SITC Tumor microenvironment
San Diego, USA
April 21st 2022

The cancer immune contexture and heterogeneity of the tumor microenvironment

Jérôme GALON

INSERM, Laboratory of Integrative Cancer Immunology, Cordeliers Research Center, Paris, France

Inserm laboratory of Integrative Cancer Immunology

INVESTISSEMENTS D'AVENIR LabEx Immuno Oncology

Université de Paris

SORBONNE UNIVERSITÉ

CRC CENTRE DE RECHERCHE DES CORDELIERS

Disclosures

Co-founder, chairman of the scientific advisory board, CSO Immuno-Oncology:

- *HalioDx – a Veracyte company*

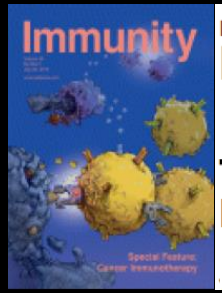
Collaborative Research Agreement (grants) :

- *Veracyte, Imcheck Therapeutics*

Participation to Scientific Advisory Boards:

- *IObiotech, Illumina, Northwest Biotherapeutics, Actelion, Amgen, Catalym, Merck MSD, Lunaphore*

The continuum of cancer immunosurveillance

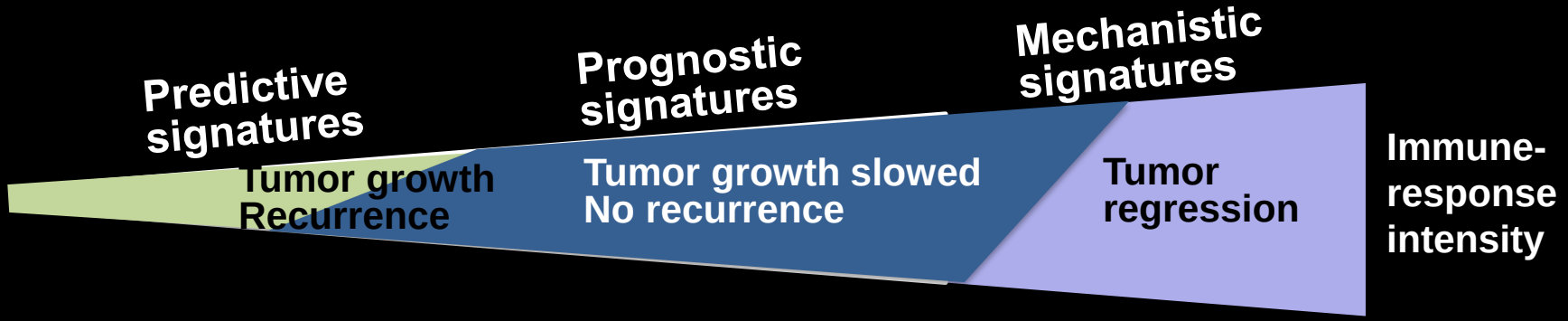


Immunity
Review

Cell PRESS

The Continuum of Cancer Immunosurveillance: Prognostic, Predictive, and Mechanistic Signatures

Jérôme Galon,[1,2,3,*] Helen K. Angell,[1,2,3] Davide Bedognetti,[4] and Francesco M. Marincola[4,5,*]



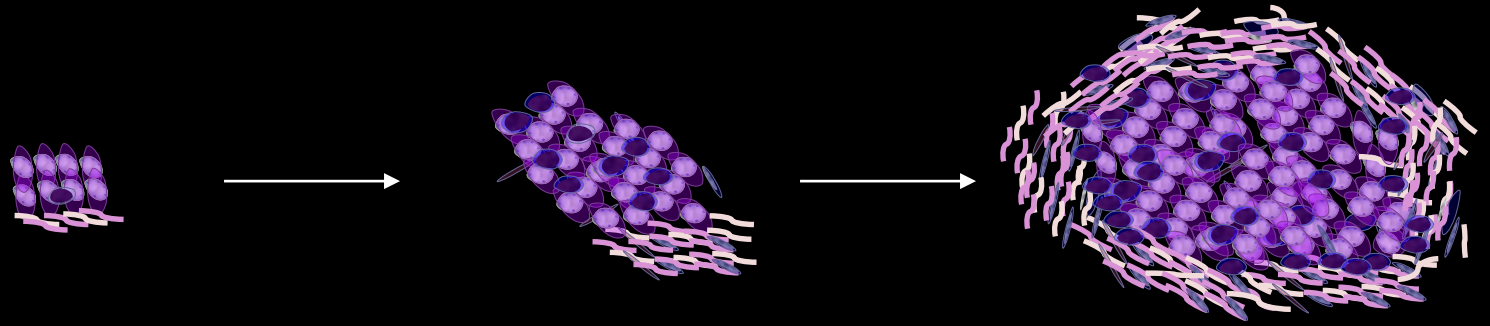
Galon J et al. ***Immunity*** 2013

The continuum of cancer immunosurveillance

Pre-cancerous lesions

Primary Carcinoma

Metastasis



Mascaux C. … Galon J. ***Nature*** 2019

Pagès F. … Galon J. ***Lancet*** 2018
Mlecnik B. … Galon J. ***JCO*** 2020

Phase 3 trials
Ann Oncol 2020, ***JNCI CS*** 2020

Angelova M. … Galon J. ***Cell*** 2018
Van den Eynde M. … Galon J. ***Cancer Cell*** 2018
Mlecnik B. … Galon J. ***JNCI*** 2018

The workdwide Immunoscore consortium

THE LANCET

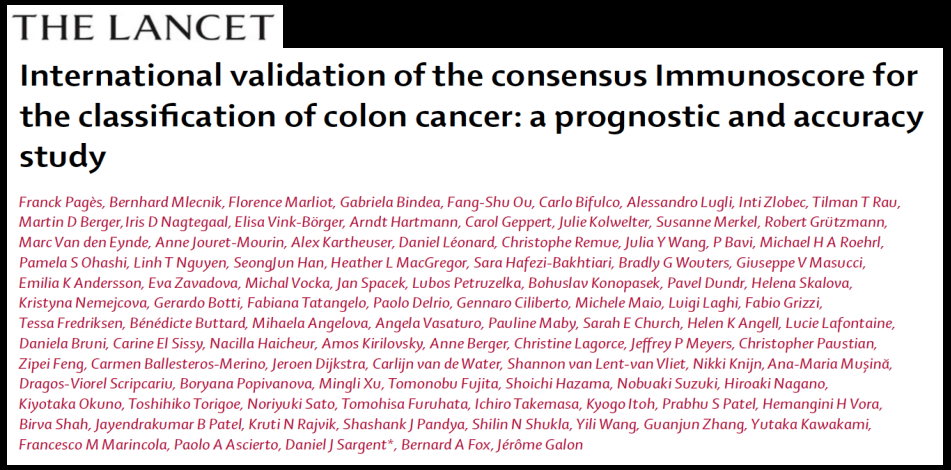
International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study

Franck Pagès, Bernhard Mlecnik, Florence Marliot, Gabriela Bindea, Fang-Shu Ou, Carlo Bifulco, Alessandro Lugli, Inti Zlobec, Tilman T Rau, Martin D Berger, Iris D Nagtegaal, Elisa Vink-Börger, Arndt Hartmann, Carol Geppert, Julie Kolwelter, Susanne Merkel, Robert Grützmann, Marc Van den Eynde, Anne Jouret-Mourin, Alex Kartheuser, Daniel Léonard, Christophe Remue, Julia Y Wang, P Bavi, Michael H A Roehrl, Pamela S Ohashi, Linh T Nguyen, SeongJun Han, Heather L MacGregor, Sara Hafezi-Bakhtiari, Bradly G Wouters, Giuseppe V Masucci, Emilia K Andersson, Eva Zavadova, Michal Vocka, Jan Spacek, Lubos Petruzelka, Bohuslav Konopasek, Pavel Dundr, Helena Skalova, Kristyna Nemejcova, Gerardo Botti, Fabiana Tatangelo, Paolo Delrio, Gennaro Ciliberto, Michele Maio, Luigi Laghi, Fabio Grizzi, Tessa Fredriksen, Bénédicte Buttard, Mihaela Angelova, Angela Vasaturo, Pauline Maby, Sarah E Church, Helen K Angell, Lucie Lafontaine, Daniela Bruni, Carine El Sissy, Nacilla Haicheur, Amos Kirilovsky, Anne Berger, Christine Lagorce, Jeffrey P Meyers, Christopher Paustian, Zipei Feng, Carmen Ballesteros-Merino, Jeroen Dijkstra, Carlijn van de Water, Shannon van Lent-van Vliet, Nikki Knijn, Ana-Maria Mușină, Dragos-Viorel Scripcariu, Boryana Popivanova, Mingli Xu, Tomonobu Fujita, Shoichi Hazama, Nobuaki Suzuki, Hiroaki Nagano, Kiyotaka Okuno, Toshihiko Torigoe, Noriyuki Sato, Tomohisa Furuhata, Ichiro Takemasa, Kyogo Itoh, Prabhu S Patel, Hemangini H Vora, Birva Shah, Jayendrakumar B Patel, Kruti N Rajvik, Shashank J Pandya, Shilin N Shukla, Yili Wang, Guanjun Zhang, Yutaka Kawakami, Francesco M Marincola, Paolo A Ascierto, Daniel J Sargent, Bernard A Fox, Jérôme Galon*

N=2681 patients

Pages et al. *The Lancet* 2018

Prognostic value of the consensus Immunoscore



THE LANCET

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Pages et al. *The Lancet* 2018

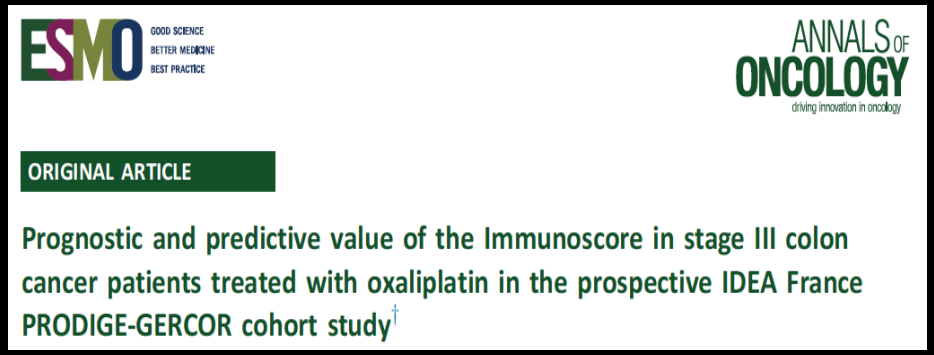
JOURNAL OF CLINICAL ONCOLOGY

original reports

Multicenter International Society for Immunotherapy of Cancer Study of the Consensus Immunoscore for the Prediction of Survival and Response to Chemotherapy in Stage III Colon Cancer

