I TUMORI DELLA TESTA E COLLO: IL PARERE DELL'ESPERTO

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Candiolo (Torino)

DISCLOSURE INFORMATION

Marco Merlano

Personal financial interests:

- Consultancy, speaker, advisory role: Merck KGaA;
- Consultancy, advisory role: Merck Sharp & Dohme, Bristol-Myers Squibb;
- Speaker: AstraZeneca;
- Stocks: Glaxo Smith Kline;

Institutional financial interests:

- Funding research project: Merck KGaA

Leadership roles:

- Vice President: Gruppo Oncologico Nord-Ovest (GONO)

STARTING FROM OLD APPROACH

SELECTING BETTER PATIENTS

HOW TO INCREASE OUTCOME ???

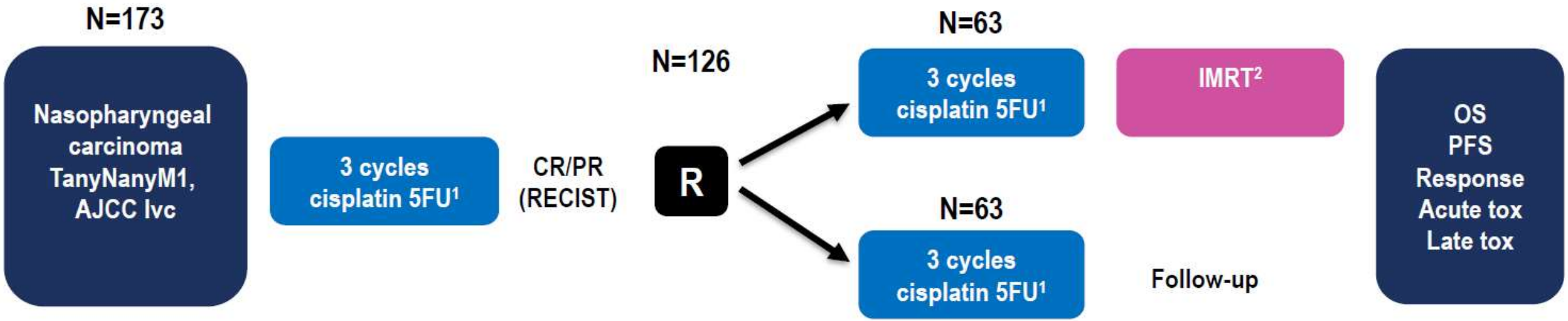
WITH NOVEL COMBINATIONS

WITH NOVEL TARGET

BARCELONA 2019 ESMO congress

CHEMOTHERAPY COMBINED WITH RADIOTHERAPY VS CHEMOTHERAPY ALONE FOR DISTANT METASTATIC NASOPHARYNGEAL CARCINOMA (1108O)

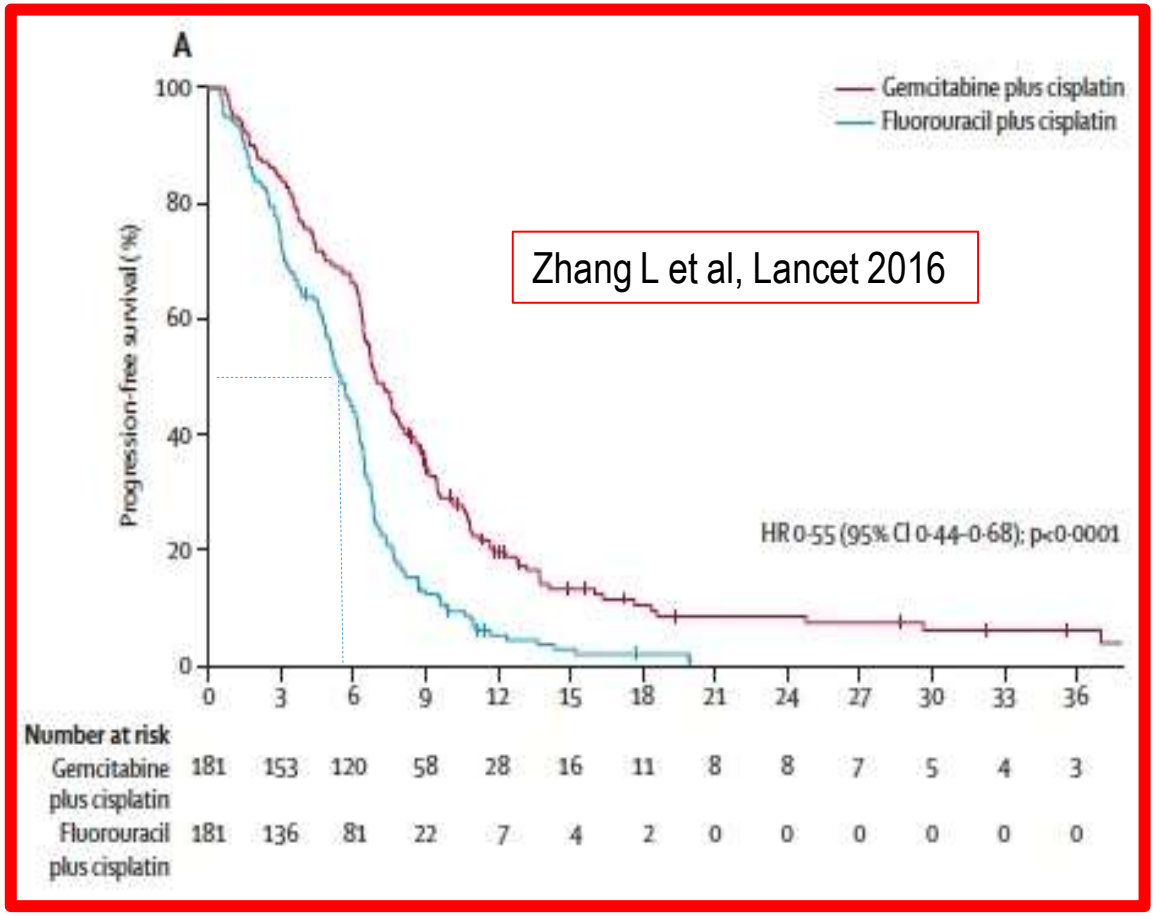
Prof. Ming-Yuan Chen, Principal Investigator (Sun Yat-sen University, Guangzhou/CHINA), R. You, L. You-Ping, P.Y. Huang, X. Zou, G.P. Shen, H.D. Zhang.



[1] cisplatin 100 mg/m^2, iv, day 1, fluorouracil 5 g/m^2 continuously iv 120 h
[2] 66-70 Gy in 28-33 fr on primary tumor, 60-66 Gy in 28-33 fr on lymph nodes

