Dr.Janbabai

Hematology & Medical oncology

Hematology oncology Research Center

Case 1

- 36-year-old male patient visited clinic because of melena on 25th March, 2014

- C.C. Melena (onset : 3 weeks ago)
- ROS : weight loss (-), epigastric pain (+), dyspnea on exertion (+)
  hematemesis (-)
- CBC : Hemoglobin 5.7 g/dL, WBC 6,200/uL, Platelet 229k/uL
- Chemistry : WNL

- What's your next examination ?



Case from Seock-Ah Im M.D. PhD.
Medical Oncologist
Cancer Research Institute
Seoul National University Hospital
Seoul National University College of Medicine

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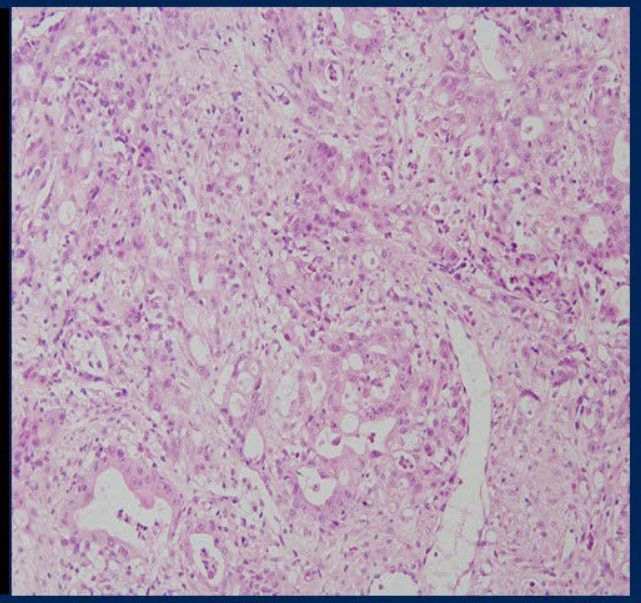
Case 1. Endoscopic Exam & CT





2014.3.25. GFS

Ulcero-infiltrative mass
Low to mid body of lesser curvature of stomach
Impression : AGC Borrmann type III
Biopsy: ADENOCARCINOMA,
Moderately Differentiated



2014.3.25 CT Stomach Preop 3D (contrast)
AGC, body LC side, Borrmann type III,
With R/O peritoneal seeding (not definitive)
Tentative staging, T3N+R/O M1

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What do you offer to the patient ?

A. Diagnostic Laparoscopy
B. Gastrectomy with lymph node dissection
C. Neoadjuvant chemoradiation
D. 1st line systemic chemotherapy

ABCD

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What's your special request to the pathologist ?

A. Presence of H. pylori & EBV
B. HER-2 IHC +/- ISH
C. PD-L1 IHC
D. MSI
E. NGS

ABCD

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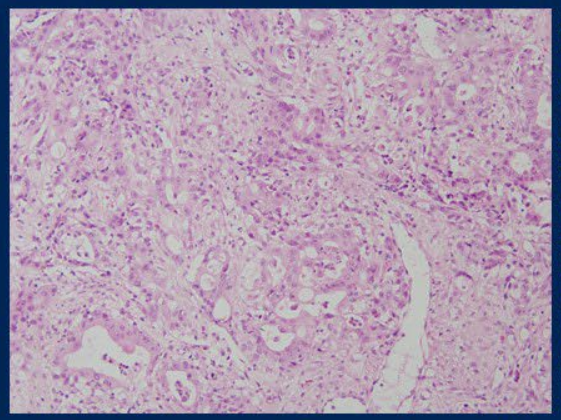
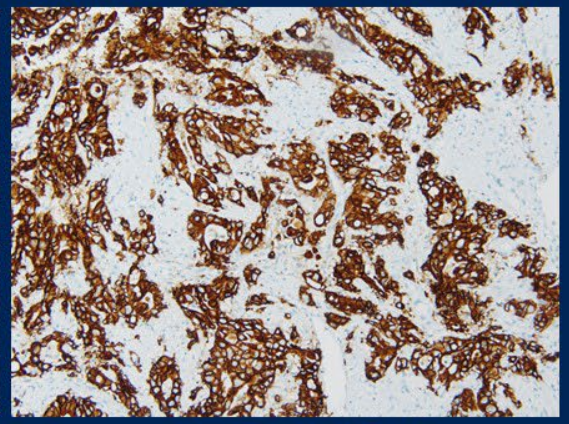
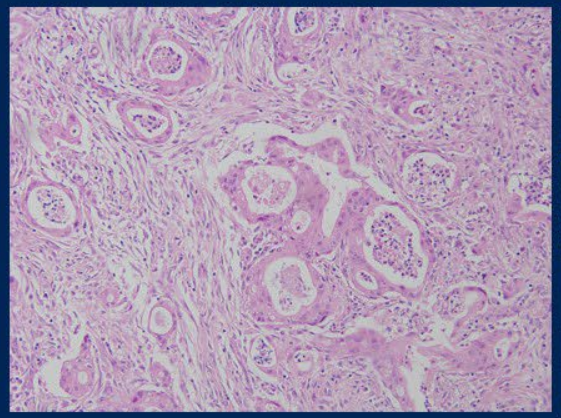
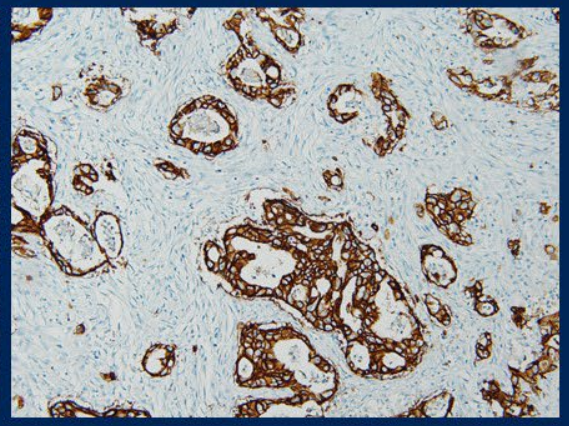
Case 1. M/36 : Adenocarcinoma, Moderately Differentiated

- GFS Bx : HER2 IHC 3+, H.pylori (-), EBV (-)

- Peritoneal Seeding Nodules : HER2 IHC 3+

EGFR (-)
Microsatellite stable (MSS)
EBV (-)

Additional Request in 2022
PD-L1(22C3) conc. : Negative [CPS < 1, TPS = 0]

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What do you offer to the patient ?

A. 5-FU or Capecitabine + Platinum + Trastuzumab
B. 5-FU or Capecitabine + Platinum + Trastuzumab + Pembrolizumab
C. Capecitabine + Oxaliplatin + Nivolumab
D. Perioperative FLOT (Fluorouracil, Leucovorin, Oxaliplatin, Docetaxel) +/- Trastuzumab



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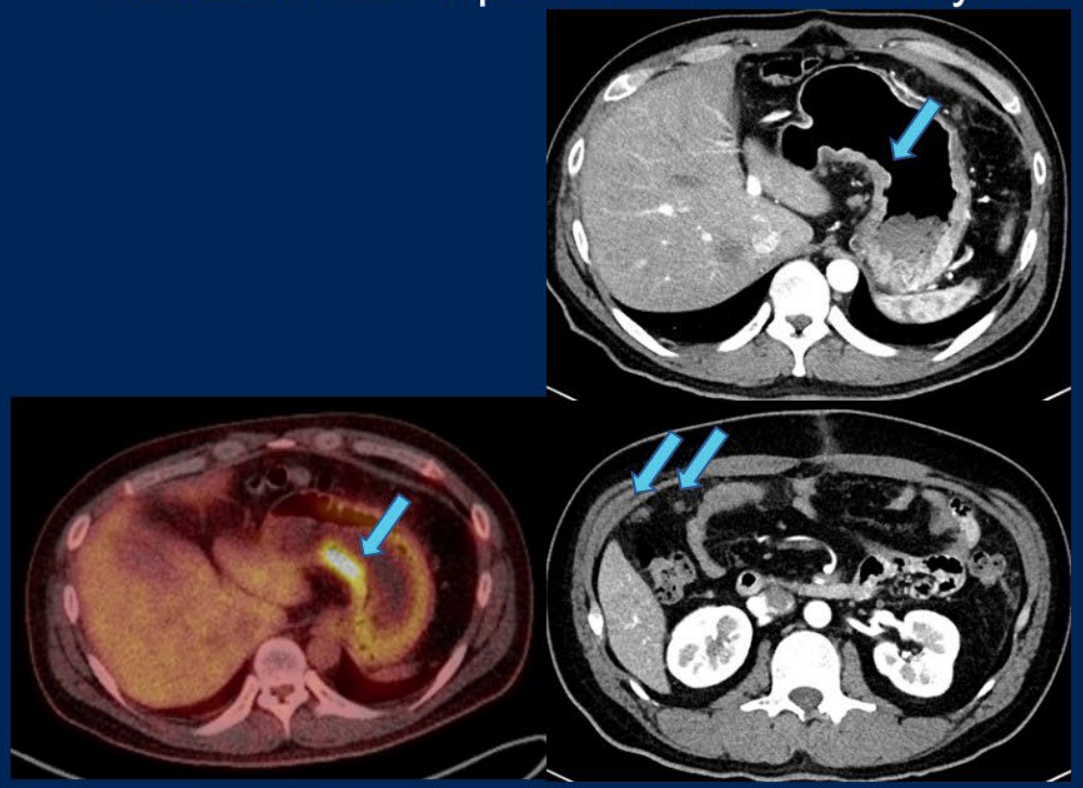
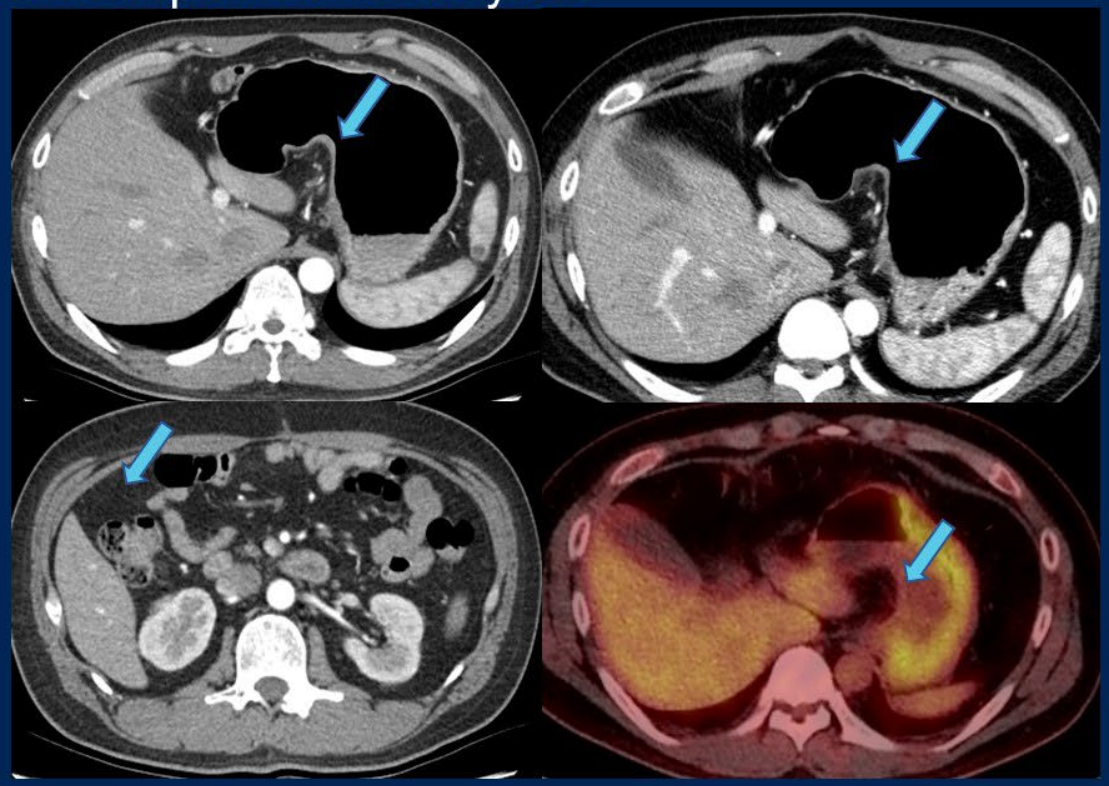
Case 1. M/36 HER2 + Stomach Ca
Stage IV (cT4N+M1) with peritoneal seeding enrolled into JACOB study

- Treated with capecitabine + cisplatin + trastuzumab +/- pertuzumab
- Started on 22nd Apr 2014 : PR after 8 cycles - omit cisplatin after 6 cycles



14 Apr 2014



27 Aug 2014

30 Dec 2015
No visible peritoneal seeding

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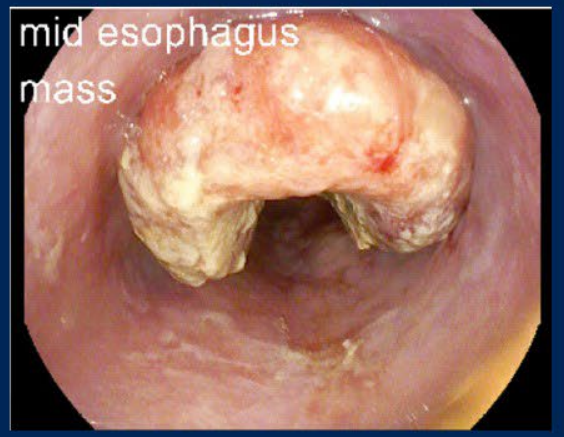
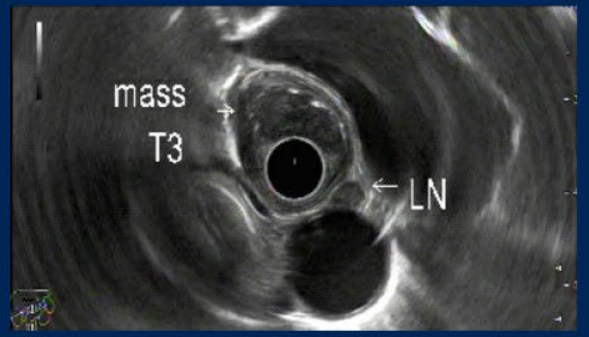
CASE 3

- 63-year-old female physician reports occasional sensation of food being stuck with swallowing and long-standing history of vertigo.
- She is otherwise healthy except for hypertension. She denies weight loss.
- EGD shows a mass in the mid-esophagus from 24cm to 36 cm from the incisors
- Pathology shows poorly differentiated non-keratinizing squamous cell carcinoma





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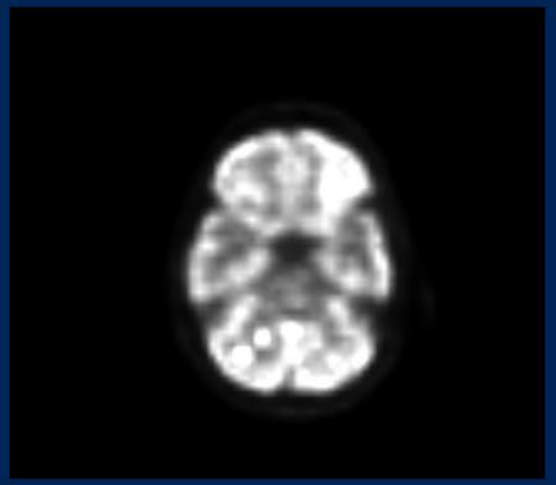
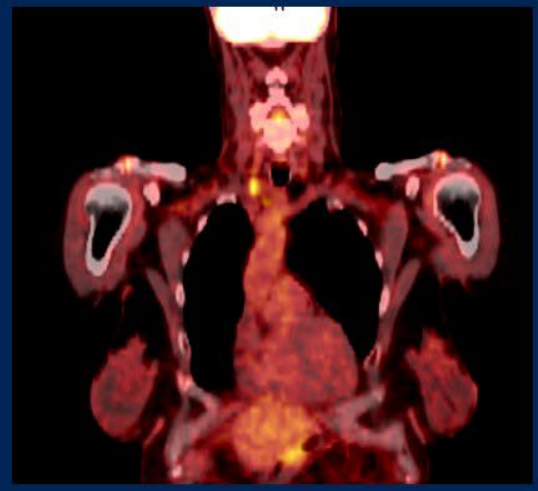
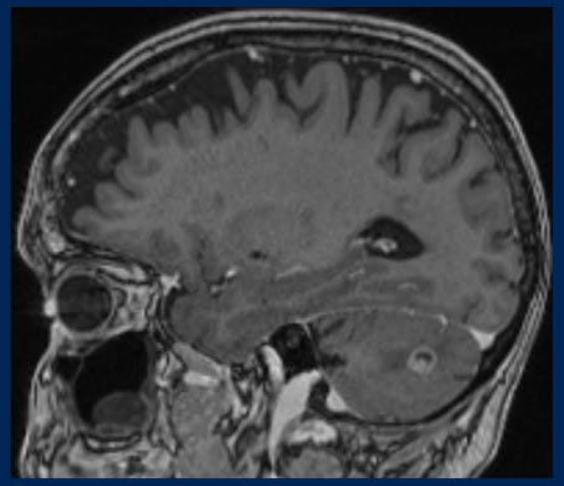
Case 3, cont'd

- PET/CT reveals hypermetabolic uptake in the mid-esophagus (SUV 86), right supraclavicular node (SUV 5.5), 3 brain lesions.
- MRI confirms 3 cerebellar (1.2 cm largest) lesions consistent with metastatic disease.
- PD-L1 CPS score 100, TMB high (11mut/Mb), Her2/Neu negative IHC, MSS, CCND1 amp, TP53 V73fs, ERCC2 Y339, CDKN2A D108N









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Case 3, cont'd

- Treated with fractionated stereotactic radiosurgery (27 Gy / 3 fractions).
- CapOx + nivolumab X 6 cycles.
- CT and brain MRI shows treatment response with resolution of node and brain lesions and minimal residual esophageal thickening.

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Multiple Choice Question: What do you offer to the patient?

A. Capecitabine + Nivolumab
B. Definitive chemoradiation
C. Preoperative intent chemoradiation
D. Not enough information

ABCD

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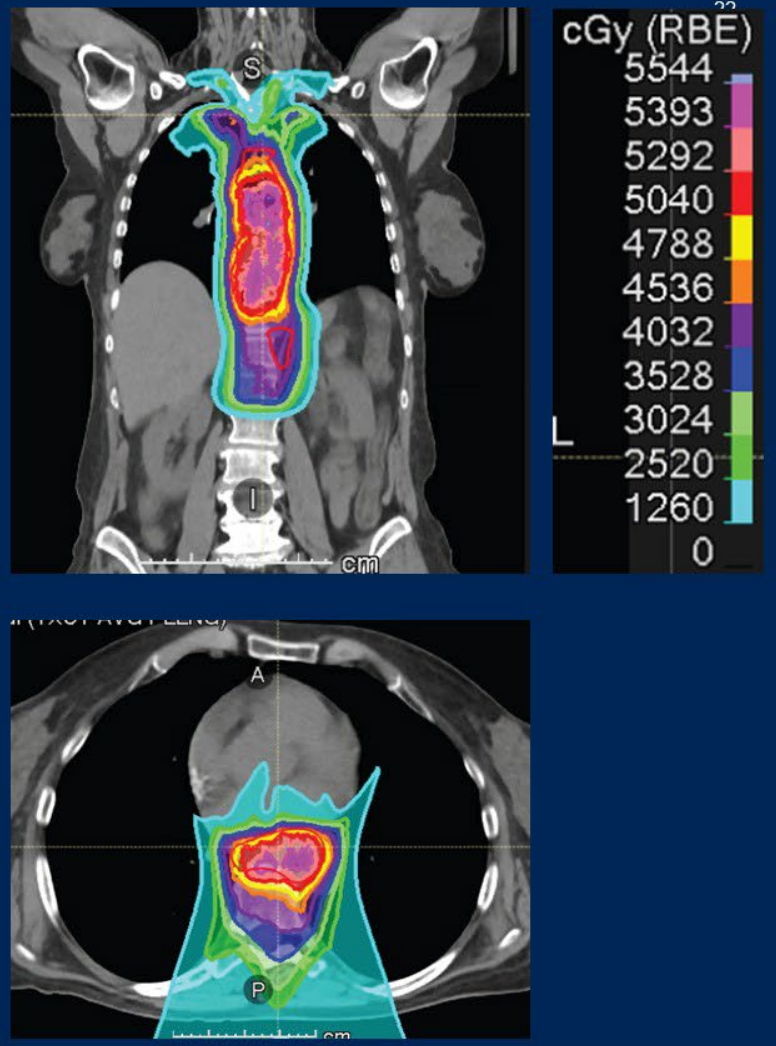
Case 3, cont'd

- Treated with chemoradiation with capecitabine
- 14 months from diagnosis remains on capecitabine and nivolumab and no evidence of disease on imaging or EGD
- Toxicities include grade 2 pneumonitis, grade 1 HFS, grade 2 hypothyroidism, grade 2 (secondary) adrenal insufficiency.



