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Beyond T cells: Targeting Other Components of the Immune Response

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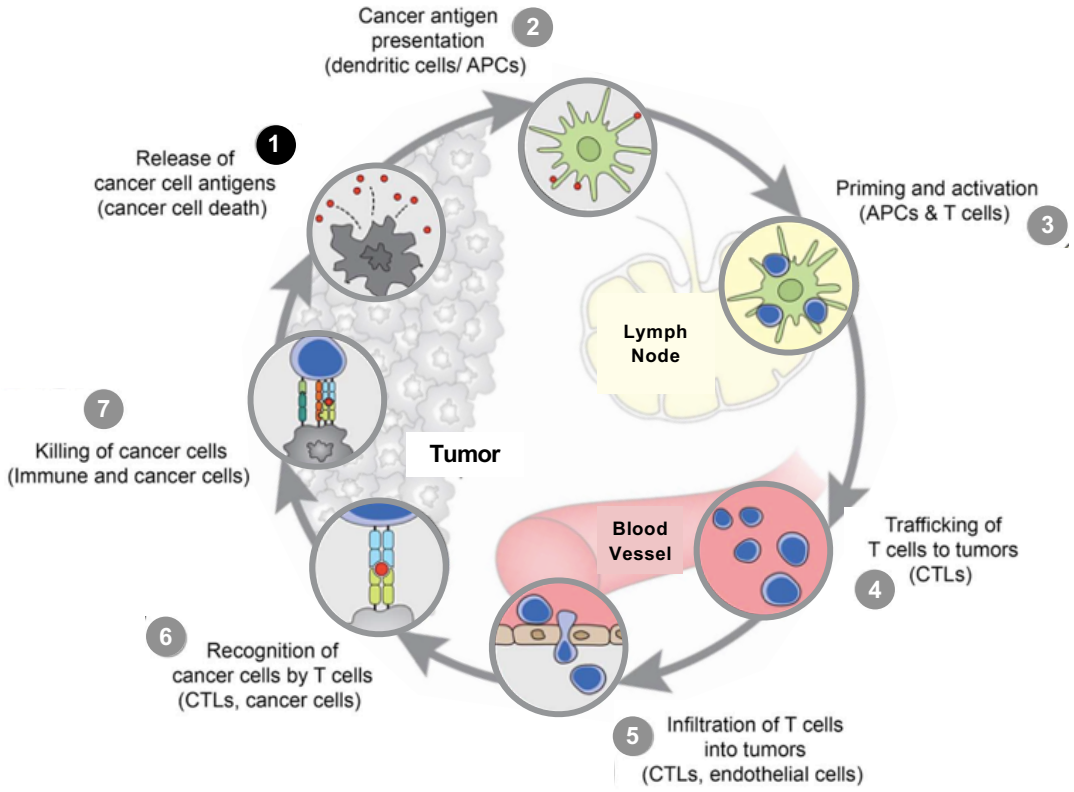
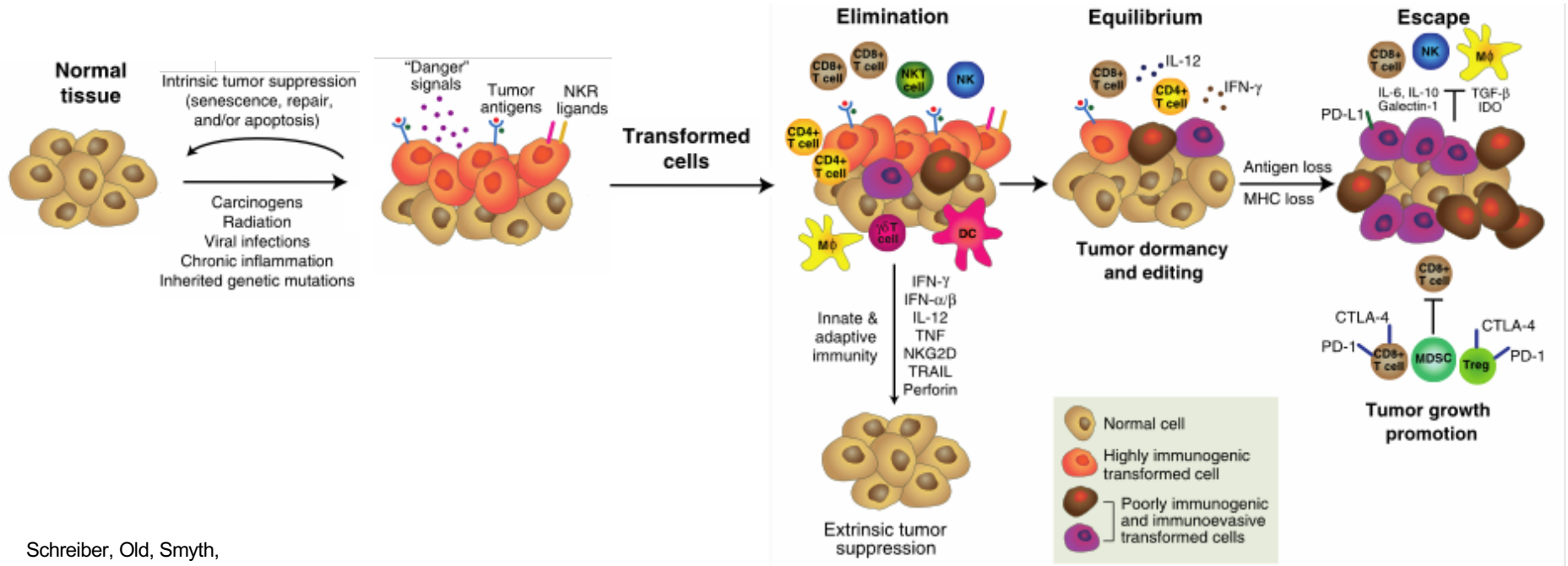
The Anti-Tumor Immune Response, a multi-step, highly regulated process



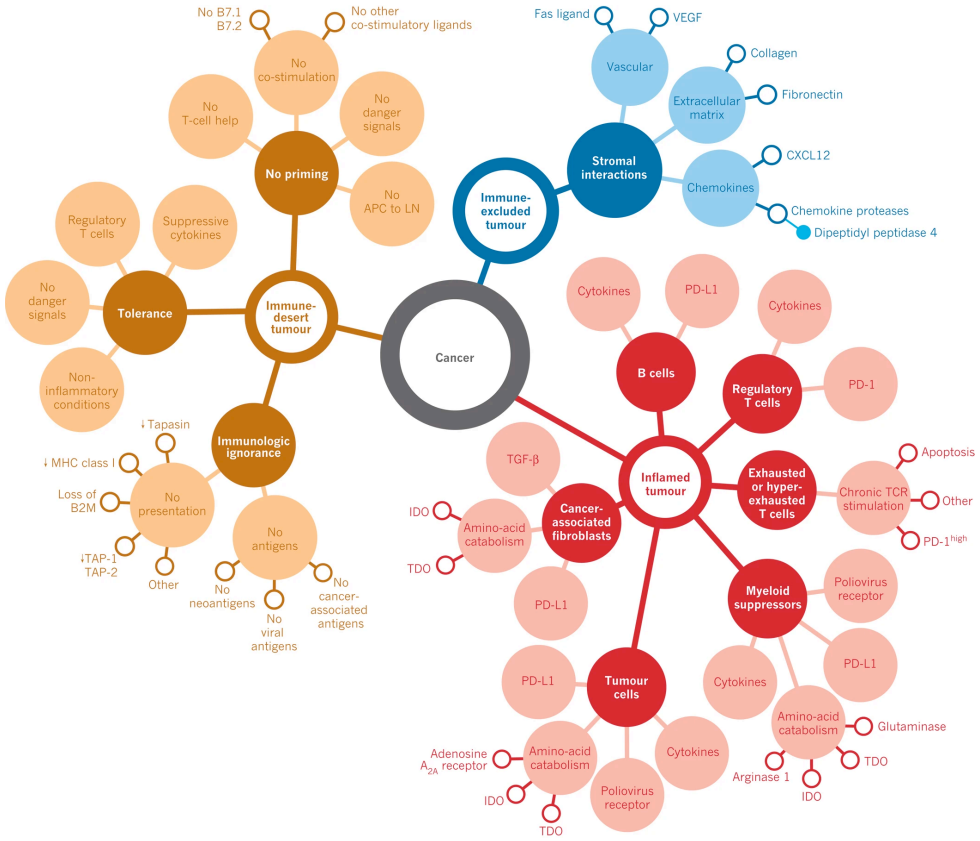
Oncology Meets Immunology:
The Cancer-Immunity Cycle.
Chen & Mellman . Immunity 2013

Cancer Immunoediting



Schreiber, Old, Smyth,
Science 331, 2011

Cancer Immune Phenotypes



Elements of cancer immunity and the cancer–immune set point. Chen & Mellman . Nature 2017

What Prevents This From Happening?

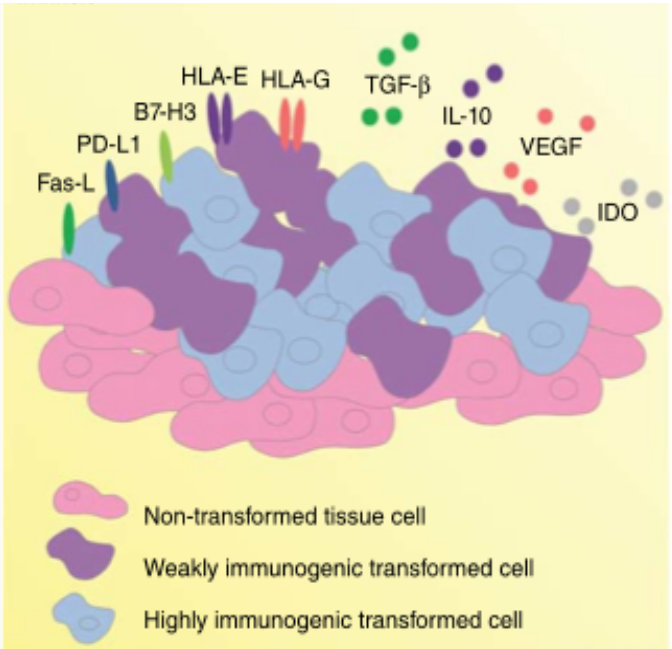
How do tumor evade immune elimination?