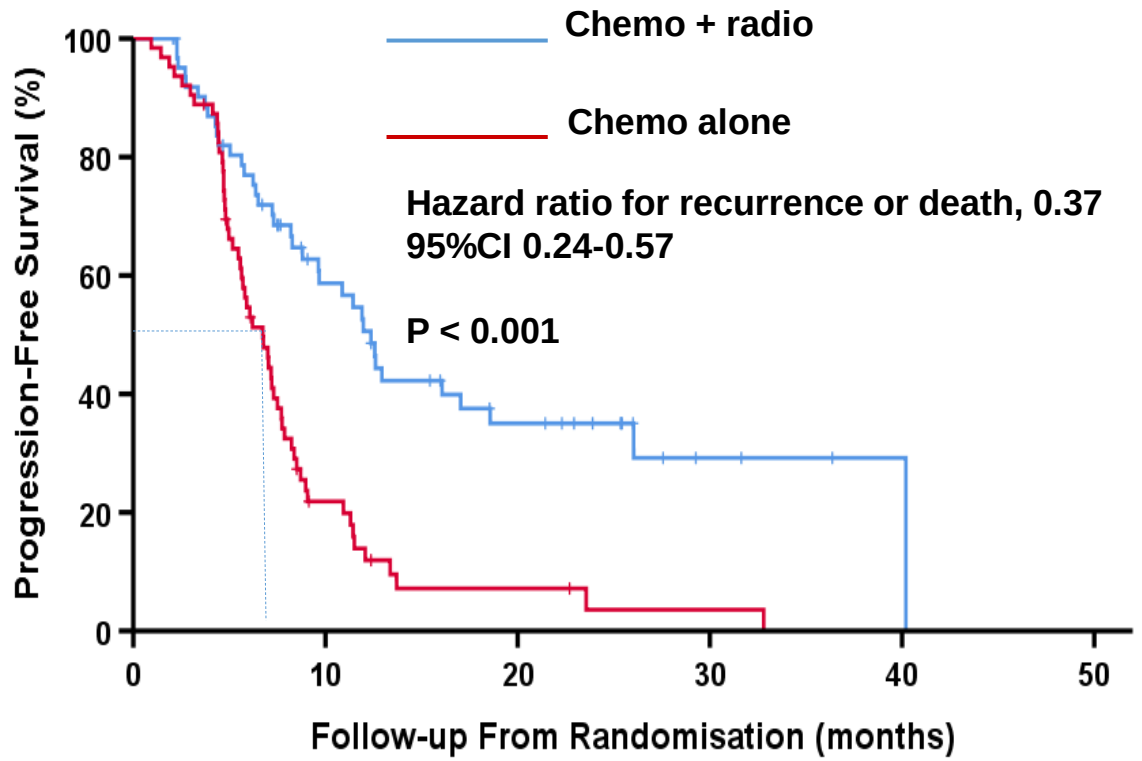
Closed at interim analysis

RESULTS② : Efficacy



Zhang L et al, Lancet 2016

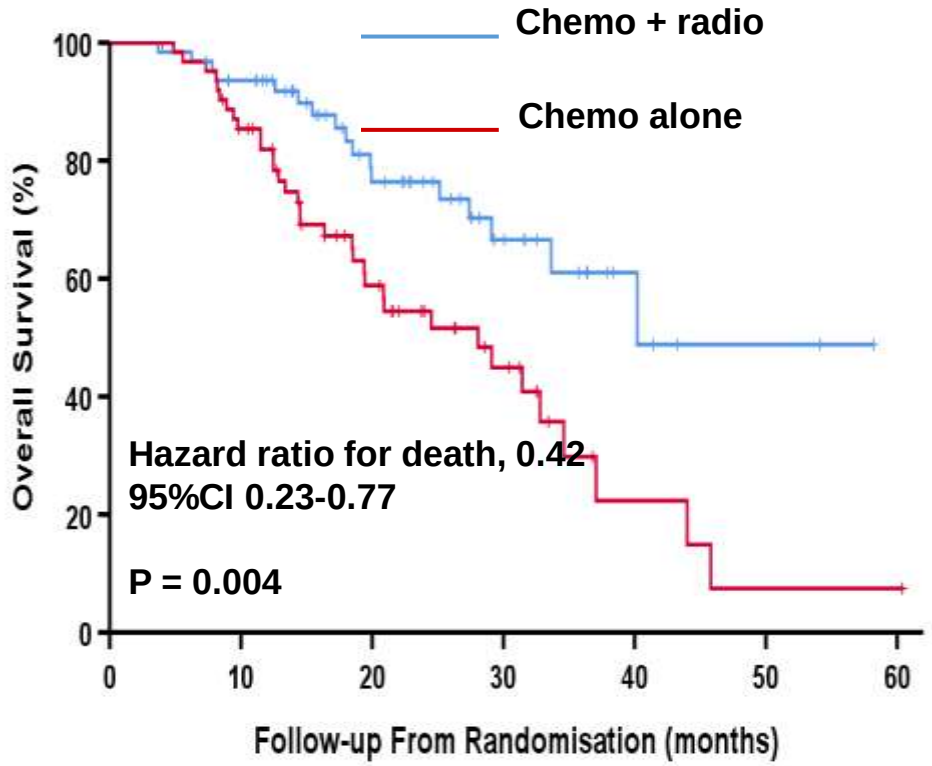
B.



Number at Risk						
Chemo + radio	63	29	14	3	1	0
Chemo alone	63	11	3	1	0	0

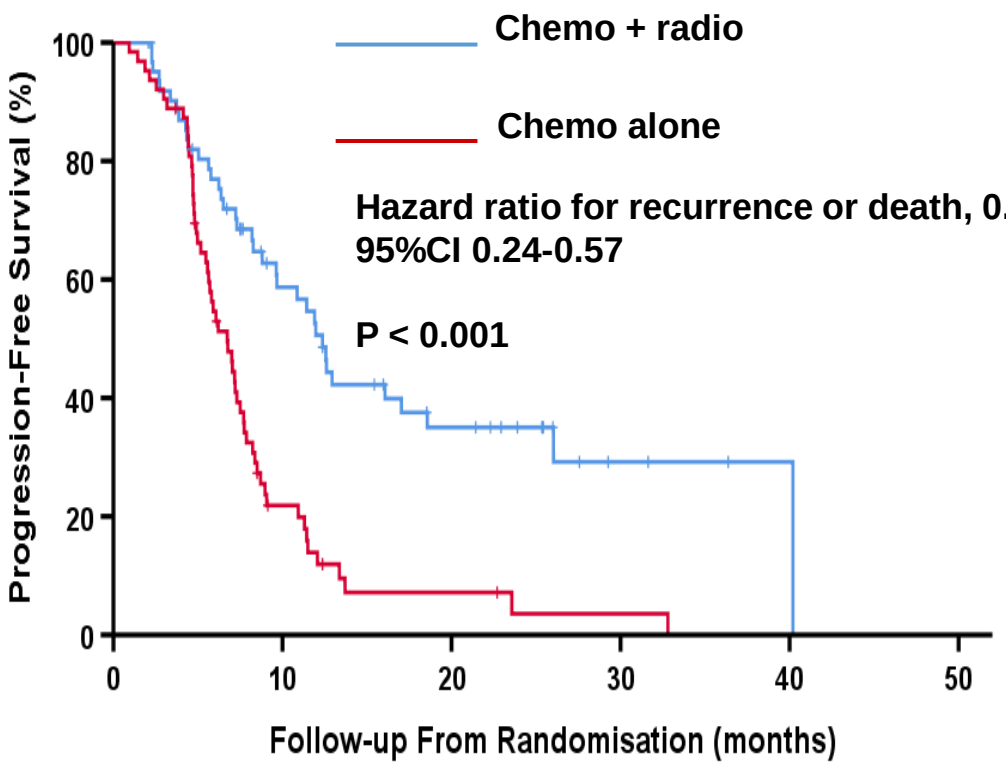
RESULTS② : Efficacy

A.



Number at Risk							
Chemo + radio	63	56	33	16	5	2	0
Chemo alone	63	51	28	13	3	1	0

B.



Number at Risk						
Chemo + radio	63	29	14	3	1	0
Chemo alone	63	11	3	1	0	0

RESULTS ② Efficacy

	Chemo + radiotherapy N = 63	Chemo alone N = 63
Overall survival		
Deaths	17 (27.0%)	34 (54.0%)
OS rate at 6 months	98.4% (95.2%-100.0%)	96.8% (92.5%-100.0%)
OS rate at 12 months	93.6% (87.5%-99.7%)	81.9% (72.3%-91.5%)
OS rate at 24 months	76.4% (64.4%-88.4%)	54.5% (41.0%-68.0%)
Progression-free survival		
Failures	37 (58.7%)	56 (88.9%)
Median PFS, months	12.4 (10.5-14.2)	6.7 (5.4-8.0)
PFS rate at 6 months	76.9% (66.3%-87.5%)	54.6% (42.1%-67.1%)
PFS rate at 12 months	50.6% (37.3%-63.9%)	13.9% (4.7%-23.1%)
PFS rate at 24 months	35.0% (21.7%-48.3%)	3.6% (0%-9.7%)

	Chemoradiotherapy N = 63	Chemo alone N = 63
Response to treatment (at the end of chemotherapy)		
Complete response	5 (7.9%)	4 (6.3%)
Partial response	46 (73.0%)	48 (76.2%)
Stable disease	5 (7.9%)	2 (3.2%)
Progressive disease	7 (11.1%)	9 (14.3%)
Overall response	51 (80.9%)	52 (82.5%)
Disease control	56 (88.9%)	55 (85.7%)
Response to treatment (at the end of radiotherapy)¶		
Complete response	10 (16.4%)	------
Partial response	36 (59.0%)	------
Stable disease	5 (8.2%)	------
Progressive disease	8 (13.1%)	------
Not assessable	2 (3.3%)	------
Overall response	46 (75.4%)	------
Disease control	51 (83.6%)	------

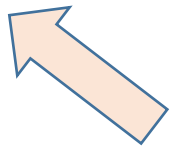
CONCLUSIONS

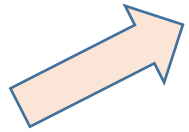
- In line with other retrospective analysis, in this prospectic randomized study radiotherapy added to chemotherapy significantly improved OS in chemotherapy-sensitive metastatic NPC patients.
- Are patients with limited (or just one) residual sites of disease (induced oligometastases[1]) those who benefit?

