Clinical Trials in GI Cancers

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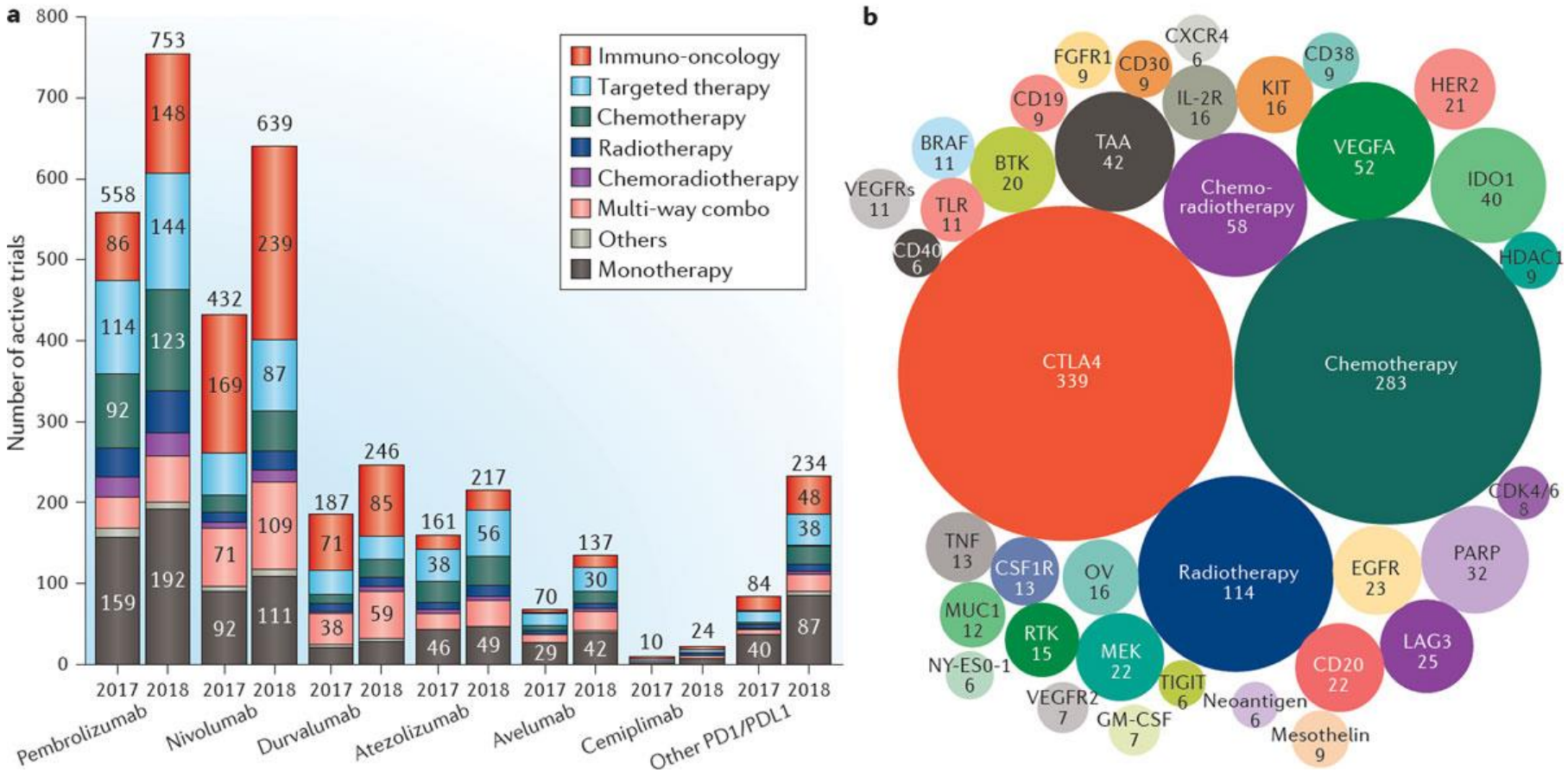
Advances in Cancer Immunotherapy

November 17th, 2021

Disclosure and Conflict of Interest

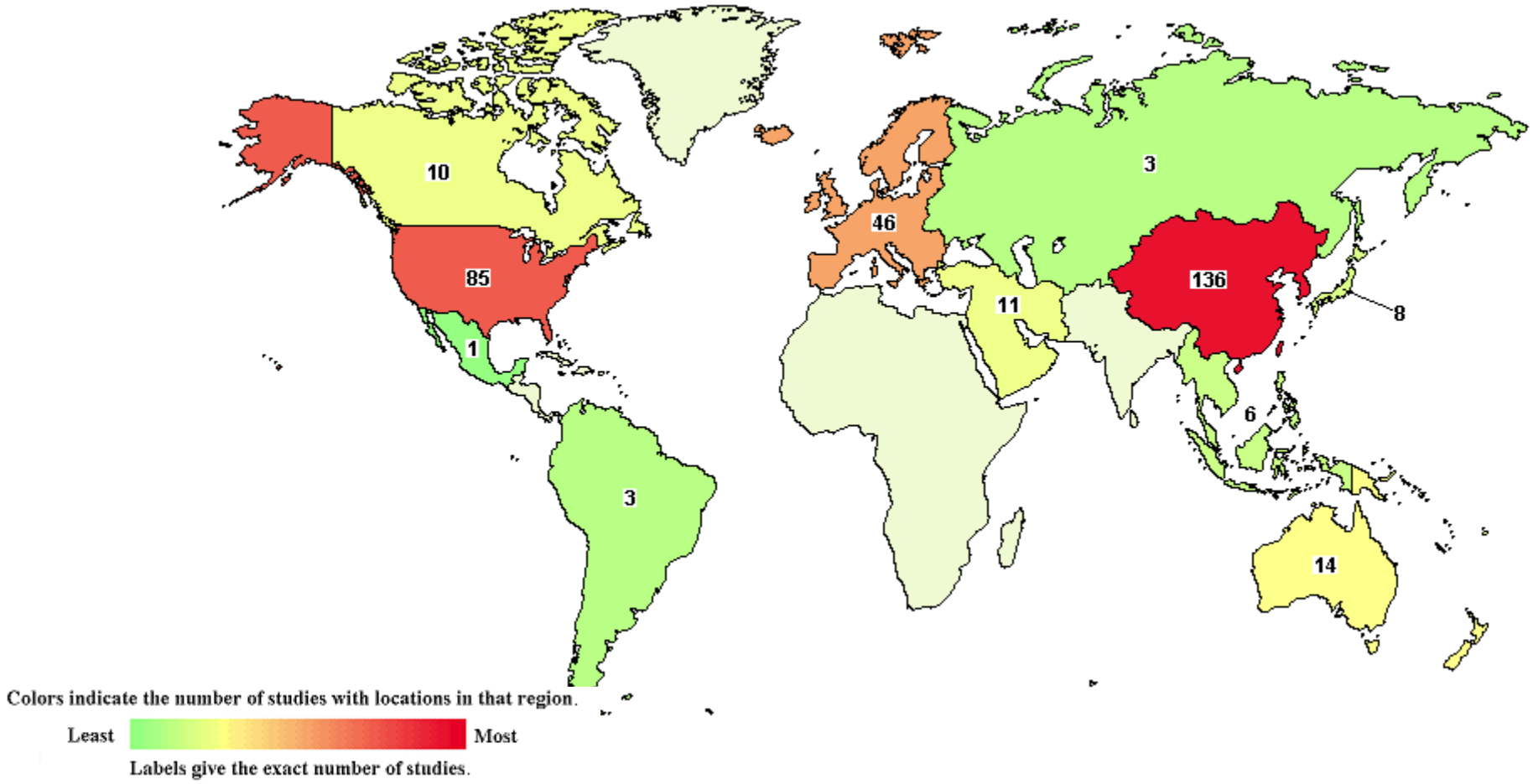
- Contracted Research: Bristol Myers Squibb, Boehringer Ingelheim, Calithera, CytomX, Genoscience, Eli Lilly, Loxo Oncology, Novartis, Pfizer, Yiviva, Zymeworks
- Consulting Fees: Adaptiimune, Bristol Myers Squibb, CytomX, Eisai, Exelexis, Merck, QED, Zymeworks

Immune Checkpoint Inhibitor (ICI) in Cancer Drug Development



Tang, J *Nat Rev Drug Discov* **17,** 854–855 (2018)

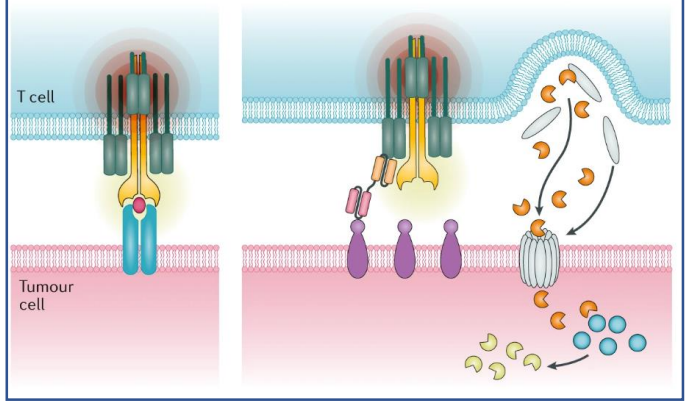
Worldwide ICI Therapeutic Trials in GI Cancers



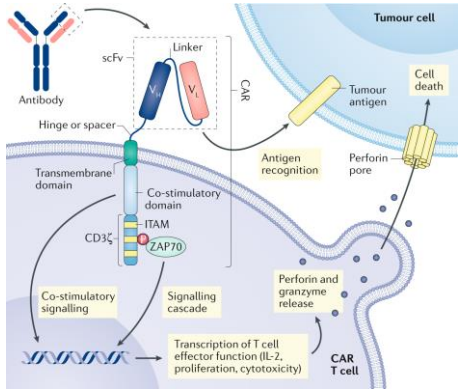
Clinicaltrials.gov search 11/2022, terms: 'gastrointestinal cancer' AND 'immunotherapy' OR 'PD-1' OR 'PD-L1' OR 'CTLA-4'

