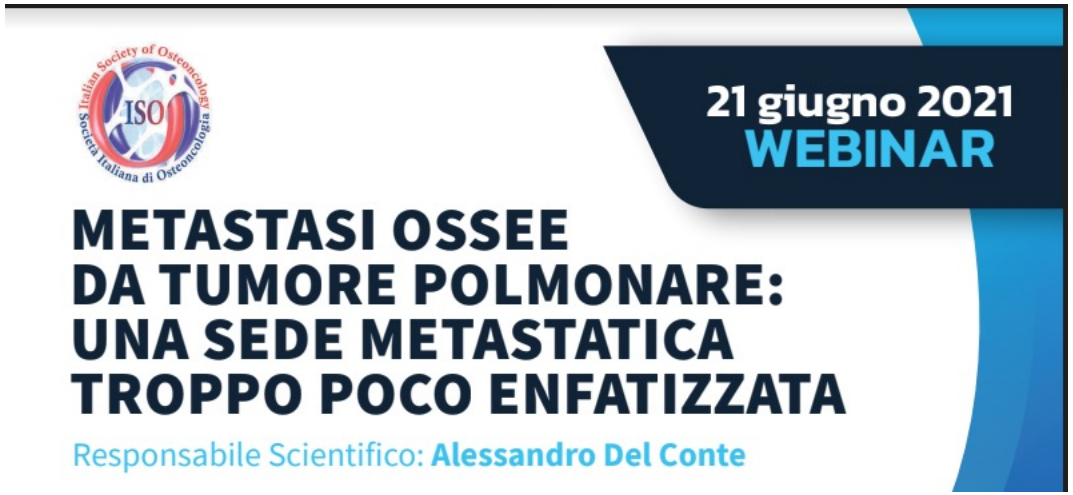


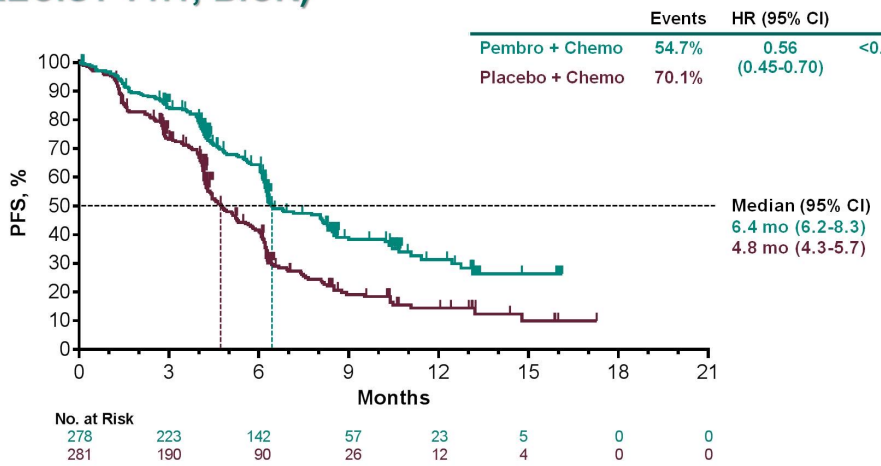
Il carcinoma polmonare con lesioni scheletriche nell'era dell'immunoterapia

Andrea Botticelli

Policlinico Umberto I, Sapienza Università di Roma

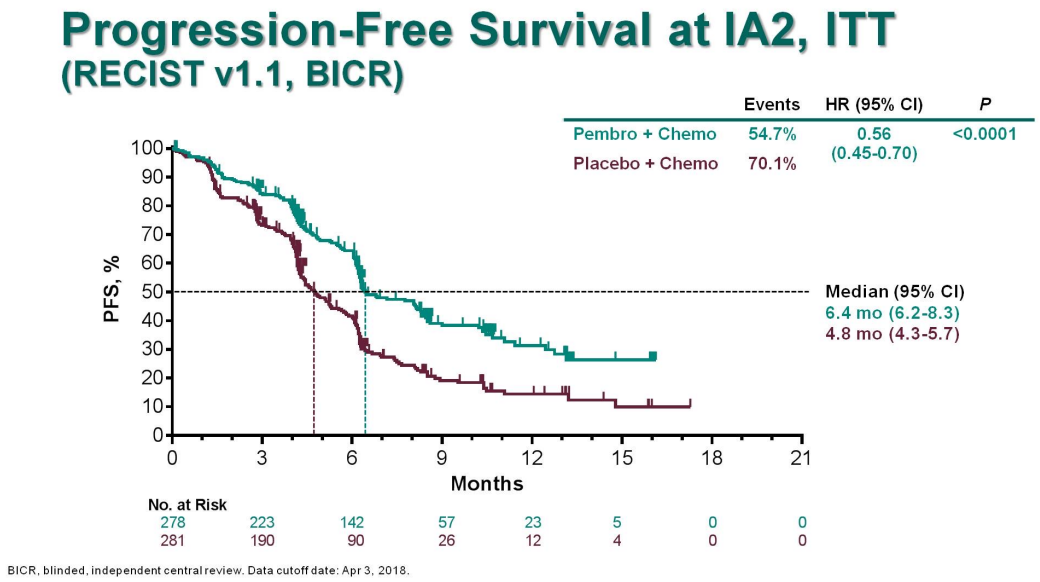
KEYNOTE 407

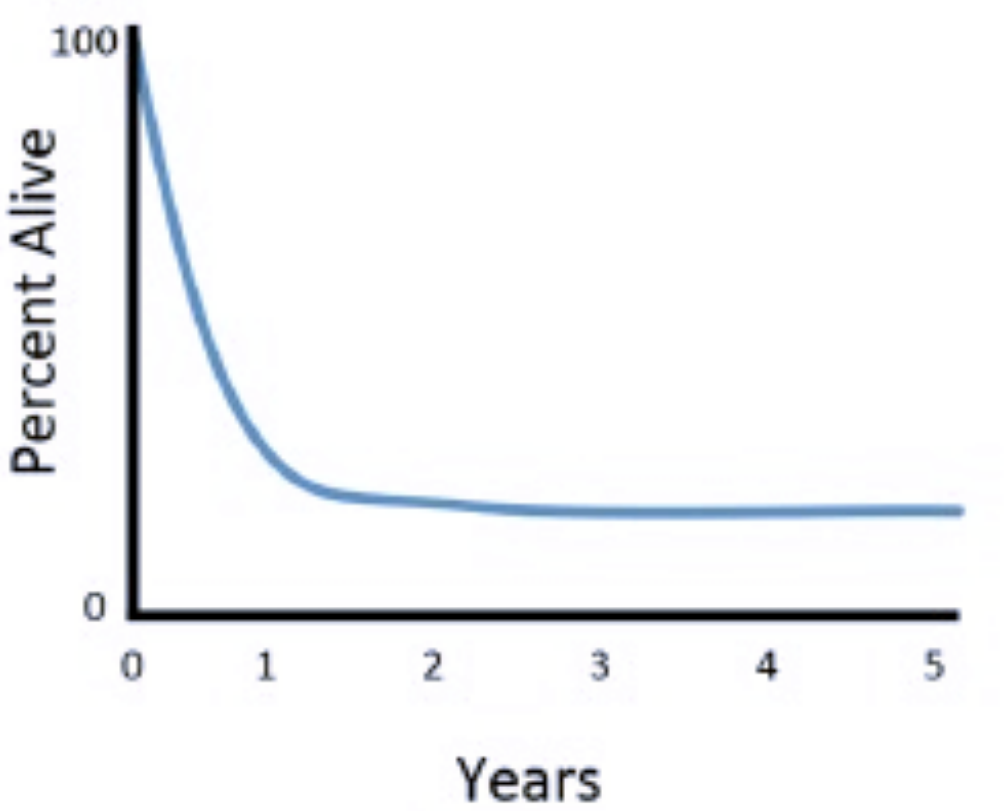
Progression-Free Survival at IA2, ITT
(RECIST v1.1, BICR)



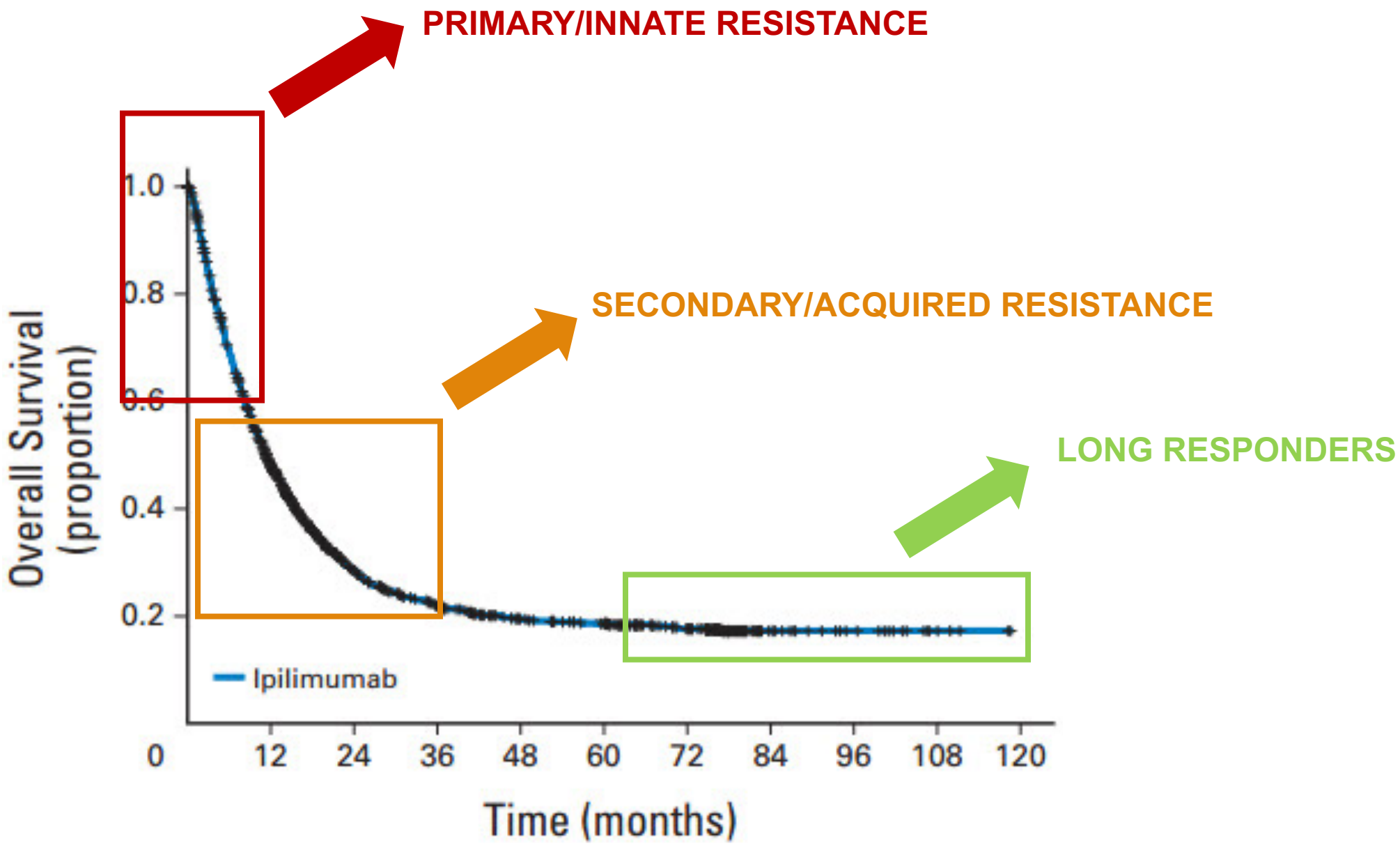
BICR, blinded, independent central review. Data cutoff date: Apr 3, 2018.

KEYNOTE 407





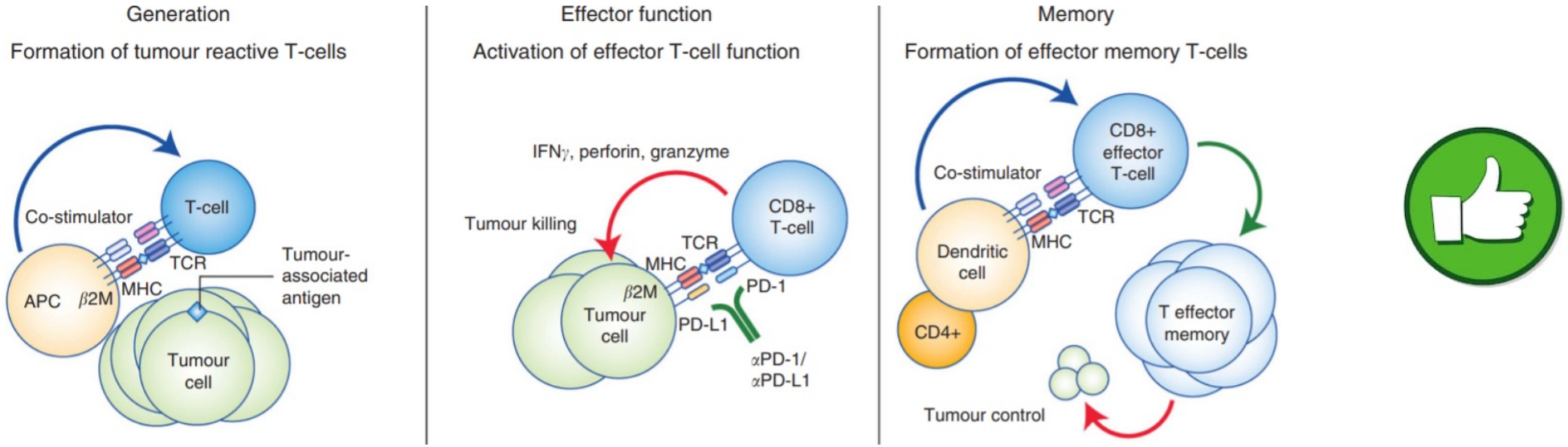
Wargo JA, et al. Cancer Discov 2014


PRIMARY/INNATE RESISTANCE
SECONDARY/ACQUIRED RESISTANCE
LONG RESPONDERS
Overall Survival (proportion)
1.0
0.8
0.6
0.4
0.2
Ipilimumab
0
12
24
36
48
60
72
84
96
108
120
Time (months)