1. Reys DK, Pienta KJ, Oncotarget 2015

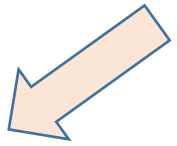
STARTING FROM OLD APPROACH

SELECTING BETTER PATIENTS





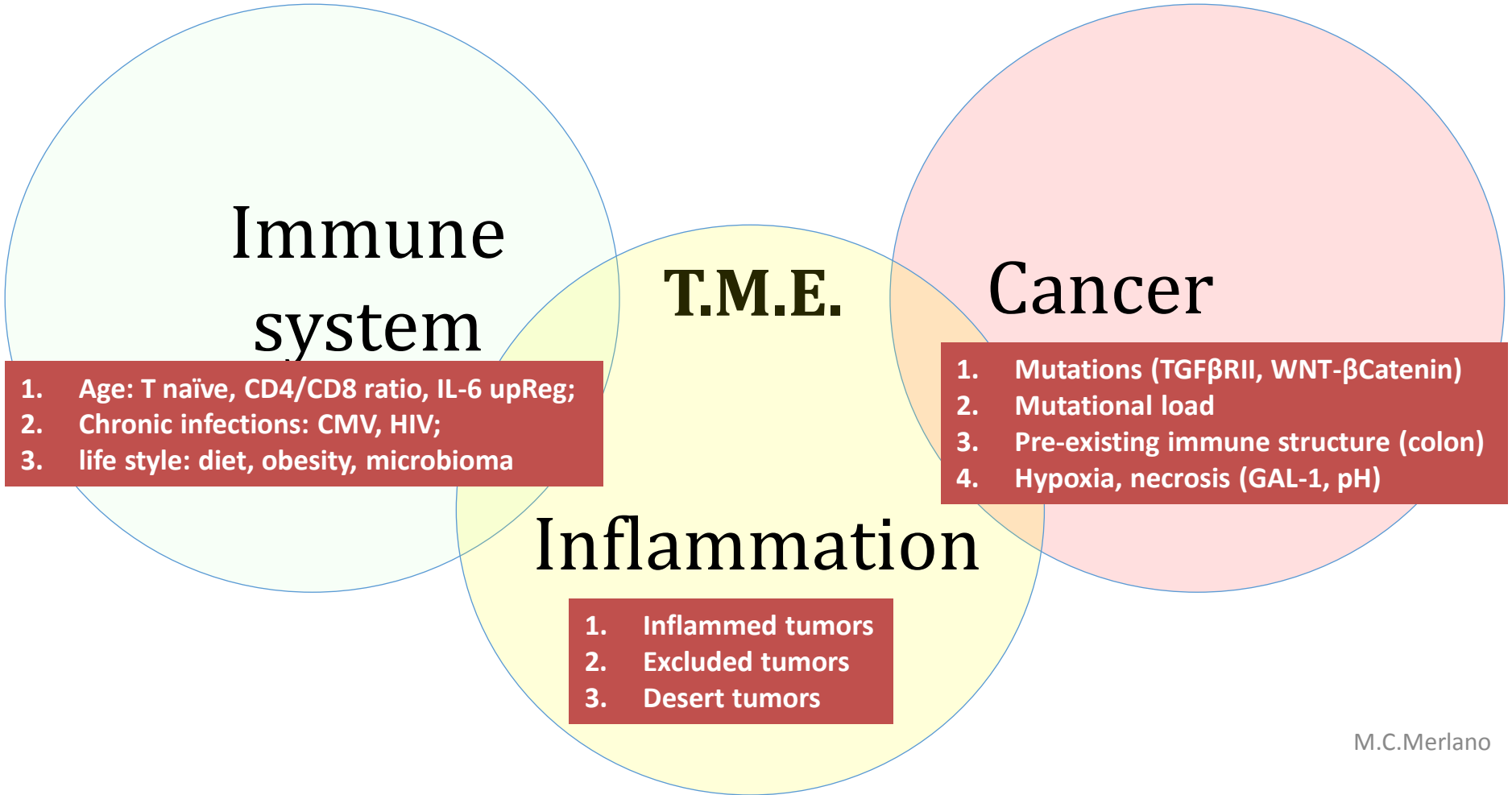
HOW TO INCREASE OUTCOME ???



WITH NOVEL COMBINATIONS

WITH NOVEL TARGET

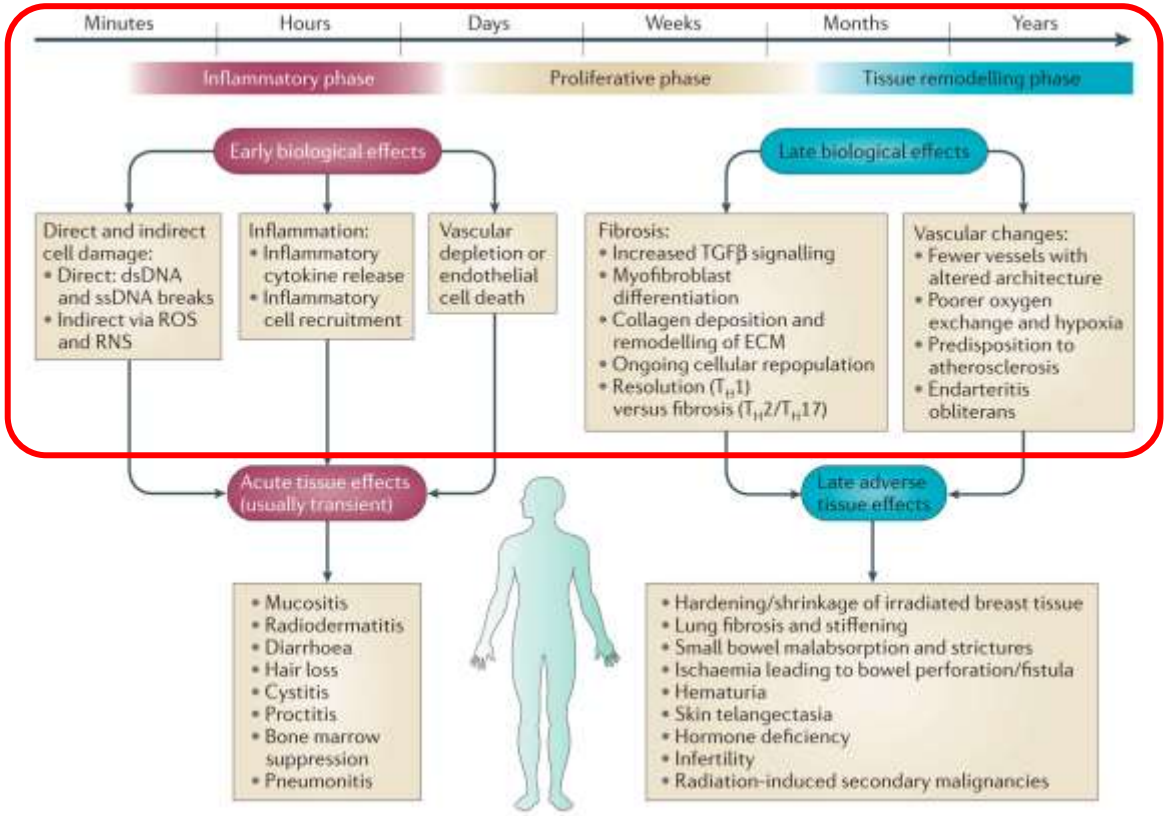
Factors affecting the TME (and response to immunotherapy)



M.C.Merlano

TREATMENT EFFECTS

Effects of RT (at curative dose) over time

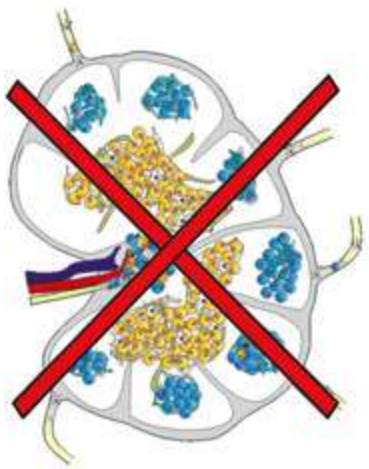


Baker HE et al, Nat Rev Cancer 2015

TREATMENT EFFECTS

Clinical and Experimental Immunology REVIEW ARTICLE doi:10.1111/j.1365-2249.2012.04602.x

