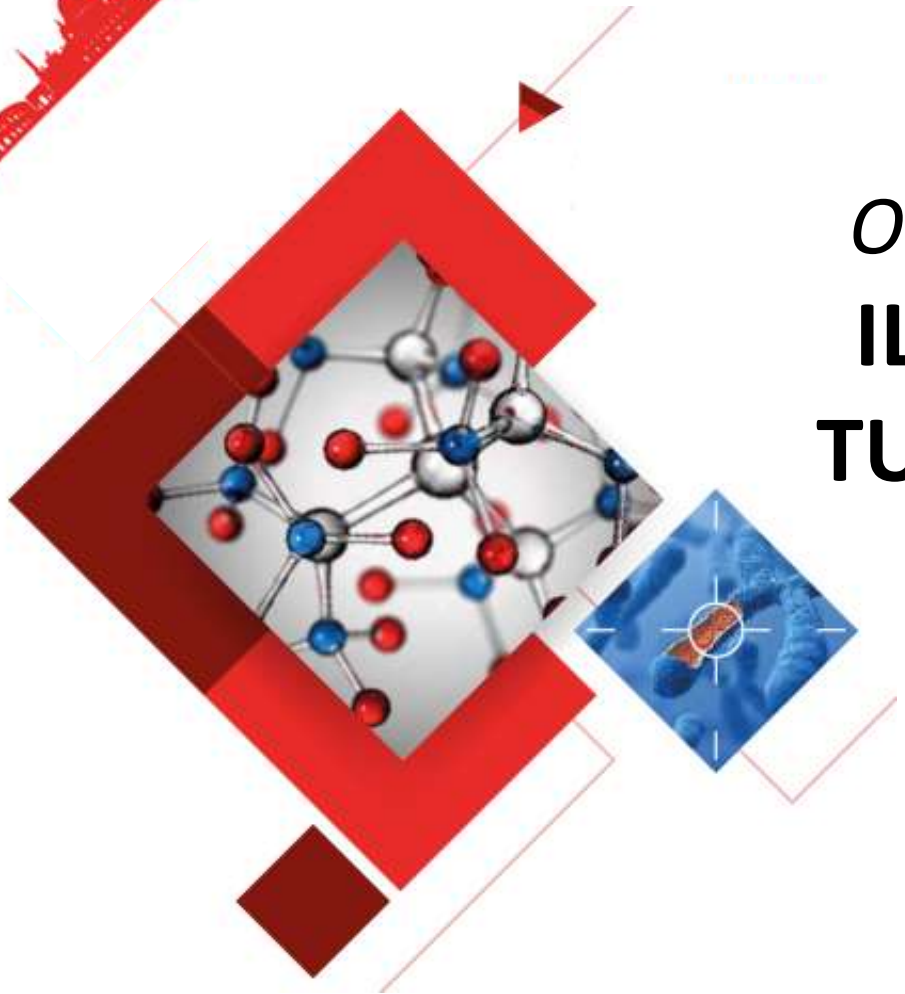


Oncologia di precisione

IL MICROAMBIENTE TUMORALE E I NUOVI FARMACI

Roma, 24 maggio 2019

Francesco Cognetti

Vanja Vaccaro

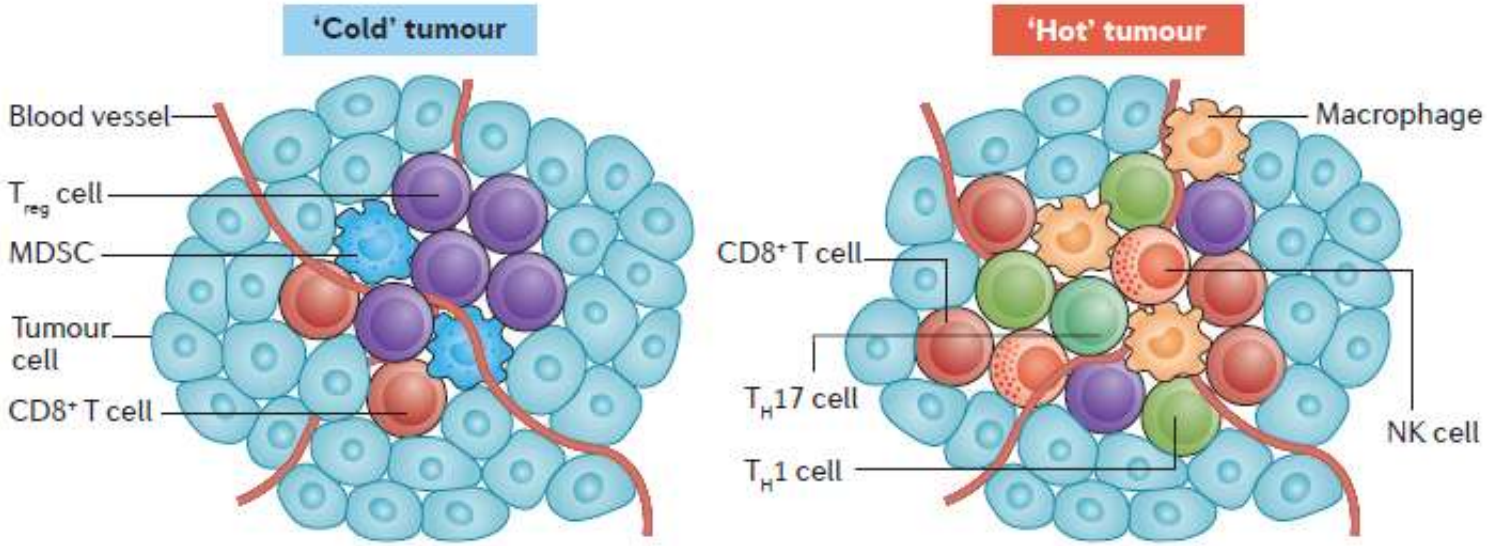
ICBs & TME

- ICBs have **improved outcomes** in solid tumors
- These therapies have **failed to produce universal durable responses**
- Serious and sometimes life-threatening **irAEs**, can result following immune activation
- Cancers with lower mutational burdens and antigen loads are generally less likely to respond to immunotherapies
- Other **inherent and adaptive resistance mechanisms may be responsible for mediating the response to ICBs**
- Successes and failures of ICBs in solid tumors are considerably dictated by the **abnormal and immunosuppressive TME**

TUMOR MICROENVIRONMENT

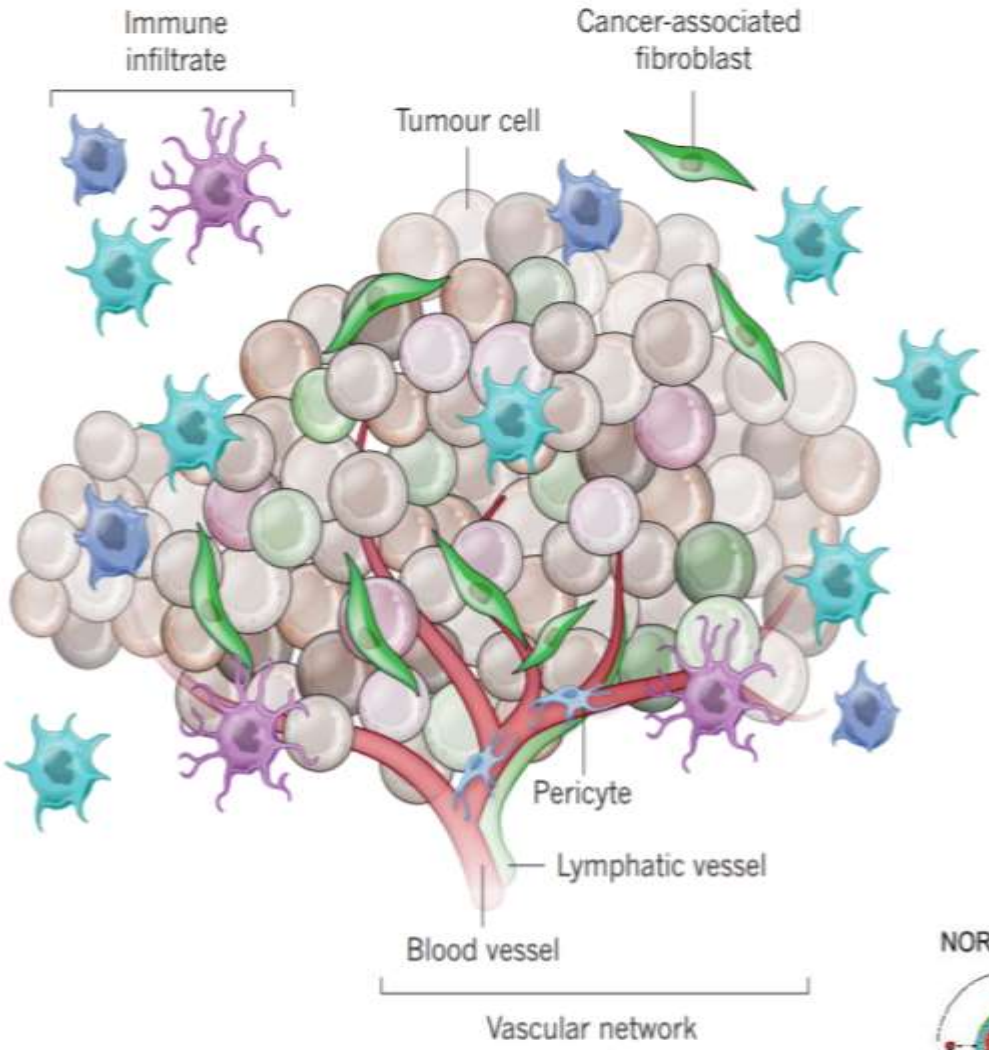
- TME comprises **stromal and immune cells, extracellular matrix molecules, and blood and lymphatic vessels**
- This complex, interactive, and highly dynamic tissue assembly cooperates to antitumor immunity and immunotherapy efficacy by a variety of mechanisms:
  - dense stromal network with increased **mechanical forces**
  - leaky and compressed blood and lymphatic vessels promote **hypoperfusion**
  - The resulting **hypoxic and acidic TME** supports resident and infiltrating **immunosuppressive cells**, induces immune checkpoint expression, and facilitates the **exclusion and exhaustion (dysfunction) of CTLs**

Tumors: «Inflamed» / «not inflamed» phnotypes

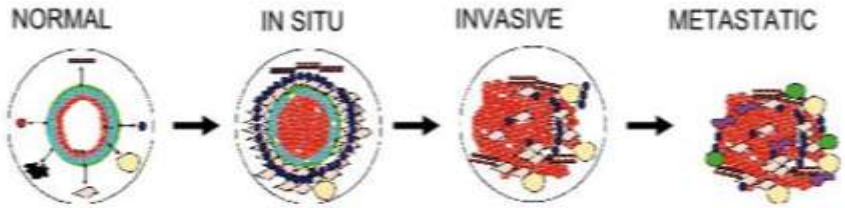


Biological characteristics	• Epigenetic silencing • Active β-catenin signalling • Mesenchymal-like cells • Stem cell-like cells • Less-differentiated cells	• Epigenetic reprogramming • Suppressed β-catenin signalling • Epithelial cells • Highly differentiated cells • High PDL1 expression
Immunological characteristics	• Enriched in immunosuppressive cytokines • High numbers of T_{reg} cells and MDSCs • Few T_H1 cells, NK cells and $CD8^+$ T cells • Few functional APCs	• Enriched in T_H1-type chemokines • High numbers of effector immune cells (T_H1 cells, NK cells and $CD8^+$ T cells) • High numbers of functional APCs

