disease-Free Survival of Colon Cancer Cohort (Paris)

UICC-TNM
Staging system



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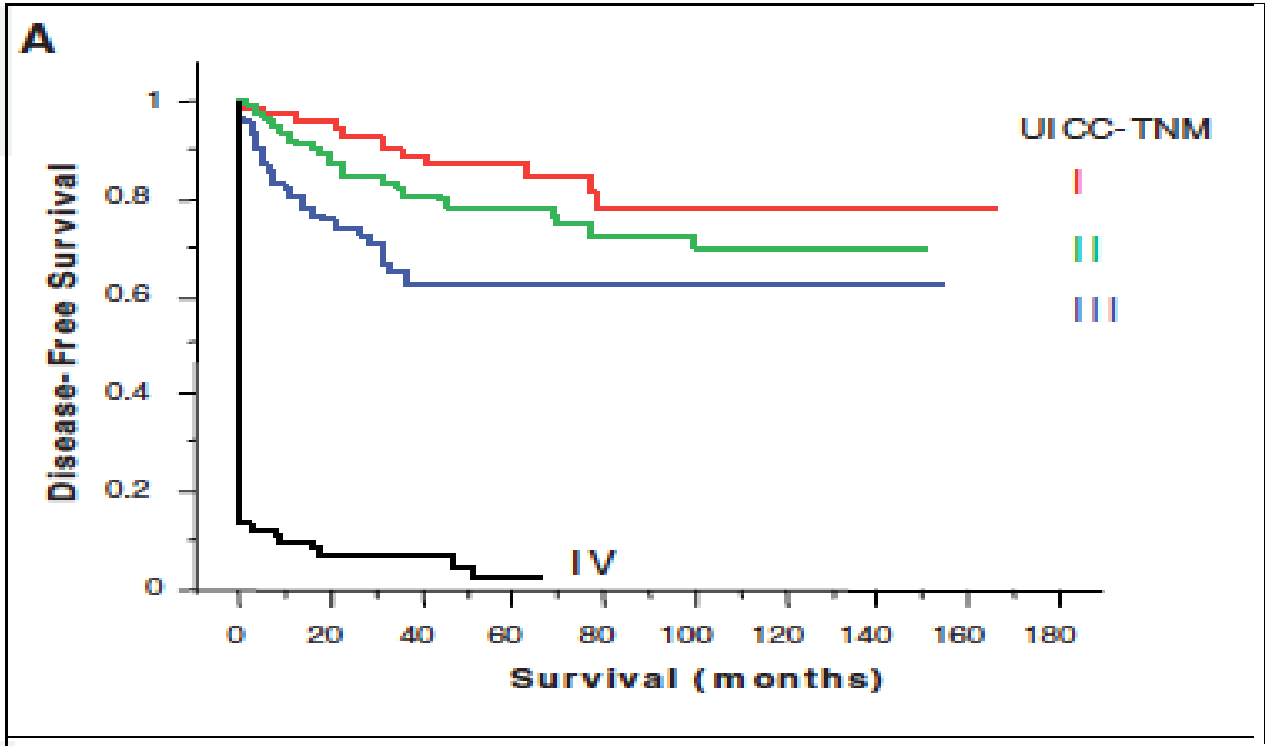
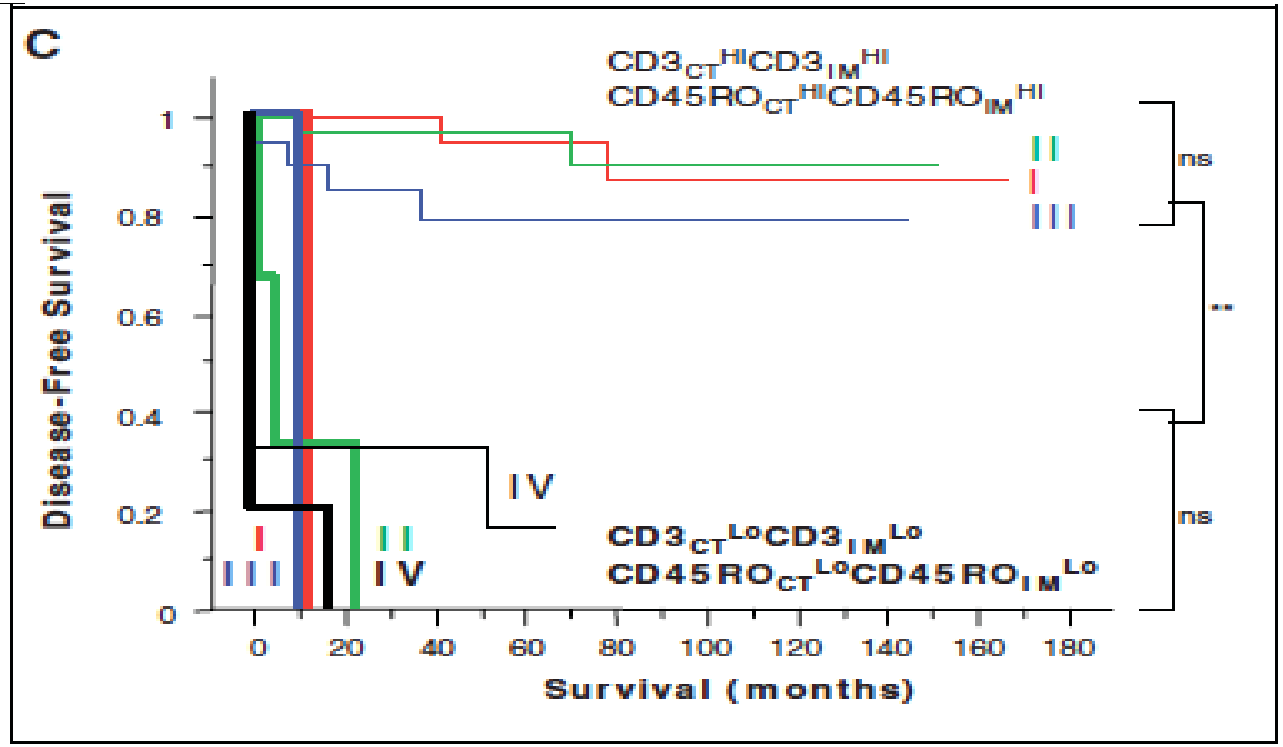
Coordinated adaptive immune response more than tumor invasion predicts outcome.

