ASCO® Gastrointestinal Cancers Symposium

Immuno-Oncology Matchmaking: Multimodality Approaches for Lower GI Cancer

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Disclosures

- Consulting
  - Synthetic Biologics
  - Novocure
  - Merck
  - Syndax
  - Nanobiotix
  - Zola Therapeutics
- Research Funding (Clinical Trials)
  - Taiho
  - Astra-Zeneca
  - BMS
  - Tesaro
  - IntraOp
  - Ipsen
  - Puma
  - SU2C/Lustgarten Pancreatic Cancer Collective

Key Takeaways

- Active hepatic metastases may constrain IO response
- Multimodality approaches may impact the negative impact of hepatic metastases
- This will be formally tested in a prospective phase III study

Radiation and Immunotherapy:
Immune Checkpoint Inhibitors in MSS GI Cancers

The NEW ENGLAND JOURNAL of MEDICINE
N ENGL J MED 366;26 NEJM.ORG JUNE 28, 2012

ORIGINAL ARTICLE

Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer

BMS-936550
RR: 0/18 CRC

VOLUME 28 · NUMBER 21 · JULY 20 2010
JOURNAL OF CLINICAL ONCOLOGY

Phase II Study of the Anti-Cytotoxic T-Lymphocyte–Associated Antigen 4 Monoclonal Antibody, Tremelimumab, in Patients With Refractory Metastatic Colorectal Cancer

Tremelimumab
RR: 1/45 CRC
(response duration 15m)

VOLUME 28 · NUMBER 19 · JULY 1 2010
JOURNAL OF CLINICAL ONCOLOGY

Phase I Study of Single-Agent Anti–Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates

Nivolumab
RR: 0/14 CRC
(response duration >21m, **MSI-H pt**)

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JUNE 28, 2012 VOL. 366 NO. 26

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Nivolumab
RR: 0/19 CRC

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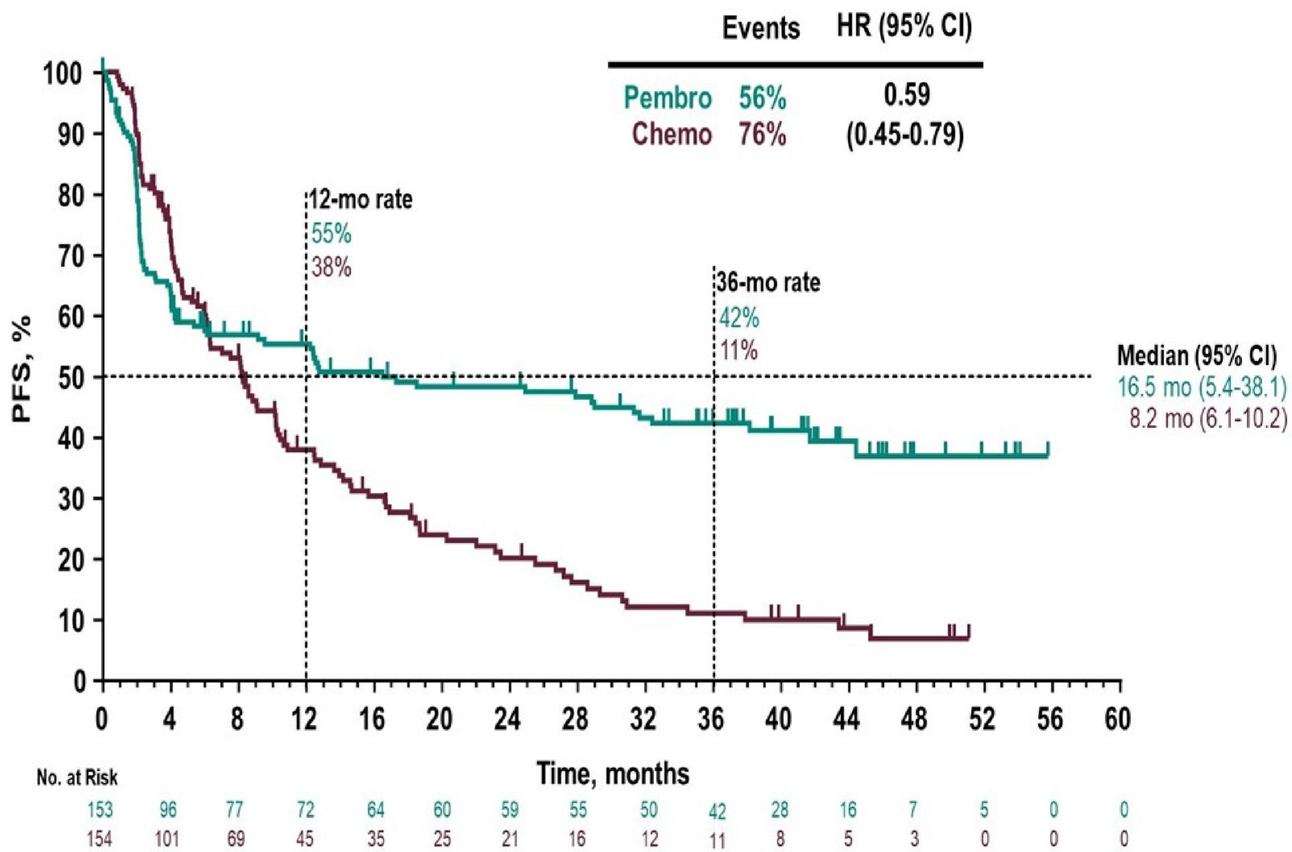
Checkpoint Blockade in MSI-H in mCRC

Objective Responses According to RECIST Criteria

Type of Response	Mismatch Repair–Deficient Colorectal Cancer (N=10)	Mismatch Repair–Proficient Colorectal Cancer (N=18)	Mismatch Repair–Deficient Noncolorectal Cancer (N=7)
Complete response — no. (%)	0	0	1 (14)*
Partial response — no. (%)	4 (40)	0	4 (57)†
Stable disease at week 12 — no. (%)	5 (50)	2 (11)	0
Progressive disease — no. (%)	1 (10)	11 (61)	2 (29)
Could not be evaluated — no. (%)‡	0	5 (28)	0
Objective response rate (95% CI) — %	40 (12–74)	0 (0–19)	71 (29–96)
Disease control rate (95% CI) — %§	90 (55–100)	11 (1–35)	71 (29–96)
Median duration of response — wk	Not reached	NA¶	Not reached
Median time to response (range) — wk	28 (13–35)	NA¶	12 (10–13)

Progression-Free Survival



Le DT, et al. N Engl J Med. 2015 Jun 25;372(26):2509-20. André T, et al. N Engl J Med. 2020 Dec 3;383(23):2207-2218.
André T, et al. Lancet Oncol. 2021 May;22(5):665-677.