MICROAMBIENTE: un sistema complesso



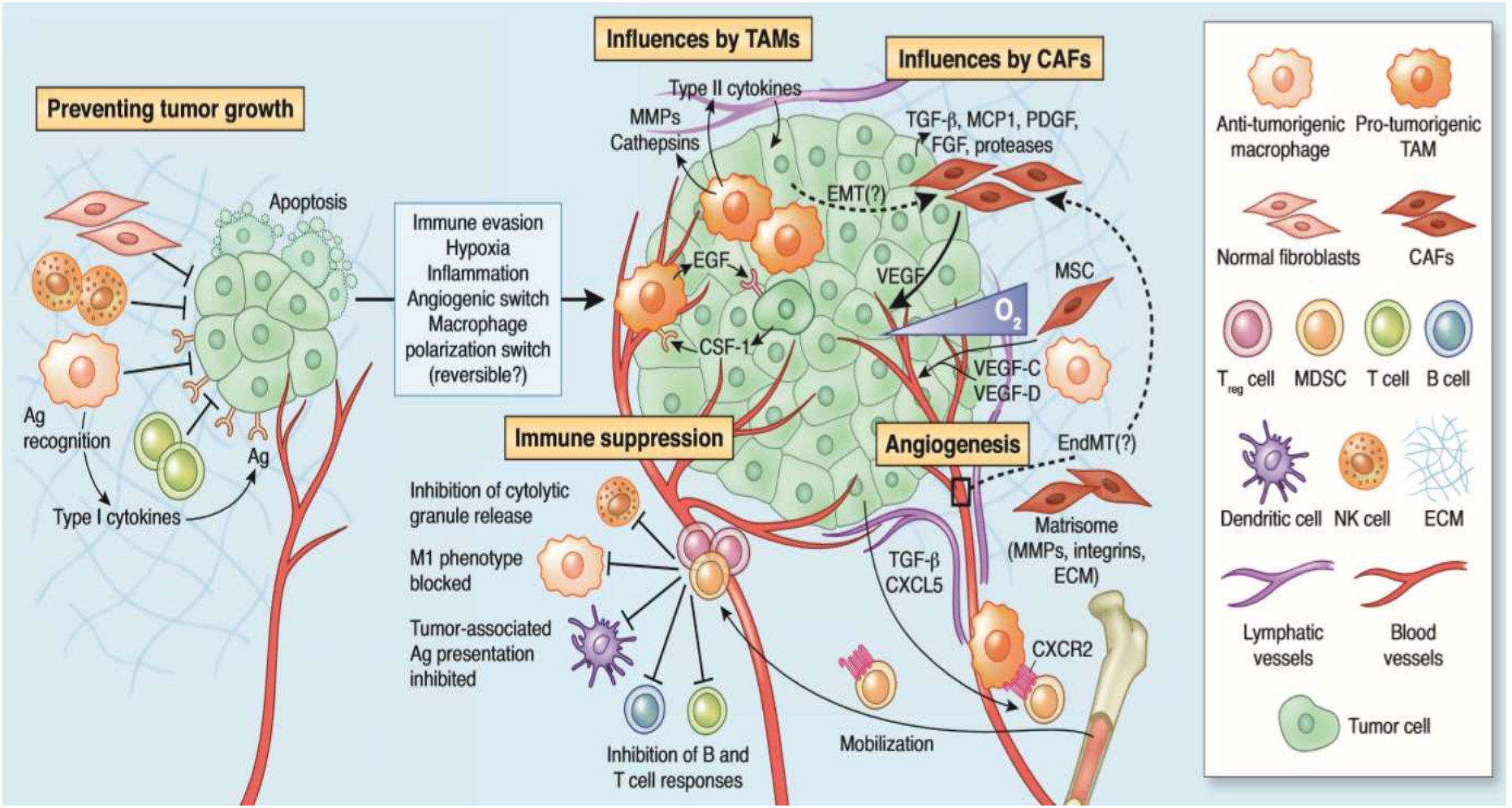
- Ha un ruolo nelle fasi iniziali di sviluppo del tumore
- Regola la crescita del tumore, la differenziazione, la polarità, l'invasione, la metastatizzazione, l'angiogenesi e la risposta ai trattamenti
- È un potenziale biomarker diagnostico, prognostico e predittivo
- È un potenziale target terapeutico



Juntilla et al; Nature 2013

SABCS 2018

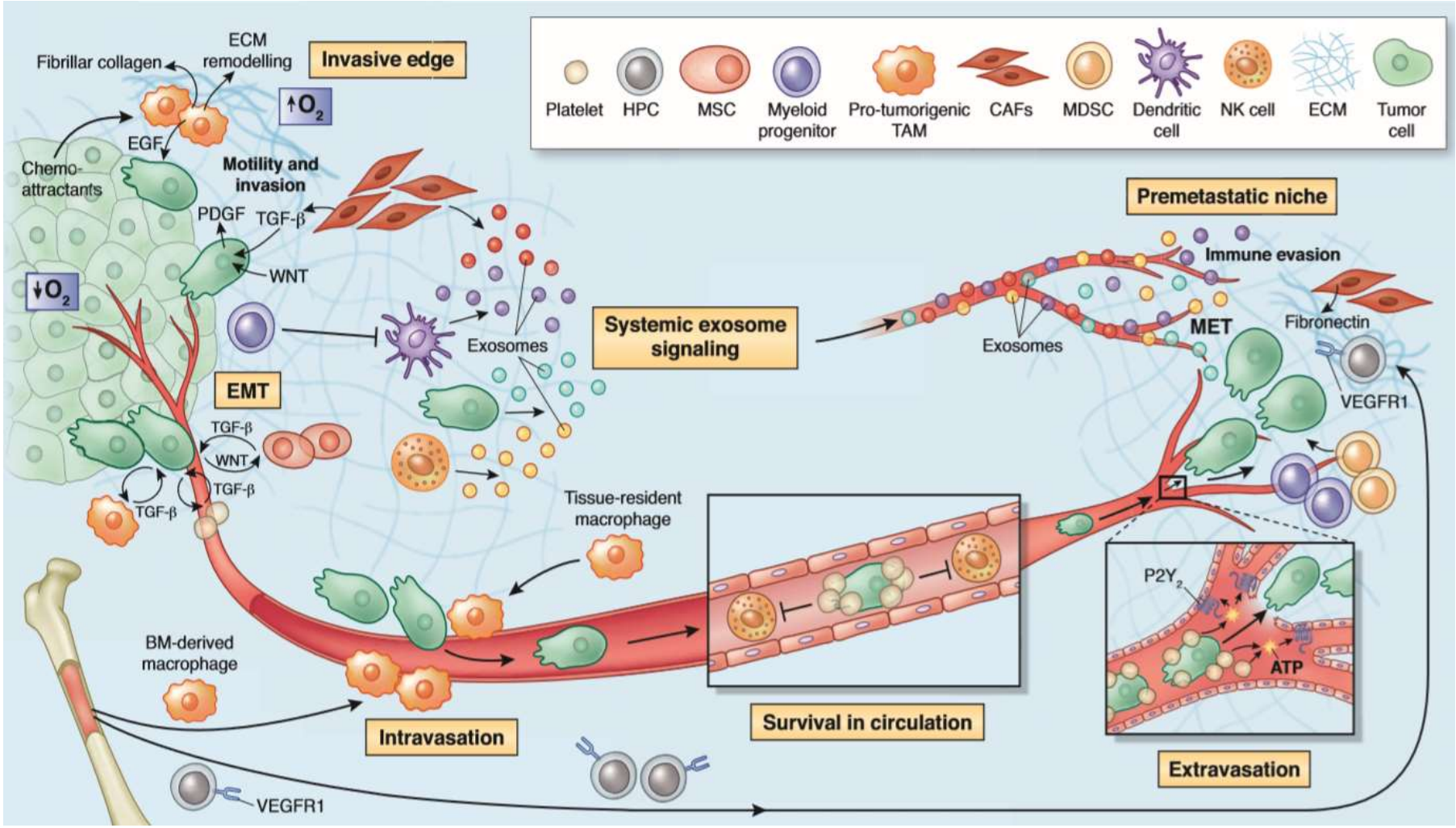
MICROAMBIEMTE: ruolo nelle fasi iniziali