Bernhard Mlecnik, PhD[1,2,3,4]; Carlo Bifulco, MD[5]; Gabriela Bindea, PhD[1,2,3]; Florence Marliot, MSc[1,2,3,6]; Alessandro Lugli, MD[7]; J. Jack Lee, PhD[8]; Inti Zlobec, PhD[7]; Tilman T. Rau, MD[7]; Martin D. Berger, MD[9]; Iris D. Nagtegaal, MD, PhD[10]; Elisa Vink-Börger, PhD[10]; Arndt Hartmann, MD[11]; Carol Geppert, MD[11]; Julie Kolwelter, MD[11]; Susanne Merkel, MD[12]; Robert Grützmann, MD[12]; Marc Van den Eynde, MD, PhD[13]; Anne Jouret-Mourin, MD, PhD[14]; Alex Kartheuser, MD, PhD[15]; Daniel Léonard, MD, PhD[15]; Christophe Remue, MD[15]; Julia Y. Wang, PhD[16,17,18]; Prashant Bavi, MD, MBBS[18]; Michael H. A. Roehrl, MD, PhD[17,18,19]; Pamela S. Ohashi, PhD[20]; Linh T. Nguyen, PhD[20]; SeongJun Han, MSc[20]; Heather L. MacGregor, PhD[20]; Sara Hafezi-Bakhtiari, MD[17]; Bradly G. Wouters, MD, PhD[20]; Giuseppe V. Masucci, MD, PhD[21]; Emilia K. Andersson, MD, PhD[21]; Eva Zavadova, MD, PhD[22]; Michal Vocka, MD[22]; Jan Spacek, MD[22]; Lubos Petruzelka, MD, PhD[22]; Bohuslav Konopasek, PhD[22]; Pavel Dundr, PhD[23]; Helena Skalova, PhD[23]; Kristyna Nemejcova, MD, PhD[23]; Gerardo Botti, MD, PhD[24]; Fabiana Tatangelo, MD, PhD[24]; Paolo Delrio, MD, PhD[25]; Gennaro Ciliberto, MD, PhD[26]; Michele Maio, MD, PhD[27]; Luigi Laghi, MD, PhD[28]; Fabio Grizzi, PhD[29]; Tessa Fredriksen, MSc[1,2,3]; Bénédicte Buttard, MSc[1,2,3]; Lucie Lafontaine, BSc[1,2,3]; Daniela Bruni, PharmD, PhD[1,2,3]; Anastasia Lanzi, PhD[1,2,3]; Carine El Sissy, MD[1,2,3,6]; Nacilla Haicheur, MSc[6]; Amos Kirilovsky, PhD[1,2,3,6]; Anne Berger, MD, PhD[1,2,330]; Christine Lagorce, MD, PhD[1,2,3,31]; Christopher Paustian, PhD[32]; Carmen Ballesteros-Merino, PhD[32]; Jeroen Dijkstra, BSc[10]; Carlijn van de Water, BSc[10]; Shannon van Lent–van Vliet, BSc[10]; Nikki Knijn, MD[10]; Ana-Maria Mușină, MD, PhD[33]; Dragos-Viorel Scripcariu, MD, PhD[33]; Boryana Popivanova, MD, PhD[34]; Mingli Xu, MD, PhD[34]; Tomonobu Fujita, PhD[34]; Shoichi Hazama, MD, PhD[35]; Nobuaki Suzuki, MD, PhD[36]; Hiroaki Nagano, MD, PhD[36]; Kiyotaka Okuno, MD, PhD[37]; Toshihiko Torigoe, MD, PhD[38]; Noriyuki Sato, MD, PhD[38]; Tomohisa Furuhata, MD, PhD[39]; Ichiro Takemasa, MD, PhD[39]; Kyogo Itoh, MD, PhD[40]; Prabhu S. Patel, PhD[41]; Hemangini H. Vora, PhD[41]; Birva Shah, MD[41]; Jayendrakumar B. Patel, PhD[41]; Kruti N. Rajvik, PhD[41]; Shashank J. Pandya, MS[41]; Shilin N. Shukla, MD[41]; Yili Wang, MD, PhD[42]; Guanjun Zhang, MD[42]; Yutaka Kawakami, MD, PhD[34]; Francesco M. Marincola, MD[43]; Paolo A. Ascierto, MD, PhD[44]; Bernard A. Fox, PhD[31,45]; Franck Pagès, MD, PhD[1,2,3,6]; and Jérôme Galon, PhD[1,2,3]

Mlecnik B. et al. *JCO* 2020



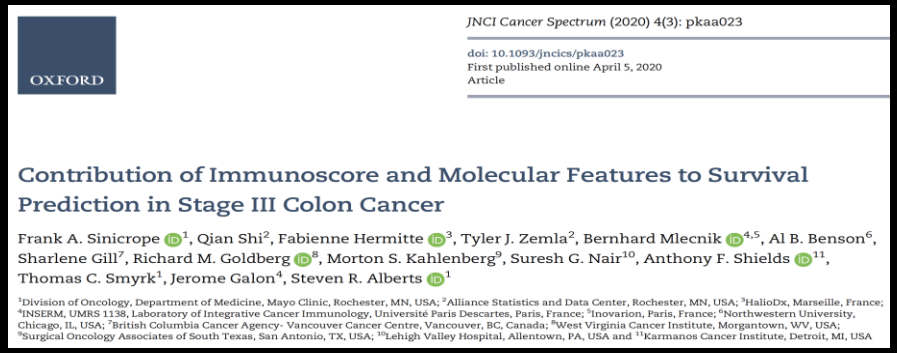
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Prognostic and predictive value of the Immunoscore in stage III colon cancer patients treated with oxaliplatin in the prospective IDEA France PRODIGE-GERCOR cohort study†

Pages F. et al. *Ann Oncol* 2020



OXFORD

JNCI Cancer Spectrum (2020) 4(3): pkaa023

doi: 10.1093/jncics/pkaa023
First published online April 5, 2020
Article

Contribution of Immunoscore and Molecular Features to Survival Prediction in Stage III Colon Cancer

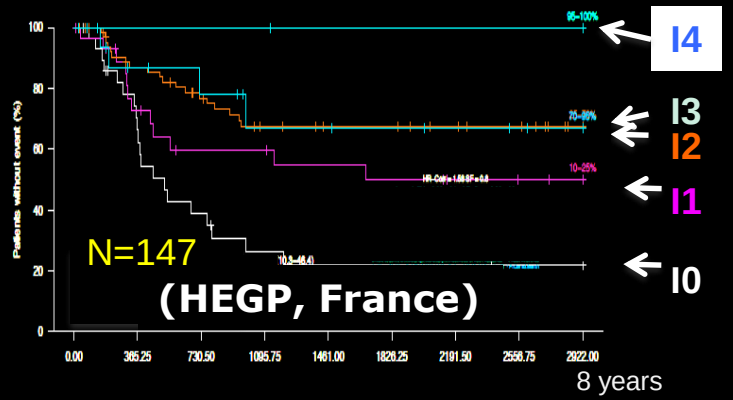
Frank A. Sinicrope[1], Qian Shi[2], Fabienne Hermitte[3], Tyler J. Zemla[2], Bernhard Mlecnik[4,5], Al B. Benson[6], Sharlene Gill[7], Richard M. Goldberg[8], Morton S. Kahlenberg[9], Suresh G. Nair[10], Anthony F. Shields[11], Thomas C. Smyrk[1], Jerome Galon[4], Steven R. Alberts[1]

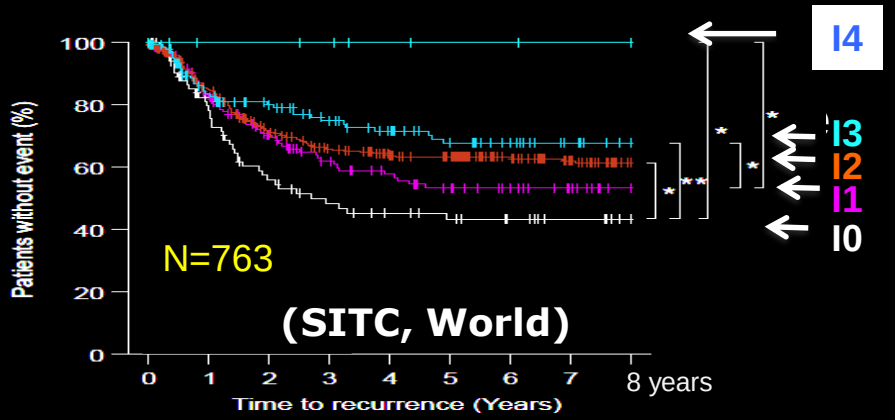
[1]Division of Oncology, Department of Medicine, Mayo Clinic, Rochester, MN, USA; [2]Alliance Statistics and Data Center, Rochester, MN, USA; [3]HalioDx, Marseille, France; [4]INSERM, UMRS 1138, Laboratory of Integrative Cancer Immunology, Université Paris Descartes, Paris, France; [5]Inovarion, Paris, France; [6]Northwestern University, Chicago, IL, USA; [7]British Columbia Cancer Agency- Vancouver Cancer Centre, Vancouver, BC, Canada; [8]West Virginia Cancer Institute, Morgantown, WV, USA; [9]Surgical Oncology Associates of South Texas, San Antonio, TX, USA; [10]Lehigh Valley Hospital, Allentown, PA, USA and [11]Karmanos Cancer Institute, Detroit, MI, USA

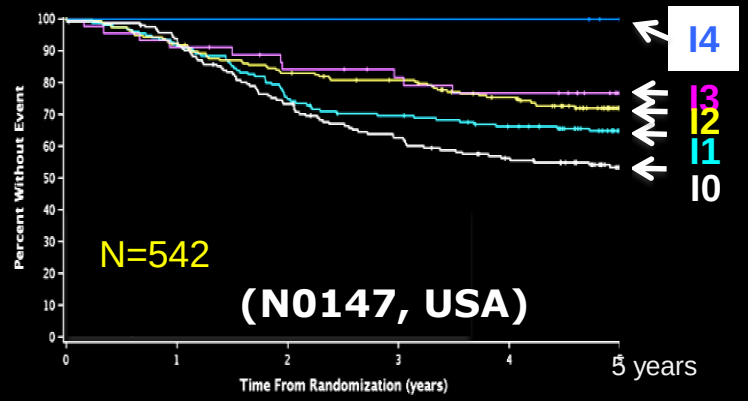
Sinicrope . et al. *JNCI Cancer Spec* 2020

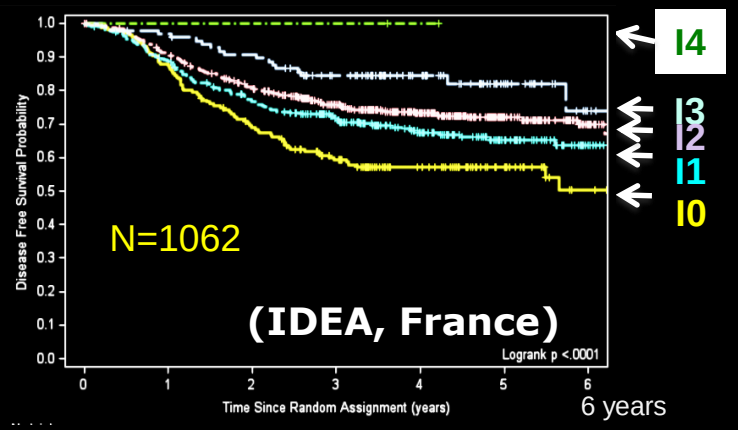
Immunoscore in stage III colon carcinoma patients

- ✓ Predefined cut-off from Worldwide SITC study, and Predefined statistical plan (Mayo Clinic)
- ✓ 4 independent cohorts, 2514 patients









Immunoscore predicts High-risk and No-risk patients in stage III colon cancer

Immunoscore: Inclusion into Cancer Guidelines

International Agency for Research on Cancer

World Health Organization

Essential and desirable diagnostic criteria for colorectal cancer

Immune response

Immune response (Immunoscore)

"*A standardized examination of the presence of lymphocytes at the invasive front of the tumour, using immunohistochemistry for CD3 and CD8, showed that this feature has significant prognostic power (Pages et al. Lancet 2018).*"

WHO Classification of Tumours, 5th Edition, 2019

Immunoscore: Inclusion into Cancer Guidelines

International Agency for Research on Cancer

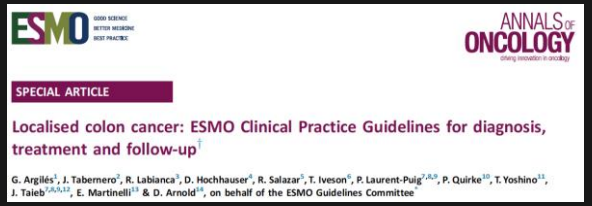
World Health Organization

Essential and desirable diagnostic criteria for colorectal cancer

➡ Immune response

Immune response (Immunoscore)
"*A standardized examination of the presence of lymphocytes at the invasive front of the tumour, using immunohistochemistry for CD3 and CD8, showed that this feature has significant prognostic power (Pages et al. Lancet 2018).*"

WHO Classification of Tumours, 5th Edition, 2019


ESMO

ANNALS OF ONCOLOGY

SPECIAL ARTICLE

Localised colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

G. Argilés[1], J. Tabernero[2], R. Labianca[3], D. Hochhauser[4], R. Salazar[5], T. Iveson[6], P. Laurent-Puig[7,8,9], P. Quirke[10], T. Yoshino[11], J. Taieb[7,8,9,12], E. Martinelli[13] & D. Arnold[14], on behalf of the ESMO Guidelines Committee*

ESMO
European Clinical Practice Guidelines for Gastrointestinal Cancers

➡ **Immunoscore** (Prognostic, Predictive)

Argiles et al. *Ann Oncol* 2020


ESMO

ANNALS OF ONCOLOGY

SPECIAL ARTICLE

Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis treatment and follow-up of patients with localised colon cancer

T. Yoshino[1*], G. Argilés[2], E. Oki[3], E. Martinelli[4], H. Taniguchi[5], D. Arnold[6], S. Mishima[7], Y. Li[8], B. K. Smruti[9], J. B. Ahn[10], I. Faud[11], C. E. Chee[12], K.-H. Yeh[13,14], P.-C. Lin[15], C. Chua[16], H. H. Hasbullah[17], M. A. Lee[18], A. Sharma[19], Y. Sun[20], G. Curigliano[21], H. Bando[22], F. Lordick[23], T. Yamanaka[23], J. Tabernero[24], E. Baba[25], A. Cervantes[26], A. Ohtsu[5], S. Peters[27], C. Ishioka[28] & G. Pentheroudakis[29]