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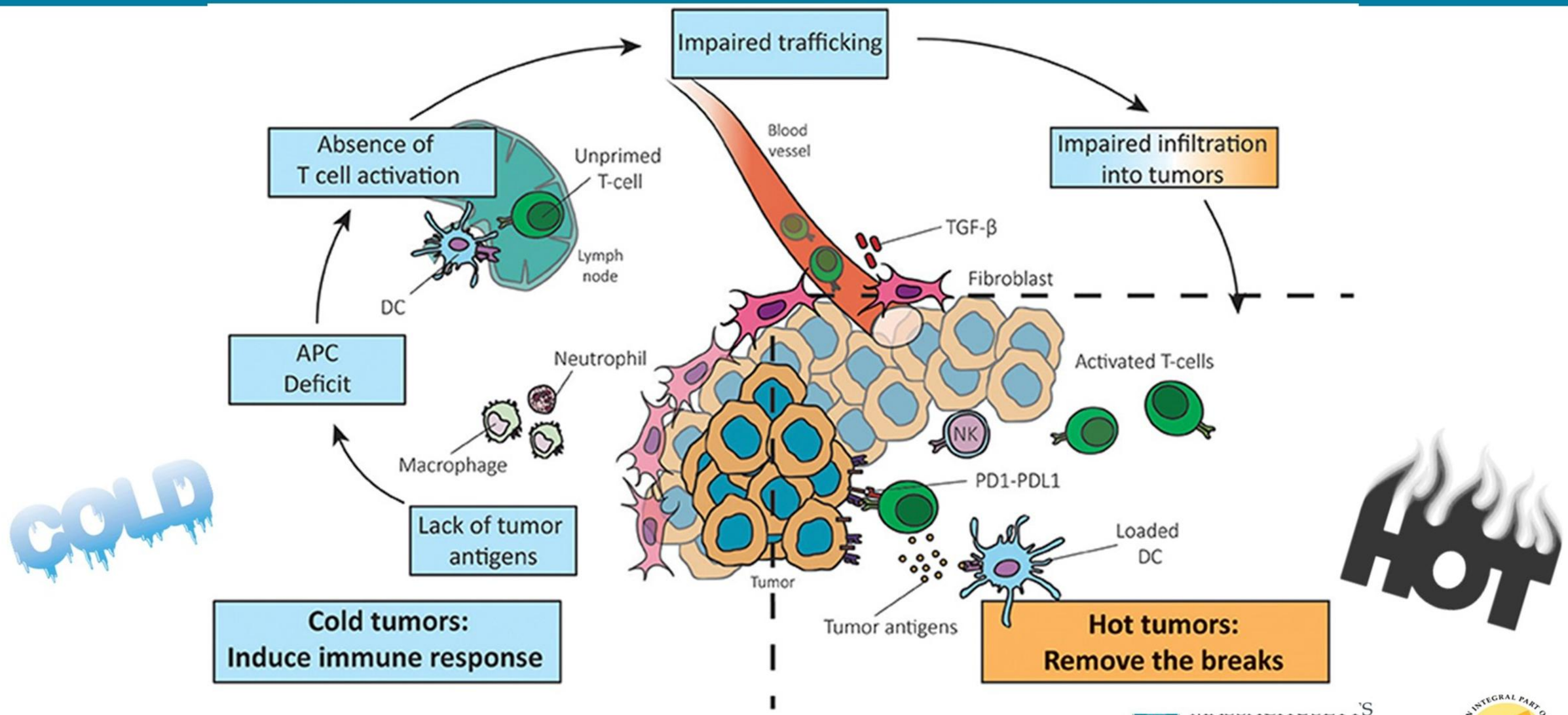
The Fundamental Problem



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Rationale for RT and Immune Checkpoint Blockade

CANCER DISCOVERY

Low Dose Radiotherapy Reverses Tumor Immune Desertification and Resistance to Immunotherapy

Fernanda G Herrera, Catherine Ronet, Maria Ochoa de Olza, et al.

Cancer Discov Published OnlineFirst September 3, 2021.

Radiotherapy induces responses of lung cancer to CTLA-4 blockade

Silvia C. Formenti ✉, Nils-Petter Rudqvist, Encouse Golden, Benjamin Cooper, Erik Wennerberg, Claire Lhuillier, Claire Vanpouille-Box, Kent Friedman, Lucas Ferrari de Andrade, Kai W. Wucherpfennig, Adriana Heguy, Naoko Imai, Sacha Gnjatic, Ryan O. Emerson, Xi Kathy Zhou, Tuo Zhang, Abraham Chachoua & Sandra Demaria ✉

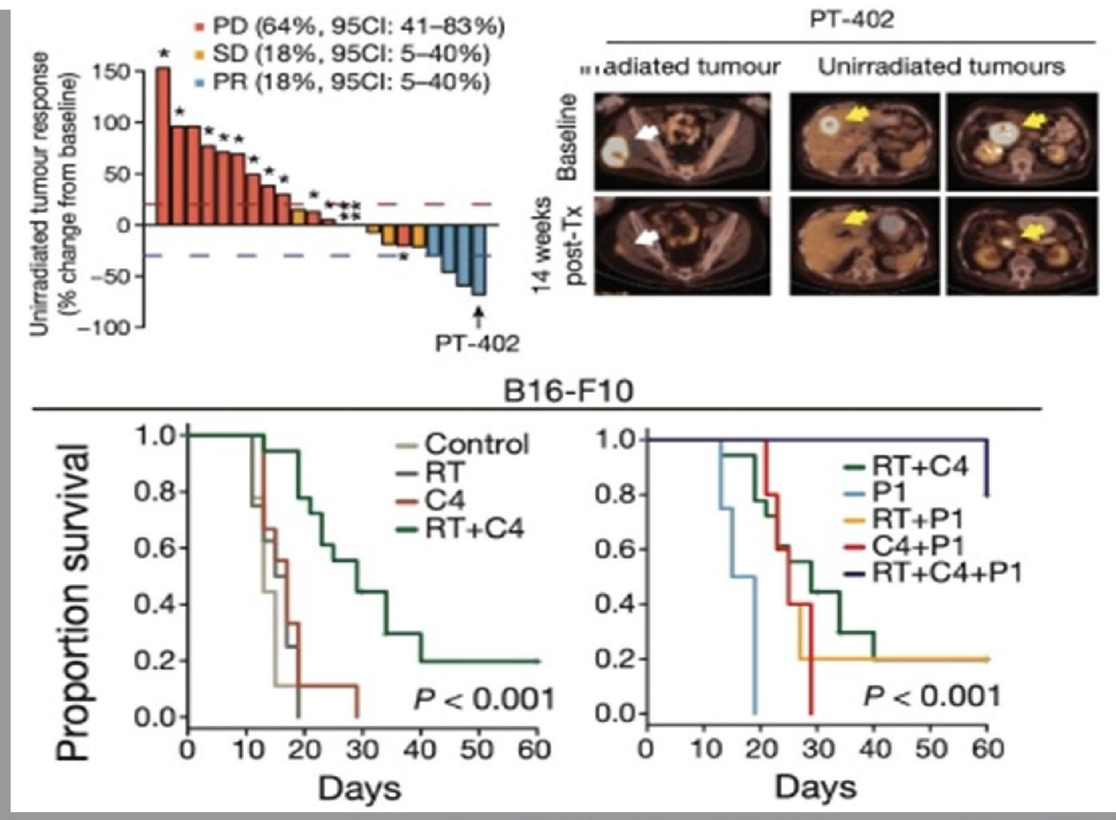
Nature Medicine **24**, 1845–1851 (2018) | Cite this article