UICC-TNM Staging system

$CD3_{CT}CD3_{IM}$ evaluation ± $CD45RO_{CT}CD45RO_{IM}$ evaluation





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JOURNAL OF CLINICAL ONCOLOGY

EDITORIALS

TNM Staging in Colorectal Cancer: T Is for T Cell and M Is for Memory

Elizabeth K. Broussard and Mary L. Disis, *Tumor Vaccine Group, Center for Translational Medicine in Women's Health, University of Washington, Seattle, WA*

Galon *et al. Journal of Translational Medicine* 2012, **10**:1
http://www.translational-medicine.com/content/10/1/1

JOURNAL OF TRANSLATIONAL MEDICINE

EDITORIAL Open Access

The Immune Score as a New Possible Approach for the Classification of Cancer

Jérôme Galon[1,2,3,4,5*], Franck Pagès[1,2,3,4], Francesco M Marincola[5,6], Magdalena Thurin[7], Giorgio Trinchieri[8], Bernard A Fox[5,9,10], Thomas F Gajewski[5,11] and Paolo A Ascierto[12,13]

SITC Immunoscore Taskforce

Cancer classification using the Immunoscore: a worldwide task force

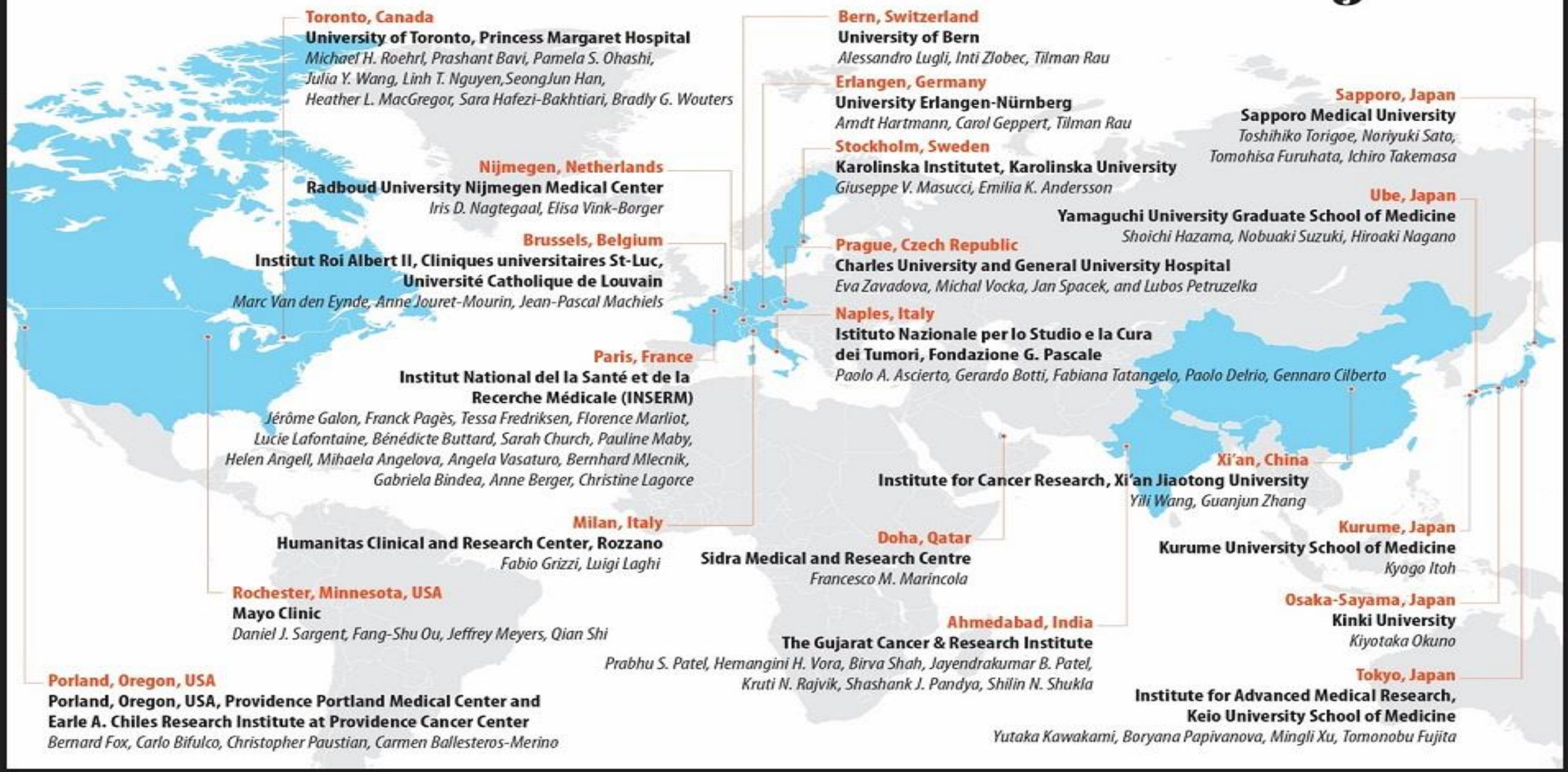