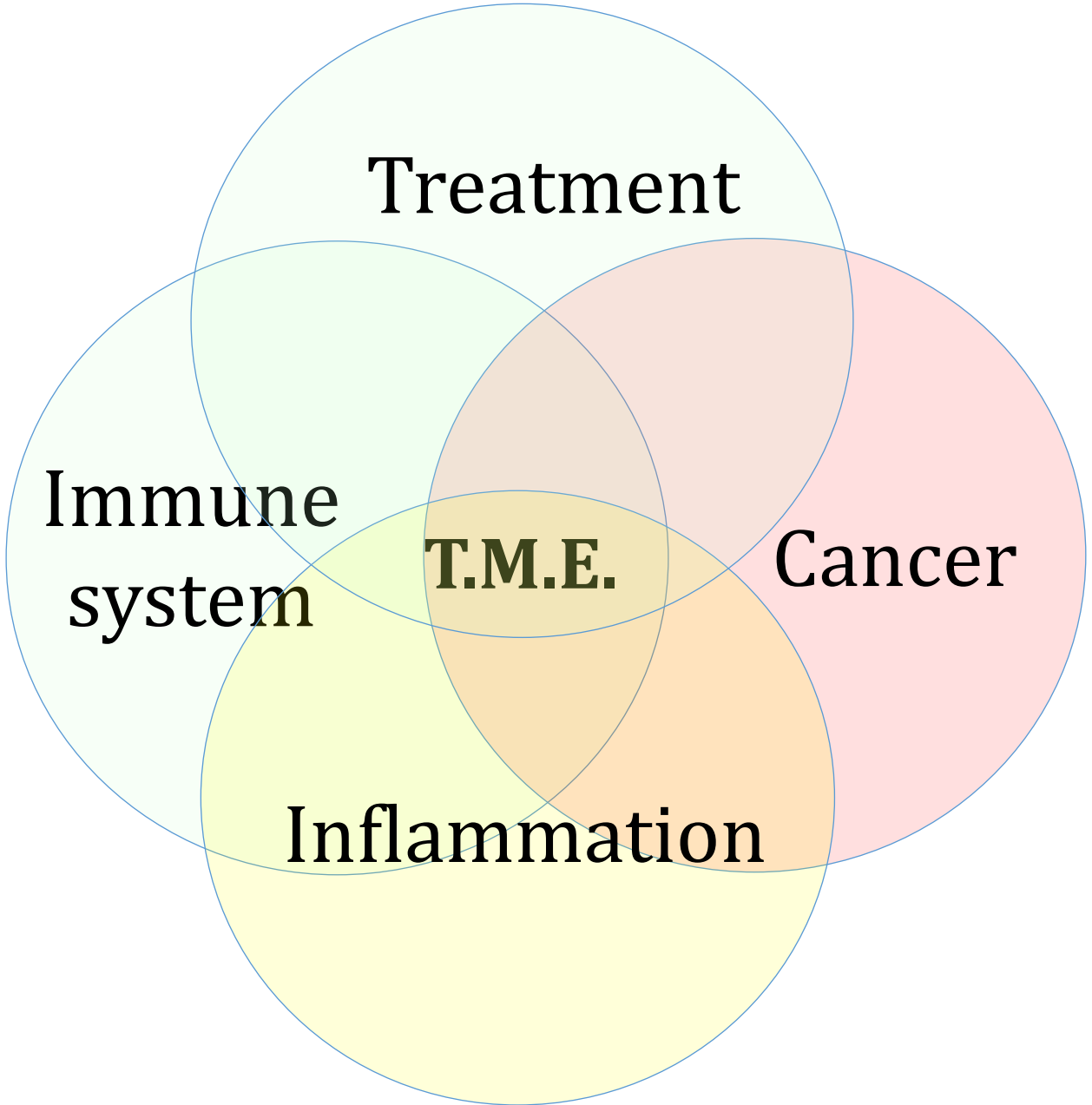
Lymph node dissection – understanding the immunological function of lymph nodes



- ↓ Immune response in the H&N region
- ↑ Immune response in the Gut
- ↓ Mucosal tolerance (infections)

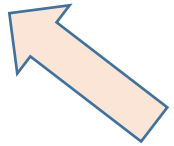
Buettner M, Clin Exp Immunology 2012

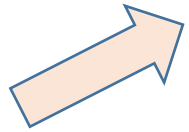

The TIME FACTOR


Treatment
Immune system
T.M.E.
Cancer
Inflammation

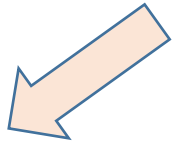
STARTING FROM OLD APPROACH

BETTER SELECTING PATIENTS





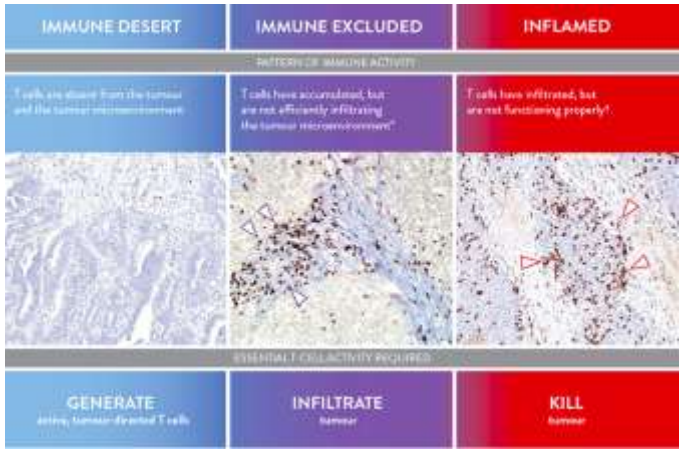
HOW TO INCREASE OUTCOME ???



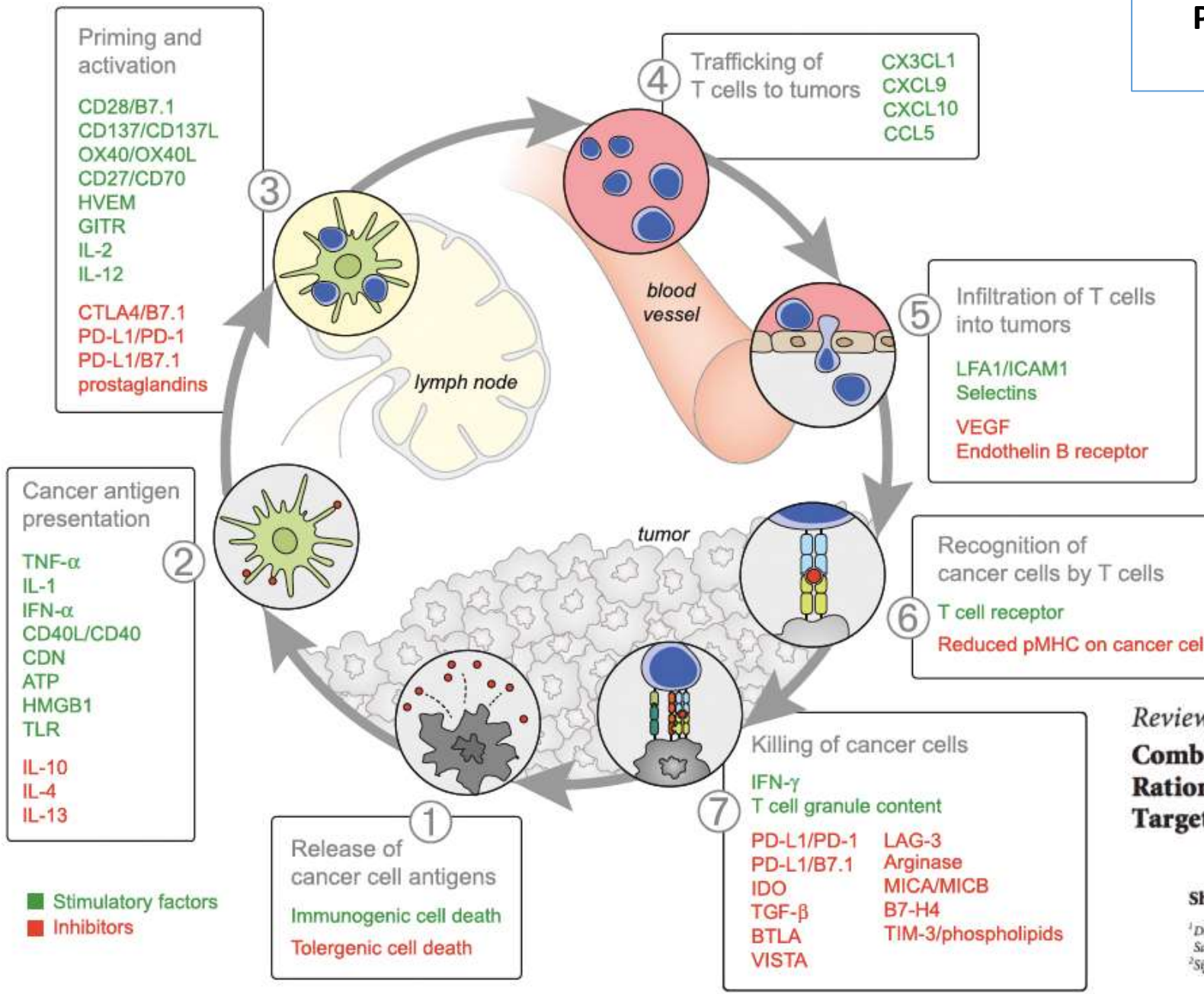
WITH NOVEL COMBINATIONS

WITH NOVEL TARGET

Perché così tante molecole non hanno dato i risultati sperati? ONE DOES NOT FIT ALL!