LETTER

doi:10.1038/nature14292

Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer

Christina Twyman-Saint Victor[1,2]*, Andrew J. Rech[2]*, Amit Maity[3,4], Ramesh Rengan[3,4]†, Kristen E. Pauken[5,6], Erietta Stelekati[5,6], Joseph L. Benci[2,3], Bihui Xu[2,3], Hannah Dada[2,3], Pamela M. Odorizzi[5,6], Ramin S. Herati[1,6], Kathleen D. Mansfield[5,6], Dana Patsch[3], Ravi K. Amaravadi[1,4], Lynn M. Schuchter[1,4], Hemant Ishwaran[7], Rosemarie Mick[4,8], Daniel A. Pryma[4,9], Xiaowei Xu[4,10], Michael D. Feldman[4,10], Tara C. Gangadhar[1,4], Stephen M. Hahn[3,4]†, E. John Wherry[4,5,6]§, Robert H. Vonderheide[1,2,4,6]§ & Andy J. Minn[2,3,4,6]§



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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

Ipilimumab and Nivolumab with Radiation for MSS CRC
PI: Hong
Nature Cancer 2021

MSS Colon Cancer
- Previously treated w 5-FU, oxaliplatin, and irinotecan in some combination
- MSS by IHC

Exploratory cohorts
- MSI-H Colon Cancer
- Pancreatic Cancer

Cycle 1
- Nivolumab 240 mg q 2 wk x 3
- Ipiliumab 1 mg/kg q 6 wk x 1

Cycle 2
- Nivolumab 240 mg q 2 wk x 3
- Ipiliumab 1 mg/kg q 6 wk x 1
- RT- 8 Gy x 3 to single lesion- start D1
  - Liver
  - Nodal
  - Lung
  - Pulmonary
  - Soft tissue (including pancreatic primary)

Cycle 3 and Beyond
- Nivolumab 240 mg q 2 wk x 3
- Ipiliumab 1 mg/kg q 6 wk x 1

Continues Until Progression

Pre-Treatment | **On Treatment**

Pre-Treatment Biopsy

Pre-Radiation Biopsy

Post-Radiation Biopsy

Parikh A, et al. Nature Cancer 2021.

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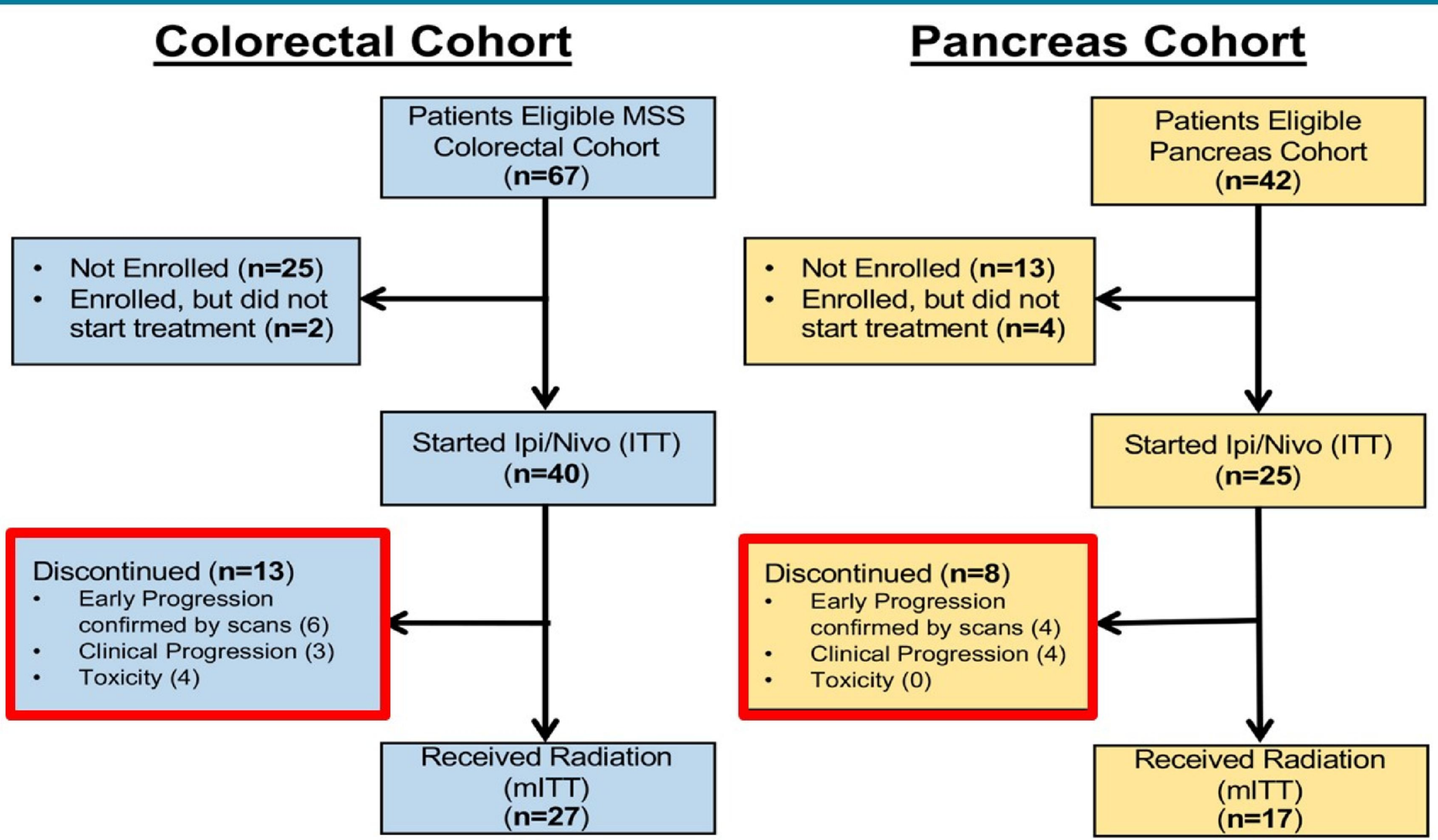
Consort Diagram