RESPONDERS VS NON-RESPONDERS

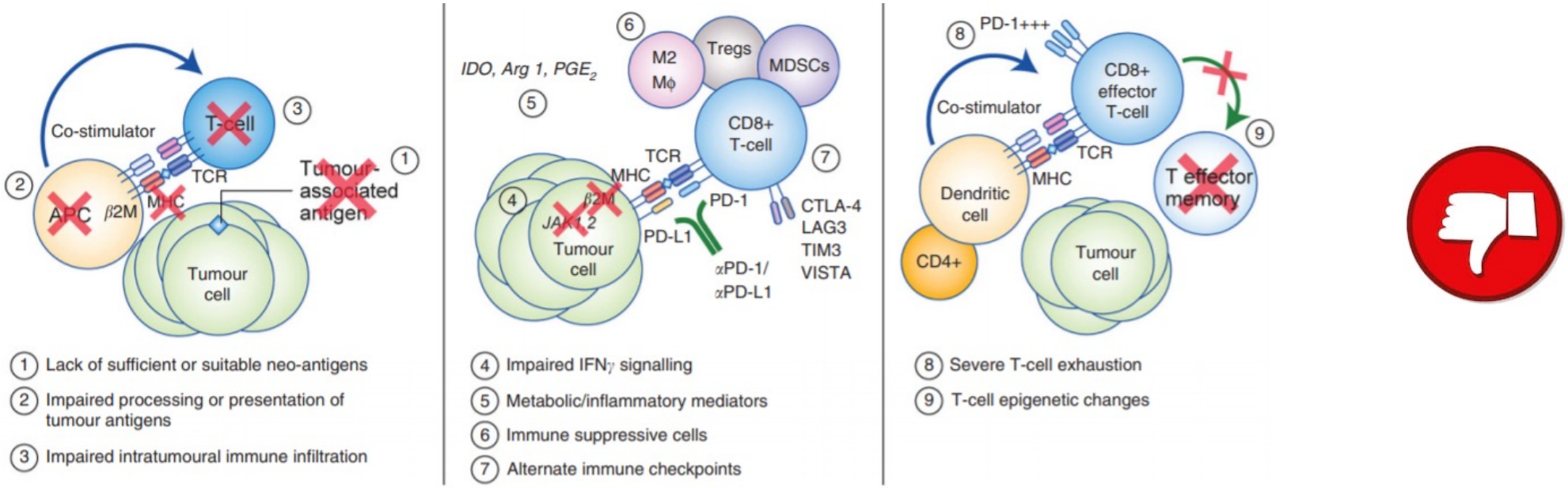
Response

RESPONDERS



Innate/ acquired resistance

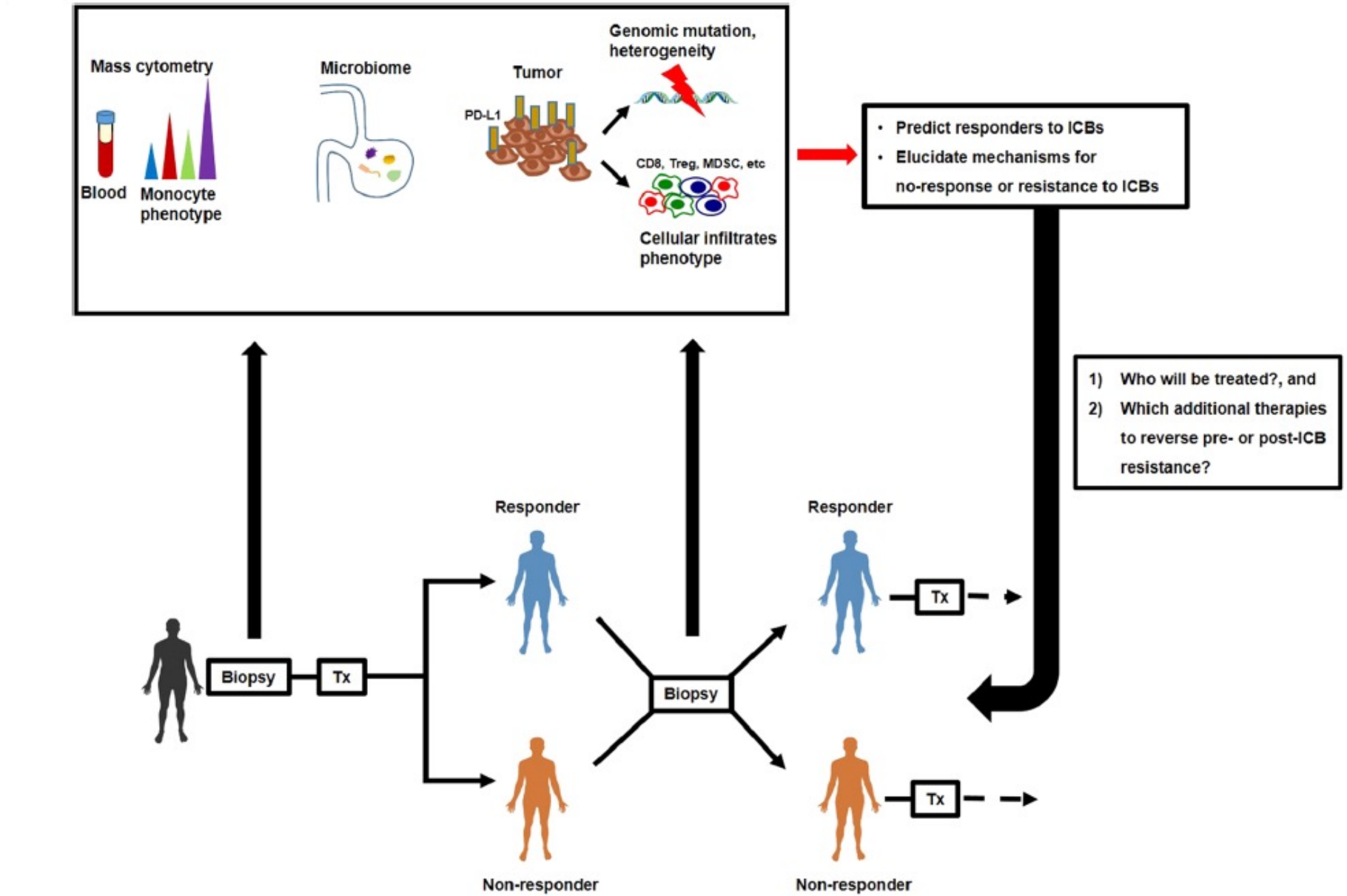
RESISTANT



1. Lack of sufficient or suitable neo-antigens
2. Impaired processing or presentation of tumour antigens
3. Impaired intratumoural immune infiltration
4. Impaired IFNγ signalling
5. Metabolic/inflammatory mediators
6. Immune suppressive cells
7. Alternate immune checkpoints
8. Severe T-cell exhaustion
9. T-cell epigenetic changes

Russel et al British Journal of Cancer (2018) 118, 9–16

IMPROVE THE SELECTION OF PATIENTS…



Park Experimental & Molecular Medicine (2018)

OSPITE

TUMORE

PD-L1 : NEVERENDING STORY…

PD-L1 : sp142 IC

PD-L1 STAINING

TPS (Tumor Proportion Score)

$$TPS = \frac{\text{Number of PD-L1 stained tumor cells}}{\text{Total number of viable tumor cells}} \times 100$$

*Reported as a **percentage***

CPS (Combined Positive Score)

$$CPS = \frac{\text{Number of PD-L1 stained cells (tumor cells, lymphocytes, macrophages)}}{\text{Total number of viable tumor cells}} \times 100$$

*Reported as a **number** (capped at 100)*

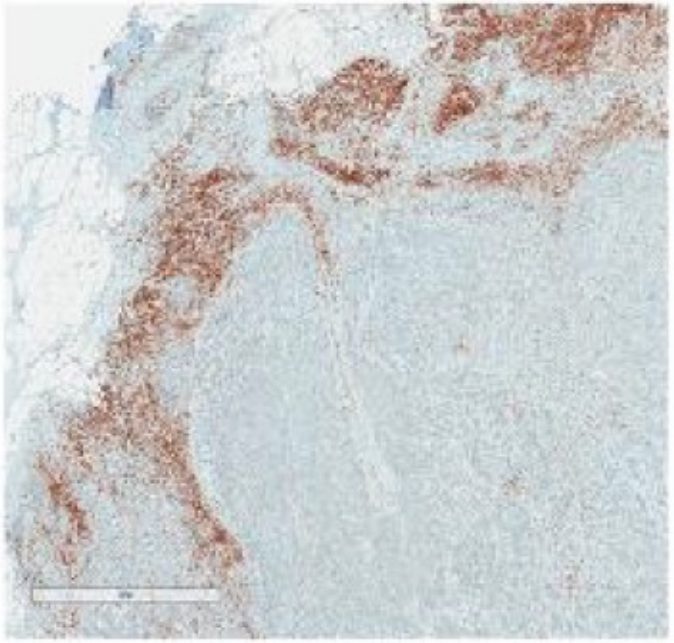
BARCELONA 2019 ESMO congress

HOT VS COLD TUMOR

Non-inflamed

Chemotherapy, XRT
HER-2-directed antibodies
Vaccines, STING agonists

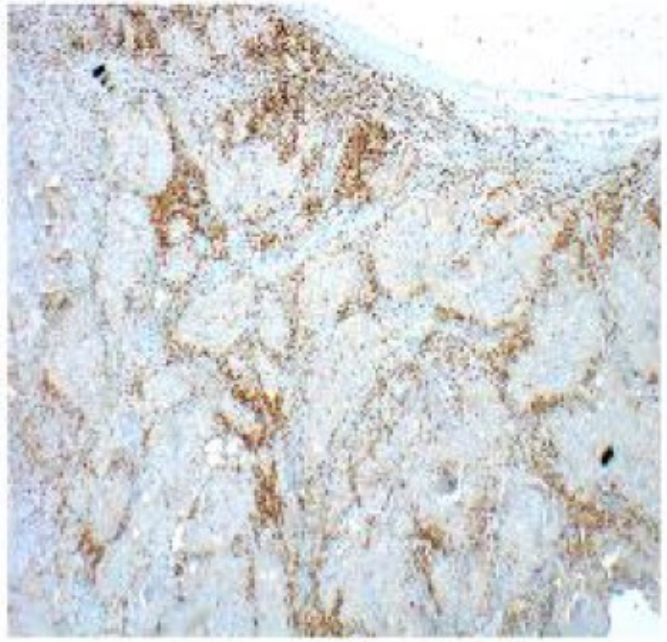
Immune-Excluded



VEGF inhibition

Gajewski TF Semin Oncol 2015 42: 663-71.
Herbst RS et al Nature 2014 515: 568-71.
Chen DS Mellman I Immunity 2013 39: 1-10.
Cimino-Mathews A/Emens LA, unpublished images.

Inflamed



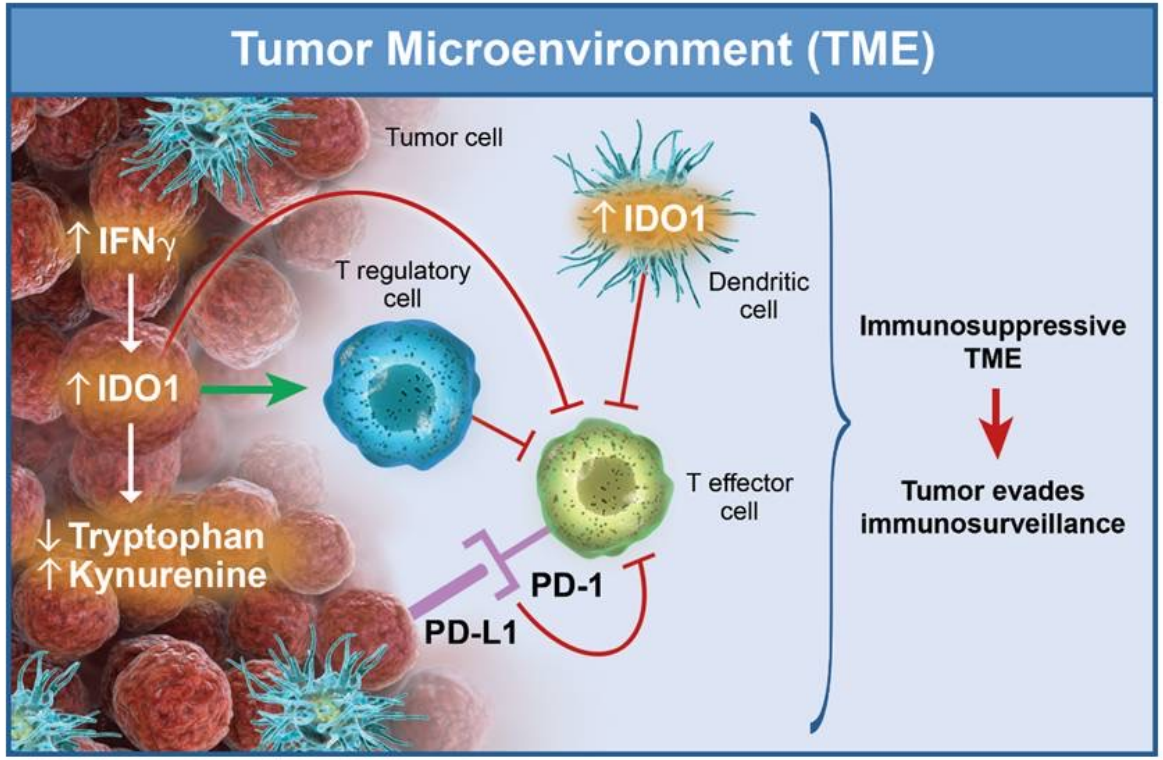
Anti-PD-1/PD-L1
IDO inhibition
A2AR inhibition

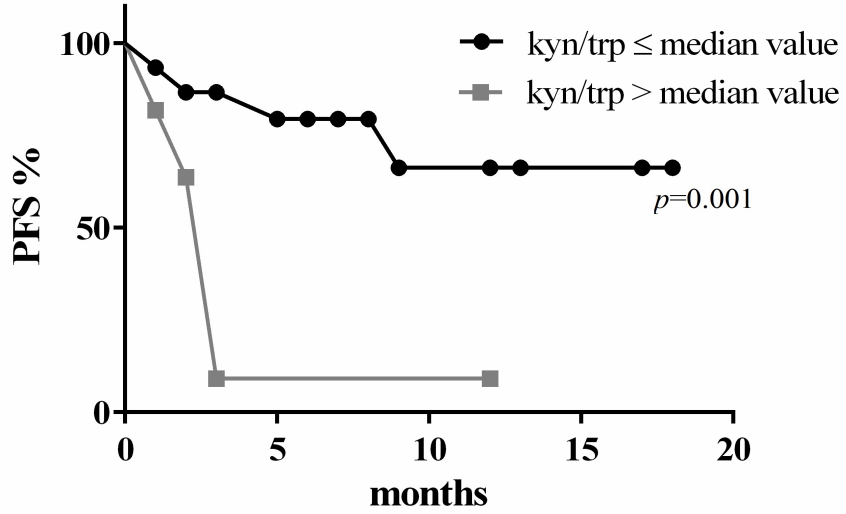
RESEARCH Open Access

Can IDO activity predict primary resistance to anti-PD-1 treatment in NSCLC?

