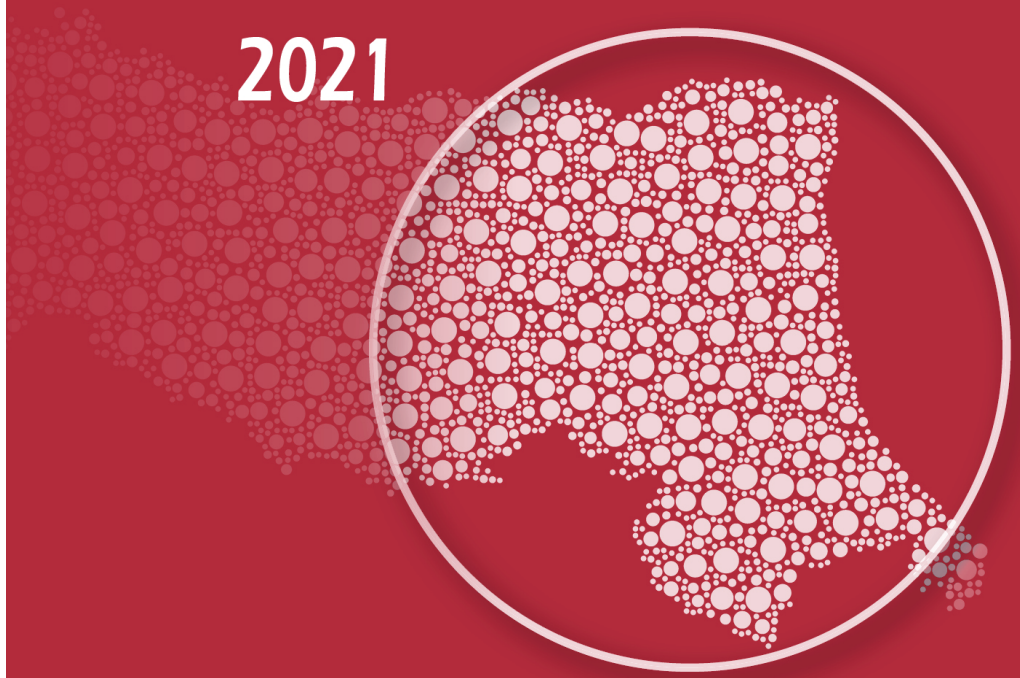


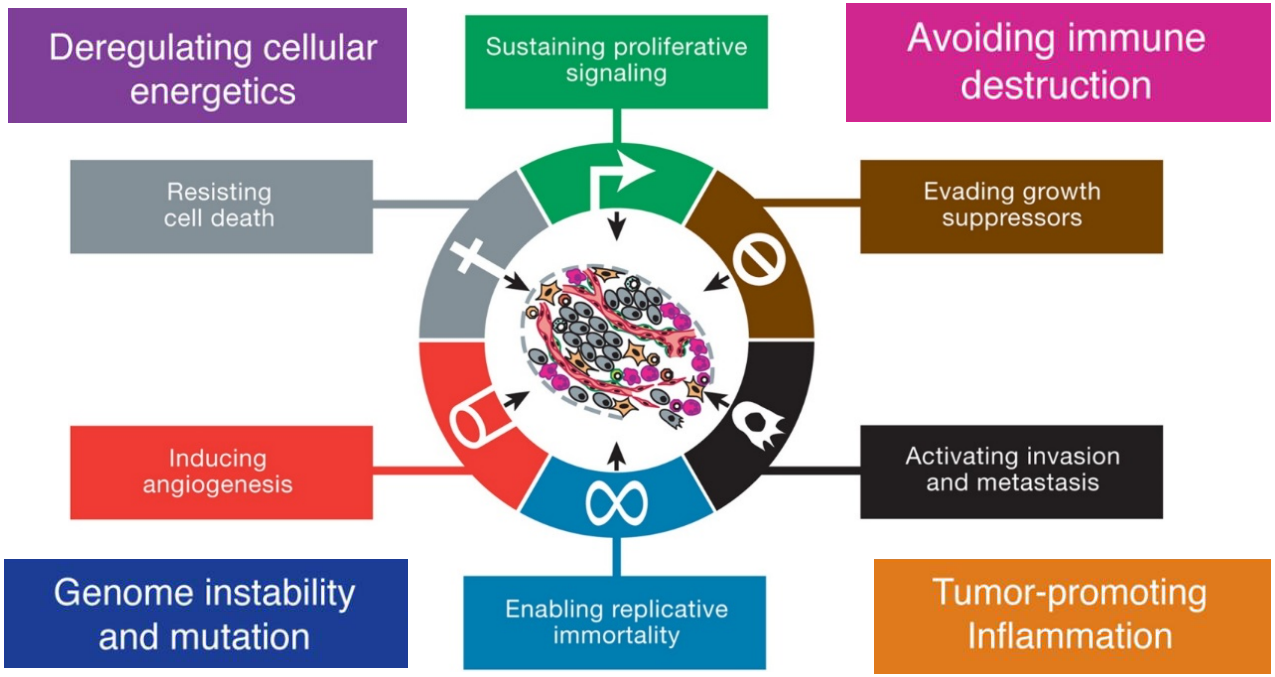
Progetto
Ematologia
Romagna

DALLA BIOLOGIA ALLA TERAPIA DELLE LEUCEMIE ACUTE MIELOIDI: NUOVI MECCANISMI E BERSAGLI TERAPEUTICI

Antonio Curti

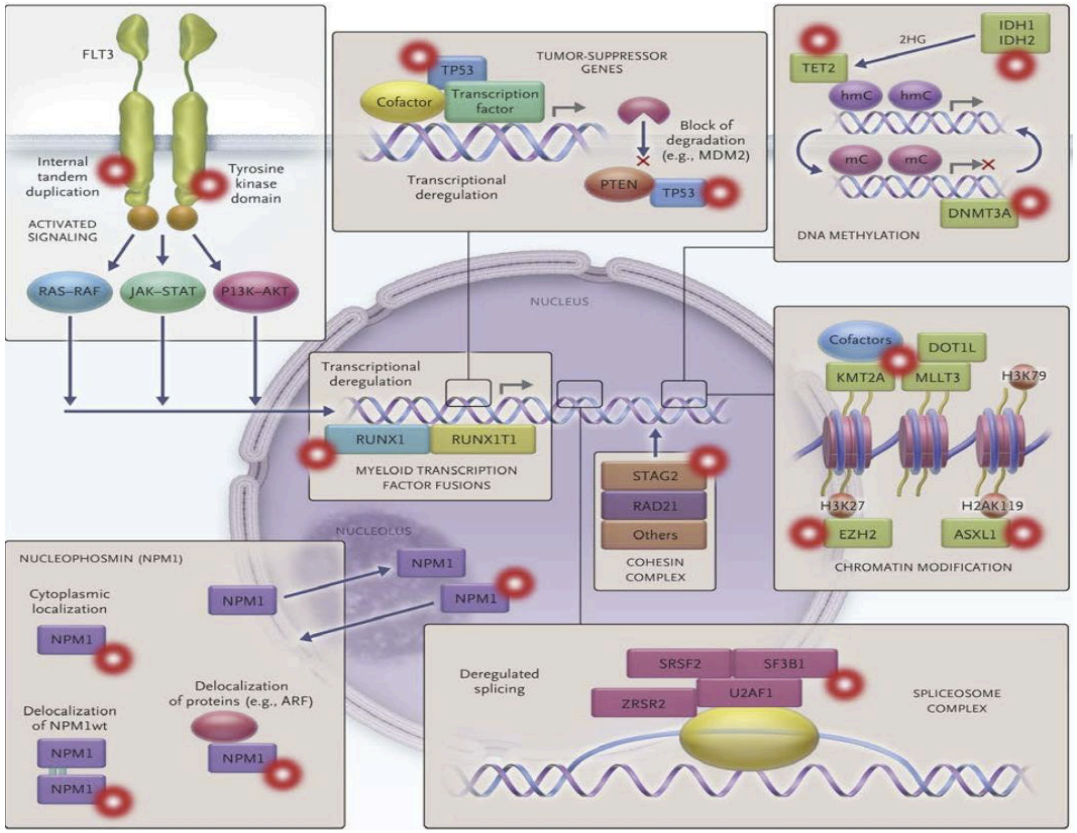
Istituto «Seràgnoli», Bologna

Emerging Hallmarks of Cancer



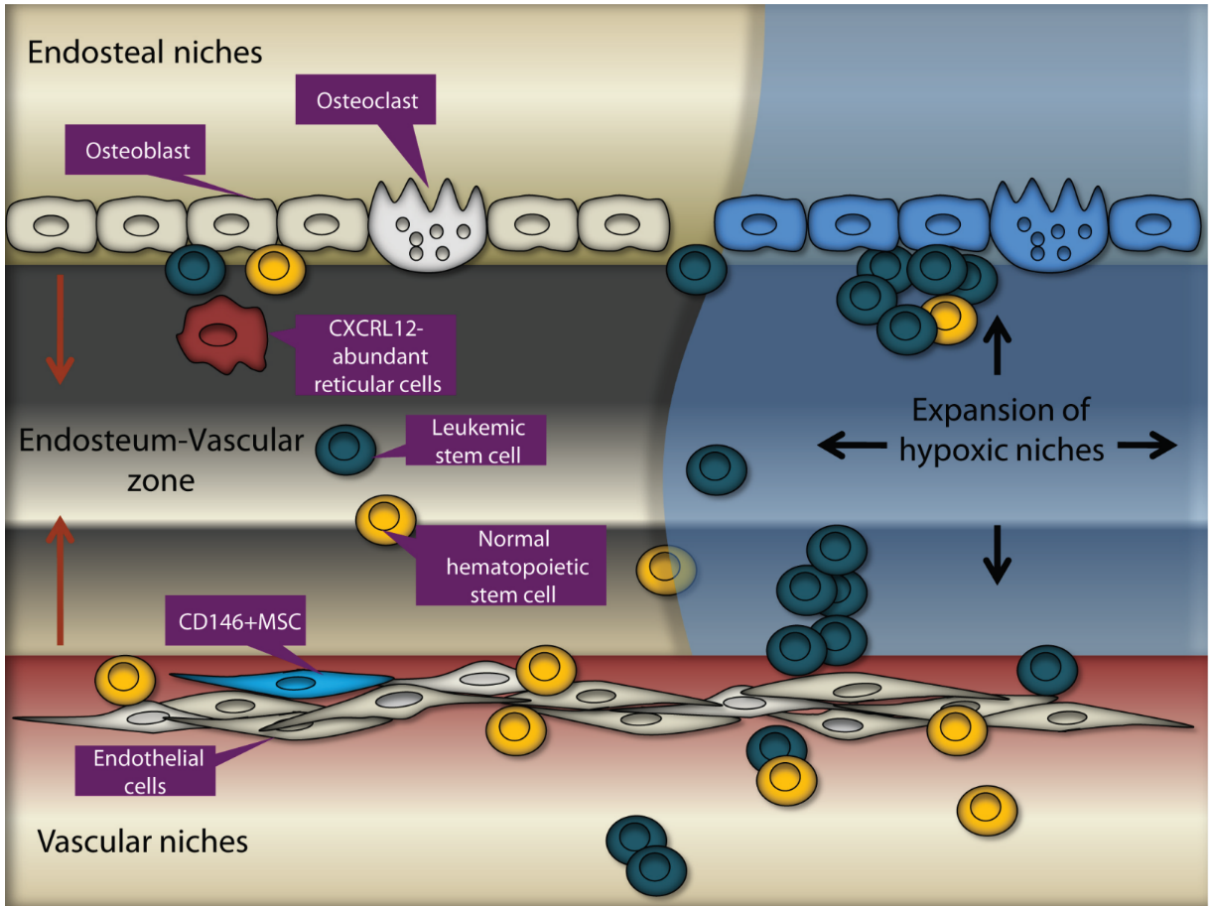
Cell 2011 144, 646-674

Pathobiology of AML



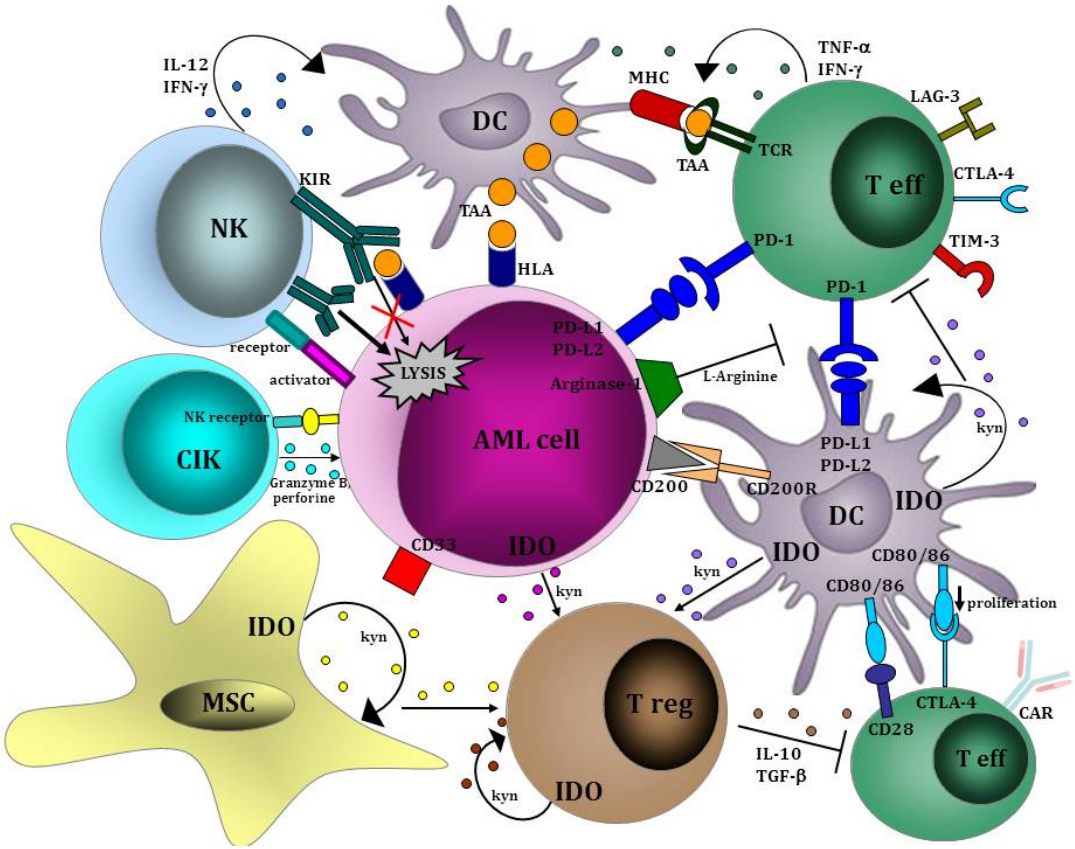