- Tumor adaptations that allow immune evasion
- Tumor microenvironment, trafficking, physical barriers
- Suppressive/Regulatory cell populations
- Regulation of anti-tumor immune cells

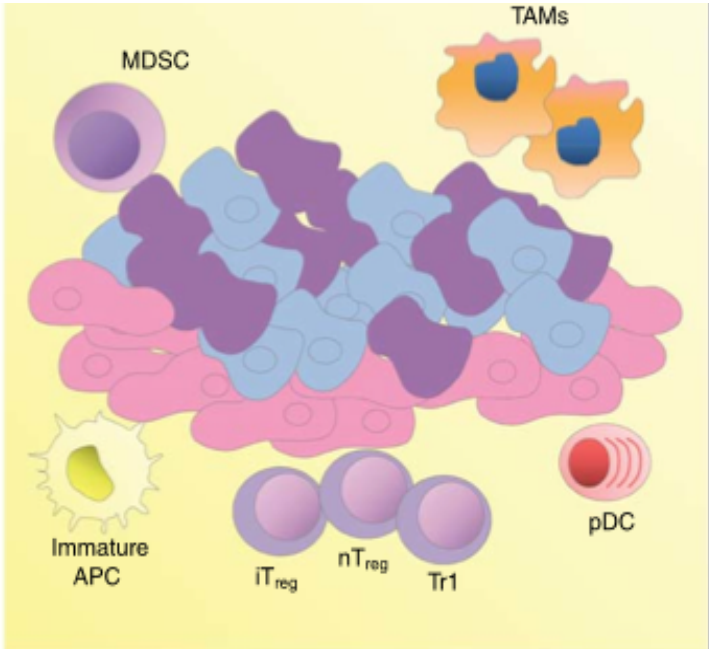
Porter DL and Antin JH. Annu Rev Med. 1999;50:369–86.

How do Tumors Evade Immune Elimination?

Intrinsic



Extrinsic

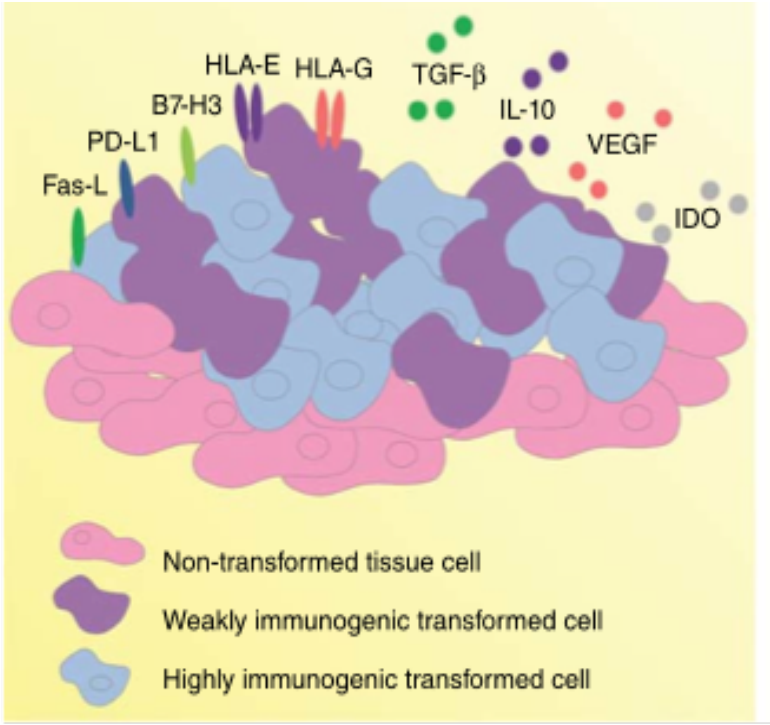


Oleinika et al.
Clinical & Exp
Immunology 2013

Tumor/Intrinsic Factors

- » Antigen Loss
- » MHC Loss (or any other step in antigen presentation)
- » Expression of molecules that impair anti-tumor immune responses (PD-L1)
- » Expression of soluble factors to down-regulate anti-tumor immune responses (TGF-b, IDO)
- » Others …

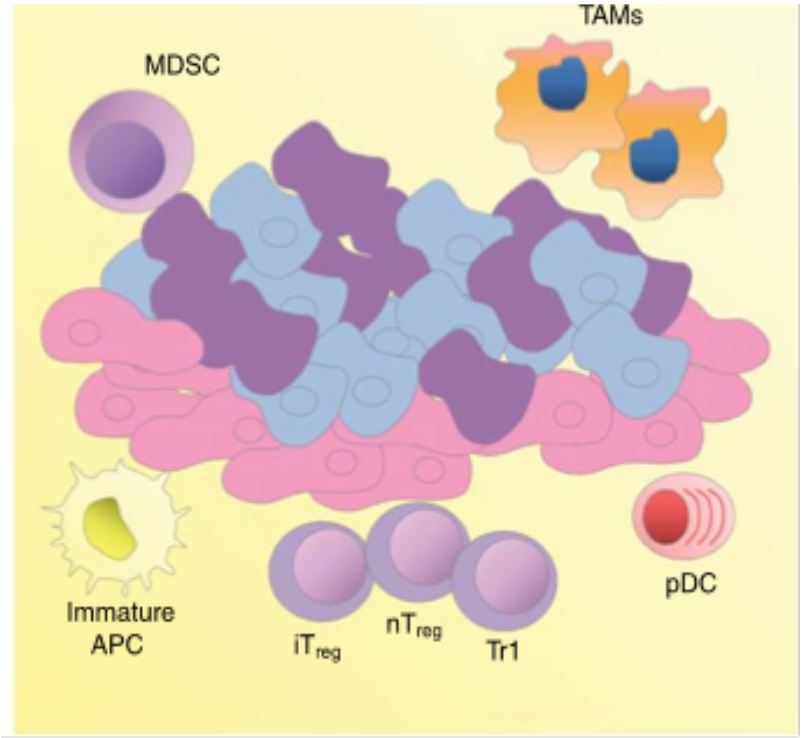
Intrinsic



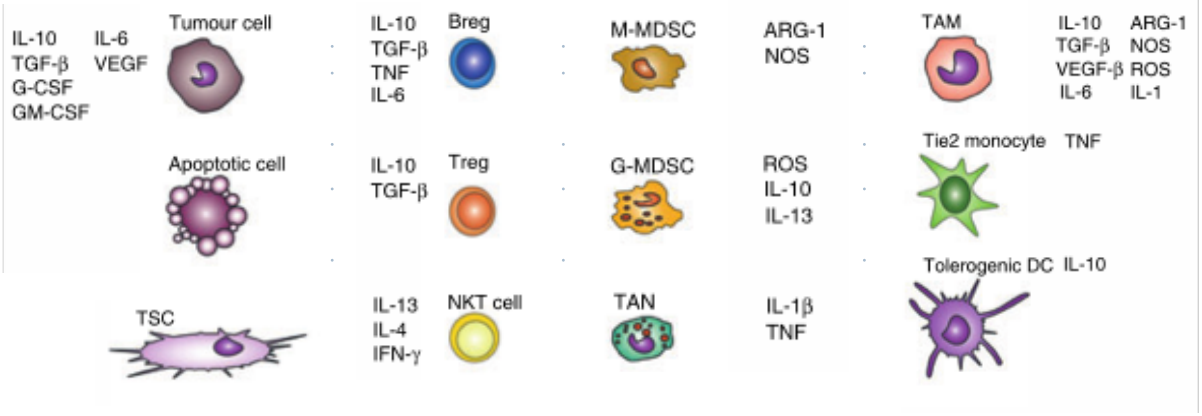
Microenvironment/Extrinsic Factors

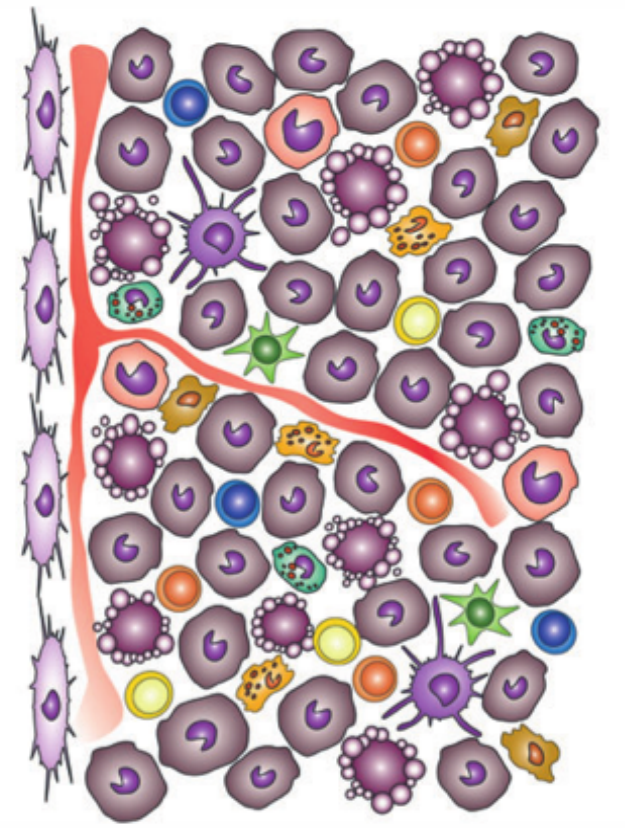
- » Geographic Barriers
- » Myeloid Derived Suppressor Cells (MDSC)
- » Regulatory T cells (iTreg, nTreg)
- » Tumor Associated Macrophages (TAMs)
- » Tolerogenic DCs
- » Others …