…AND REDUNDANT MECHANISMS IN EACH ONE



Review Article

Combinatorial Approach to Improve Cancer Immunotherapy: Rational Drug Design Strategy to Simultaneously Hit Multiple Targets to Kill Tumor Cells and to Activate the Immune System

Shweta Joshi[1] **and Donald L. Durden**[1,2]

[1]*Division of Pediatric Hematology-Oncology, Department of Pediatrics, Moores Cancer Center, University of California, San Diego, CA, USA*
[2]*SignalRx Pharmaceuticals, Inc., San Diego, CA, USA*

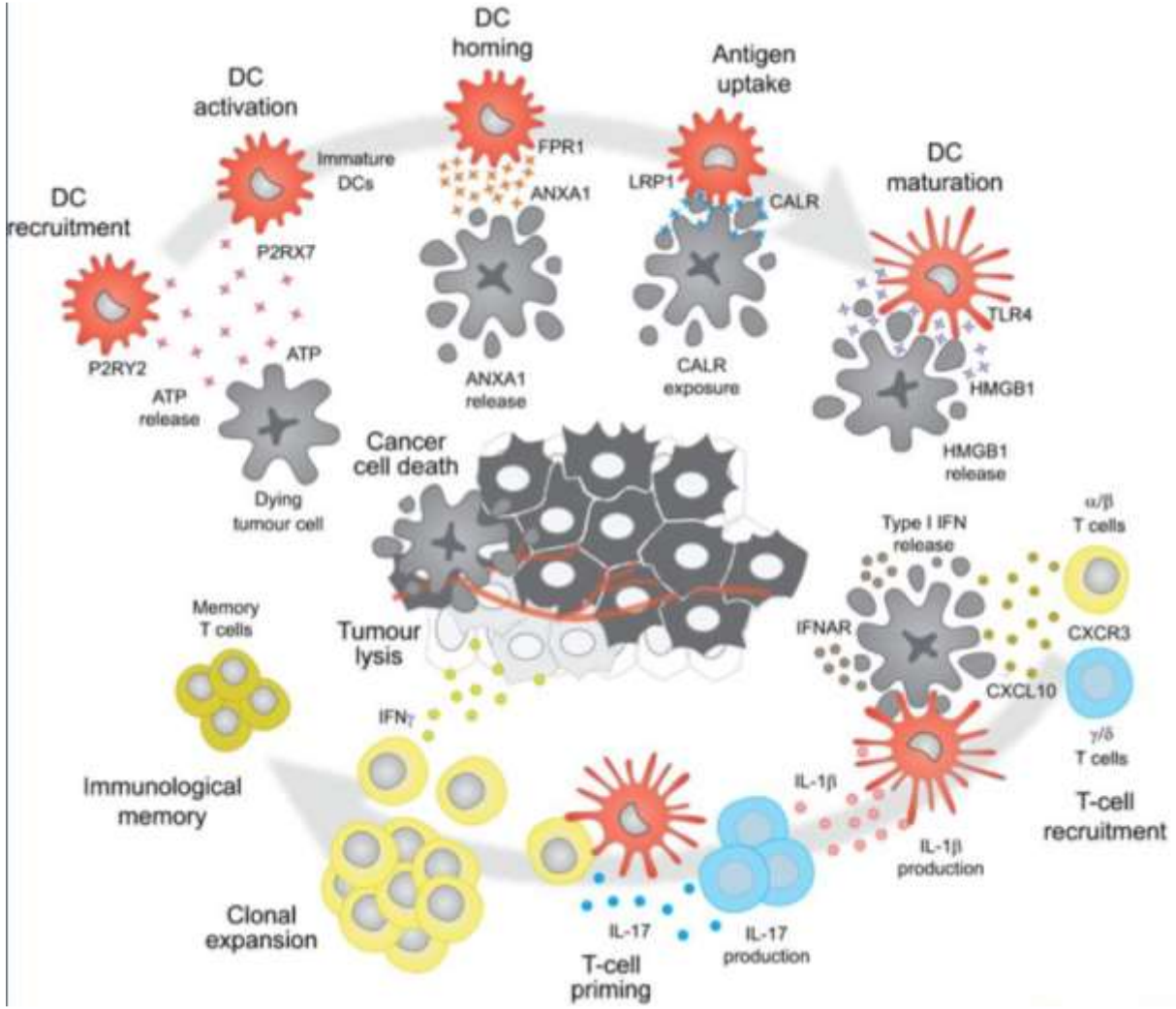
J. Oncol 2019

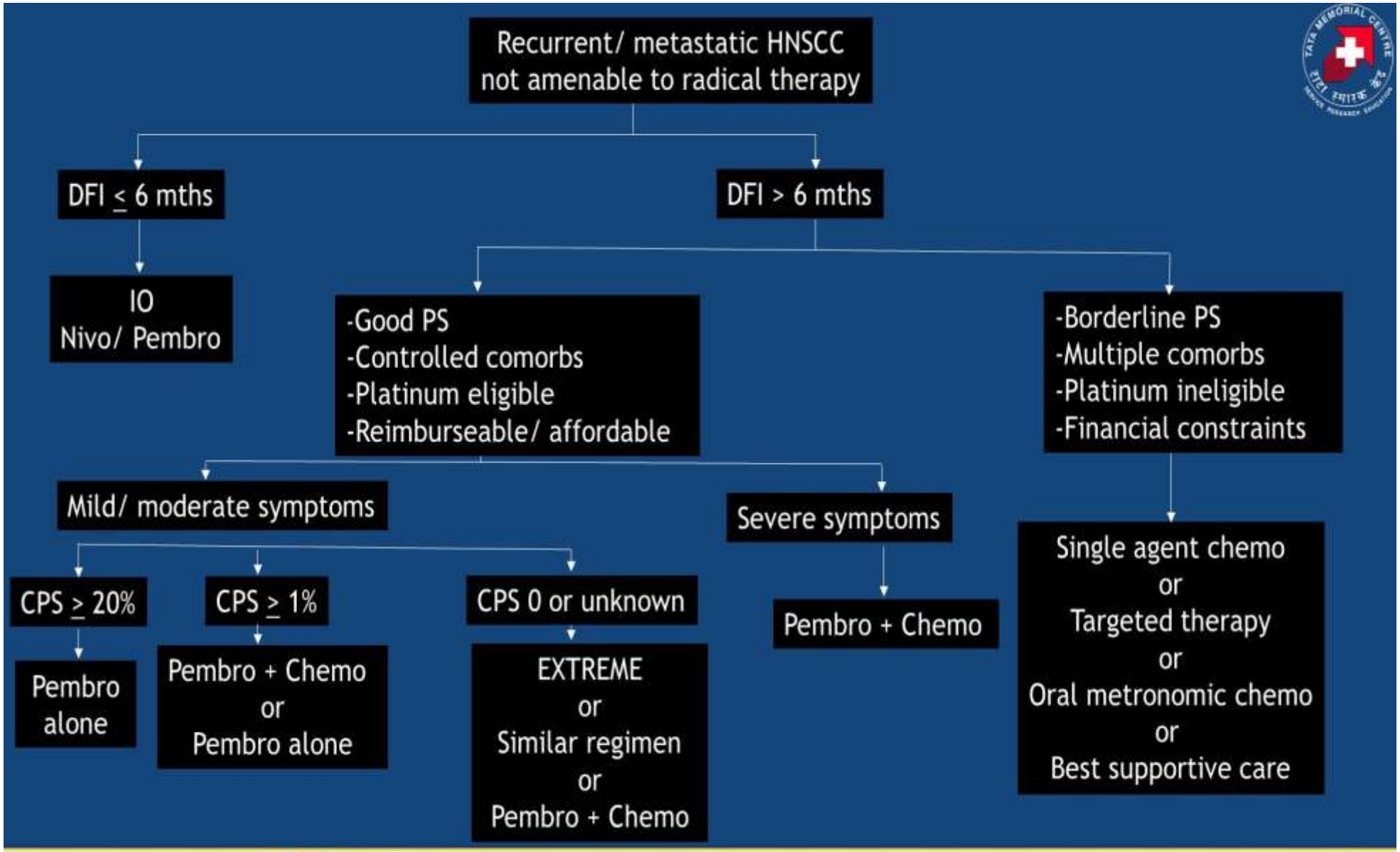
Protocol-Specified Final Results of the KEYNOTE-048 Trial of Pembrolizumab as First-Line Therapy for Recurrent/ Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC)