Dohner et al. N Engl J Med 2015

Leukemia Stem Cells and Microenvironment: Biology and Therapeutic Targeting

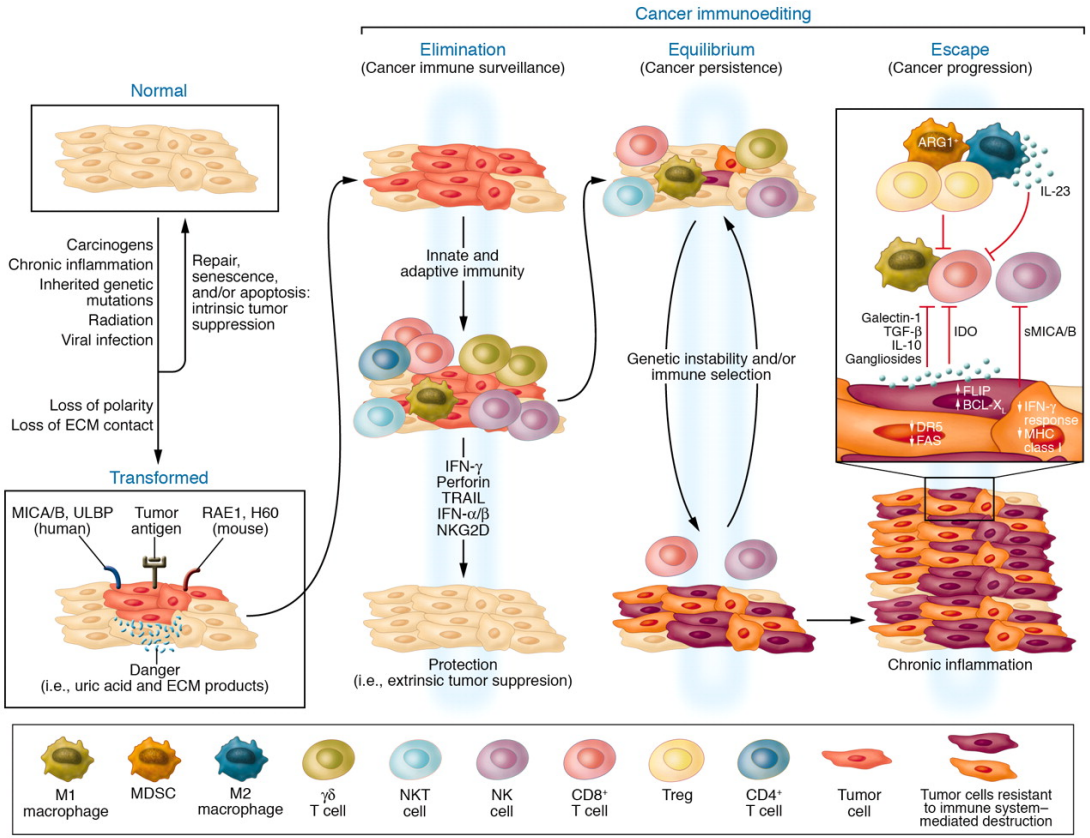


J Clin Oncol 29:591-599. 2011

AML and immunological microenvironment

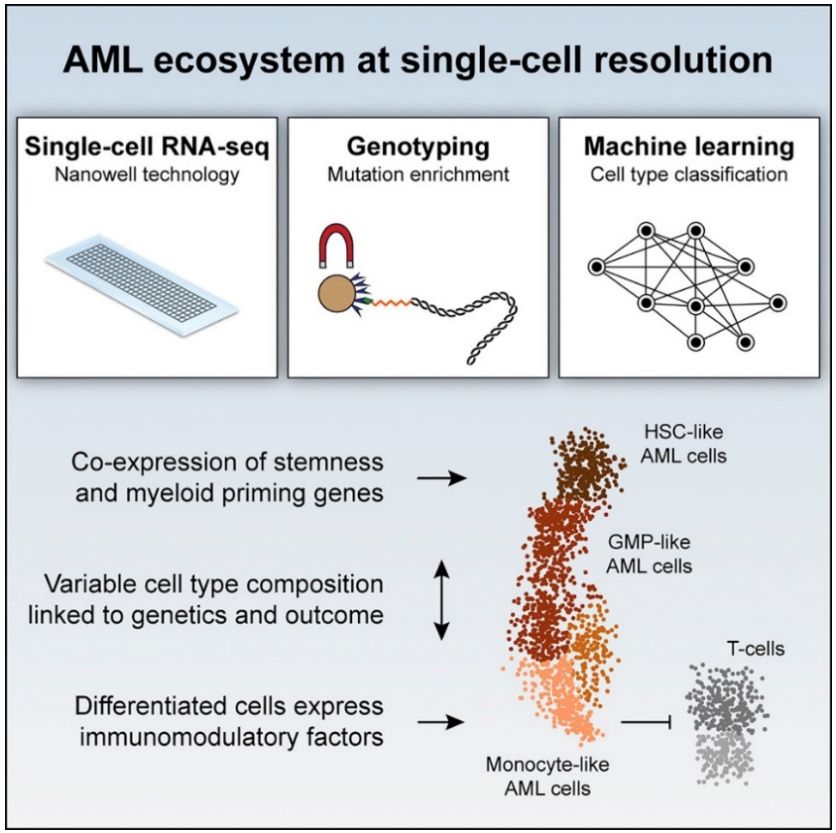


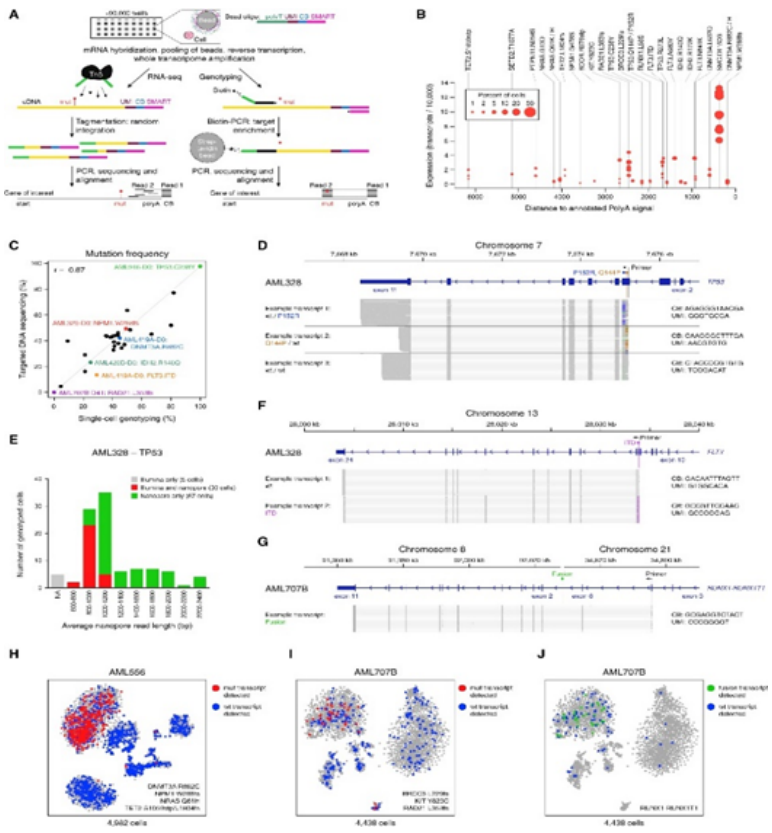
Cancer immunoediting: the three «E» theory



Swann and Smyth *J. Clin. Invest.* (2007)

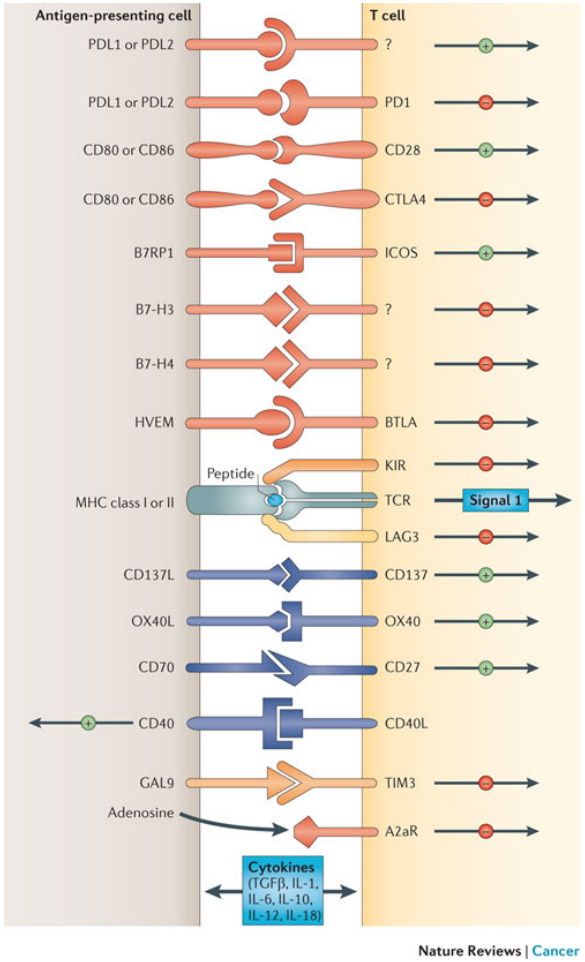