Extrinsic



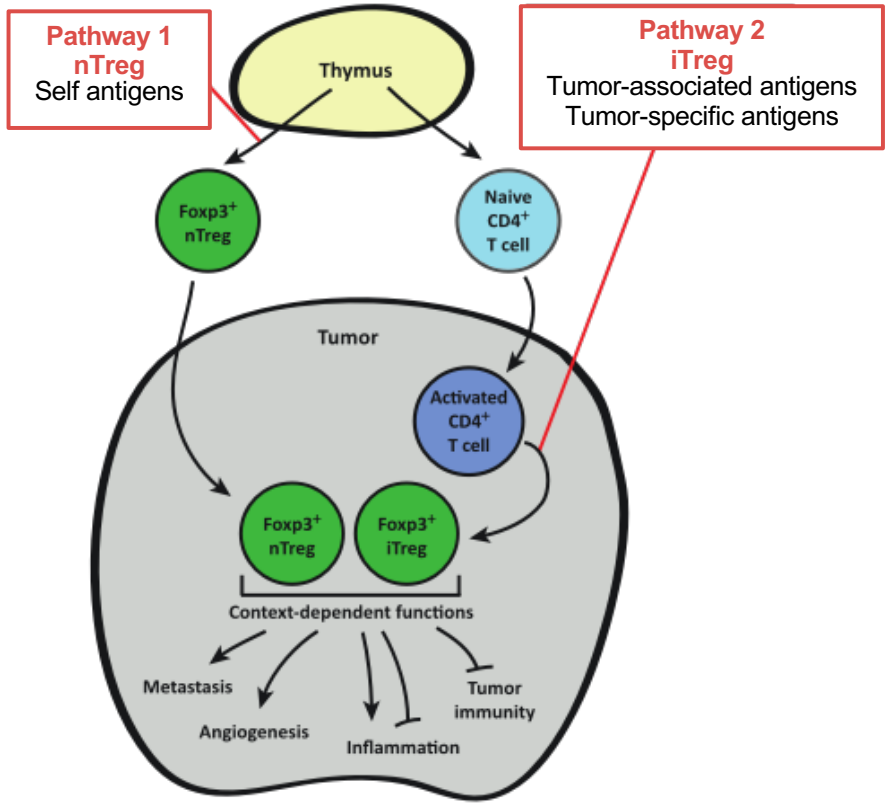
The Immunosuppressive Tumor Microenvironment





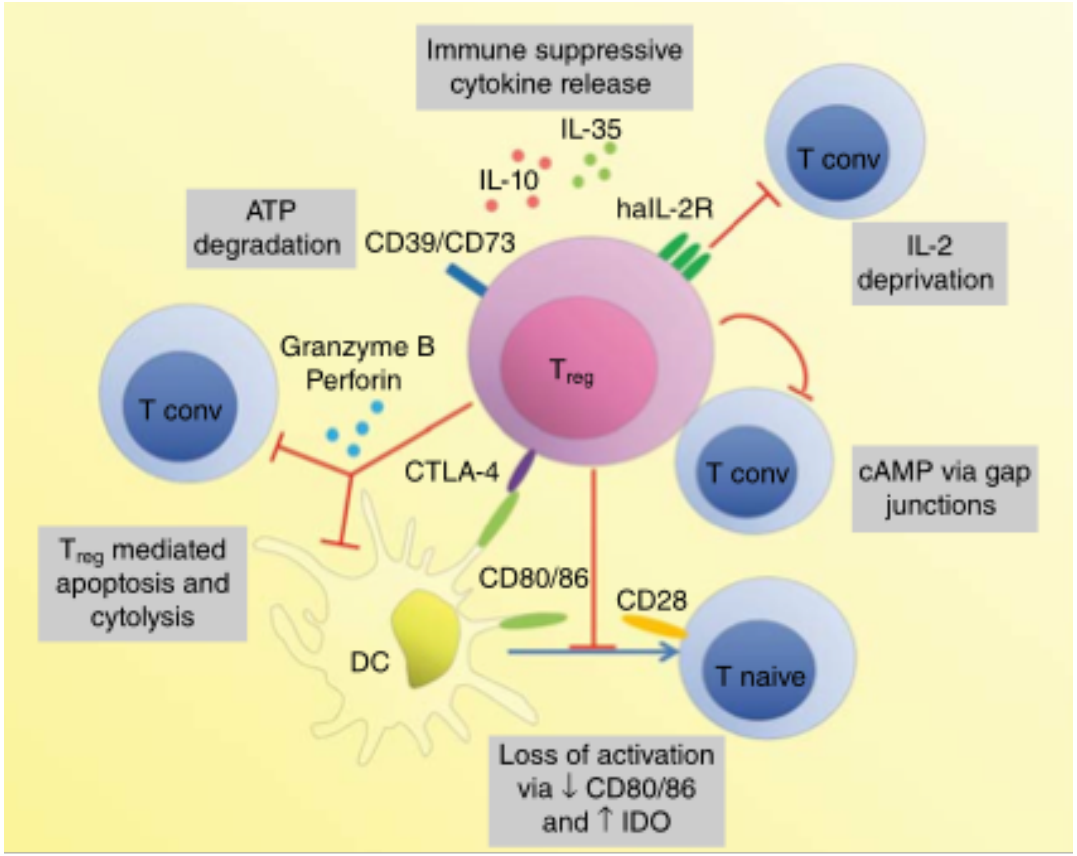
Lindau et al. The immunosuppressive tumor network: myeloid derived suppressor cell, regulatory T cells and natural killer cells. Immunology. 2012

Regulatory T cells



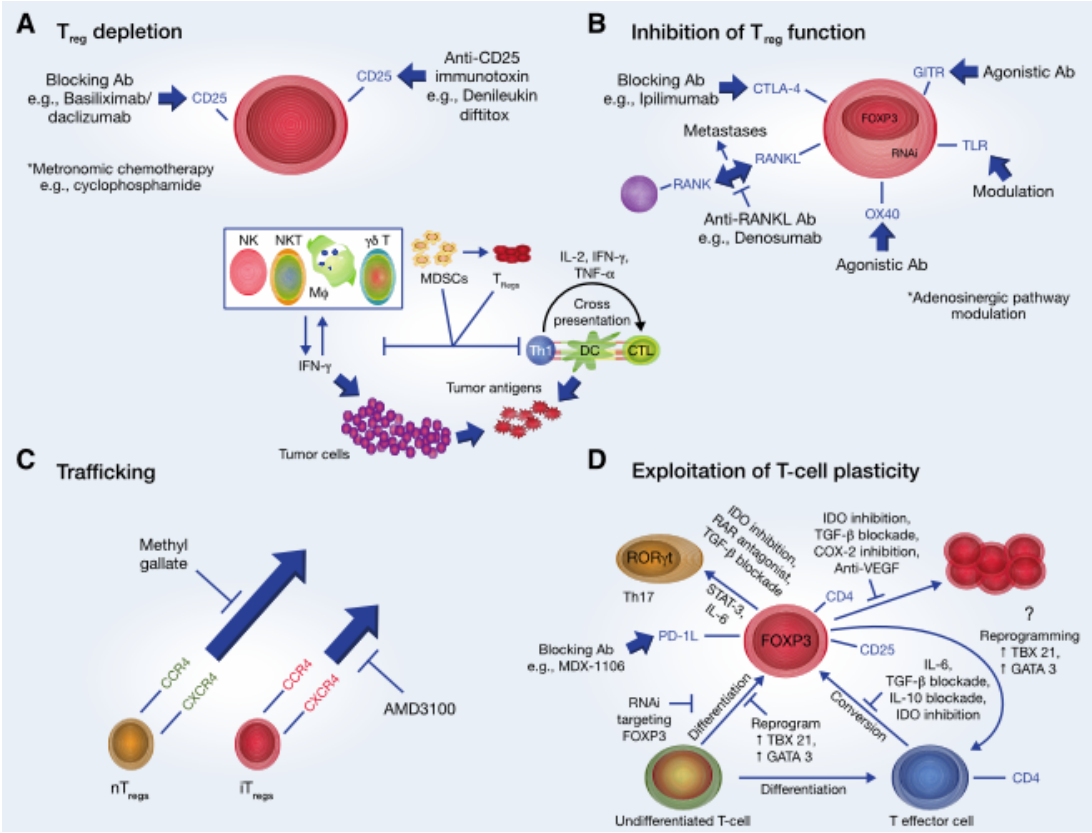
Basic principles of tumor-associated regulatory T cell biology. Peter A. Savage, Sven Malchow, and Daniel S. Leventhal

Regulatory T cells in anti-tumor immunity



Oleinika et al. Clinical & Exp Immunology 2013

Opportunities for Targeting Tregs ?

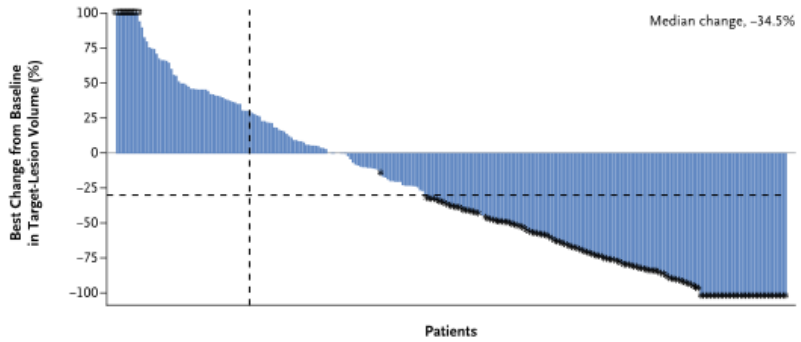


Strategies for Targeting Tregs – Monoclonal Antibodies

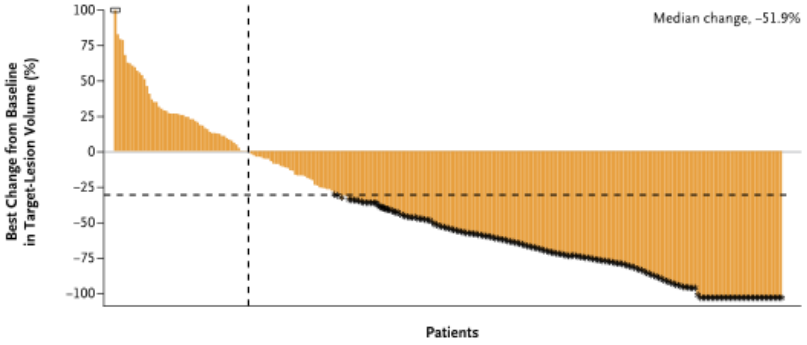
- Cell surface molecules selectively enriched include CD25, CTLA-4, GITR, 4-1BB, OX-40, LAG3, and TIGIT, and some chemokine receptors such as CCR4 and CCR8
- Ipilimumab predominantly kills CTLA-4-expressing Tregs in tumor tissues by antibody-dependent cellular cytotoxicity (ADCC) in mouse models
- Clinical responders among ipilimumab-treated melanoma patients showed a significant reduction of tumor Tregs