Drug Development Not restricted to ICI

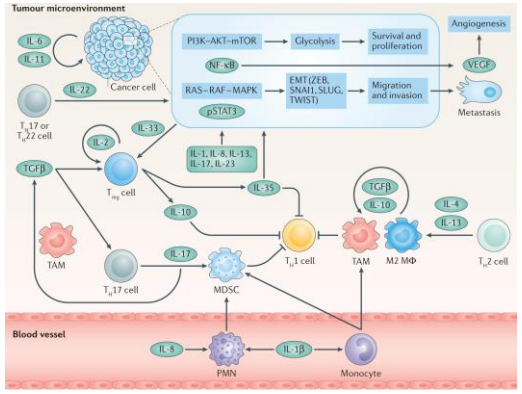
Bispecific and T-cell Engagers



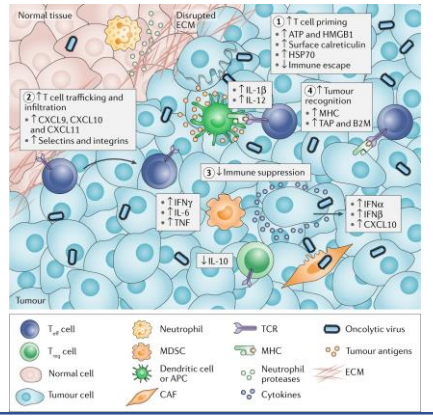
Adoptive Cellular Therapy



Cytokines



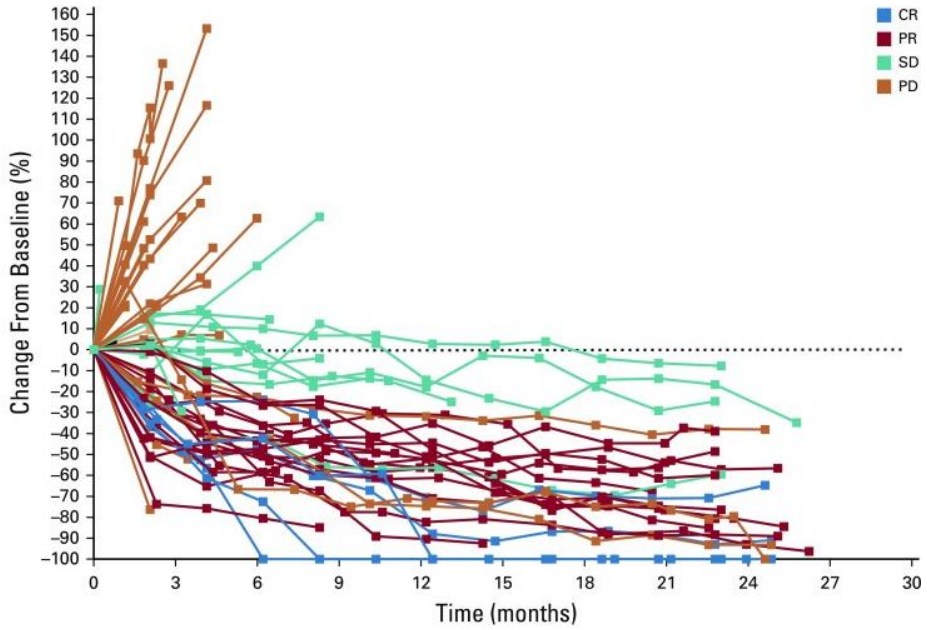
Vaccines and Viruses



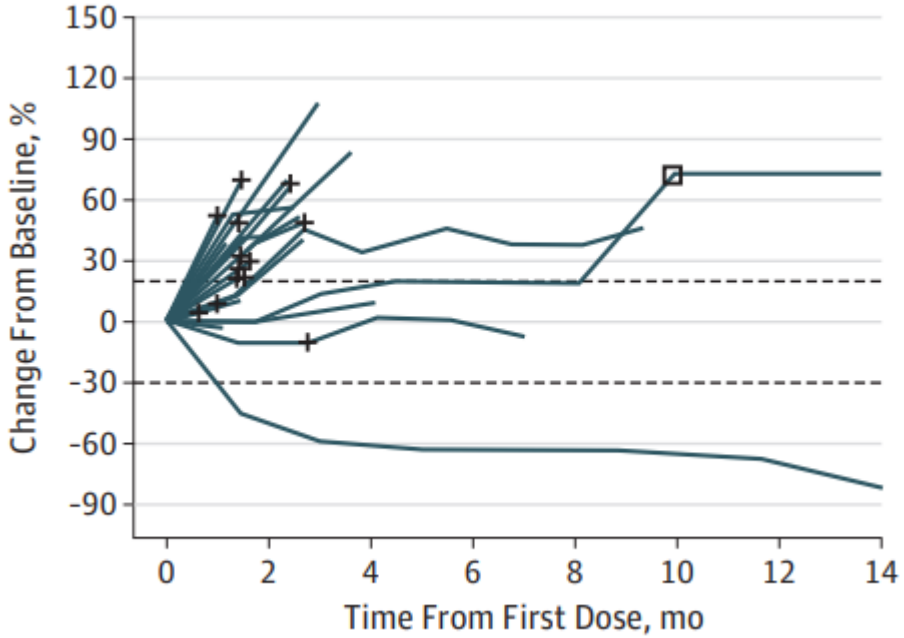
Goebler Nature et al. Cancer Review 2020; Larson et al. Nature Reviews Cancer 2021; Nature Reviews Cancer 2021; Nature Reviews Cancer 2018

GI Tumors Exhibit Variable Immunogenicity Across

MSI-high
Single Agent Anti-PD1
ORR 33%



PDAC
Combination Anti-CTLA4/PDL1
ORR 3.1%



Le et al. JCO 2020; O'Reilly JAMA Onc 2019

Key Questions for Ongoing ICI Studies in GI Cancers

- ***Biomarker Selection***
  - MSI-high
  - TMB
  - PD-1/PD-L1 status
  - Cytolytic score
- ***Combinations in the Advanced Disease State***
  - Antiangiogenics
  - Tyrosine Kinase Inhibitors
  - Chemotherapy
  - IO-IO (i.e. PD-1 + CTLA4, ± Lag-3)
  - Radiotherapy
  - BITEs, Vaccines, Cytokines, CARs
- ***Earlier Disease State as Adjuvant or Neoadjuvant***

Ongoing Studies
MSI-High Colorectal and Other GI Cancers

dMMR/MSI-H in Colorectal Cancer

- DNA mismatch repair deficiency (dMMR) or high frequency microsatellite instability (MSI-H) in CRC

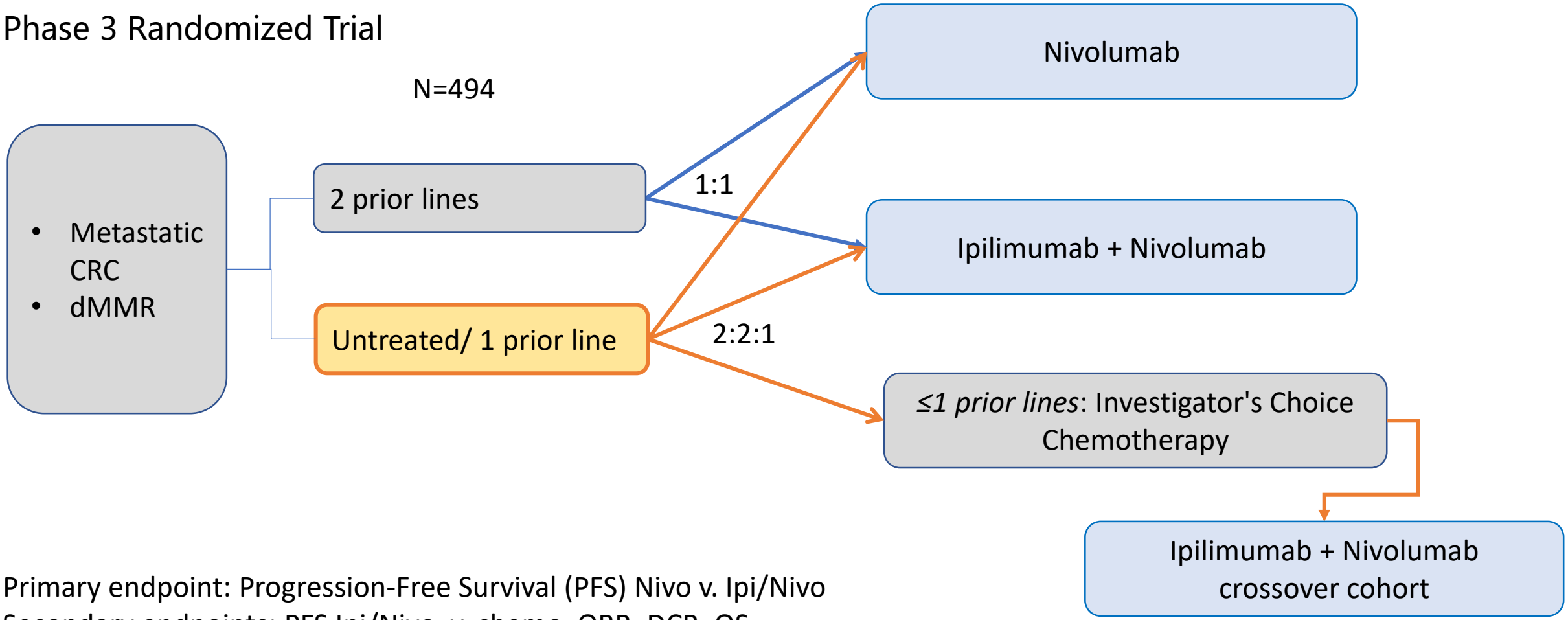
Stage	Frequency of dMMR/MSI-H
I/II	~20%
III	~12%
IV	~4%

Anti-PD-1 Monotherapy and Combinations for MSI-high/dMMR CRC

Checkpoint inhibitor	Trial type	Study treatment groups	Trial identifier
Atezolizumab	• Phase III • Stage 3 CRC	Adjuvant atezolizumab + FOLFOX versus FOLFOX alone	NCT02912559
	• Phase III • First-line metastatic CRC	Atezolizumab versus atezolizumab + FOLFOX + bevacizumab versus FOLFOX + bevacizumab	NCT02997228
Pembrolizumab	• Phase III • First-line metastatic CRC	Pembrolizumab versus standard-of-care chemotherapy	NCT02563002
	• Phase II • mCRC: refractory or ≥1 prior therapy	Pembrolizumab	NCT02460198
Avelumab	• Phase II • mCRC: >1 prior therapy	Avelumab	NCT03150706
Nivolumab ± ipilimumab	• Phase II • Refractory CRC	Nivolumab ± ipilimumab or daratumumab or anti-LAG3 antibody	NCT02060188
Atezolizumab	• Phase I • Locally advanced or metastatic solid tumours	• Atezolizumab + bevacizumab • Atezolizumab + bevacizumab + FOLFOX • Atezolizumab + carboplatin + paclitaxel • Atezolizumab + carboplatin + pemetrexed • Atezolizumab + carboplatin + nab-paclitaxel • Atezolizumab + nab-paclitaxel	NCT01633970