AML genotype influences immunological microenvironement toward tolerance





Van Galen P, Cell, 7 March 2019, Pages 1265-1281

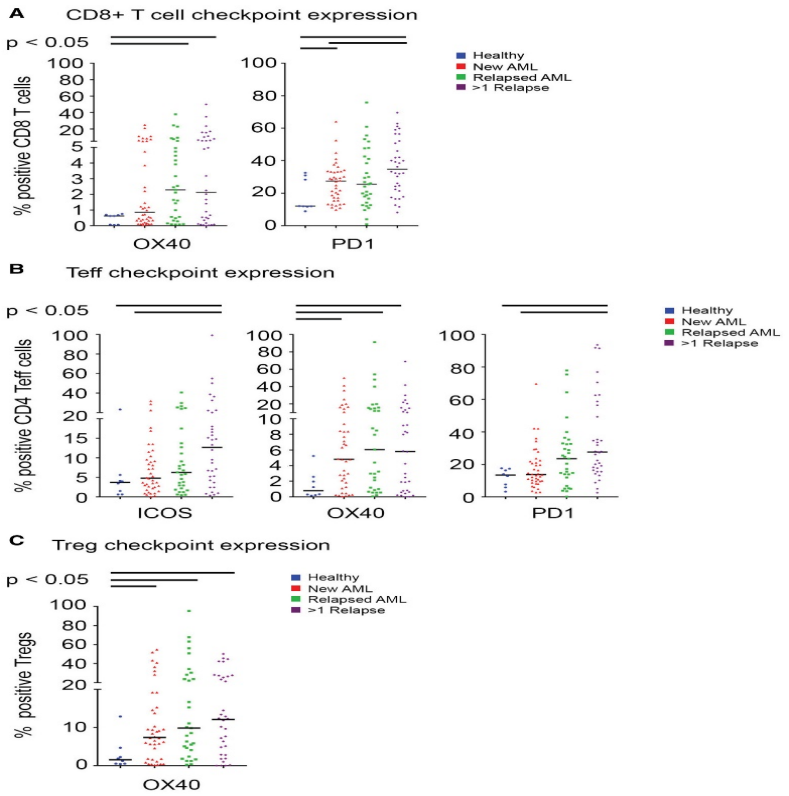
Multiple co-stimulatory and inhibitory interactions regulate T cell responses



Ligand–receptor interactions between T cells and (APCs) can occur at the initiation of T cell responses in lymph nodes (where the major APCs are dendritic cells) or in peripheral tissues or tumours (where effector responses are regulated).