Jérôme Galon[1,2,3,4,5*], Franck Pagès[1,2,3,4], Francesco M Marincola[5,6], Helen K Angell[1,2,3], Magdalena Thurin[7], Alessandro Lugli[8], Inti Zlobec[8], Anne Berger[4], Carlo Bifulco[9], Gerardo Botti[10], Fabiana Tatangelo[10], Cedrik M Britten[11], Sebastian Kreiter[11], Lotfi Chouchane[12], Paolo Delrio[13], Hartmann Arndt[14], Martin Asslaber[15], Michele Maio[16], Giuseppe V Masucci[17], Martin Mihm[18], Fernando Vidal-Vanaclocha[19], James P Allison[20], Sacha Gnjatic[20], Leif Hakansson[21], Christoph Huber[11], Harpreet Singh-Jasuja[22], Christian Ottensmeier[23], Heinz Zwierzina[24], Luigi Laghi[25], Fabio Grizzi[25], Pamela S Ohashi[26], Patricia A Shaw[27], Blaise A Clarke[27], Bradly G Wouters[27], Yutaka Kawakami[28], Shoichi Hazama[29], Kiyotaka Okuno[30], Ena Wang[6], Jill O'Donnell-Tormey[31], Christine Lagorce[32], Graham Pawelec[33], Michael I Nishimura[34], Robert Hawkins[35], Réjean Lapointe[36], Andreas Lundqvist[37], Samir N Khleif[38], Shuji Ogino[39], Peter Gibbs[40], Paul Waring[41], Noriyuki Sato[42], Toshihiko Torigoe[42], Kyogo Itoh[43], Prabhu S Patel[44], Shilin N Shukla[44], Richard Palmqvist[45], Iris D Nagtegaal[46], Yili Wang[47], Corrado D'Arrigo[48], Scott Kopetz[49], Frank A Sinicrope[50], Giorgio Trinchieri[51], Thomas F Gajewski[5,52], Paolo A Ascierto[53,54] and Bernard A Fox[5,55,56]