Ganesh et al. Nature Reviews Gastroenterology and Hepatology 2020

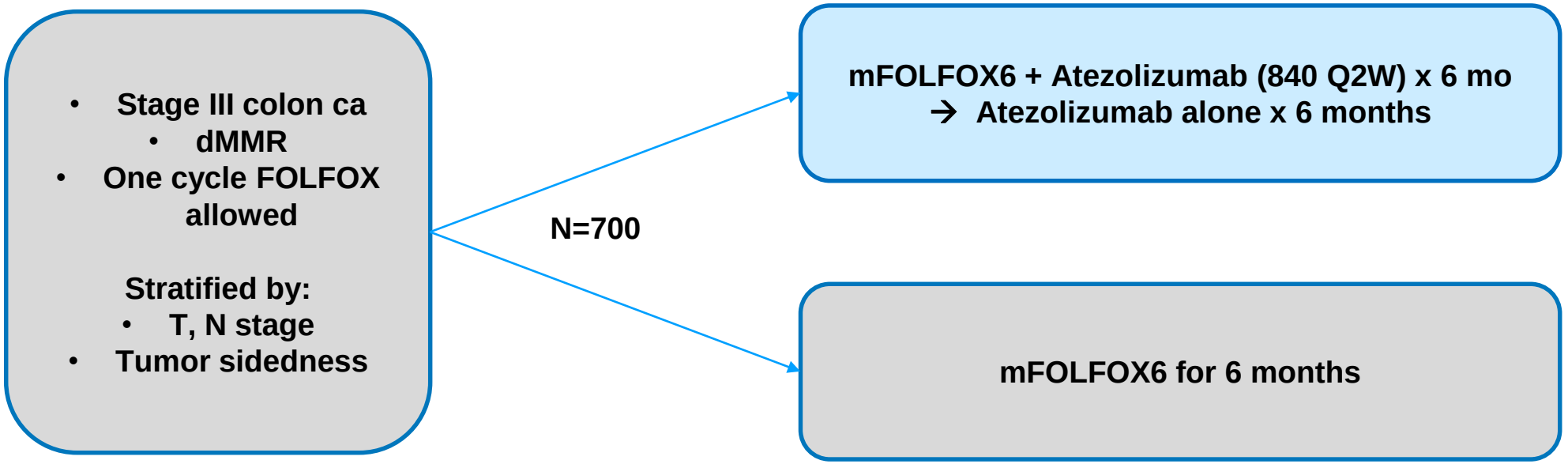
Phase III randomized study of Nivolumab, Nivolumab Plus Ipilimumab, or Investigator's Choice Chemotherapy for the Treatment of Patients With dMMR/ MSI-H Metastatic Colorectal Cancer (CheckMate 8HW, NCT04008030)



Primary endpoint: Progression-Free Survival (PFS) Nivo v. Ipi/Nivo
Secondary endpoints: PFS Ipi/Nivo v. chemo, ORR, DCR, OS

https://clinicaltrials.gov/ct2/show/NCT04008030

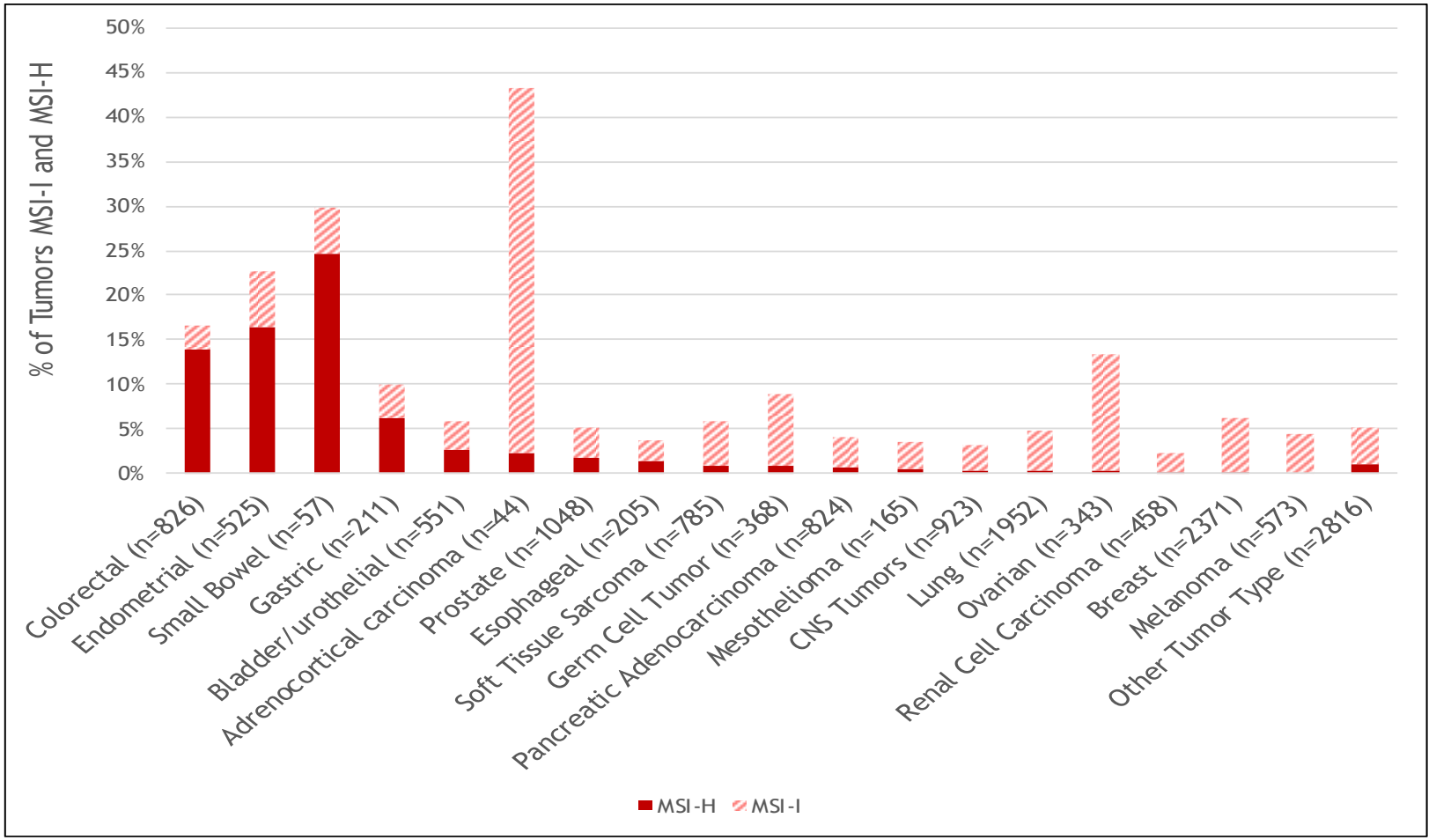
Combination Chemotherapy With or Without Atezolizumab in Treating Patients With Stage III Colon Cancer and Deficient DNA Mismatch Repair (Alliance A021502, NCT02912559)



Primary endpoint: DFS at two-sided alpha of 0.05.
Secondary endpoints: overall survival, treatment tolerability, and quality of life.

https://clinicaltrials.gov/ct2/show/NCT02912559

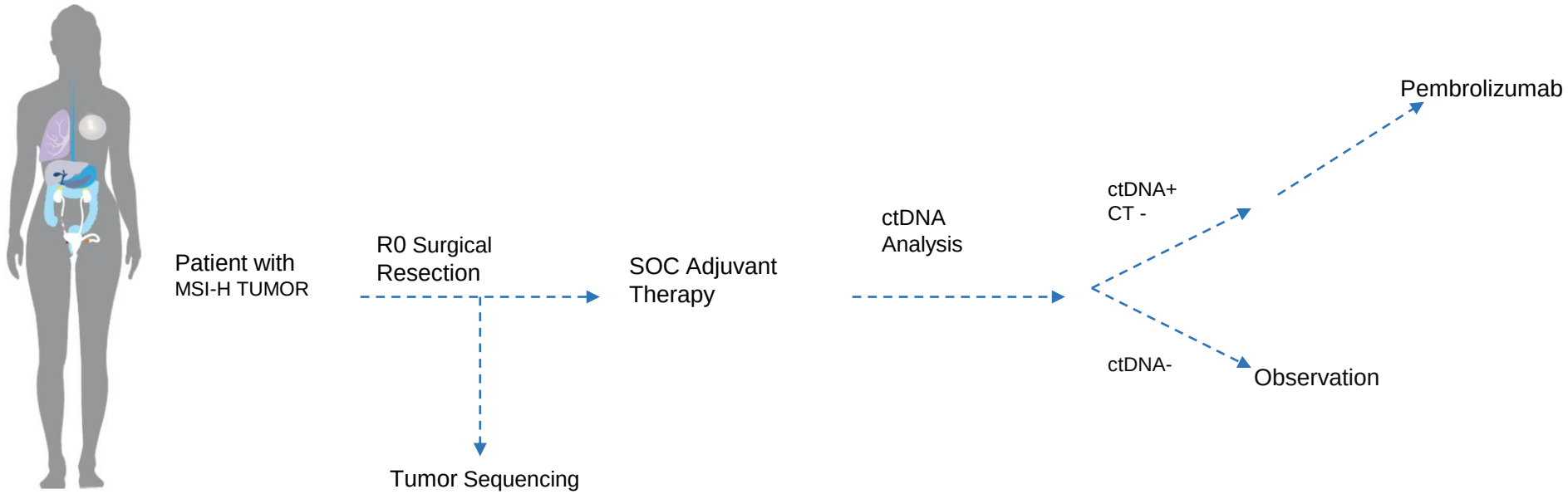
Distribution of MSI Across Cancer Types (N=15,045)



- **MSI-H tumors**
  - **small bowel cancer (25%; 14/57)**
  - endometrial (16%; 86/525)
  - **colorectal (14%; 115/826)**
  - **gastric (6%; 13/211)**

Latham, Srinivasan, Berger, Stadler *JCO 2018*

A Randomized Double-Blind Study of Adjuvant Pembrolizumab vs. Placebo In Patients with MSI-H Tumors with Persistent ctDNA Following Surgery (NCT03832569)



Year 1 Objective: To demonstrate clearance of ctDNA at 12 months.

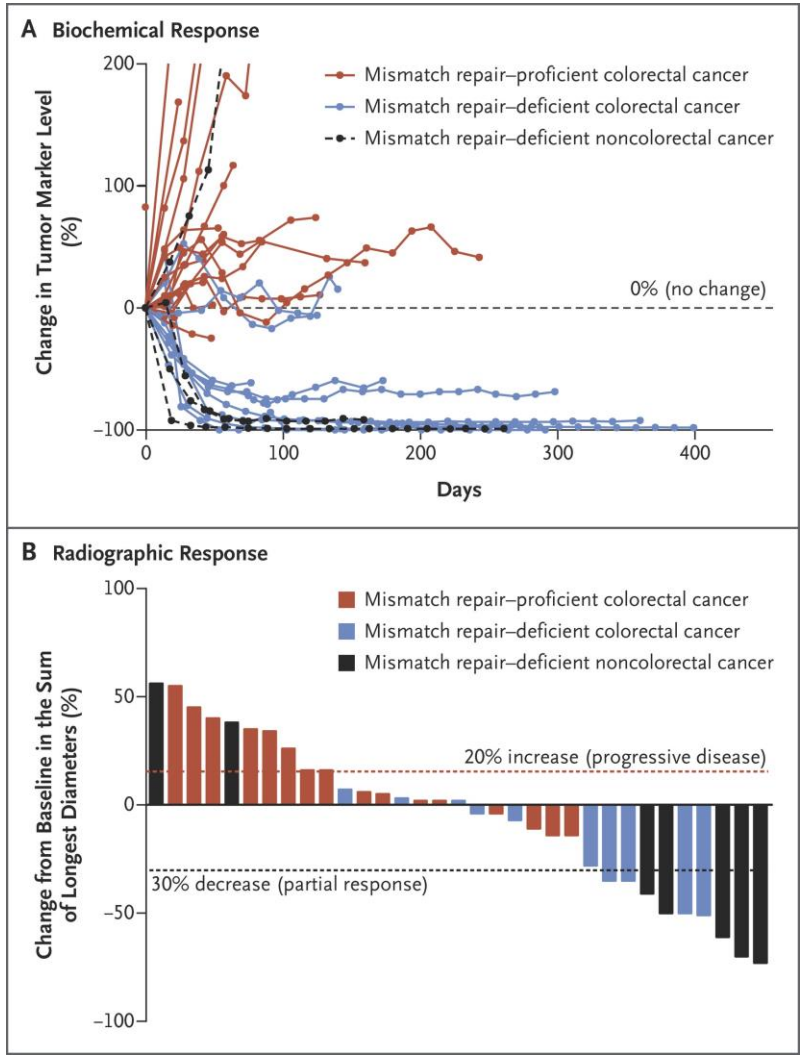
Year 2, 3 and 5 Objectives: To demonstrate improvement in DFS and OS.