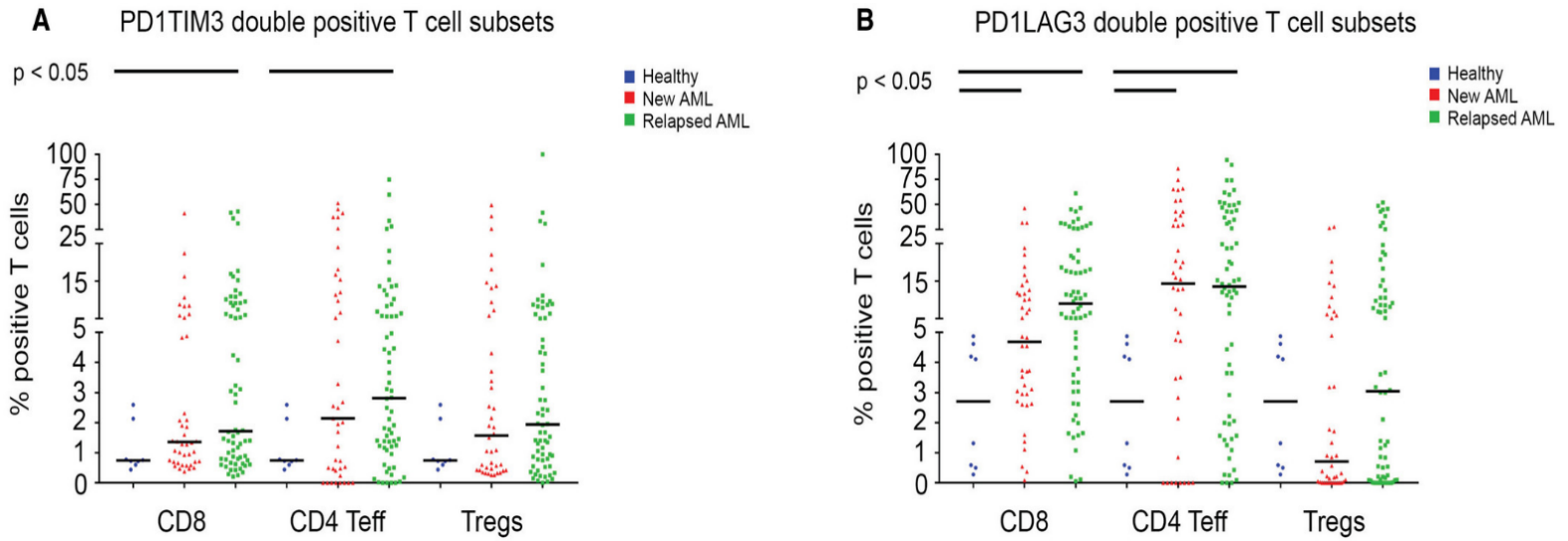
Drew M. Pardoll Nature Reviews Cancer 12, 2012

Checkpoint Receptors PD1, OX40, and ICOS Are Expressed on T Cells in BMAs From AML Patients



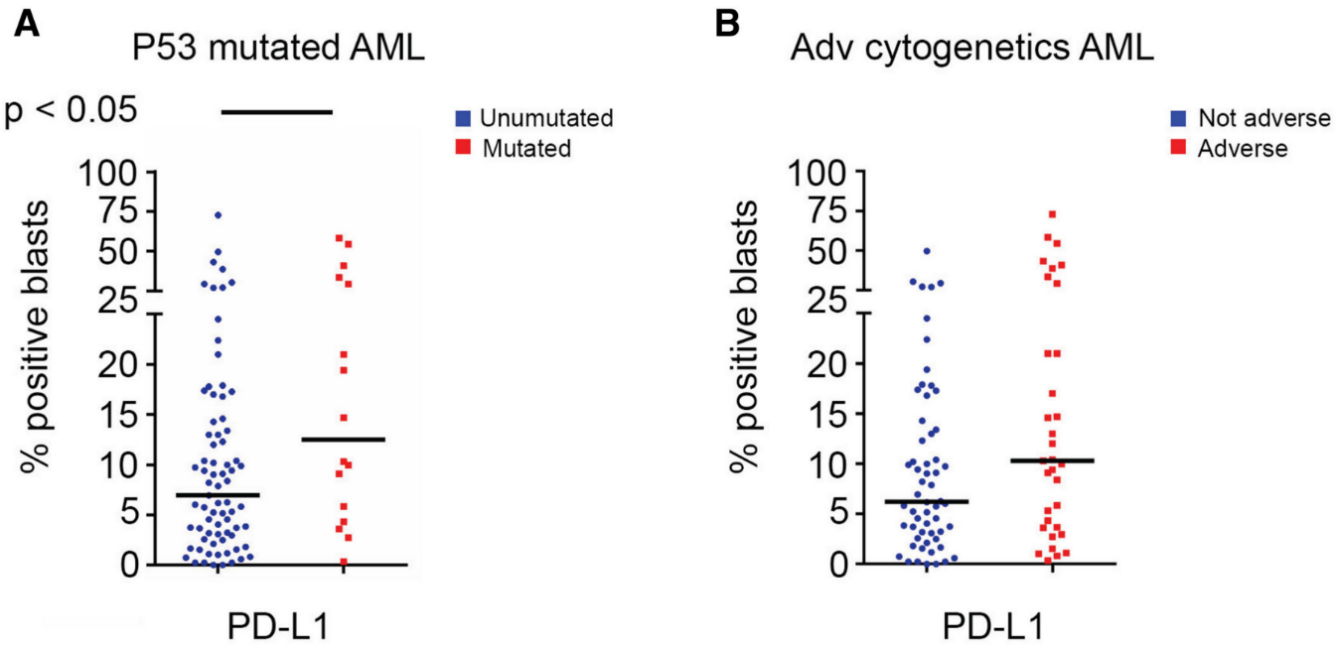
Cancer, 30 November 2018, DOI: (10.1002/cncr.31896)

TIM3 and LAG3 Are Coexpressed More Frequently With PD1 on T Cells Isolated From AML BMAs



Cancer, 30 November 2018, DOI: (10.1002/cncr.31896)

Age, Mutational Profile, and Karyotypic Status Influence the Composition of T-Cell Subsets and Immune-Checkpoint

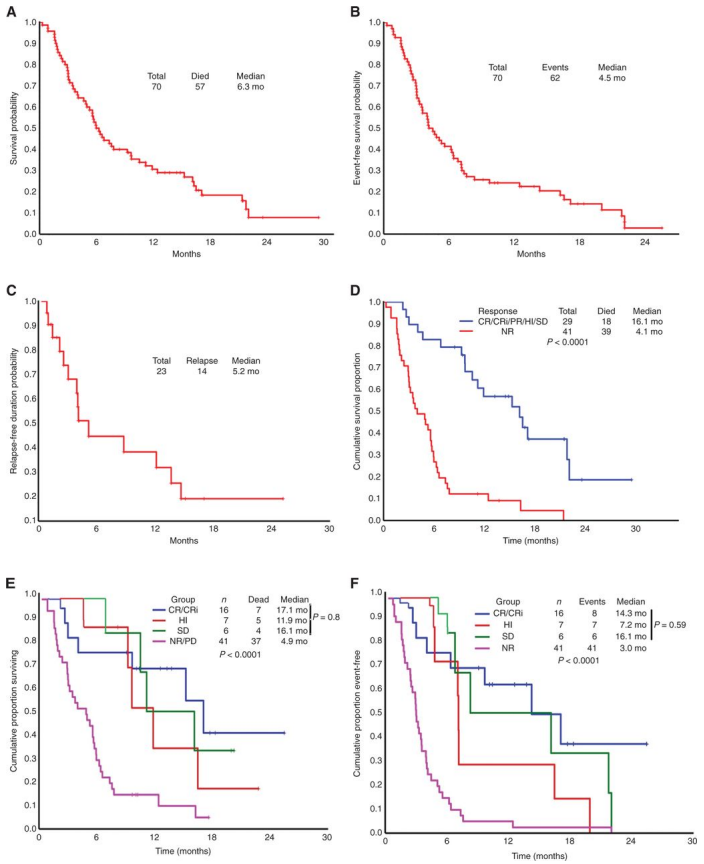


Cancer, 30 November 2018, DOI: (10.1002/cncr.31896)