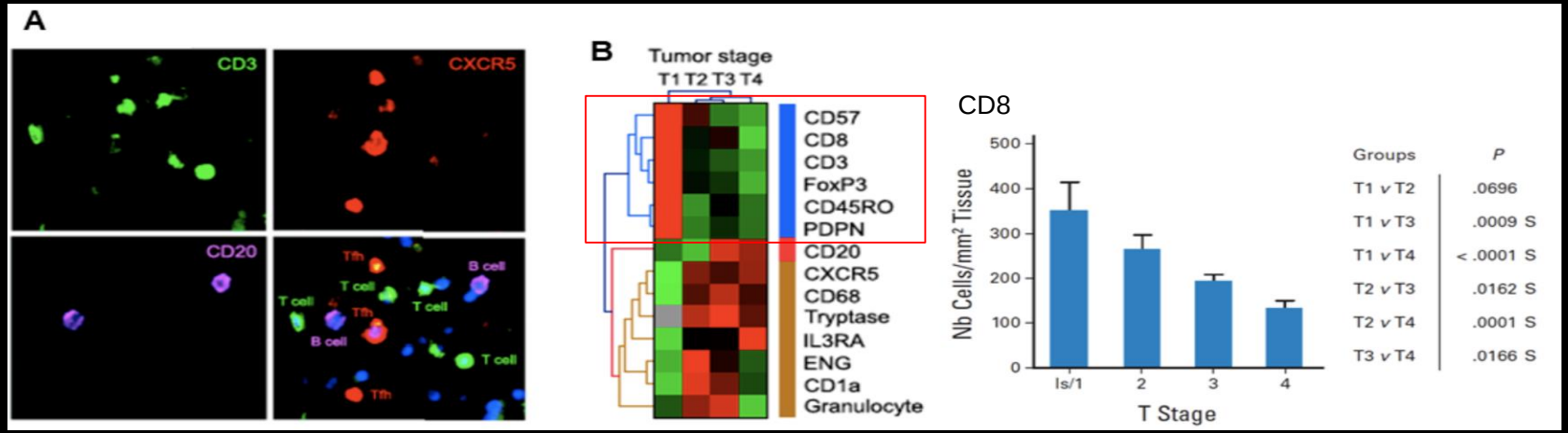
ESMO
Pan-Asian Guidelines 2021 for localised Colon Cancers

Japan (JSMO), China (CSCO), India (ISMPO), Malasya (MOS), Taiwan (TOS)

➡ **Immunoscore** is considered for its full range indication in colon cancers, stage II and stage III, with inclusion of all risk groups, with 100% consensus voted for recommendation

Yoshino et al. *Ann Oncol* 2021

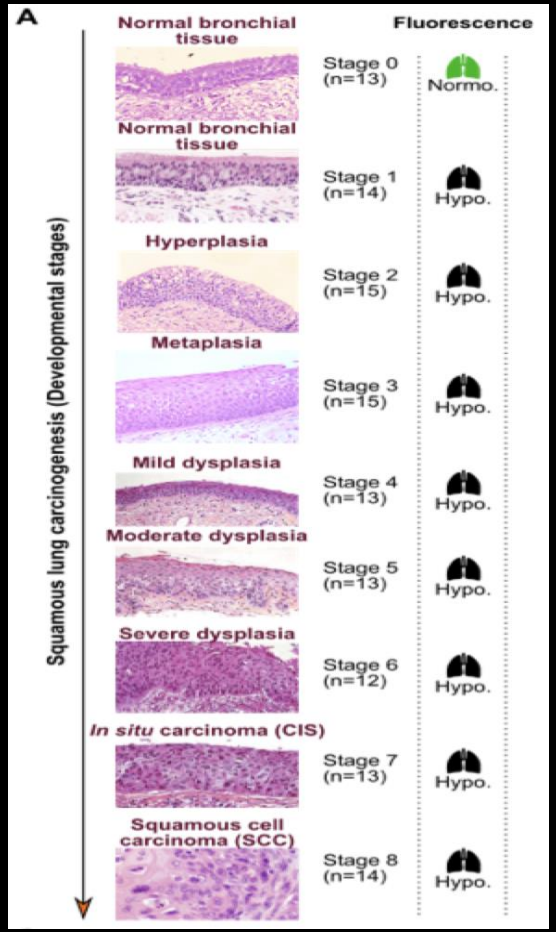
Adaptive immunity decreases with tumor progression



Bindea G. et al. ***Immunity*** 2013

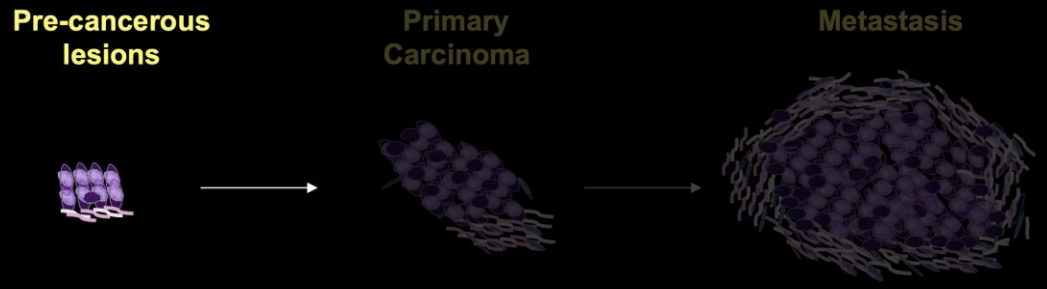
Mlecnik B. et al. ***J Clin Oncol*** 2011

Oncogenesis of lung squamous cell carcinoma



- ✓ Analysis of 122 pre-cancer lesions across 9 developmental stages

Mascaux C et al. ***Nature*** 2019



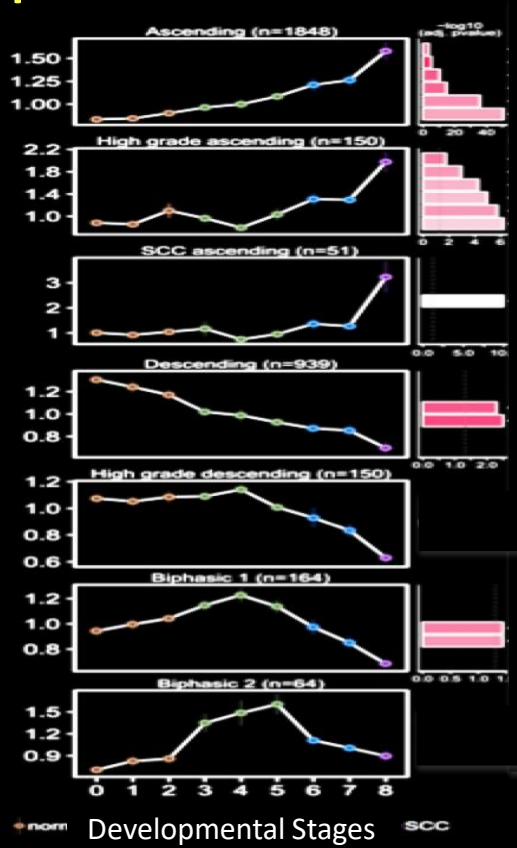
nature
International journal of science

Immune evasion before tumour invasion in early lung squamous carcinogenesis

Céline Mascaux[1,2,3,4,14,15,18]*, Mihaela Angelova[5,6,7,8,16,18], Angela Vasaturo[5,6,7,8], Jennifer Beane[2], Kahkeshan Hijazi[2], Geraldine Anthoine[1], Bénédicte Buttard[5,6,7,8], Françoise Rothe[9], Karen Willard-Gallo[10], Annick Haller[11,17], Vincent Ninane[12], Arsène Burny[13], Jean-Paul Sculier[1], Avi Spira[2] & Jérôme Galon[5,6,7,8]*

Mascaux C et al. ***Nature*** 2019

Main gene expression patterns across 9 developmental stages

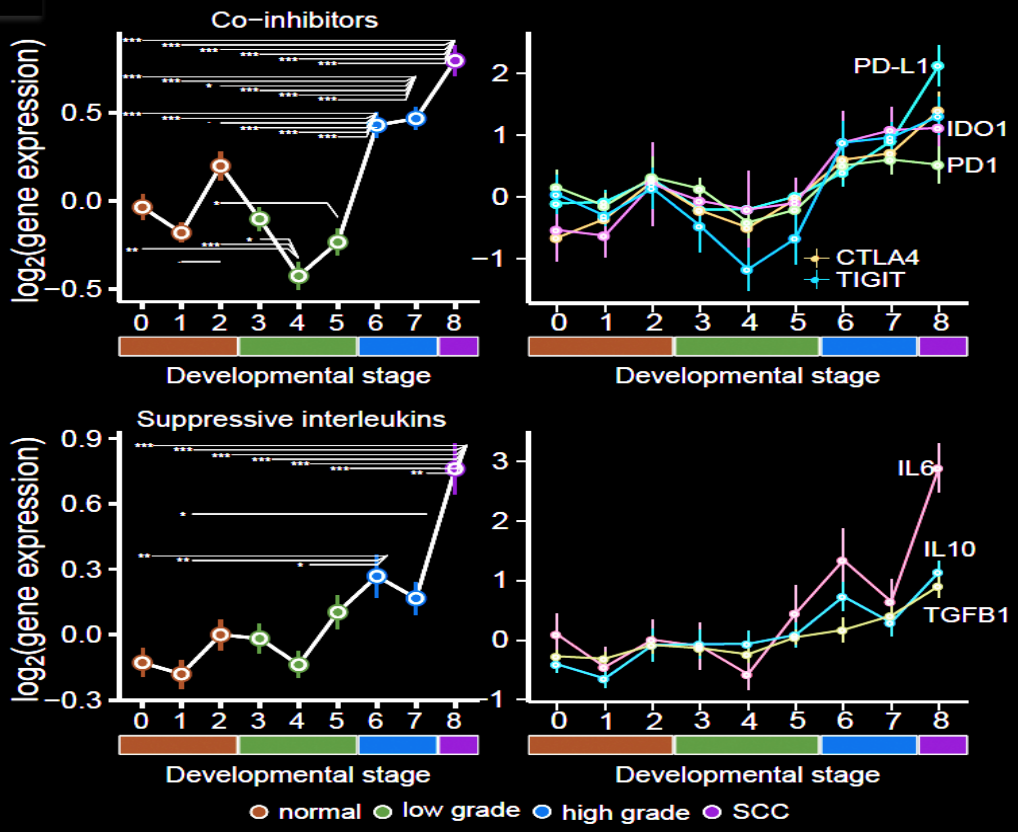


Ascending	Proliferation
Ascending from High-Grade	**Immune**
SCC Ascending	Develomental (EMT)
Descending	DNA damage
Descending from High-Grade	Heterogeneous
Biphasic 1	Metabolism
Biphasic 2	Heterogeneous

Immune functions mostly associated with genes ascending from high-Grade

Mascaux C et al. ***Nature*** *2019*

Immune escape mechanisms in pre-cancer lesions



✓ Decreased expression of co-inhibitors in Low-Grade

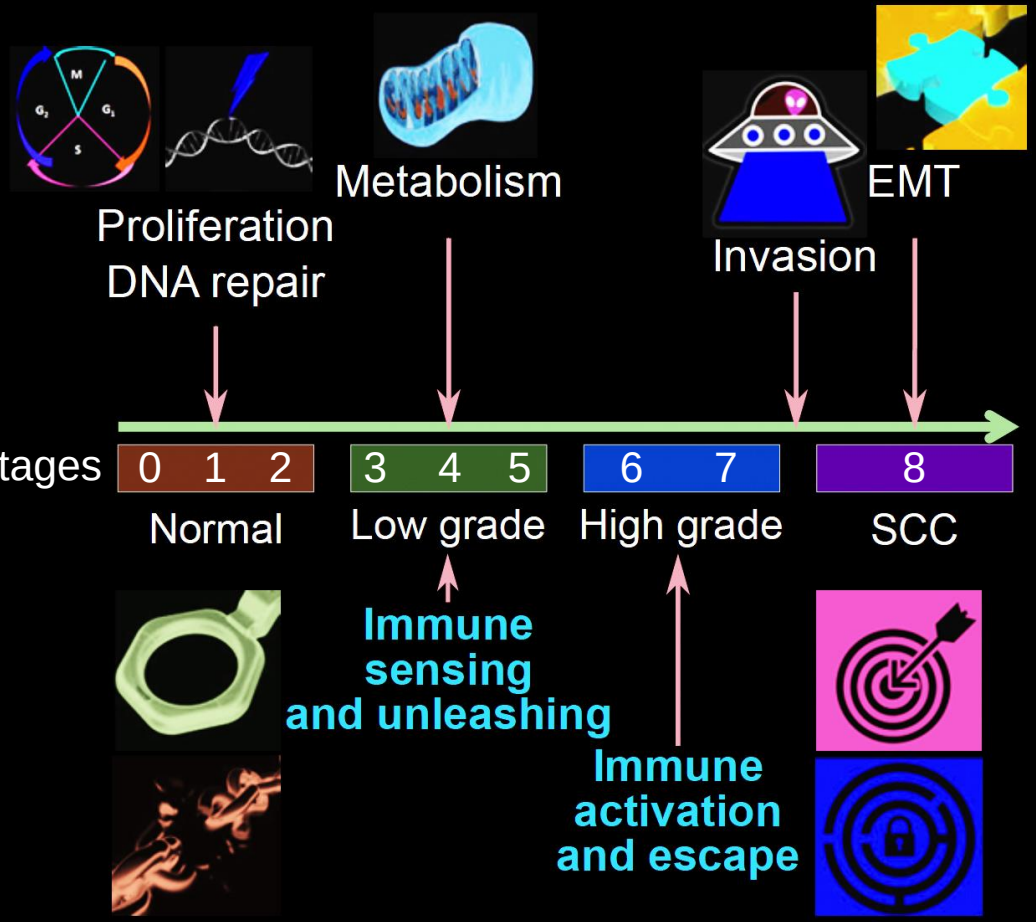
✓ Increased expression of co-inhibitors in High-Grade