EQUILIBRIUM → PROMOTING/ESCAPE

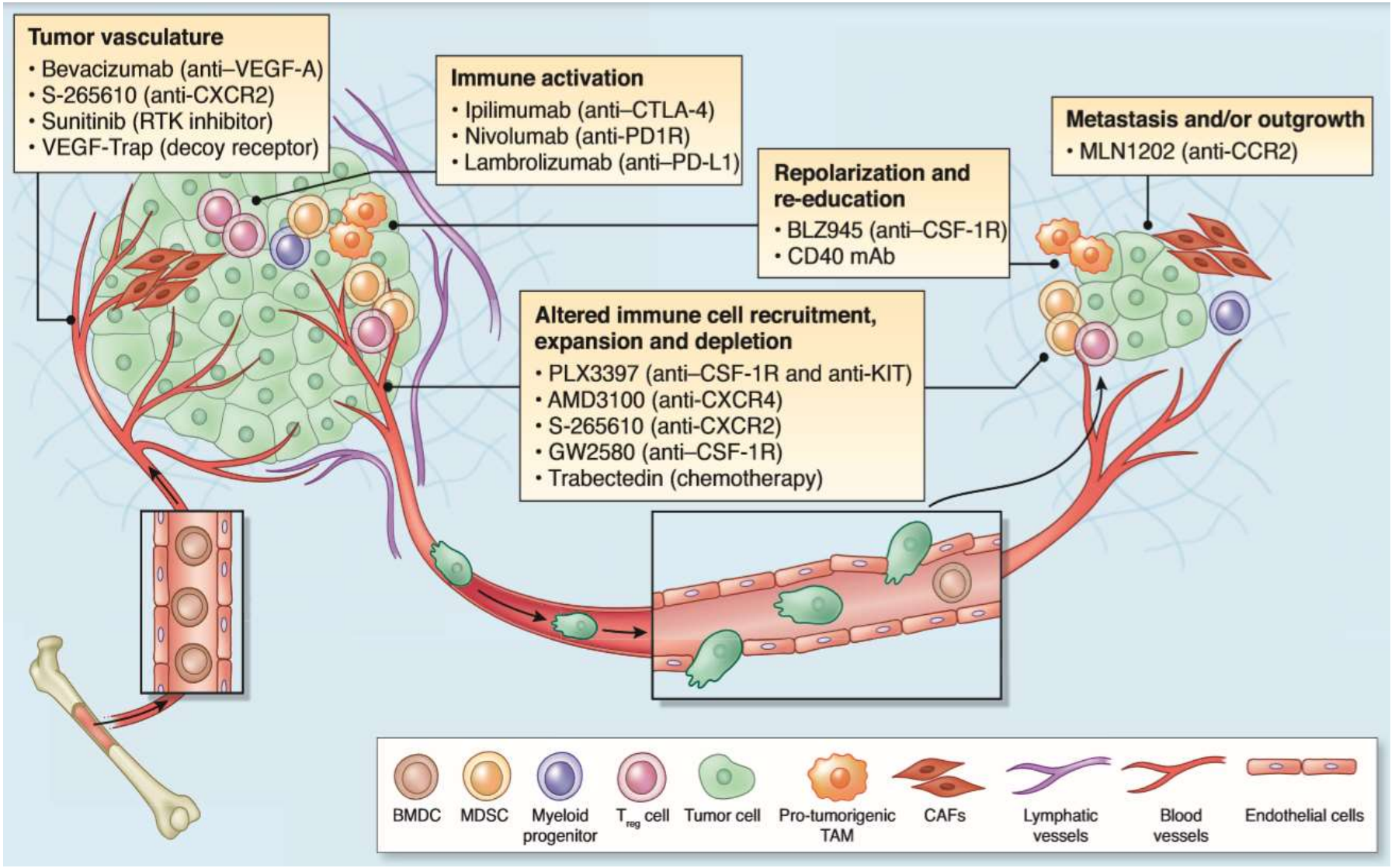
Quail et al. Nature Medicine 2013

MICROAMBIEMTE: ruolo nella metastatizzazione



Quail et al. Nature Medicine 2013

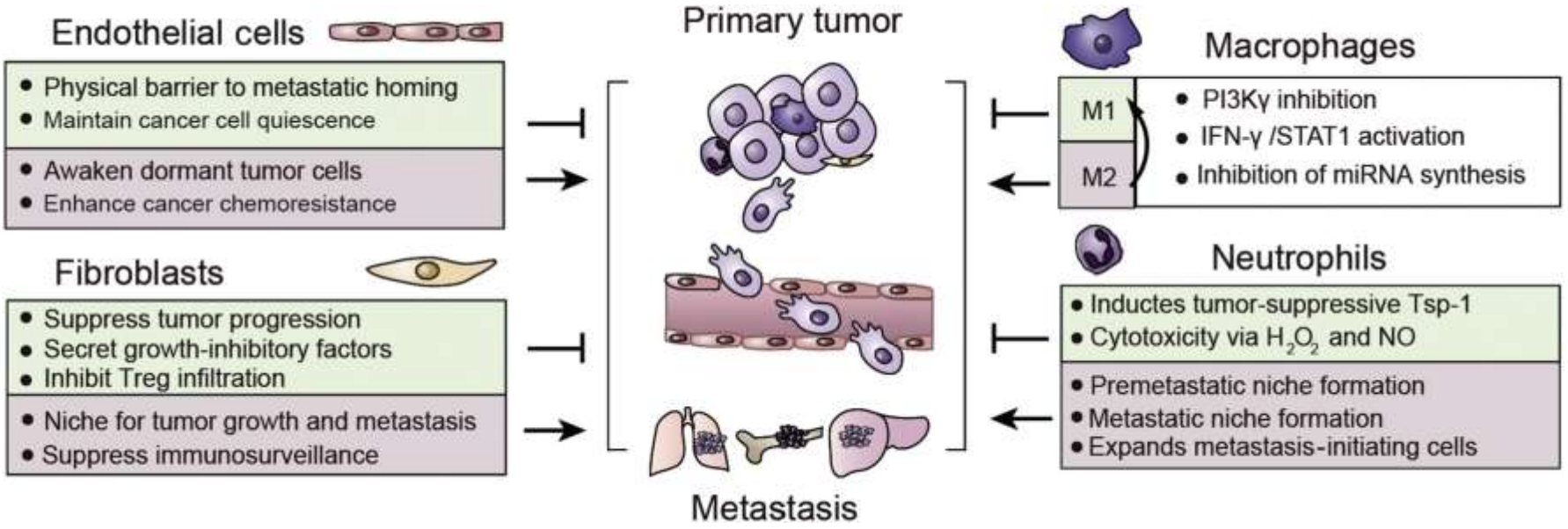
MICROAMBIEMTE: possibili «target»



Quail et al. Nature Medicine 2013

CellPress
REVIEWS

Cellular components of the tumor microenvironment (TME) that play opposite roles in metastasis



During metastatic growth, different TME cells exert **seemingly contradictory regulatory effects** on tumor cell dissemination and metastatic colonization. These cells include, but are not limited to, endothelial cells, fibroblasts, neutrophils, and macrophages.

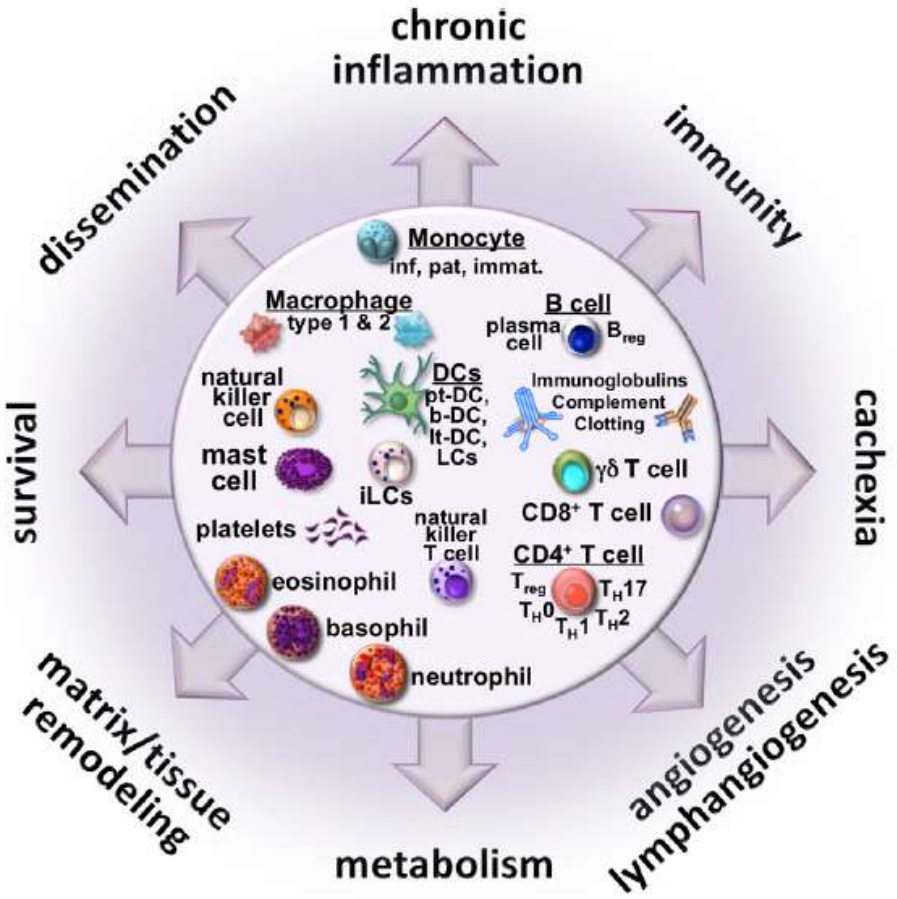
Reprogramming the Tumor Microenvironment to Improve Immunotherapy: Emerging Strategies and Combination Therapies

- The TME releases factors into circulation that promote systemic immunosuppression and further inhibit antitumor immunity
- **Reprogramming specific facets of the immune compartment**, such as immunosuppressive myeloid and lymphoid cell subsets, **may overcome microenvironment-induced resistance mechanisms and enhance antitumor immunity**.

2019 ASCO EDUCATIONAL BOOK

The Tumor-Immune Microenvironment mediates tumor progression and treatment response

protumor and antitumor immune cells promote and cooperate with other pathophysiologic features to promote the major hallmarks of cancer progression, immunosuppression, and treatment resistance



Immunotherapeutic strategies (as combination therapies)

must be carefully orchestrated to promote antitumor immunity for efficacious outcomes

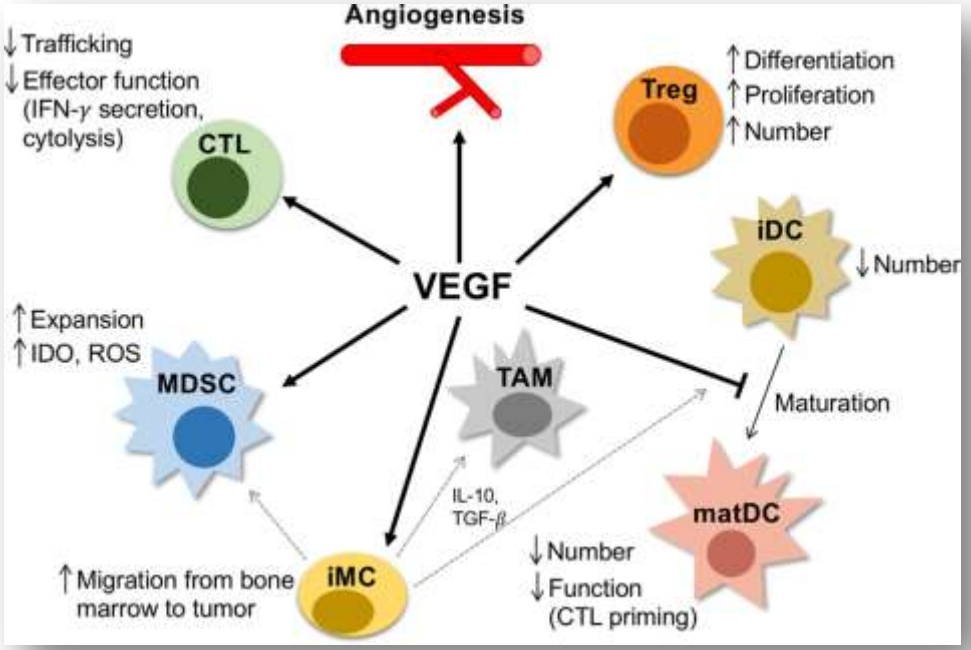
THERAPEUTIC STRATEGIES

- **Targeting non-immune components of the TME**
  - by **normalizing or decompressing the vasculature** represents a clinically translatable strategy to overcoming resistance to ICBs and other immunotherapies.
- A bench-to-bedside-and-back approach for microenvironment-based strategies may not only enhance immunotherapies for solid tumors but also **abrogate irAEs**

NORMALIZING THE TUMOR VASCULATURE TO IMPROVE IMMUNOTHERAPY

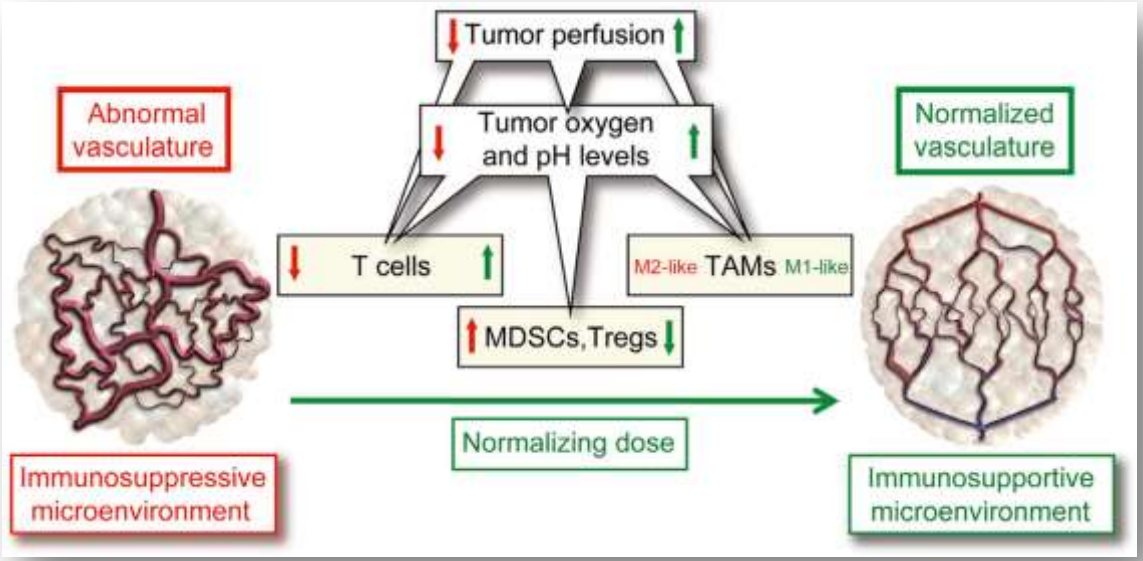
VEGF modulates immune cells to promote an immunosuppressive tumor microenvironment

indirectly promoting immunosuppression via an **abnormal tumor vasculature**



directly influencing immune cells in the tumor microenvironment and **promoting immunosuppressive** cells such as Tregs, MDSCs, and protumor TAMs, while inhibiting antigenpresenting cells (such as DCs and antitumor TAMs) and CTLs.