Regulatory T Cells and Human Disease
Sakaguchi et al, Annual Review of Immunology 2020 38:1, 541-566

A Nivolumab

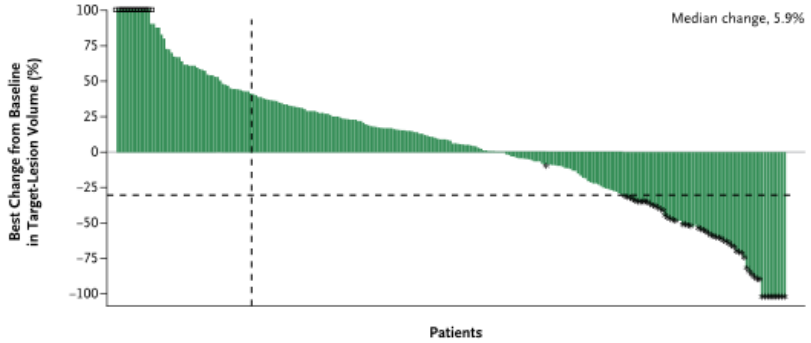


B Nivolumab plus Ipilimumab



(Wolchok et al, 2017)

C Ipilimumab

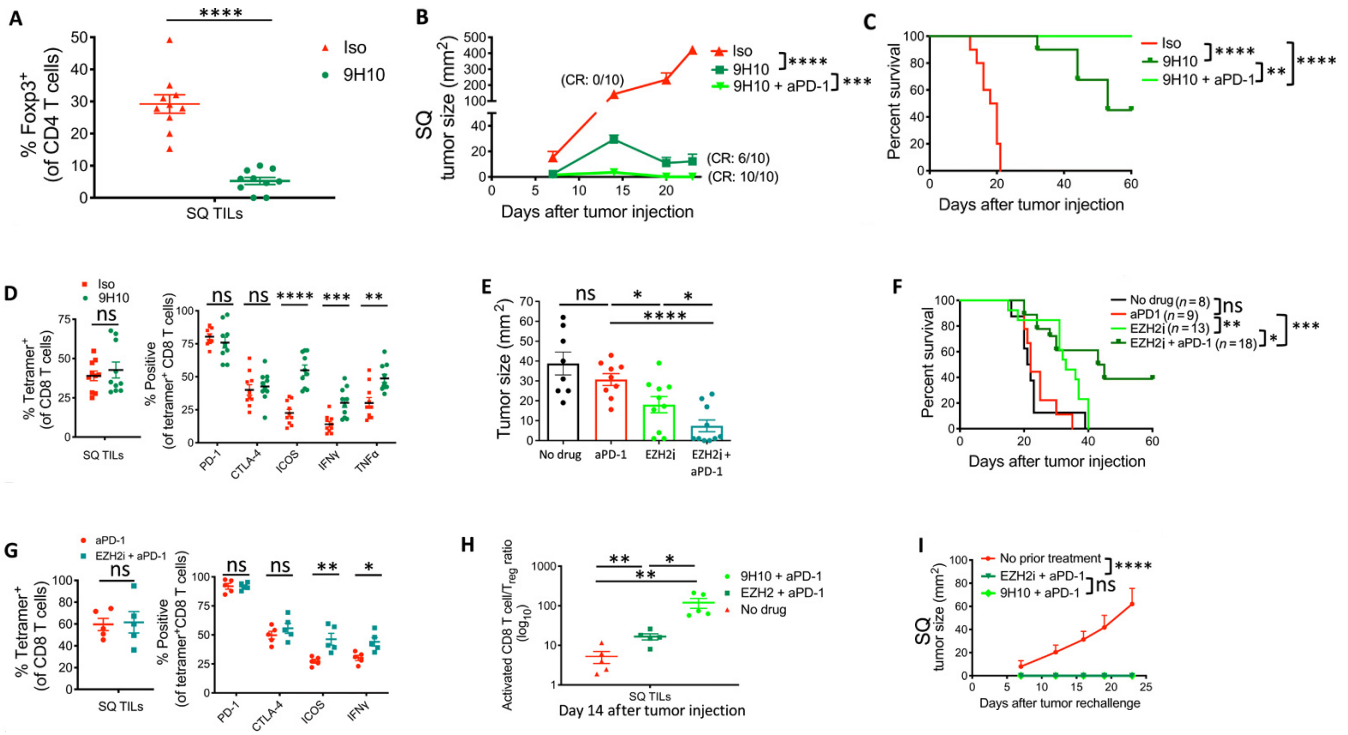


» 3-year median OS was 58% in nivo+ipi, 52% nivo alone, 34% ipi alone

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

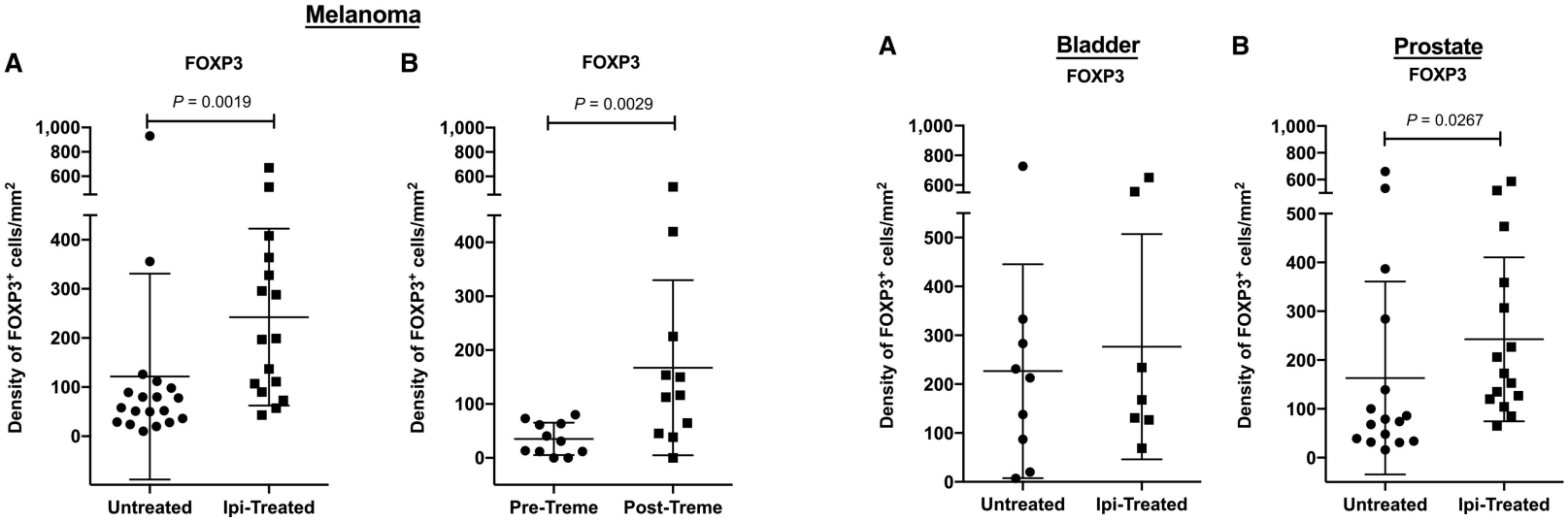
J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob, C.L. Cowey, C.D. Lao, D. Schadendorf, R. Dummer, M. Smylie, P. Rutkowski, P.F. Ferrucci, A. Hill, J. Wagstaff, M.S. Carlino, J.B. Haanen, M. Maio, I. Marquez-Rodas, G.A. McArthur, P.A. Ascierto, G.V. Long, M.K. Callahan, M.A. Postow, K. Grossmann, M. Sznol, B. Dreno, L. Bastholt, A. Yang, L.M. Rollin, C. Horak, F.S. Hodi, and J.D. Wolchok

Treg targeting immunotherapy enhances reverses immune dysfunction in liver metastasis



James C. Lee et al. Sci. Immunol. 2020;5:eaba0759

Effect of CTLA-4 blockade on FOXP3+ cells in human melanoma and GU tumors



Anu Sharma et al. Clin Cancer Res 2019;25:1233-1238

Tiragolumab, an Anti-TIGIT Antibody

» Tiragolumab is a fully human IgG1/kappa anti-TIGIT monoclonal antibody with an intact Fc region that blocks the binding of TIGIT to its receptor PVR

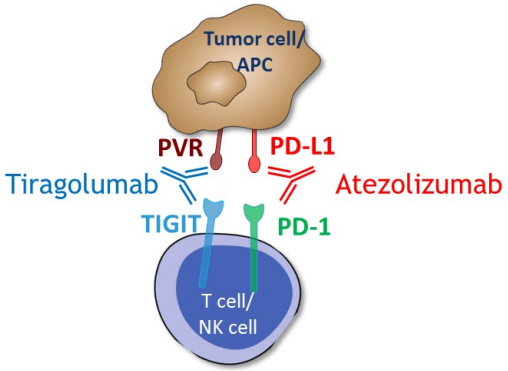
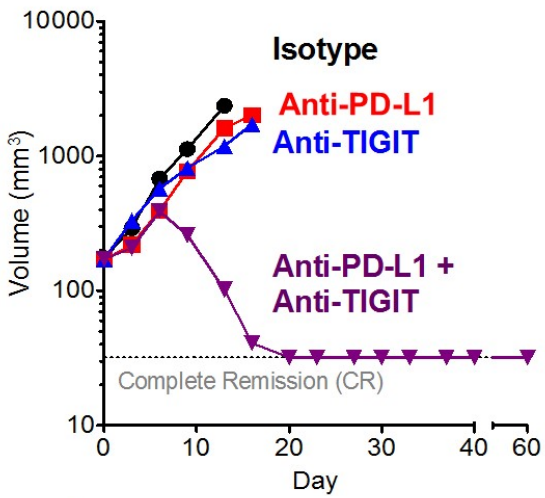