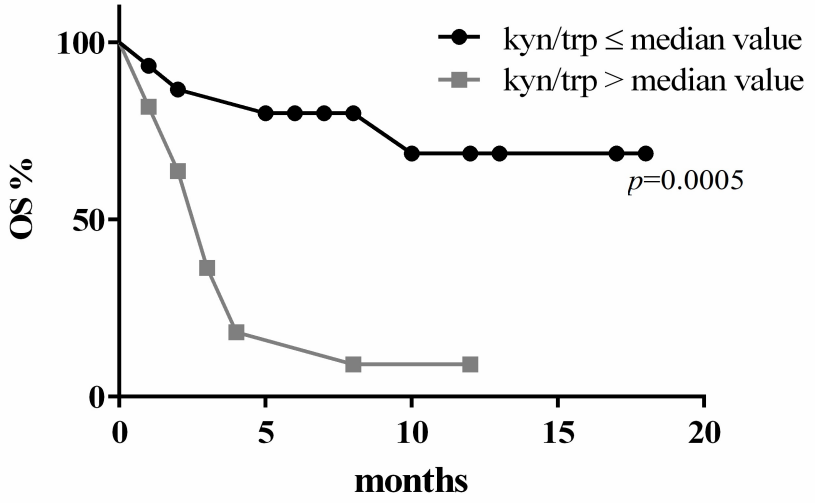
Andrea Botticelli[1*], Bruna Cerbelli[2], Luana Lionetto[3], Ilaria Zizzari[4], Massimiliano Salati[5], Annalinda Pisano[2], Mazzuca Federica[1], Maurizio Simmaco[6], Marianna Nuti[4] and Paolo Marchetti[1]

B





KYN/TRP



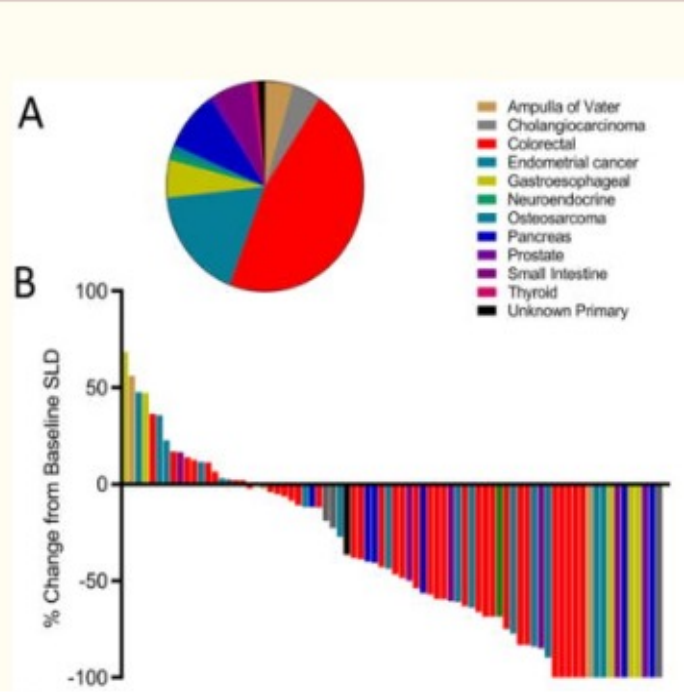
Science. 2017 July 28; 357(6349): 409–413. doi:10.1126/science.aan6733.

Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade

ORR : 53%

DISEASE CONTROL : 77%

CR : 21%

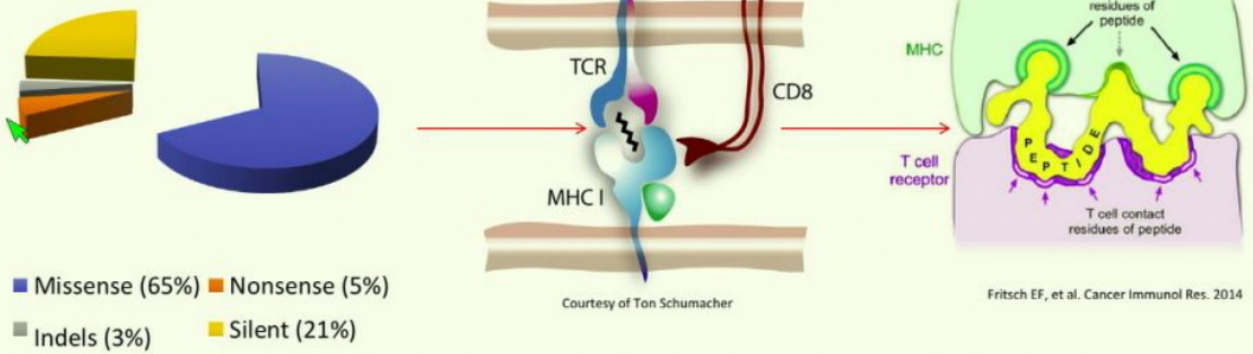


FDA Approves First Cancer Site Agnostic Biomarker/Drug Combination: May 23 2017

- Pembrolizumab accelerated approval for MSI-H or dMMR solid tumors
- 149 patients in 5 phase II single arm trials
  - 90 metastatic CRC patients refractory to 5FU/oxali/irino
  - 59 with 14 other tumor types
- 40% response rates, many durable, a few complete (7%)

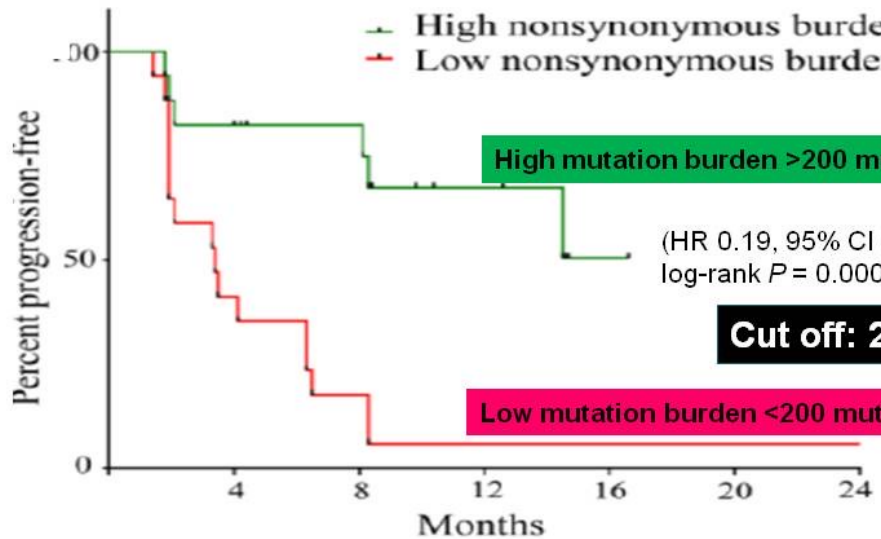
PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17 Presented by: D. Schrag MD MPH

TMB is a surrogate for (predicted) neoantigens



High Mutational Burden Predicts Response to Pembrolizumab (anti-PD1) in NSCLC

PFS
High burden (n=17) vs. low burden (n = 17



High mutation burden >200 mutations

(HR 0.19, 95% CI 0.08-0.47
log-rank *P* = 0.0004)

Cut off: 200 mutations

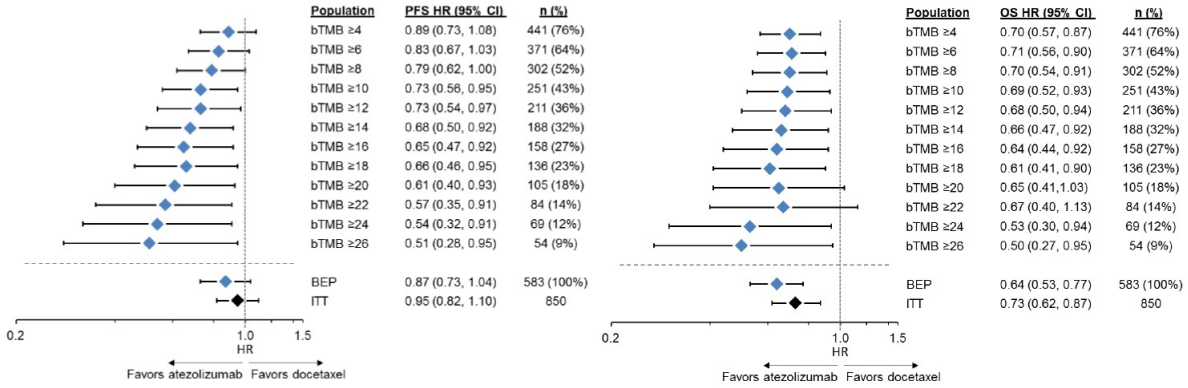
Low mutation burden <200 mutations

Rizvi Na et al; Science 10: 1126 (2014)

BLOOD-BASED BIOMARKERS FOR CANCER IMMUNOTHERAPY: TUMOR MUTATIONAL BURDEN IN BLOOD (bTMB) IS ASSOCIATED WITH IMPROVED ATEZOLIZUMAB EFFICACY IN 2L+ NSCLC (POPLAR AND OAK)

INCREASING ATEZOLIZUMAB BENEFIT WITH HIGHER bTMB CUT-POINTS IN OAK

Progression-Free Survival – OAK



Population	PFS HR (95% CI)	n (%)
bTMB ≥4	0.89 (0.73, 1.08)	441 (76%)
bTMB ≥6	0.83 (0.67, 1.03)	371 (64%)
bTMB ≥8	0.79 (0.62, 1.00)	302 (52%)
bTMB ≥10	0.73 (0.56, 0.95)	251 (43%)
bTMB ≥12	0.73 (0.54, 0.97)	211 (36%)
bTMB ≥14	0.68 (0.50, 0.92)	188 (32%)
bTMB ≥16	0.65 (0.47, 0.92)	158 (27%)
bTMB ≥18	0.66 (0.46, 0.95)	136 (23%)
bTMB ≥20	0.61 (0.40, 0.93)	105 (18%)
bTMB ≥22	0.57 (0.35, 0.91)	84 (14%)
bTMB ≥24	0.54 (0.32, 0.91)	69 (12%)
bTMB ≥26	0.51 (0.28, 0.95)	54 (9%)
BEP	0.87 (0.73, 1.04)	583 (100%)
ITT	0.95 (0.82, 1.10)	850

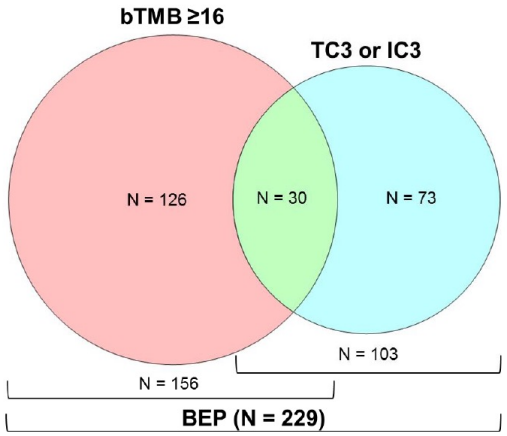
Overall Survival – OAK

Population	OS HR (95% CI)	n (%)
bTMB ≥4	0.70 (0.57, 0.87)	441 (76%)
bTMB ≥6	0.71 (0.56, 0.90)	371 (64%)
bTMB ≥8	0.70 (0.54, 0.91)	302 (52%)
bTMB ≥10	0.69 (0.52, 0.93)	251 (43%)
bTMB ≥12	0.68 (0.50, 0.94)	211 (36%)
bTMB ≥14	0.66 (0.47, 0.92)	188 (32%)
bTMB ≥16	0.64 (0.44, 0.92)	158 (27%)
bTMB ≥18	0.61 (0.41, 0.90)	136 (23%)
bTMB ≥20	0.65 (0.41,1.03)	105 (18%)
bTMB ≥22	0.67 (0.40, 1.13)	84 (14%)
bTMB ≥24	0.53 (0.30, 0.94)	69 (12%)
bTMB ≥26	0.50 (0.27, 0.95)	54 (9%)
BEP	0.64 (0.53, 0.77)	583 (100%)
ITT	0.73 (0.62, 0.87)	850

- Enrichment of PFS benefit was observed in the bTMB ≥16 subgroup, while OS was consistent between the bTMB ≥16 subgroup and the BEP

BEP, biomarker-evaluable population; ITT, intention-to-treat.