Immune checkpoint inhibitors for AML: on-going clinical trials

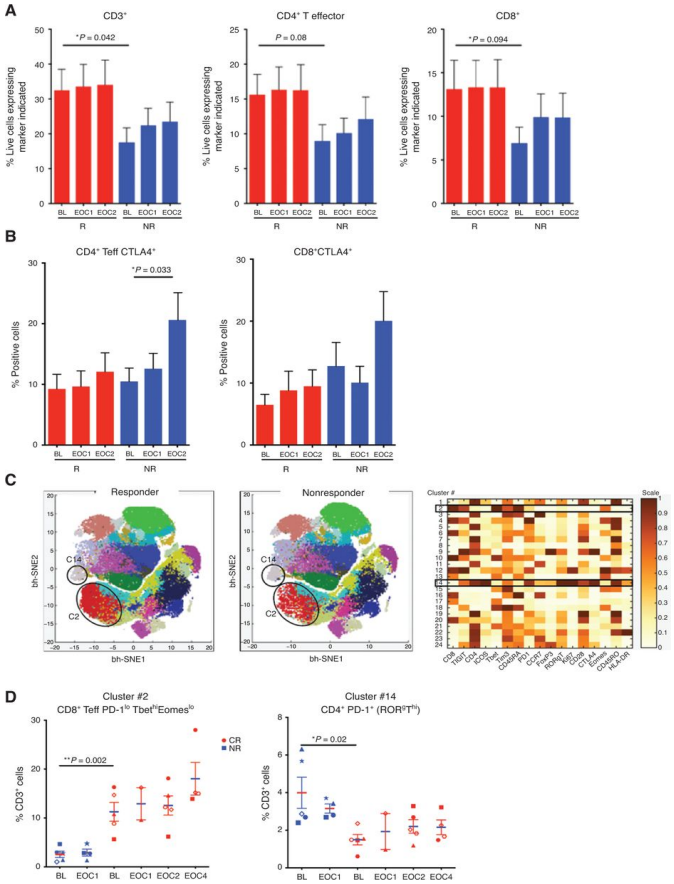
Study design	Phase	Code	Starting date
Anti-PD1 + DC AML vax	Phase 2	NCT01096602	March 2010
Ipilimimab in R/R MDS and AML with MRD	Phase 1	NCT017557639	December 2012
Ipilimumab or Nivolumab in relapsed HMs after SCT	Phase 1	NCT01822509	April 2013
Nivolumab in AML	Phase 1/2	NCT02464657	July 2015
Nivolumab in CR AML at high risk for relapse	Phase 2	NCT02532231	October 2015
Nivolumab in CR AML with MRD+	Phase 2	NCT02275533	May 2015
Nivolumab plus 5-azacytidine in R/R AML	Phase 2	NCT02397720	April 2015

Efficacy, Safety, and Biomarkers of Response to Azacitidine and Nivolumab in Relapsed/Refractory Acute Myeloid Leukemia: A Nonrandomized, Open-Label, Phase II Study



Daver et al. Cancer Discov 2019;9:370-383

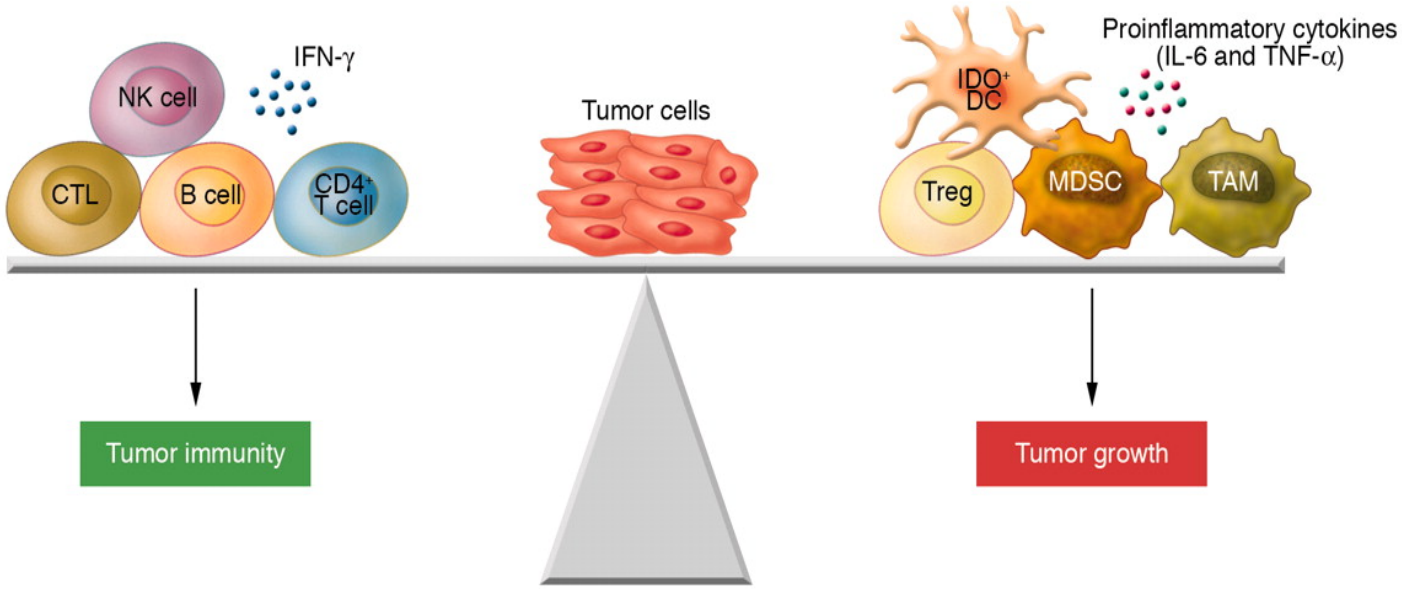
Efficacy, Safety, and Biomarkers of Response to Azacitidine and Nivolumab in Relapsed/Refractory Acute Myeloid Leukemia: A Nonrandomized, Open-Label, Phase II Study



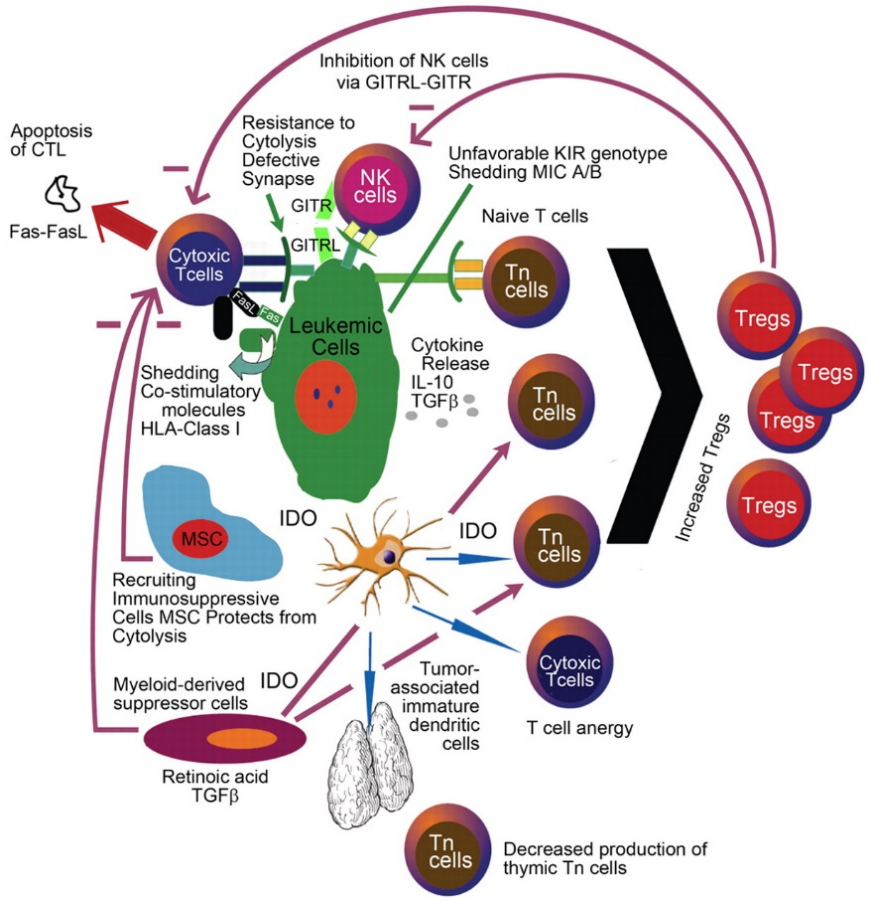
Bone marrow T-cell profile and checkpoint expression in responders (R) versus nonresponders (NR).