https://clinicaltrials.gov/ct2/show/NCT03832569

Ongoing Studies
pMMR/MSS Colorectal and Anal

pMMR/MSS Colorectal Cancer

pMMR/MSS CRC is not sensitive to ICI



Le et al NEJM 2018

Multiple Combinations Strategies in Phase 1/2 testing

Checkpoint inhibitor	Trial type	Combination treatment (target)	Trial identifier
Atezolizumab	• Phase I • mCRC	Cobimetinib (MEK) and bevacizumab (VEGFA)	NCT02876224
	• Randomized phase II • Refractory CRC	Capecitabine and bevacizumab (VEGFA)	NCT02873195
	• Phase III • mCRC	Cobimetinib (MEK) and regorafenib	NCT02788279
	• Phase II • First-line metastatic CRC	Cobimetinib (MEK)	NCT02291289
Durvalumab	• Phase I/II • Refractory CRC	Cediranib (VEGFR and KIT)	NCT02484404
Durvalumab ± tremelimumab	• Phase I • mCRC	Radiation	NCT02888743
	• Phase II • mCRC	Radiation or ablation	NCT03122509
	• Phase II • mCRC	Radiation	NCT03007407
Durvalumab	• Phase II • mCRC	Trametinib (MEK)	NCT03428126
	• Phase II • mCRC	Azacitidine (DNMT)	NCT02811497
Nivolumab	• Phase I/II • CRC and solid tumours	Epacadostat (IDO1)	NCT02327078
	• Phase I/II • Locally advanced rectal cancer	Chemoradiation	NCT02948348
	• Phase II • Refractory CRC	TAS-102	NCT0280546
Nivolumab ± ipilimumab	• Phase II • Refractory CRC	• Cobimetinib (MEK) • Daratumumab (CD38)	NCT02060188
	• Phase I/II • Metastatic pretreated CRC	Binimetinib (MEK)	NCT03271047
	• Phase II • CRC arm	Radiation	NCT03104439
	• Phase I/II • Metastatic pretreated CRC	Trametinib (MEK)	NCT03377361
	• Phase II • RAS-wild-type CRC	Panitumumab (EGFR)	NCT03442569
	• Phase II • Stage 1–3 CRC	Celecoxib (COX2)	NCT03026140
Pembrolizumab	• Phase I • Metastatic pretreated CRC	Oral azacitidine (DNMT) and romidepsin (HDAC1 and/or HDAC2)	NCT02512172
	• Phase Ib • mCRC	• Binimetinib (MEK) • ± FOLFOX or FOLFIRI	NCT03374254
	• Phase I/II • mCRC	Nintedanib (VEGFR, PDGFR and FGFR)	NCT02856425
	• Phase I/II • Refractory CRC and NSCLC	Azacitidine (DNMT) and epacadostat (IDO1)	NCT02959437
	• Phase Ib/II • Metastatic pretreated CRC	Cetuximab (EGFR)	NCT02713373
	• Phase II • GI tumours and CRC arm	Tumour-infiltrating lymphocytes, IL-2, cytoxan and fludarabine	NCT01174121
	• Phase II • mCRC	Binimetinib (MEK), FOLFOX and FOLFIRI	NCT03374254
PDR001	• Phase I • First-line metastatic CRC	FOLFOX and bevacizumab (VEGFA)	NCT03176264
	• Phase I • Metastatic pretreated CRC	Regorafenib (multikinase)	NCT03061494
Avelumab	Phase II	eFT508 (MNK)	NCT03258398

Combinations

Antiangiogenics

MAPK Pathway

DNA Damage

Chemotherapy

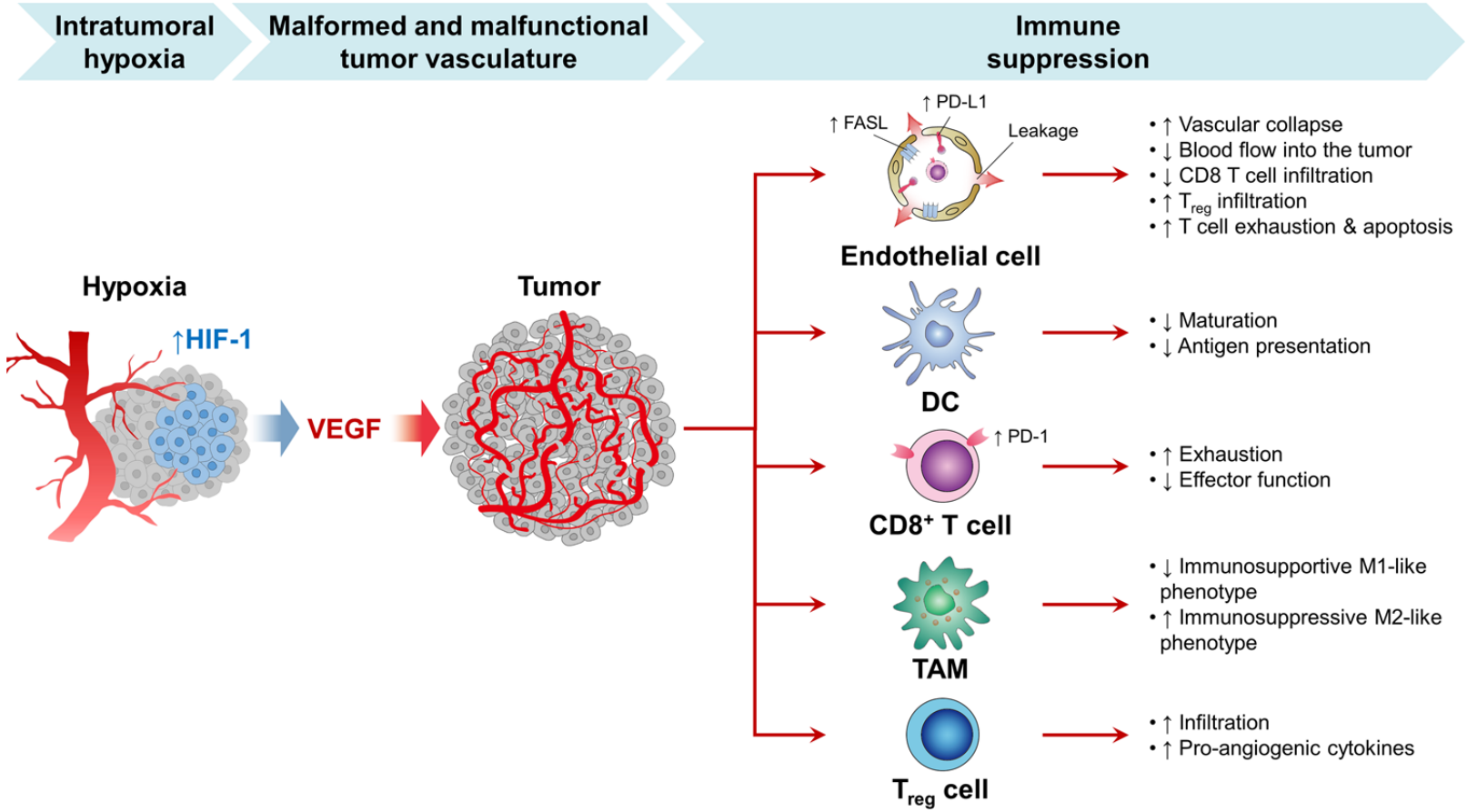
Radiation Therapy

Metabolomics

Novel Agents
-BITE/DARTs
-CARs
-Vaccines

Ganesh et al. Nature Reviews Gastroenterology and Hepatology 2020

Targeting Angiogenesis in MMS/pMMR CRC (and other GI tumors)

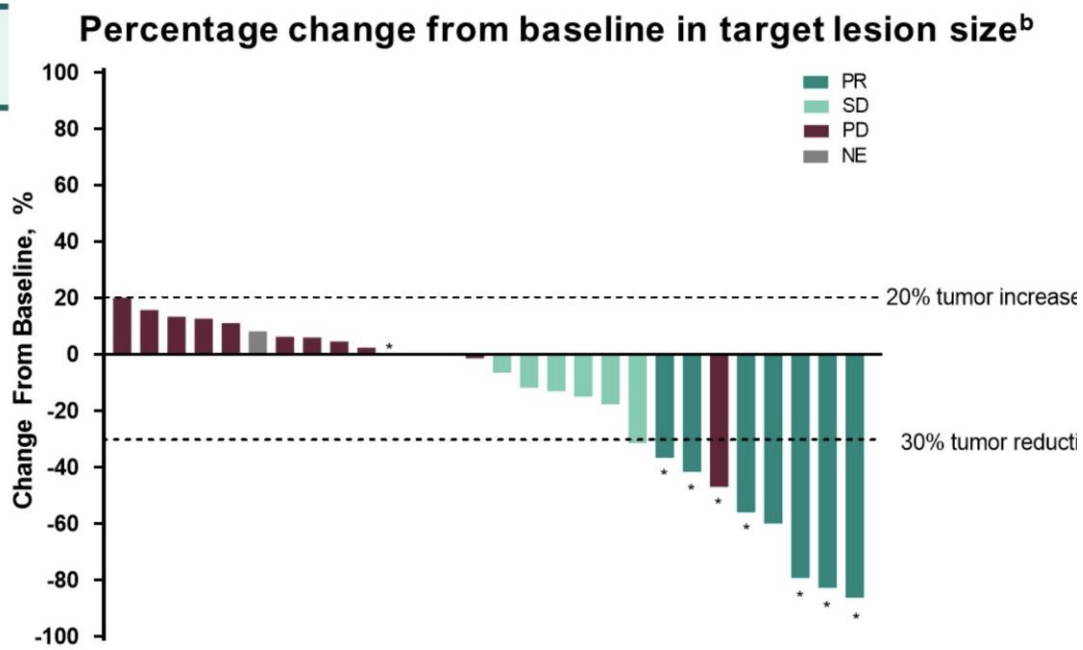


Experimental and Molecular Medicine 2020; Dvorak. JCO. 2002; Chen. The Cancer Journal. 2018; Rini. Lancet. 2019; Lii-Cheng. ESMO. 2019; Liu. JAMA Onc. 2019

Lenvatinib plus pembrolizumab in CRC

Antitumor Activity
(Confirmed Objective Responses, RECIST v1.1 by BICR)

	N = 32
ORR, % (95% CI)	22 (9–40)
DCR,[a] % (95% CI)	47 (29–65)
Best overall response, n (%)	
CR	0
PR	7 (22)[b]
SD	8 (25)
PD	12 (38)
Non-evaluable[c]	1 (3)
No assessment[d]	4 (13)
DOR, median (range), mo	NR (2.1+ to 10.4+)



CI, confidence interval; CR, complete response; NR, not reached; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Defined as best overall response of CR, PR or SD. [b]All responders had a PD-L1 CPS score ≥1. [c]Patient had post-baseline imaging and the best overall response was determined to be non-evaluable per RECIST version 1.1. [d]Patient had no post-baseline imaging. *Patient with treatment ongoing.
Data cutoff date: April 10, 2020.