LIMITED OVERLAP BETWEEN bTMB ≥16 AND PD-L1 EXPRESSION[a] (OAK BEP)

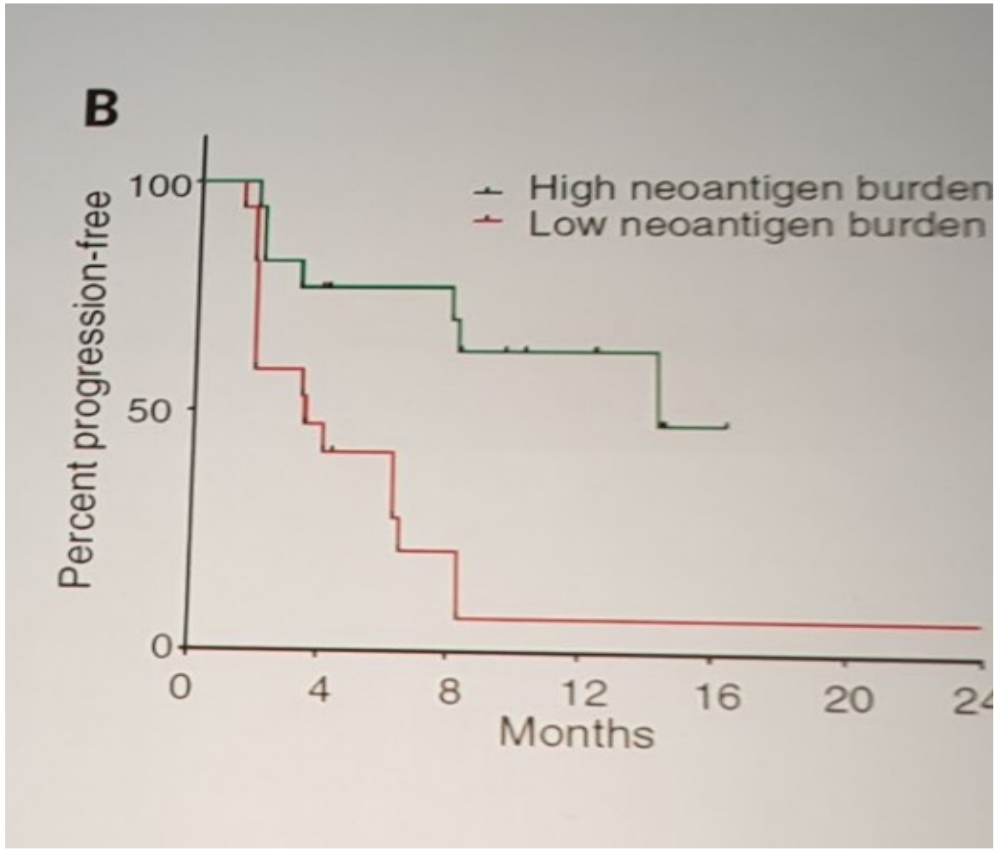


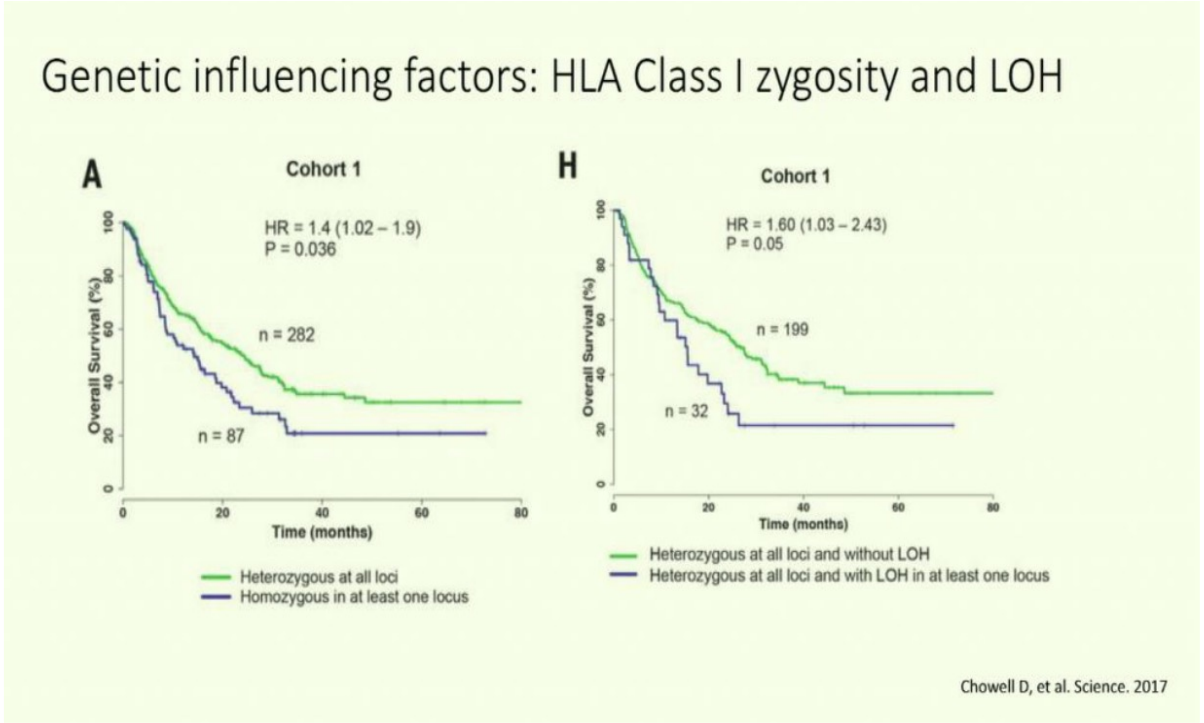
- Non-significant overlap between the bTMB ≥16 and TC3 or IC3 subgroups (Fisher exact test, $P = 0.62$)
  - **19.2%** of tumors with bTMB ≥16 were also TC3 or IC3
  - **29.1%** of tumors with TC3 or IC3 also had bTMB ≥16

	PFS HR (95% CI)	OS HR (95% CI)
bTMB ≥16	0.64 (0.46, 0.91)	0.64 (0.44, 0.93)
TC3 or IC3	0.62 (0.41, 0.93)	0.44 (0.27, 0.71)
bTMB ≥16 and TC3 or IC3	0.38 (0.17, 0.85)	0.23 (0.09, 0.58)

[a] PD-L1 expression was evaluated by immunohistochemistry (IHC) using the VENTANA SP142 assay; TC3 or IC3, ≥50% of TC or ≥10% of IC express PD-L1.
BEP, biomarker-evaluable population; IC, tumor-infiltrating immune cell; TC, tumor cell.

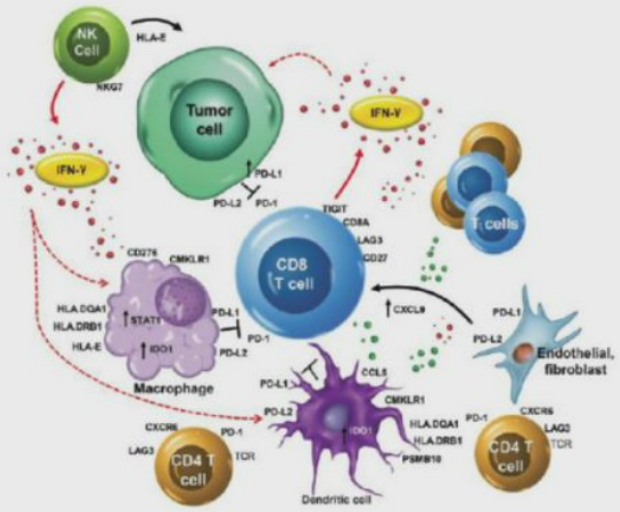
LIMITI DEL TMB :





OLTRE LE MUTAZIONI : L'ESPRESSIONE

An 18 Gene "Interferon" Signature

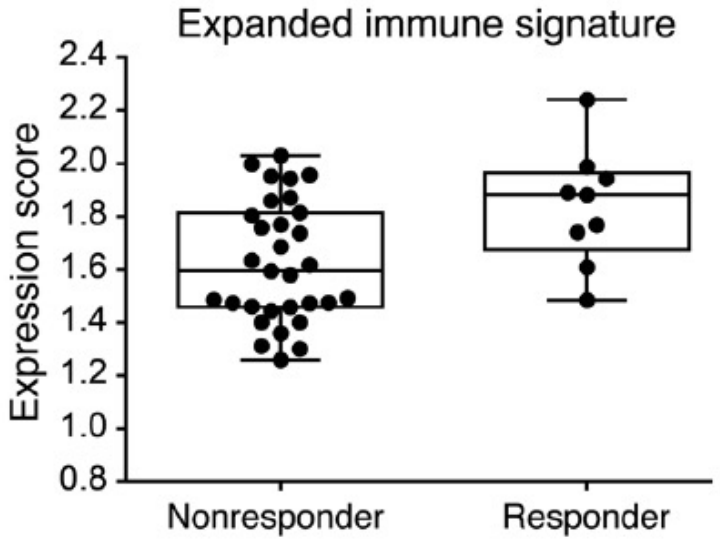


IFNγ Biology	T Cell Exhaustion
CCL5	TIGIT
CXCL9	CD8A
CD27	LAG3
CXCR6	PD-L1
IDO1	PD-L2
STAT1	CD276

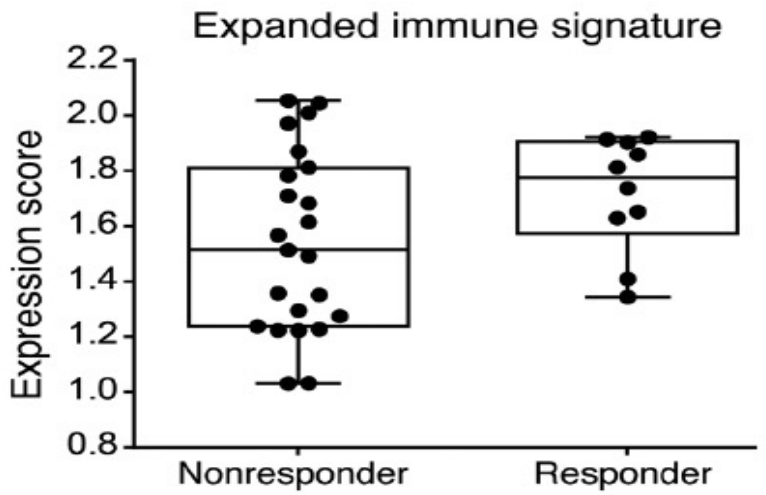
T Cell/NK Signature	Antigen Presenting Cell Signature
HLA-E	PSMB10
NKG7	HLA-DQA1
CMKLR1	HLA-DRB1

ASCO 2016; Poster #1536

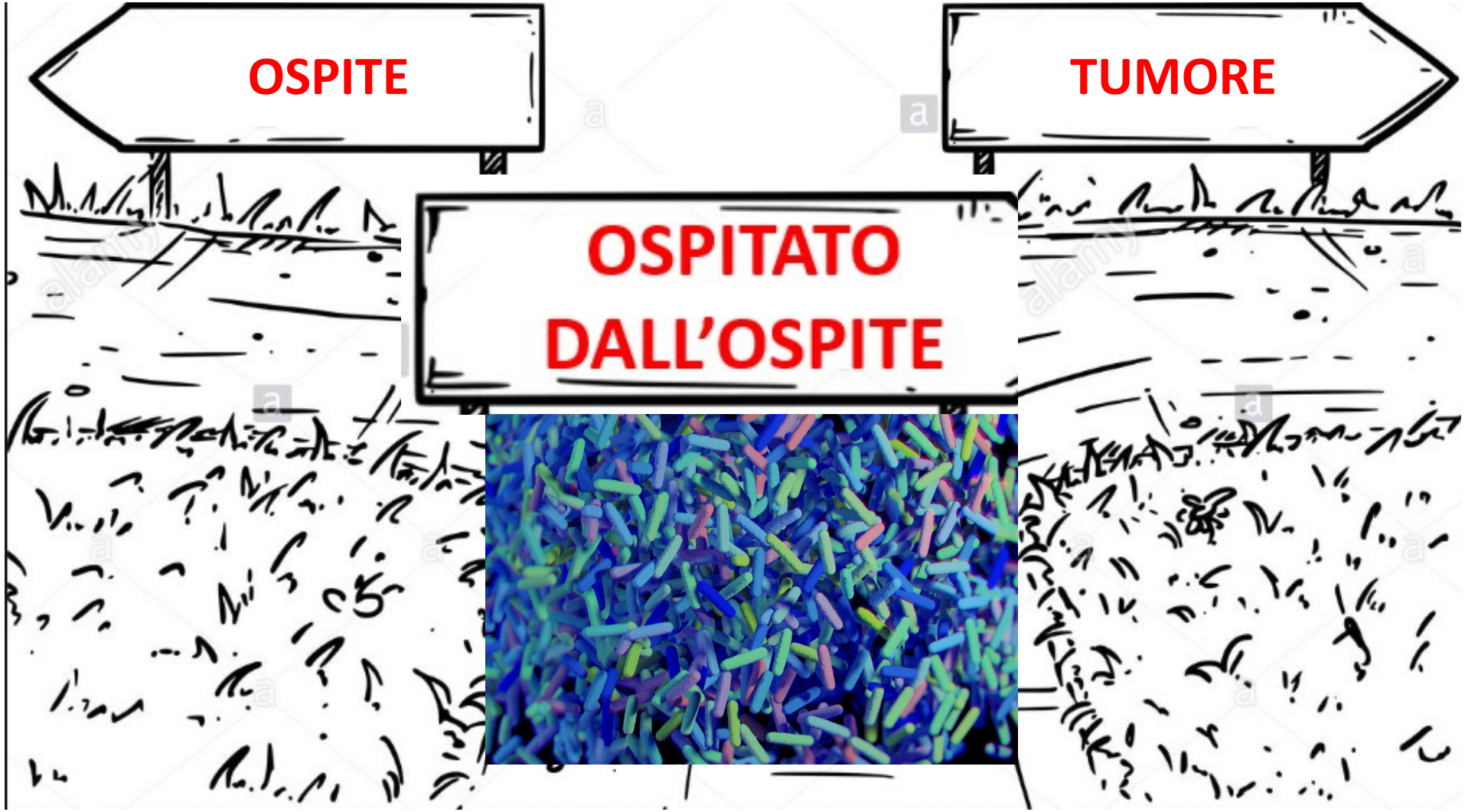
ASCO 2016: Abstract 1536 / Courtesy of Alessandra Cesano



HN



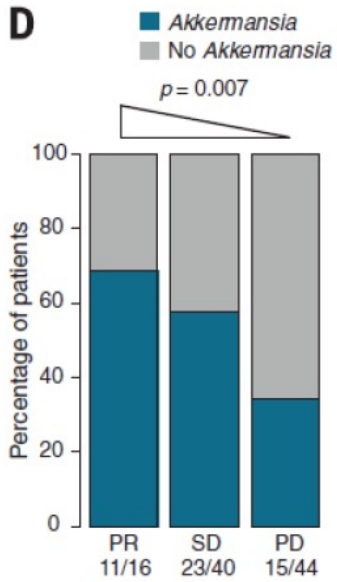
GASTRIC


OSPITE
TUMORE
OSPITATO
DALL'OSPITE

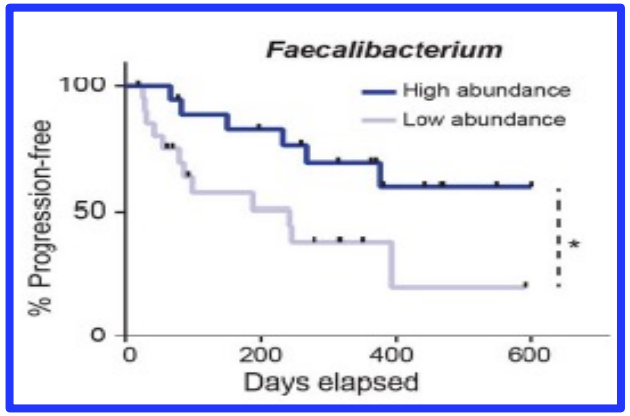
MICROBIOTA E RISPOSTA ALL'IMMUNOTERAPIA

CANCER IMMUNOTHERAPY

Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors



Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients



Routy Science 2018
Gopalakishnan, Science 2018

nature genetics

LETTERS

https://doi.org/10.1038/s41588-018-0135-7

The fecal metabolome as a functional readout of the gut microbiome

…The fecal metabolome provides a functional readout of microbial activity and can be used as an intermediate

phenotype mediating host–microbiome interactions…

Botticelli *et al. J Transl Med* (2020) 18:49
https://doi.org/10.1186/s12967-020-02231-0