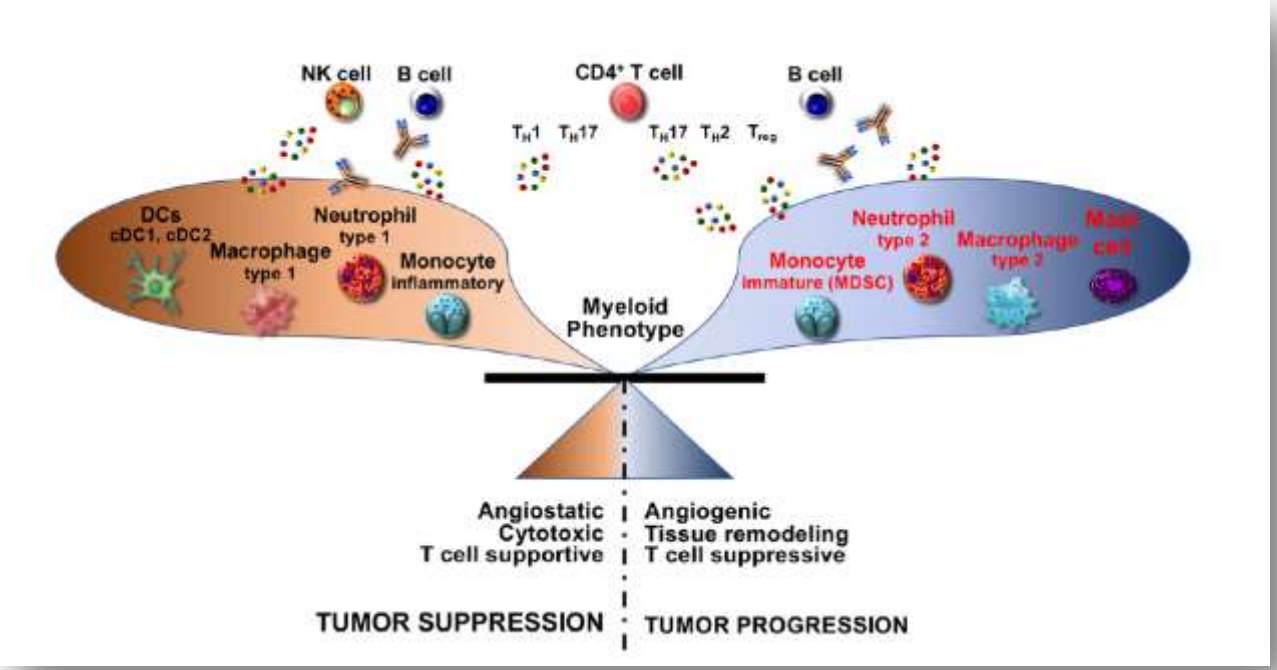
Vascular normalization can reprogram the immunosuppressive tumor microenvironment



Antiangiogenic therapies

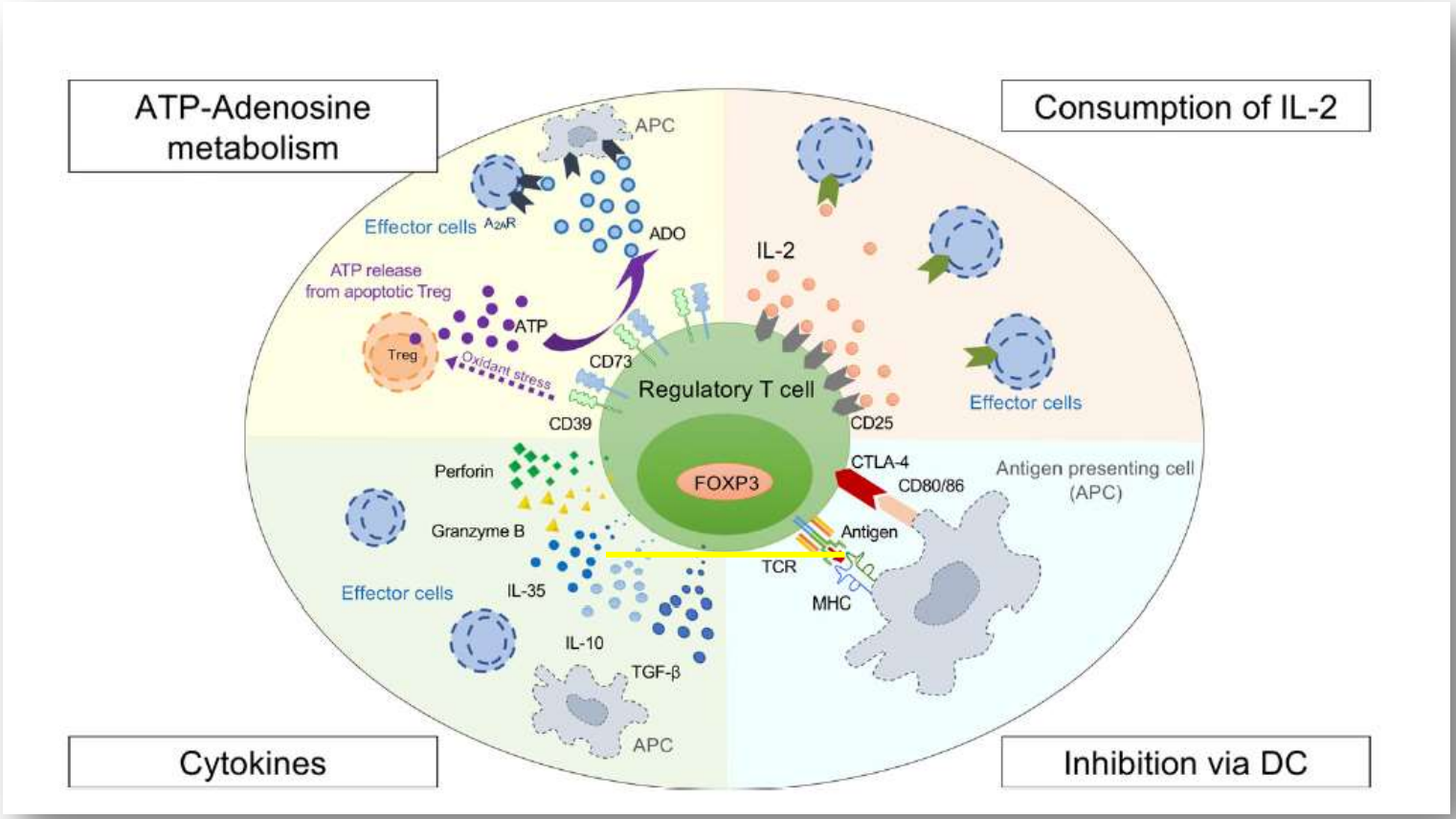
- can reprogram the tumor microenvironment to an immunostimulatory milieu by normalizing the vasculature to facilitate T effector cell infiltration and antitumor function,
- reduce MDSC and Treg accumulation, and alleviate hypoxia, which can induce conversion of TAMs to an “M1-like” antitumor phenotype.

Adaptive immune responses dictate myeloid cell activity to influence tumor progression



- Although regulation of **adaptive and innate immune responses** is likely bidirectional and can be altered by treatment modalities, **different adaptive cells can also promote either pro- or antitumor myeloid cell phenotype** and function and together influence tumor progression.
- In cases where the immune response to cancer results in increased **TH1 cytokines** by adaptive cells (e.g., CD4+ T cells and natural killer [NK] cells), this induces myeloid cell bioactivity that promotes tumor stabilization or regression.
- On the other hand, when the responding adaptive response includes chronic B cell, **TH2**, and regulatory T-cell activation, myeloid cells upregulate programs that promote tumor progression, including angiogenesis and **immunosuppression**.

Mechanisms of regulatory T-Cell suppression in the tumor microenvironment



Tregs are a specialized **subset of CD4 T cells** that are required in normal physiologic conditions to balance effector immune responses and maintain immune homeostasis and self-tolerance

In the TME, however, Tregs are **co-opted to suppress antitumor immune responses and promote tumor progression**

- **Tregs are able to inhibit the function of antigen-presenting cells (APCs) and T effector cells by three main mechanisms:**

1. Tregs support their own **immunosuppressive function by consuming interleukin (IL)-2** (via the IL-2 receptor CD25).
2. Tregs **inhibit APCs** (via CTLA-4 binding to CD80/CD86) to downregulate costimulatory signals to T effector cells.
3. Tregs **directly inhibit T effector cells and APCs with suppressive cytokines** (IL-10, IL-35, and transforming growth factor [TGF]-β) or by inducing apoptosis (perforin and granzyme).

REPROGRAMMING REGULATORY T CELLS IN THE TME TO OVERCOME IMMUNOSUPPRESSION

- Tregs are emerging as a **target** in cancer immunotherapy
- **Inhibition** of Treg-mediated suppression:
  - **selective depletion of intratumoral Tregs,**
  - **reprogramming intratumoral Tregs to an antitumor effector phenotype**
- VEGF signaling and overexpression promotes Treg proliferation and activation.
- **VEGF pathway inhibition**
  - **reduced immune checkpoint expression and Treg infiltration** in both preclinical and clinical studies

Treg cell- targeted treatments in clinical trials

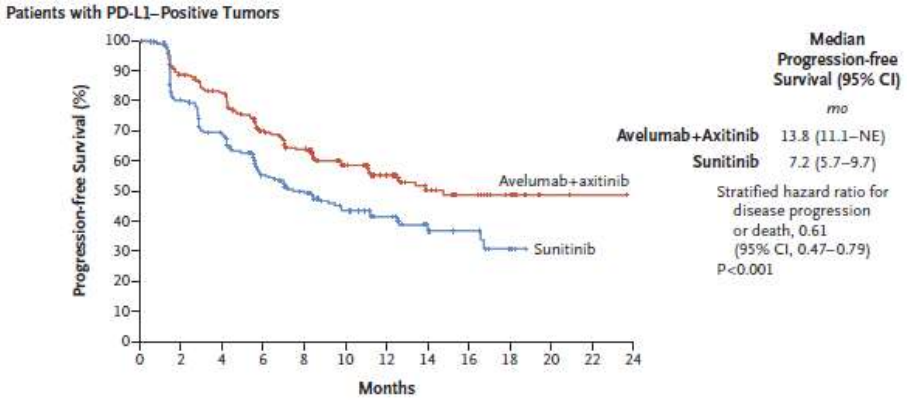
Therapeutic approach	Target	Representative agents (drug type)
Targeting receptors on T_{reg} cells	CD25 (IL-2Rα)	Daclizumab (anti-CD25 antibody) and photoimmunotherapy (CD25-targeted near-infrared photoimmunotherapy)[132,133,190]
	CTLA-4	Ipilimumab (anti-CTLA-4 antibody)[21,107,108]
	CCR4	Mogamulizumab (anti-CCR4 antibody)[136,137]
	OX40	PF-04518600 (agonistic anti-OX40 antibody) and MEDI6383 (OX40L–Fc fusion protein)[142,143]
	GITR	MEDI1873 (agonistic hexameric GITR ligand fusion protein; NCT02583165), TRX518 (NCT02628574) and MK-1248 (agonistic anti-GITR antibodies)[144]
	ICOS	JTX-2011 (agonistic anti-ICOS antibody)[146,147]
Targeting intracellular signalling	PI3Kδ	Parsaclisib (also known as INCB050465; small-molecule PI3Kδ inhibitor; NCT02646748)
	LCK	Dasatinib and imatinib (multi-targeted TKIs)[151]
Targeting the tumour microenvironment	IDO1	Epacadostat (small-molecule IDO1 inhibitor)[156,157]
	VEGF signalling	Bevacizumab (anti-VEGF antibody), ramucirumab (anti-VEGFR2 antibody), sorafenib and lenvatinib (VEGFR-targeted TKIs)[162–166]
	TGFβ	Galunisertib (TGFR1 kinase inhibitor; NCT02423343 and NCT02734160) and M7824 (anti-PD-L1–TGFβ trap)[172,173]
	FAK	Defactinib (NCT02758587)
Other	HSP90	XL888 (NCT03095781), ganetespib (NCT01173523) and TAS-116 (UMIN000032801) (small-molecule HSP90 inhibitors)
	DNA (immunomodulatory chemotherapy)	Cyclophosphamide[182–185]