Lenvatinib plus pembrolizumab demonstrated antitumor activity and manageable safety
Enrollment in the CRC cohort was expanded to 100 pts

Gomez-Roca. ASCO. 2021

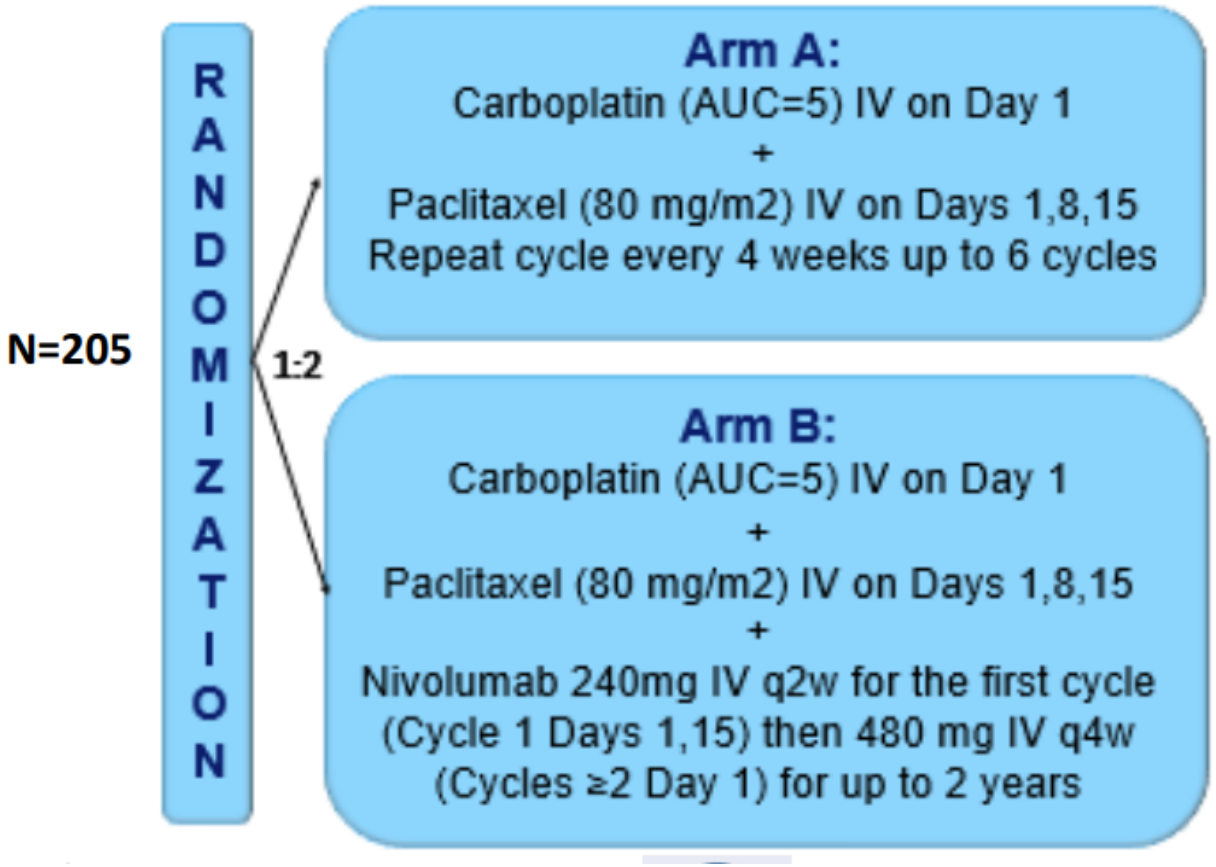
Anal Squamous Cell Carcinoma

Identifier (phase)	Patients, *n* (estimated)	Protocol	Setting	Primary endpoint
NCT02314169 (2)	137	Arm I: nivolumab Arm II: nivolumab + ipilimumab	Refractory metastatic SCCA (2L+)	PFS
NCT02408861 (1)	96	Nivolumab + ipilimumab	HIV-associated relapsed or refractory metastatic or unresectable classical Hodgkin lymphoma or solid tumors (1 L)	MTD of nivolumab
NCT03233711 (2)	200	Arm I: nivolumab Arm II: observation	High risk stage II–IIIB anal cancer (1L)	DFS
NCT02488759 (1/2)	1100	Arm I: nivolumab Arm II: nivolumab + ipililumab Arm III: nivolumab + relatlinib Arm IV: nivolumab + daratumumab	Virus-Associated Tumors, including SCCA (1 L)	Safety and tolerability
NCT03074513 (2)	160	Atezolizumab + bevacizumab	Metastatic SCCA (2L+); rare solid tumors	ORR
NCT03944252 (2)	54	Arm I: avelumab Arm II: avelumab + cetuximab	Metastatic or unresectable, locally advanced SCCA (2 L+)	ORR
NCT03519295 (2)	99	Arm I: mDCF + atezolizumab Arm II: mDCF	Metastatic or unresectable, locally advanced recurrent SCCA (1L)	PFS
NCT04046133 (1b/2)	50	Pembrolizumab	Stage IIIA or IIIB SCCA (1L)	Safety and tolerability

Carboplatin and Paclitaxel +/- Nivolumab in Metastatic Anal Cancer Patients

Key Eligibility Criteria:

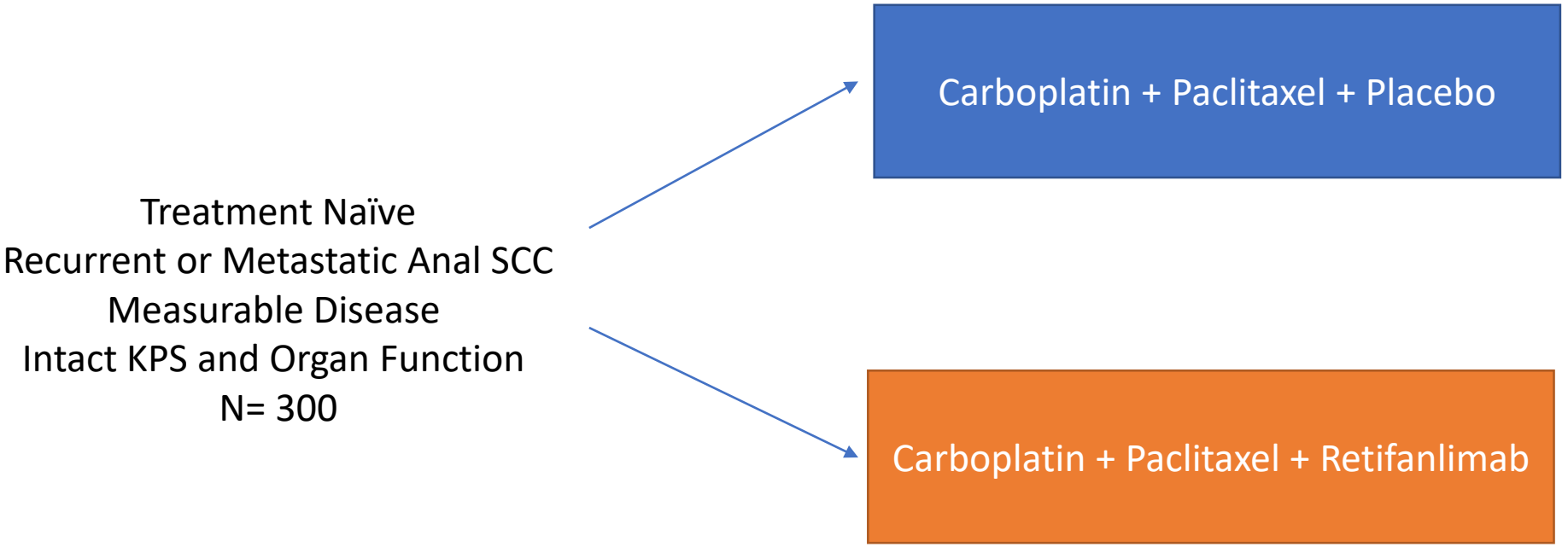
- Inoperable, recurrent, or metastatic anal squamous cell carcinoma
- ≥ 18 years of age
- ECOG Performance Status ≤ 0-1
- RECIST v1.1 measurable disease
- Patients with asymptomatic brain lesions are eligible if treatment ended >3 months
- HIV+ patients on effective anti-retroviral therapy with undetectable viral load are eligible
- No prior systemic chemo or other investigational therapy; no prior immunotherapy



https://clinicaltrials.gov/ct2/show/NCT04444921

Carboplatin-paclitaxel ± Retifanlimab in Locally Advanced or Metastatic Squamous Cell Anal Carcinoma (POD1UM-303/InterAACT 2)

- Global, Multicenter, Double-Blind Randomized Study



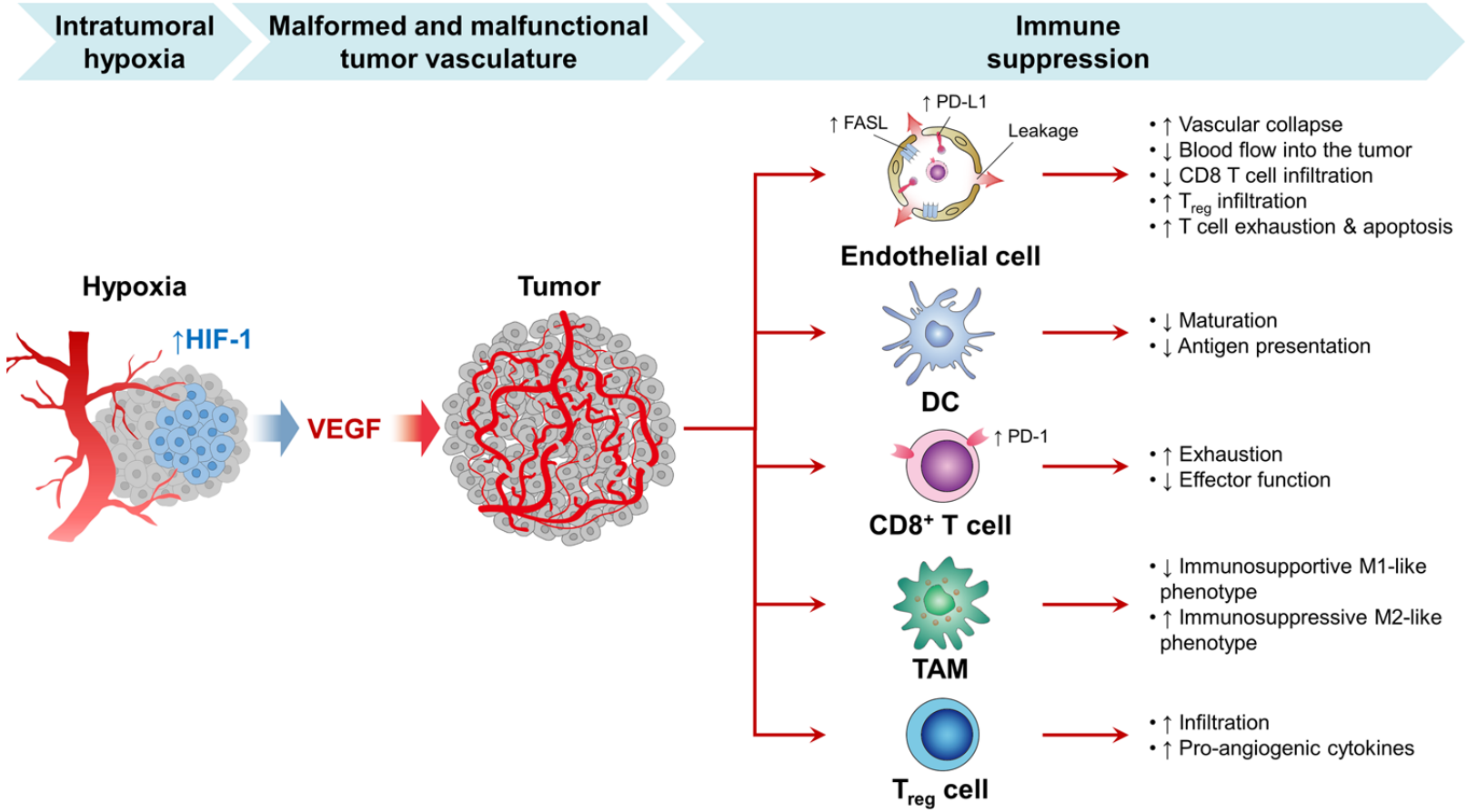
- Primary Endpoint: PFS

https://www.clinicaltrials.gov/ct2/show/NCT04472429

Ongoing Studies

Hepatobiliary, Esophagogastric, Pancreas

Targeting Angiogenesis in HCC (and other GI tumors)