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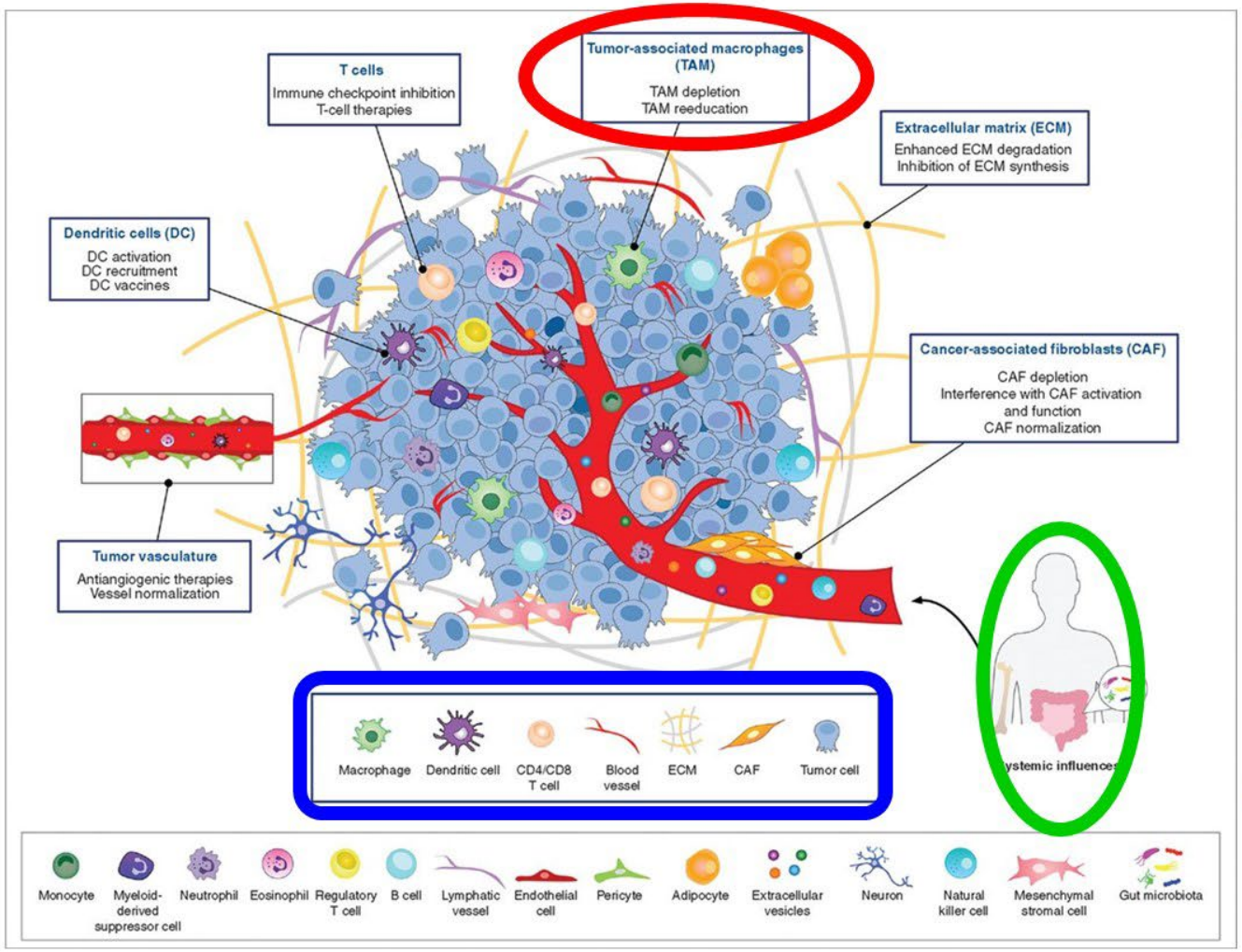
GI tumors harbor a hostile microenvironment

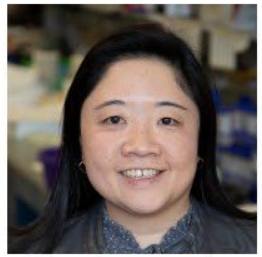




Dougan



Hong



Tsukamoto
Kagohara



Alqahtani

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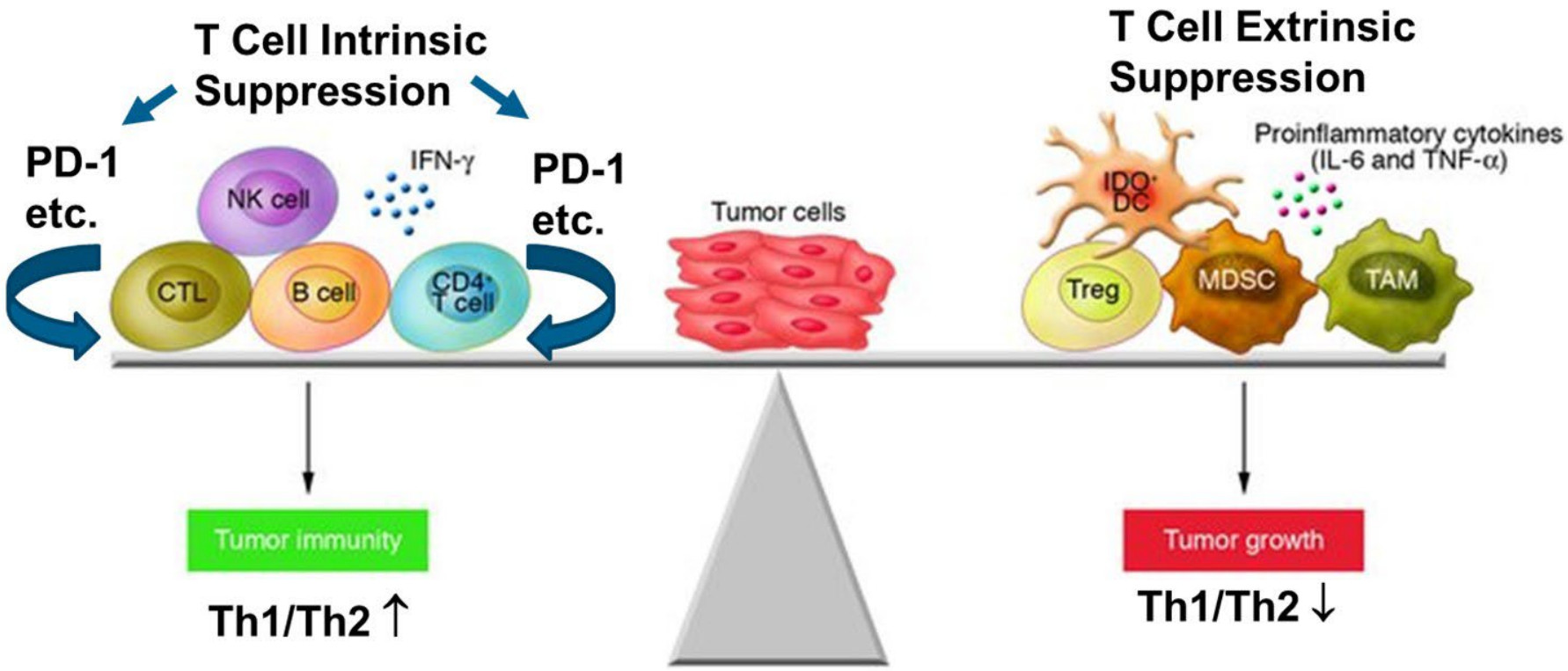
Simplifying suppressed anti-tumor immunity



Adapted from Bhardwaj, N. Journal of Clinical Investigation. 2007

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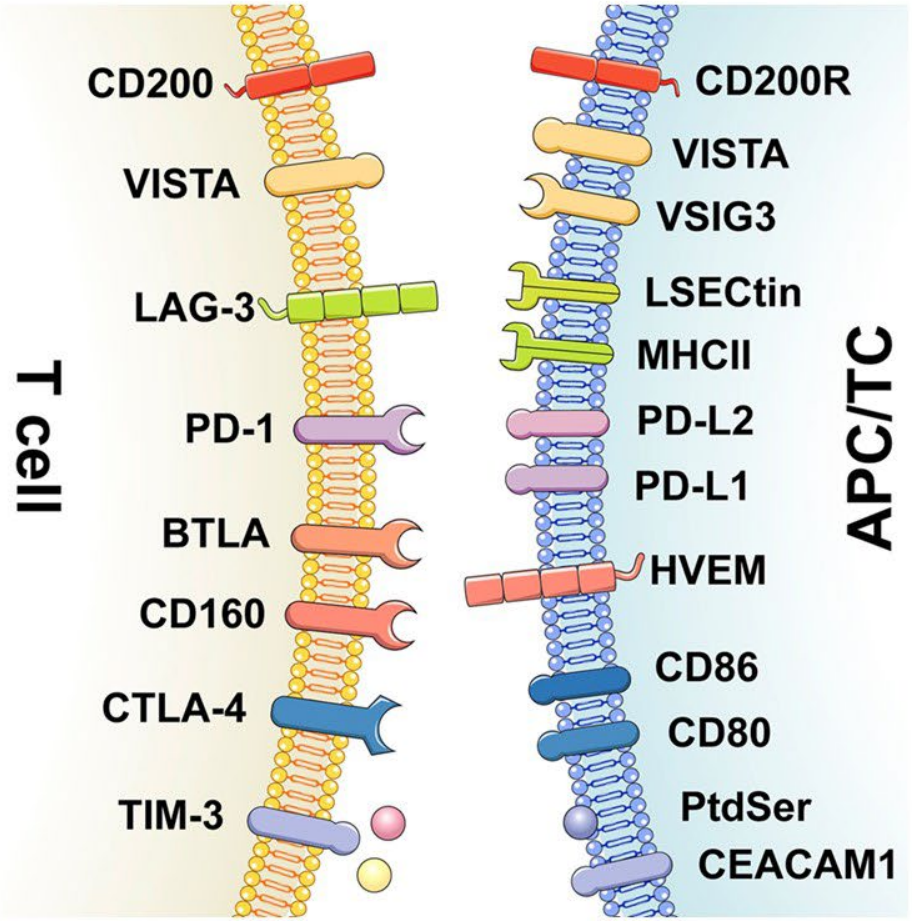
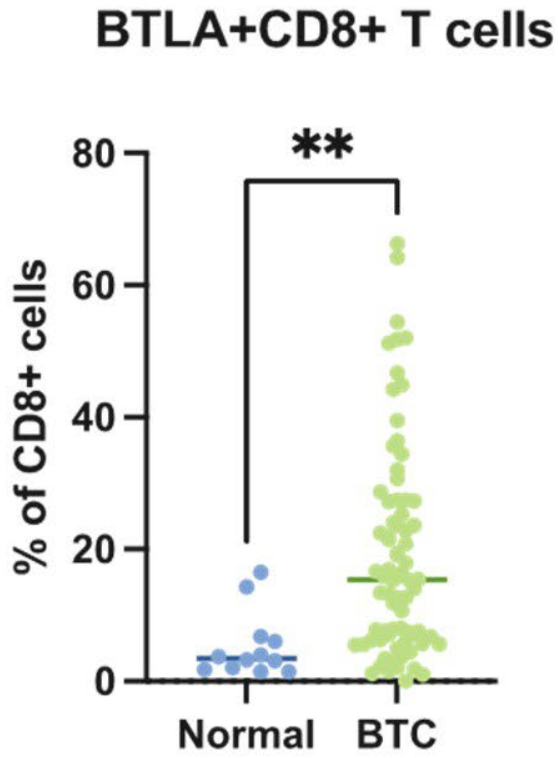
Redundancy in immune checkpoints limits anti-tumor immunity



Huang *et al*. Journal of Autoimmunity, 2019



Ruggieri *et al*. Clin Cancer Res, 2022

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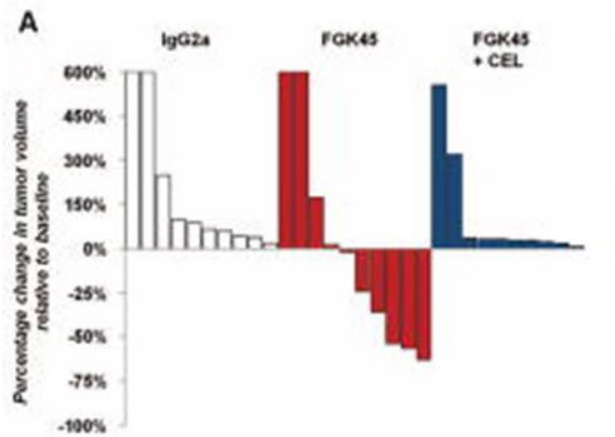
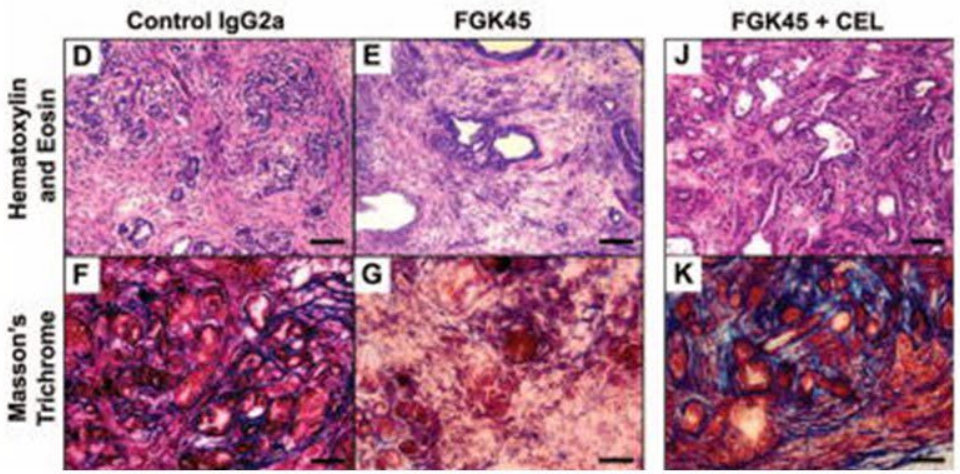
Strategies to reprogram myeloid cells

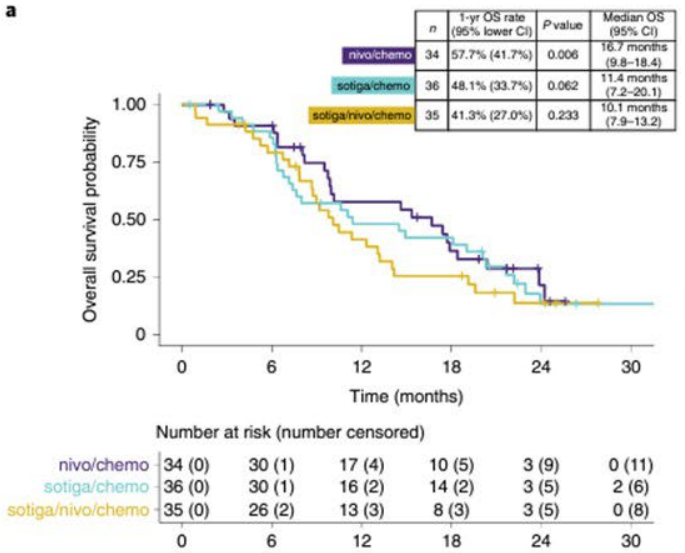
Pros/cons:
Also activates dendritic cells – enhanced T cell priming

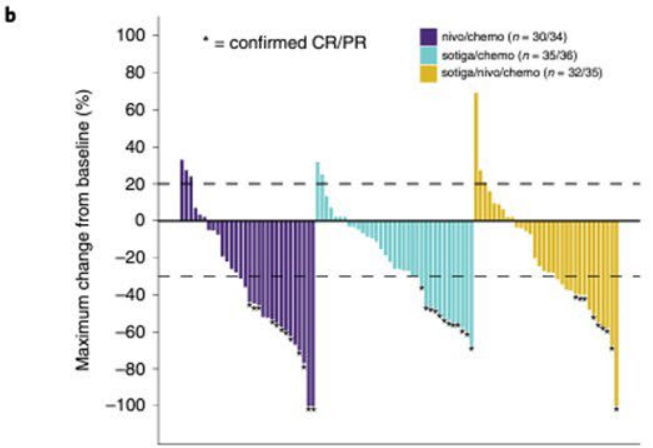
Safety concerns (CRS) require local delivery or other thoughtful strategy





Beatty, Vonderheide et al. Science 2011





Padron, Vonderheide et al. Nature Medicine 2022

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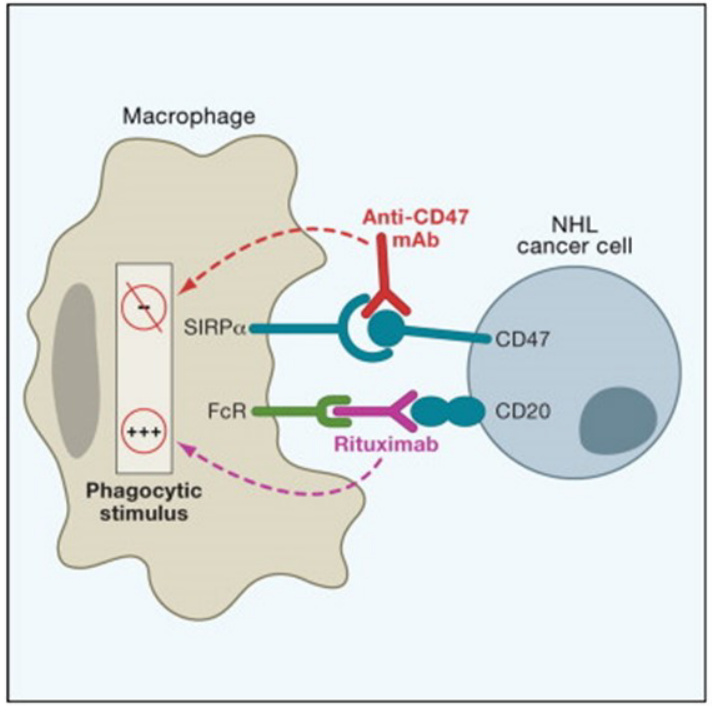
Strategies to enhance phagocytosis