Danny Rischin[1], Kevin Harrington,[2] Richard Greil,[3] Denis Soulières,[4] Makoto Tahara,[5] Gilberto de Castro,[6] Amanda Psyrri,[7] Neus Basté,[8] Prakash Neupane,[9] Åse Bratland,[10] Thorsten Fuereder,[11] Brett GM Hughes,[12] Ricard Mesia,[13] Nuttapong Ngamphaiboon,[14] Tamara Rordorf,[15] Wan Zamaniah Wan Ishak,[16] Yayan Zhang,[17] Fan Jin,[17] Burak Gumuscu,[17] Barbara Burtness[18]

[1]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [2]The Institute of Cancer Research/The Royal Marsden NHS Foundation Trust National Institute of Health Research Biomedical Research Centre, London, UK; [3]Paracelsus Medical University, Salzburg Cancer Research Institute, and Cancer Cluster Salzburg, Salzburg, Austria; [4]Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada; [5]National Cancer Center Hospital East, Kashiwa, Japan; [6]Instituto do Cancer do Estado de Sao Paulo, Sao Paulo, Brazil; [7]National Kapodistrian University of Athens, Attikon University Hospital, Athens, Greece; [8]Vall d'Hebron University Hospital, Barcelona, Spain; [9]University of Kansas Medical Center, Kansas City, KS, USA; [10]Oslo University Hospital, Oslo, Norway; [11]Medical University of Vienna, Vienna, Austria; [12]Royal Brisbane and Women's Hospital and University of Queensland, Brisbane, QLD, Australia; [13]Catalan Institute of Oncology, Hospitalet de Llobregat, Barcelona, Spain; [14]Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [15]University Hospital, Zurich, Switzerland; [16]University Malaya, Kuala Lumpur, Malaysia; [17]Merck & Co., Inc., Kenilworth, NJ, USA; [18]Yale School of Medicine and Yale Cancer Center, New Haven, CT, USA

CHT + IMMUNO

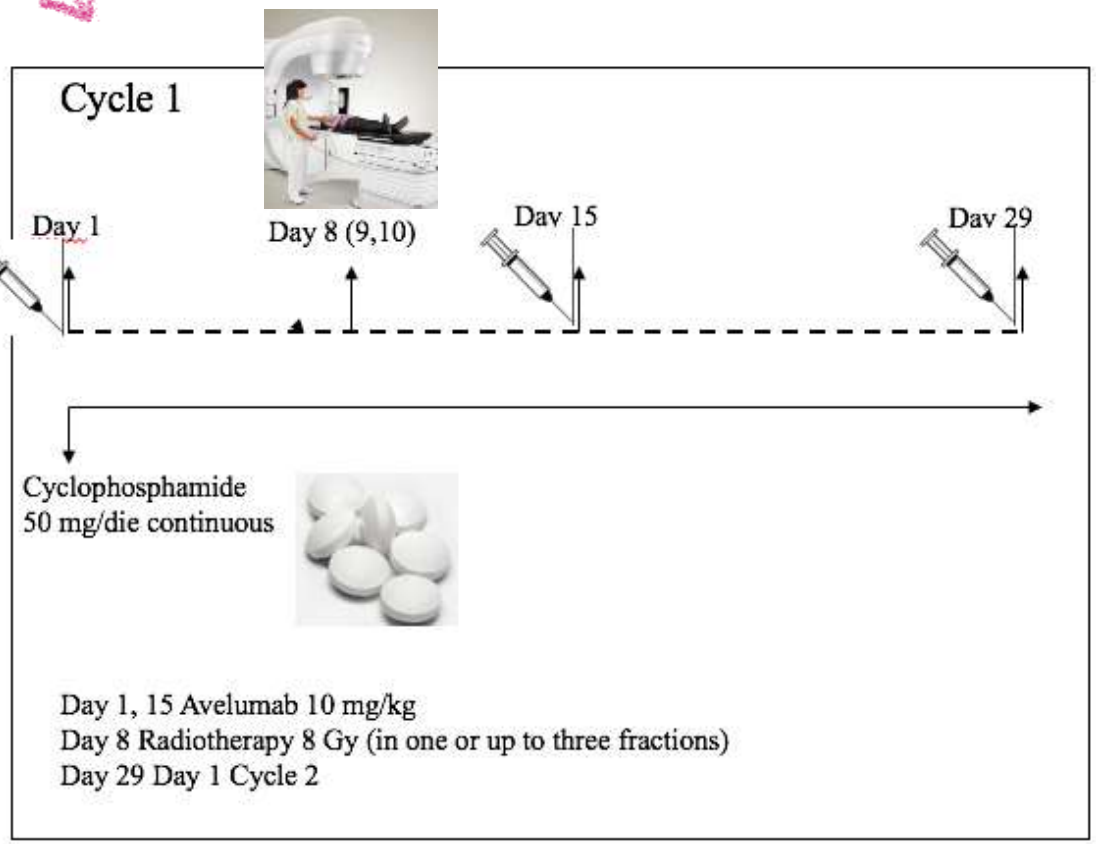


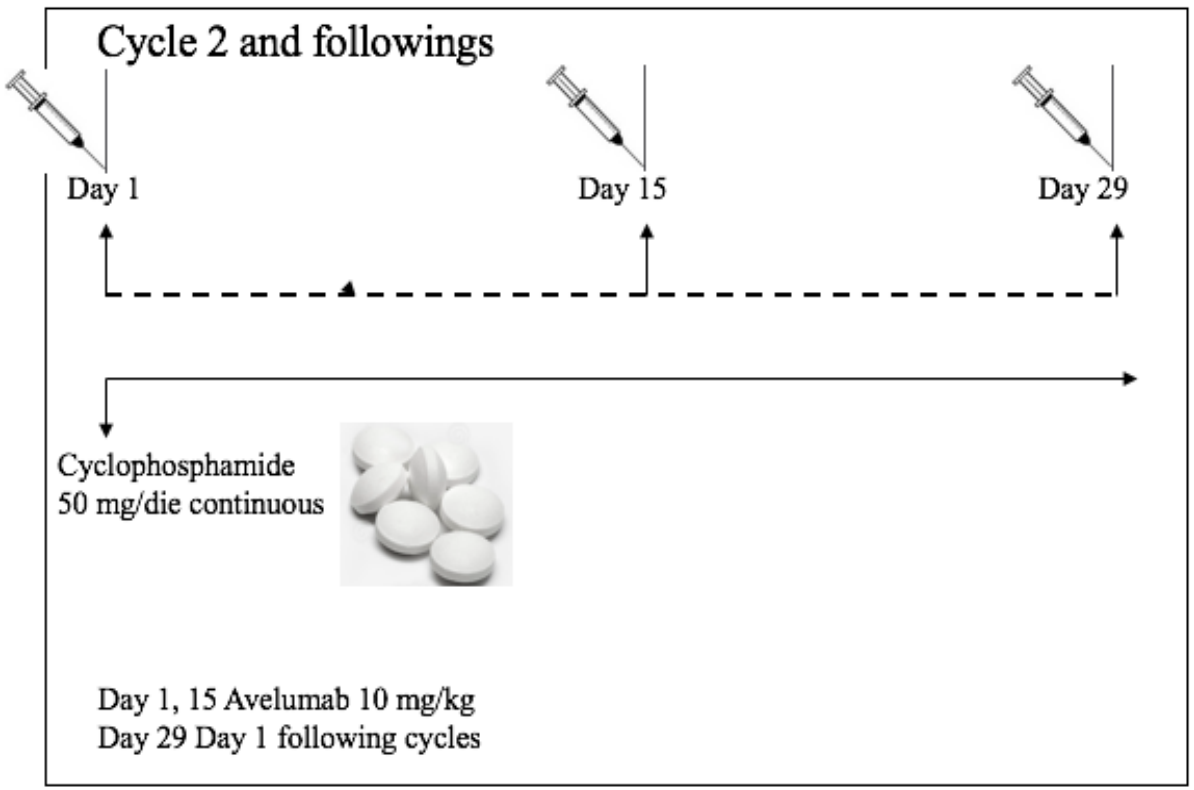


Clin Transl Radiat Oncol. 2018 Aug 13;12:47-52. doi: 10.1016/j.ctro.2018.08.001. eCollection 2018 Aug.

Activation of immune responses in patients with relapsed-metastatic head and neck cancer (CONFRONT phase I-II trial): Multimodality immunotherapy with avelumab, short-course radiotherapy, and cyclophosphamide.