Experimental and Molecular Medicine 2020

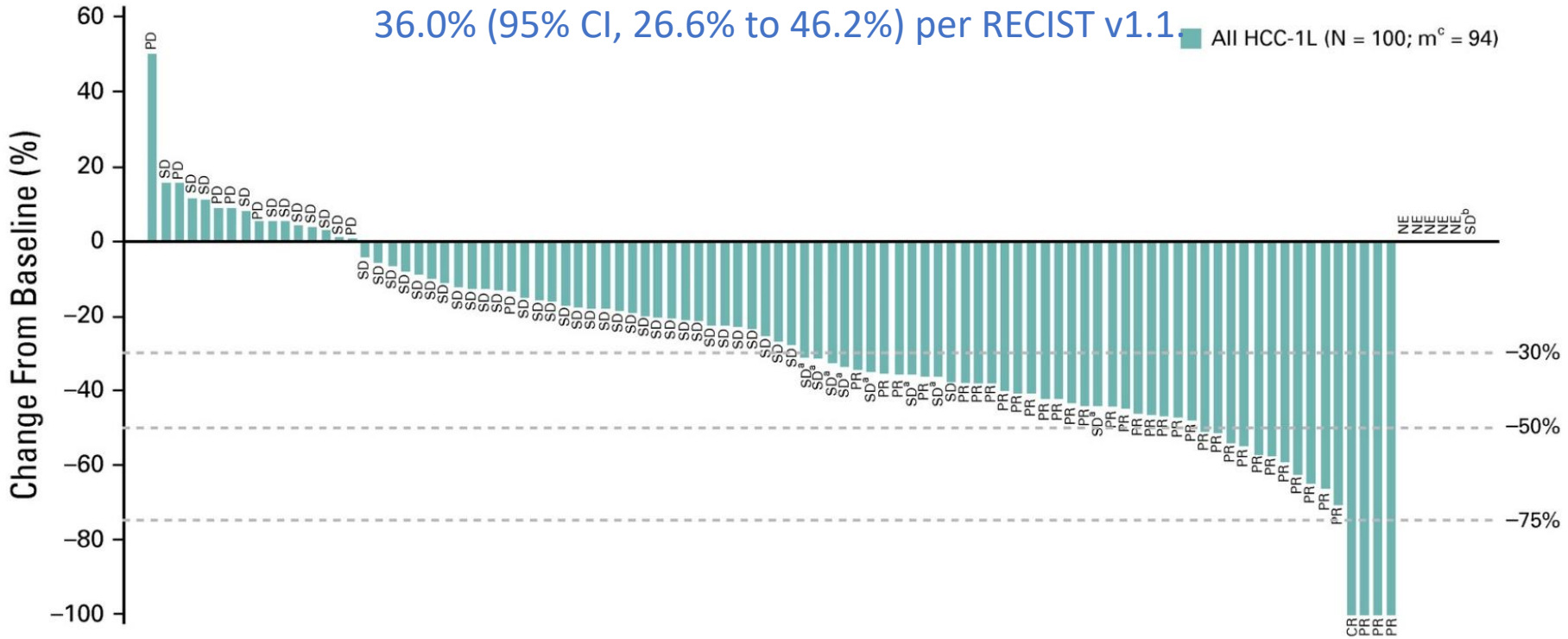
Multiple TKI or Anti-VEGFR combinations ongoing or resulted in HCC

Pivotal Phase 3 in the front-line				
IMbrave 150 NCT03434379	Atezolizumab + Bevacizumab vs. Sorafenib	PD-L1 + VEGFR	Phase III	ORR/OS
Leap-02 NCT03713593	Pembrolizumab + Lenvatenib Vs Lenvatenib	PD-1 + TKI	Phase III	PFS/OS
Cosmic-312 NCT03755791	Atezolizumab + Cabozantnib Vs. Sorafenib	PD-1 + TKI	Phase III	PFS/OS
NCT01658878	Nivolumab + Cabozantinib	PD-1 + TKI	Phase I/II	Safety/ORR
NCT02988440	PDR001 + Sorafenib	PD-1 + TKI	Phase I/II	Safety
NCT03006926	Pembrolizumab + Lenvatinib	PD-1 + TKI	Phase I	Safety
NCT03289533	Avelumab + Axitinib	PD-L1 + TKI	Phase 1	Safety
NCT03347292	Pembrolizumab + Regorafenib	PD-1 + TKI	Phase I	Safety
NCT03418922	Nivolumab + Lenvatinib	PD-1 + TKI	Phase I	Safety
NCT03439891	Nivolumab + Sorafenib	PD-1 + TKI	Phase I/II	Safety/ORR
NCT03382886	Nivolumab + Bevacizumab	PD-1 + VEGF	Phase 1	Safety

Adapted from El Dika. Cancer 2020

Hypothesis generating data for Lenvatinib + Pembrolizumab in HCC

36.0% (95% CI, 26.6% to 46.2%) per RECIST v1.1

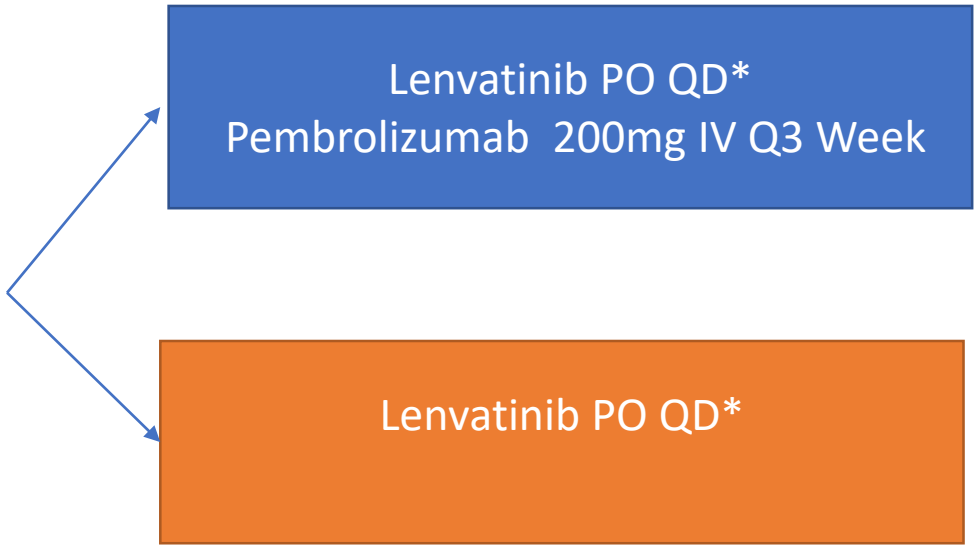


Finn et al. JCO 2020

LEAP-002: First-line Lenvatinib Plus Pembrolizumab vs Lenvatinib Plus Placebo in Advanced HCC

- Multicenter, double-blind phase III trial

HCC (BCLC C or BCLC B that is not amenable to locoregional/curative therapy); no previous systemic therapy; Child-Pugh A; ECOG PS ≤ 1; (planned N = 750)



Treatment until PD, intolerable toxicity, or 36 cycles of pembrolizumab or placebo

*Body weight < 60 kg, 8 mg; body weight ≥ 60 kg, 12 mg.

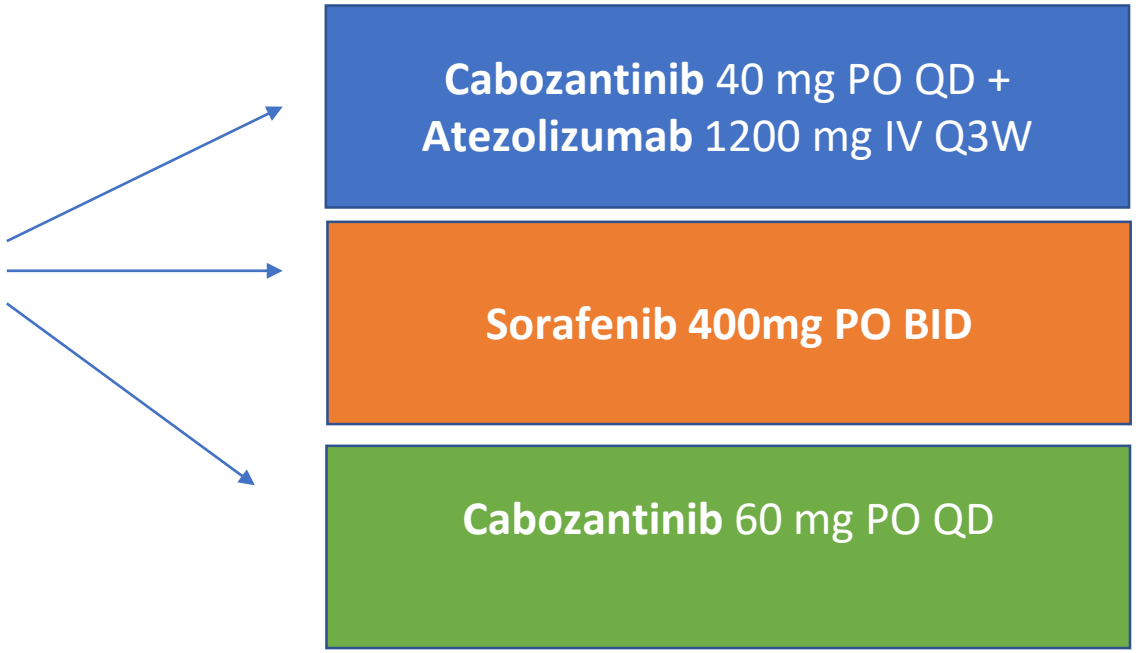
- Primary endpoints: PFS, OS
- Secondary endpoints: ORR, DoR, DCR, TTP, safety

Llovet. ASCO 2019. Abstr TPS4152. NCT03713593.