Figure adapted from Manieri et al. *Trends Immunology* 2017

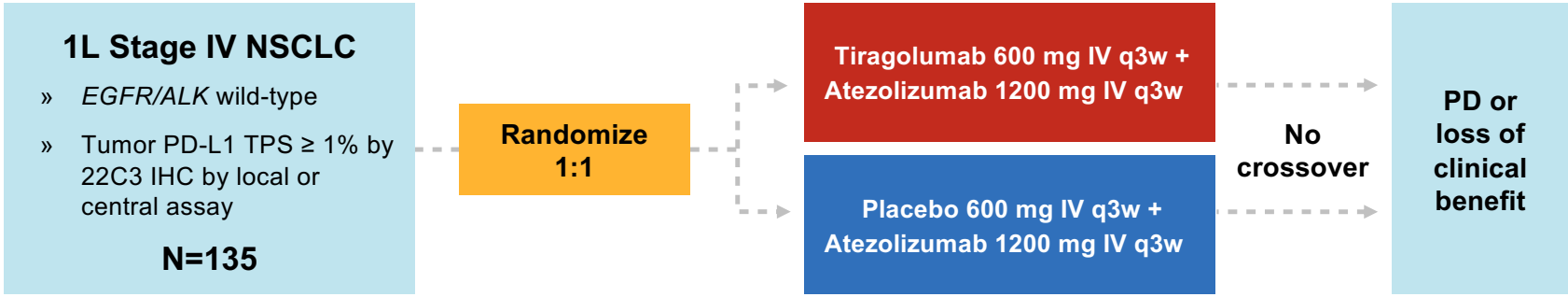
» In preclinical models, combination treatment with anti-TIGIT and anti-PD-L1 antibodies synergistically improves tumor control and prolongs survival in mice[1]



[1] Johnston et al. *Cancer Cell* 2014

Primary analysis of a randomized, double-blind, phase II study of the anti-TIGIT antibody tiragolumab (tira) plus atezolizumab (atezo) versus placebo plus atezo as first-line (1L) treatment in patients with PD-L1-selected NSCLC (CITYSCAPE). Delvys Rodriguez-Abreu et al, Journal of Clinical Oncology 2020 38:15_suppl, 9503-9503

CITYSCAPE Study Design



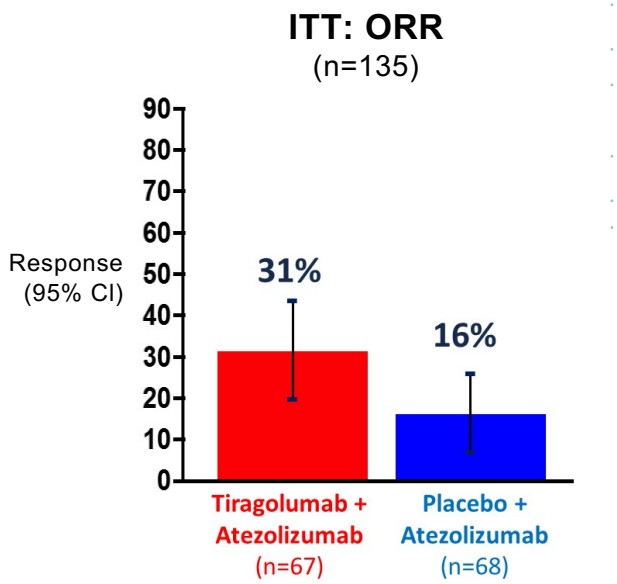
Stratification Factors:

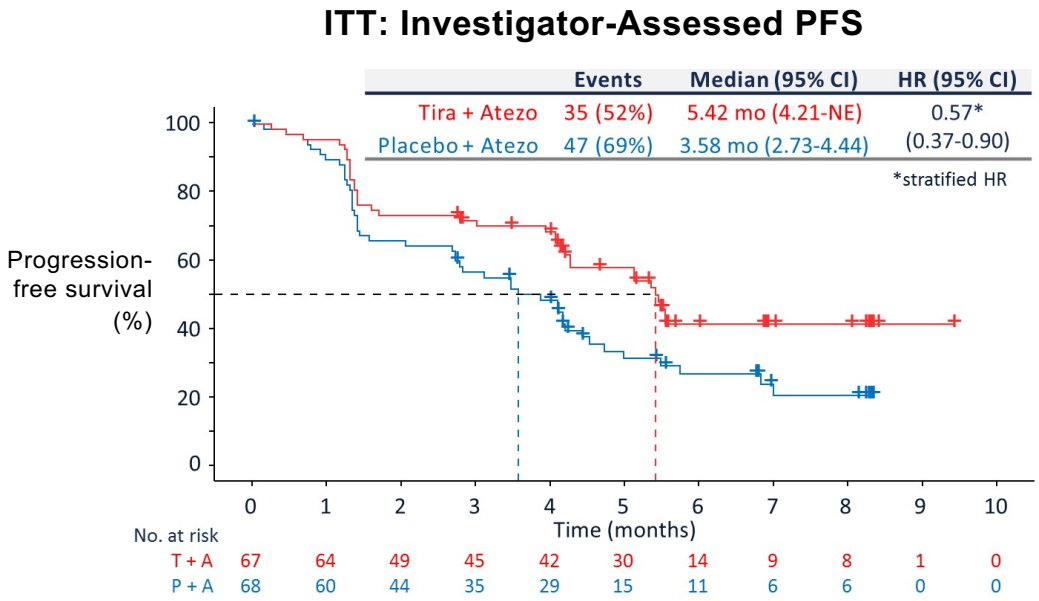
- PD-L1 TPS (1-49% vs ≥50%
- Hisytology (Non-Squamous vs Squamous)
- Tobacco use (yes vs no)

- **Co-Primary Endpoints: ORR** and **PFS**
- **Key Secondary Endpoints: Safety,** DOR, OS, Patient-reported outcomes (PROs)
- **Exploratory Endpoints:** Efficacy analysis by PD-L1 status

Porter DL and Antin JH. Annu Rev Med. 1999;50:369–86.

Clinical Response Rate





ITT = intention-to-treat; NE = non-evaluable, P+A = placebo + atezolizumab; T+A = tiragolumab + atezolizumab

Primary analysis data cutoff: 30 June 2019

Strategies for Targeting Tregs – Small Molecules

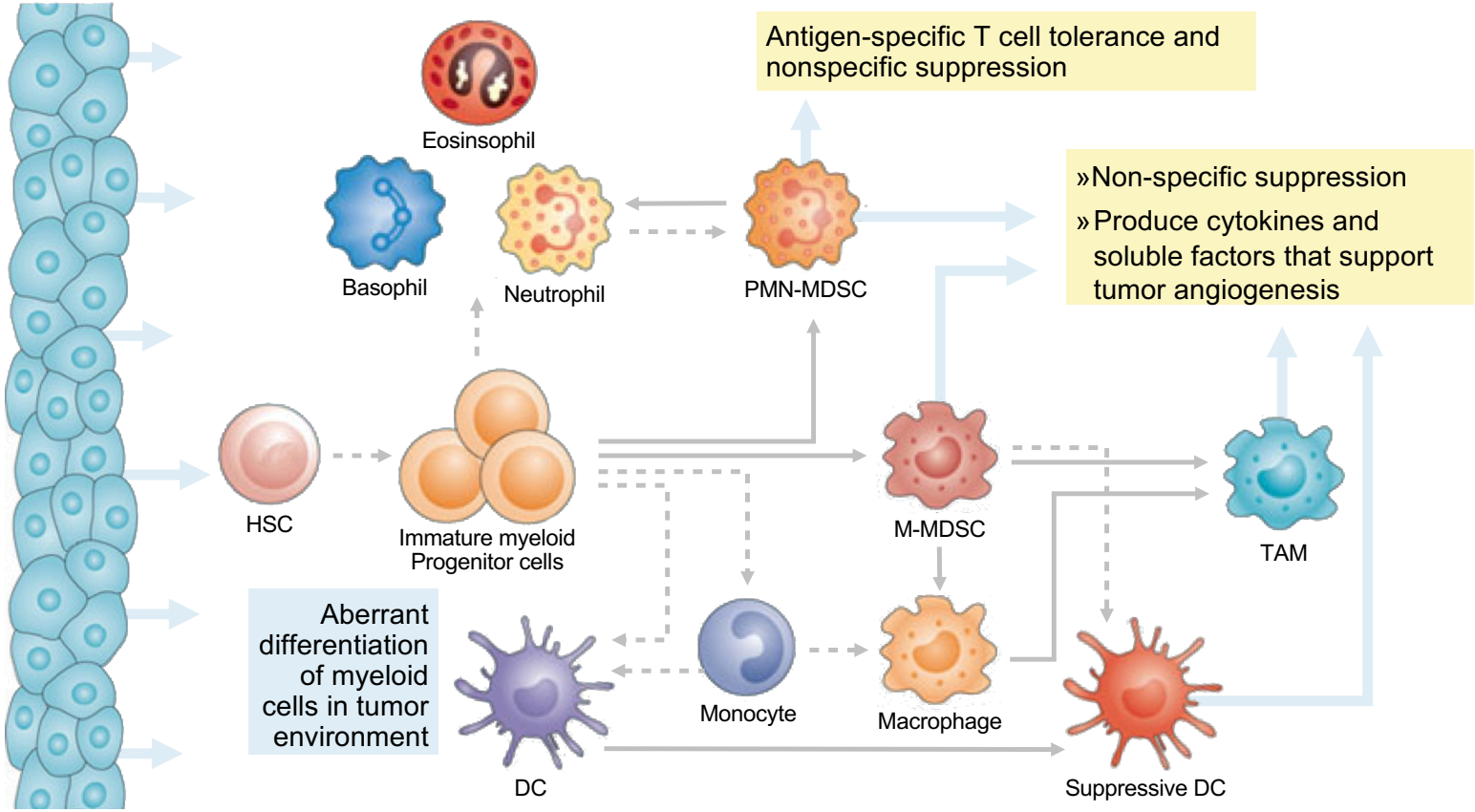
» Long-term imatinib-treated CML patients in complete molecular remission with no detectable BCR-ABL mRNA in the blood showed selective depletion of FoxP3+ effector Tregs