CD47 blockade +
Fc-optimized antibodies

Blockade of “don’t eat me”
Add “do eat me” signal



Chao, Weissman, Majeti et al. Cell 2010

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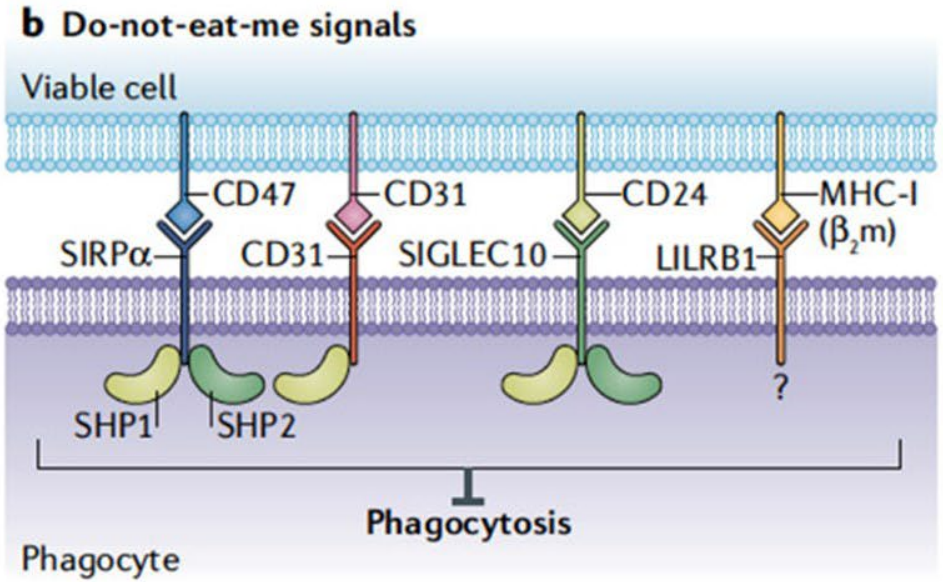
Strategies to enhance phagocytosis

Pros/cons:
Can synergize with anti-tumor antibodies

Need tumor-specific antibody or other "do eat me" signal

Fc enhanced CTLA-4 antibodies exploit this pathway for Treg depletion

Unclear long-term solution in the absence of a T cell response



Boada-Romero, Green DR et al. Nature Rev Mol Cell Bio, 2020

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Strategies to enhance phagocytosis

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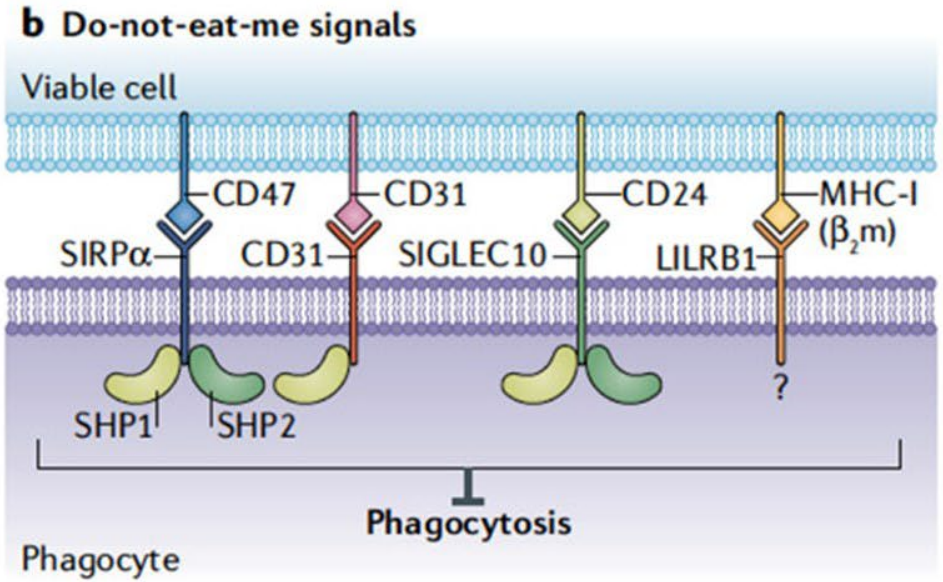

Boada-Romero, Green DR et al. Nature Rev Mol Cell Bio, 2020

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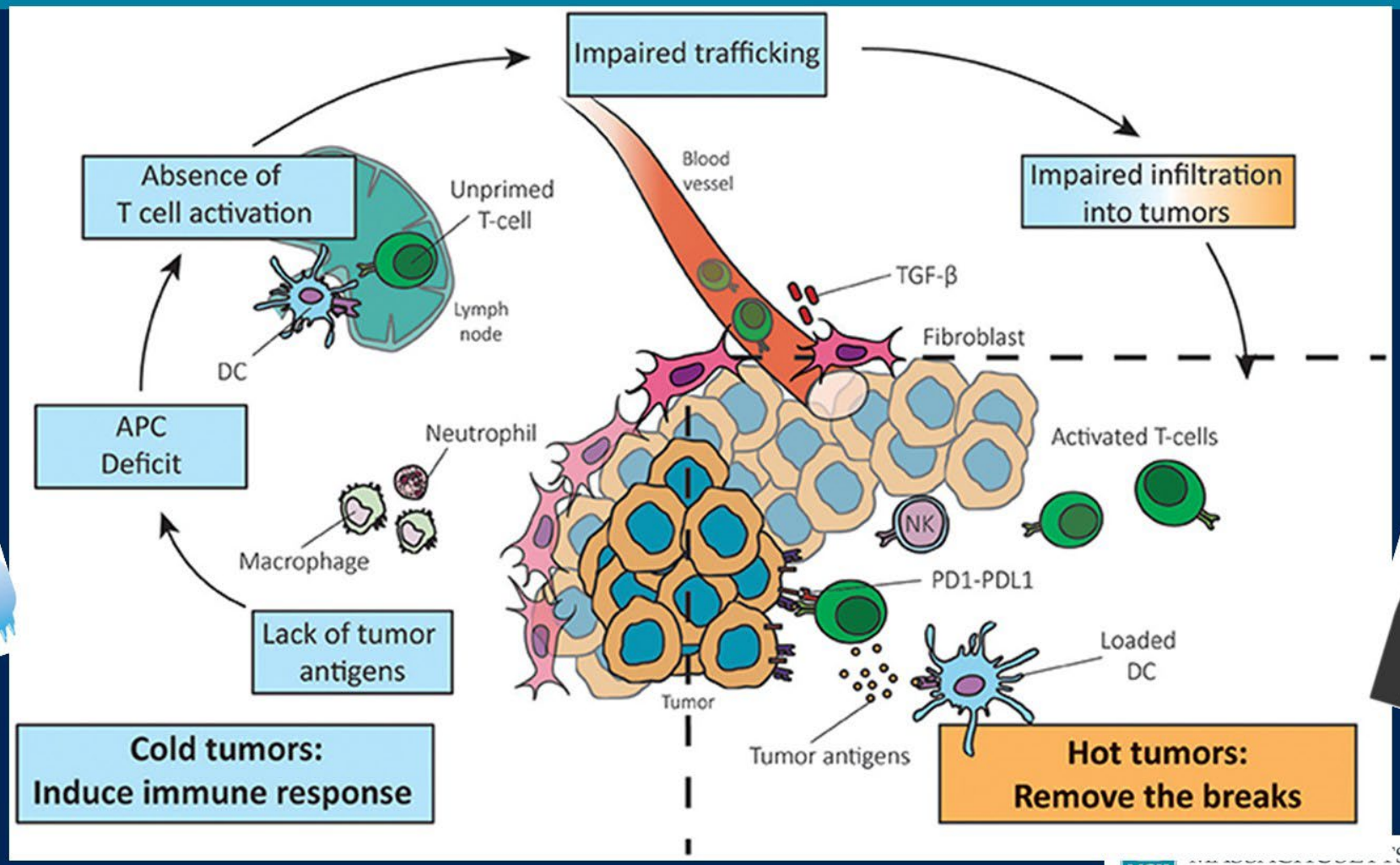
The Fundamental Problem







Courtesy of Dr. Aparna Parikh

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Rationale for RT with IO

- Enhanced diversity promotes T cell infiltration, antigen presentation and shapes the TCR repertoire
- Promotes T-cell infiltration and enables responsiveness to IO in IFN dependent manner
- Promotes in situ “vaccination” through release of tumor-associated antigens
- RT activation of dendritic cells
- Anti-CTLA4 promotes expansion of T cells, inhibits T-regs, increasing CD8/Treg ratio
- PD-L1 blockade reverses T-cell exhaustion to mitigate depression in the CD8/Treg ratio and further encourages oligoclonal T-cell expansion
- Plasticity of tumors and their microenvironment upregulates diverse inhibitory signals
- Engages adaptive and innate immune responses
- Activation of non-redundant immune activation mechanisms with CPI and RT
- Combinatorial approaches to sustain tumor control by T cells critical

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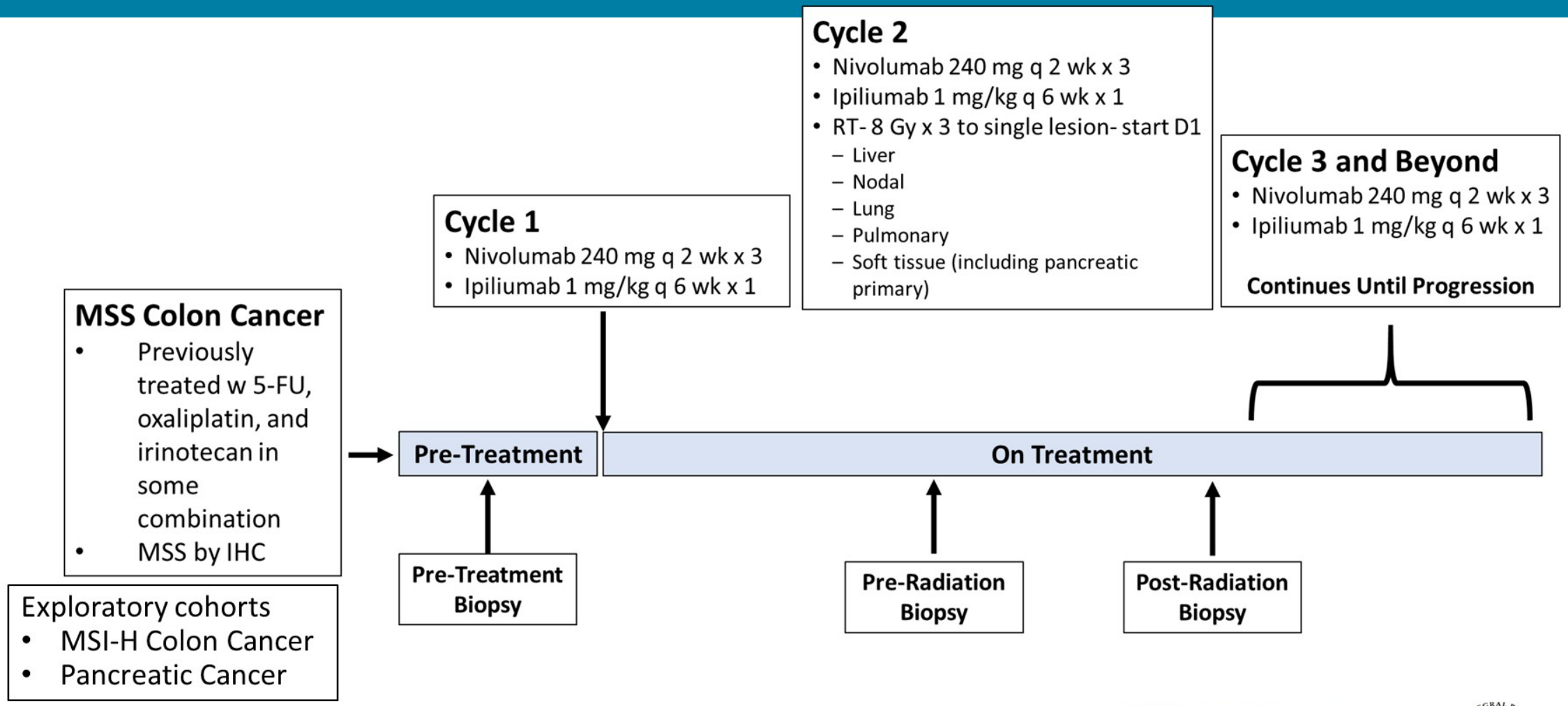
Ipilimumab/Nivolumab/Radiation Schema



Parikh A, ... Ting DT, Hong TS. Nature Cancer 2021.

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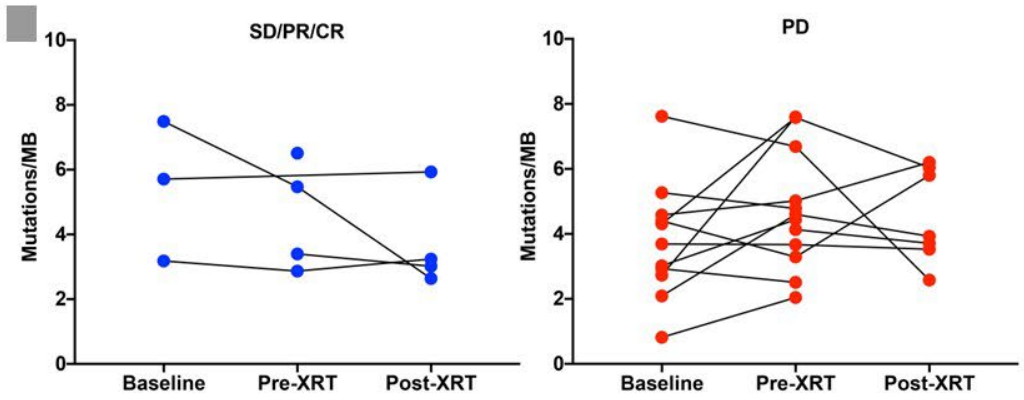
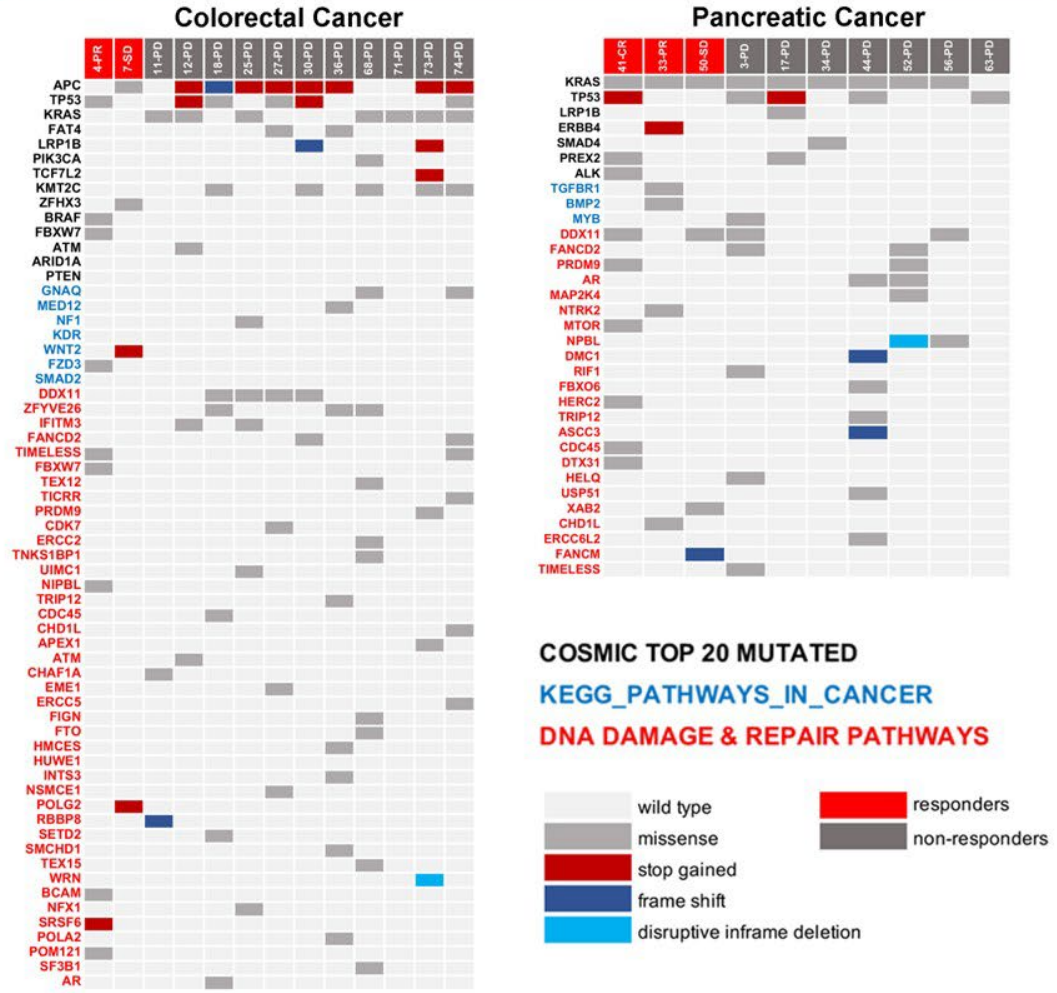
TMB and Coding Gene Mutational Analysis

All low TMB and no clear mutations associated with response

- 41 samples paired germline DNA WES
- 17 patients with RT analyzed
- All **low** TMB with < 10 mutations/Mb
- No change in TMB before, during, or after treatment
- Profiling c/w expected mutations *KRAS, TP53, APC*
- Notable mutations in DDR genes with shared mutations in *DDX11* (CRC 4/13; PDAC 4/10) and *FANCD2* (CRC 2/13; PDAC 2/10)
  - 1 CRC PR and 1 PDAC CR had 6 mutations in DNA damage and repair genes

Add a





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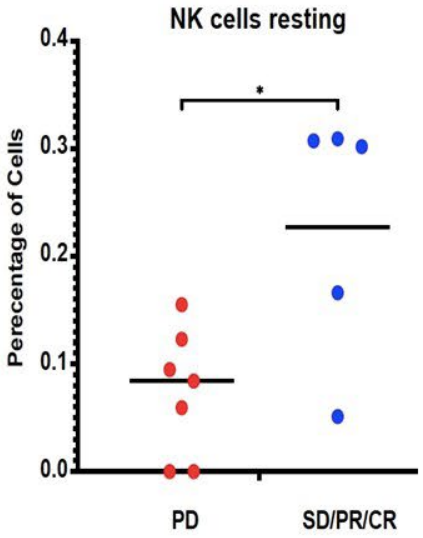
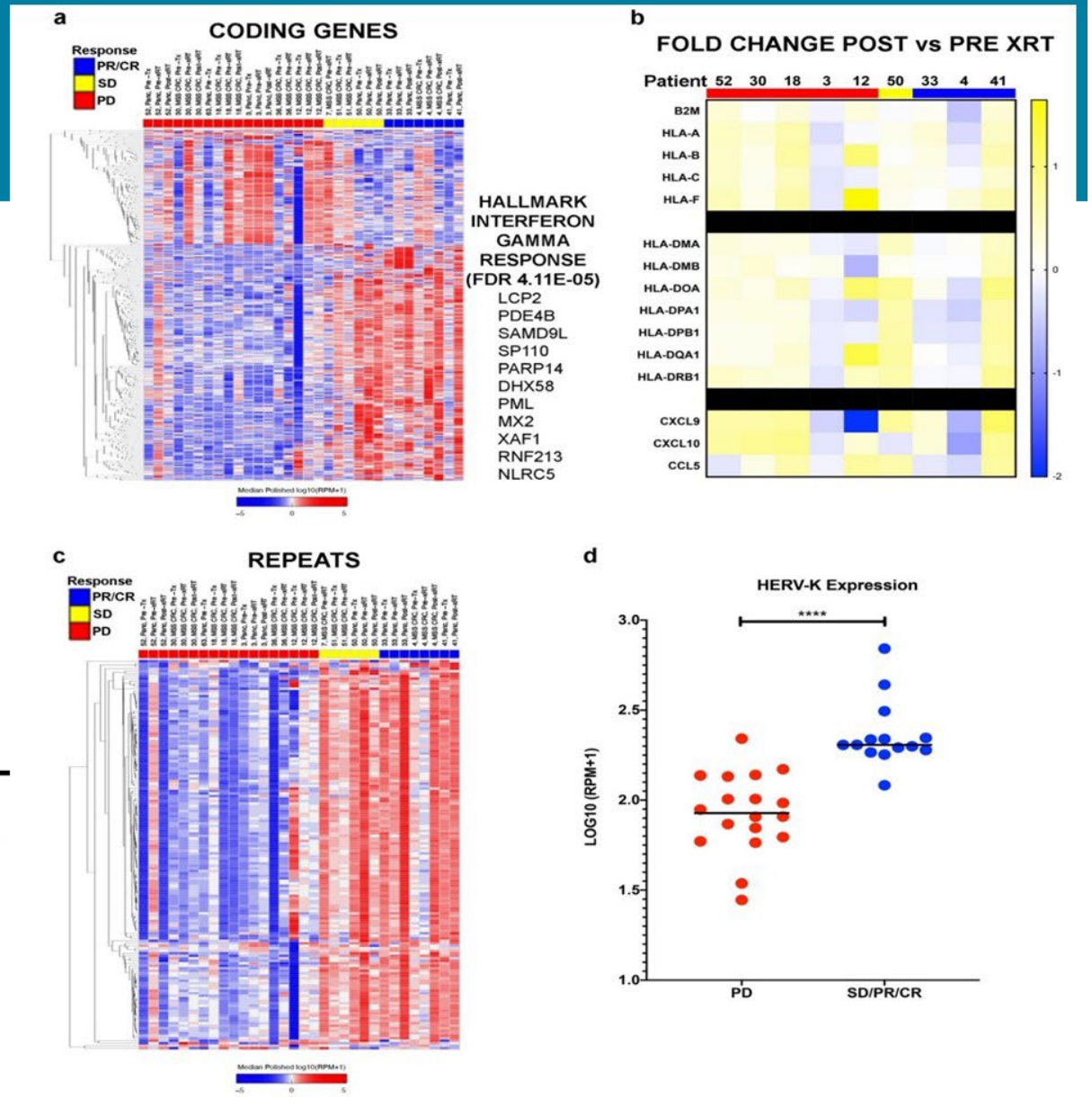
IFN signatures and repeats

32 samples from 13 pts with RT

- IFN-g response genes most enriched in responders compared to non-responders
- Change of MHC1 genes and recruitment cytokines with differential expression genes before and after radiation in available specimens
- Differential expression of repeat RNAs in all biopsies from responders compared to non-responders





Parikh A, et al. Nature Cancer 2021. With Ted Hong, MD and David T. Ting MD, PhD.