COSMIC-312: Cabozantinib ± Atezolizumab vs Sorafenib in Advanced HCC

- Multicenter, randomized, open-label phase III trial

Patients with HCC not amenable to curative treatment;
no prior systemic therapy;
BCLC stage B or C
Child-Pugh A
ECOG PS ≤ 1
(planned N = 740)

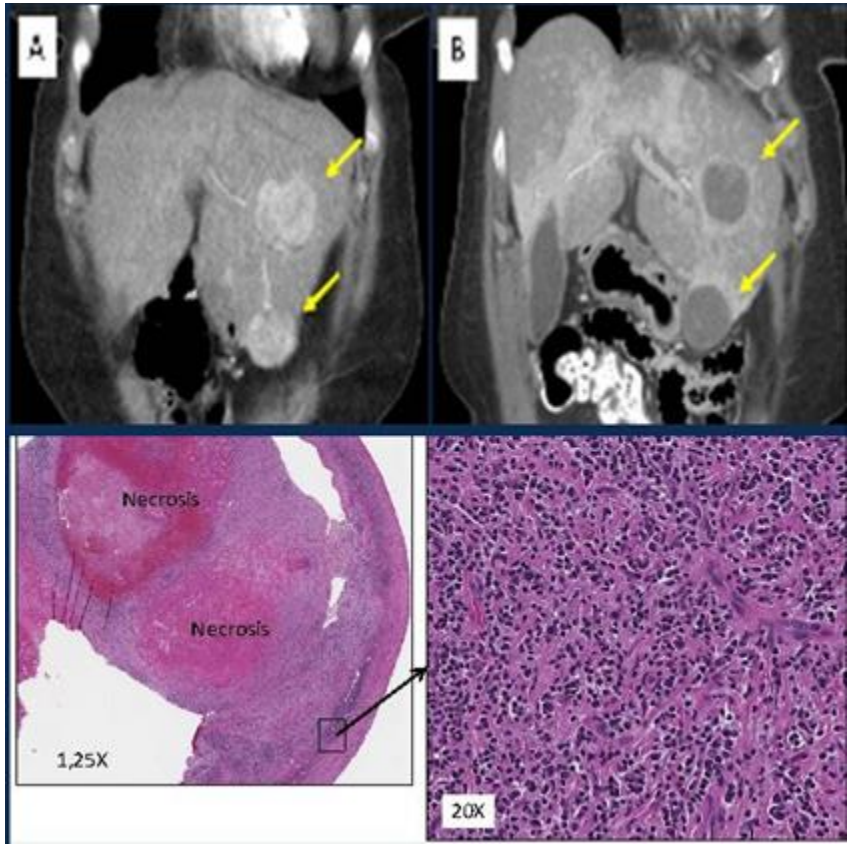


- Primary endpoints: PFS (cabozantinib + atezolizumab vs sorafenib), OS
- Secondary endpoints: PFS (cabozantinib vs sorafenib), ORR, TTP, DoR, safety

Kelley. ASCO 2019. Abstr TPS4157. NCT03755791.

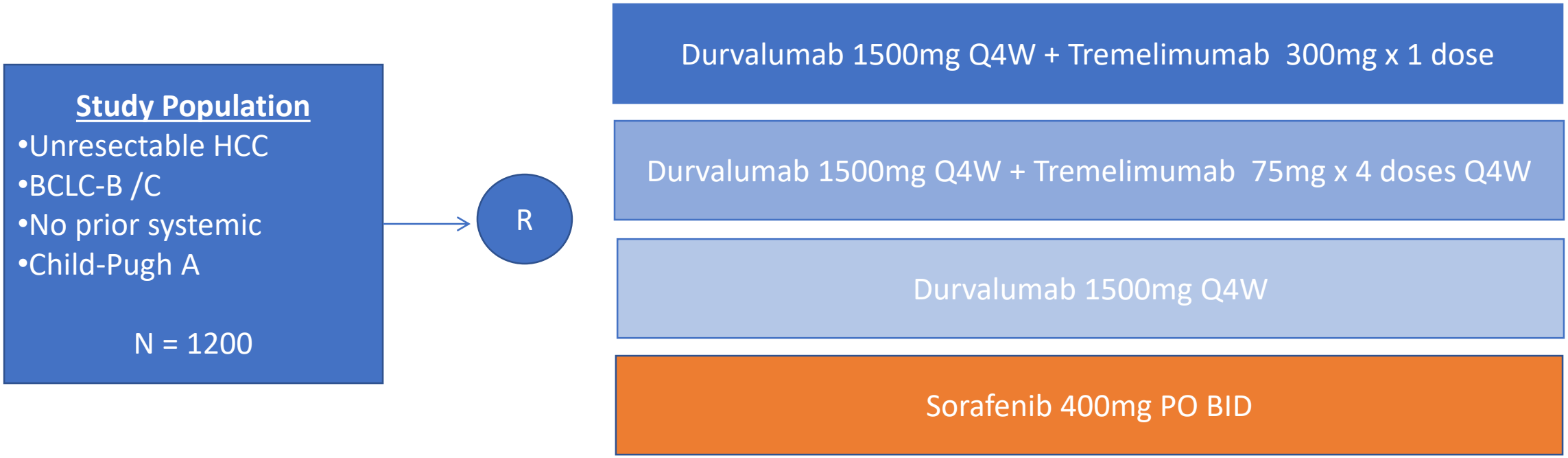
Efficacy data for CTLA-4 and PD1/PD-L1 in HCC

	Checkmate-040			NCT02519348
	NIVO1/IPI3 Q3W (n = 50)	**NIVO3/IPI1 Q3W (n = 49)**	**NIVO3 Q2/IPI1 Q6W (n = 49)**	**Durva/Treme (N =40)**
ORR, n (%)	16 (32)	15 (31)	15 (31)	6 (17.5)
DCR, % (95% CI)	54 (39–68)	43 (29–58)	49 (34–64)	57.5 (40.9-73.0)
mOS, mo (95% CI)	23 (9–NA)	12 (8–15)	13 (7–33)	
12-mo OS rate, % (95% CI)	61 (46–73)	56 (41–69)	51 (36–64)	
24-mo OS rate, % (95% CI)	48 (34–61)	30 (18–44)	42 (28–56)	



Yao et al J Clin Oncol 37, 2019 (suppl; abstr 4012); Kelley et al. J Clin Oncol 35, 2017 (suppl; abstr 4073); Kaseb et al. J Clin Oncol 37, 2019 (suppl 4; abstr 185);

HIMALAYA: Open-label, randomized, multicentered phase 3 study in advanced HCC



Stratification

- MVI
- Etiology: HBV vs HCV vs. non-viral
- Performance status

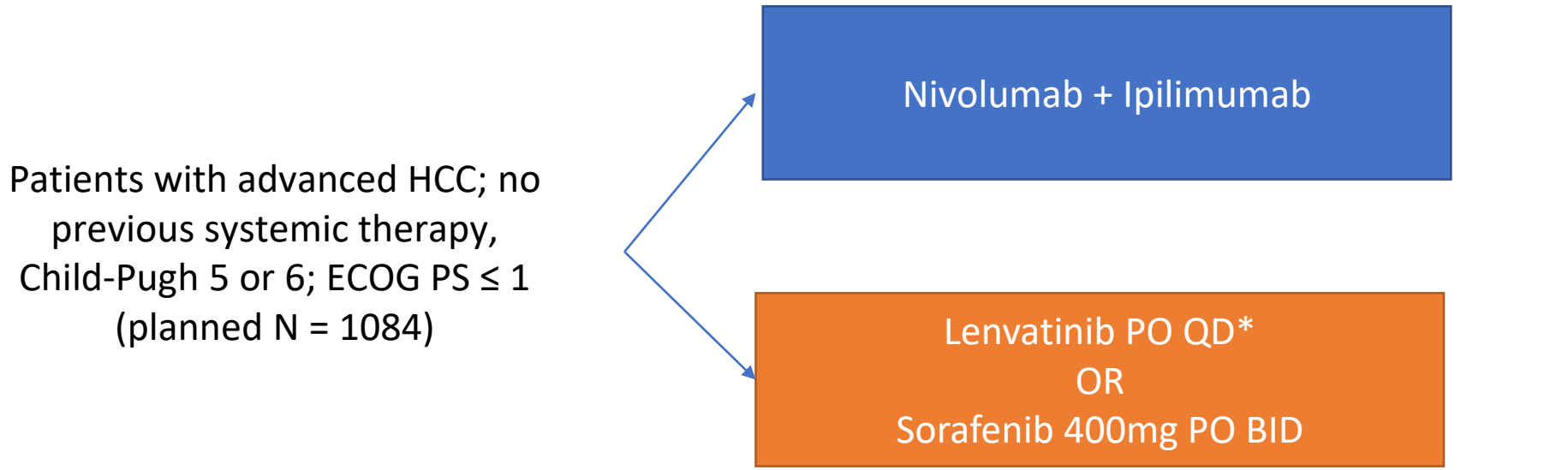
Endpoints

- Primary: OS
- Secondary: ORR, PFS, Safety, QOL, biomarker

Abou-Alfa. ASCO 2018. Abstr TPS4144. NCT03298451.

CheckMate 9DW: Nivolumab + Ipilimumab vs Sorafenib or Lenvatinib as First-Line Treatment for Advanced HCC

- Multicenter, phase III trial



*Body weight < 60 kg, 8 mg; body weight ≥ 60 kg, 12 mg.

- Primary endpoints: OS
- Secondary endpoints: ORR, DoR, DCR, TTSD

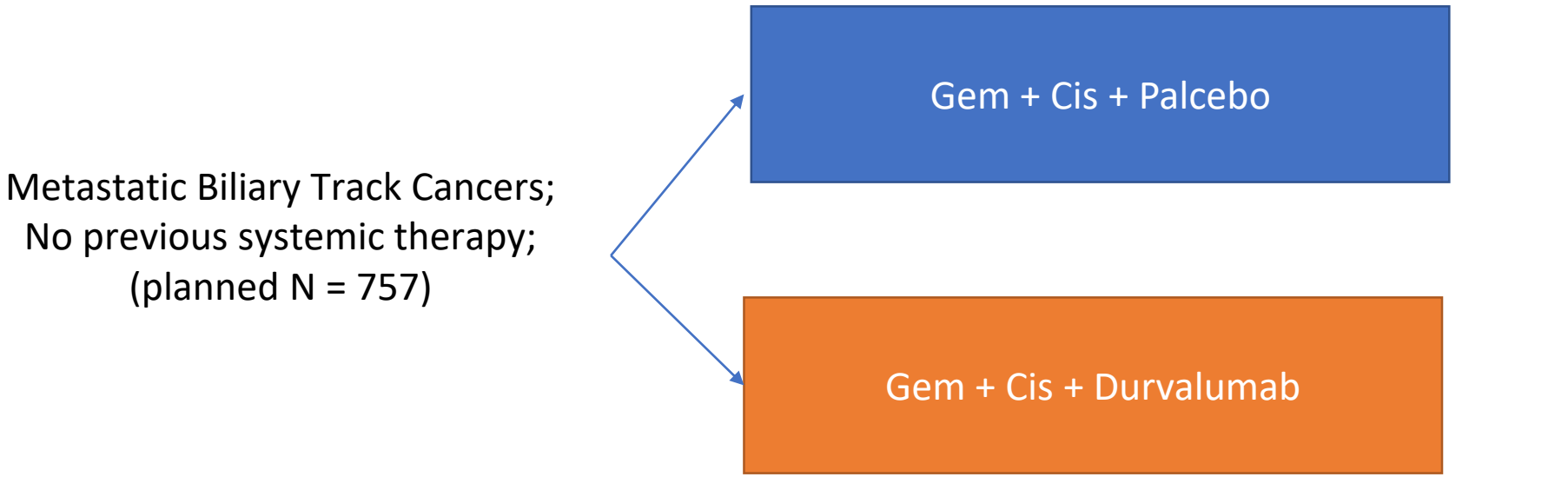
NCT04039607

ICI in Biliary Track Cancer

Agent	N	ORR	Ref
Nivolumab	30	3%	Uneno et al. Lancet Gastro and Hepatology 2019
	54	9% central review	Kim et al. JAMA ONC 2020
Pembrolizumab	40	10%	Kang et al. Cancer Res Treat. 2020
	104	5.8%	Piha-Paul et al. Int J Cancer. 2020
	24	13.0%	
Ipilimumab + Nivolumab	39	23%	Klein et al. JAMA ONC 2020
Nivolumab + GEMCIS	32	46%	Feng et al. JITC 2020
Nivolumab + GEMCIS	30	36%	Uneno et al. Lancet Gastro and Hepatology 2019
Durvalumab + GEMCIS	45	73.5%	Oh et al. GI ASCO 2021