» The drug inhibits tyrosine phosphorylation of lymphocyte-specific protein tyrosine kinase (LCK)

» LCK inhibition by imatinib reduces the TCR proximal signal more severely in activated Tregs than in activated Tconvs

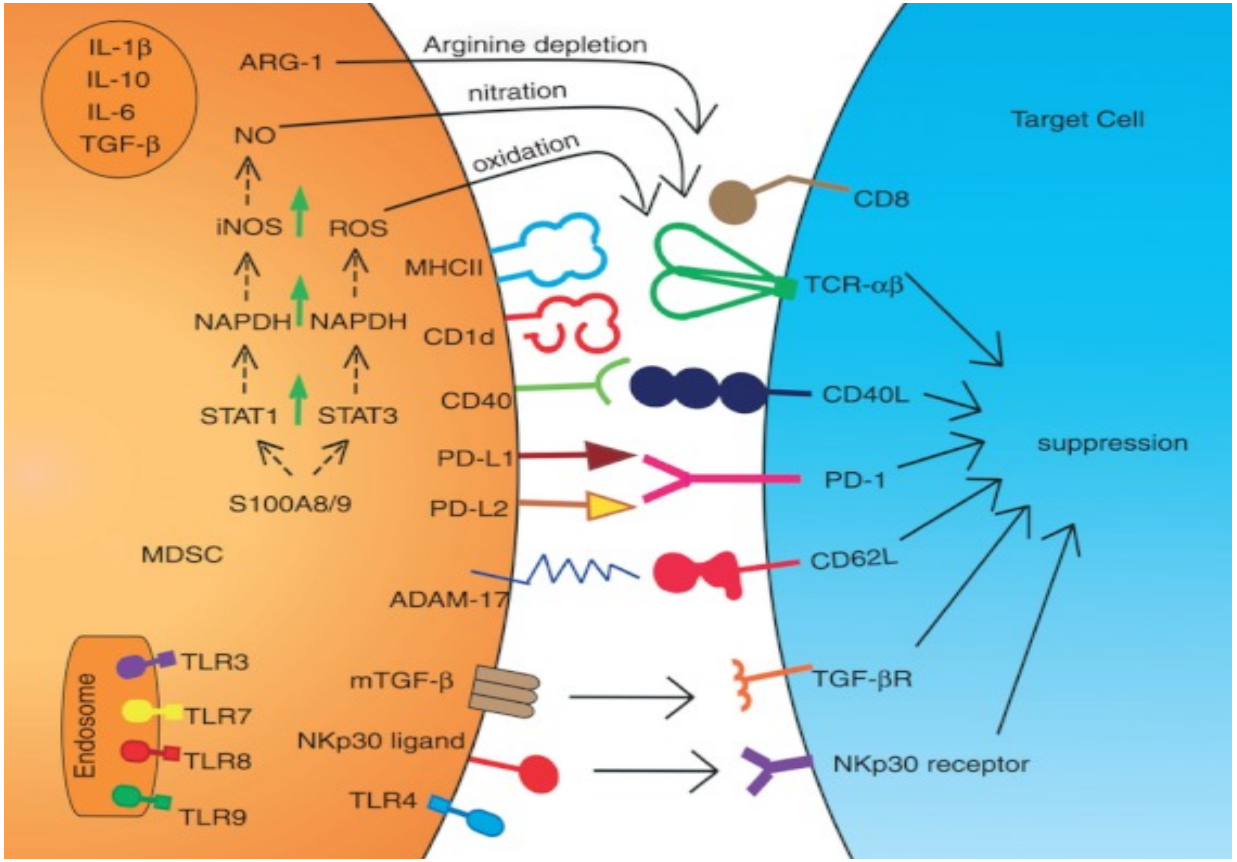
Regulatory T Cells and Human Disease
Sakaguchi et al, Annual Review of Immunology 2020 38:1, 541-566

MDSC



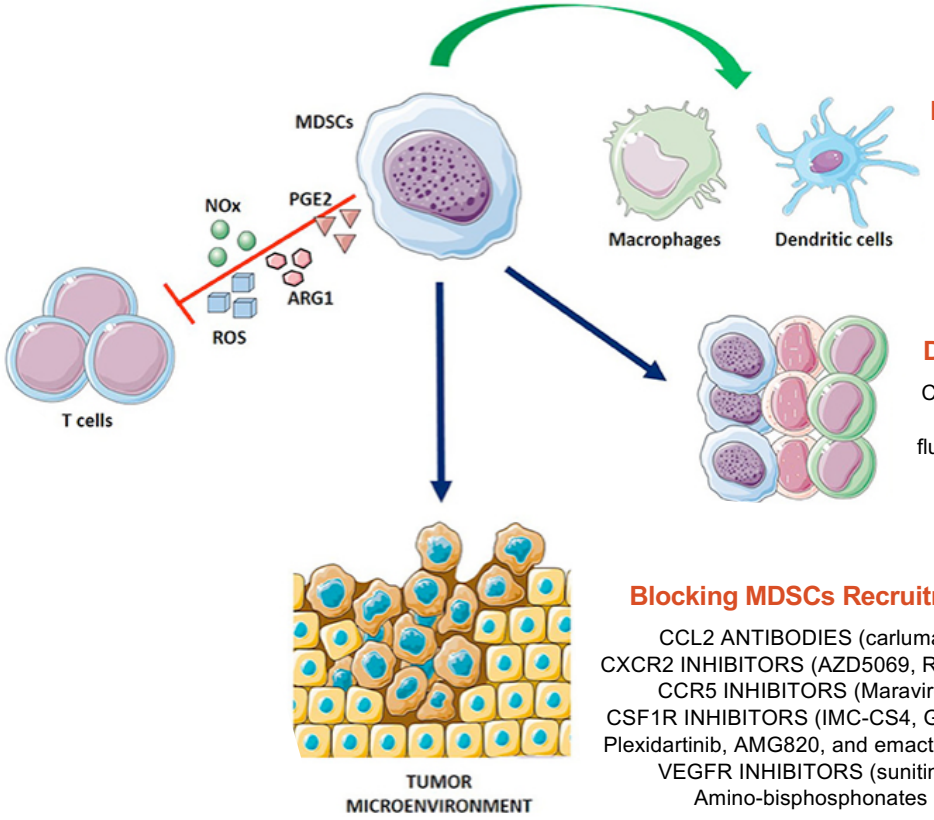
Gabrilovich et al. Coordinated regulation of myeloid cells by tumours. Nat Rev Immunology. 2012

Myeloid-Derived Suppressor Cells



Lindau et al. The immunosuppressive tumor network: myeloid derived suppressor cell, regulatory T cells and natural killer cells. Immunology. 2012

Approaches for Targeting MDSCs



Promoting MDSCs DIFFERENTIATION

ATRA,
Vitamin D3,
STAT3 Inhibitors

Inhibition oF MDSCs-Mediated Immunosuppression

CCL2 ANTIBODIES (carlumab)
CXCR2 INHIBITORS (AZD5069, Reparixin)
CCR5 INHIBITORS (Maraviroc)
CSF1R INHIBITORS (IMC-CS4, GW2580, Plexidartinib, AMG820, and emactuzumab)
VEGFR INHIBITORS (sunitinib)
Amino-bisphosphonates

Depletion of MDSCs

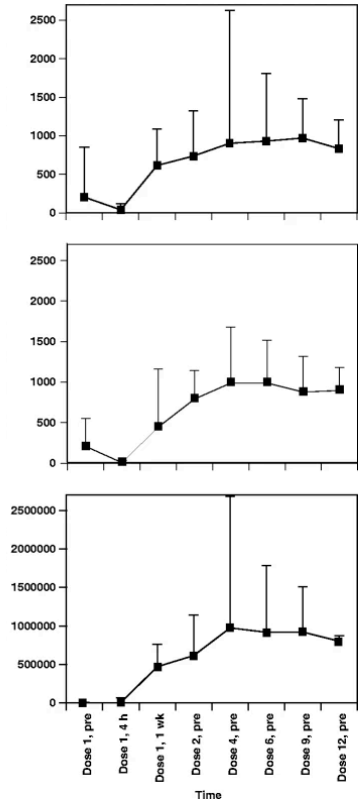
CHEMOTHERAPEUTICS (gemcitabine, 5-fluorouracil, paclitaxel, and doxorubicin)
PEPTIBODIES

Blocking MDSCs Recruitment

CCL2 ANTIBODIES (carlumab)
CXCR2 INHIBITORS (AZD5069, Reparixin)
CCR5 INHIBITORS (Maraviroc)
CSF1R INHIBITORS (IMC-CS4, GW2580, Plexidartinib, AMG820, and emactuzumab)
VEGFR INHIBITORS (sunitinib)
Amino-bisphosphonates

Case Study: Carlumab

- Carlumab: IgG that binds to to human CCL2.
- In preclinical studies, carlumab significantly slowed prostate tumor growth in mice and reduced macrophage infiltration
- In a phase 2 study of 46 CRPC patients, there were zero responses
- Median OS 10 months