32% drop off

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

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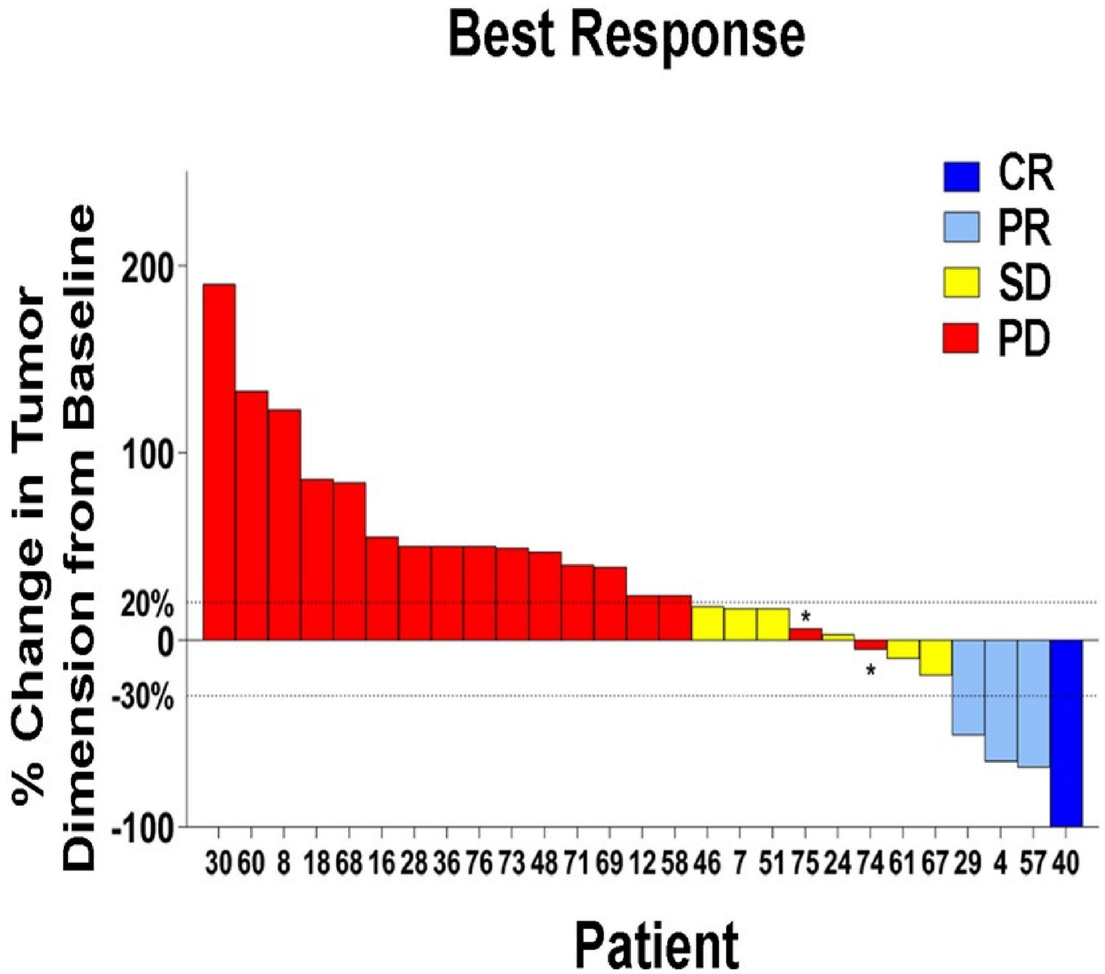
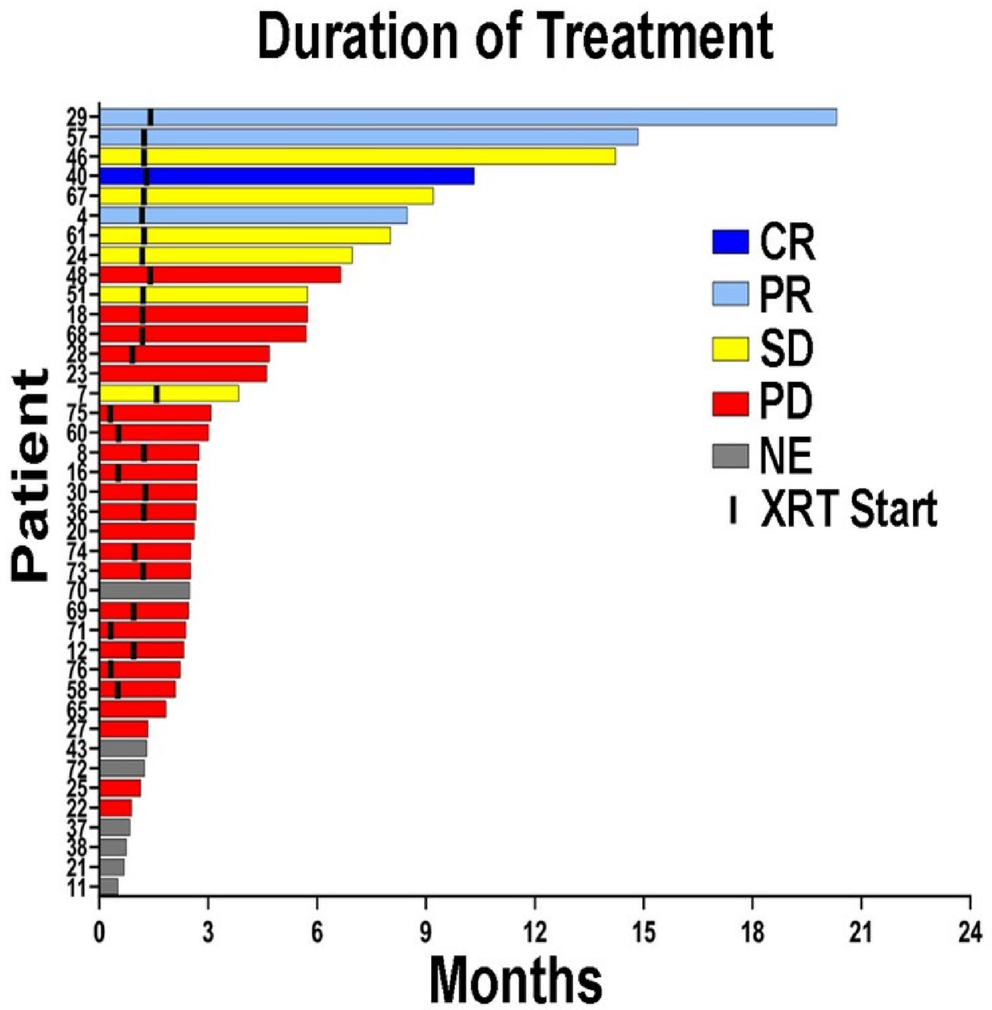
MSS CRC Cohort (per-protocol)