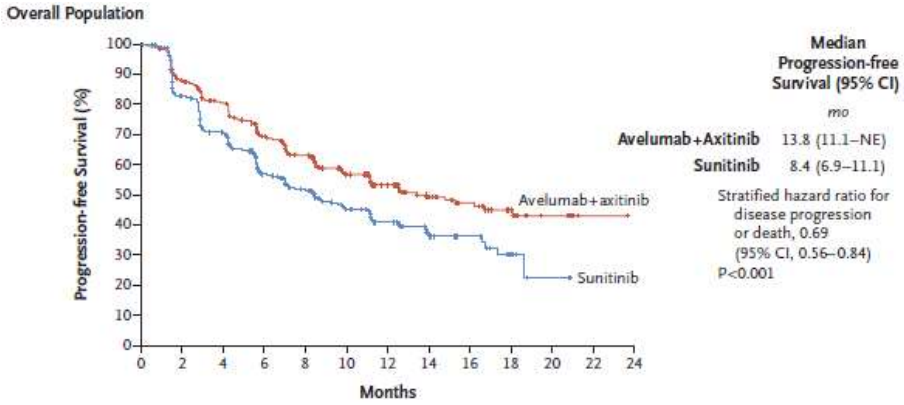
Yosuke Togashi

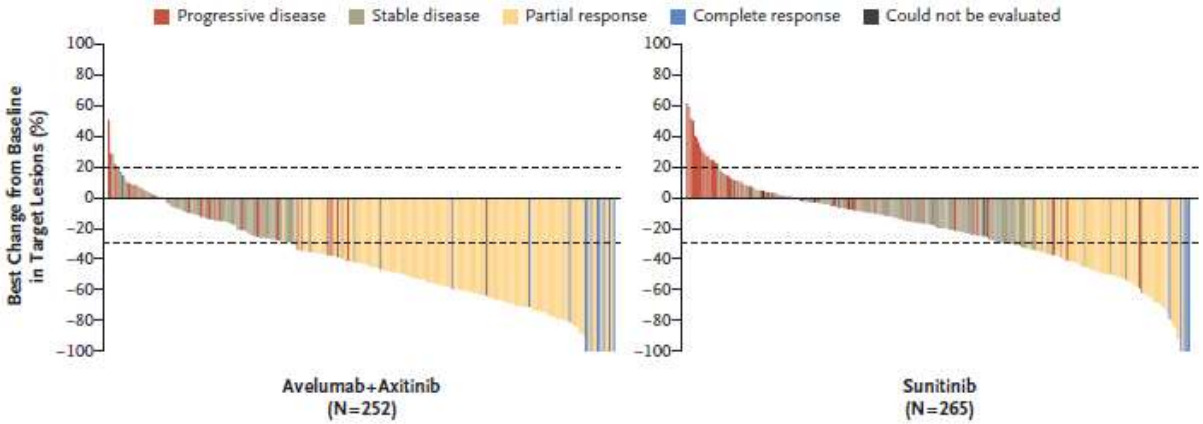
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 21, 2019 VOL. 380 NO. 12

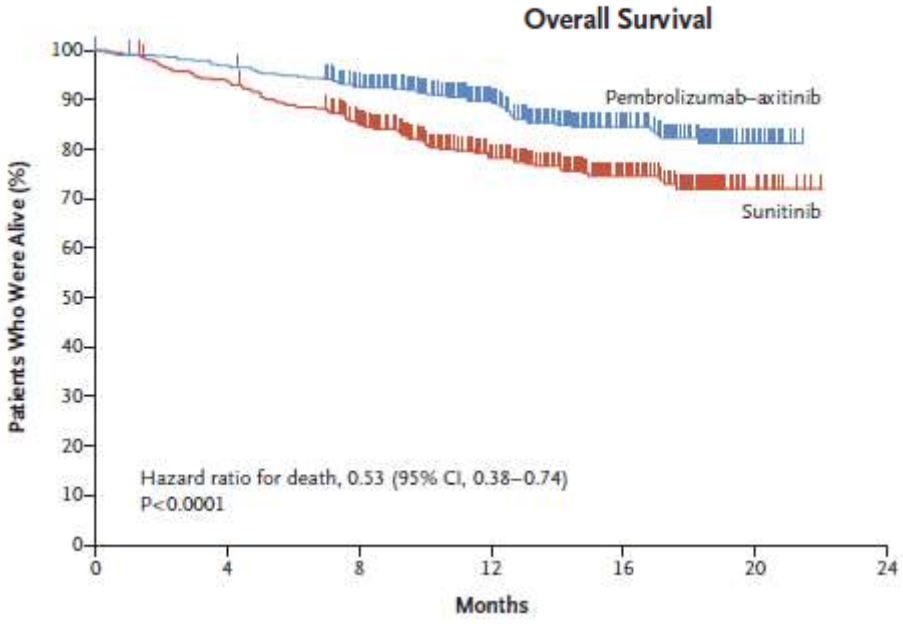
Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

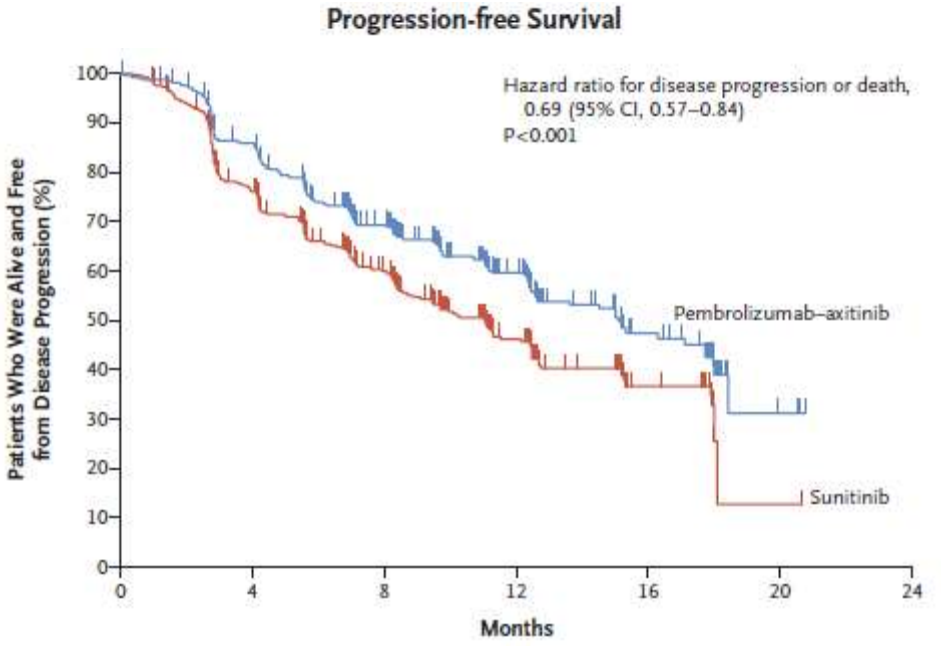




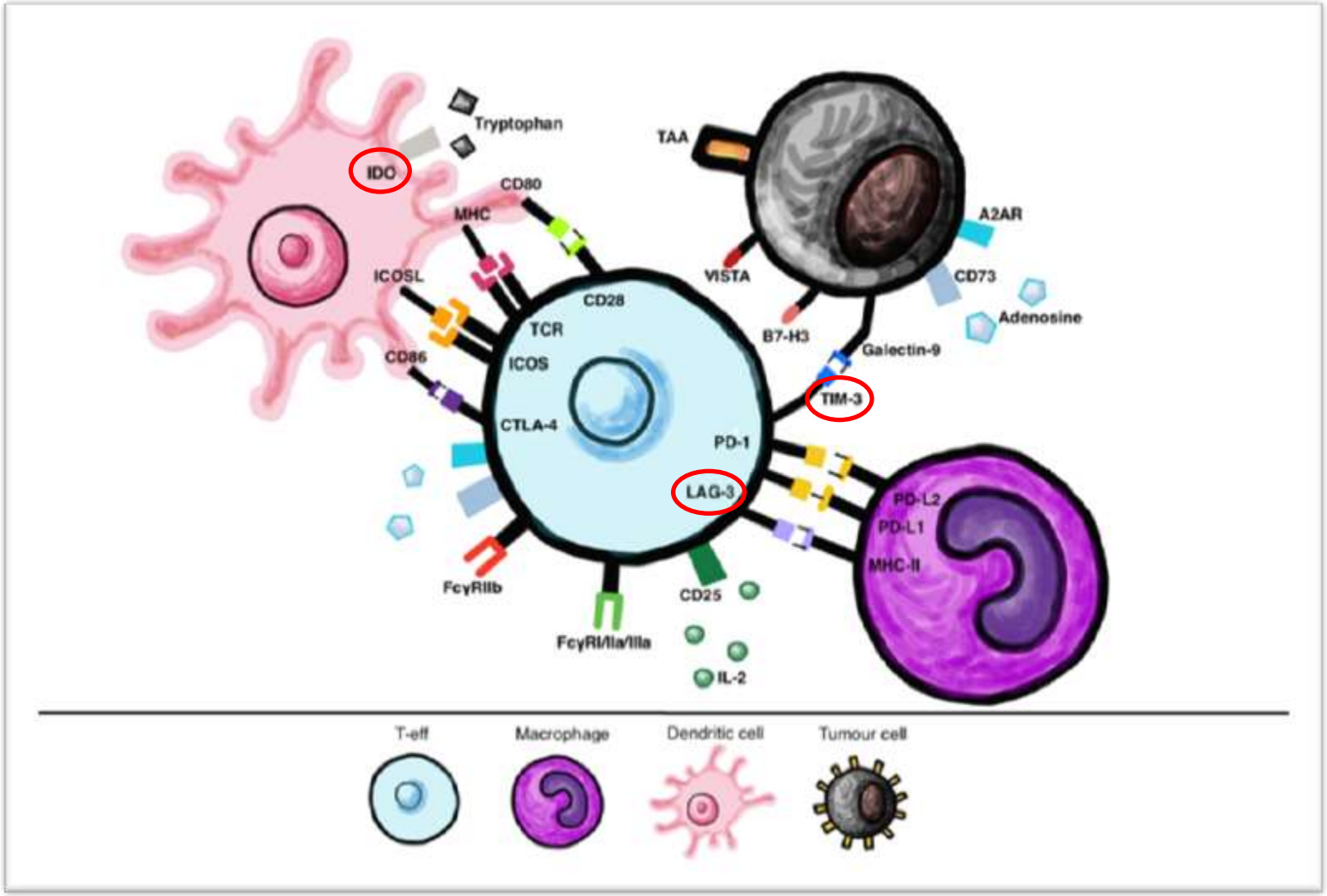


Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma





Immune cell interactions via checkpoint molecules and their ligands



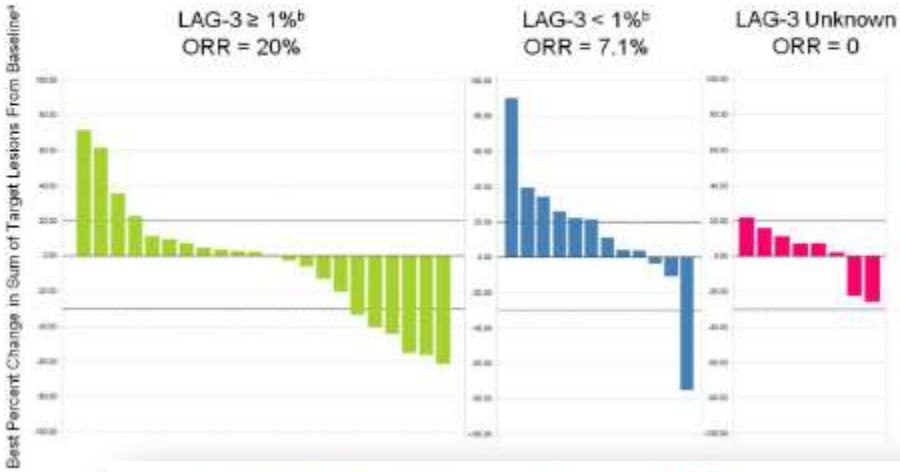
Various interactions between checkpoint molecules and their ligands expressed by different cells, such as immune cells (dendritic cells (DC)s, T-effector cells (T-eff), macrophages) and between T-eff and tumor cells, that may be targeted with therapy

Khair et al.