Galon *et al. Journal of Translational Medicine* 2012, **10**:205

SITC Organized

- Logistical and infrastructure support
- Brought World Immunotherapy Council (WIC) Together / Support
- Organized meetings with major pharma to try and raise $
- Provided platforms for Updates
  - Taskforce Meetings
  - Publications: JTM, JITC
  - Annual Meeting – Update to Membership

SITC Immunoscore Validation Project



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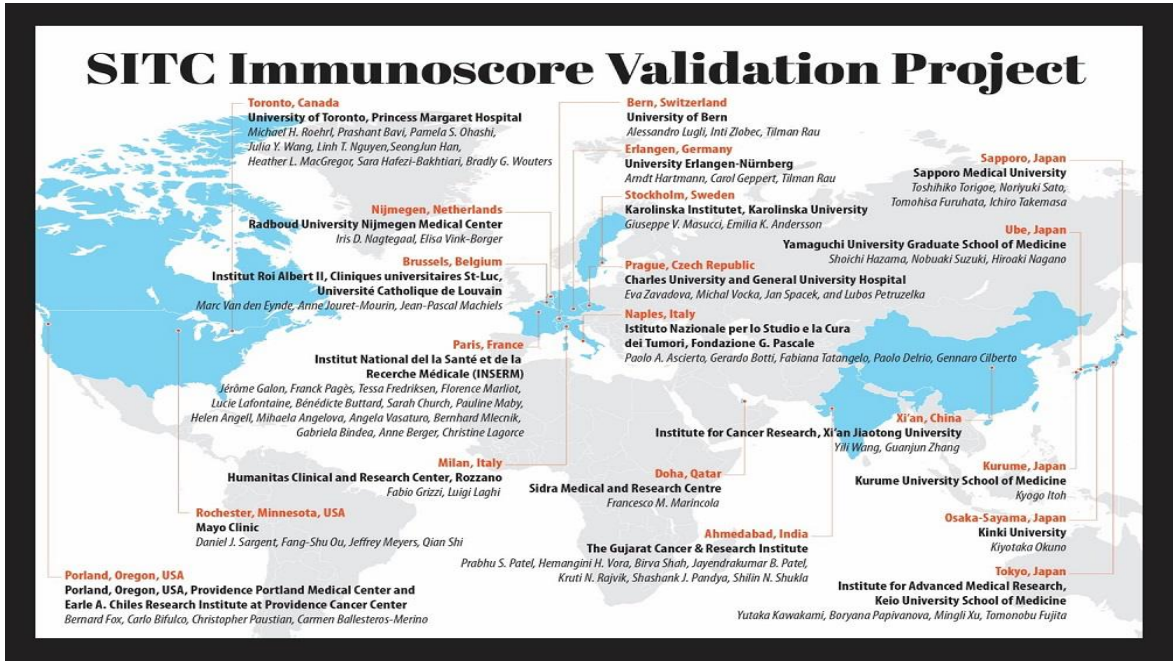
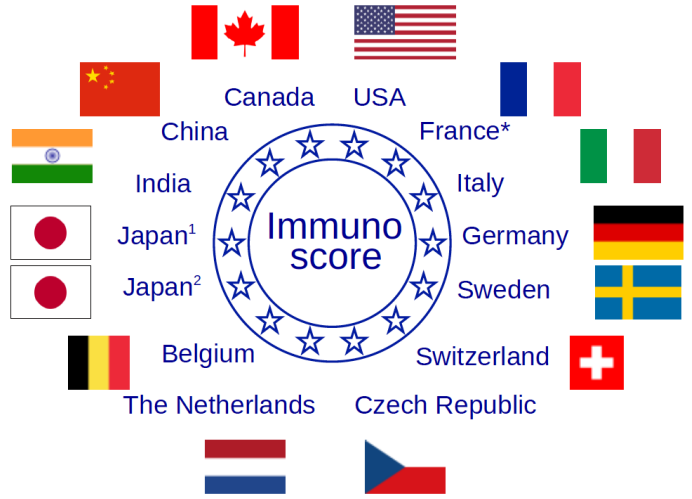
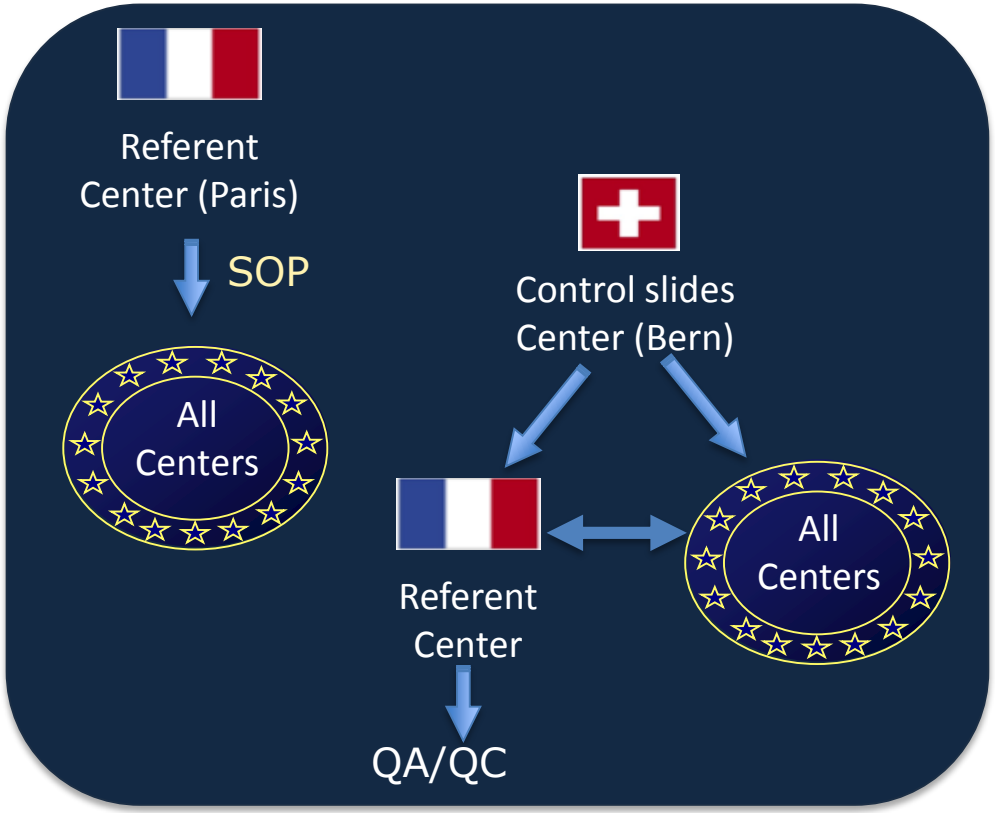
Population Diversity