Daver et al. Cancer Discov 2019;9:370-383

How to harness the immune system against cancer

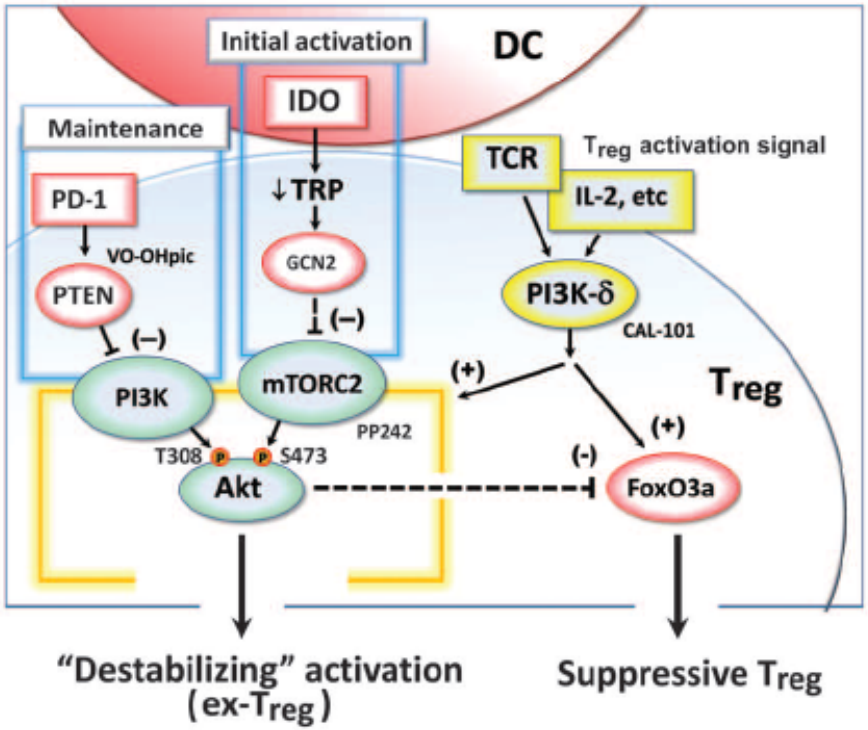


AML immunological microenvironment: the crucial role of Tregs



Ustun C et al. Blood 2011;118:5084-5095

Initial activation of Tregs within tumor microenvironment depends on IDO1 expression



Sharma et al, Science, 2015

IDO inhibitors

A phase II study to determine the safety and efficacy of an oral inhibitor of indoleamine 2,3-dioxygenase (IDO) enzyme in patients with myelodysplastic syndrome and AML with 20-30% of marrow blasts

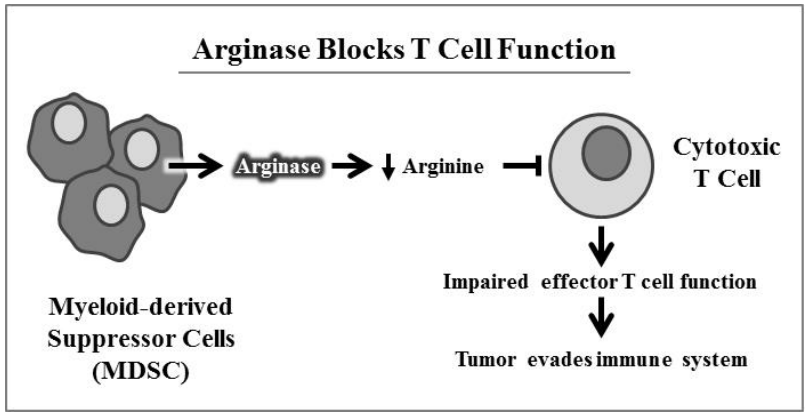
Primary endpoint: overall response
Secondary endpoints: 1) IDO suppression, 2) change in Treg and 3) the percentage of bone marrow MDSC change after treatment with INCB024360

Methods: All patients were treated with 600 mg oral twice a day for 16 weeks until progression or unless toxicity was evident.

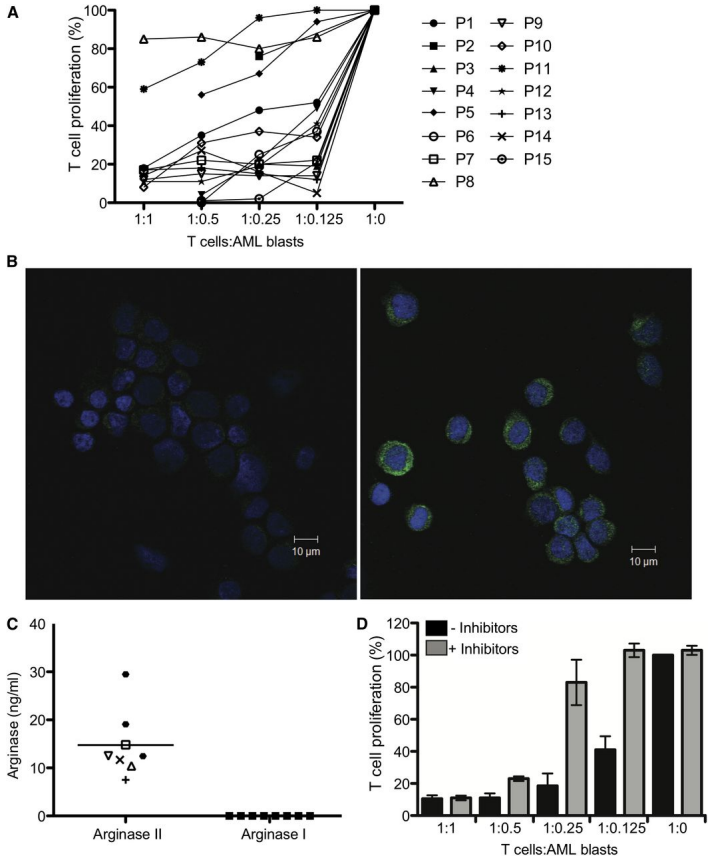
Results: 15 patients
SD (80%)
PD (20%)
No grade 3/4 events
Evidence of activity (laboratory)

Conclusions: well-tolerated. Significant activity. To be tested in combination

Arginine metabolism regulates the suppressive activity of AML blasts



A Phase II Study of Arginine Deiminase in Relapsed/Refractory or Poor-Risk Acute Myeloid Leukemia Patients