CA224-020

CONFIDENTIAL DRAFT
DISCUSSANT SLIDES

Promising Response With BMS-986016 + Nivolumab in Patients With Melanoma Who Received Prior Anti–PD-1/PD-L1 Therapy



- LAG-3 expression enriches for responses in IO-experienced patients with melanoma
- Nearly a 3-fold increase in ORR was observed in patients with LAG-3 ≥ 1% vs LAG-3 < 1% (20% vs 7.1%)
- Overall response rate was 12.5%

Figure will be redrawn.

ASCO Meeting Library

Updated phase I trial of anti-LAG-3 or anti-CD137 alone and in combination with anti-PD-1 in patients with recurrent GBM.

Presented Sunday, June 2, 2019

CA224-060: A randomized, open label, phase II trial of relatlimab (anti-LAG-3) and nivolumab with chemotherapy versus nivolumab with chemotherapy as first-line treatment in patients with gastric or gastroesophageal junction adenocarcinoma.

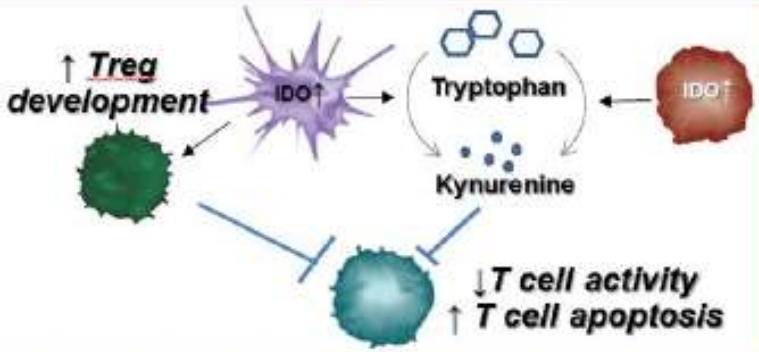
Presented Monday, June 3, 2019

IDO Pathway

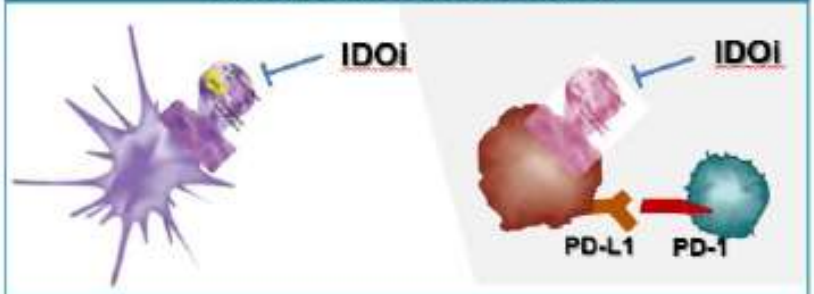
	Enzyme	Substrate
	IDO	**Tryptophan**
Expression	• APCs	• Released by cells within the tumor microenvironment
Biological function(s)	• Regulates T-cell activity via metabolism of tryptophan into immunosuppressive metabolites (eg, kynurenine)	
Status in cancer	• Increased metabolism of tryptophan via tumor-dependent IDO upregulation • Increased tryptophan in the tumor microenvironment triggers Treg development and causes T cell starvation	

IDO Inhibitor	
Intervention	IDO blockade by inhibitor • Reduces Treg numbers and restores T-cell function Preclinical data suggest that IDO inhibition in combination with PD-1 blockade demonstrates antitumor activity
Current investigations	• Phase I/IIa trial for advanced solid tumors in combination with anti-PD-1

Pathway in Cancer

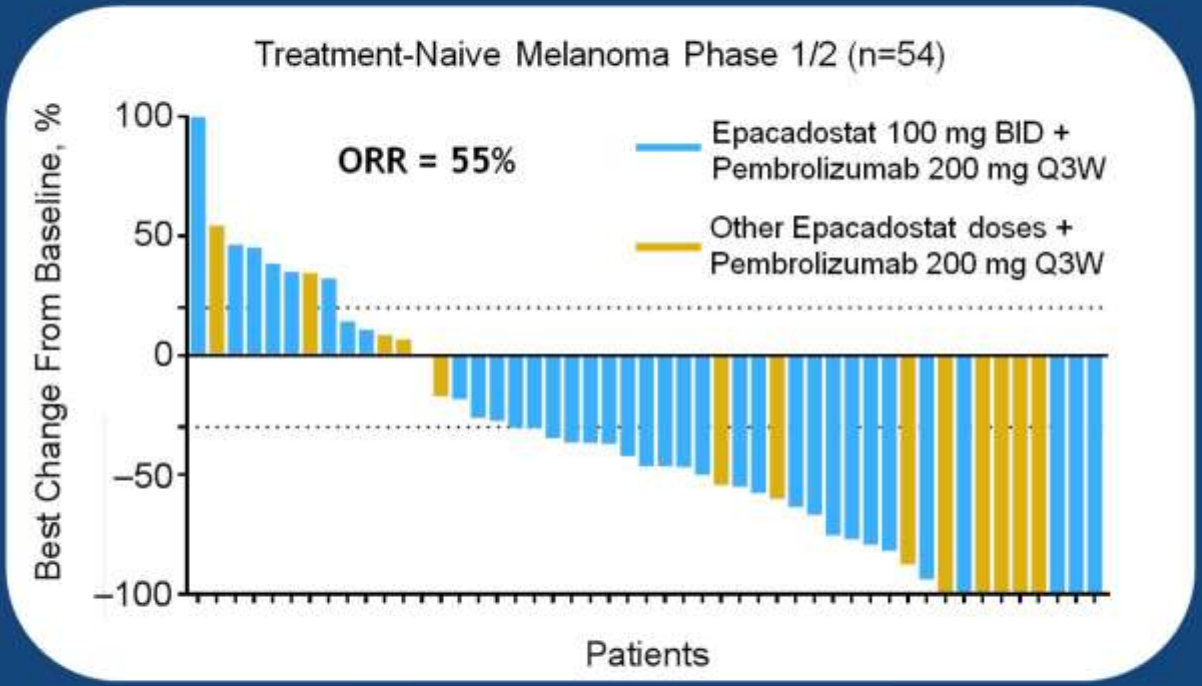


Therapeutic Intervention



1. Mellor AL et al. *Immunol Today*. 1999;20:469-473.
2. Munn DH et al. *Science* 2002;297:1867-1870.
3. Löb S et al. *Cancer Immunol Immunother*. 2009;58:153-157.
4. Uyttenhove C et al. *Nat Med*. 2003;9:1269-1274.

Background: Rationale for Combination and Dosing



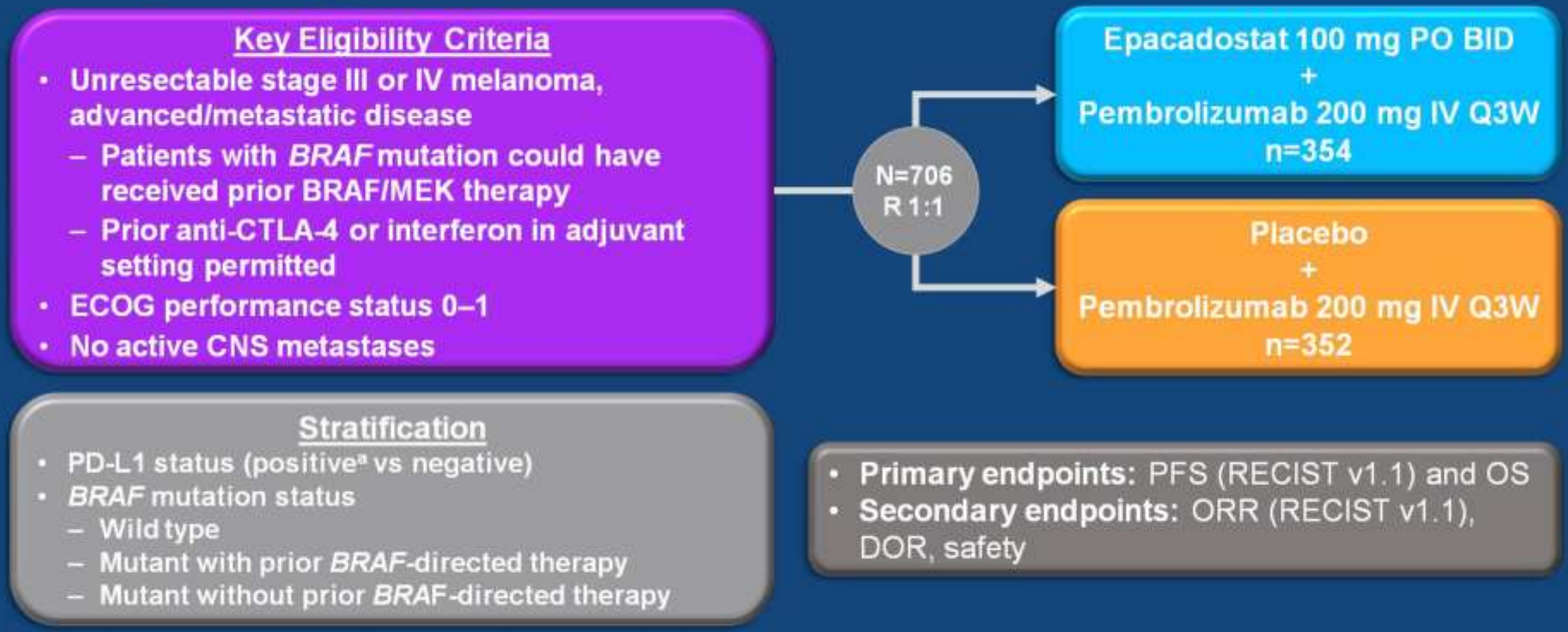
ECHO-202 / KEYNOTE-037

- Phase 1: Epacadostat 50, 100, or 300 mg PO BID + Pembrolizumab 200 mg IV Q3W
- MTD of epacadostat not reached
- Phase 2: Epacadostat 100 mg PO BID
- Phase 1/2 efficacy in treatment-naive melanoma:
  - ORR = 55%
  - Median PFS = 22.8 mo (12.4 mo all melanoma)

BID, twice daily; MTD, maximally tolerated dose; PD-L1, programmed death ligand-1; Q3W, every 3 weeks.
Hamid O, et al. *Ann Oncol.* 2017;28(suppl 5):1214O.

Presented By Georgina Long at 2018 ASCO Annual Meeting

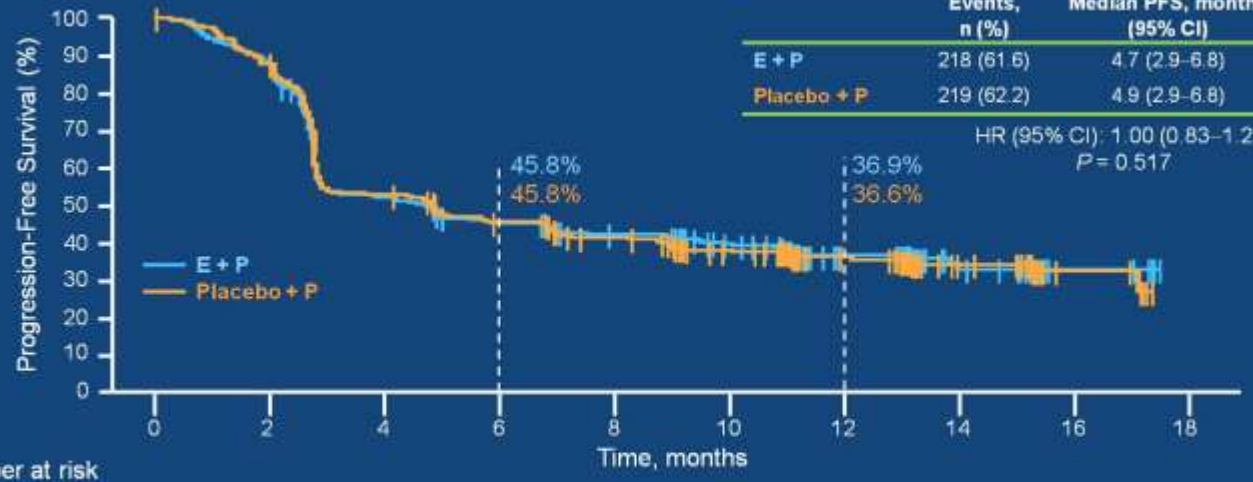
Study Design: Phase III Randomized Controlled Trial



BID, twice daily; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.
[a]≥1% staining in tumor and adjacent immune cells as assessed by IHC (22C3 antibody).