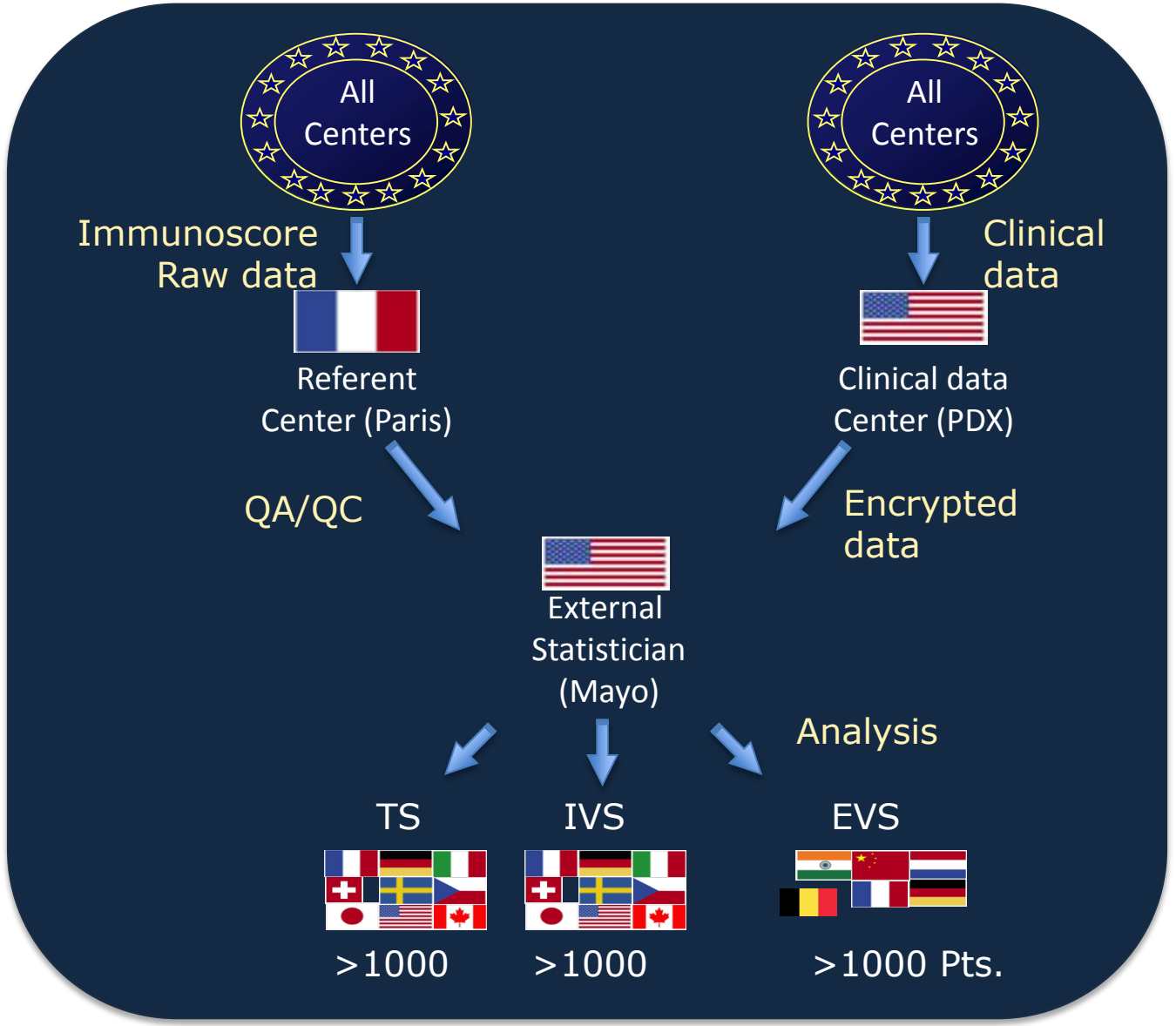


- Genetic / Ancestry Differences
- HLA Haplotypes
  - Varied capabilities to present peptides
- Microbiome
  - Different microbes may influence



SITC- Led Immunoscore Consortium Study design





Patient population and clinical characteristics

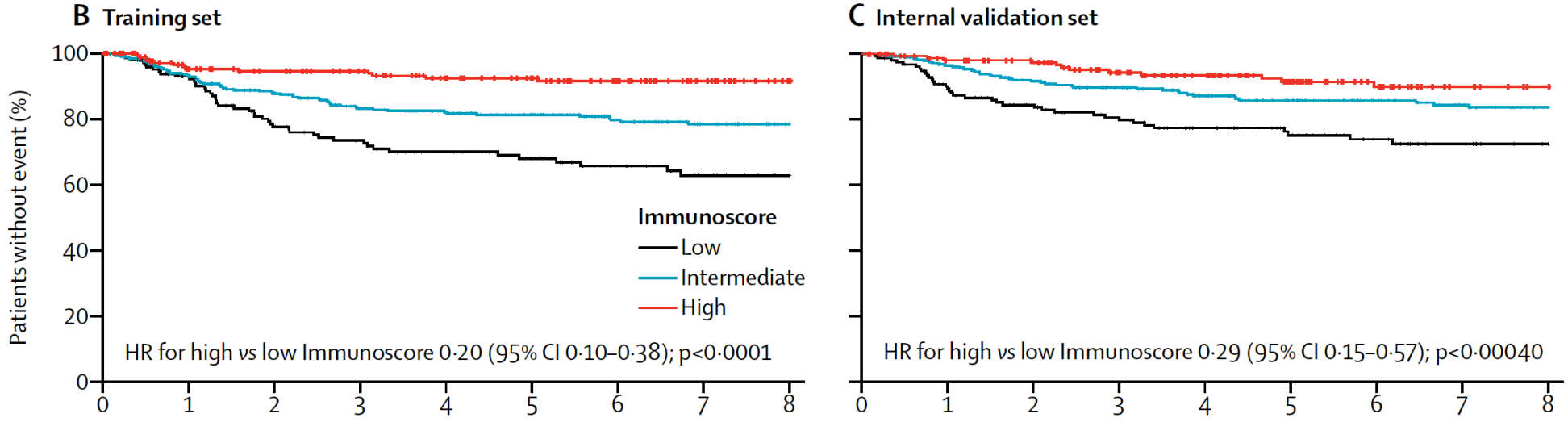
Inclusion criteria:

- Colon Cancer
- Stages I/II/III (T1-T4, N0-N2, M0)
- No neo-adjuvant treatments
- clinical data and follow-up ---------- **3855 patients**

Exclusion criteria:

- Rectum cancer (n=255)
- Stage IV (M1) (n=81)
- Neo-adjuvant treatments (n=6)
- Missing Clinical data (n=45)
- Missing follow-up (n=127)
- Staining intensity <152 (n=86)
- Missing/incomplete biomarker data (n=490) ---------- **2667 patients**