- **DCR 37% (10/27)**
- **ORR 15% (4/17)**

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

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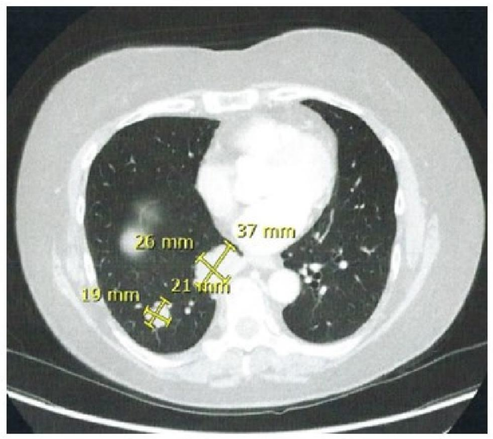
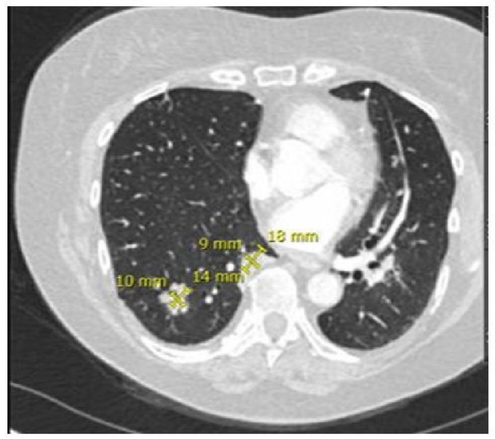
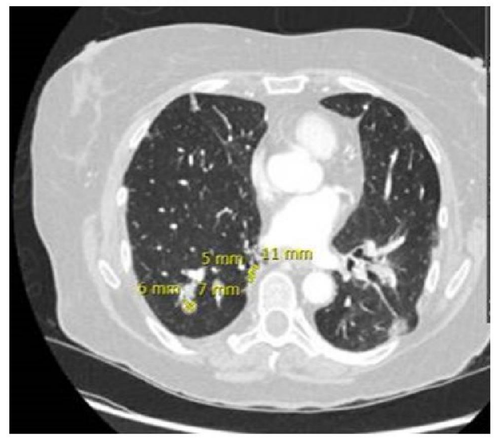
Out of Field Response (liver radiated)