✓ Increased expression of suppressive cytokines in High-Grade

-> Immune evasion before tumor invasion (SCC)

Mascaux C et al. ***Nature*** *2019*

Pre-Neoplastic / Pre-Cancer Lesion evolution



n=122 lesions

Epithelial cells
Stroma
Tumor cells

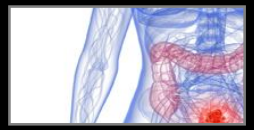
Immune microenvironment

Mascaux C. … Galon J. ***Nature*** 2019

Metastasis analysis

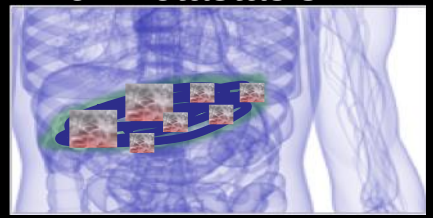
One primary tumor

Colorectal cancer



Multiple metastatic sites

Liver Metastasis



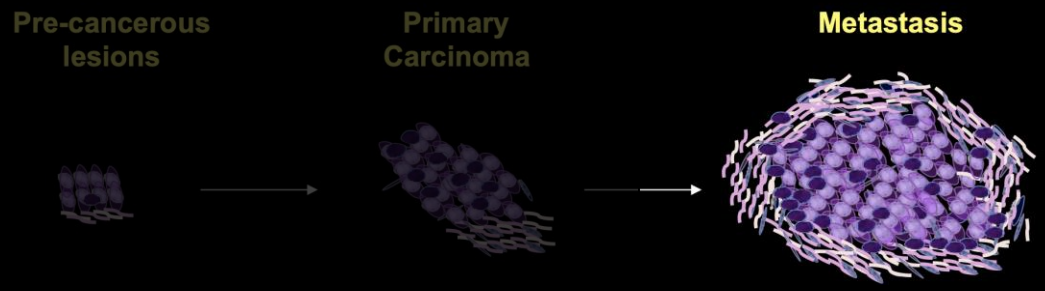
Lung Metastasis

N=603 metastases

- Immunoscore within multiple metastases at different sites

Mlecnik et al. ***JNCI*** 2018

Van den Eynde M. *et al*. ***Cancer Cell 2018***



What drives metastasis

What are the metastatic escape mechanisms

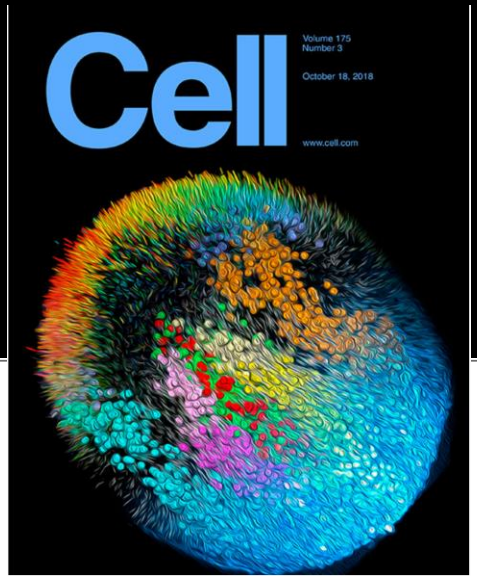
A Novel theory of cancer evolution

Current theories of cancer evolution

Models

LINEAR	NEUTRAL	BIG-BANG	BRANCHED
			
Immune pressure from Darwinian selection			
NO	**NO**	**NO**	**NO**

- The 4 proposed theories of cancer evolution
- All theories are tumor cell-centric. None involves a role of the immune system.



Article

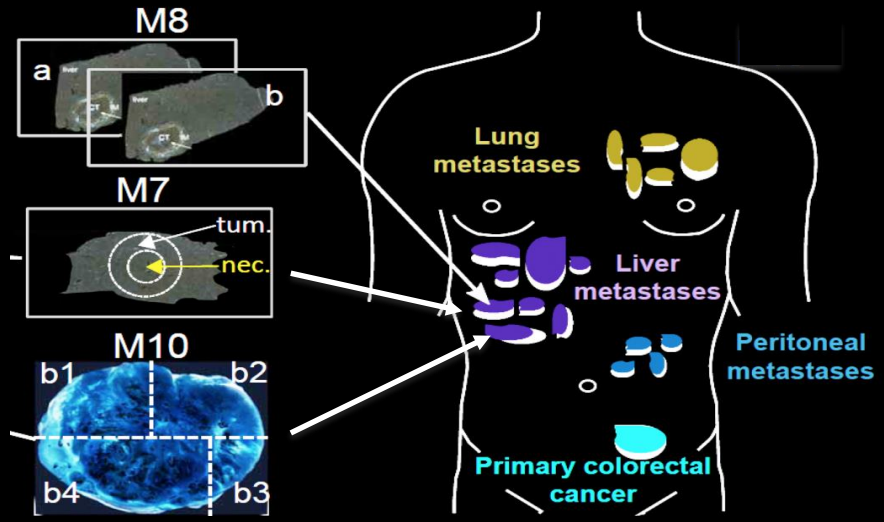
Cell

Evolution of Metastases in Space and Time under Immune Selection

Mihaela Angelova,[1] Bernhard Mlecnik,[1,2] Angela Vasaturo,[1] Gabriela Bindea,[1] Tessa Fredriksen,[1] Lucie Lafontaine,[1] Bénédicte Buttard,[1] Erwan Morgand,[1] Daniela Bruni,[1] Anne Jouret-Mourin,[3] Catherine Hubert,[3] Alex Kartheuser,[3] Yves Humblet,[3] Michele Ceccarelli,[4,5] Najeeb Syed,[6] Francesco M. Marincola,[7,8] Davide Bedognetti,[9,10] Marc Van den Eynde,[1,3,10] and Jérôme Galon[1,11,*]