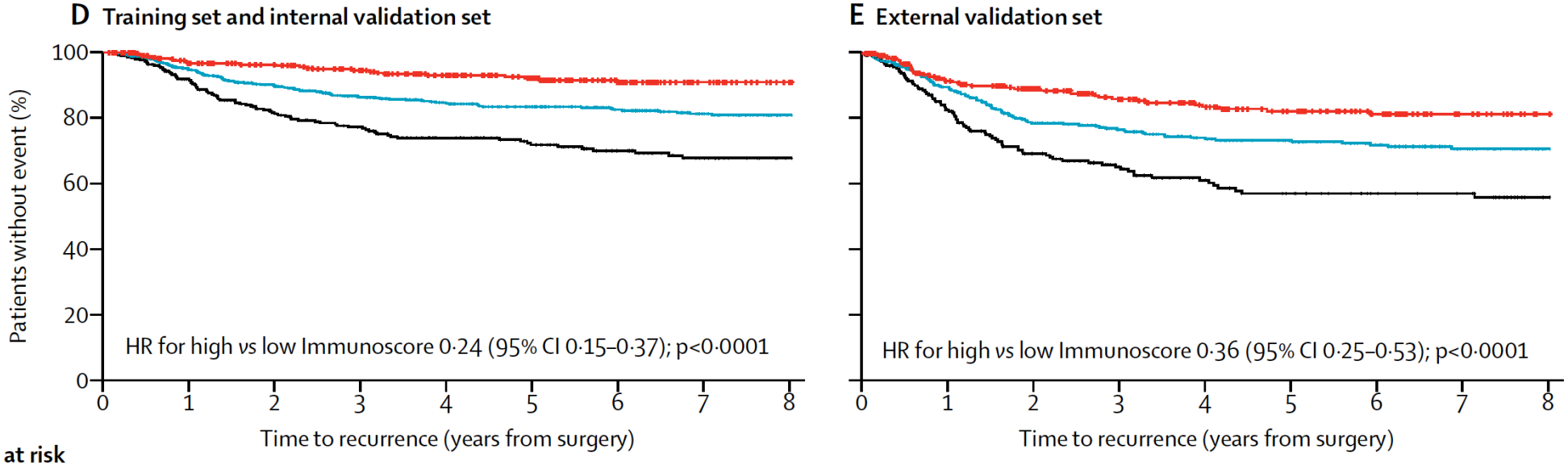
analyzed after QC and exclusion following a pre-defined statistical analysis workplan



Number at risk

Low	155	127	95	86	74	66	51	39	32
Intermediate	357	294	262	232	213	175	141	113	91
High	188	156	144	135	120	108	86	70	53

Low	162	130	114	101	84	69	56	45	38
Intermediate	304	268	243	223	199	171	135	117	100
High	170	149	139	117	104	81	64	47	41

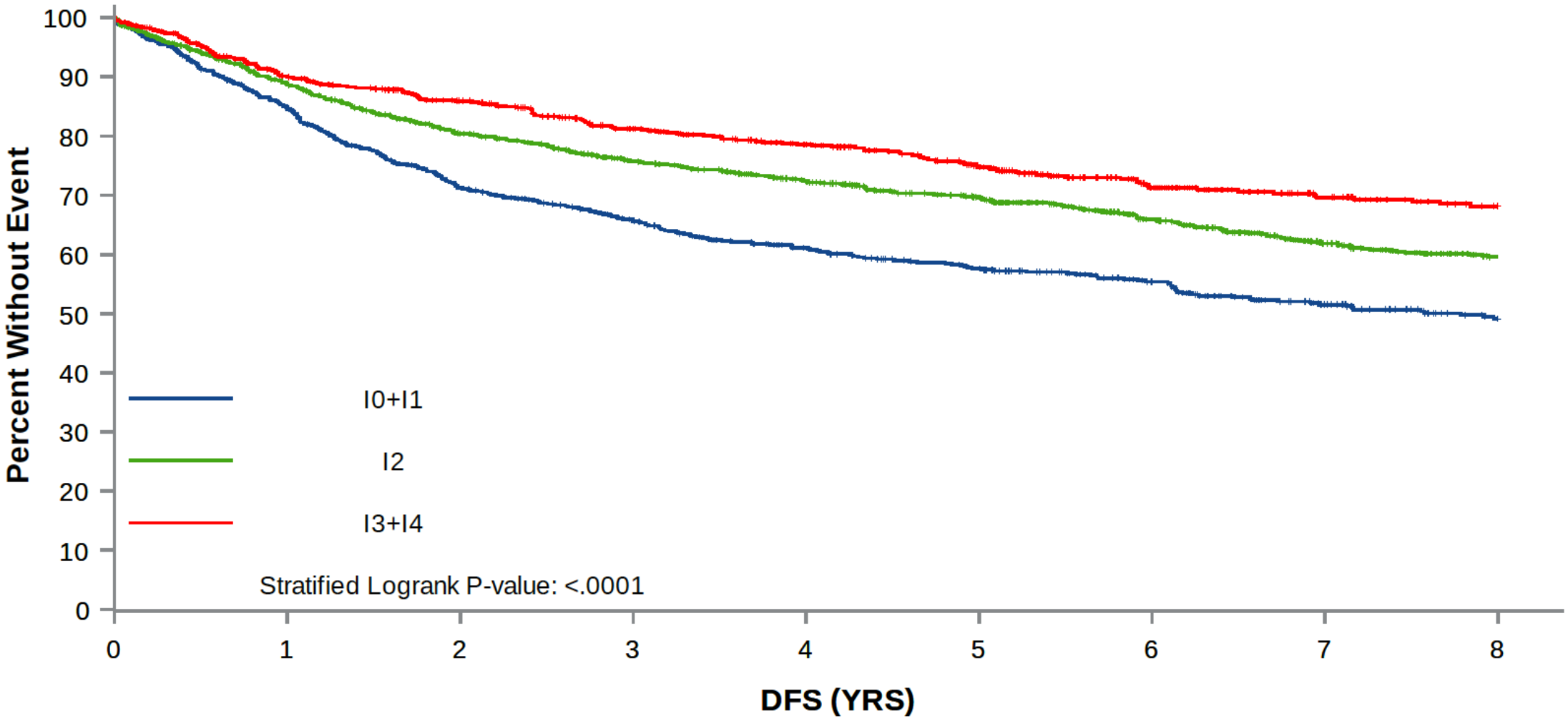


Number at risk

Low	317	257	209	187	158	135	107	84	70
Intermediate	661	562	505	455	412	346	276	230	191
High	358	305	283	252	224	189	150	117	94