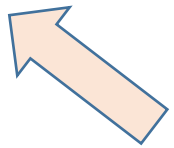
Merlano MC[1], Merlotti AM[2], Licitra L[3], Denaro N[1], Fea E[1], Galizia D[4], Di Maio M[5], Fruttero C[6], Curcio P[7], Vecchio S[8], Russi EG[2], Corvò R[9].

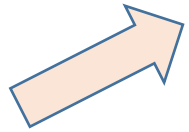




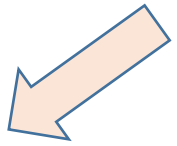
STARTING FROM OLD APPROACH

BETTER SELECTING PATIENTS





HOW TO INCREASE OUTCOME ???



WITH NOVEL COMBINATIONS

WITH NOVEL TARGET

JAMA Oncology | Brief Report

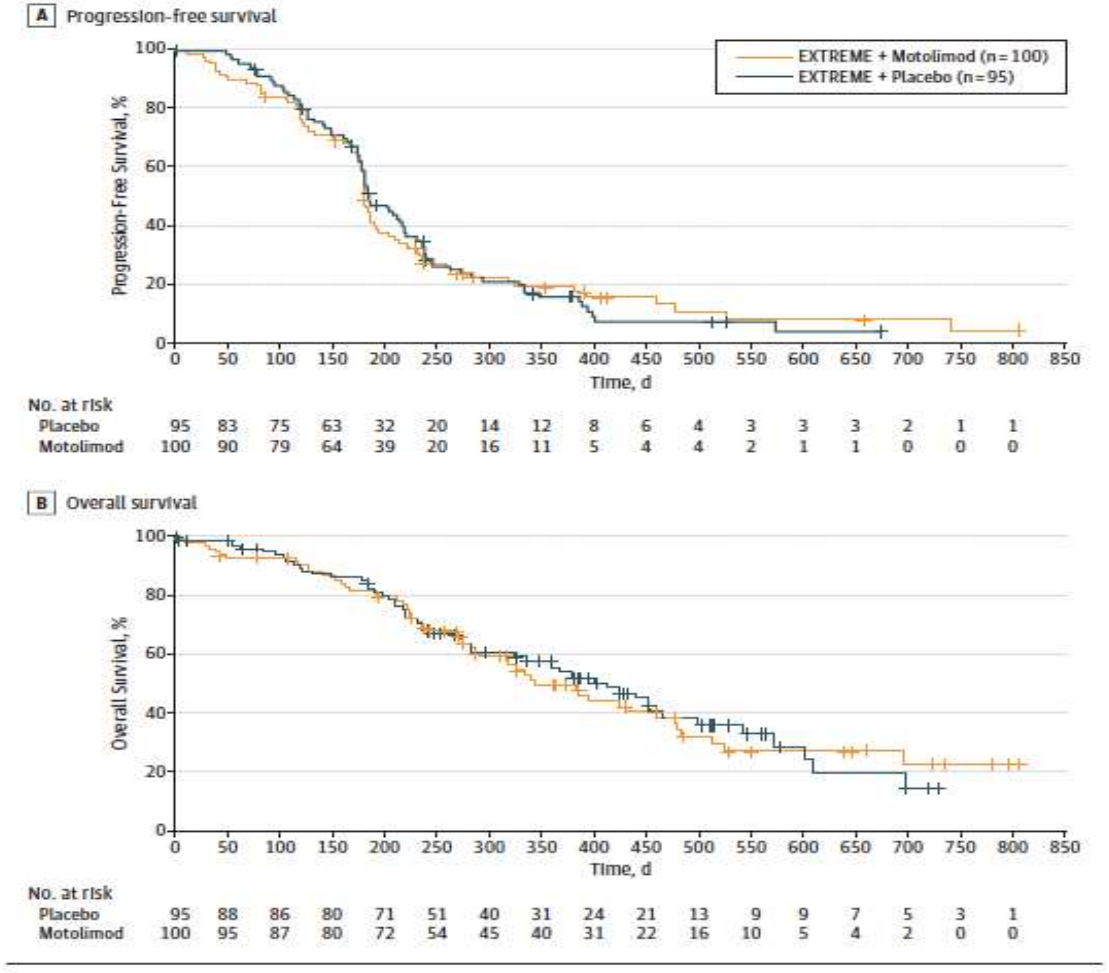
Effect of Adding Motolimod to Standard Combination Chemotherapy and Cetuximab Treatment of Patients With Squamous Cell Carcinoma of the Head and Neck
The Active8 Randomized Clinical Trial

Robert L. Ferris, MD, PhD; Nabil F. Saba, MD; Barbara J. Gitlitz, MD; Robert Haddad, MD; Ammar Sukari, MD; Prakash Neupane, MD; John C. Morris, MD; Krzysztof Misiukiewicz, MD; Julie E. Bauman, MD, MPH; Moon Fenton, MD, PhD; Antonio Jimeno, MD; Douglas R. Adkins, MD; Charles J. Schneider, MD; Assuntina G. Sacco, MD; Keisuke Shirai, MD; Daniel W. Bowles, MD; Michael Gibson, MD, PhD; Tobenna Nwizu, MD; Raphael Gottardo, PhD; Kristi L. Manjarrez, BS; Gregory N. Dietsch, PhD; James Kyle Bryan, MD; Robert M. Hershberg, MD, PhD; Ezra E. W. Cohen, MD

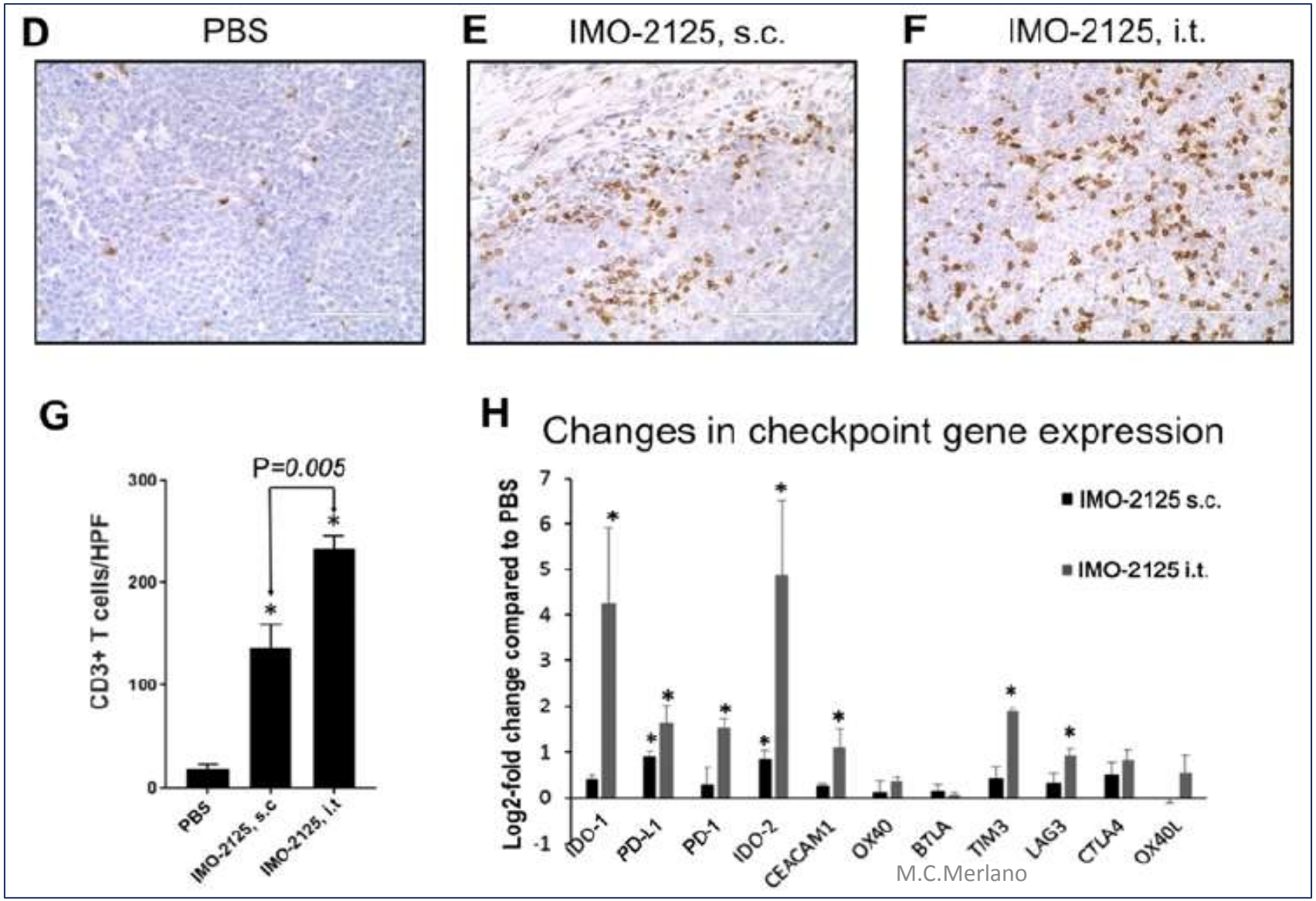
Methods

P-F-Cmab + six 21-day cycles of weekly subcutaneous motolimod (3 mg/m2) or placebo.