Angelova M. *et al.* ***Cell*** 2018

What drives metastasis



Primary tumors

↓

Synchronous metastases

↓

Metachronous metastases

↓

Metachronous metastases

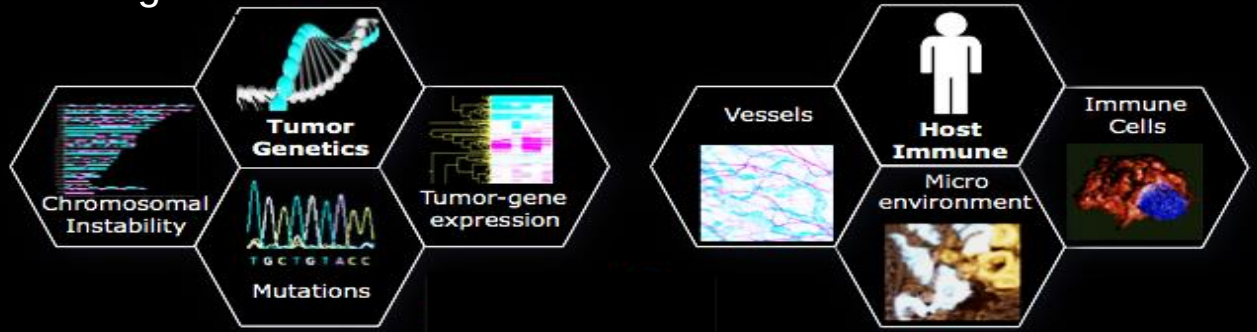
↓

Metachronous metastases

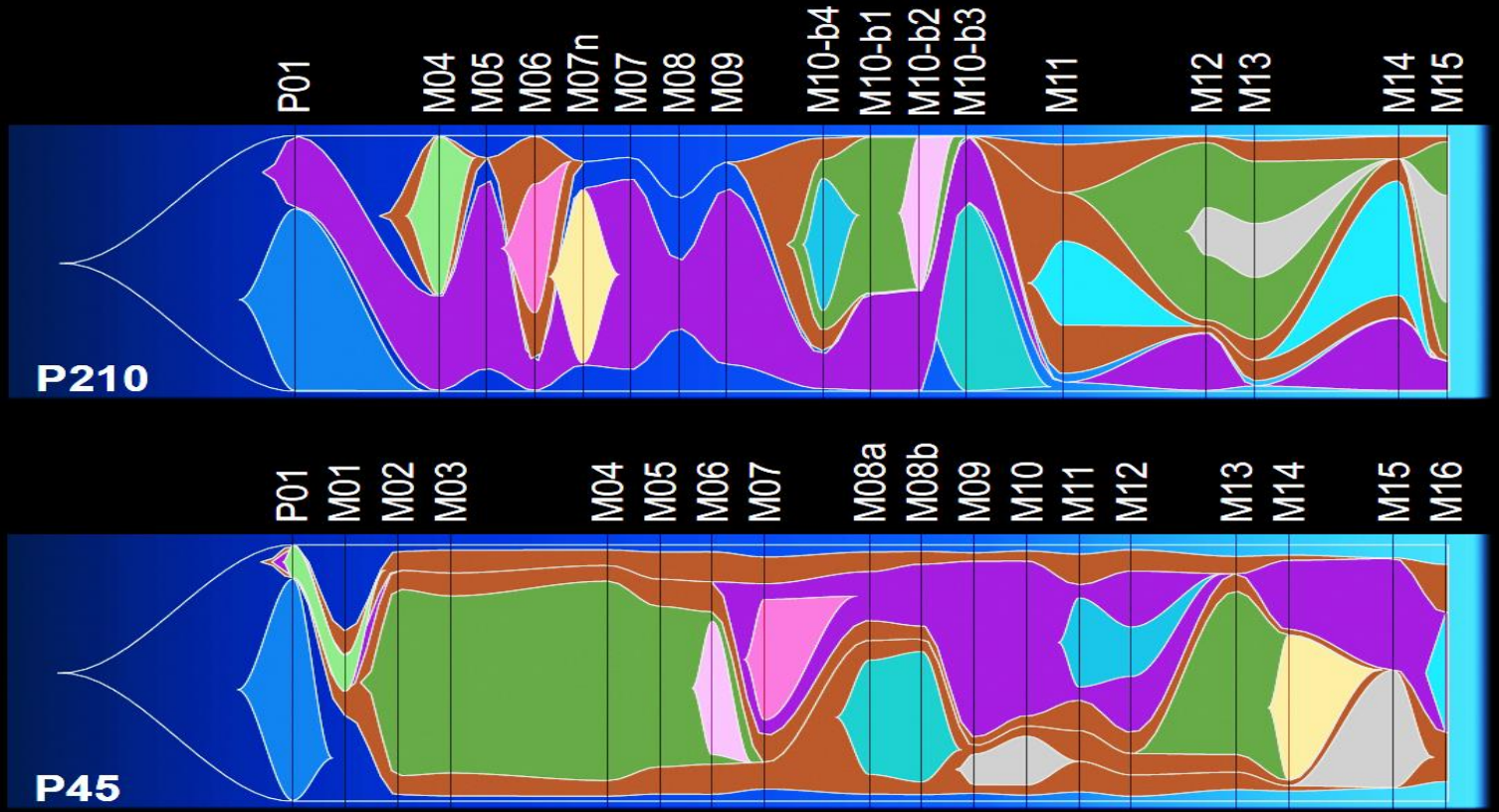
↓

> 11 years

Multi-Omics technologies

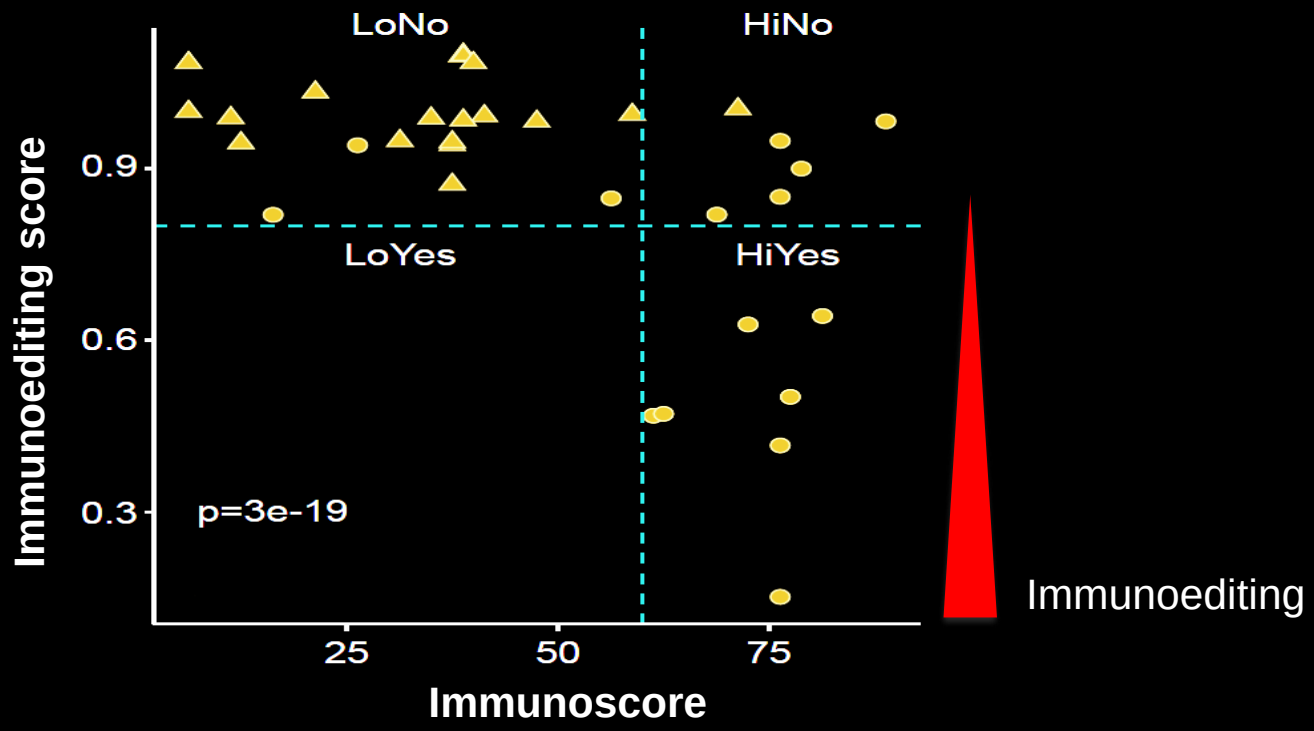


Evolvogram of tumor clones



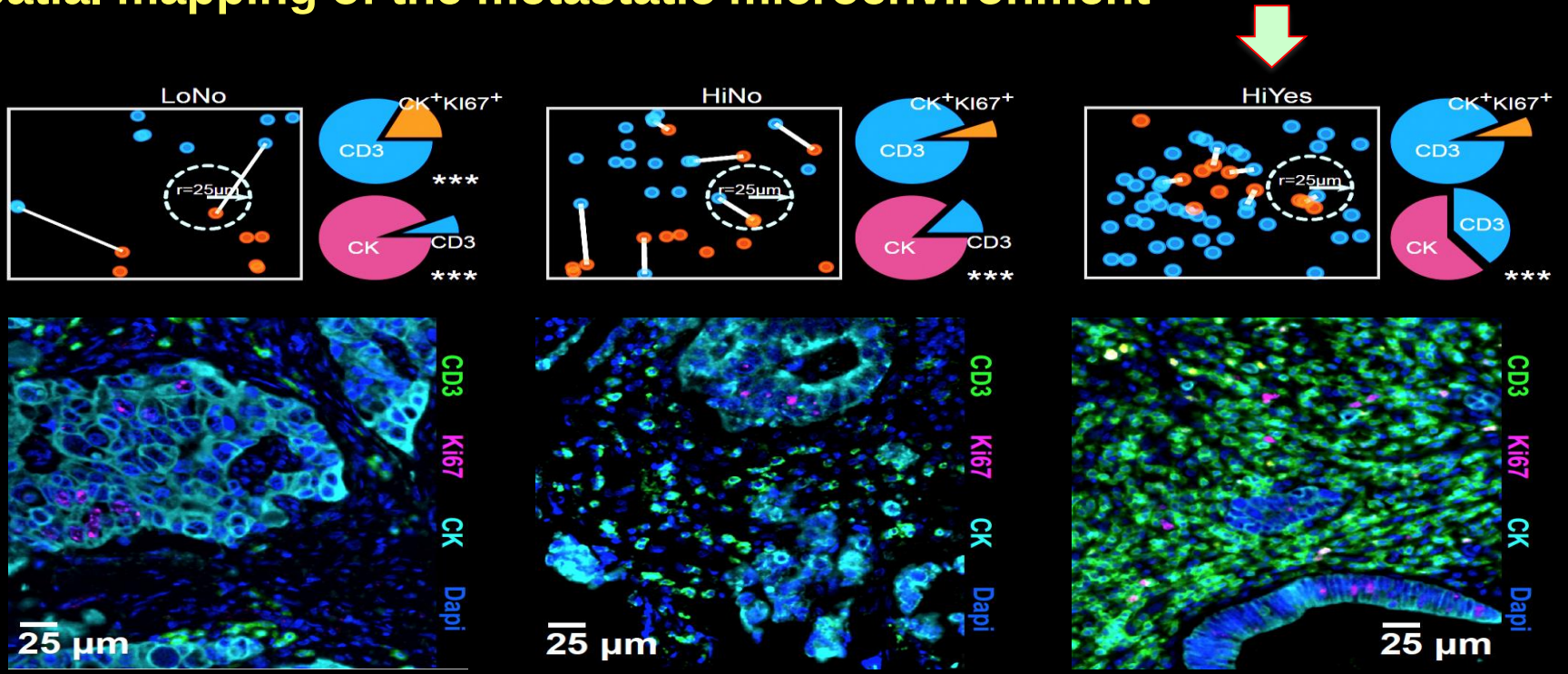
- ✓ Clonal evolution and cancer evolvogram
- ✓ Non-recurrent clones are immunoedited. Progressing clones are immune privileged

Immunoscore and Immunoediting within metastases



- ✓ For Immunoediting to occur, High-Immunoscore is necessary
- ✓ Immunoscore is not sufficient, since High-Immunoscore may not show immunoediting

Spatial mapping of the metastatic microenvironment



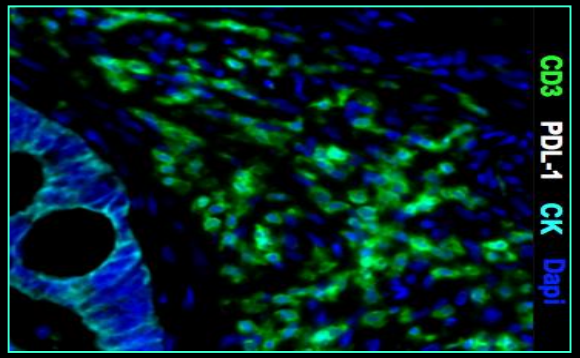
- Distance between CD3 + cells and tumor cells Ki67+ are associated with Immunoscore and Immunoediting groups, and with metastasis recurrence.

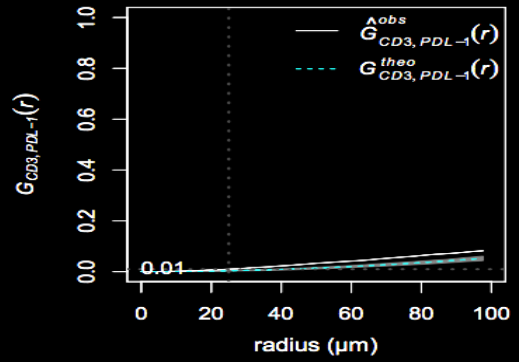
Spatial mapping of the metastatic microenvironment

Cumulative distribution function of nearest neighbors between CD3+ and PD-L1+

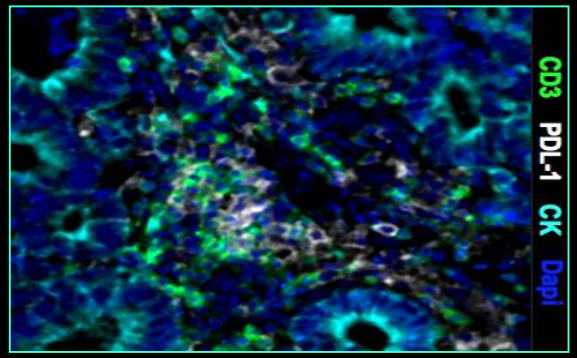
Immunoscore - Immunoediting

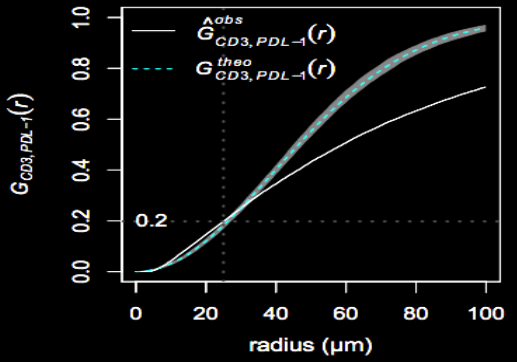
Lo-No



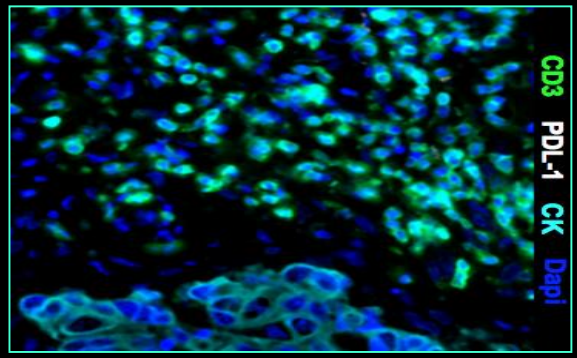


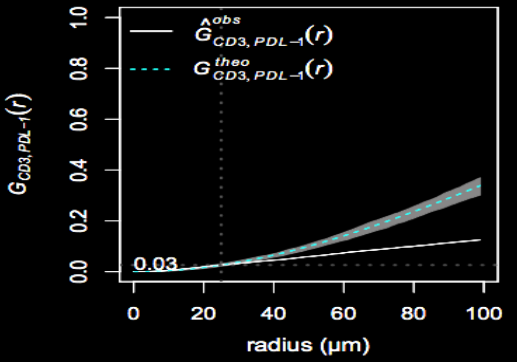
Hi-No





Hi-Yes





HiNo metastases have a higher percentage of T cells ($CD3^{+}$) that have the nearest PD-L1+ within a radius of 25μm

A Novel theory of cancer evolution

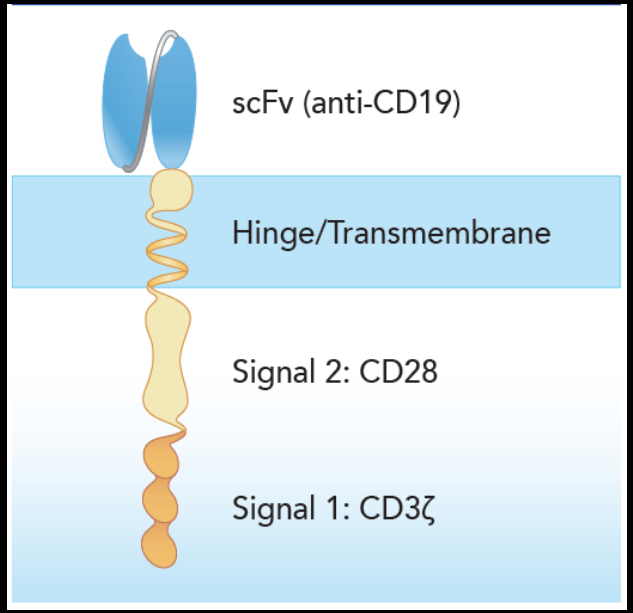
Models

LINEAR	NEUTRAL	BIG-BANG	BRANCHED	SELECTION
				
Immune pressure from Darwinian selection				
NO	**NO**	**NO**	**NO**	**YES**

- **Parallel immune selection model**
- Dynamic interaction of tumor-cells with immune-cells and Darwinian selection of immune escape variant, with parallel evolution and multiverse of metastases.

Anti-CD19 CAR T Cell Therapy in DLBCL

- Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 CAR T therapy with CD3ζ/CD28-based signaling directed to CD19-expressing cells
- Axi-cel approved for the treatment of relapsed or refractory large B cell lymphoma after ≥ 2 lines of systemic therapy



CAR, chimeric antigen receptor; scFv, single-chain variable fragment.