Gemcitabine/Cisplatin ± Durvalumab in Advanced Biliary Tract Cancer (TOPAZ-1)

- Multicenter, double blind, phase III trial



*Body weight < 60 kg, 8 mg; body weight ≥ 60 kg, 12 mg.

- Primary endpoints: OS
- Secondary endpoints: PFS, ORR, DoR, DCR, ADA, QoL

https://clinicaltrials.gov/ct2/show/NCT03875235

Advanced Gastric/GEJ Cancers

- Her2 Positive

Study	Groups	Endpoint	NCT
KEYNOTE-811	Pembro/tras/chemo vs. tras/chemo (732 Pts)	PFS/ OS	NCT03615326
MAHOGANY	Margetuximab/IO/ chemo vs. tras/chemo (500 Pts)	OS	NCT04082364

- Her2 Negative

Study	Groups	Endpoint	NCT
LEAP-015	Pembro/lenvatinib/chemo vs. chemo	PFS and OS	NCT04662710

Locally Advanced Disease

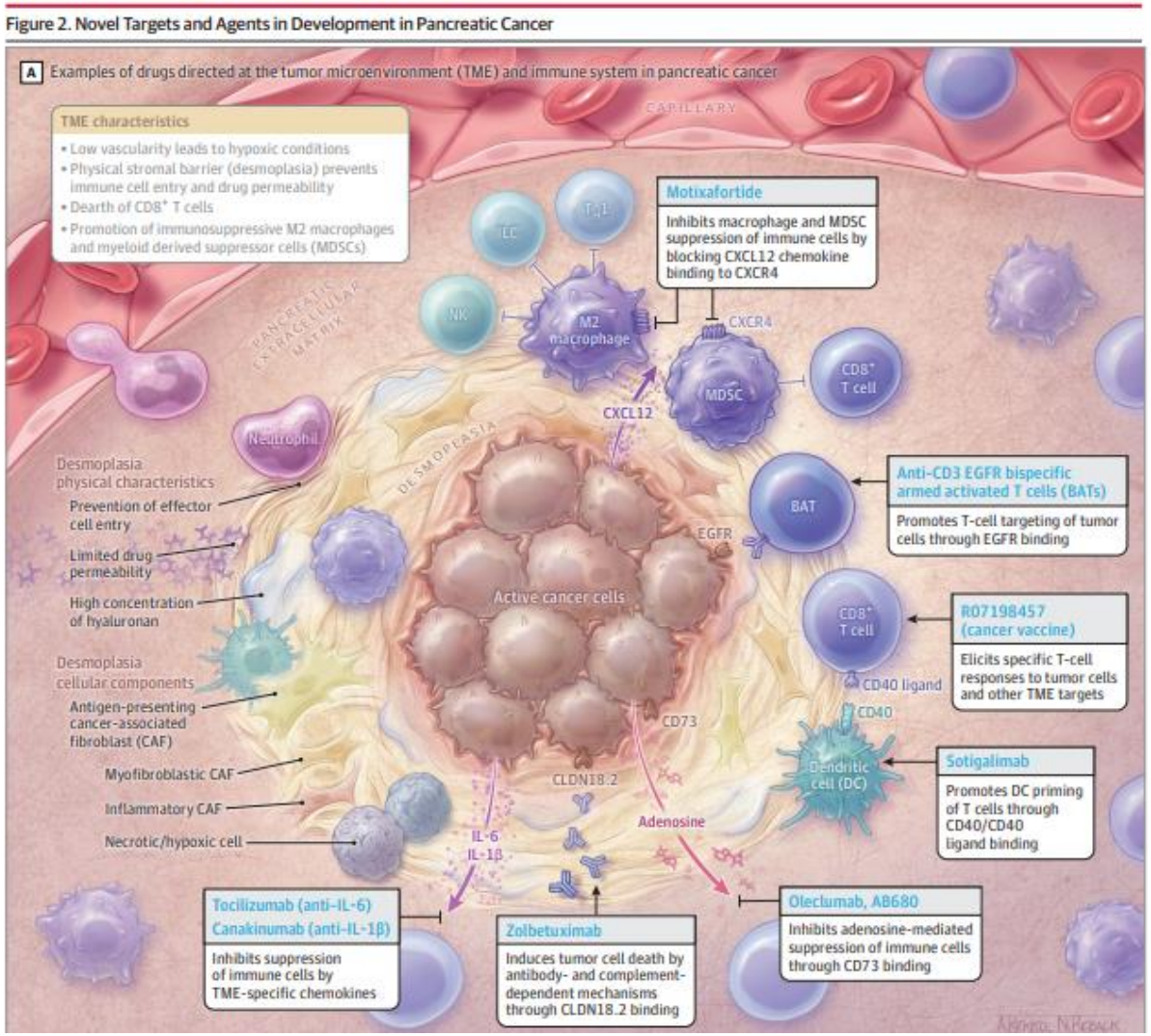
- Gastric

Study	Groups	Endpoint	NCT no.
KEYNOTE-585	Pembro/peri-op chemo vs. peri-op chemo (1ooo Pts)	EFS OS	NCT03221426
MATTERHORN	Durvalumab/peri-op chemo vs. peri-op chemo (900 Pts)	EFS	NCT04592913

- Esophagus/GEJ

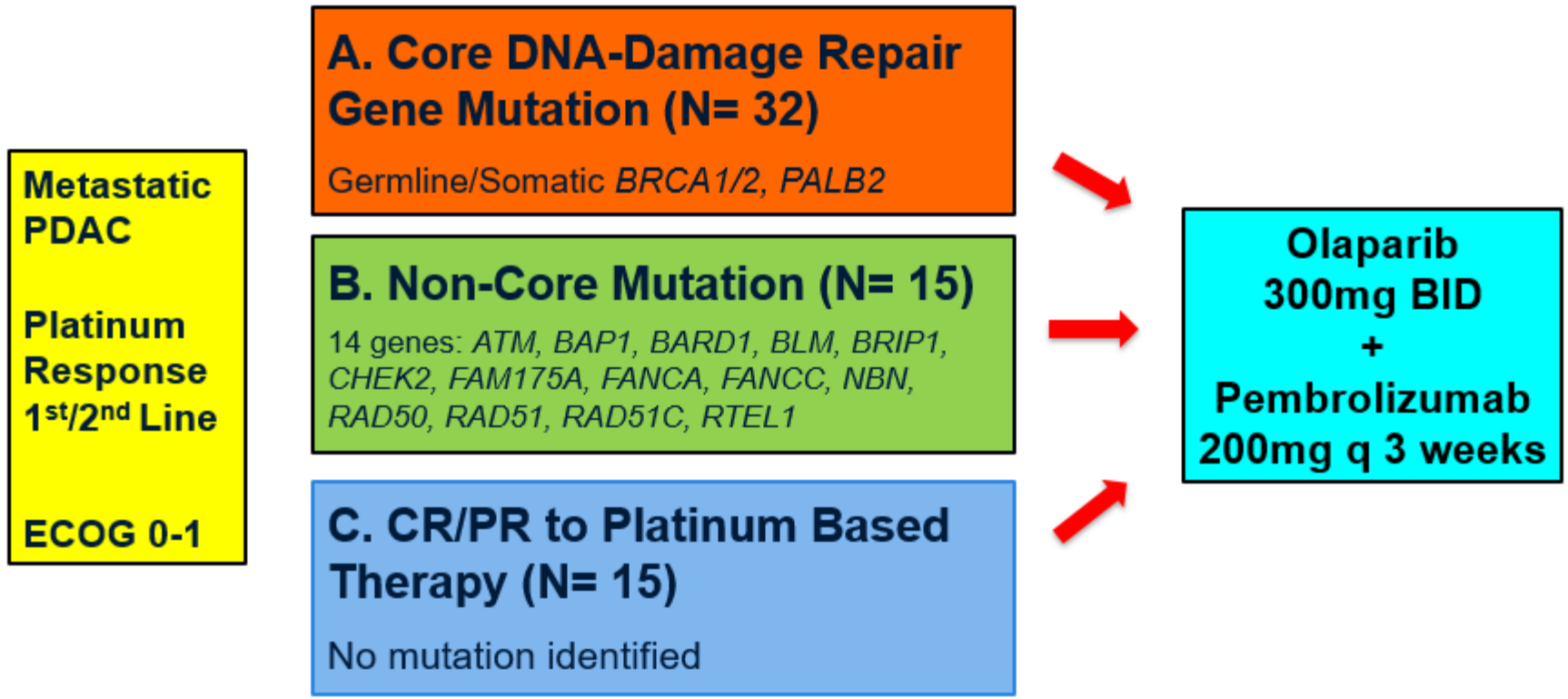
Study	Groups	1^0 endpoint	NCT no.
KEYNOTE-975	Pembro/chemoRT vs. chemoRT [adenoCA/SCC] (600 Pts)	EFS OS	NCT04210115
ECOG/ACRIN	Nivo/chemoRT vs. chemoRT → surgery → ipi/nivo vs. nivo [adenoCA] (278 Pts)	pCR DFS	NCT03604991
KUNLUN	Durvalumab/chemoRT vs. chemoRT [SCC] (600 Pts)	PFS	NCT04550260

Pancreatic Ductal Adenocarcinoma



Park et al. JAMA 2021

MSK Phase II IIT: Olaparib and Pembrolizumab Maintenance in PDAC (POLAR)



Co-Primary: ORR and 6-months PFS rate, Simon-2 stage for Cohort A
Exploratory single arm for Cohort B and C

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Conclusions

- Immune checkpoint molecules have a role an important role in cancers of digestive tract
- Although antitumor activity is observed with anti-PD1/L1 monotherapy, most GI cancers are not sensitive to this approach
- Combination strategies are now approved and are ongoing investigation to improve outcomes across GI cancers
- Rational combinations seek to make GI cancers more immunogenic
- More data to come in the upcoming months…