Figure 2. Kaplan-Meier Analyses of Progression-Free Survival and Overall Survival in the Intent-to-Treat Population



TLR9 Agonist IMO-2125. s.c. = sub-cutaneous; i.t. = intra-tu



Intra-tumor delivery extends antitumor immune response to uninjected distal tumors resulting in a systemic efficacy

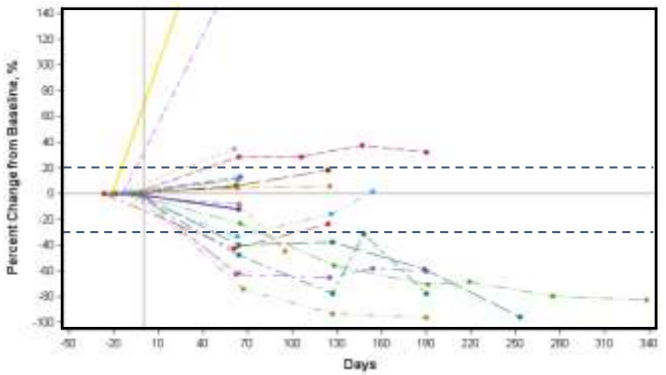
Wang D et al, Int. J. Oncol. 2018

EFFICACY

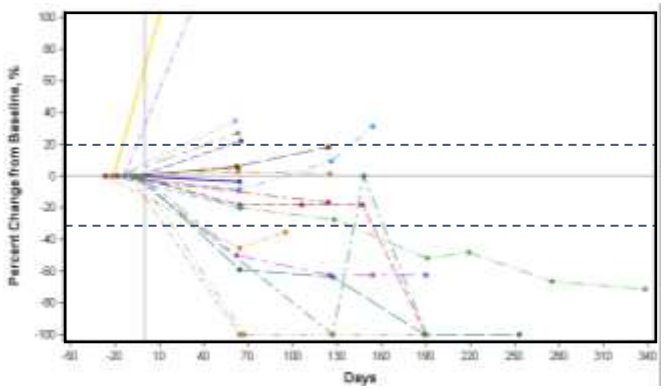
	8 mg	2 mg
mITT patients, n*	**22**	**2**
Objective response rate, n (%)	6 (27.3)	
95% confidence interval	(16, 56)	
Best overall response, n (%)		
Complete response	0	
Partial response	6 (27.3)	
Stable disease	4 (18.2)	2 (100)
Progressive disease	10 (45.5)	
Time to response (months)		
Median (min, max)	2.1 (2.0, 4.2)	
Duration of response (months)		
Median (min, max)	3.6+ (0.0, 6.9)	

* mITT: patients on treatment but did not yet have their first CT scan and tumor assessment

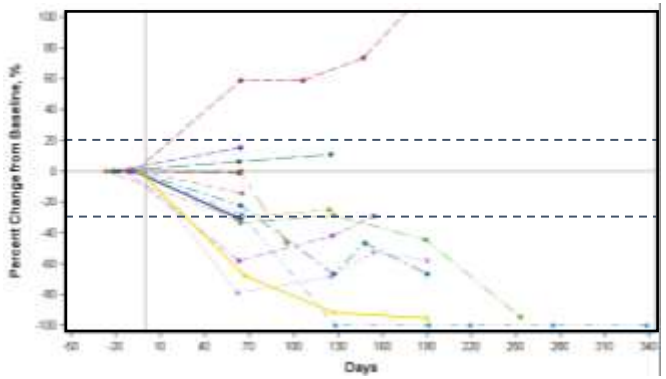
Percent Change From Baseline for Target Lesions: SD-101 8 mg



All Target Lesions



Injected Target Lesions



Non-Injected Target Lesions

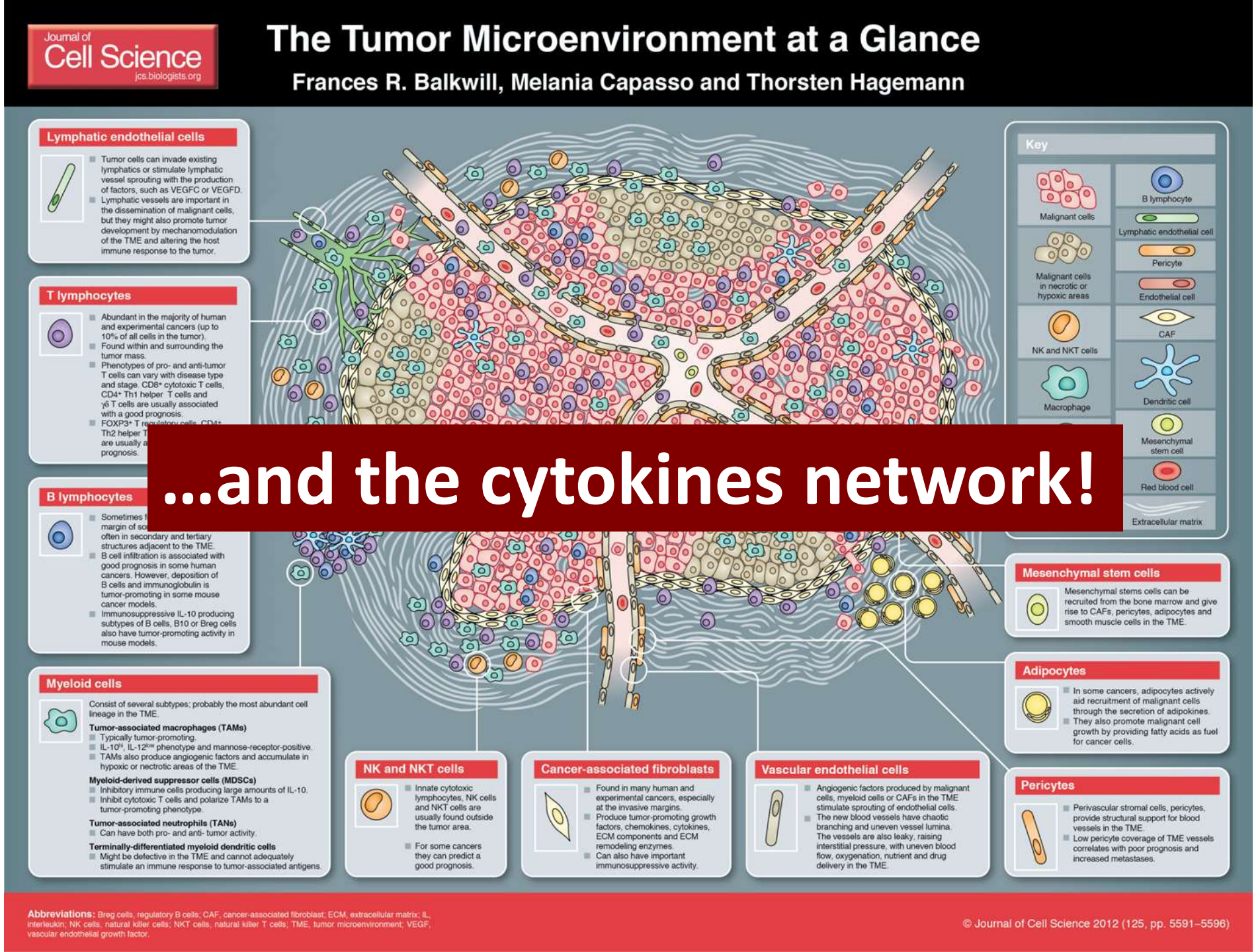
Cohen E, et al. Abstract 3560

May be a problem of scheduling?

TLR9 Agonist SD 101 Intra Tumoral administration[1,2] ↑
TLR7 Agonist Imiquinod Topic administration[3] ↕
TLR8 Agonist Motolimod S.C. administration[4]

not: it's a problem of concentration!

1. Cohen EE, ESMO 2018, Abstr 1050PD
2. Ribas A et al, Cancer Discovery 2018
3. Chi H et al, Frontiers in pharmacol 2017
4. Siu LL et al, JAMA 2018



…and the cytokines network!

Thank You!