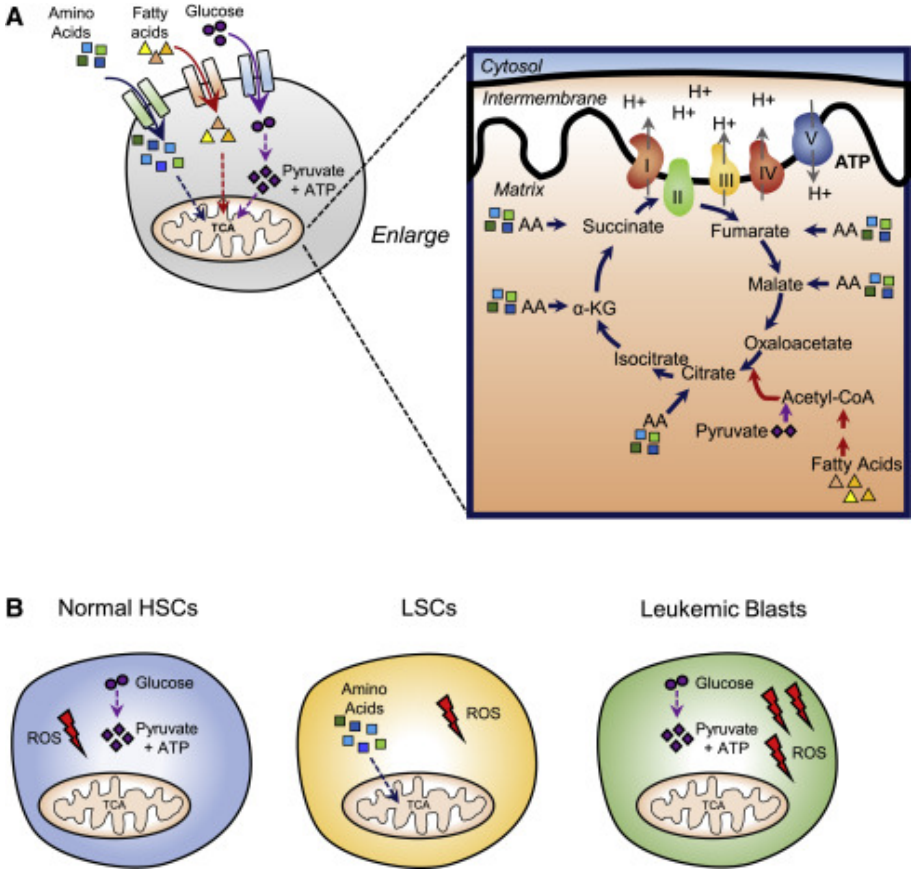


Francis Mussai et al. Blood 2013;122:749-758

Novel pathways as target for immunological therapies in AML

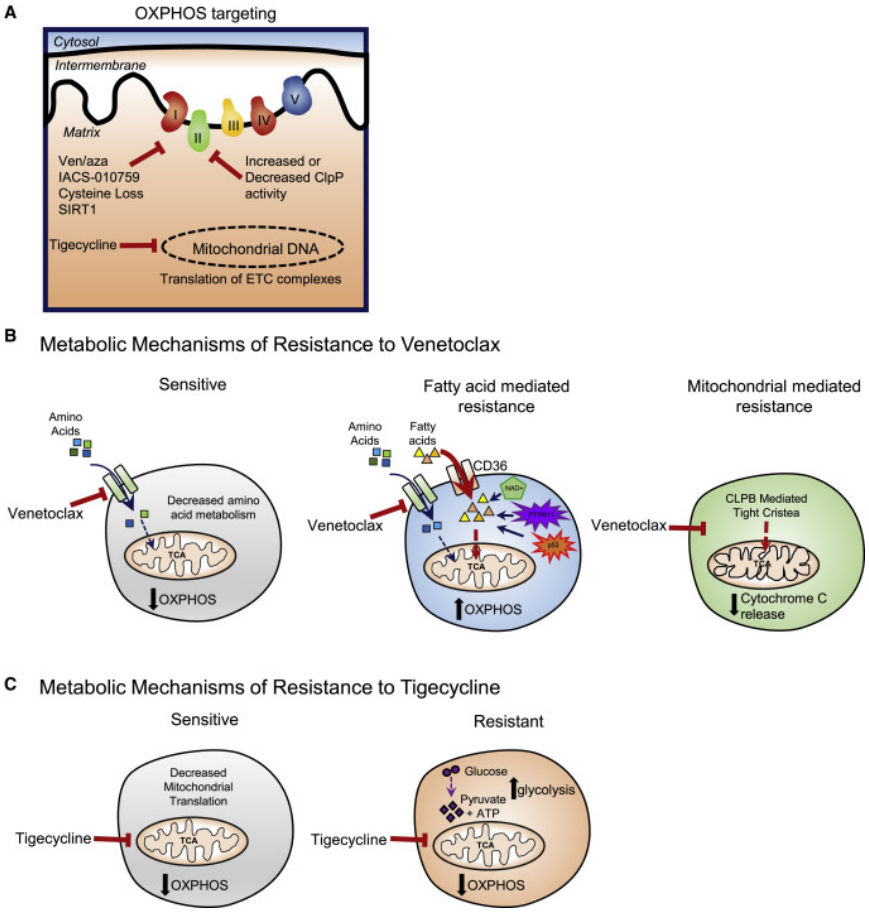
PATHWAY	THERAPEUTICAL ACTION	EFFECTS
PD-1/PD-L1/TIM-3/LAG-3	-mAb anti-PD-1/TIM-3/LAG-3 -mAb anti-PD-L1	- Increased T-cell cytotoxicity - Increased DC function as APCs
CD33	mAb anti-CD33	- AML cell lysis
CTLA-4	mAb anti-CTLA-4	- Increased T-cell cytotoxicity - Increased DC function as APCs
CD200	mAb anti-CD200	- Increased T/NK-cell cytotoxicity - Increased DC function as APCs
IDO	IDO1 inhibitor	- Prevention of T-cell tolerance
NK cells	adoptive cell therapy	- AML cell lysis
CAR-T cells	adoptive cell therapy	- AML cell lysis
Tregs	lymphodepletion therapy	- Prevention of T-cell tolerance
KIR	mAb anti-KIR	- AML cell lysis
Arginine	human recombinant arginase	- Prevention of immune tolerance
CIK cells	adoptive cell therapy	- AML cell lysis
TAAs (WT1, RHAMM..)	immunotherapy-peptide vaccines	- Specific AML cell lysis

Leukemic stem cells utilize OXPHOS for energy production



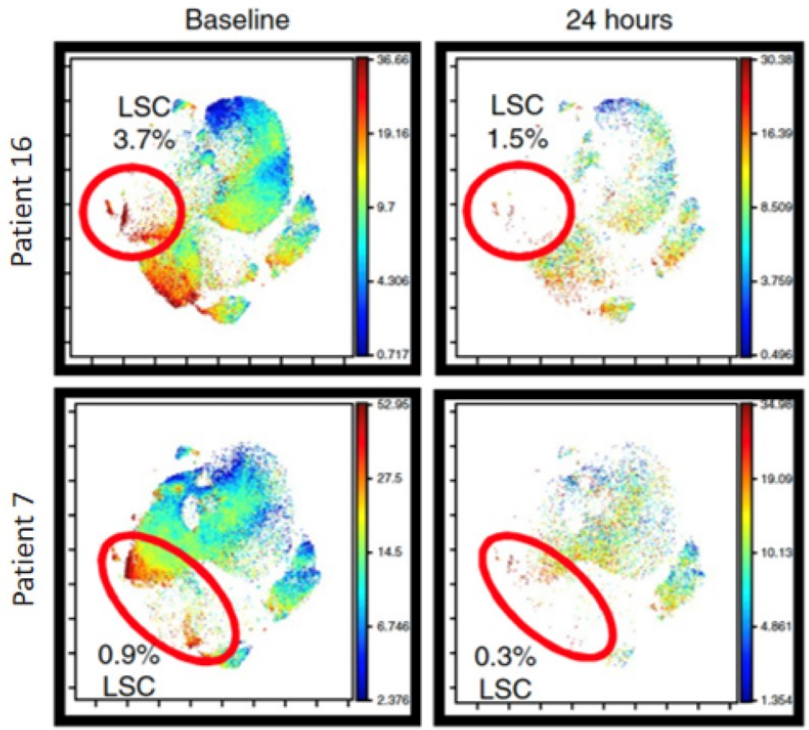
Jones et al, Cell Stem Cell, March 2021, Pages 378-393

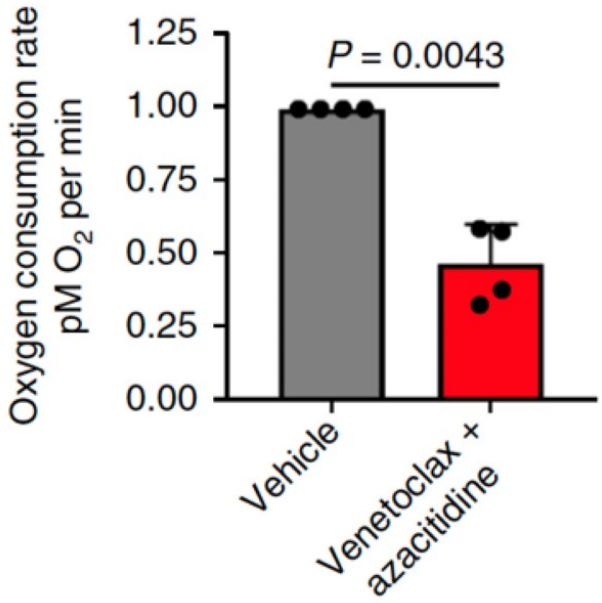
Targeting OXPHOS and Therapy Resistance in LSCs