Modified from A Bot, Kite

CAR-T cells

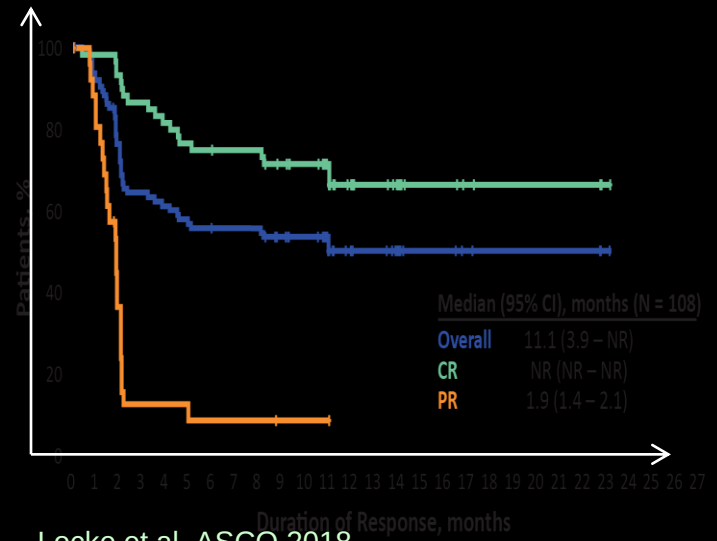
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

S.S. Neelapu, F.L. Locke, N.L. Bartlett, L.J. Lekakis, D.B. Miklos, C.A. Jacobson, I. Braunschweig, O.O. Oluwole, T. Siddiqi, Y. Lin, J.M. Timmerman, P.J. Stiff, J.W. Friedberg, I.W. Flinn, A. Goy, B.T. Hill, M.R. Smith, A. Deol, U. Farooq, P. McSweeney, J. Munoz, I. Avivi, J.E. Castro, J.R. Westin, J.C. Chavez, A. Ghobadi, K.V. Komanduri, R. Levy, E.D. Jacobsen, T.E. Witzig, P. Reagan, A. Bot, J. Rossi, L. Navale, Y. Jiang, J. Aycock, M. Elias, D. Chang, J. Wiezorek, and W.Y. Go

ZUMA-1 Trial: Long-Term Follow Up



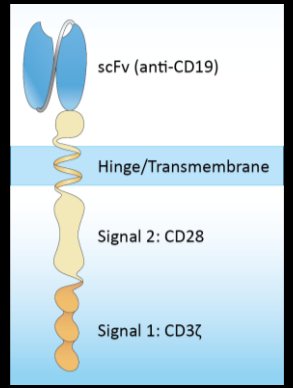
Locke et al, ASCO 2018

ZUMA-1 with refractory large B cell lymphoma treated with axi-cel have 83% ORR and 58% CR

Axi-Cel Maintained Ongoing Responses at Median Follow-Up of 27.1 Months

Improval of CAR-T cell therapy

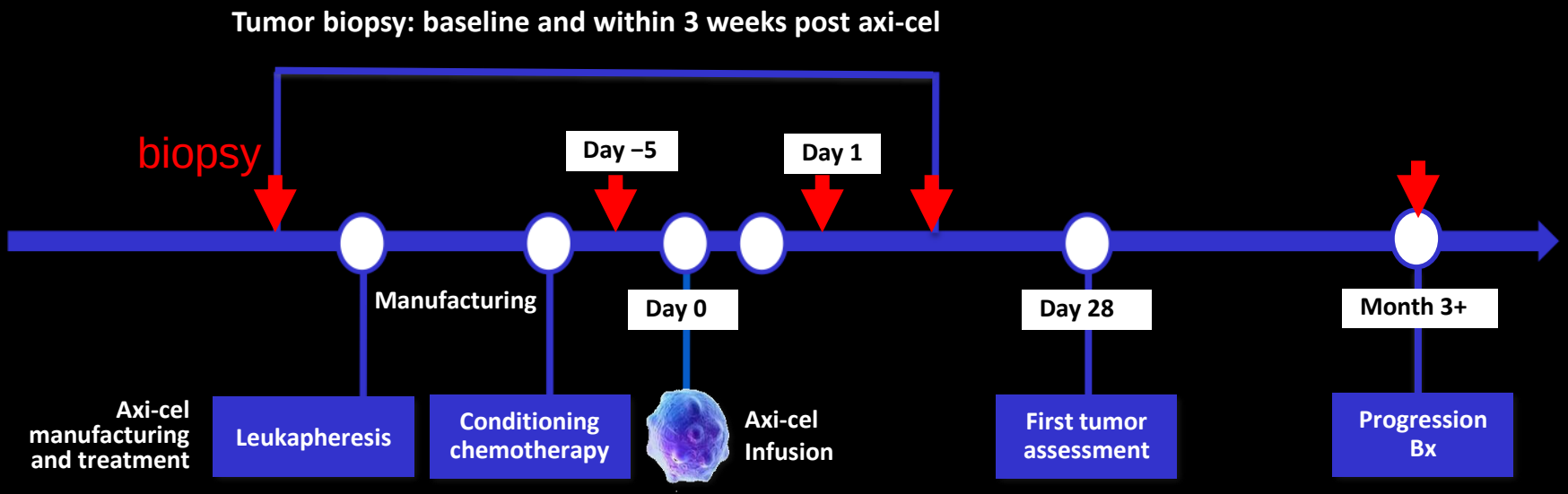
- ✓ Improved CAR constructs
- ✓ Get better intracellular CAR signaling (1st, 2nd, 3rd generation CARs)
- ✓ Get better targets (especially for solid tumors)
- ✓ Get dual targets, inducible CAR, killing-construct CAR
- ✓ Select subtypes of T-cells for infusion



But,

- ✓ Ignoring the fact that a cancer is not tumor cells in a test-tube
- ✓ and that adoptive CAR-T cells are not working alone, but within a patient

Tumor microenvironment analysis: Zuma 1 - Protocol and Timing of Paired Biopsies



axi-cel, axicabtagene ciloleucel.

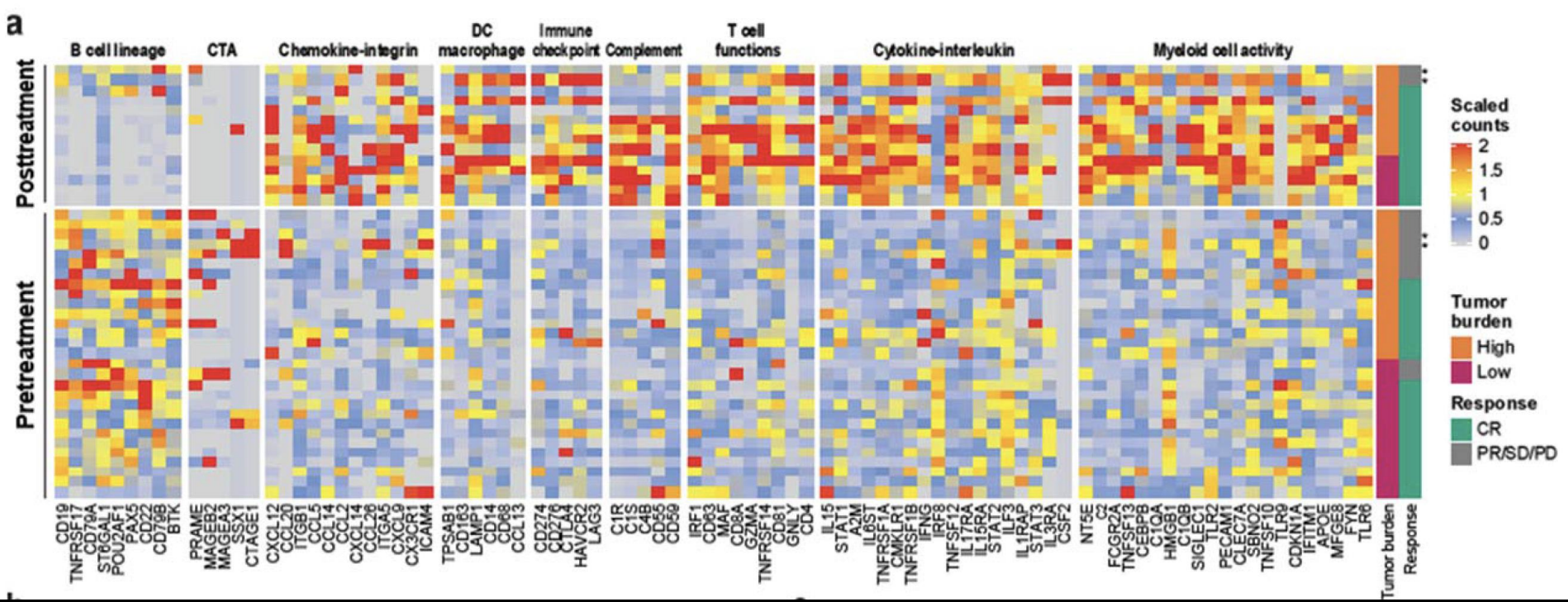
ZUMA-1 clinical trial Translational Biomarkers analysis

- *Which patients are responding to CAR-T based on pre-treatment biopsies?*
- *What are the changes in TME Post-CAR-T?*
- *What are the mechanisms of relapse?*
- *Can we predict toxicities?*

- Zuma-1 trial (DLBCL): tumor biopsies (n=135)
- Zuma-7 trial (DLBCL): tumor biopsies (n=252)
- DLBCL patients: tumor biopsies (n=249)

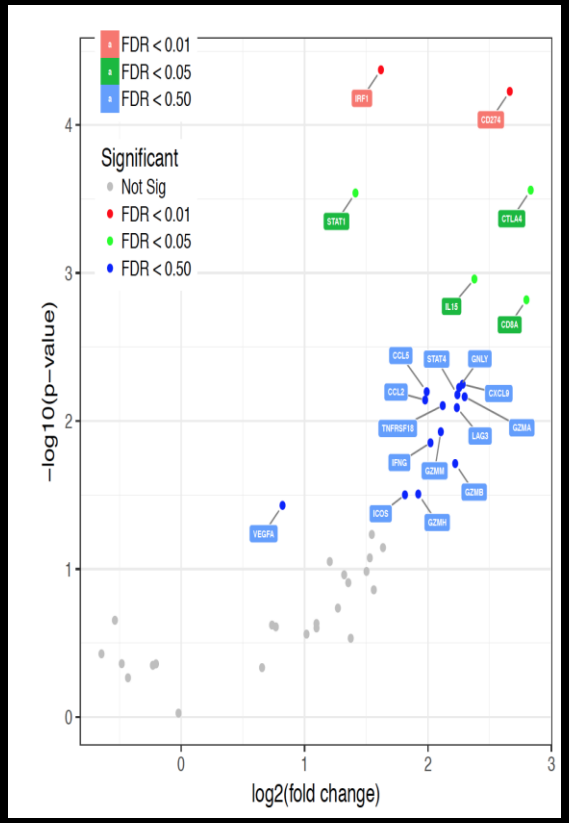
TME: Tumor MicroEnvironment

ZUMA-1 Pre and Post-CAR-T cell treatment analysis



Scholler et al. *In revision*

Treatment with Axi-Cel Results in Rapid and Dramatic Changes in the Tumor Immune Microenvironment



Top transcripts from a pre-specified 43 immune gene panel upregulated in tumor 7-21 days after treatment. IDO1 and other genes not in the 43 panel are pending.