Low	239	166	128	100	77	68	55	51	36
Intermediate	445	332	259	223	189	170	139	102	77
High	294	227	190	160	133	111	88	64	52

Training set, Internal and External Validations



702	566	468	411	358	321	259	194	150
1271	1069	930	839	763	675	526	406	324
708	594	535	469	417	359	273	208	172

3-level Immunoscore Derived From TS+IVS, Training+IV+EV+Japan/China Dataset adjusting for MSI status

	TTR Model (314/1562)*			DFS Model (590/1562)*			OS Model (491/1562)*		
	Hazard Ratio (95% CI)	P-value	C-Index (95% CI)	Hazard Ratio (95% CI)	P-value	C-Index (95% CI)	Hazard Ratio (95% CI)	P-value	C-Index (95% CI)
Unadjusted Stratified Cox Model			0.62 (0.56-0.68)			0.58 (0.54-0.63)			0.58 (0.53-0.63)
Immunoscore, 3-level (CD3/CD8 CT/IM)		<.0001[1]			<.0001[1]			<.0001[1]	
I2 vs I0+I1	0.447 (0.349-0.572)	<.0001[2]		0.588 (0.487-0.710)	<.0001[2]		0.617 (0.503-0.757)	<.0001[2]	
I3+I4 vs I0+I1	0.239 (0.168-0.341)	<.0001[2]		0.429 (0.338-0.545)	<.0001[2]		0.496 (0.384-0.640)	<.0001[2]	
Multivariable Stratified Cox Model			0.74 (0.67-0.80)			0.66 (0.61-0.71)			0.64 (0.58-0.69)
Immunoscore, 3-level (CD3/CD8 CT/IM)		<.0001[1]			<.0001[1]			<.0001[1]	
I2 vs I0+I1	0.488 (0.381-0.626)	<.0001[2]		0.622 (0.515-0.753)	<.0001[2]		0.654 (0.532-0.805)	<.0001[2]	
I3+I4 vs I0+I1	0.328 (0.229-0.472)	<.0001[2]		0.511 (0.401-0.652)	<.0001[2]		0.558 (0.429-0.726)	<.0001[2]	
Gender		0.0696[1]			0.0894[1]			0.1355[1]	
Female vs Male	0.811 (0.646-1.017)	0.0696[2]		0.867 (0.735-1.022)	0.0894[2]		0.872 (0.728-1.044)	0.1355[2]	
T-stage (Grouped T4 Version)		<.0001[1]			<.0001[1]			0.0059[1]	
T2 vs T1	1.611 (0.551-4.710)	0.3839[2]		1.491 (0.778-2.860)	0.2289[2]		1.636 (0.800-3.345)	0.1774[2]	
T3 vs T1	2.707 (0.994-7.371)	0.0514[2]		2.084 (1.133-3.833)	0.0182[2]		2.088 (1.065-4.096)	0.0322[2]	
T4 vs T1	4.991 (1.803-13.818)	0.0020[2]		2.850 (1.518-5.351)	0.0011[2]		2.657 (1.322-5.339)	0.0061[2]	
N-stage		<.0001[1]			<.0001[1]			<.0001[1]	
N1 vs N0	1.943 (1.477-2.555)	<.0001[2]		1.563 (1.274-1.918)	<.0001[2]		1.327 (1.056-1.667)	0.0150[2]	
N2 vs N0	3.118 (2.315-4.200)	<.0001[2]		2.272 (1.793-2.879)	<.0001[2]		1.992 (1.530-2.594)	<.0001[2]	
MSI Status (Derived)		0.0064[1]			0.6677[1]			0.6107[1]	
dMMR vs pMMR	0.608 (0.425-0.870)	0.0064[2]		0.953 (0.767-1.185)	0.6677[2]		1.063 (0.841-1.343)	0.6107[2]	
Age	0.999 (0.995-1.003)	0.5695[1]		1.001 (1.000-1.002)	0.2023[1]		1.002 (1.000-1.003)	0.0143[1]	