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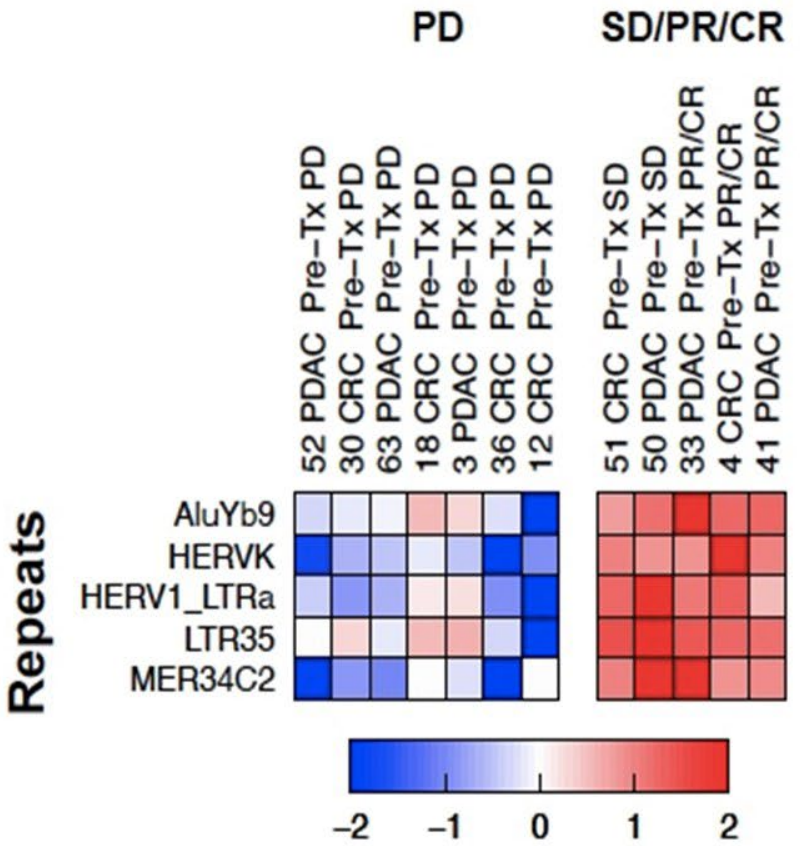
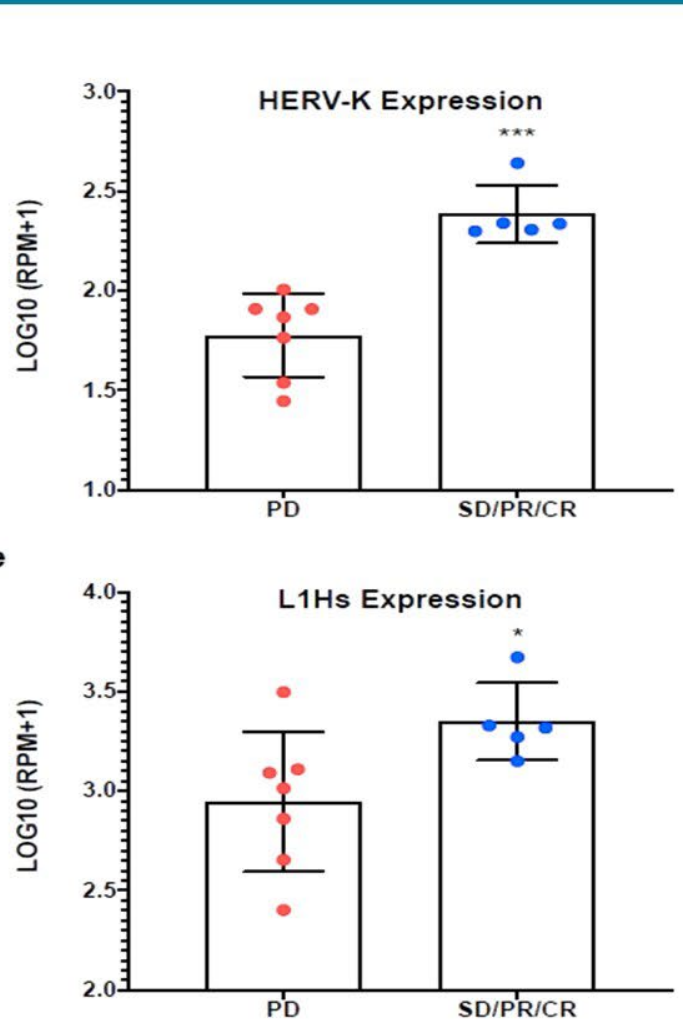
Differential Expression in Majority of Repeat RNAs is Responders

- Certain repeats were higher in responders
- HERVK protein coding repeat elevated in responders
- HERVK association with NK activation
- HERVK with response in urothelial CA
- Innate immunity to HERVK and potential adaptive immunity to protein coding elements





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What did we learn?

- Dual CTLA-4 and PD1 with RT in IO refractory disease has some activity in a subset of patients
- Schedule of treatment should be considered in follow up studies due to toxicity and patient decline
  - Move radiation up earlier
- Alternative dosing schedules for ideal immune modulation
  - Recent data PD1 blockade prior to antigen priming may lead to T cell exhaustion inducing dysfunctional CD8+s
- Ongoing biomarker and subset considerations

So, what's next?

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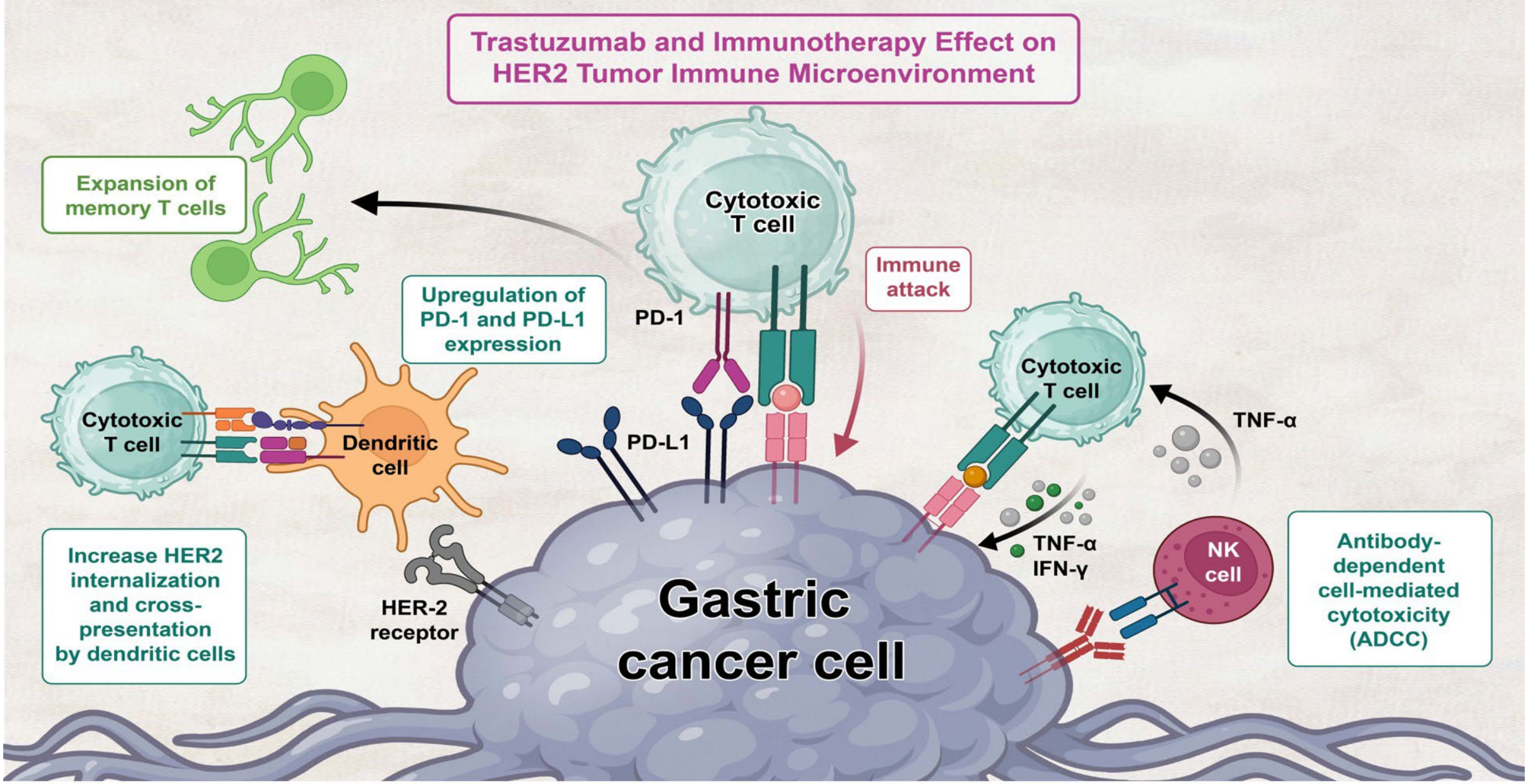

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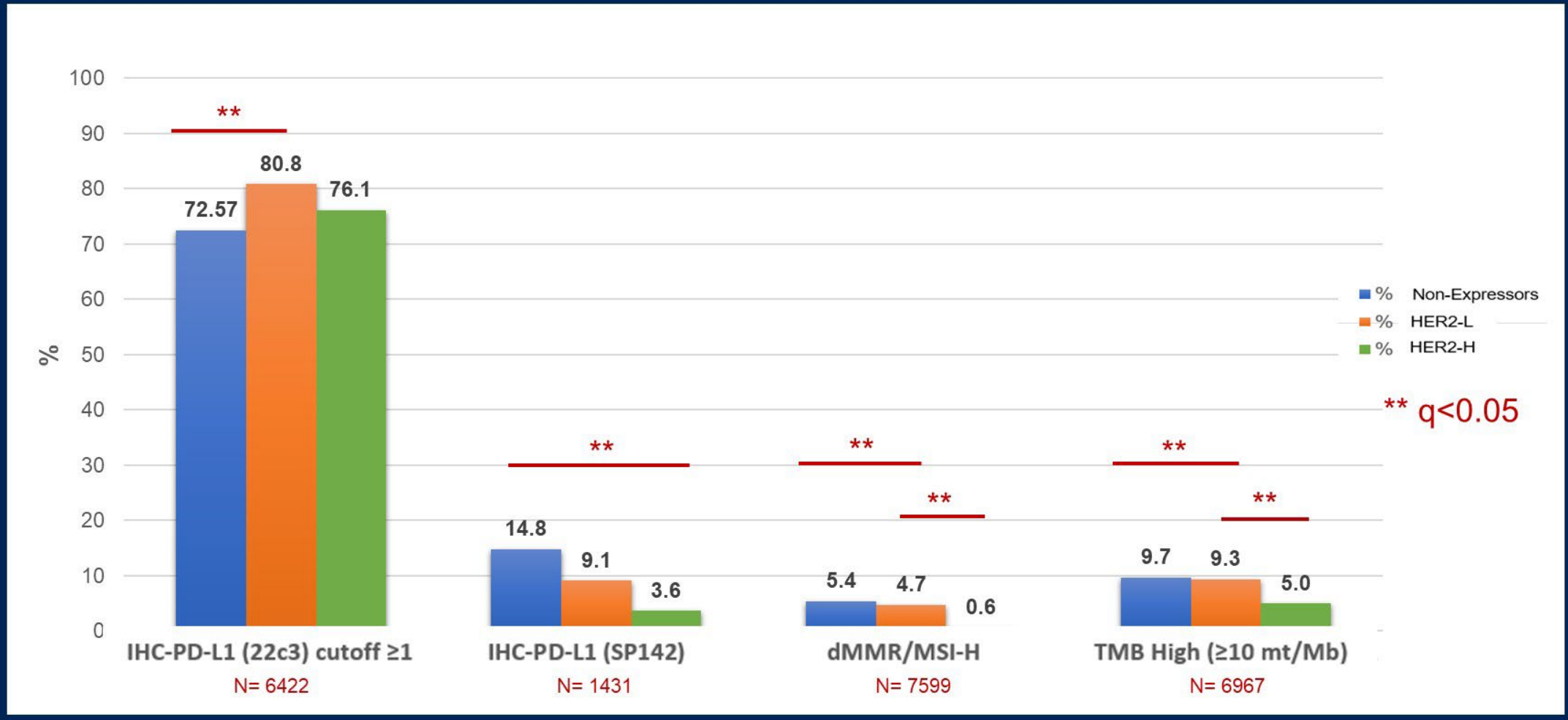
IO markers in HER2 cohorts



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ASCO Gastrointestinal Cancers Symposium

‘Other’ targeted therapy in metastatic esophagogastric cancer

Prof. dr. dr. Hanneke W.M. van Laarhoven

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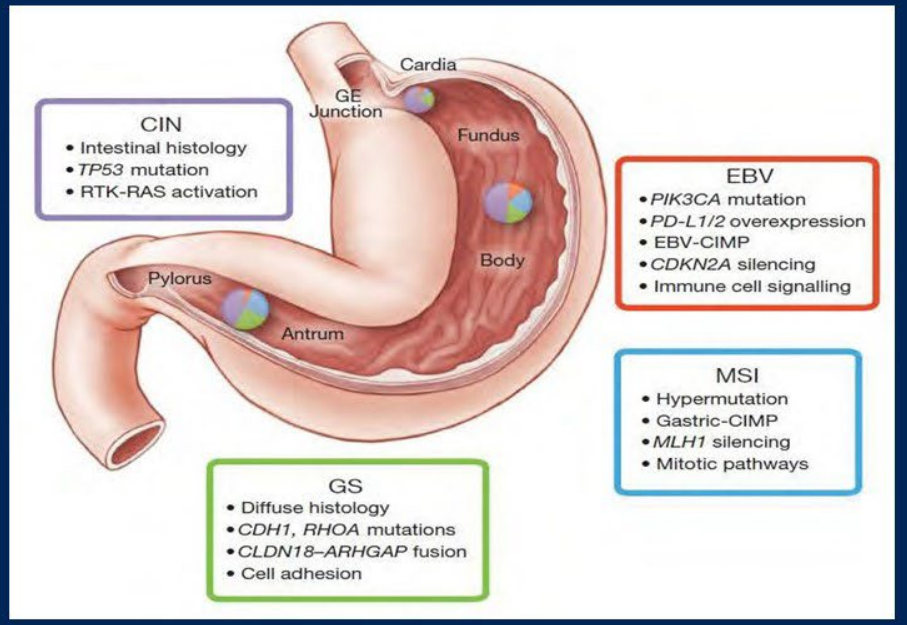
To be discussed – other targets, other therapies

- GS subtype: Claudin 18.2
- CIN/GS subtype: FGFR
- CIN subtype: HER2
- Other targets: the tumor microenvironment …



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To be discussed

- **GS subtype: Claudin 18.2**
- CIN/GS subtype: FGFR
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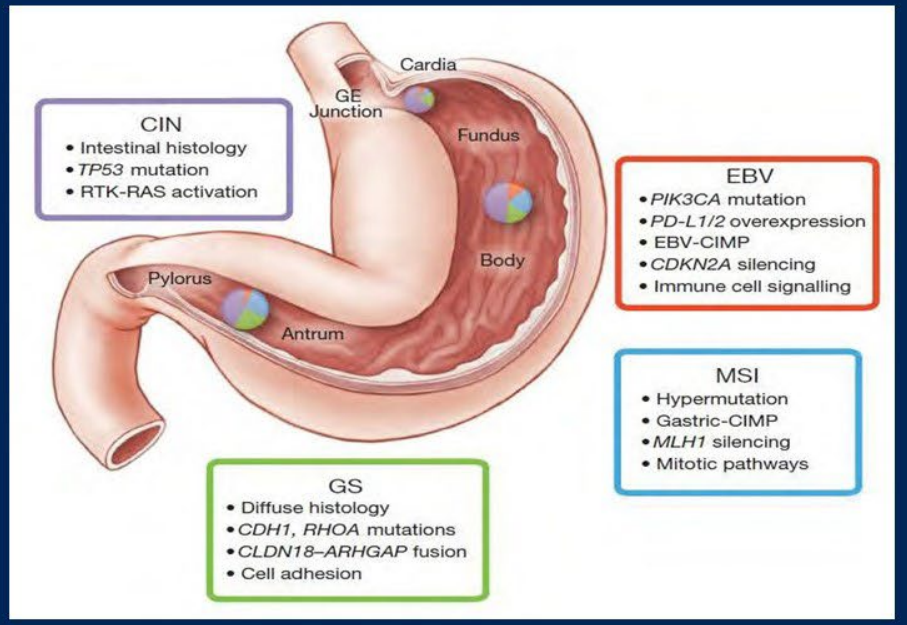
- Other targets: the tumor microenvironment …