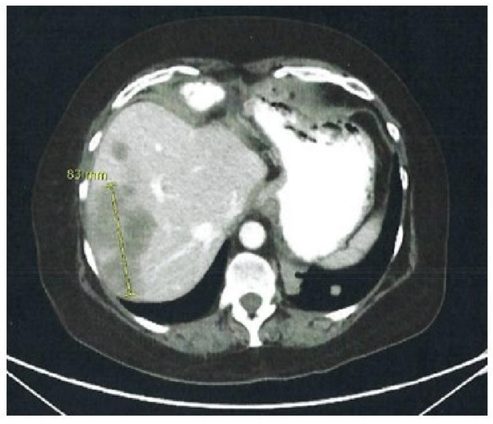
Out of Field Lesions



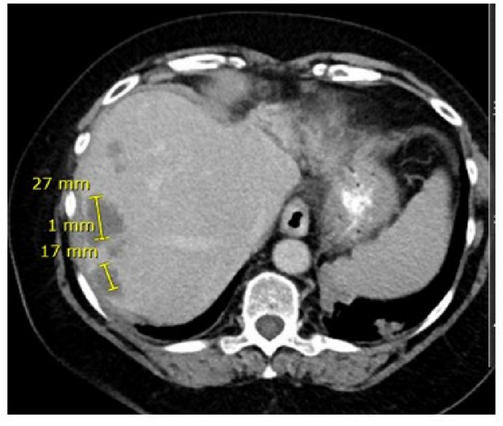




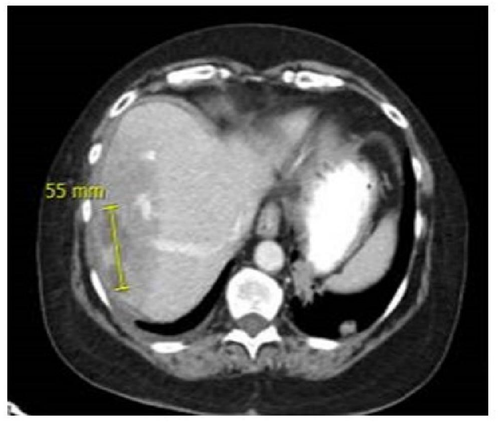
Radiation Target Lesion



Baseline



1M Post-xRT



4M Post-xRT

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KM Curves

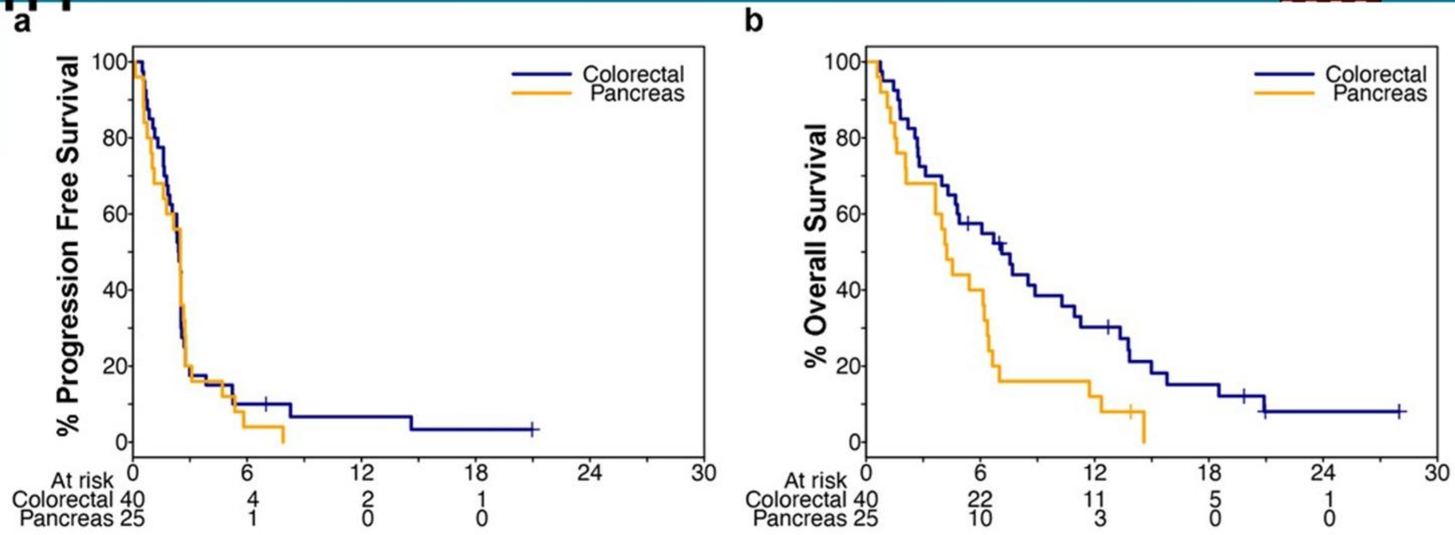
CRC

- Median PFS
  5.2 months (95% CI: 2.5-14.6) vs
  2.4 months (95% CI: 1.8-2.5)
- Median OS
  20.9 months (95% CI: 4.9-not reached) vs
  7.7 months (95% CI: 4.0-11.3)

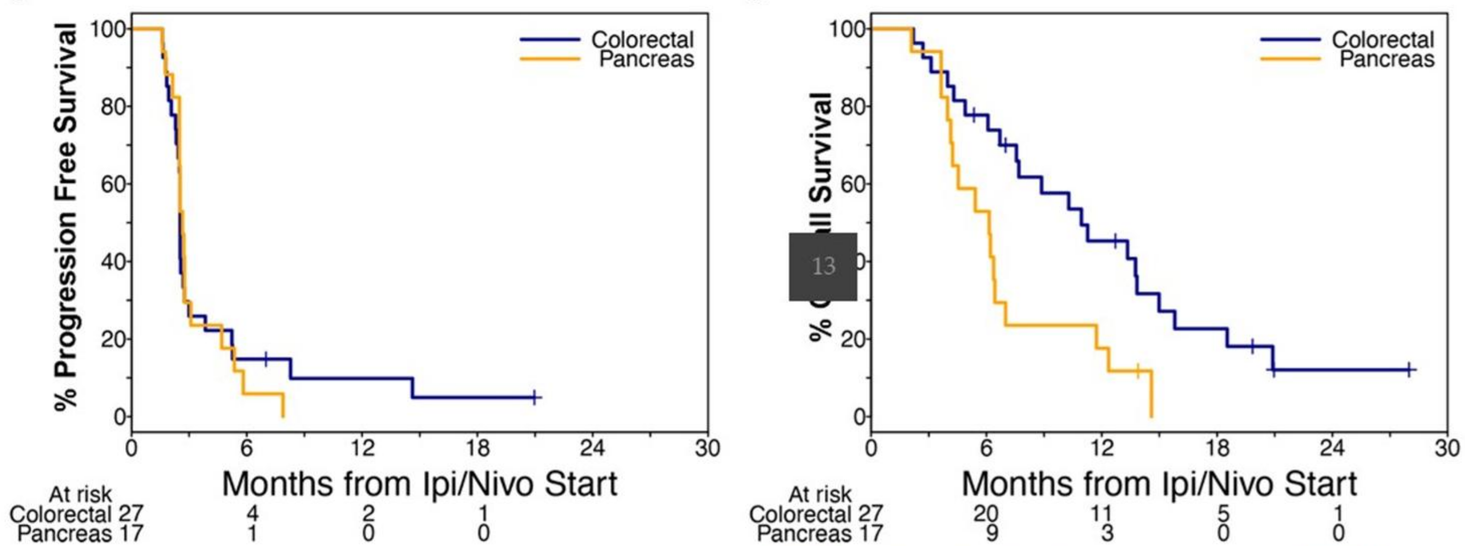
PDAC

- Median PFS
  5.5 months (95% CI: 2.5-7.9) vs
  2.5 months (95% CI: 1.8-2.8)
- Median OS
  11.7 months (95% CI: 5.4-14.6) vs
  4.4 months (95% CI: 3.6-6.4)