Checkpoints	IFN related	Effectors	Proliferative	Chemokines
PD-L1	IRF1	CD8A	IL15	CXCL9
CTLA4	STAT1	GNLY		CCL2
		GZMA		CCL5
	STAT4			
LAG3				
TNFRSF18				
	IFNγ	GZMM		
		GZMB		
ICOS		GZMH		

Scholler et al. *In revision*

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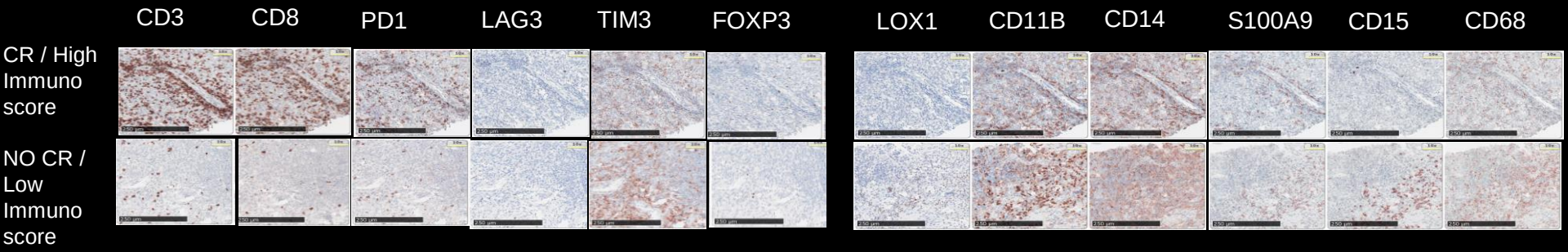
Treatment with Axi-Cel Results in Rapid and Dramatic Changes in the Tumor Immune Microenvironment asssociated with CR

Multiplex chromogenic brightfield stains using BrightPlex® technology



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Scholler et al. *In revision*

Pre-specified Immunosign separates Responders from non-Responders

In **pre-treatment** Samples

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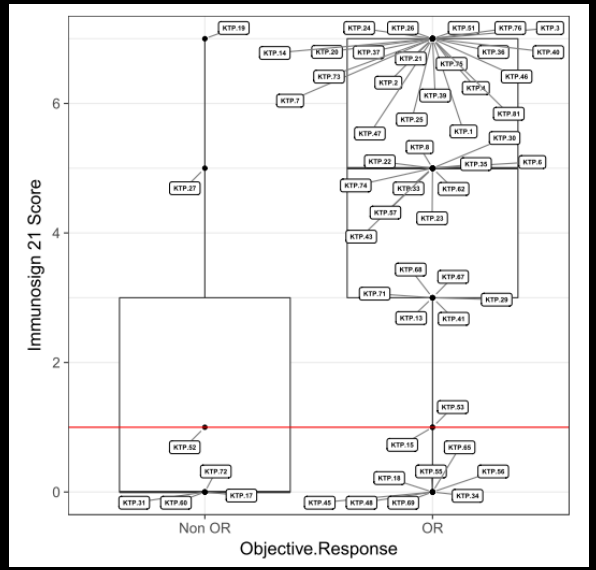
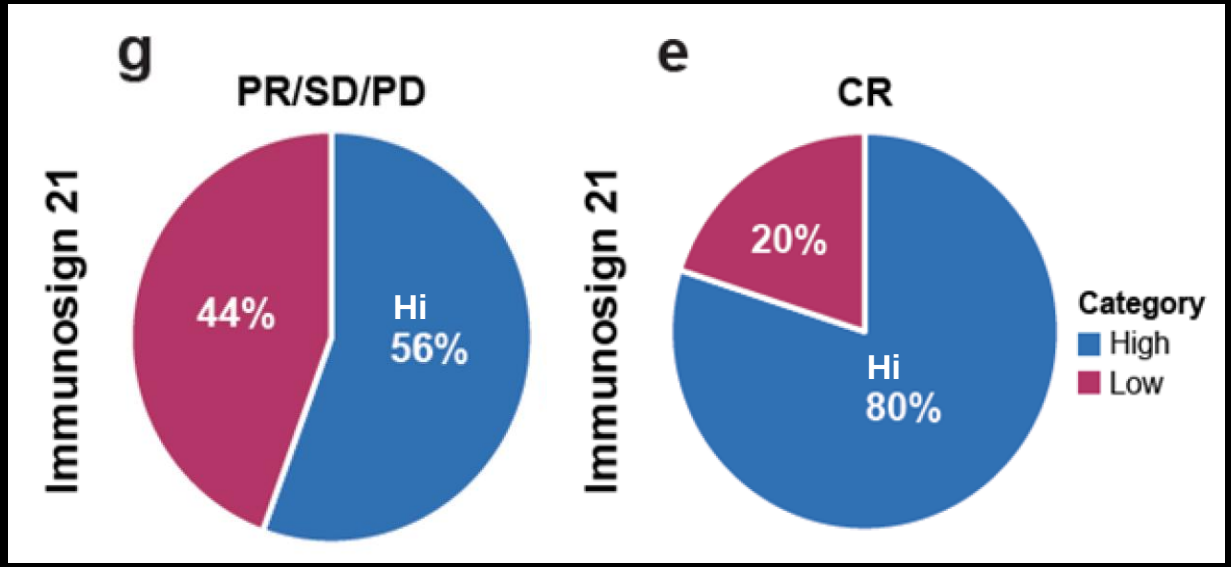
OR vs No OR (Objective.Response)

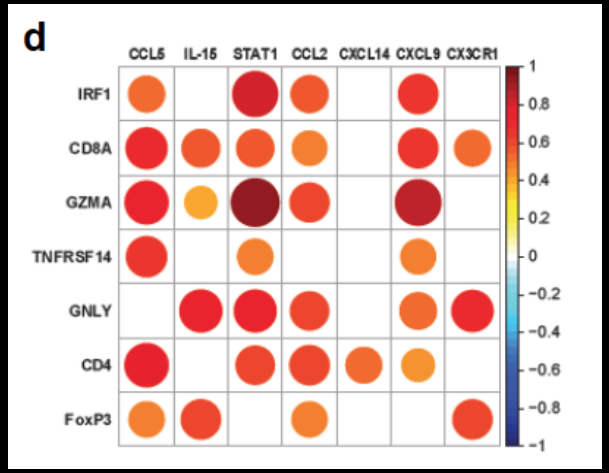




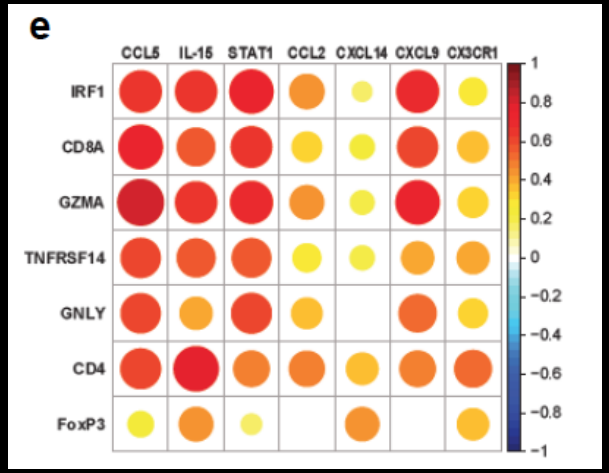
Immunosign® 21 pre-CAR-T infusion predicts clinical Response (OR and CR)

Scholler et al. *In revision*

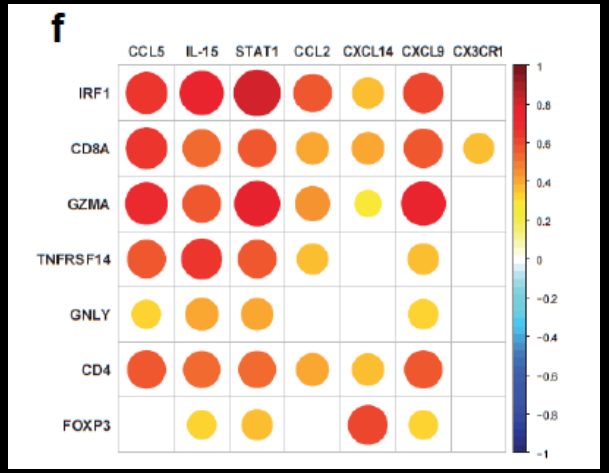
Mechanistic link between pre-treatment immune contexture and T-cell parameters



CAR-T cell treated patients
(Zuma-1 trial, n=19)



CAR-T cell treated patients
(Zuma-7 trial, n=252)



Treatmnt-naive patients
(DLBCL, n=67)

Correlation matrix for myeloid-secreted and T cell-produced cytokine and chemokines (horizontal axis) with T-cell subset–related genes (vertical axis) in the baseline TME from 3 independent cohorts of DLBCL patients

Scholler et al. *In revision*

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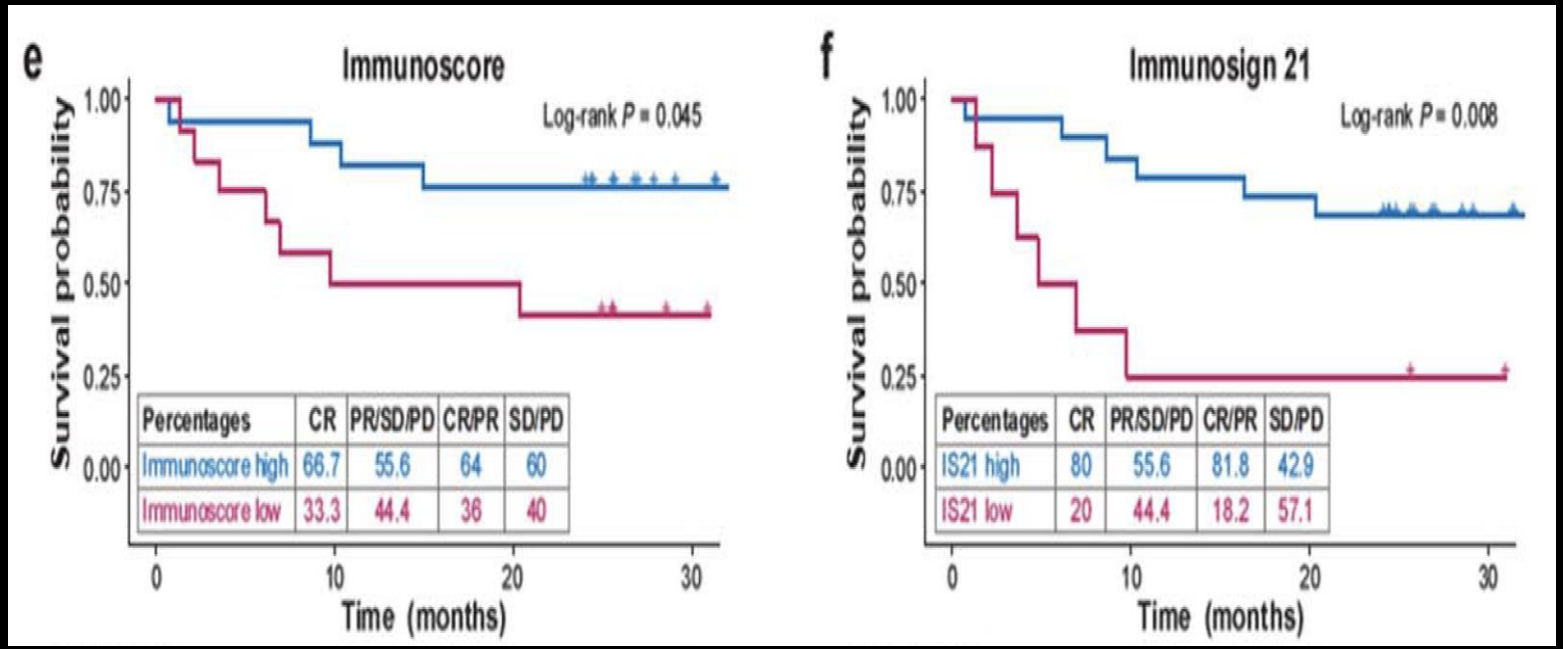
Pre-treatment immune contexture predicts response to CAR-T cell therapy and prolonged survival



High

Low

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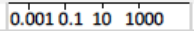
Scholler et al. *In revision*

Pre-treatment immune contexture predicts response to CAR-T cell therapy and prolonged survival

Variable		N	Hazard ratio (95% CI)	*P* value
Immunosign 21				
	High	19	Reference	
	Low	8	42.91 (1.88, 977.60)	0.020
Gender				
	F	14	Reference	
	M	12	0.33 (0.04, 2.78)	0.31
Subtypes				
	GCB	15	Reference	
	ABC	4	2.30 (0.06, 88.39)	0.65
	Unknown	8	0.37 (0.00, 44.69)	0.68
IPI				
	Low	7	Reference	
	Intermediate	9	0.57 ((.004, 7.56)	0.67
	High	11	0.08 (0.00, 9.03)	0.29
Baseline Tumor Burden (SPD)		27	1.00 (1.00, 1.00)	0.03
BCL2 overexpression				
	Y	15	Reference	
	N	6	0.24 (0.03, 2.20)	0.21
	Unknown	6	0.00 (0.00, Inf)	1.000
MYC overexpression				
	Y	8	Reference	
	N	13	4.21 (0.29, 60.77)	0.29
	Unknown	6	0.00 (0.00, Inf)	1.000
BCL6 overexpression				
	Y	12	Reference	
	N	10	8.84 (0.79, 99.00)	0.08
	Unknown	5	6.54 1018 (0.00, Inf)	1.000



Survival hazard ratios from cox multivariate analyses of ZUMA-1 patient and clinical characteristics