Journal of Translational Medicine

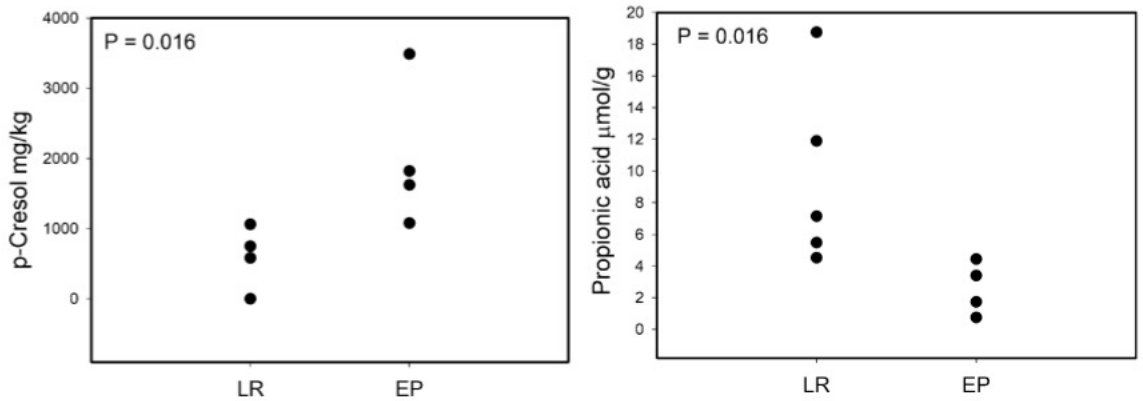
RESEARCH Open Access

Gut metabolomics profiling of non-small cell lung cancer (NSCLC) patients under immunotherapy treatment

Andrea Botticelli[1,2†], Pamela Vernocchi[3†], Federico Marini[4,5], Andrea Quagliariello[3], Bruna Cerbelli[6], Sofia Reddel[3], Federica Del Chierico[3], Francesca Di Pietro[7], Raffaele Giusti[7], Alberta Tomassini[4,5], Ottavia Giampaoli[4], Alfredo Miccheli[5,8], Ilaria Grazia Zizzari[9], Marianna Nuti[9], Lorenza Putignani[10*†] and Paolo Marchetti[1,2,7†]

HIGH ALCOHOLS,ESTERS AND PHENOLS:
Associated with ***fast progressor***

ORGANIC ACID AND SHORT CHAIN FATTY ACIDS:
Associated with ***long term benefit***



GENOMICA

METAGENOMICA

METABOLICA

TRASCRITTOMICA

PROTEOMICA

Cerchiamo biomarkers nella clinica…

www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 59), pp: 99336-99346

Research Paper: Immunology

The sexist behaviour of immune checkpoint inhibitors in cancer therapy?

Andrea Botticelli[1,2], Concetta Elisa Onesti[1,2], Ilaria Zizzari[3], Bruna Cerbelli[4], Paolo Sciattella[5], Mario Occhipinti[1], Michela Roberto[1,2], Francesca Di Pietro[1,2], Adriana Bonifacino[6], Michele Ghidini[7], Patrizia Vici[8], Laura Pizzuti[8], Chiara Napoletano[3], Lidia Strigari[9], Giulia D'Amati[4], Federica Mazzuca[1,2], Marianna Nuti[3] and Paolo Marchetti[1,2]

[1]Medical Oncology Department, Sant'Andrea Hospital, Rome, Italy

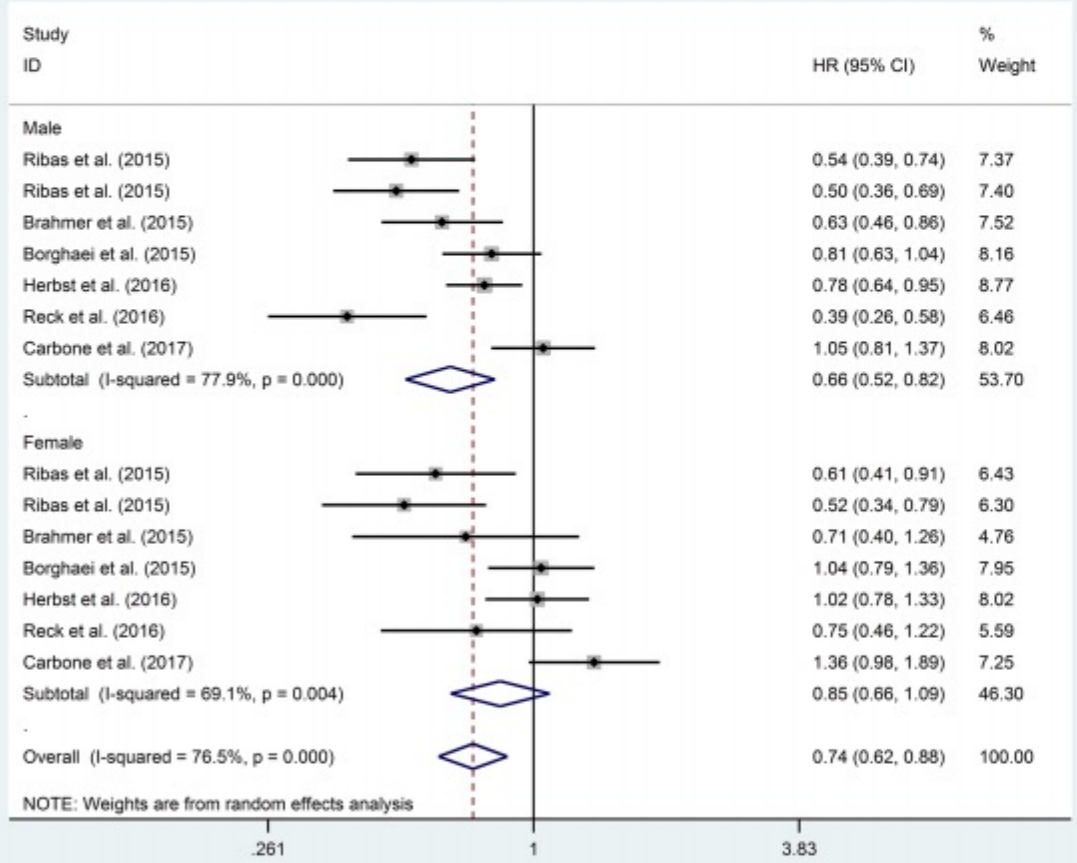


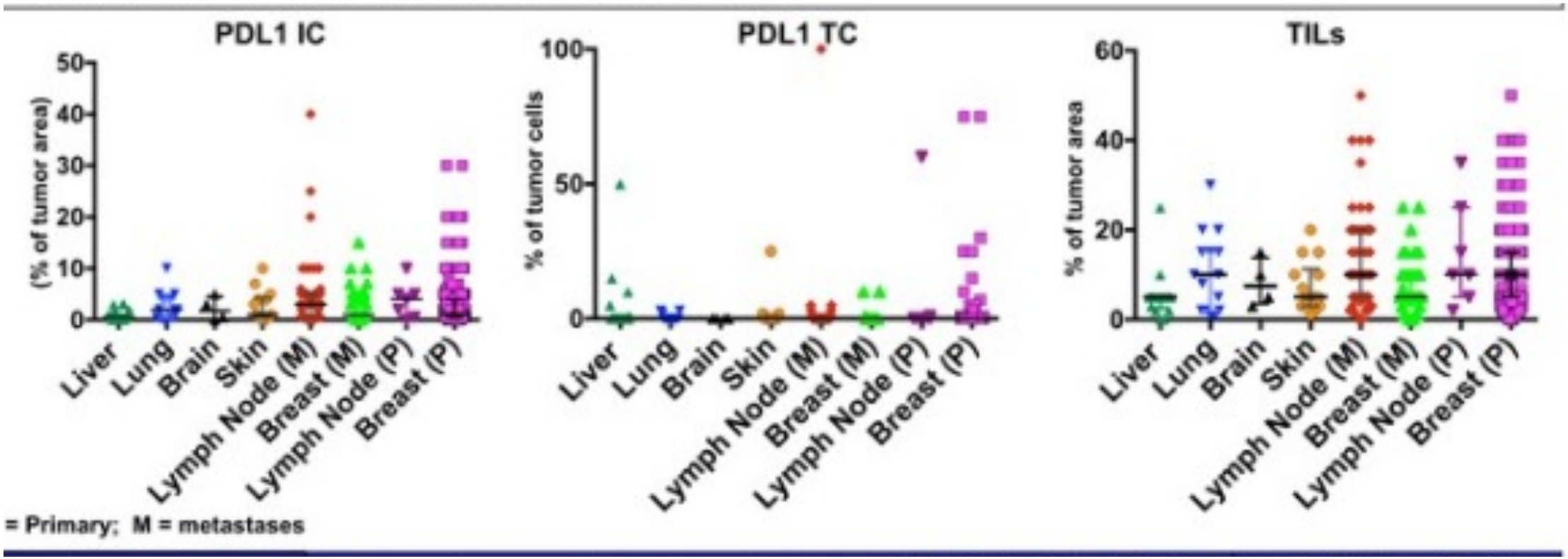
Figure 4: Forest Plot for PFS with anti-PD-1.

DIFFERENZE TRA PRIMITIVO E METASTASI

Prevalence of PDL1 and Tumor Infiltrating Lymphocytes (TILs) in Primary and Metastatic TNBC

Yijin Li, Ching-Wei Chang, David Tran, Mitchell Denkert, Priti Hedge, and Luciana Molinero
Genentech, South San Francisco, California, USA. 94080

Poster PD6-01



Botticelli et al. J Transl Med (2019) 17:99
https://doi.org/10.1186/s12967-019-1847-x

Journal of
Translational Medicine

RESEARCH Open Access

A nomogram to predict survival in non-small cell lung cancer patients treated with nivolumab

Andrea Botticelli[1], Massimiliano Salati[2,3*], Francesca Romana Di Pietro[1], Lidia Strigari[4], Bruna Cerbelli[5], Ilaria Grazia Zizzari[6], Raffaele Giusti[1], Marco Mazzotta[1], Federica Mazzuca[1], Michela Roberto[1], Patrizia Vici[7], Laura Pizzuti[7], Marianna Nuti[6] and Paolo Marchetti[1]