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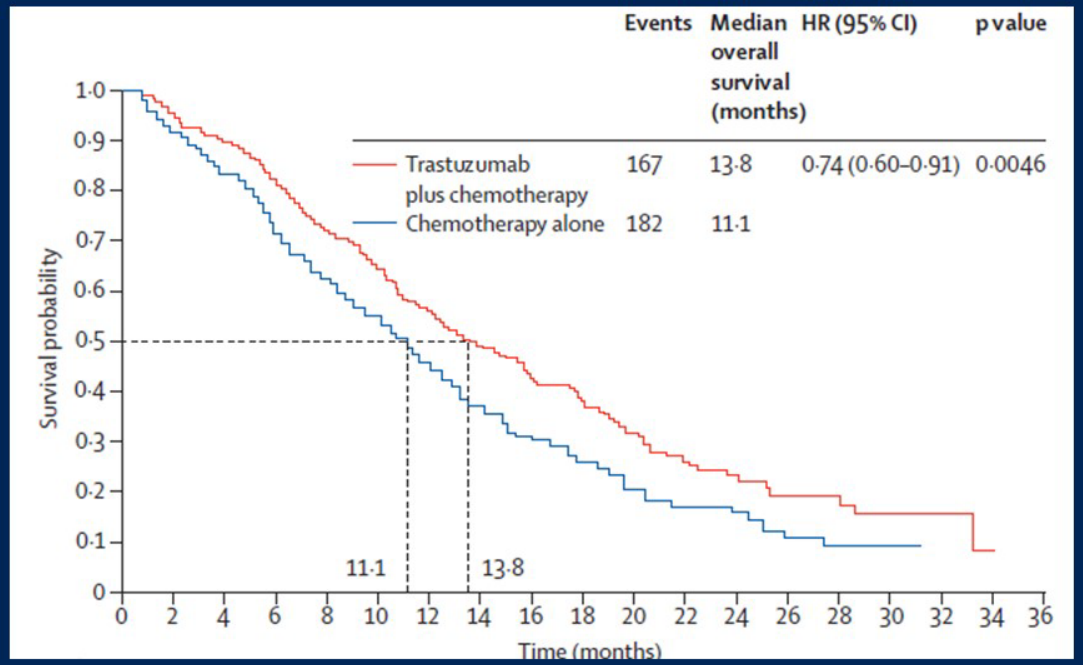
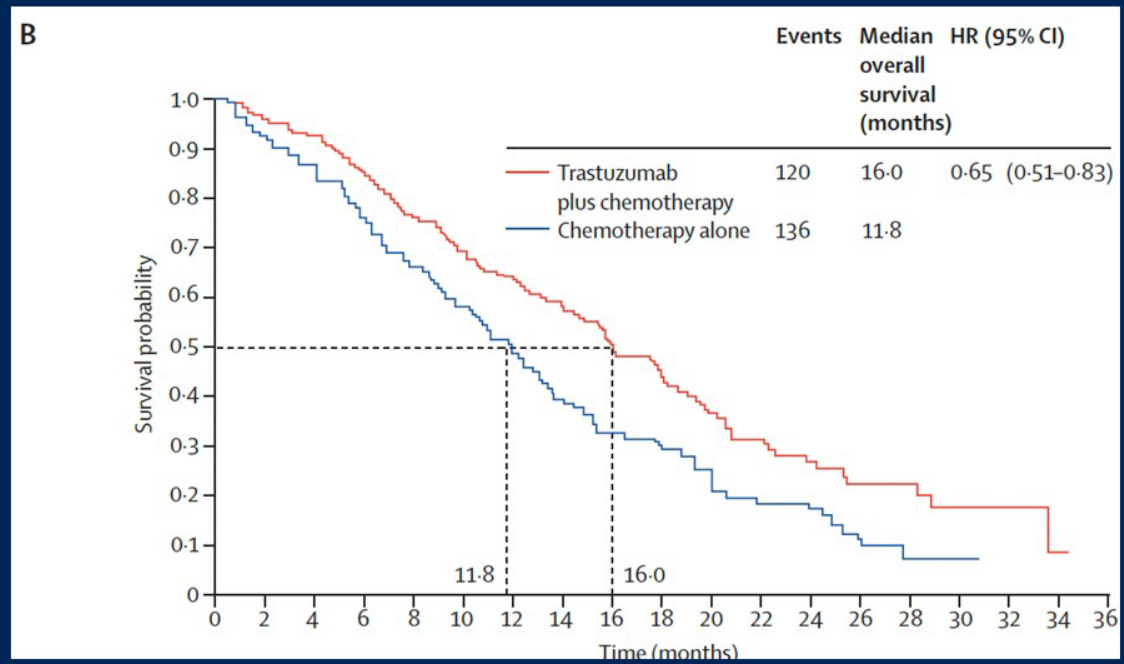
Trastuzumab standard of care in first line in HER2+ adenocarcinoma





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Bang, Lancet 2010

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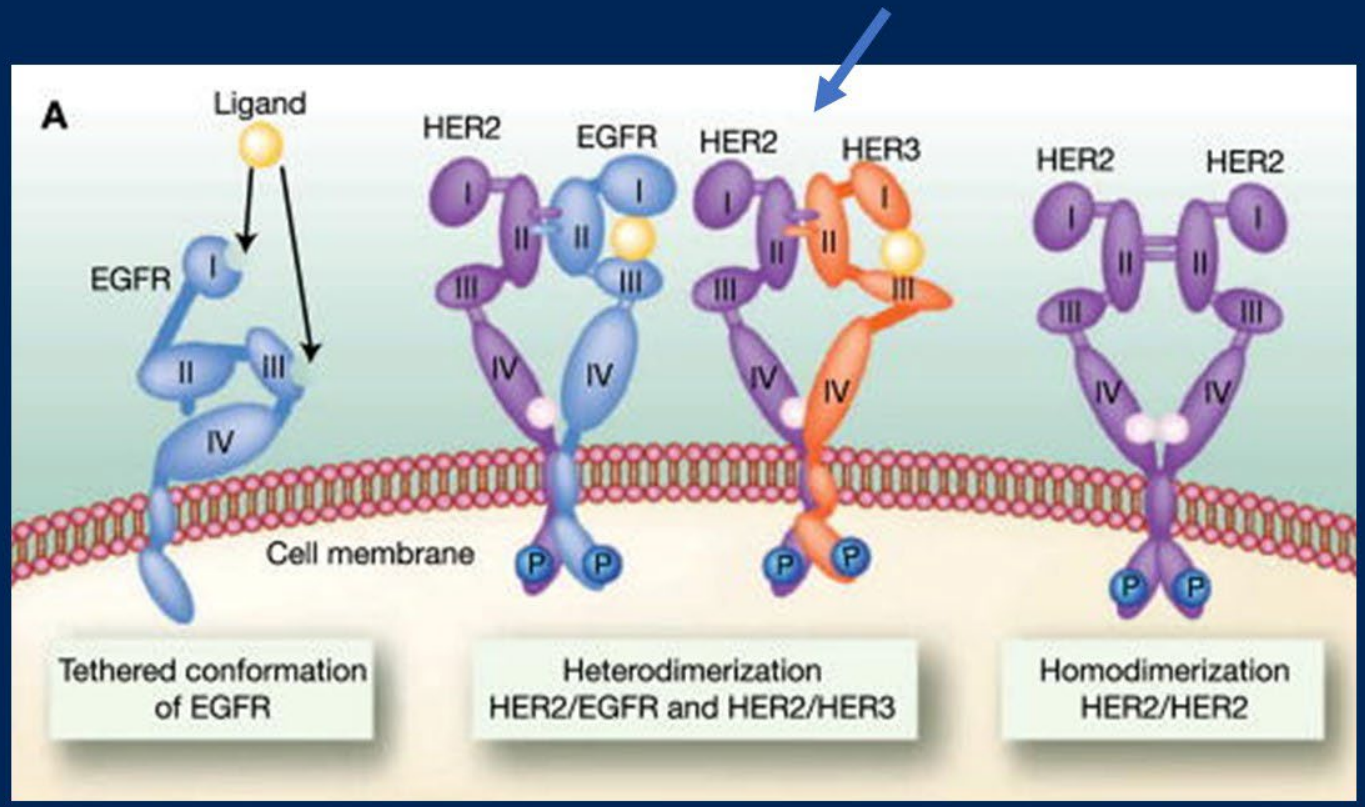
HER2 targeting revisited – circumventing resistance



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Pohlman, Clin Cancer Res 2009

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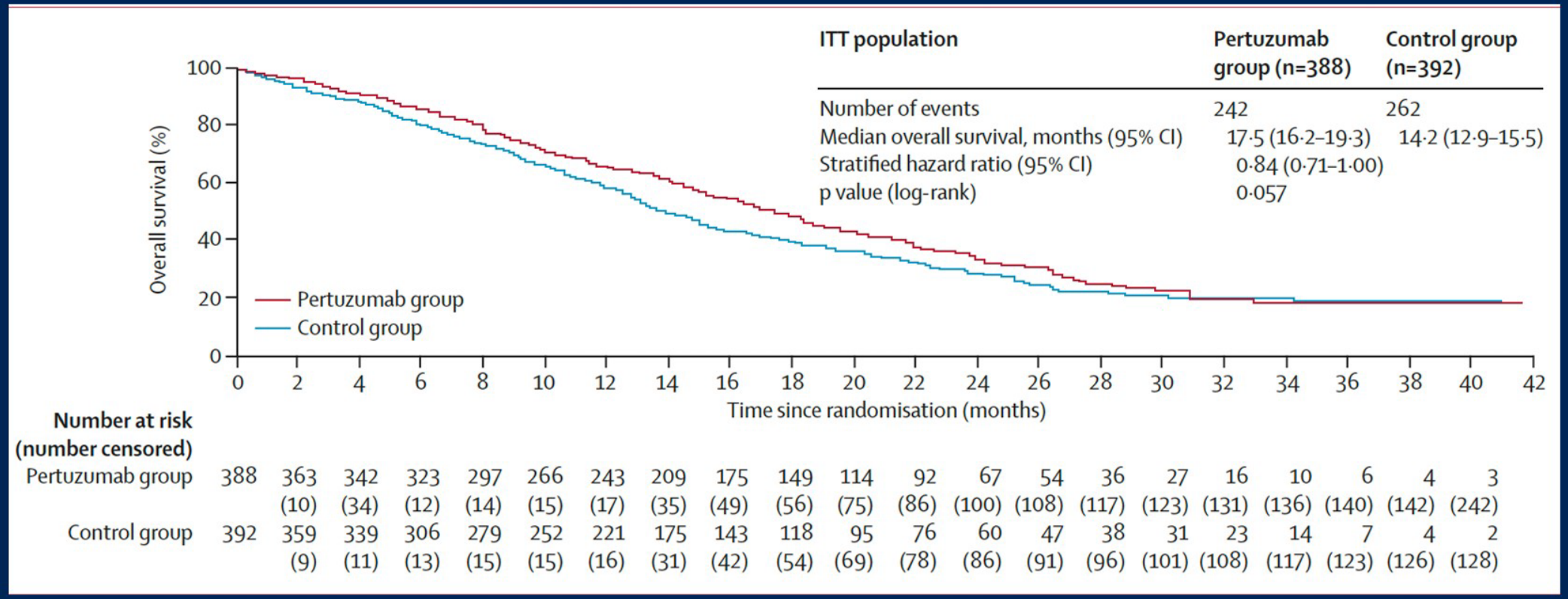
HER2/HER3 targeting: pertuzumab – M1 setting



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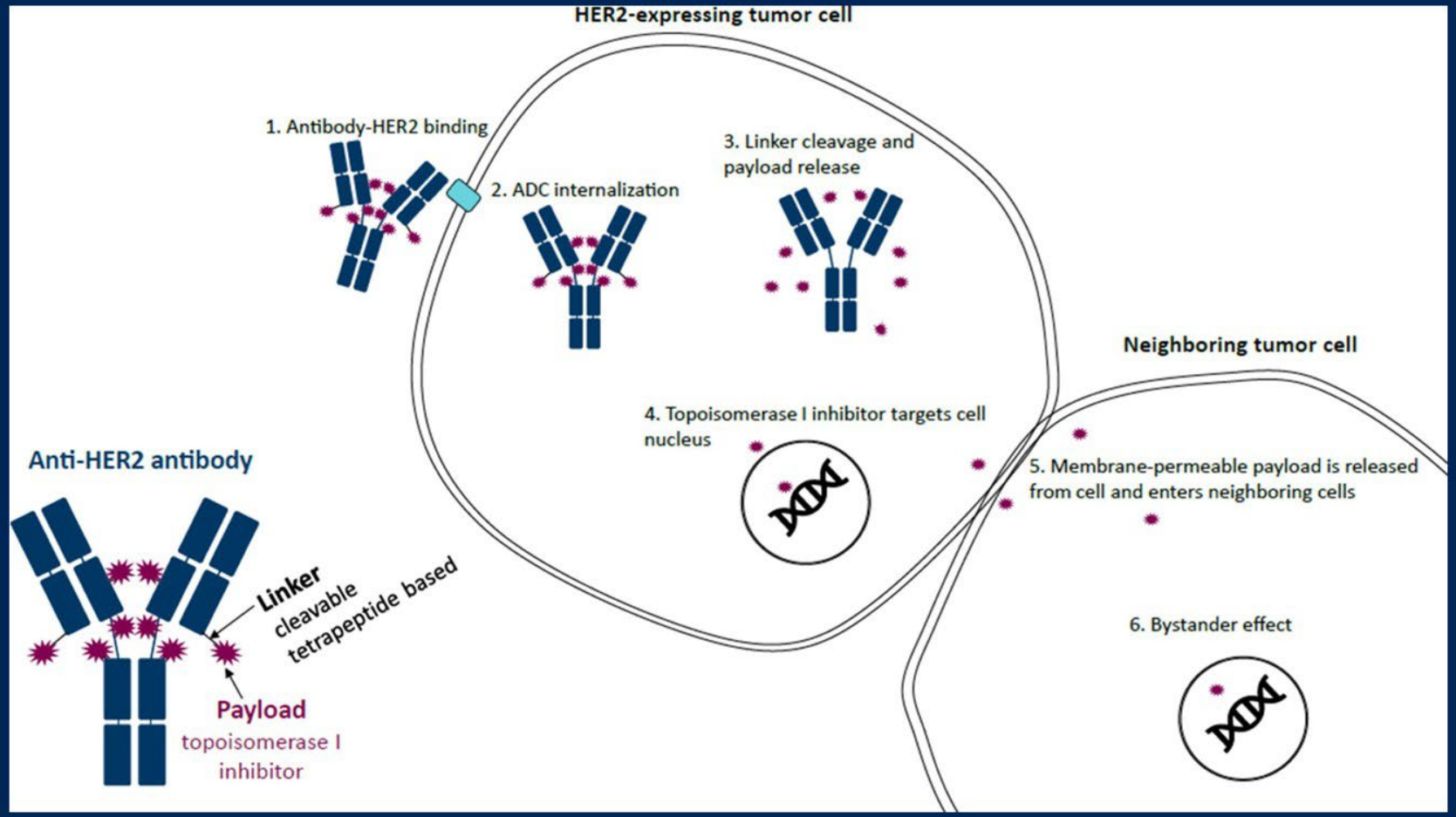
HER2 targeting – trastuzumab deruxtecan



Swain, Cancer Treat Rev 2022

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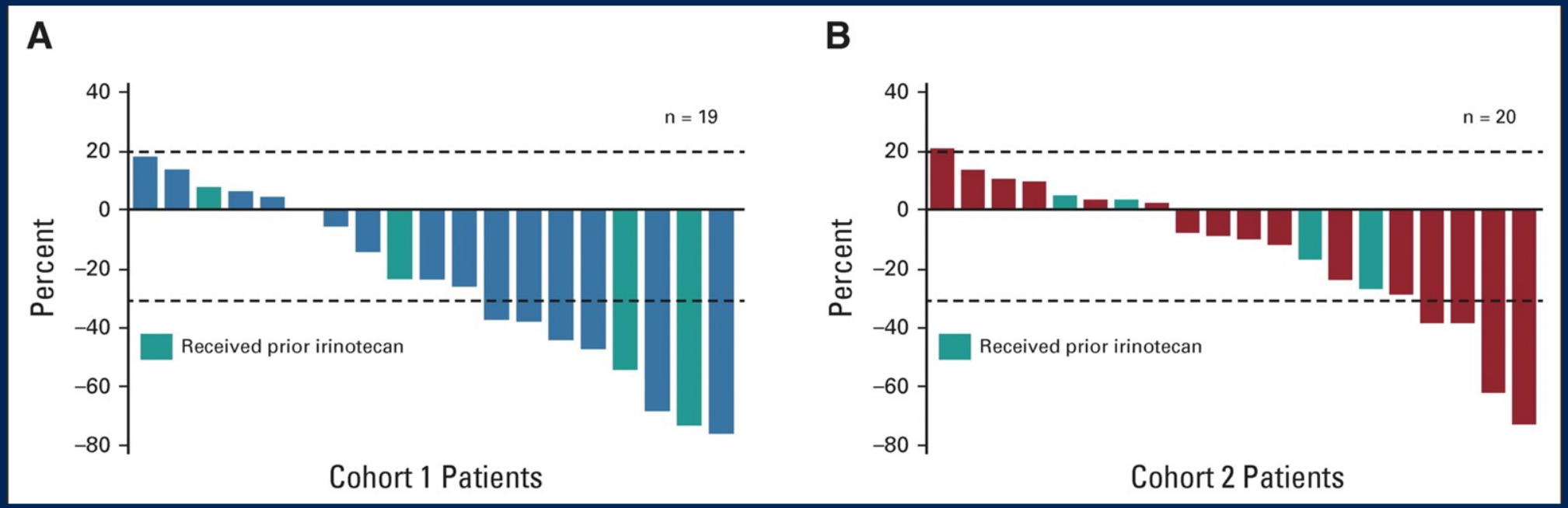
HER2 targeting – trastuzumab deruxtecan