Presented By Georgina Long at 2018 ASCO Annual Meeting

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



	Events, n (%)	Median PFS, months (95% CI)
E + P	218 (61.6)	4.7 (2.9–6.8)
Placebo + P	219 (62.2)	4.9 (2.9–6.8)

HR (95% CI): 1.00 (0.83–1.21)
P = 0.517

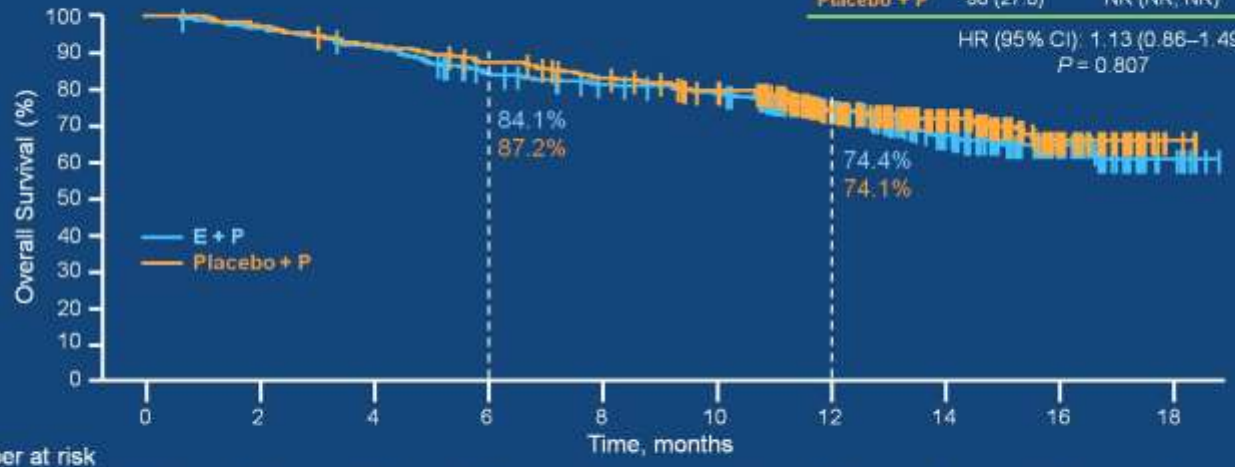
Number at risk

E + P	354	309
Placebo + P	352	304

BICR, blinded independent central review; CI, confidence interval; E, [illegible]
PFS defined as time from randomization to disease progression or de[illegible]

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

Overall Survival



	Events, n (%)	Median OS, months (95% CI)
E + P	106 (29.9)	NR (NR, NR)
Placebo + P	98 (27.8)	NR (NR, NR)

HR (95% CI): 1.13 (0.86–1.49)
P = 0.807

Number at risk

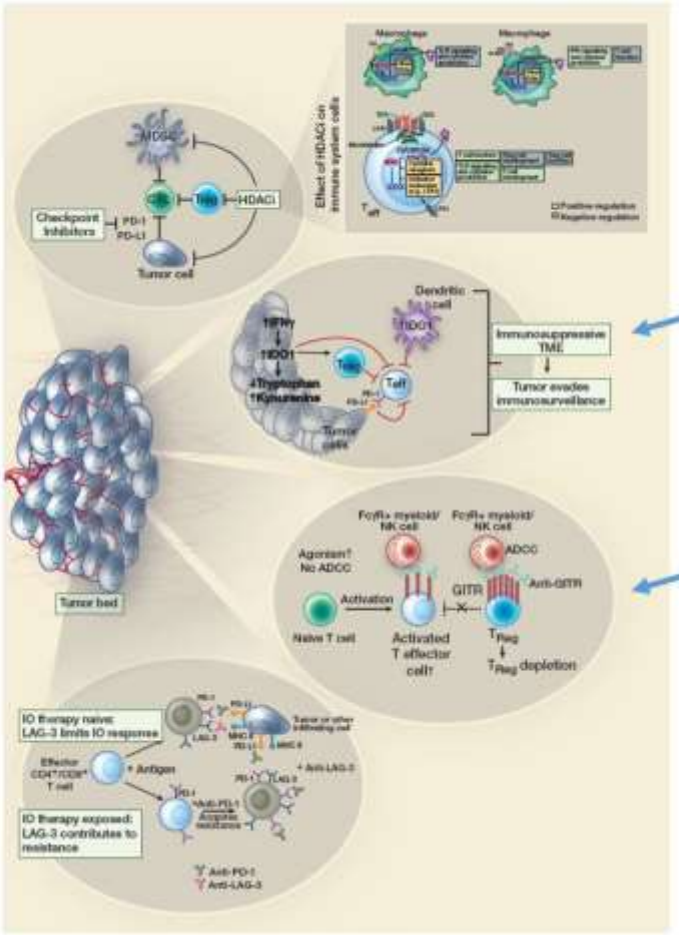
E + P	354	340	322	290	274	263	183	96	42	5
Placebo + P	352	342	323	304	285	263	186	115	43	2

CI, confidence interval; E, epacadostat; HR, hazard ratio; NR, not reached; OS, overall survival; P, pembrolizumab.

Presented By Georgina Long at 2018 ASCO Annual Meeting

New emerging pathways for future combination with anti-PD-1/PD-L1 compounds

HDAC inhibitor
(eg., entinostat [Ph 2])



IDO1 inhibitor
(eg., epacadostat [Ph 3], etc.)

Anti-GITR
(eg., BMS-986156 (Ph 1/2])

Anti-LAG-3
(eg., relatlimab [Ph 1/2])

GITR, glucocorticoid-induced TNFR-related protein; HDAC, histone deacetylases; IDO1, indoleamine 2,3-dioxygenase 1; LAG-3, lymphocyte-activation gene 3

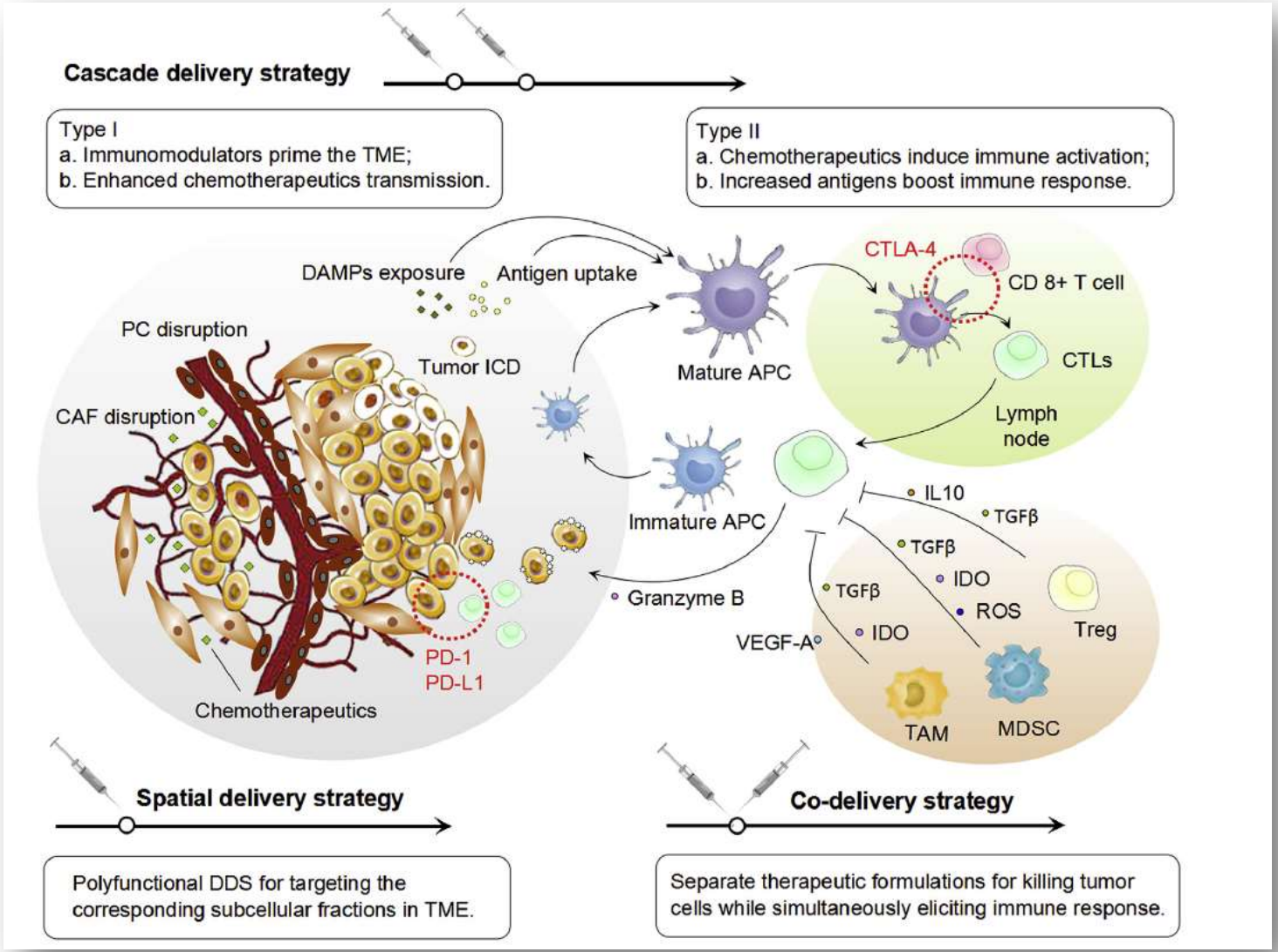
Presented by Paolo A. Ascierto at ASCO 2018

Ascierto PA & McArthur JA. *J Transl Med* 2017;15:173

Strategies in cancer combination therapies using chemotherapy with immunotherapy

- Chemotherapeutic drugs could elicit immune-potentiating effects by either inducing immunogenicity or relieving tumor-induced immunosuppression
- Some also leave tumors directly susceptible to cytotoxic T cell attacks.
- Mounting evidence accumulated from preclinical and clinical studies suggests that these two treatment modalities might be mutually reinforcing