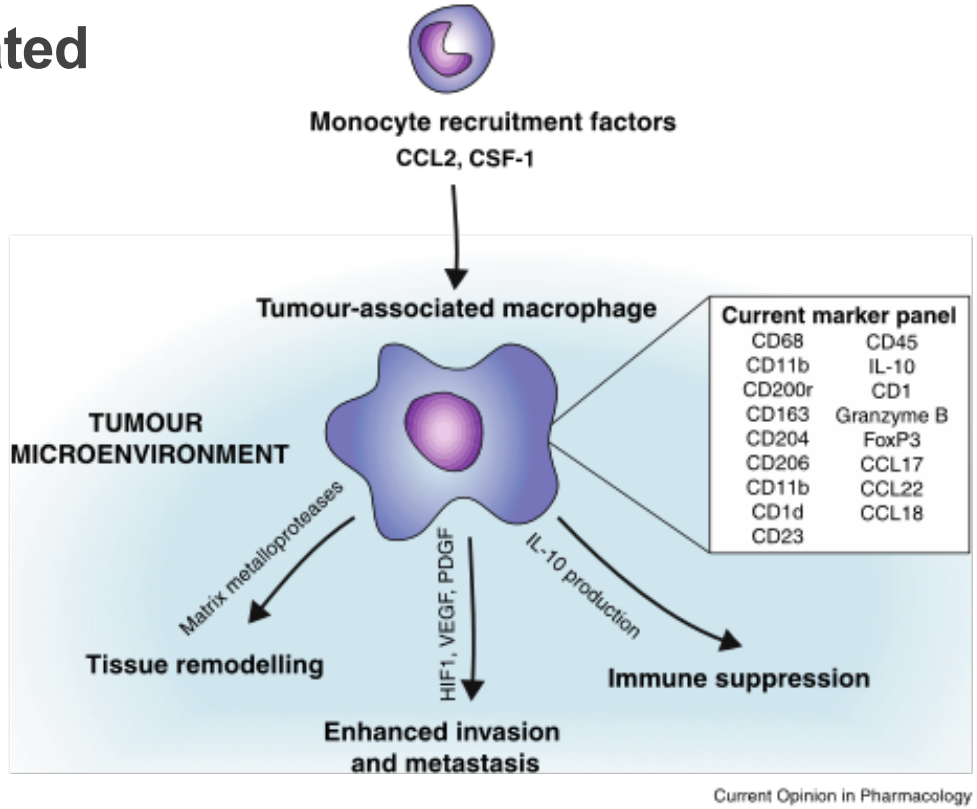
Media free CCL2 (pg/mL), Column Method

Media free CCL2 (pg/mL), MSD Method

Median total CCL2 (pg/mL)

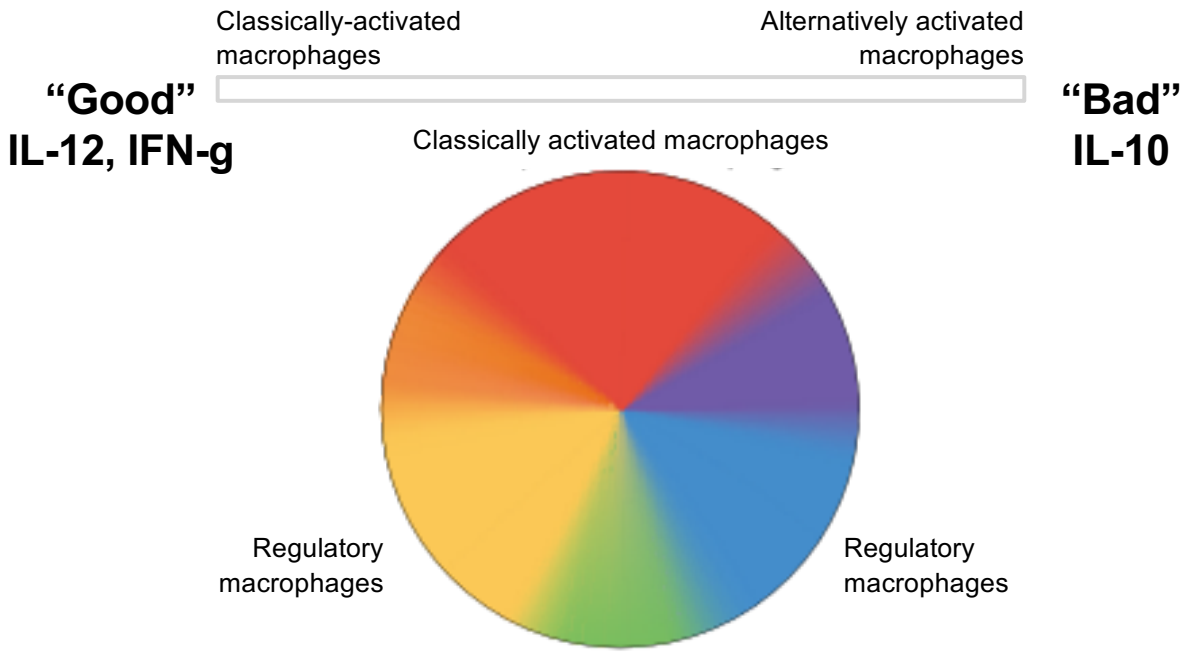
Pienta, K.J., Machiels, JP., Schrijvers, D. et al. Phase 2 study of carlumab (CNTO 888), a human monoclonal antibody against CC-chemokine ligand 2 (CCL2), in metastatic castration-resistant prostate cancer. Invest New Drugs 31, 760–768 (2013).

Tumor Associated Macrophages



Cook and Hagemann. Tumour-associated macrophages and cancer. Curr. Opinion in Pharmacology. 2013.

TAMs may have positive or negative effects on anti-tumor immunity



Color wheel of macrophage evolution

Moser and Edwards. Exploring the full spectrum of macrophage activation. Nat Rev Immunol. 2008

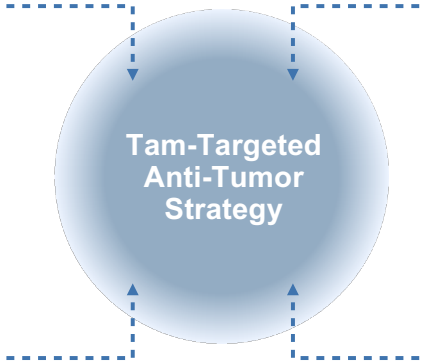
Opportunities for Targeting TAMs?

Inhibiting macrophage recruitment

- Inhibitors of CCL2/CCR2 (e.g. Yondeli and RS102895)
- Inhibitors of M-CSF/M-CSFR (e.g. anti-M-CSF mAb, JNJ-28312141 and GW2580)
- Inhibitors of other chemoattractants (e.g. CCL5, CSCL-12 and VEGF) and their receptors
- Inhibitors of the pathways for recruitment (e.g. inhibitors of HIFs)

Enhancing M1 tumoricidal activity of TAMs

- Agonists of NF-κB (e.g. TLR agonists, anti-CD40 mAb and anti-IL-10R mAb)
- Agonists of STAT1 (e.g. interferon)
- Agonists of other M1 pathways (e.g. SHIP)
- Other agents (e.g. GM-CSF, IL-12 and thymosin α1)



Suppressing TAM survival

- Chemical drugs (e.g. bisphosphonates, dasatinib) that deplete macrophages directly
- Immunotoxin-conjugated mAbs (e.g. anti-FRβ mAb) targeting membrane molecules of TAMs
- Attenuated bacteria (e.g. *Shigella flexneri*) that induce apoptosis of macrophages
- Agents that induce macrophages to express molecules (e.g. legumain and CD1d) that can be targeted by cytotoxic T lymphocytes

Blocking M2 tumor-promoting activity of TAMs

- Inhibitors of STAT3 (e.g. sunitinib, sorafenib, WP1066, corosolic acid and oleanolic acid)
- Inhibitors of other M2 pathways (e.g. c-Myc, PPAR-α/γ, PI3K, KLF4, HIFs, Ets2, DcR3, mTOR)
- Other agents (e.g. HRG, CuNG, MDXAA, silibinin and PPZ)

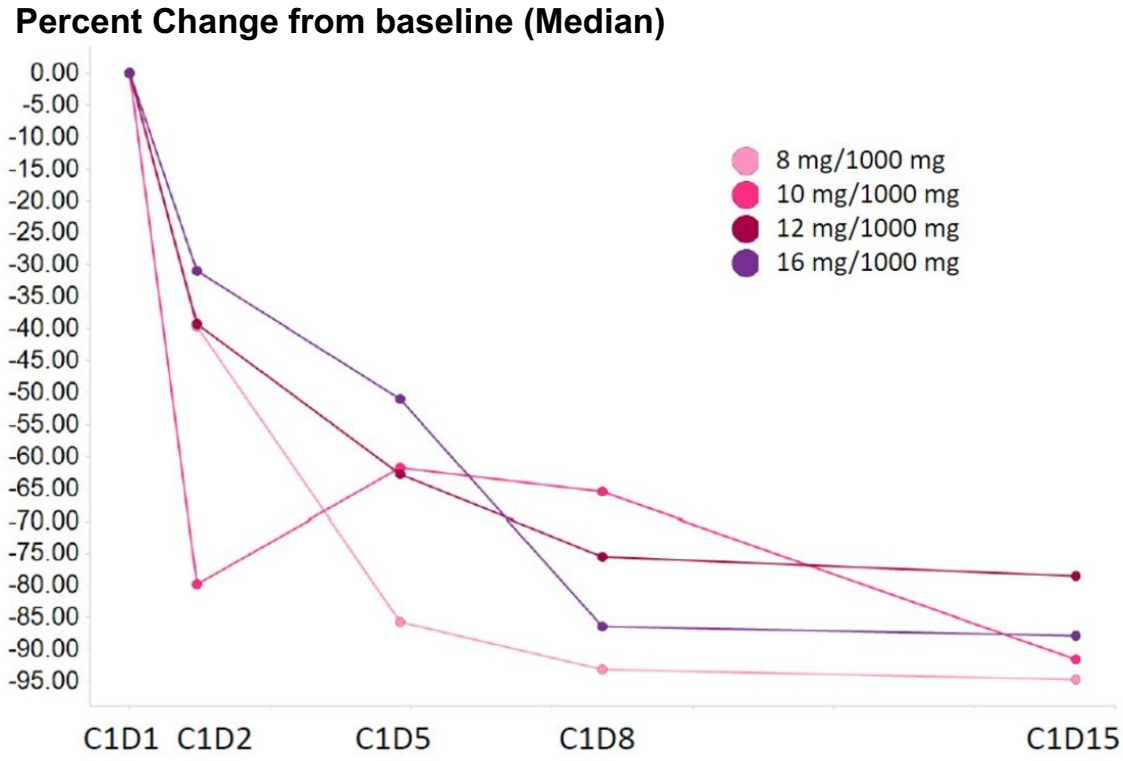
Tang et al. Anti-tumour strategies aiming to target tumour-associated macrophages. Immunology. 2012

Case Study: Emactuzumab

- Emactuzumab is a recombinant, humanized mAb directed against CSF-1R
- Inhibition of CSF-1R signaling by various CSF-1R inhibitors acts as an amplifier of aCD40-regulated general immune activation via TAM reprogramming
- In a Phase 1b study of 37 advanced solid tumor patients, there were zero responses when combined with a CD40 agonist