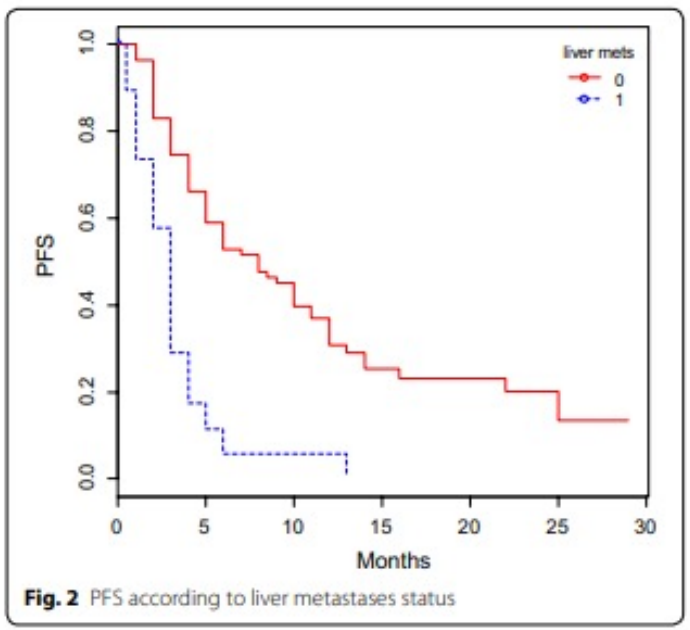


Fig. 2 PFS according to liver metastases status

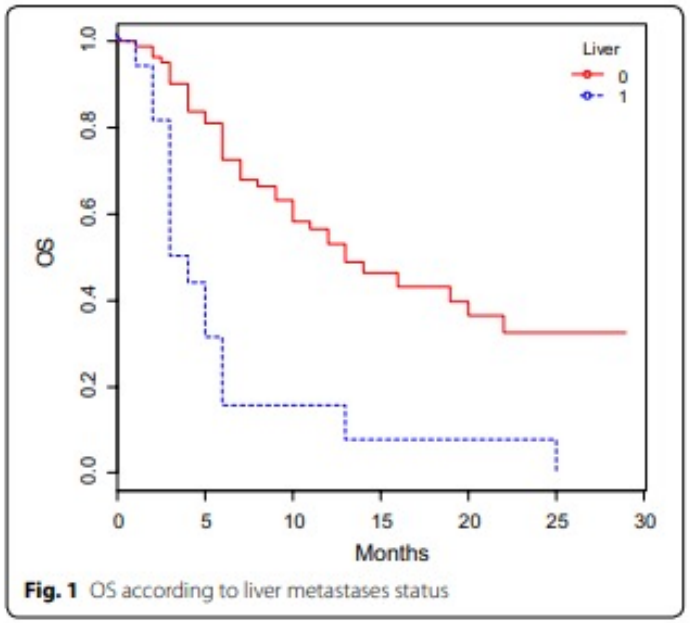


Fig. 1 OS according to liver metastases status

vaccines

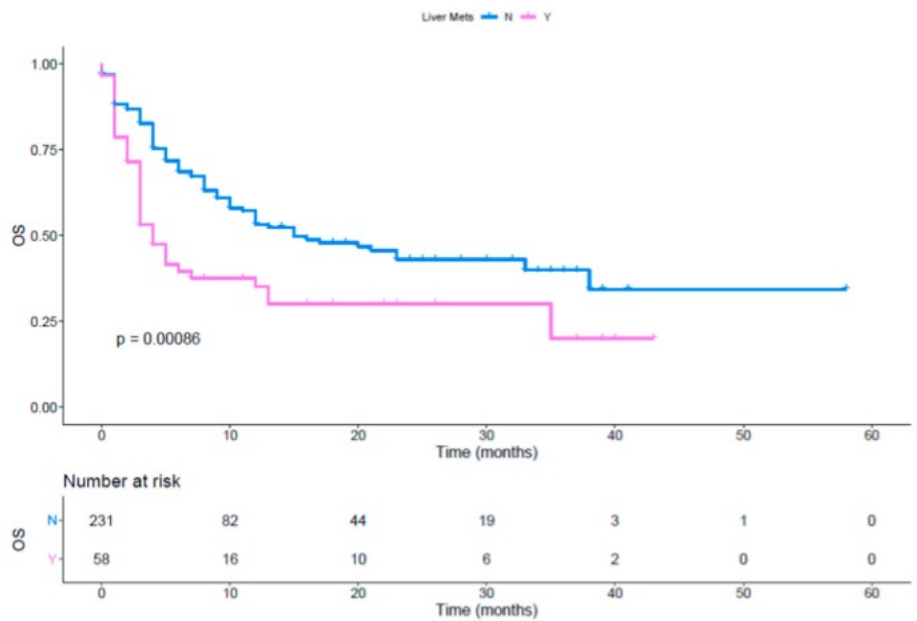
MDPI

Article

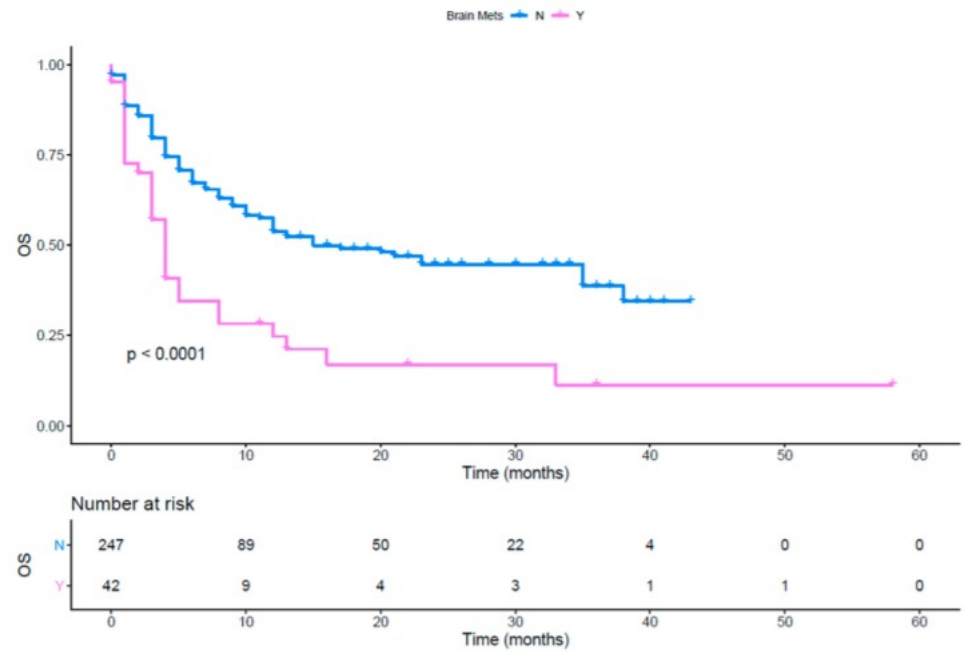
The Agnostic Role of Site of Metastasis in Predicting Outcomes in Cancer Patients Treated with Immunotherapy

Andrea Botticelli [1], Alessio Cirillo [2], Simone Scagnoli [3,*], Bruna Cerbelli [2], Lidia Strigari [4], Alessio Cortellini [5], Laura Pizzuti [5], Patrizia Vici [6], Federica De Galitiis [7], Francesca Romana Di Pietro [7], Edoardo Cerbelli [2], Michele Ghidini [8], Giulia D'Amati [2], Carlo Della Rocca [9], Silvia Mezi [2], Alain Gelibter [2], Raffaele Giusti [10], Enrico Cortesi [2], Paolo Antonio Ascierto [11], Marianna Nuti [12] and Paolo Marchetti [1]

[1] Department of Clinical and molecular oncology, University of Rome "Sapienza", 00185 Rome, Italy;



(a)



(b)

Figure 1. *Cont.*

vaccines

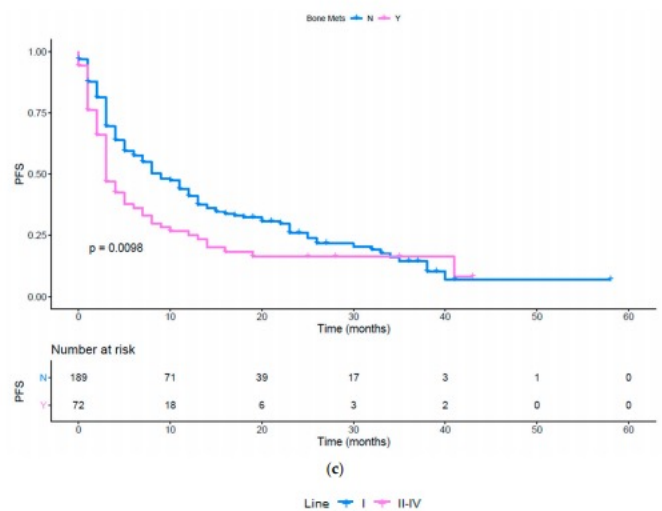
MDPI

Article

The Agnostic Role of Site of Metastasis in Predicting Outcomes in Cancer Patients Treated with Immunotherapy

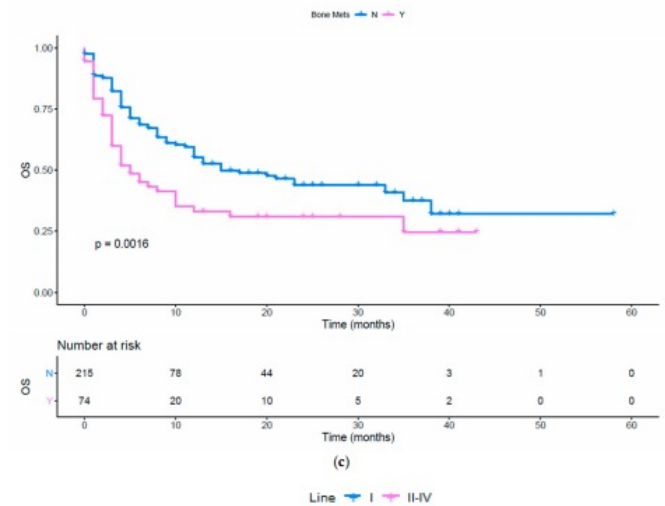
Andrea Botticelli [1], Alessio Cirillo [2], Simone Scagnoli [3,*], Bruna Cerbelli [2], Lidia Strigari [4], Alessio Cortellini [5], Laura Pizzuti [5], Patrizia Vici [6], Federica De Galitiis [7], Francesca Romana Di Pietro [7], Edoardo Cerbelli [2], Michele Ghidini [8], Giulia D'Amati [2], Carlo Della Rocca [9], Silvia Mezi [2], Alain Gelibter [2], Raffaele Giusti [10], Enrico Cortesi [2], Paolo Antonio Ascierto [11], Marianna Nuti [12] and Paolo Marchetti [1]

[1] Department of Clinical and molecular oncology, University of Rome "Sapienza", 00185 Rome, Italy;



(c)

Line I II-IV



(c)

Line I II-IV

La nicchia e la MDSC

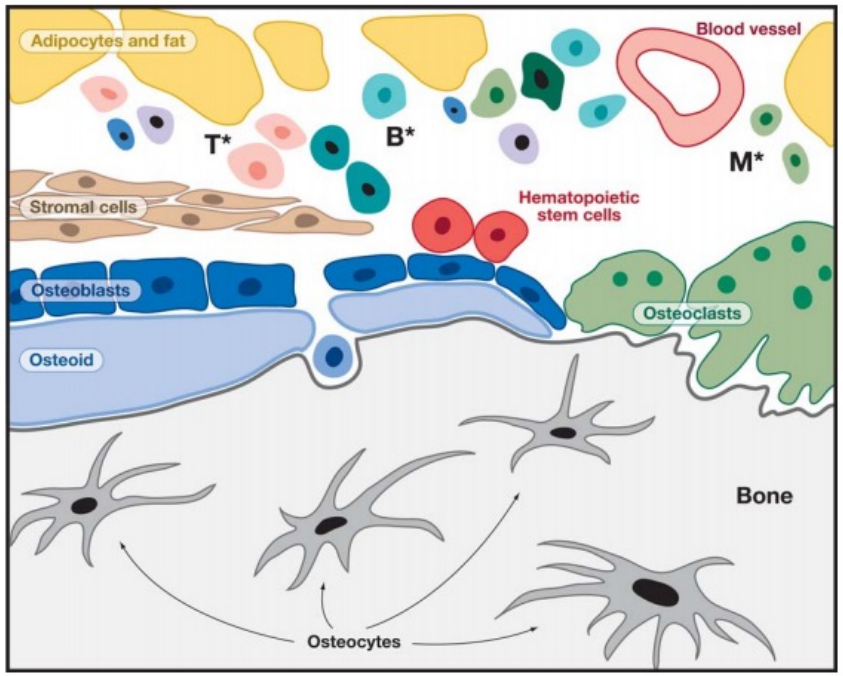


Figure 1

Schematic diagram of the bone microenvironment as a loosely compartmentalized lymphoid organ: T* (memory T cells and circulating T cells), B* (B cells, differentiation of which occurs via interaction with stromal cells; memory B cells also interact with stromal cells; in addition, there are circulating mature B cells), stromal cells (bone marrow stromal cells are of mesenchymal origin, but not fully characterized), M* (monocyte and its derivatives), and osteoid [newly formed, but not yet calcified matrix, composed mostly of type I collagen (~90%) and noncollagenous proteins (~10%)].

Review Article

The Impact of Immune System in Regulating Bone Metastasis Formation by Osteotropic Tumors

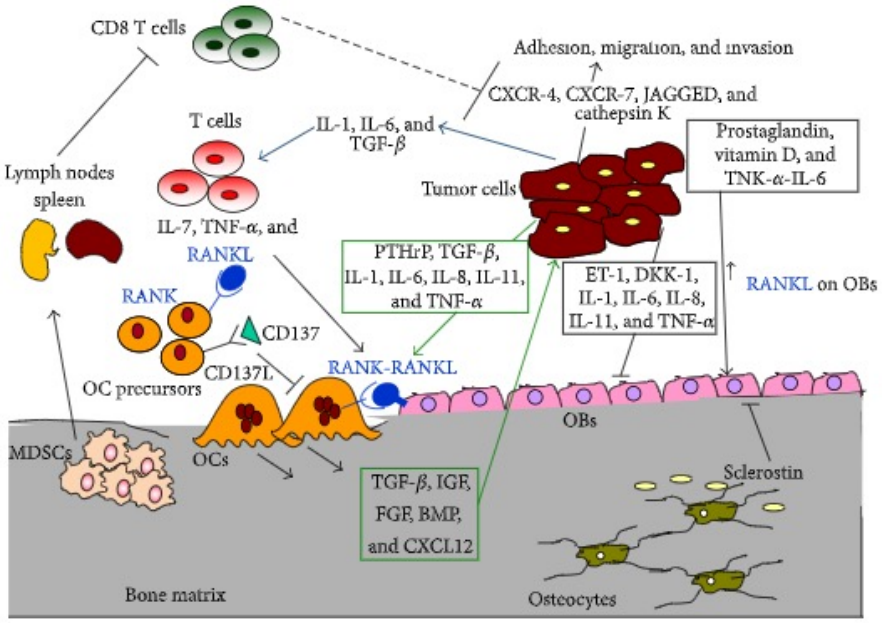


Figure 1

Interactions among bone, immune, and tumor cells sustain the vicious cycle of bone metastasis. Tumor cells release cytokines that activate T cells to produce proosteoclastogenic factors, such as RANKL, which activate OCs. In turn, the release of bone matrix growth factors during bone resorption enhances the tumor growth. MDSCs originate from BM and migrate to secondary lymphoid organs where they inhibit the antitumor immune response mediated by CD8 T cells. Consequently, the increased tumor growth induces the production of osteolytic factors which activates the OCs, the cells responsible for bone destruction.

OSTEOIMMUNOLOGIA

frontiers in Immunology

REVIEW
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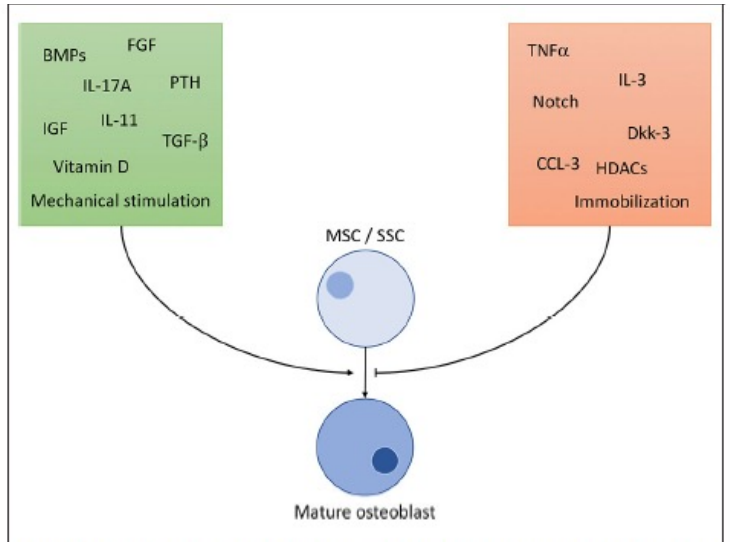
Osteoimmunology: A Current Update of the Interplay Between Bone and the Immune System

*Christian Guder[1], Sascha Gravius[1,2], Christof Burger[1], Dieter C. Wirtz[1] and Frank A. Schildberg[1]**

[1] Clinic for Orthopedics and Trauma Surgery, University Hospital Bonn, Bonn, Germany, [2] Department of Orthopedics and Trauma Surgery, University Medical Center Mannheim of University Heidelberg, Mannheim, Germany