ITT



Per Protocol



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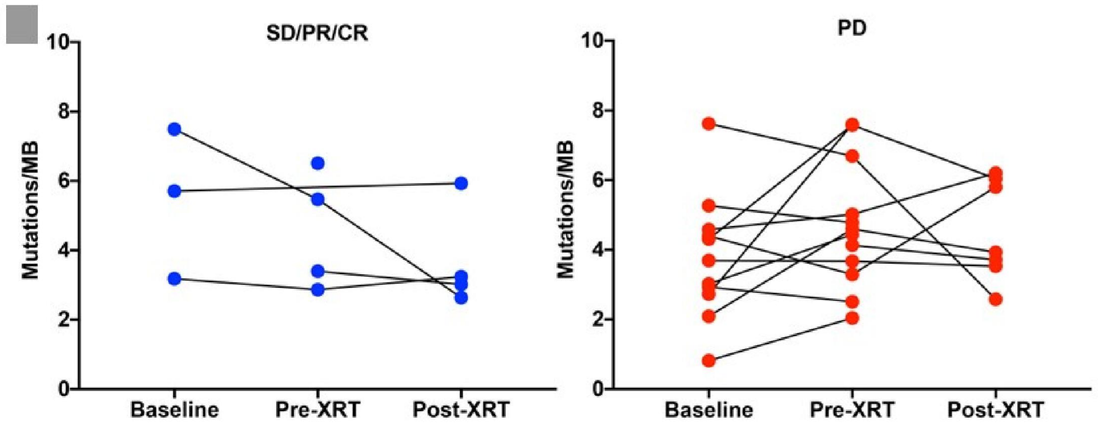
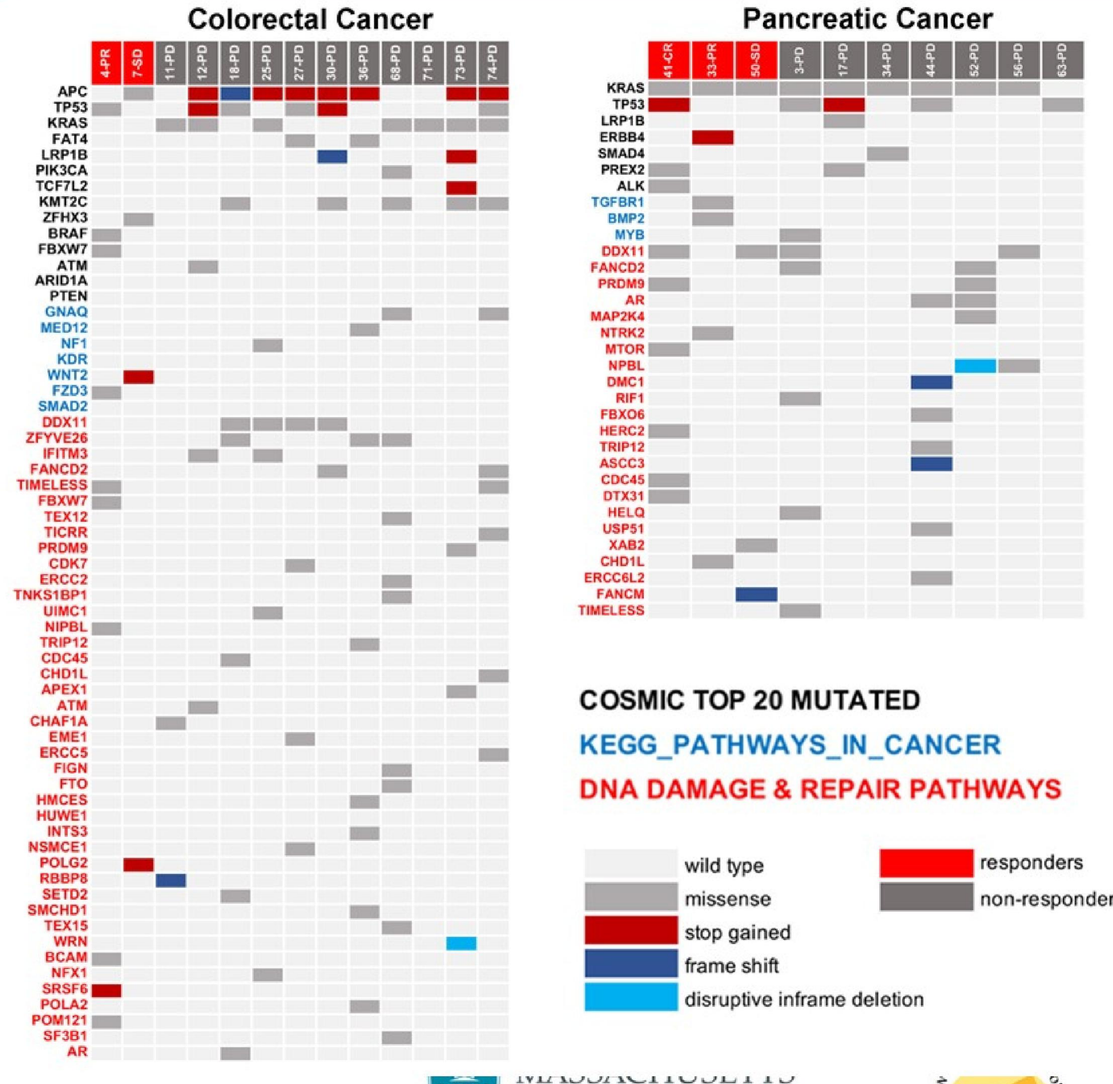
TMB and Coding Gene Mutational Analysis

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





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Ipi/Nivo/Upfront Radiation: MSS Colon Cancer

N=30

MSS Colon Cancer
- Previously treated w 5-FU, oxaliplatin, and irinotecan in some combination
- MSS by IHC

→

Cycle 1
Nivolumab 240 mg q 2 wk x 3
Ipiliumab 1 mg/kg q 6 wk x 1
RT- 8 Gy x 3 to single lesion- start D1
- Liver
- Nodal
- Lung
- Pulmonary
- Soft tissue

→

Cycle 2-4
Nivolumab 240 mg q 2 wk x 3
Ipiliumab 1 mg/kg q 6 wk x 1

→

Cycle 5 and beyond
Nivolumab 240 mg q 2 wk x 3

N=30

- Single cell RNA seq/MERFISH
  - WHAT cells are in the tumor?
- Multiplex IHC/ Immunofluorescence
  - WHERE in the tumor are different cells located?
- Monitoring response- ctDNA

Ph II Ipilimumab and Nivolumab with radiation for MSS CRC
PI: Hong
ASCO 2023

Koenig JL, et al. ASCO 2023.