HER2 2+, ISH neg

HER2 1+

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Yamaguchi, JCO 2022

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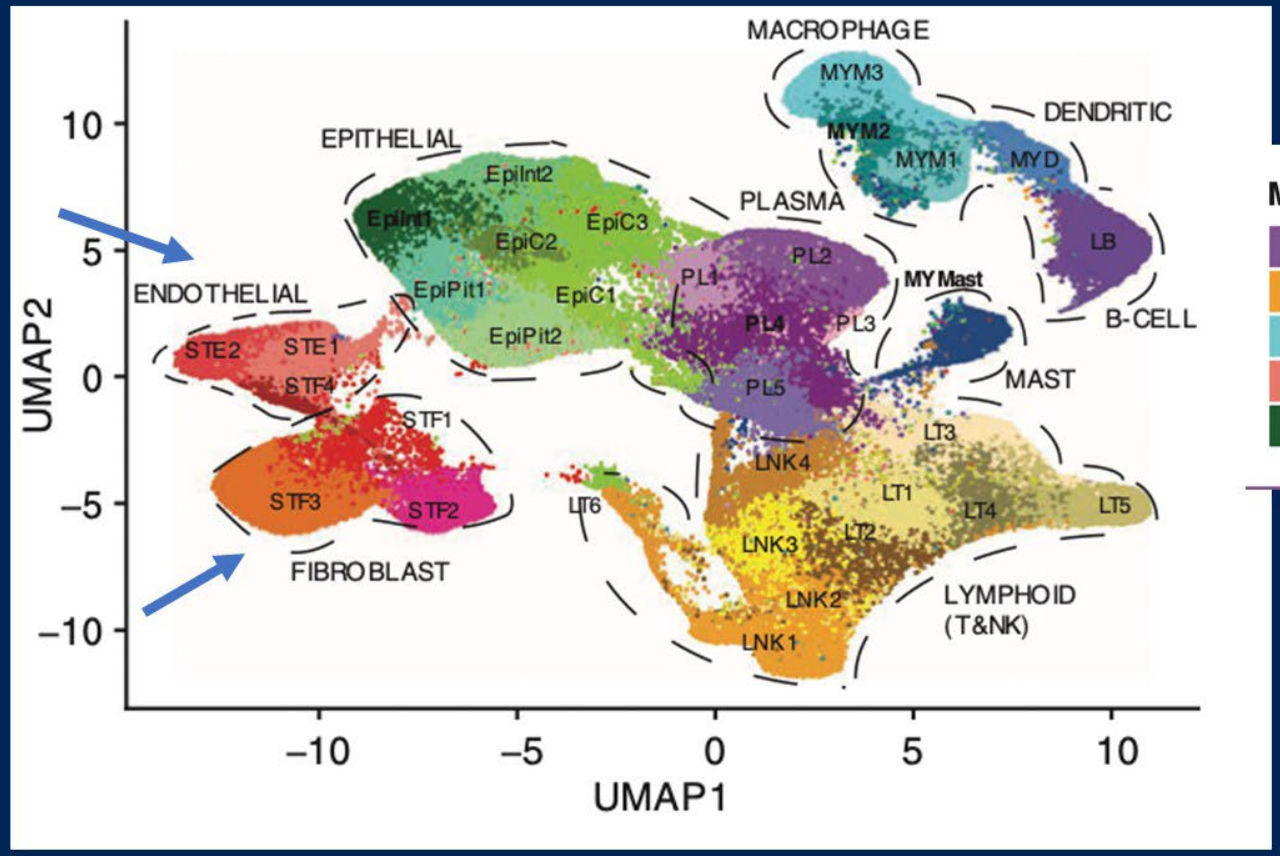
Tumor microenvironment





Kumar, Cancer Discov 2022

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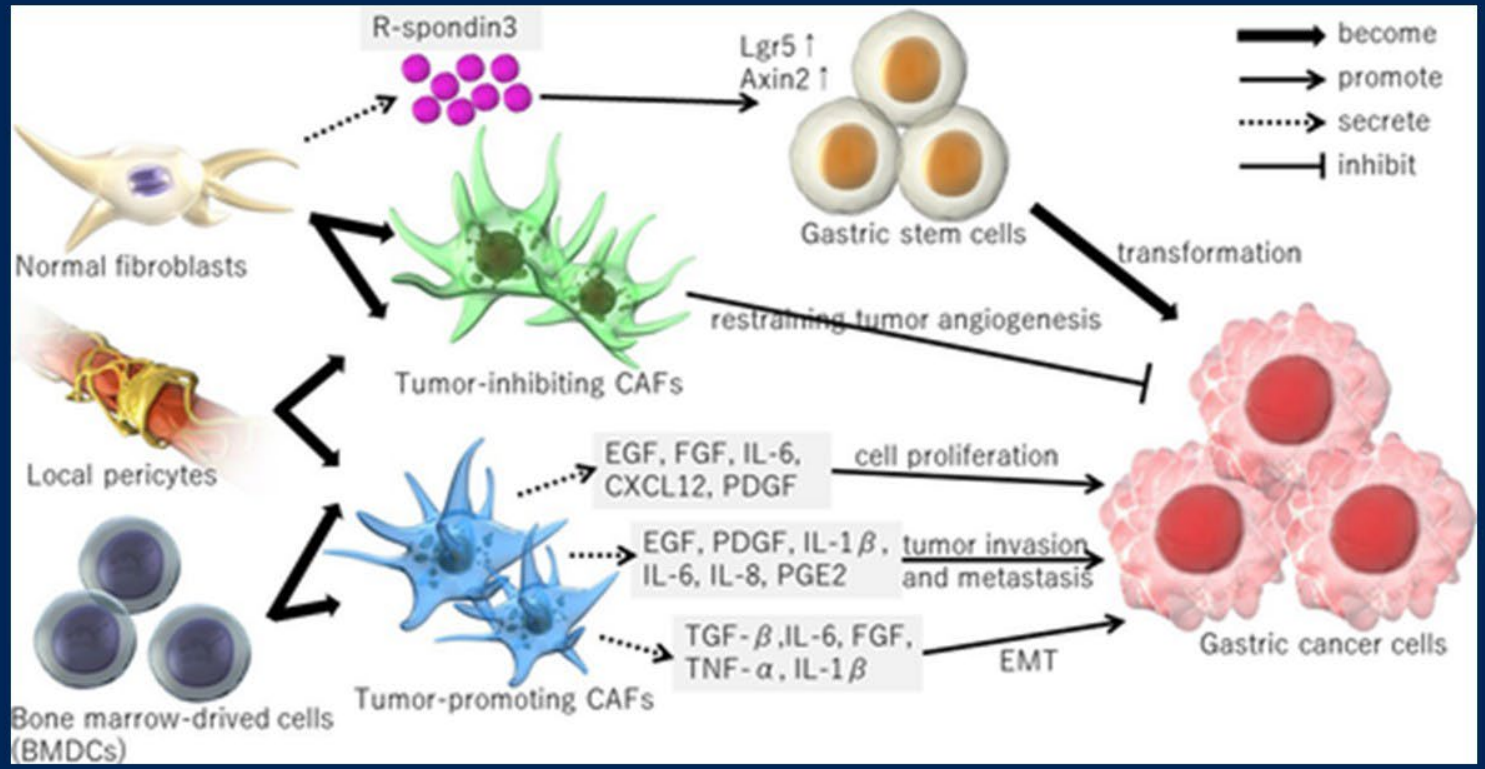
Cancer associated fibroblasts



Oya, Cancer Science 2020

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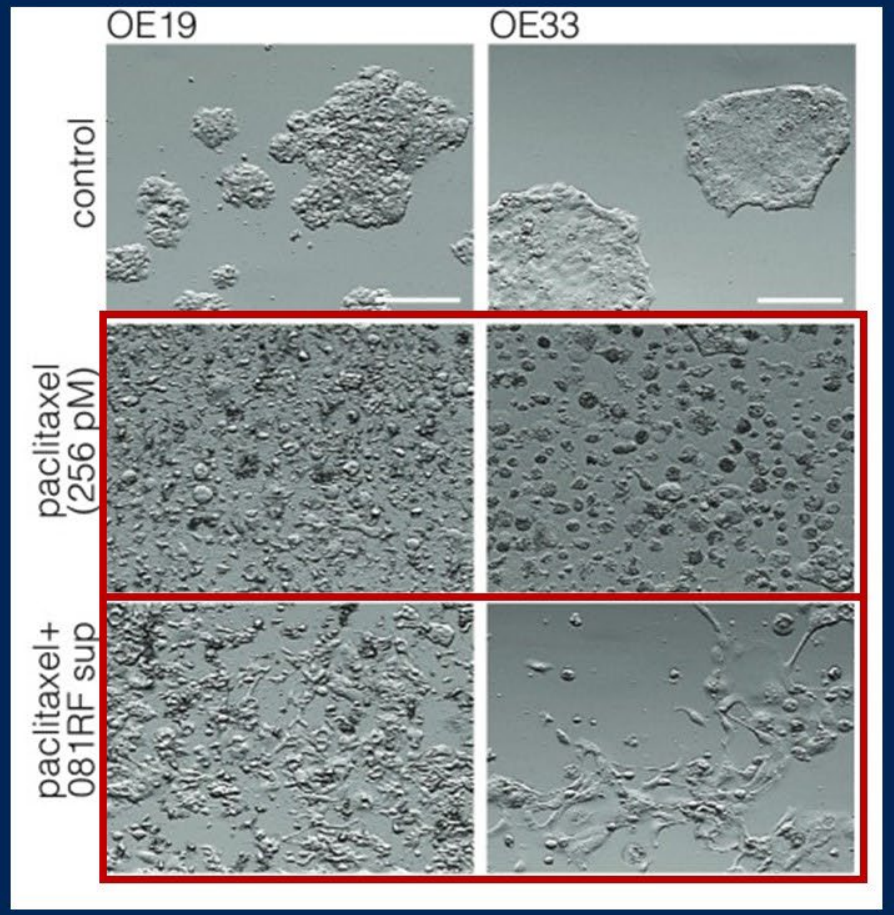
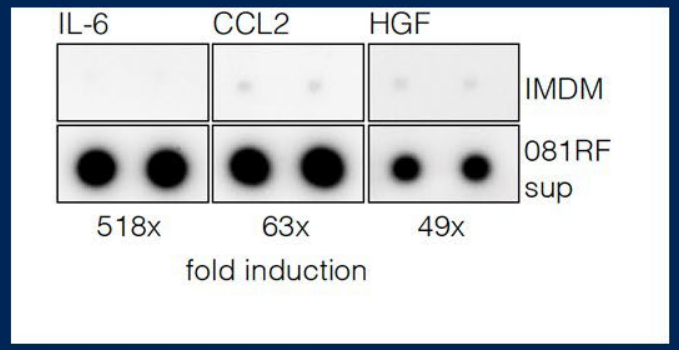
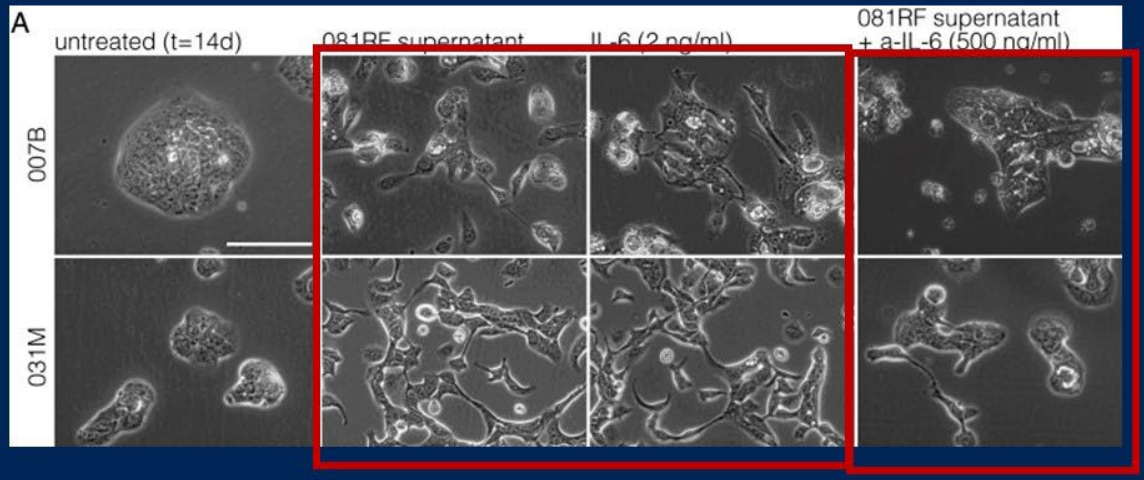
Cancer associated fibroblasts – treatment resistance through EMT induction





BASALT
(NCT04554771)



Ebbing, PNAS 2021

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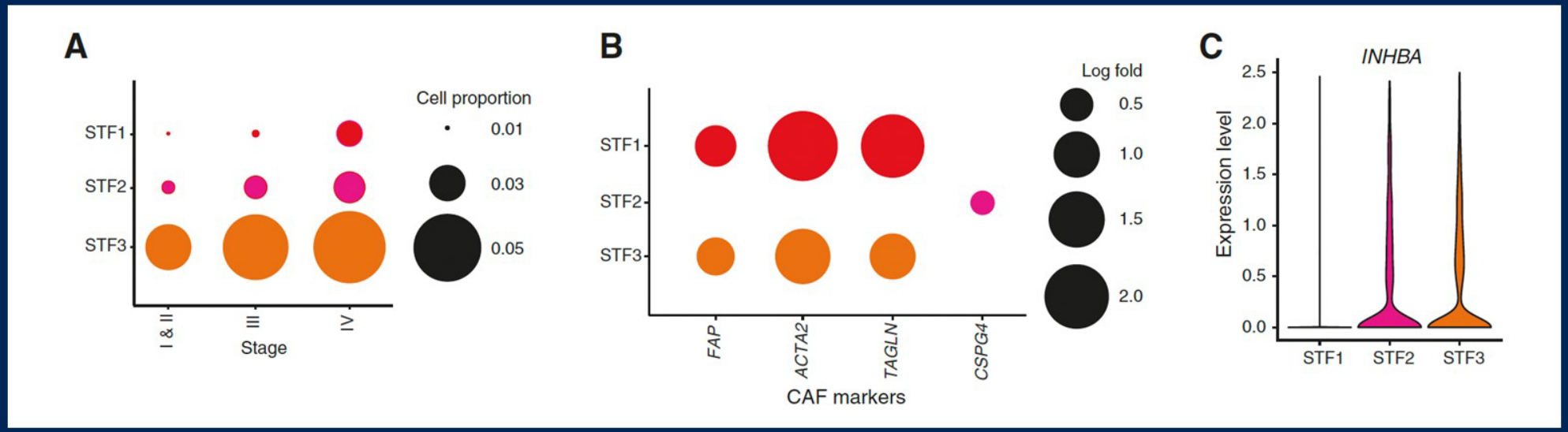
Cancer associated fibroblasts – different subtypes



Kumar, Cancer Discov 2022

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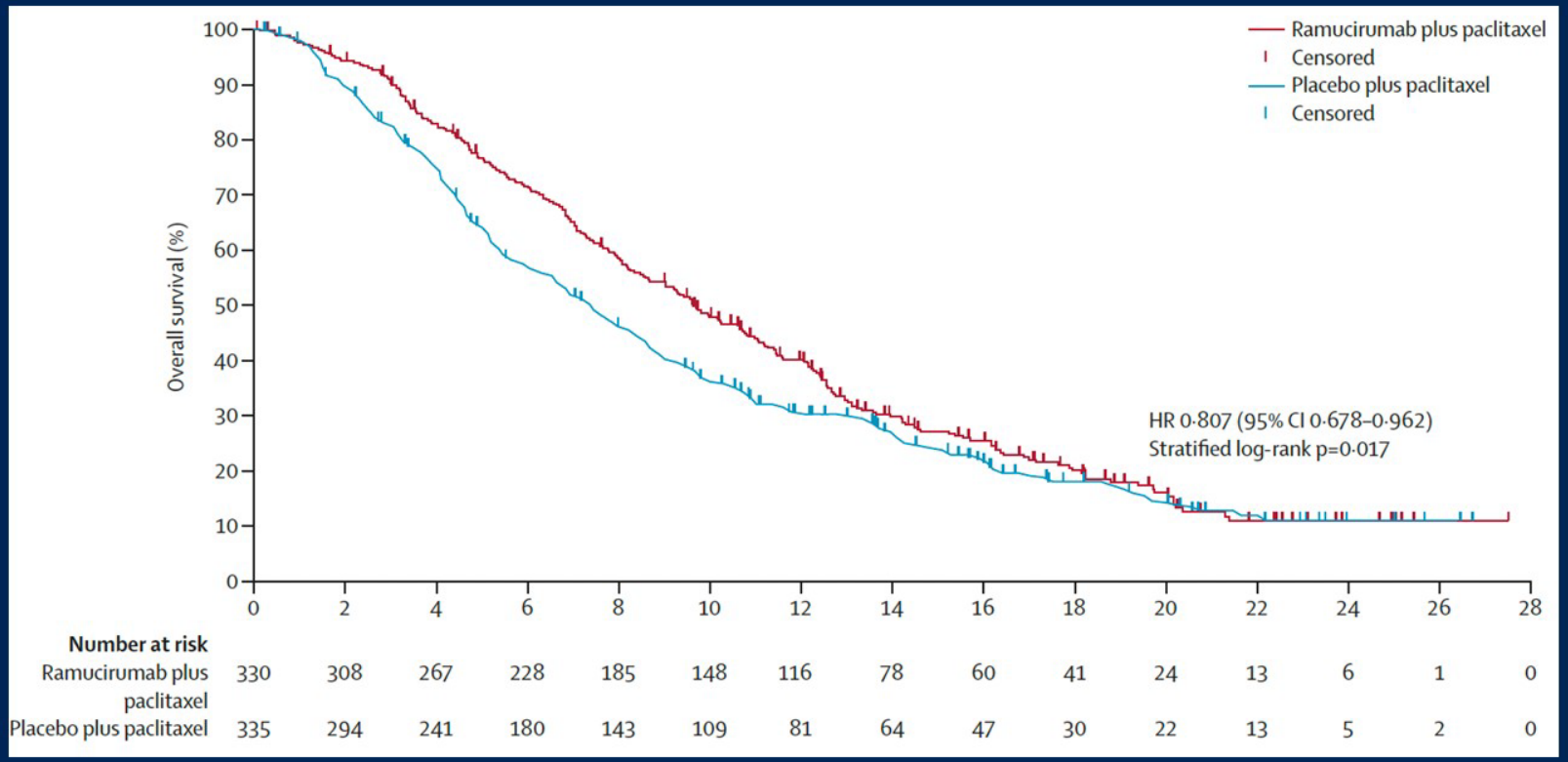
Endothelial cells, angiogenesis - ramucirumab



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Wilke, Lancet Oncol, 2014

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Endothelial cells, angiogenesis - regorafenib

Rapid Abstract Session Level 3, Ballroom

Rapid Abstract Session A: Cancers of the Esophagus and Stomach

Primary Track: Esophageal and Gastric Cancer

Presentations

11:15 PST

INTEGRATE IIa: A randomised, double-blind, phase III study of regorafenib versus placebo in refractory advanced gastro-oesophageal cancer (AGOC)—A study led by the Australasian Gastro-intestinal Trials Group (AGITG).

Presenter: Nick Pavlakis, PhD, MBBS, FRACP | Royal North Shore Hospital

Abstract: LBA294

11:20 PST

Neo-AEGIS (Neoadjuvant Trial in Adenocarcinoma of the Esophagus and Esophago-Gastric Junction International Study): Final primary outcome analysis.