Jones et al, Cell Stem Cell, March 2021, Pages 378-393

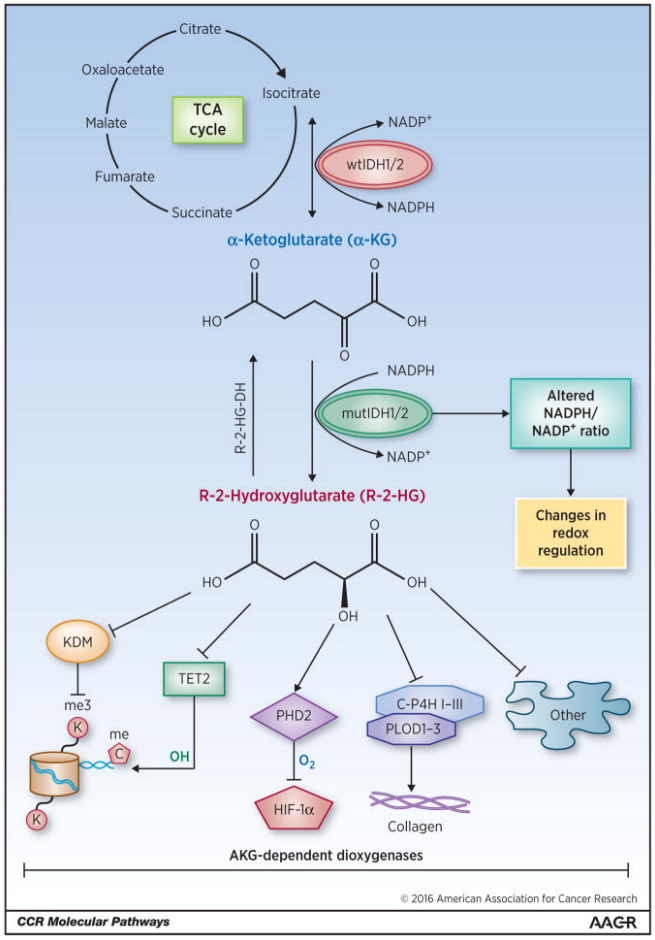
Venetoclax + AZA disrupts energy metabolism and target LSCs in AML





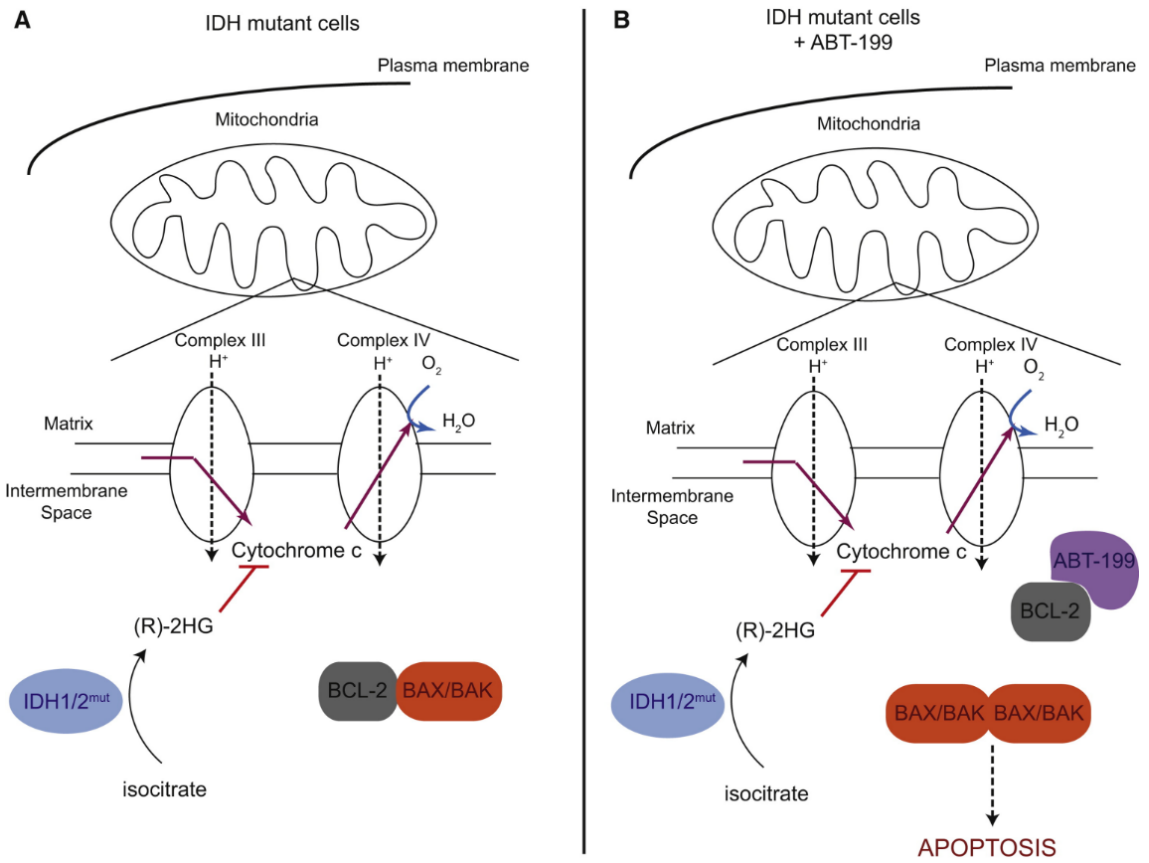
Pollyea DA, et al. *Nat Med.* 2018;24:1859-1866.

Molecular mechanisms of IDH-associated tumorigenesis



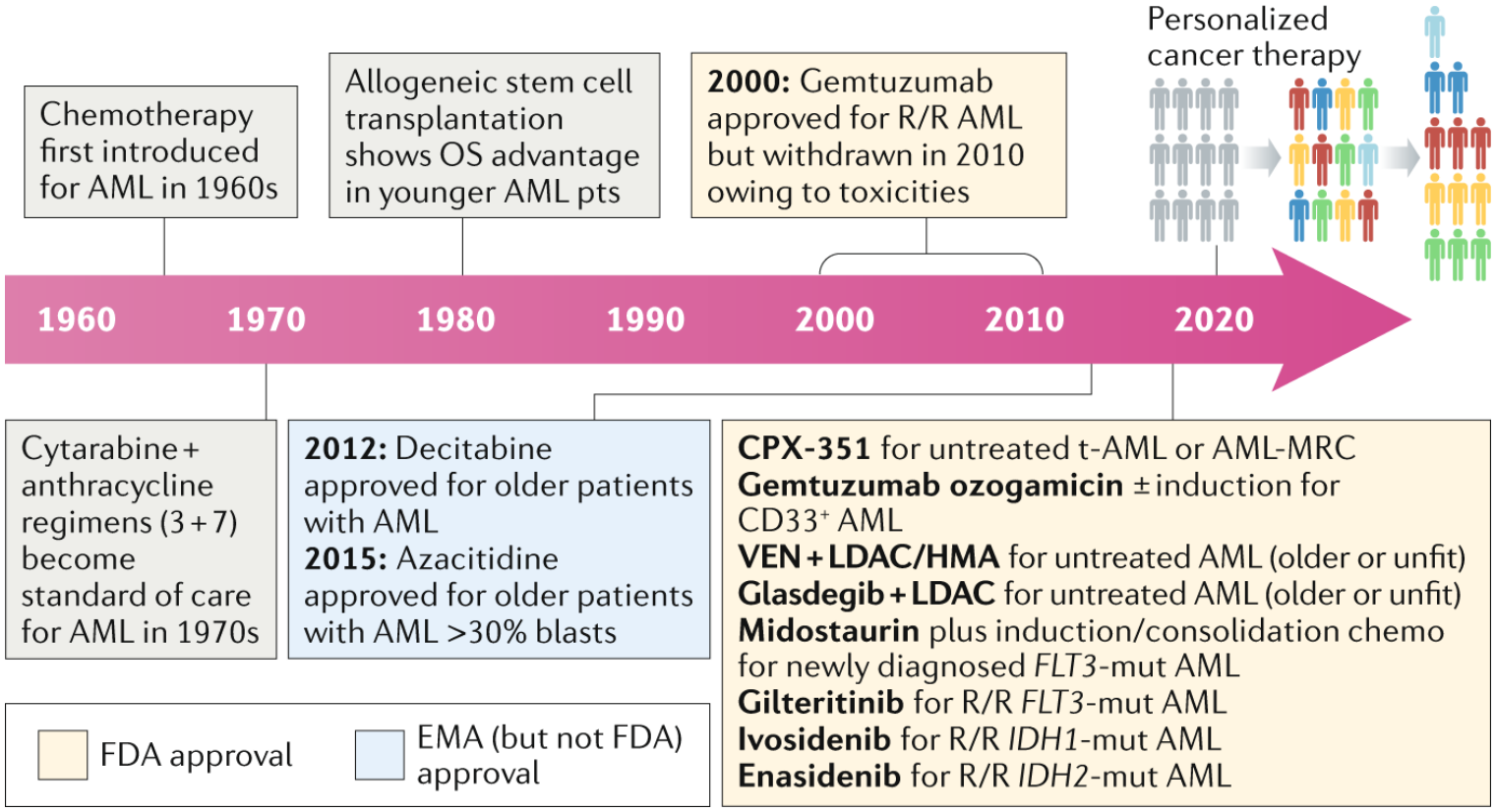
Clin Cancer Res. 2016 Apr 15; 22(8): 1837–1842.

IDH1/2 Mutations and BCL-2 Dependence: An Unexpected Chink in AML's Armour



Cancer Cell 27, March 9, 2015

Advances in AML patient care through increasingly individualized therapy



Courtney D. DiNardo & Alexander E. Perl *Nature Reviews Clinical Oncology* (2019)