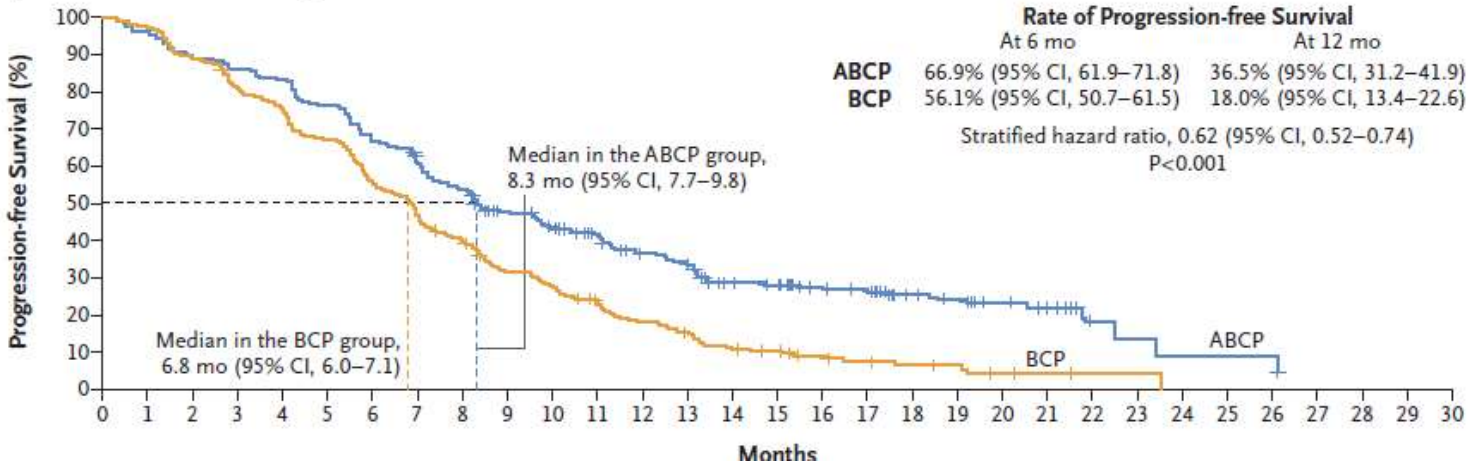
Chemo-immunotherapy



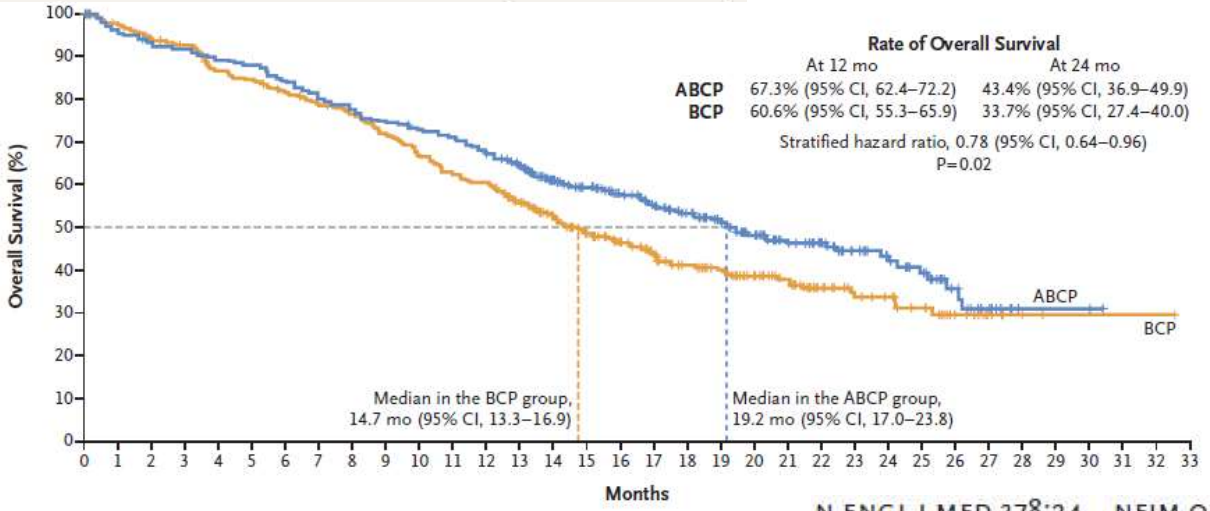
Cancer Letters 454 (2019) 191–203

Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC

Kaplan–Meier Estimates of Progression-free Survival

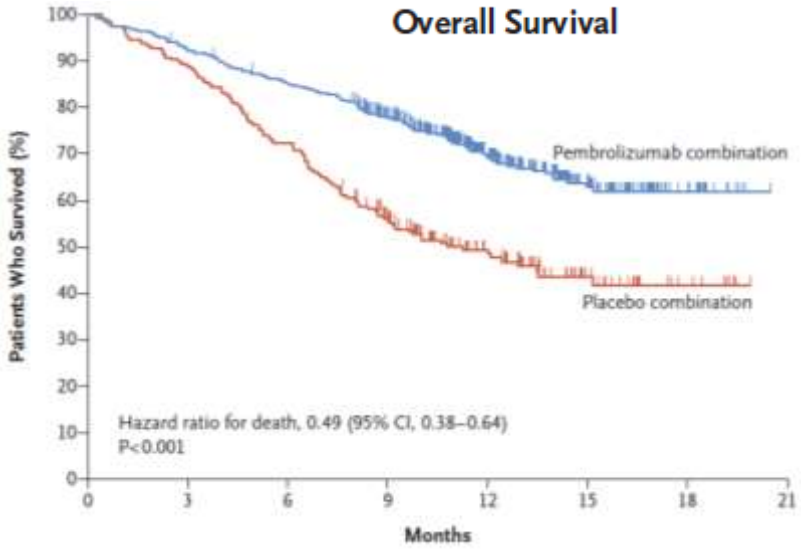


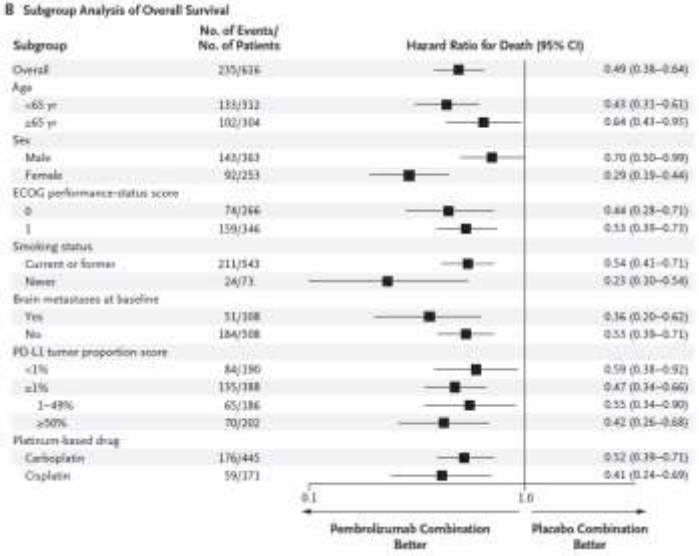
Interim Analysis of Overall Survival in the ABCP Group and the BCP Group.

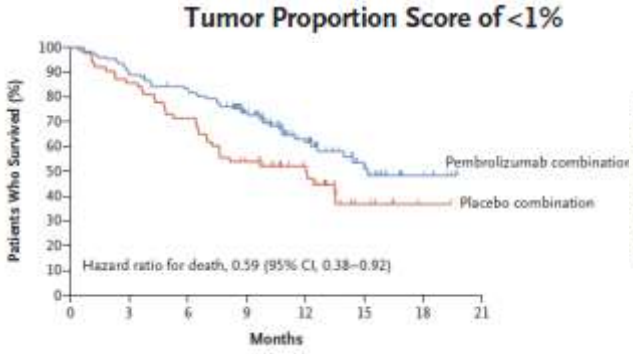


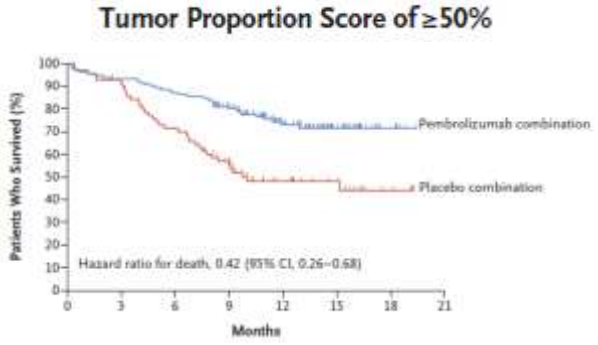
The NEW ENGLAND JOURNAL of MEDICINE

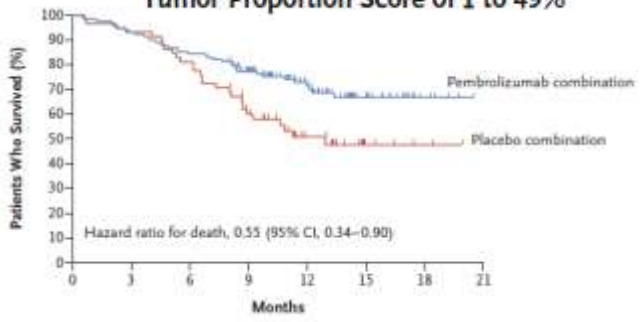
Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer











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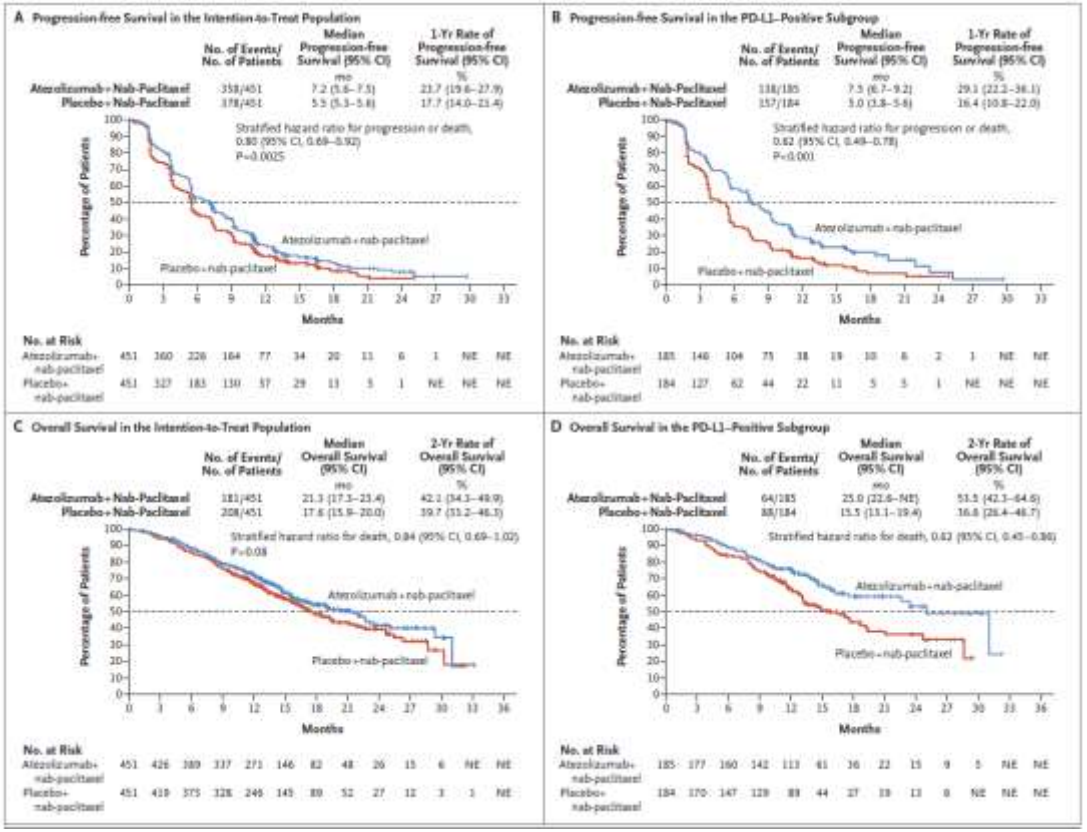
Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer

P. Schmid, S. Adams, H.S. Rugo, A. Schneeweiss, C.H. Barrios, H. Iwata, V. Diéras, R. Hegg, S.-A. Im, G. Shaw Wright, V. Henschel, L. Molinero, S.Y. Chui, R. Funke, A. Husain, E.P. Winer, S. Loi, and L.A. Emens, for the IMpassion130 Trial Investigators*

HTPOTESIS - Chemotherapy may enhance tumor-antigen release and antitumor responses to immune checkpoint inhibition. Taxanes in particular may additionally activate tolllike receptor activity and promote dendritic-cell activity.



Atezolizumab plus nab-paclitaxel prolonged progression-free survival among patients with metastatic triple-negative breast cancer in both the intention-to-treat population and the PD-L1–positive subgroup.

CONCLUSIONS

- Careful consideration must be given to how TME-specific features are incorporated into emerging personalized strategies for combination approaches with immunotherapy to close the gap between responders and nonresponders.

- TME factors should be included in biomarker development for predicting immunotherapeutic efficacy.

- TME-driven resistance mechanisms can be overcome with effective combination therapies to enhance immunotherapy efficacy and durability for patients while reducing adverse effects.