Presenter: Maeve Aine Lowery, MD | St James's Hospital

Abstract: 295

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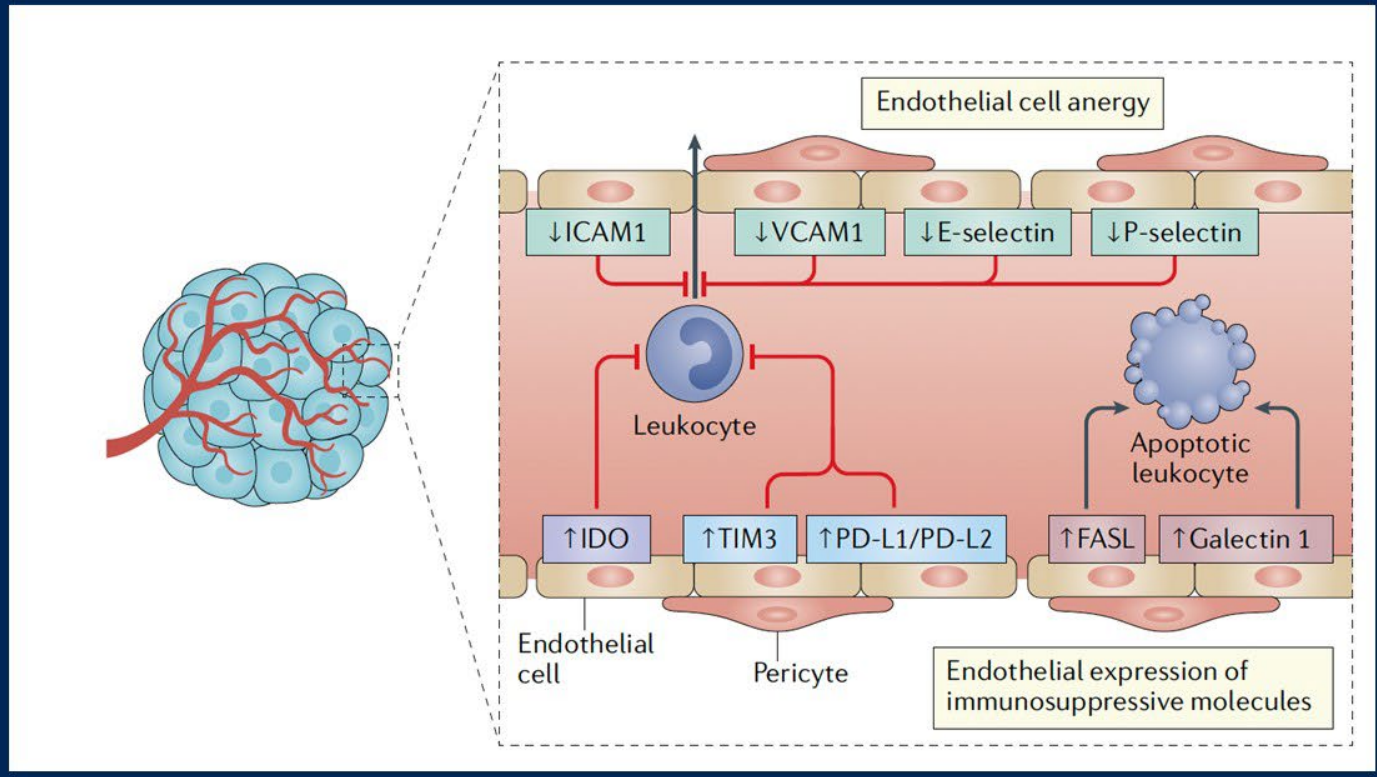
Endothelial cells, angiogenesis





Huinen, Nat Rev Clin Oncol. 2021

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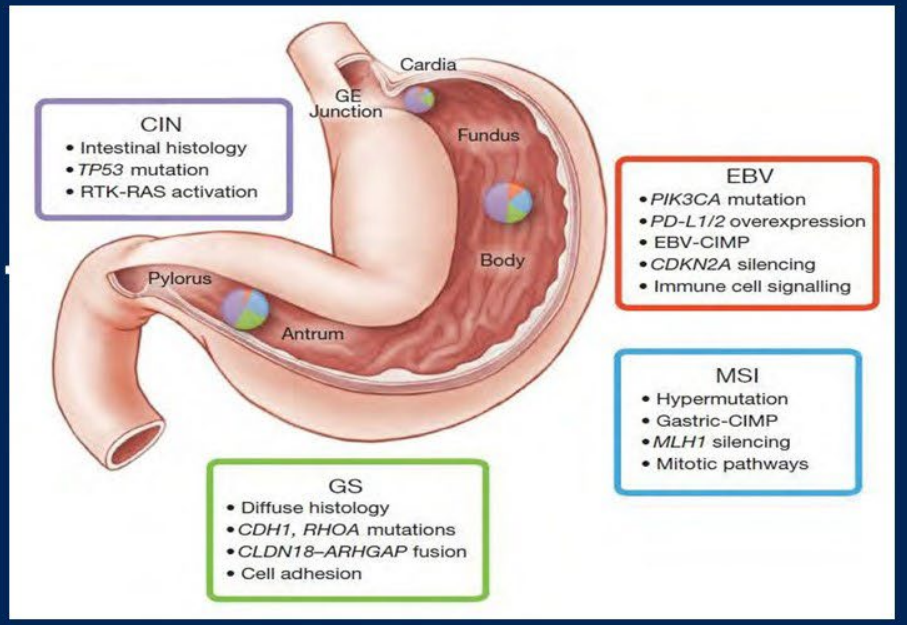
To be discussed

- GS subtype: Claudin 18.2
- CIN/GS subtype: FGFR
- CIN subtype: HER2
- **Other targets: the tumor microenvironment .**



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Multiple immunotherapies are approved.
‘One Size Does Not Fit All.’
‘Gastrointestinal cancers’ is not one disease.

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Immunotherapy in MSS CRC

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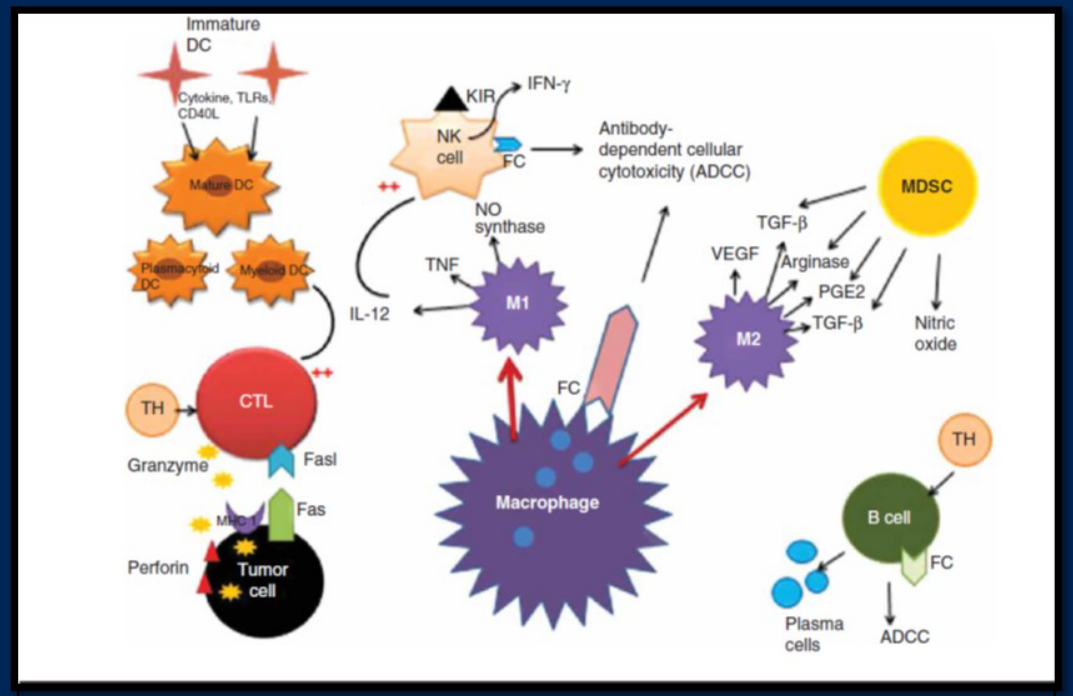
Tumor microenvironment in MSS CRC



Amin M and Lockhart AC, Expert Opin Investig Drugs 2015 Mar;24(3):329-44

Immunologically Cold:

- Low tumor neo-antigen load
- Low tumor mutation burden (average TMB of 6-8 mutations/MB)
- Lack of immune surveillance
- Low anti-tumor immune response

Interplay of immunosuppressive cells (Treg, immature DC, MDSC)and immunomodulatory cells (CD8, CD4, mature DC)

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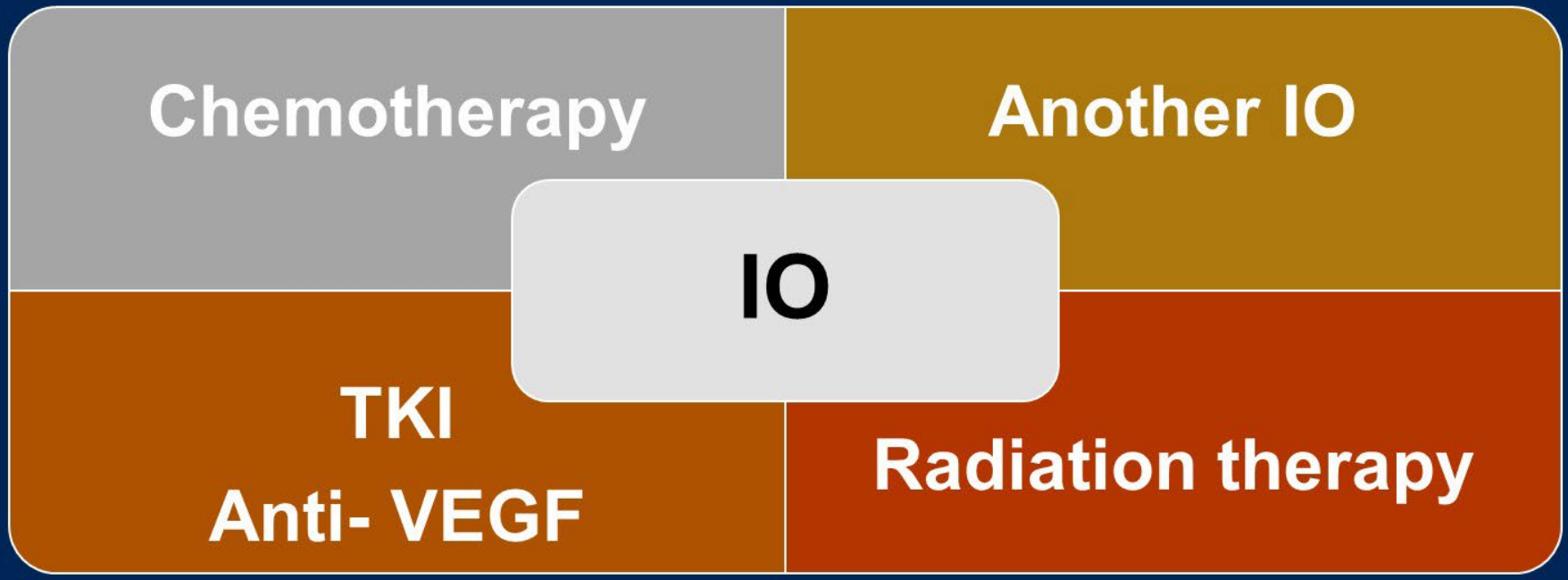
Common strategies for IO combination in MSS CRC



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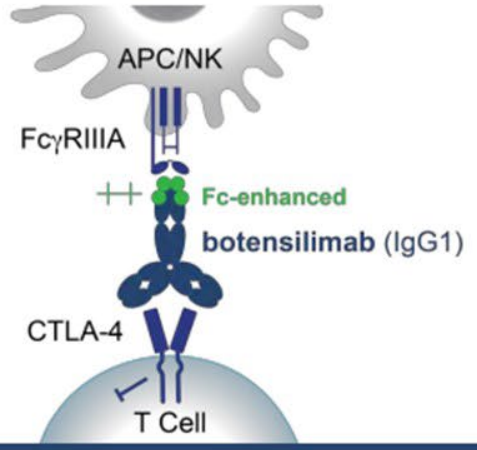
A look at upcoming novel strategies in MSS CRC: Anti-PD1 + Anti-CTLA-4

Novel Immunotherapy Agents

botensilimab

Fc-enhanced CTLA-4 Inhibitor

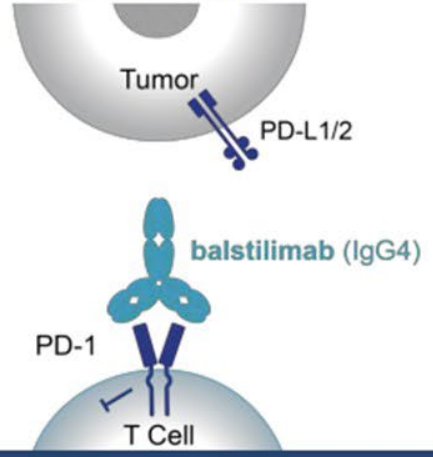


Active in cold and IO refractory tumors[1]:

- ↑ T cell priming, expansion, memory[2]
- ↑ Treg depletion
- ↓ Complement mediated toxicity

balstilimab

PD-1 Inhibitor



Safety and efficacy analogous to approved anti-PD-1 mAbs[3,4]

- > 650 patients treated; 8 ongoing trials / 2 completed
- Complete blocker of PD-1-PD-L1/2 interactions
- Enhanced T cell activation and effector function

1. El-Khoueiry AB. SITC 2021 Annual Meeting. Poster #479. 2. Waight et al. *Cancer Cell*. 2018;33(6): 1033-1047. 3. O'Malley, et al. *Gynecol Oncol*. 2021; 163: 274-280. 4. O'Malley et al, *J Clin Oncol*. 2022; 40(7): 762-771.

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Novel Strategies in MSS CRC:
IO + TKI combination

- REGONIVO Japan, REGONIVO US, REGOTORI (China)Regorafenib + Toripalimab)), Fruquintinib + Sintilimab (China), Fruquintinib + Geptanolimab (china), Lenvatinib + Pembrolizumab, CAMILLA trial: Duravalumab + Cabozantinib (benefit in Kras WT)

- Variable efficacy in MSS CRC.

- ORR ranges from 7-40 %
- OS ranges from 7 to 16 months.

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LEAP-005: Phase 2 Trial of Pembrolizumab Plus Lenvatinib in Previously Treated Patients With Select Solid Tumors: CRC cohort (NCT03797326)

CRC patients:
- Has received 2 prior lines of therapy
- Non-MSI-H/pMMR tumor

Primary end point:
ORR, safety, tolerability
Secondary end point:
DCR, DOR, PFS, OS

Outcome	N = 32
ORR (CR+PR), % (95% CI)	22 (9-40)
DCR (CR+PR+SD[a]), % (95% CI)	47 (29-65)
DOR, median (range), mos	NR (2.1+-10.4+)
PFS, median (95% CI), mos	2.3 (2.0-5.2)
OS, median (95% CI), mos	7.5 (3.9-NR)

LEAP-017 : Phase IIII randomized trial of Pembrolizumab + Lenvatinib versus standard of care in metastatic colorectal cancer who have previously received treatment. N=434 (NCT04776148)

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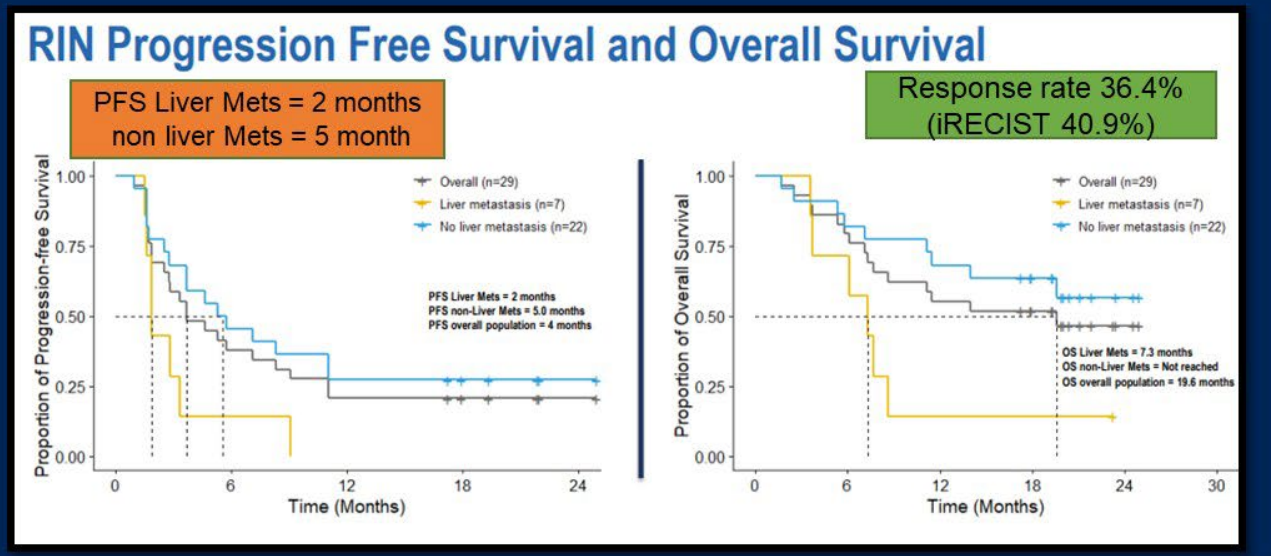
IO + TKI combination

Does the site of the metastasis matter ?

REGONIVO Phase II: US data

Response, n (%)	Without liver metastases (n=23)	With liver metastases (n=47)	All patients (N=70)
Complete response	0	0	0
Partial response	5 (22)	0	5 (7)
Stable disease	8 (35)	14 (30)	22 (31)
Progressive disease	9 (39)	27 (57)	36 (51)
Not evaluable	1 (4)	6 (13)	7 (10)
Objective response rate	5 (22)	0	5 (7)
Disease control rate ≥8 weeks	13 (57)	14 (30)	27 (39)
Median duration of stable disease, weeks	30	21	30

RIN Phase I: Regorafenib + Ipilimumab + Nivolumab



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Upcoming Immune targets: Second Generation ICIs

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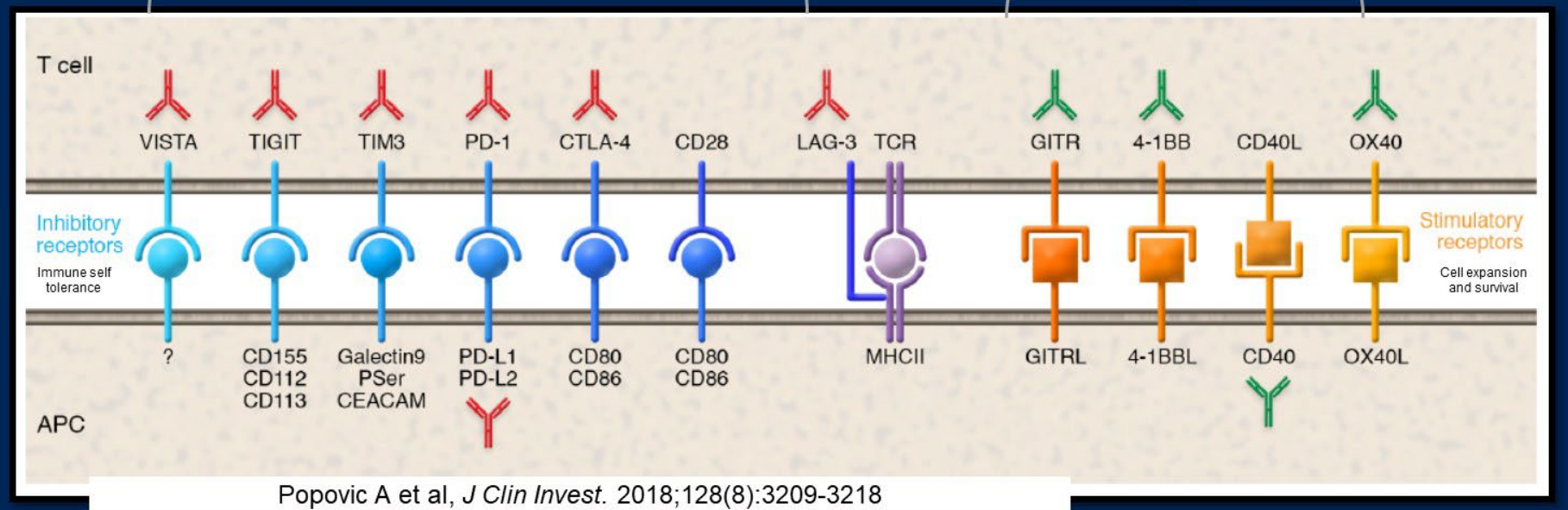
Second Generation Immune Checkpoints

Inhibitory Immune Checkpoints

Co-stimulatory Immune Checkpoints



Popovic A et al, *J Clin Invest.* 2018;128(8):3209-3218

CTLA4: Cytotoxic T Lymphocyte Antigen 4
LAG-3: Lymphocyte-Activation Gene 3
VISTA: V-domain Immunoglobulin Suppressor of T cell Activation
TIGIT: T cell Immunoreceptor with immunoglobulin and ITIM domains
TIM3: T-cell Immunoglobulin and Mucin domain 3

GITR: Glucocorticoid-induced tumour necrosis factor (TNF) receptor
4-1BB: CD 137
CD40
OX40: CD134

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LAG-3

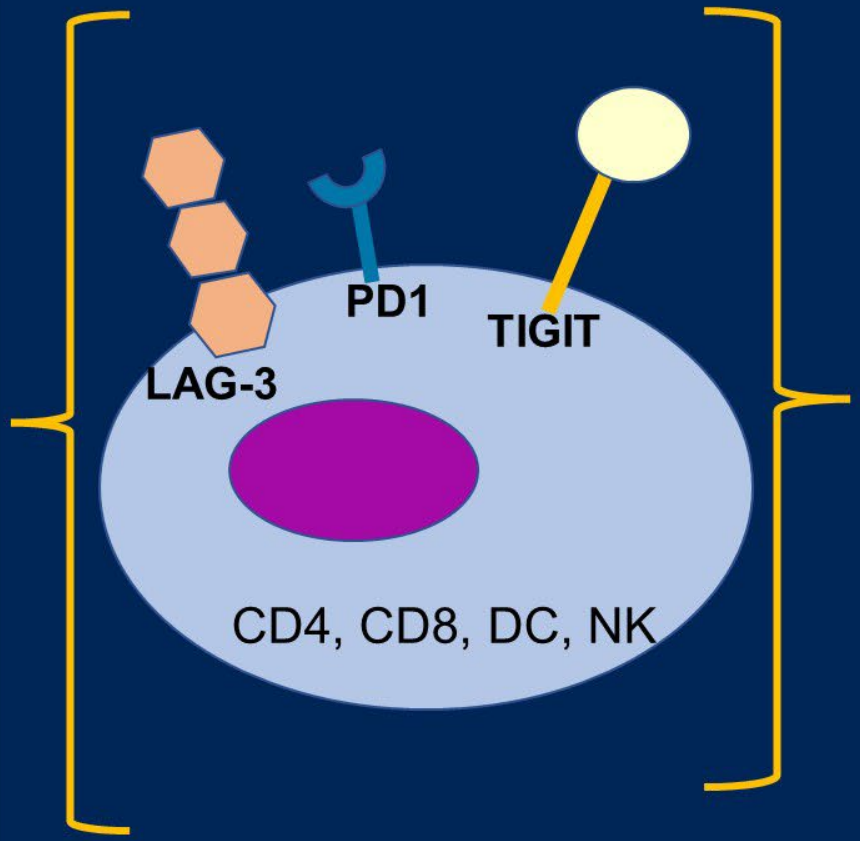
Expressed on CD4, CD8,DC, NK cells

Structurally similarly to CD4 Binds to MHC class II on APC.