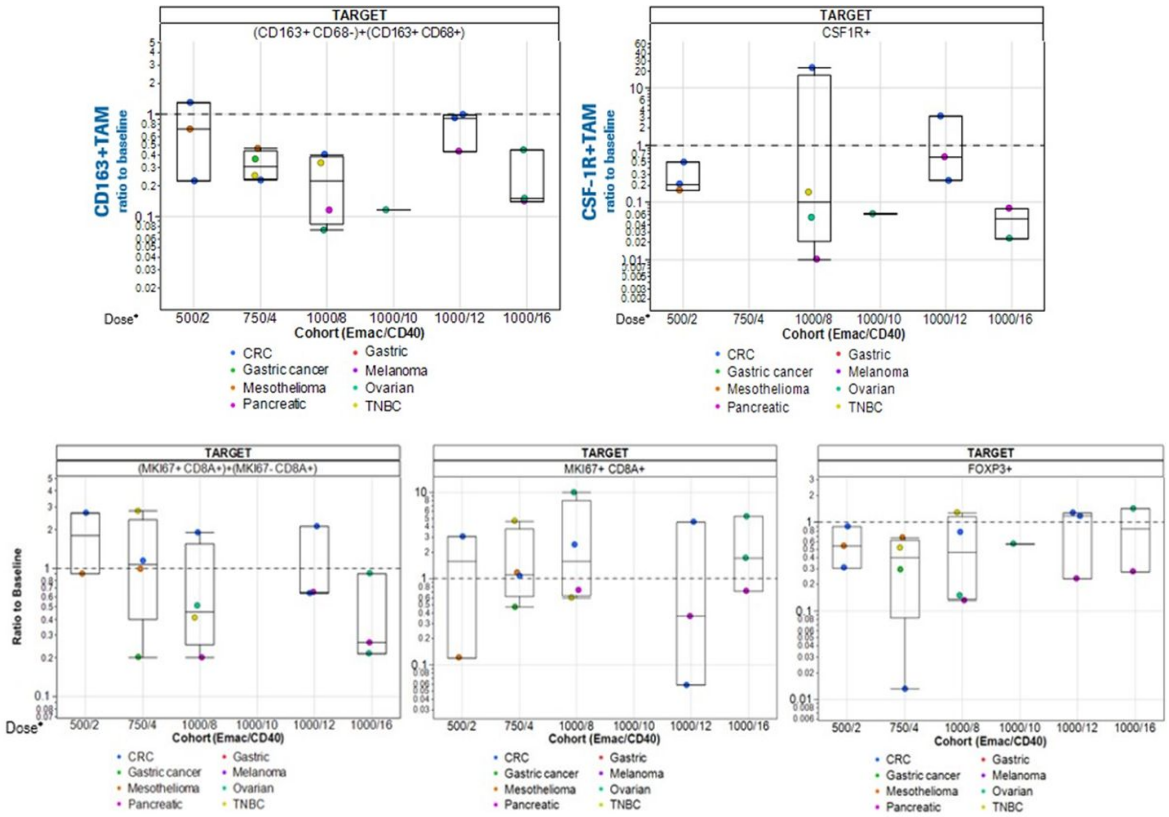
Jean-Pascal Machiels et al. J Immunother Cancer 2020;8:e001153

Percent change of peripheral CD14dim CD16high monocytes from baseline



Jean-Pascal Machiels et al. J Immunother Cancer 2020;8:e001153

Change from baseline of TAMs and Tregs in paired biopsies



Jean-Pascal Machiels et al. J Immunother Cancer 2020;8:e001153

Lenvatinib plus Pembrolizumab – Case Study

» Until 2018, Megace was the only FDA-approved drug for endometrial cancer

» Area of therapeutic need → ORR to single agent chemotherapy is 5-15%

» Lenvatinib selectively inhibits VEGFR1–3 and other receptor tyrosine kinases (RTKs), including FGFR1–4, PDGFRα, KIT, and RET

Key Eligibility Criteria

» Aged ≥ 18 years
» Pathologically confirmed and metastatic endometrial carcinoma
» ≤ 2 Prior systemic therapies
» Measurable disease by irRECIST
» ECOG performance status ≤ 1
» Life expectancy ≥ 12 weeks

Lenvatinib
20 mg/day (oral)
+
Pembrolizumab
200 mg/3 weeks (IV)

Phase 2
Open-label; single-arm

Primary End Point

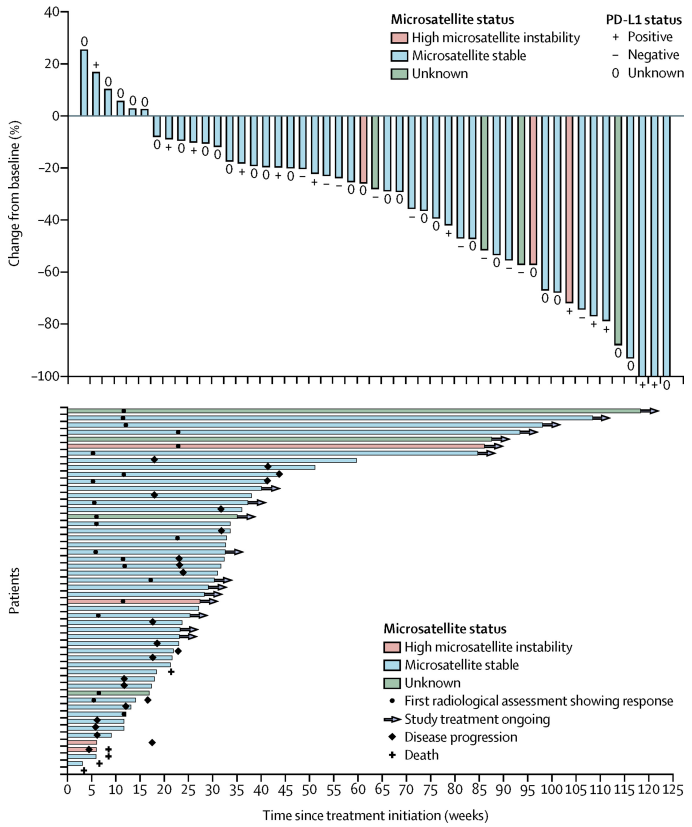
» ORR_{Week24}

Primary End Point

» Overall ORR
» DOR
» PFS
» Safety and tolerability

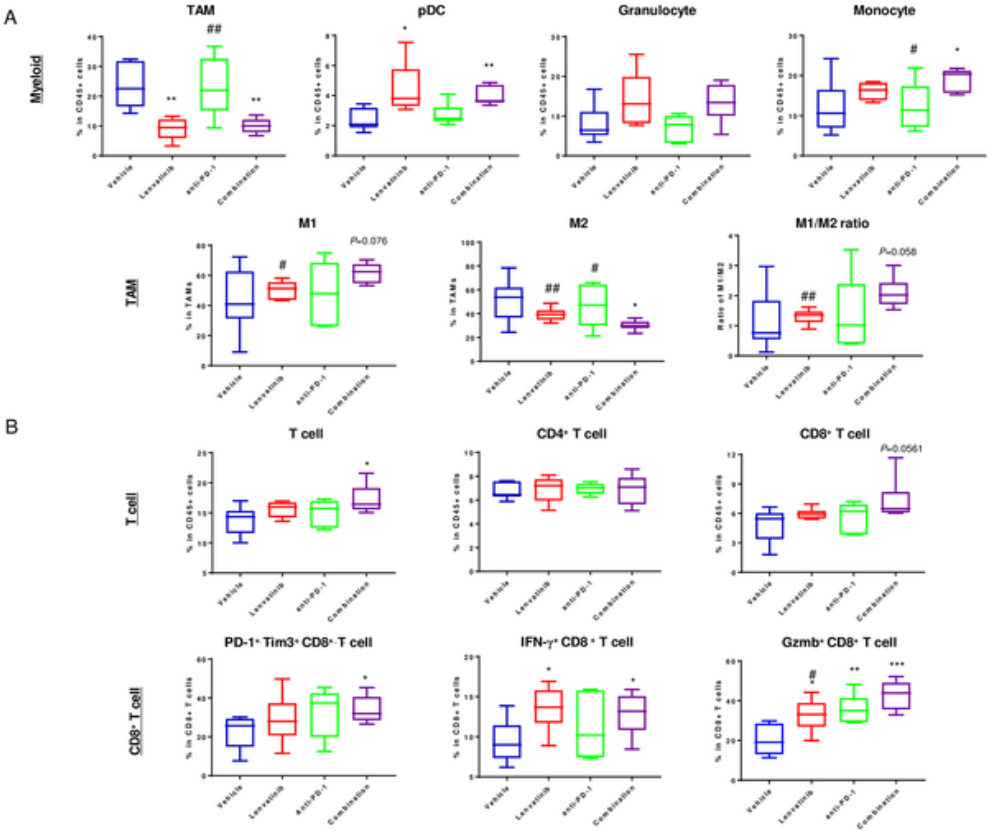
Len/Pem is Active in Recurrent Endometrial Cancer Regardless of MSI

- ORR was 39.6%
- PD-L1 staining was not predictive of response
- **83·0% (95% CI 55·9–94·2) had a duration of response of at least 6 months and 64·5% (32·8–84·2) had a response of at least 12 months' duration**
- **Objective responses in 2/4 MSI-H (50% [95% CI 6·8–93·2]) and 16/45 MSS (35·6% [21·9–51·2])**



The Lancet Oncology 2019 20711-718DOI: (10.1016/S1470-2045(19)30020-8)

Immune cell population analysis in a colon adenocarcinoma murine model



Kato Y, Tabata K, Kimura T, Yachie-Kinoshita A, Ozawa Y, et al. (2019) Lenvatinib plus anti-PD-1 antibody combination treatment activates CD8+ T cells through reduction of tumor-associated macrophage and activation of the interferon pathway. PLOS ONE 14(2): e0212513. https://

Conclusions

- Many immune populations play a role in the cancer immune phenotype beyond T cells
- Negative regulators of immune response
- Multiple attempts to target these immunosuppressive populations have been unrewarding
  - Few success stories to light the way forward

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Beyond T cells: Targeting Other Components of the Immune Response

Questions