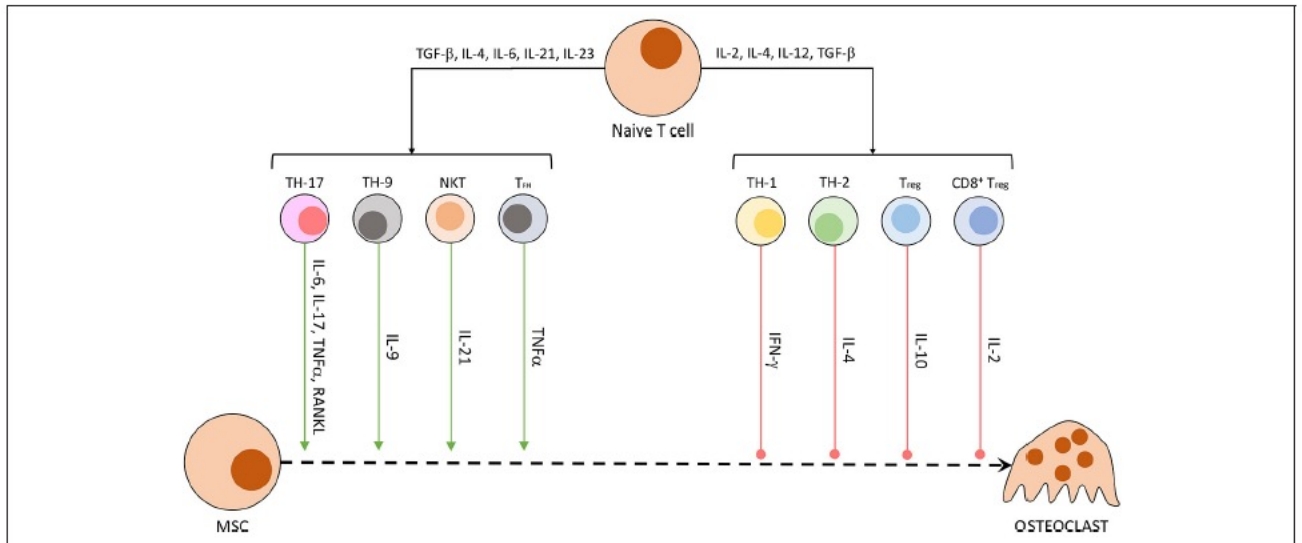
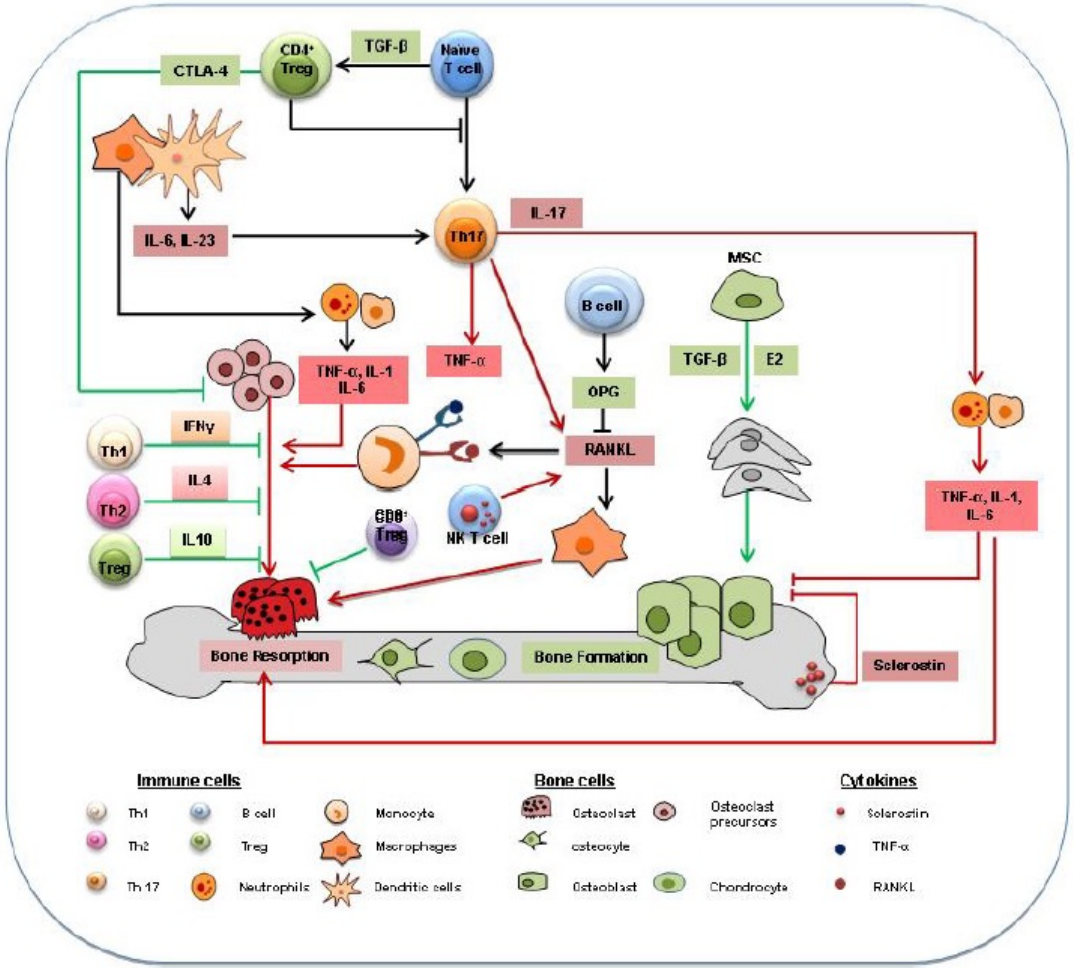


FIGURE 3 | Secreted T cell factors modulating osteoclastogenesis. Naïve T cells undergo differentiation in dependency of exposed factors. A mix of pro-inflammatory and anti-inflammatory conditions leads to the development of differentiated T cell subtypes. These specialized cells then produce a characteristic fingerprint of soluble molecules, which induce or hamper OC development and activity.

UN COMPLESSO NETWORK

Interplay between Bone and Immune system



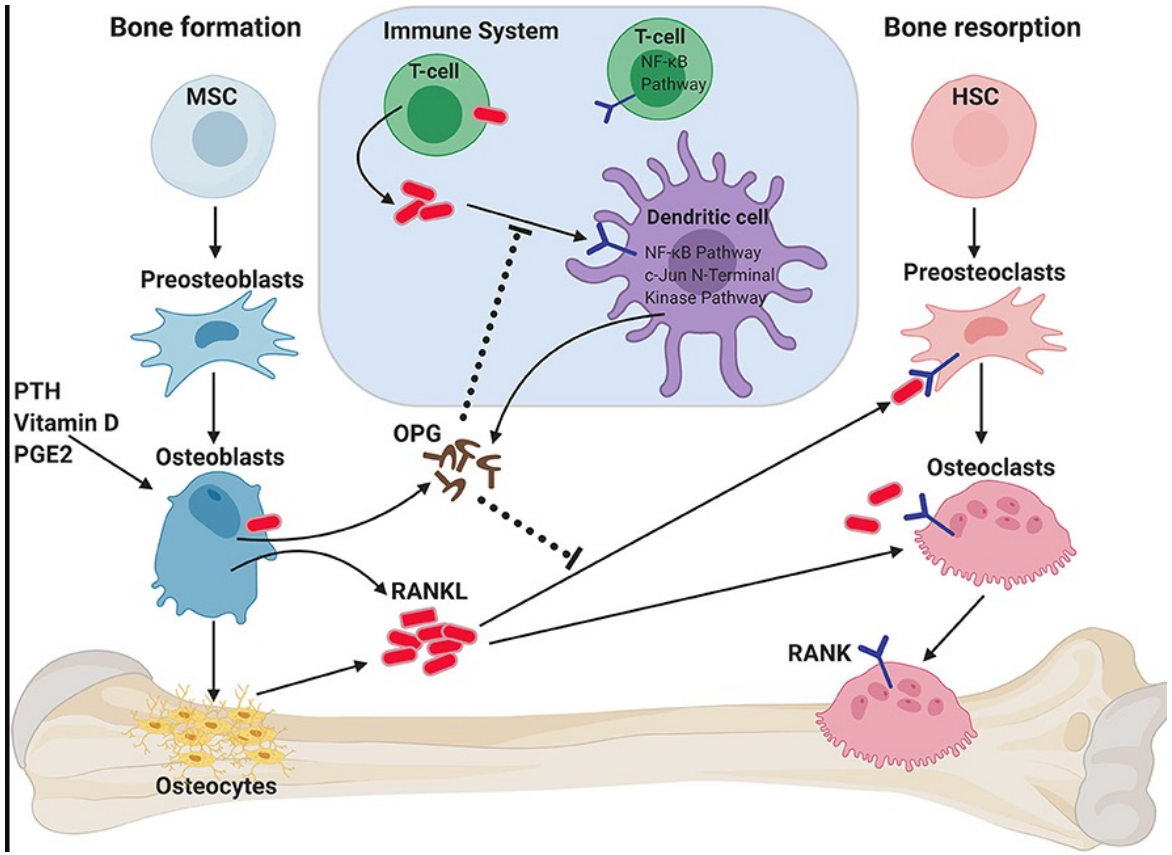
Interplay between Bone and Immune system

Table 1. Role of cytokines/factors in Osteoimmune system

Cytokine	Source	Effect on OCs	Effect on immunity	Function in bone Homeostasis	Ref.
IL-1	Macrophage and DCs	OC↑	Pro-inflammation	Directly activates RANK signaling to promote osteoclastogenesis	(51)
IL-3	Activated T cells	OB↑	Blocks RANKL induced osteoclast	Inhibits osteoclastogenesis	(60, 199–202)
IL-4	Th2	OC↓	Humoral Immunity	Inhibits osteoclastogenesis	(201)
IL-6	Macrophage, DCs	OC↑	Pro-inflammation, Th17 induction	Activation of osteoclastogenesis	(203)
IL-7	BMSC	OC↑	Promotion of T/B cell development	B cell development	(80)
IL-10	Treg	OC↓	Anti-inflammation	Suppress bone resorption	(58)
IL-17	T cells	OC↑	Pro-inflammatory cytokine	RANKL expression and vigorous pro-inflammatory potency	(2)
IL-18	Macrophage	OC↓	Th1 differentiation, IFN-γ Induction	Inhibits TNF-α mediated osteoclast formation in a T cell independent manner	(204)
IL-23	Macrophage and DCs	OC↑	Th17 induction	Indirect osteoclast activation	(135)
IL-27	Macrophage and DCs	OC↓	Th1and Treg↑; Th17 induction	Inhibits osteoclast formation, blocking RANK dependent osteoclastogenesis	(205)
GM-CSF	Th1	OC↓	Pro-inflammation	Inhibits osteoclastogenesis	(52)
IFN- γ	Th1, NK cells	OC↓	Cellular immunity	Inhibits osteoclastogenesis	(203)
OPG	Osteoclasts	OC↓	Decoy receptor for RANKL	Inhibits osteoclastogenesis	(46)
RANK	Osteoclasts, DCs	OC↑	DCs activation	Osteoclast differentiation and activation	(52)
RANKL	Osteoblast, Th cells	OC↑	DCs maturation and osteoclast differentiation	Direct osteoclast activation through RANK	(206)
TNF-α	Th17, Macrophage DCs	OC↑	Pro-inflammatory cytokine	Indirect osteoclastic activation through RANKL	(206)
TGF-β	Multiple cell lines	OC↑	Blocks activation of lymphocytes and monocytes derived phagocytosis	Indirect osteoclast activation, Inhibits osteoblast differentiation	(52, 207)

Abbreviations: IL: Interleukin; OC: osteoclast; OB: Osteoblast; DCs: Dendritic Cell (s); RANK: Receptor activator for nuclear factor κB; RANKL: Receptor activator for nuclear factor κB ligand; IFN-γ: Interferon-γ; BMSC: Bone marrow stromal cells; TNF-α: Tumor necrosis factor; TGF-β: Transforming growth factor; GMCSF: Granulocyte macrophage colony stimulating factor; OPG: Osteoprotegerin; NK cells: Natural killer cells.

RUOLO CENTRALE DI RANK/RANKL



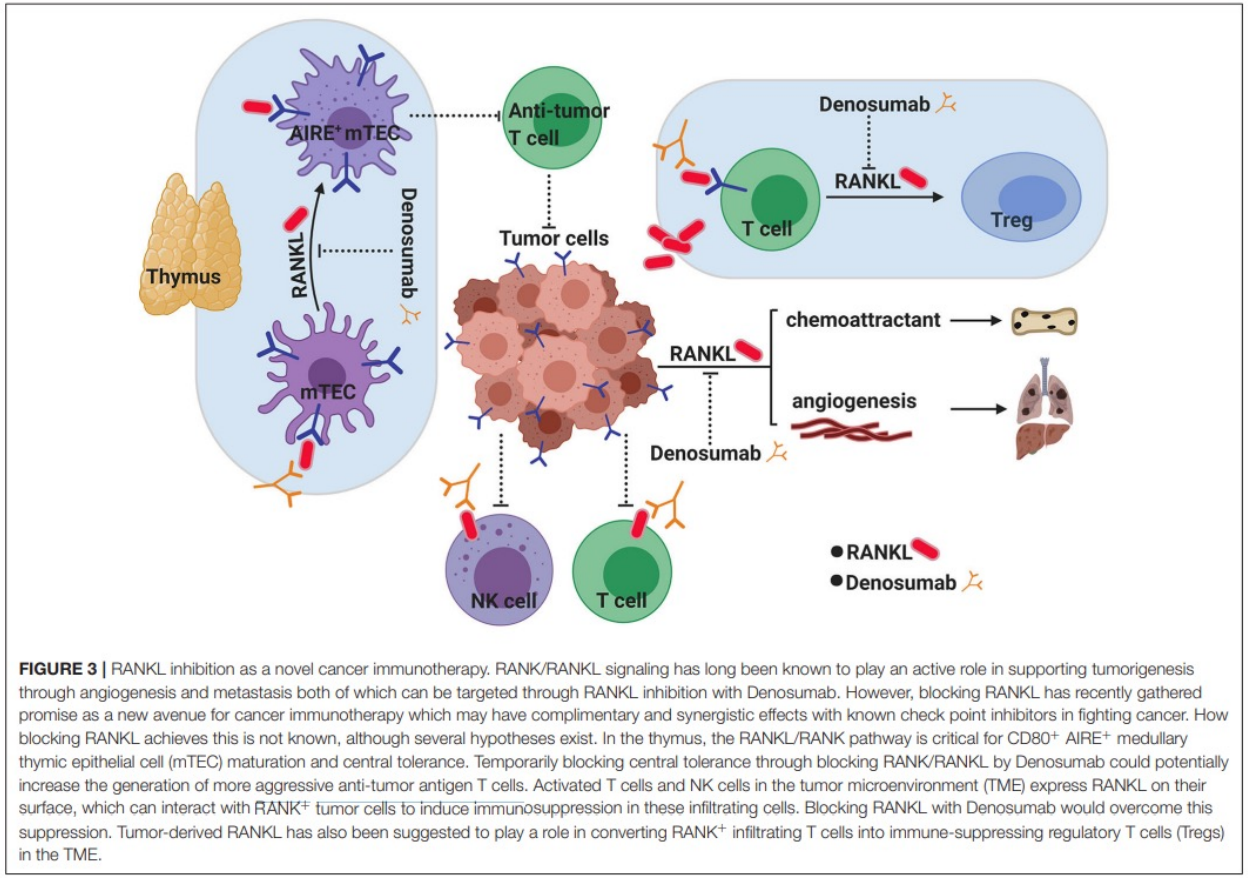
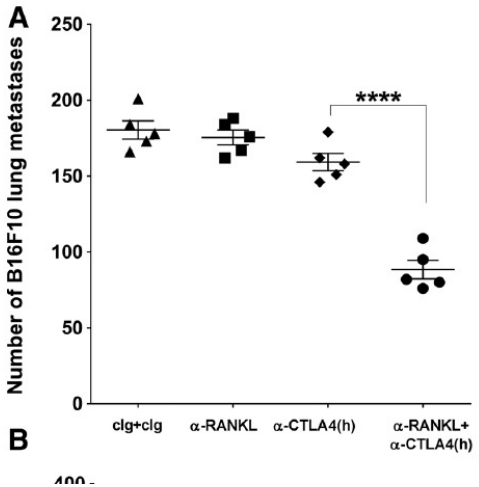