Negative regulatory function in T cells.

Treg mediated immune suppression.

Co-expression of PD1 and LAG-3 lead to T cell exhaustion.



TIGIT

Expressed on effector CD4, CD8, Tregs, NK cells.

Binds to CD155 on APC with high affinity.

Negative regulatory function in T cells.

Treg mediated immune suppression.

Co-expression of TIGIT with PD1 or TIM3 lead to T cell exhaustion.

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Anti-LAG-3, Anti-TIGIT combinations with IO in phase III trials in GI cancers

Type of cancer	Trial Phase	Patient population	Drug combination	Primary outcome	Secondary outcome	Clincialtrials.gov
MSS mCRC	III	PDL1 positive MSS mCRC	**Favezelimab** + pembrolizumab	OS	PFS, ORR, DoR, QOL	NCT05064059
MSS mCRC RELATIVITY-123	III		Nivolumab + **Relatilmab** Versus Regorafenib or TAS 102	OS	ORR, PFS, DoR	NCT05328908
Gastric/GEJ HER2-Positive (First line)	II/III		Margetuximab + Retifanlimab + **Tebotelimab**	ORR	PFS, DCR, DoR	NCT04082364
Unresectable Esophageal Squamous Cell SKYSCRAPER-07	III		Atezolizumab +/- **Tiragolumab** (Anti- TIGIT Antibody)	PFS, OS	ORR	NCT04543617

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Early phase trials ongoing with other inhibitory and co-stimulatory checkpoint inhibitors such as anti-CD40, Anti-VISTA, Anti-OX40 + IO combinations.

Data needs to mature in GI cancers.

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Personalized Immunotherapy: Adoptive cell therapy

Utilizing TIL and genetically engineered cells (TCR gene therapy, CAR-T therapy)

ASCO Gastrointestinal Cancers Symposium

#GI23

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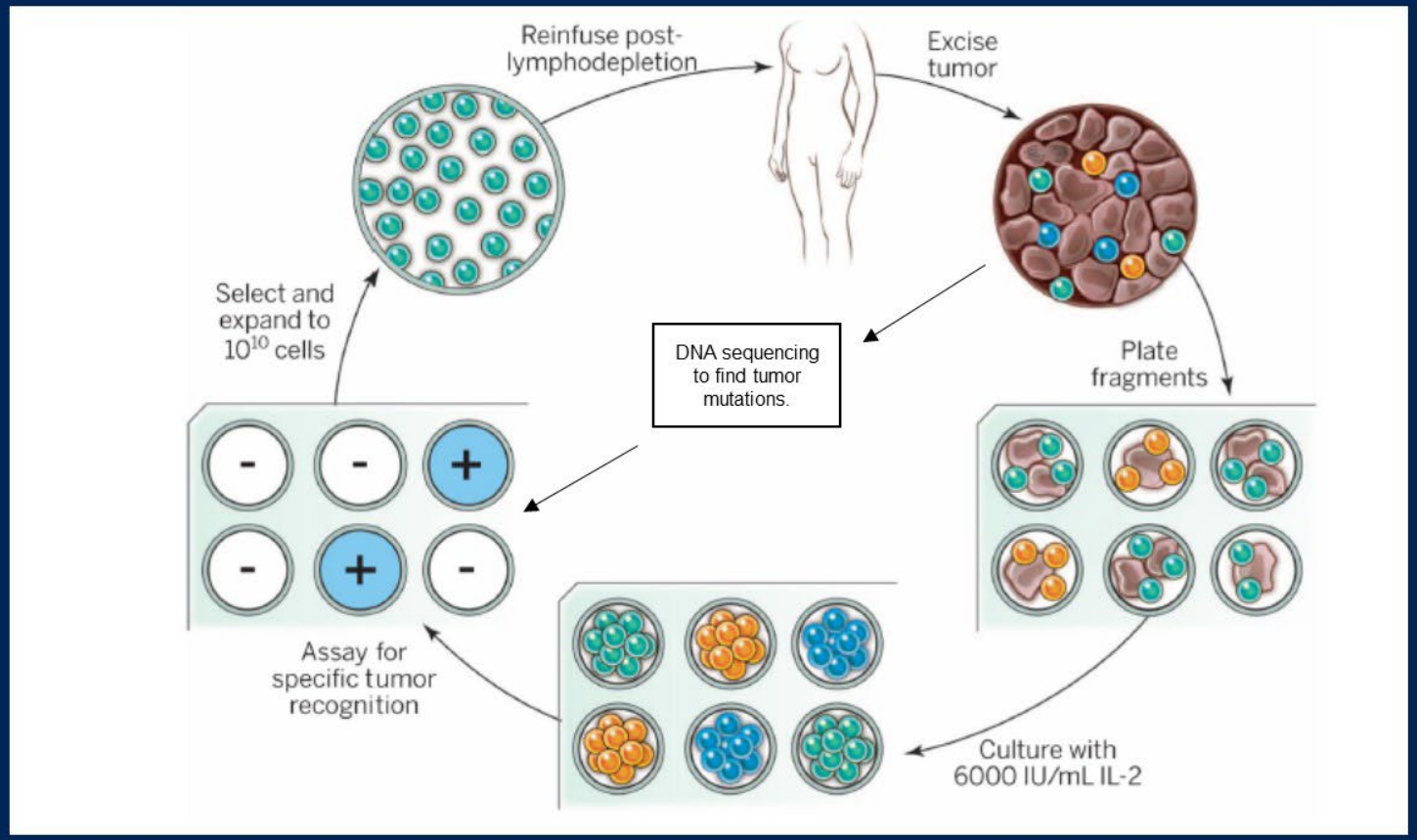
Adoptive Cell Therapy:
Utilizing Tumor Infiltrating lymphocytes (TIL)



Steven A. Rosenberg and Nicholas P. Restifo, Science. 2015 April 03; 348(6230): 62–68.

Lymphodepletion

↓

TIL infusion

↓

High dose IL2 to stimulate TIL activity

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Ongoing GI trials with TIL

Location	Trial	Objectives	Source
Masonic Cancer Center, University of Minnesota	A Phase I/II trial of Tumor infiltrating lymphocytes (TIL) in which the gene encoding CISH was inactivated using CRISPER/Cas9 system in Gastrointestinal malignancies.	MTD, safety and efficacy	NCT04426669
UPMC Hillman cancer Center	A Phase II Study to Evaluate the Efficacy and Safety of Adoptive Transfer of Autologous Tumor Infiltrating Lymphocytes (TIL) in Patients With Locally Advanced, Recurrent, or Metastatic Biliary Tract Cancers.	ORR CR DCR DoR	NCT03801083

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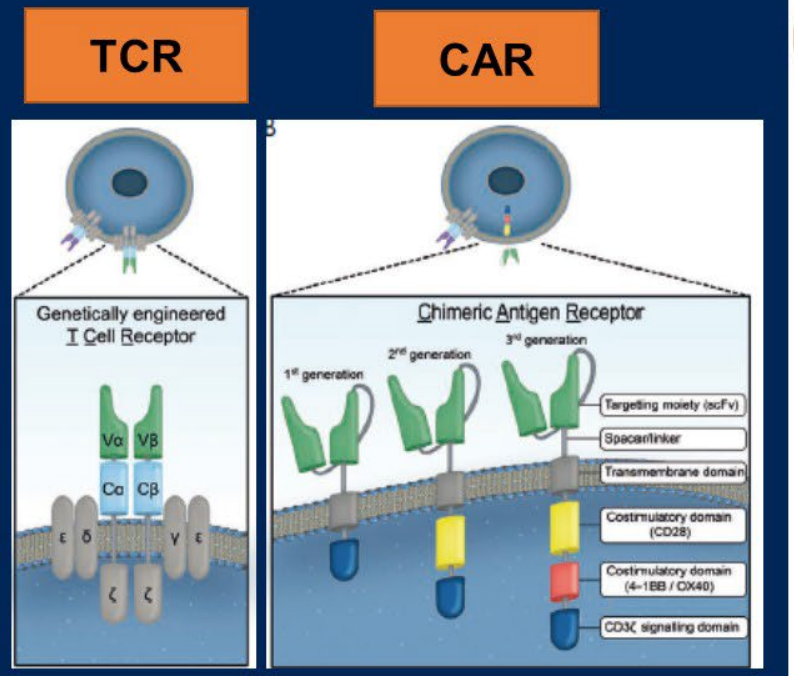
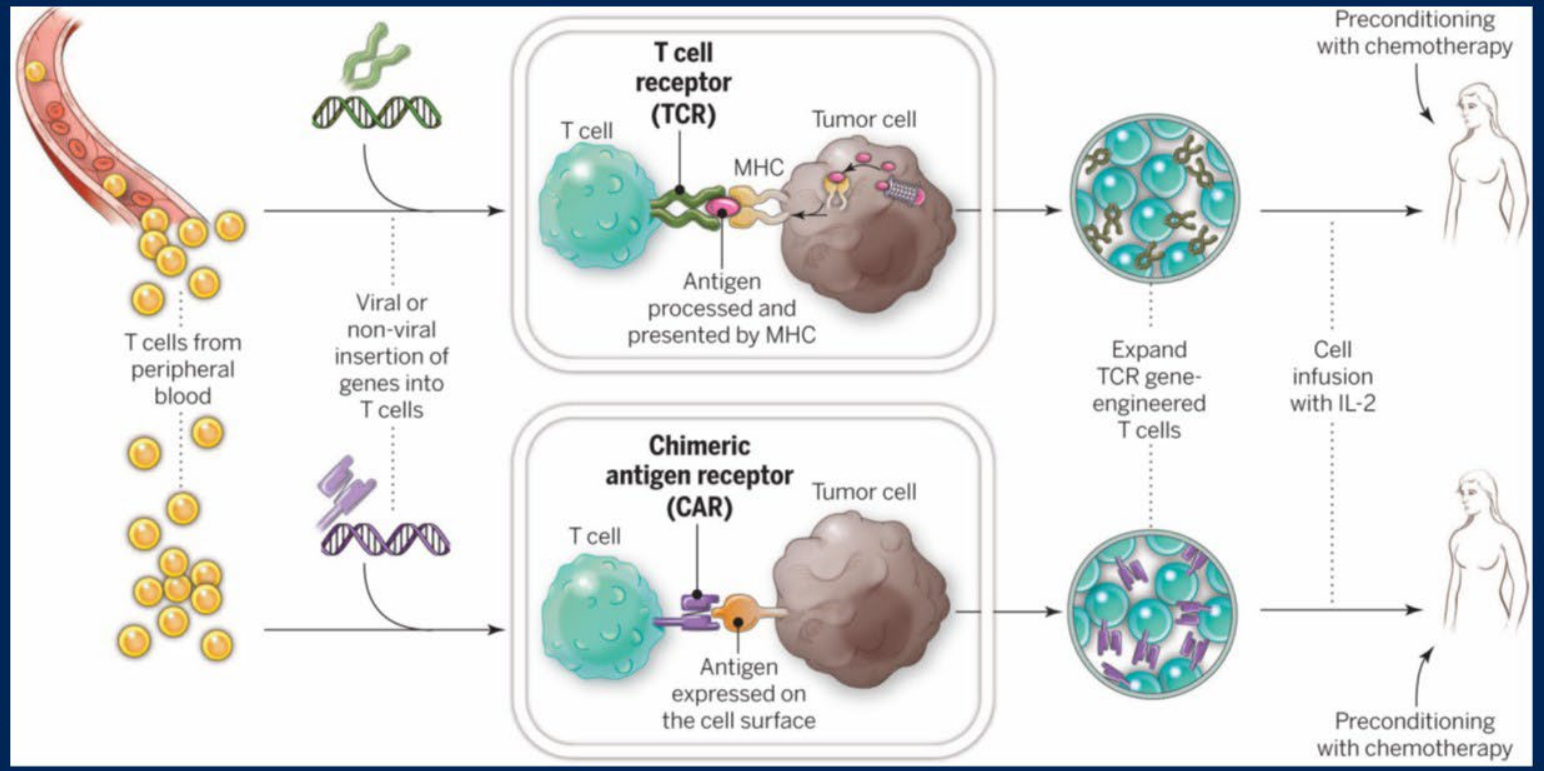
Adoptive Cell Therapy:
Utilizing Genetically Engineered Cells (TCR, CAR)



Ozcan Met et all, Seminars in Immunopathology (2019) 41:49–58



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Barriers to Adoptive Cell Therapy:

- Difficult antigen selection due to high antigen heterogeneity.
- On-Target Off-tumor toxicity.
- Insufficient T cell localization to the tumor site
- Physical barriers preventing the tumor infiltration by T cells
- Dysfunctional T cells due to immune suppressive factors in TME
- Difficulties with toxicities from lymphodepletion and HD IL2 infusion- cytokine storm

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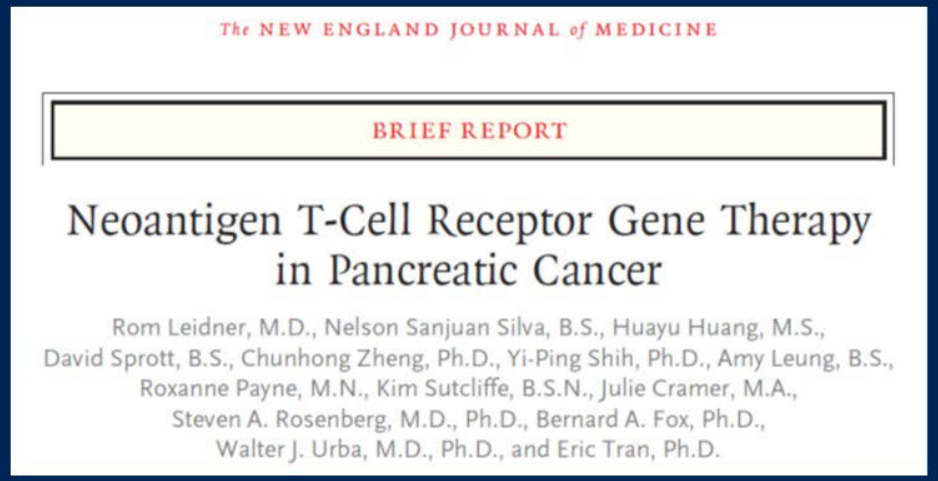
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer

Eric Tran, Ph.D., Paul F. Robbins, Ph.D., Yong-Chen Lu, Ph.D., Todd D. Prickett, Ph.D., Jared J. Gartner, M.Sc., Li Jia, M.Sc., Anna Pasetto, Ph.D., Zhili Zheng, Ph.D., Satyajit Ray, Ph.D., Eric M. Groh, M.D., Isaac R. Kriley, M.D., and Steven A. Rosenberg, M.D., Ph.D.



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Neoantigen T-Cell Receptor Gene Therapy in Pancreatic Cancer

Rom Leidner, M.D., Nelson Sanjuan Silva, B.S., Huayu Huang, M.S., David Sprott, B.S., Chunhong Zheng, Ph.D., Yi-Ping Shih, Ph.D., Amy Leung, B.S., Roxanne Payne, M.N., Kim Sutcliffe, B.S.N., Julie Cramer, M.A., Steven A. Rosenberg, M.D., Ph.D., Bernard A. Fox, Ph.D., Walter J. Urba, M.D., Ph.D., and Eric Tran, Ph.D.

HLA-C*08:02–restricted TCR gene therapy targeting the KRAS G12D driver mutation in colon cancer and pancreatic cancer.

-Patients had durable response > 6 months

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TCR-T Gene Therapy Trials in GI Cancers

Location	Trial	TCR-T Gene Target	source
Providence Portland Medical center	A Phase I/Ib Study of TCR-T Targeting Tumor-Specific Neoantigens, With in Vivo CD40 Activation and PD-1 Blockade.	**KRAS G12V with HLA-A*11:01 or HLA-DRB1*07:01** **KRAS G12D with HLA-A*11:01 or HLA-C*08:02**	NCT04520711
NCI	A Phase I/II Study Administering Peripheral Blood Lymphocytes Transduced With a Murine T-Cell Receptor. Recognizing the KRAS G12D and KRAS G12V in patients	**KRAS G12D with HLA-A*11:01** **KRAS G12V with HLA-A*11:01**	NCT03745326 NCT03190941

CAR-T Therapy trials

Targets for CAR-T in GI cancers:	**Epithelial cell adhesion molecule (EpCAM), HER2, CEA, B7-H3, mesothelin expressing cells, AFP, Glypican-3, Claudine 18.2**

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Future directions:

- Vaccine Therapies
  (Dendritic cell, peptide, DNA, RNA vaccines, Oncolytic Viruses)
- Bispecific antibodies and Bispecific T cell engagers (BiTE)
- Novel Cytokine Therapies

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Conclusions/Take-Away

- Future of Immunotherapy in GI cancers is ‘Optimistic’ and ‘Opportunistic’.
- Expectations from next generation ICIs: stay tuned.
- Personalized Immunotherapy (Adoptive cell therapies): Challenging, but success stories bring hope.
- MSS CRC:
  - There may be a role of anti-PD1 and anti-CTLA-4 combination. Need to wait for future data.
  - Site of metastasis matters. More metastatic site-specific trials and predictive biomarkers needed.

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