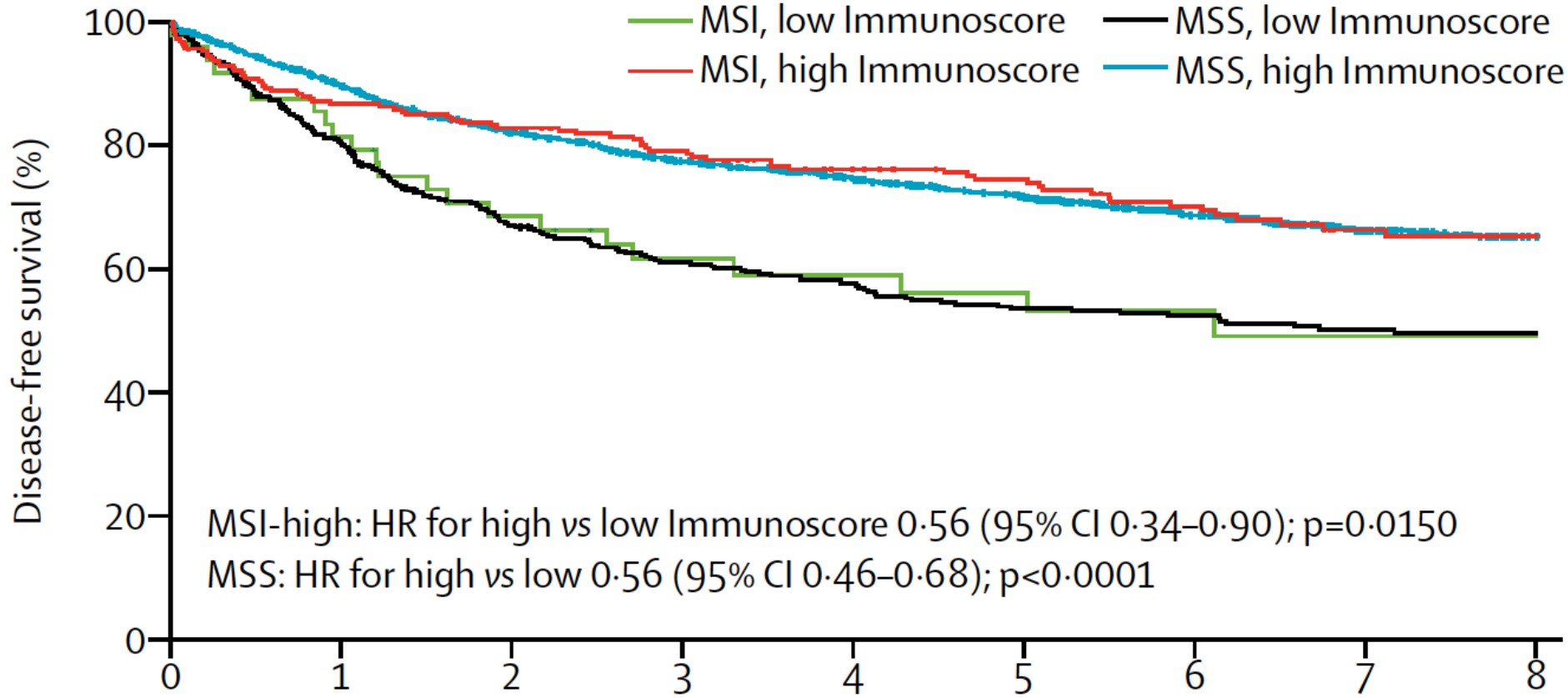
* (Events/Total); [1]Stratified type 3 Wald p-value; [2]Stratified covariate Wald p-value; Stratified by center city, adjusted by MSI status; d/p MMR: deficient/proficient Miss Match Repair

Summary of Results:

- The primary objective (significance of Immunoscore 2 categories (High/Low) significant for TTR) was pre-specified in the statistical workplan and was reached. (P<0.0001) differences for TTR, DFS and OS.
- Multivariable analyses showed that Immunoscore adds substantial power to discriminate cohorts with varied survival characteristics beyond that provided by established prognostic variables.
- Immunoscore's association to outcomes was independent of the patient's age, gender, T-stage, and N-stage (*P*< 0.0001).
- Immunoscore high and low in 3 categories for TTR was validated for North America, Asia and Europe (significant (P<0.05).

MSI – Microsatellite Instable Colon Cancers

- Highly mutated cancers –
  - Large number of neoantigens
  - Increased response to checkpoint blockade
  - FDA approved use of anti-PD-1 for all MSI high cancers



Number at risk

MSI, low Immunoscore	49	39	31	23	21	19	13	11	9
MSI, high Immunoscore	255	206	178	164	146	130	101	71	58
MSS, low Immunoscore	353	273	225	200	174	155	127	94	72
MSS, high Immunoscore	922	791	690	621	565	502	379	286	234

MSI / MSS – Immunoscore Predicts Outcome

- Immunoscore's association to outcomes was independent of the patient's microsatellite instability (MSI) status ($P < 0.0001$).
- Immune surveillance: Is real
  - Questions:
    - Inflammed signature distributed across range of mutated/nonmutated tumors
    - Immunity against overexpressed non-mutated "self" epitopes?
- Evidence in support of T cells against non-mutated epitopes
  - Parkhurst MR, et al., Mol. Ther 2011 – Colon CA
  - Gee MH et al., Cell 2018 – Colon CA
  - Tripathi et al., PNAS 2016 - NSCLC

Is the Immunoscore Ready for Prime Time?

Is the Immunoscore Ready for Prime Time?

YES!

Clinical Implications:

- Basis for the first standardized immune-based assay for the classification of cancer
- Stratification of patients on clinical trials – ANY TRIAL?
- Sets stage for clinical trials exploring adjuvant therapy in stage II colon cancer patients with a low Immunoscore
    - NCI Colon Cancer Vaccine Study?
- Role for clinical trial evaluating whether chemotherapy *versus* reducing the duration of the adjuvant chemotherapy or watchful waiting, plus or minus immunotherapy, might provide benefit for this cohort of patients.

Trial Design Developed By: **Daniel J. Sargent, PhD**

08/22/1970 - 09/22/2016

- Research was in the area of oncology clinical trials
- Led multiple international groups including;
  -ACCENT in adjuvant colon cancer,
  - Prospective IDEA in colon cancer
- In 2014, Dr. Sargent was awarded a $37.7 million, 5-year grant by the NCI to lead the Alliance for Clinical Trials in Oncology Statistics and Data Center, at the Mayo Clinic
- Published extensively in colorectal cancer treatment, optimal clinical trial design and endpoints, and prognostic and predictive biomarkers.

Fang-Shu Ou, PhD
Oncology Statistics
Mayo Clinic

Review Session
ASCO 2016

Immunoscore: Future Plans

- SITC and the Scientific Community
  - Immunoscore: TCGA-Like Image database of the 9000 images
  - *Possible – Multiplex Images?*

- Next – Pathology Taskforce to address “Hurdles” to multiplex
  - Accademics
  - Industry
  - Govt

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