Only tumor immune contexture and tumor burden predicted survival

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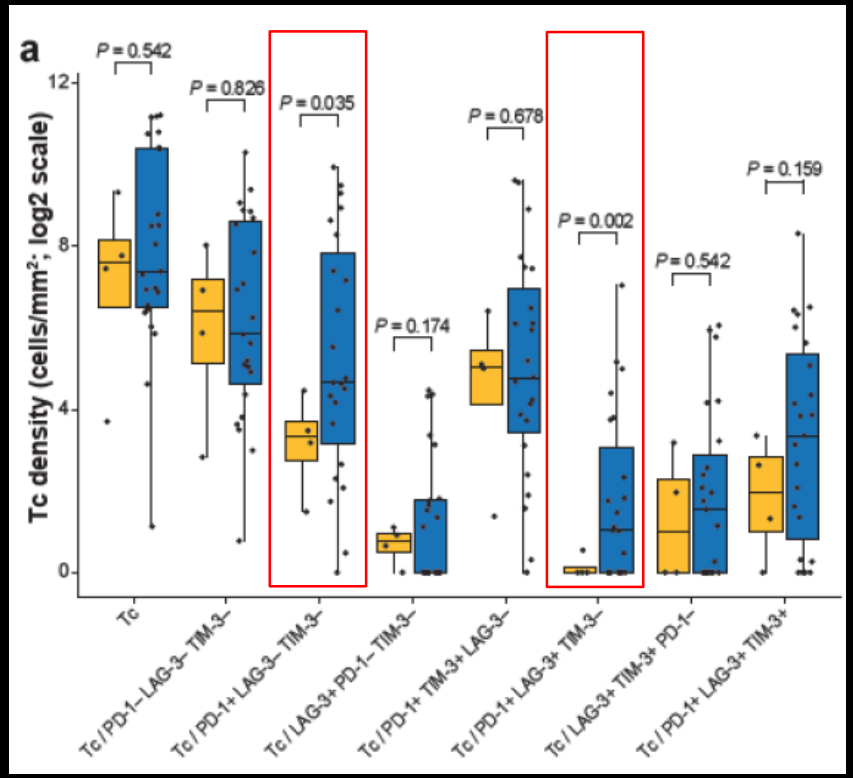
Scholler et al. *In revision*

T-cell subset densities in pretreatment tumour biopsies associated with response to CAR-T

CD3
CD4
CD8
FoxP3
PD1
TIM3
LAG3



High densities of subsets of Cytotoxic T-cells (CD3+CD8+ expressing PD1+LAG3+/-TIM3-) are significantly associated with response to CAR-T cells

Scholler et al. *In revision*

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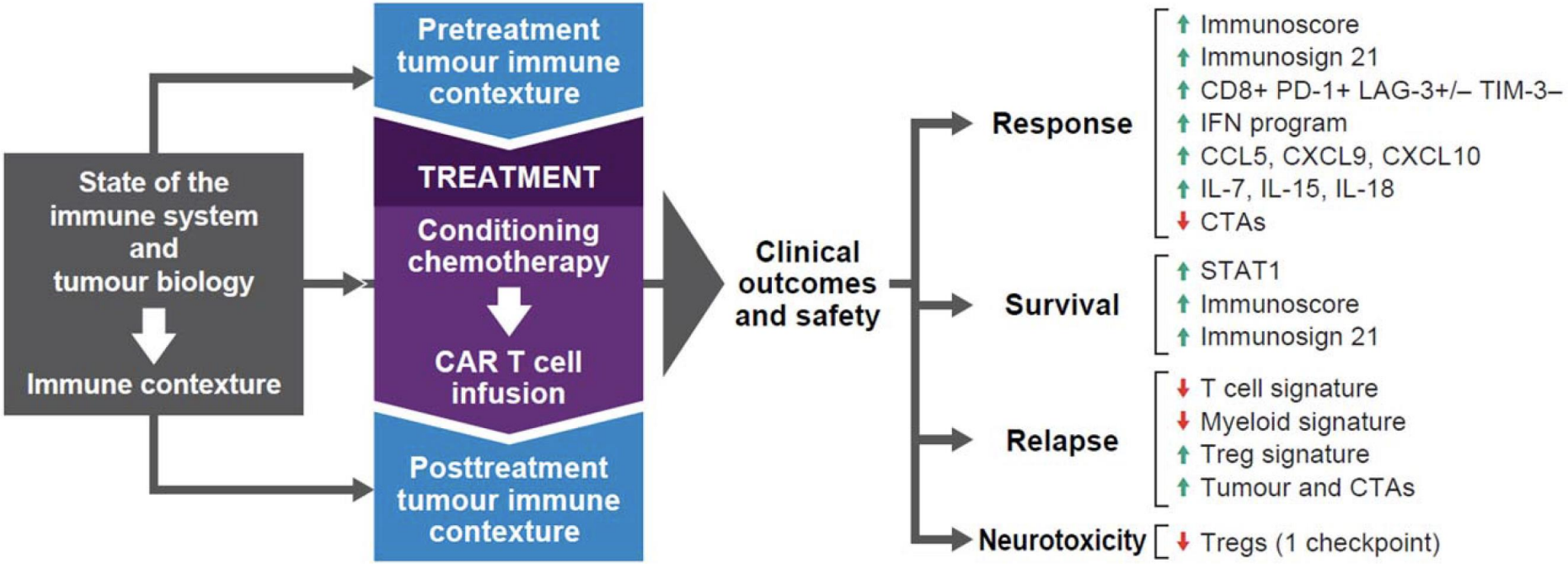
CAR-T : A Mechanistic Model of Efficacy and Toxicities



Scholler et al. *In revision*

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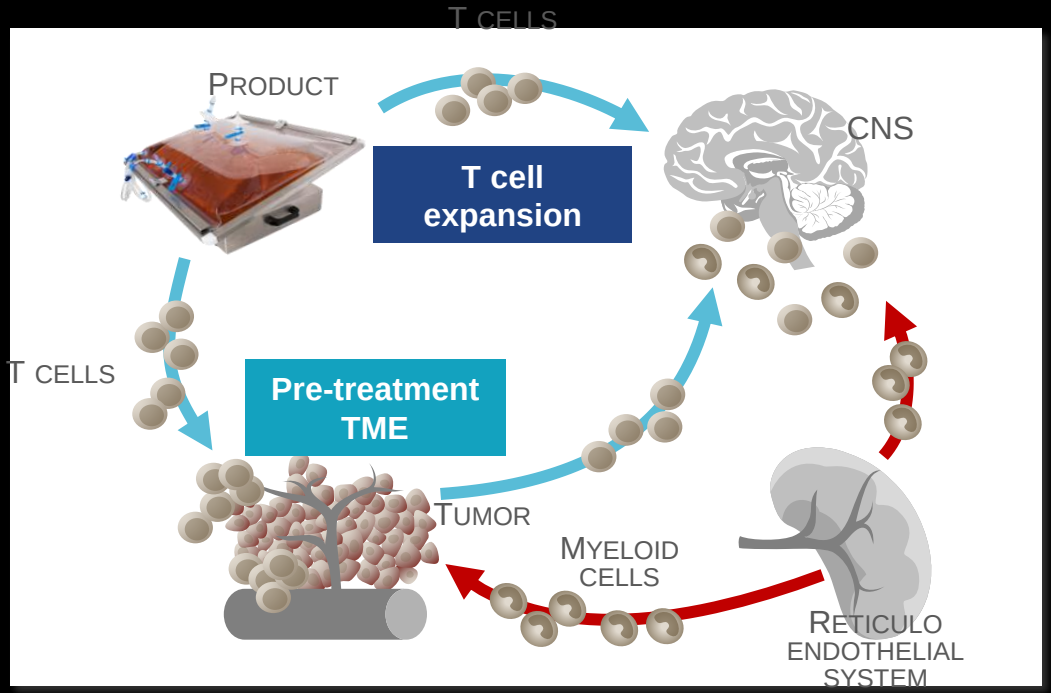
CAR-T : A Mechanistic Model of Efficacy and Toxicities

- T cell "fitness" (juvenile, proliferative, polyfunctional)
- Dose of CD8 T cells
- Pre-treatment tumor burden
- Pre-treatment pre-existing immunity / tumor microenvironment
- Target antigen "loss"



Efficacy
Toxicities
Both

*Based on: Kochenderfer, JCO 2017; Neelapu, NEJM 2017; Locke, AACR 2017; Galon, ASCO 2017; Rossi, SITC 2017; Locke, ASH 2017; Rossi, Blood 201Z, ASH 2018, AACR2018, AACR 2019. TME – Tumor microenvironment .

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nature reviews cancer

REVIEWS

The immune contexture and Immunoscore in cancer prognosis and therapeutic efficacy

Daniela Bruni[1,3], *Helen K. Angell*[2,3] *and Jérôme Galon*[1]✉

Bruni et al. ***Nature Reviews Cancer*** 2020

Galon lab.
INSERM, CRC, Paris, France

Franck Pagès
Tessa Fredriksen
Florence Marliot
Lucie Lafontaine
Stéphanie Mauger
Amélie Bilocq
Amos Kirilovsky
Marie Tosolini
Maximilian Waldner
Sarah Church
Pauline Maby
Helen Angell
Mihaela Angelova
Angela Vasaturo
Daniela Bruni
Bernhard Mlecnik
Gabriela Bindea
Bénédicte Buttard
Erwan Morgand
Anne-Françoise Batto
Louis Berthet

Institute for Bioinformatics, Innsbruck, Austria

Pornpimol Charaoetong
Zlatko Trajanoski

LabEx Immuno-oncology

Kroemer G, Zitvogel L, Tartour E, Sautès-*Fridman* C, Fridman H, *Zucman*-Rossi J,

Institut Curie, Paris, France

Hervé Brisse
Sylvie Bonvalot

SIDRA, Doha, Qatar

Davide Bedognetti

UCSF, CA, USA

Rosalyn W. Sayaman
Elad Ziv

Rouen University, France

Jean Baptiste Latouche

Dpt. of General and Digestive Surgery, HEGP, Paris, France

Anne Berger

Dpt. of Pathology, HEGP, Paris, France

Tchao Meatchi
Christine Lagorce

CHU Strasbourg, France

Celine Mascaux

Kite Pharma, Gilead

Adrian Bot, John Rossi,
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Galon lab.
INSERM, Cordeliers Research Center, Paris, France
Franck Pagès, Tessa Fredriksen, Florence Marliot, Lucie Lafontaine, Bénédicte Buttard, Sarah Church, Pauline Maby, Helen Angell, Mihaela Angelova, Angela Vasaturo, Bernhard Mlecnik, Gabriela Bindea

Dpts. of Pathology *, Surgery $, Immunology #, HEGP, Paris, France
*Christine Lagorce *, Patrick Bruneval *, Anne Berger $, Franck Pagès #, Florence Marliot #, Nacilla Haicheur #*

Department of Pathology, Providence Portland Medical Center, Portland, OR, USA
Carlo Bifulco

Laboratory of Molecular and Tumor Immunology, Earle A. Chiles Research Institute, Robert W. Franz Cancer Center, Portland, OR, USA
Bernard Fox

Princess Margaret Hospital, University Health Network, Department of Pathology , Toronto, ON, Canada
Pamela S. Ohashi, Michael Roehrl, Prashant Bavi, Sara Hafezi-Bakhtiari, Bradly G. Wouters, Linh Nguyen

Department of Pathology and Oncology, Istituto Nazionale per lo Studio e la Cura dei Tumori, "Fondazione G.Pascale" Naples-Italy
Paolo A Ascierto, Gerardo Botti, Fabiana Tatangelo, Paolo Delrio, Gennaro Cilberto

Humanitas Clinical and Research Center, Rozzano, Milan, Italy
Fabio Grizzi, Luigi Laghi

Institute of Pathology, University of Bern, Bern, Switzerland
Alessandro Lugli, Inti Zlobec, Tilman Rau

Research Branch, Sidra Medical and Research Centre, Doha, Qatar
Francesco M. Marincola

Institut Roi Albert II, Cliniques universitaires St-Luc, Université Catholique de Louvain, Brussels, Belgium
Marc Van den Eynde, Jean-Pierre Machiels

Department of Pathology, University of Erlangen, Erlangen, Germany
Arndt Hartmann, Tilman Rau, Carol Geppert

Pathology Department, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands
Iris D. Nagtegaal, Elisa Vink-Borger

Department of Oncology-Pathology, Karolinska Institutet, Karolinska University, Stockholm, Sweden
Giuseppe V. Masucci, Emilia K. Andersson

Department of Oncology, Medical School and general hospital, Prague, Czech Republic
Eva Zavadova, Michal Vocka

Institute for Cancer Research, Center of Translational medicine, Xi'an Jiaotong university, Xian, China
Yili Wang

The Gujarat Cancer & Research Institute, Asarwa, Ahmedabad, India
Prabhu S. Patel, Shilin N. Shukla, Hemangini H. Vora, Birva Shah, Jayendrakumar B. Patel, Kruti N. Rajvik, Shashank J. Pandya

Institute for Advanced Medical Research, Keio University School of Medicine, Tokyo, Japan
Yutaka Kawakami, Shoichi Hazama, Kiyotaka Okuno, Kyogo Itoh, Boryana Papivanova

Department of Pathology, Sapporo Medical University School of Medicine, Sapporo, Japan
Toshihiko Torigoe, Noriyuki Sato