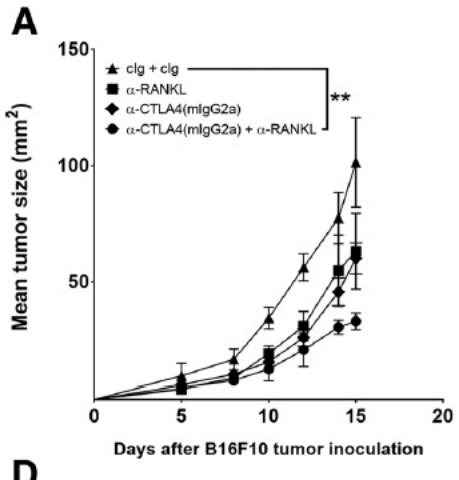
FIGURE 3 | RANKL inhibition as a novel cancer immunotherapy. RANK/RANKL signaling has long been known to play an active role in supporting tumorigenesis through angiogenesis and metastasis both of which can be targeted through RANKL inhibition with Denosumab. However, blocking RANKL has recently gathered promise as a new avenue for cancer immunotherapy which may have complimentary and synergistic effects with known check point inhibitors in fighting cancer. How blocking RANKL achieves this is not known, although several hypotheses exist. In the thymus, the RANKL/RANK pathway is critical for $CD80^+$ $AIRE^+$ medullary thymic epithelial cell (mTEC) maturation and central tolerance. Temporarily blocking central tolerance through blocking RANK/RANKL by Denosumab could potentially increase the generation of more aggressive anti-tumor antigen T cells. Activated T cells and NK cells in the tumor microenvironment (TME) express RANKL on their surface, which can interact with $RANK^+$ tumor cells to induce immunosuppression in these infiltrating cells. Blocking RANKL with Denosumab would overcome this suppression. Tumor-derived RANKL has also been suggested to play a role in converting $RANK^+$ infiltrating T cells into immune-suppressing regulatory T cells (Tregs) in the TME.

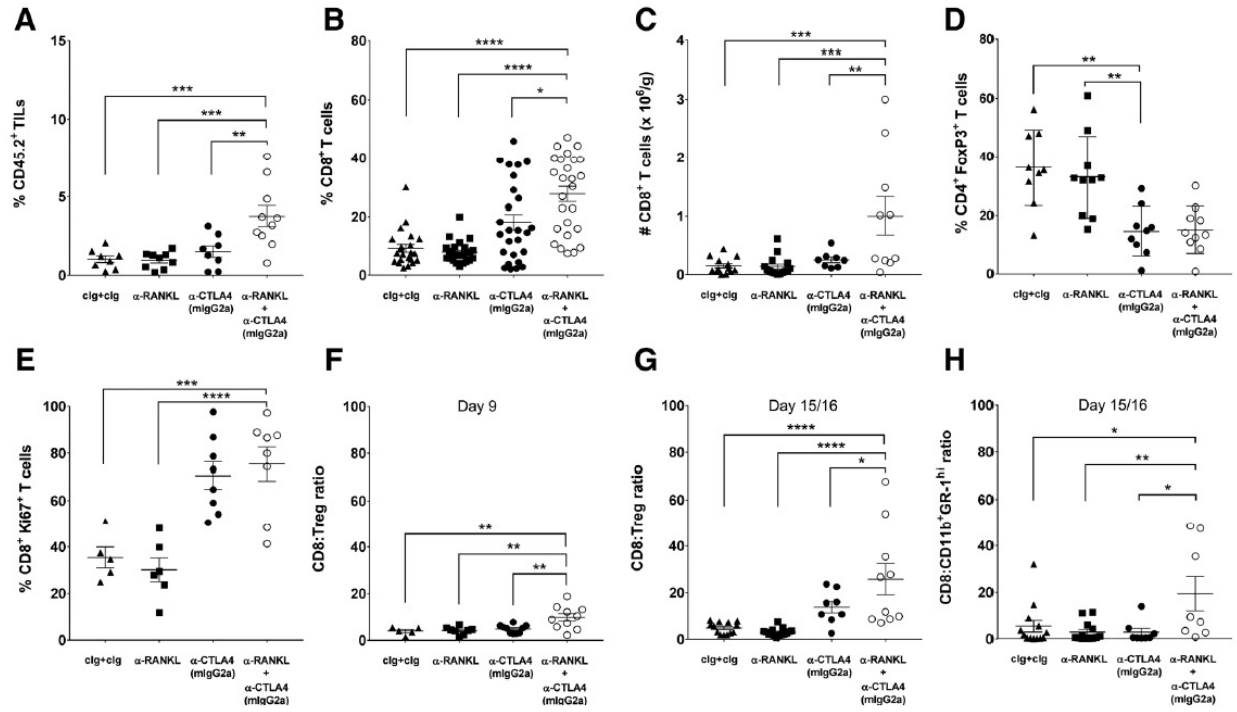
Clinical Cancer Research

Co-administration of RANKL and CTLA4 Antibodies Enhances Lymphocyte-Mediated Antitumor Immunity in Mice

Elizabeth Ahern[1,2,3,4], Heidi Harjunpää[2,3], Deborah Barkauskas[1], Stacey Allen[2], Kazuyoshi Takeda[5], Hideo Yagita[6], David Wyld[3,4], William C. Dougall[1,3], Michele W.L. Teng[2,3], and Mark J. Smyth[1,3]







IL DISEGNO DI UN NUOVO ASSE …

Calcif Tissue Int
DOI 10.1007/s00223-017-0331-y

REVIEW

Gut Microbiota, Immune System, and Bone

P. D'Amelio[1] · F. Sassi[1]

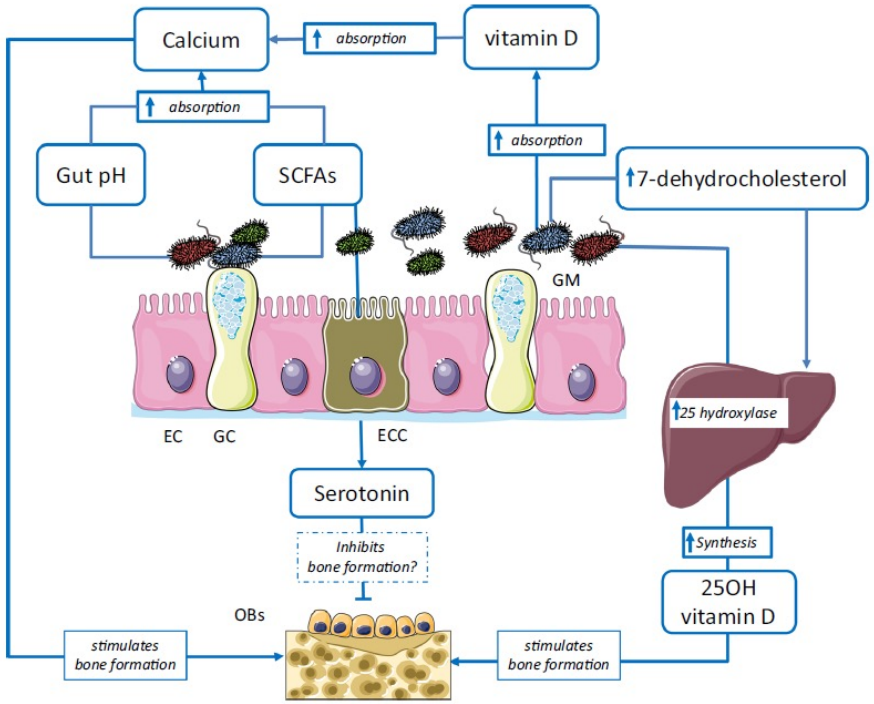


Fig. 3 The link between gut microbiota and bone turnover beyond immune system. *GM* gut microbiota, *EC* enteral cells, *ECC* enterochromaffin cells, *OBs* osteoblasts

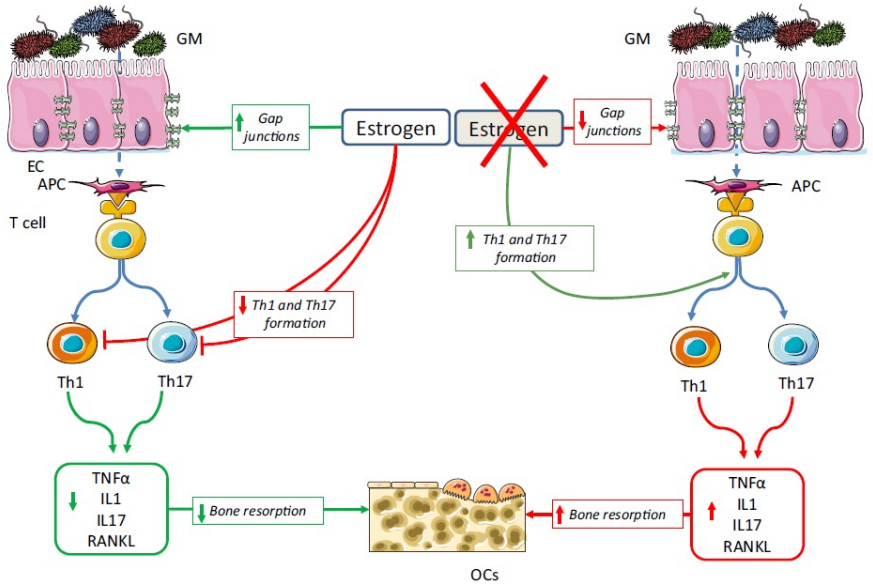


Fig. 2 The complex relationships between immune system, estrogen deficiency-bone loss, and gut microbiota: enteral barrier integrity, cytokine production, immune, and bone cells are involved. *GM* gut microbiota, *EC* enteral cells, *APC* antigen-presenting cells, *Treg* T regulatory cells, *Th1* T helper-1, *Th17* T helper-17 cells, *OBs* osteoblasts, *OCs* osteoclasts

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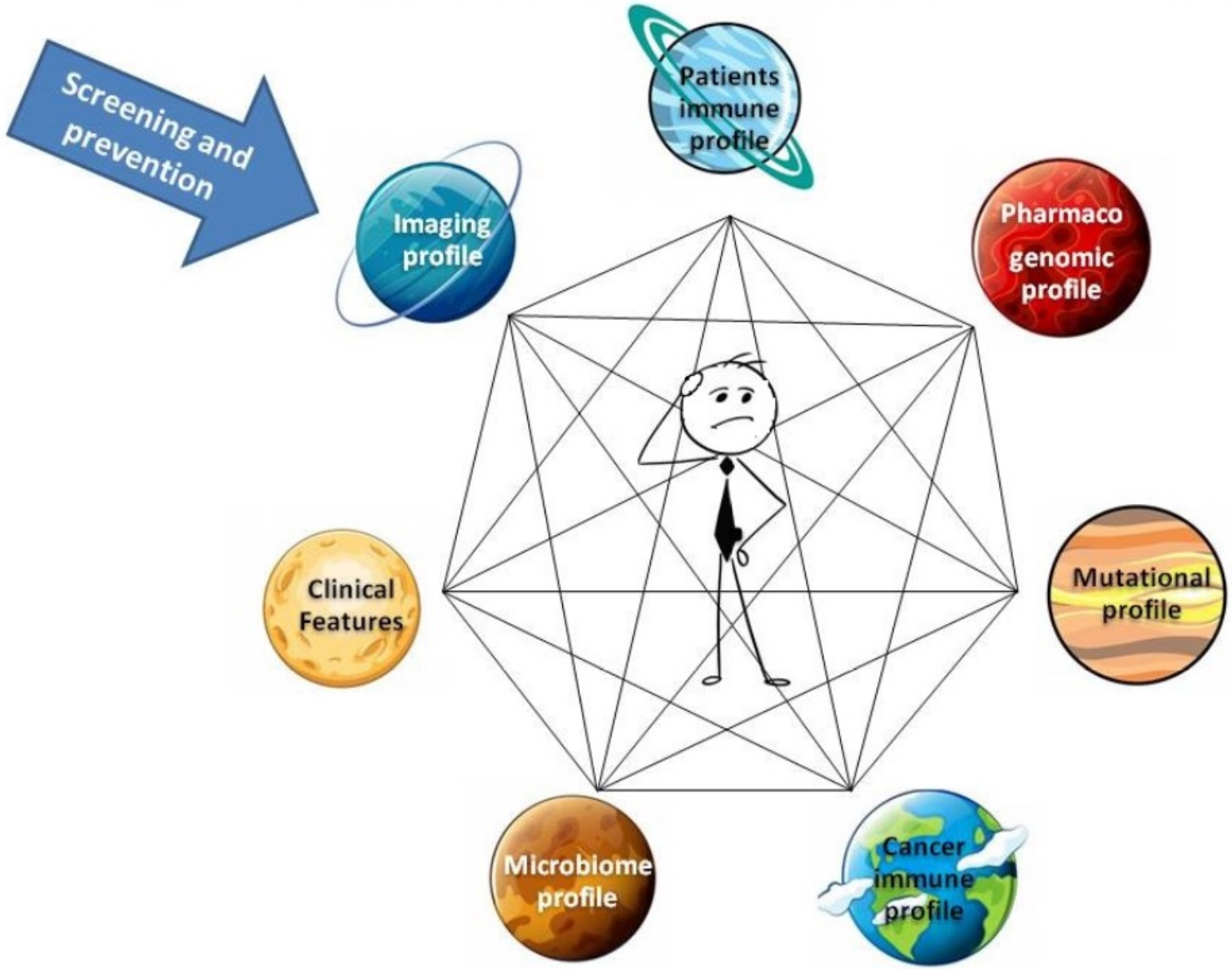
Comprehensive cancer profile in head and neck cancer

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