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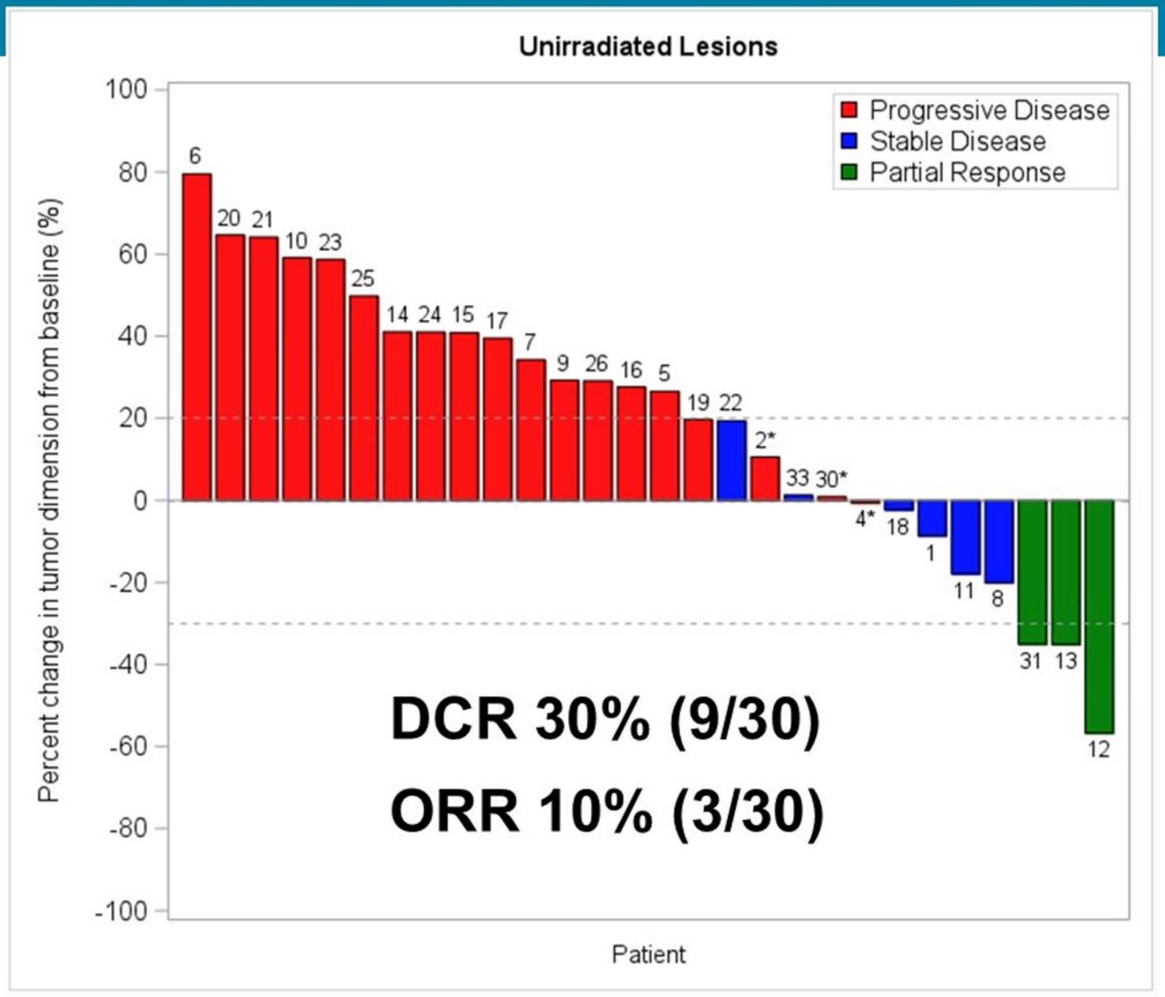
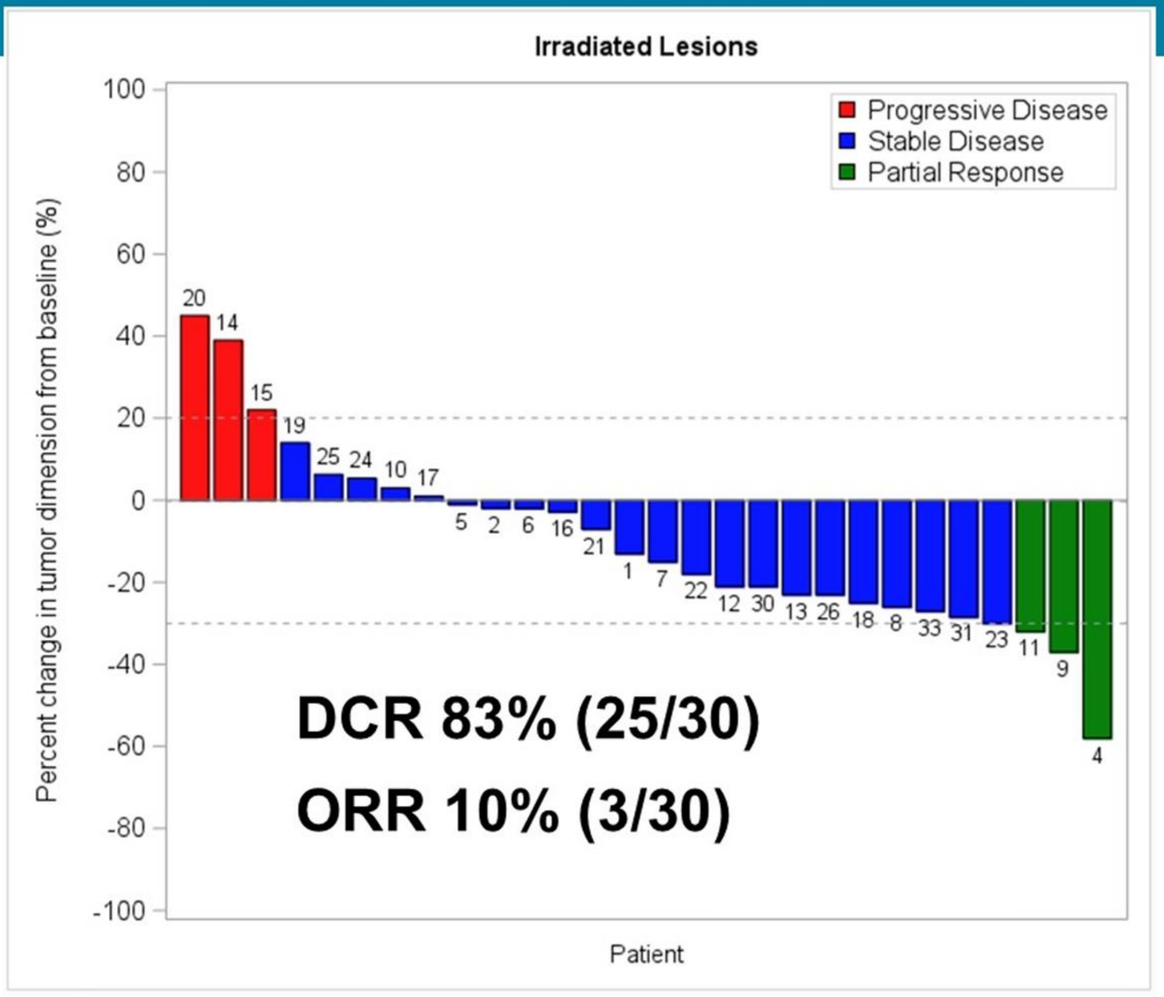
Response to treatment





Koenig JL, et al. ASCO 2023.

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nature medicine

ARTICLES

https://doi.org/10.1038/s41591-020-1131-x

Check for updates

Liver metastasis restrains immunotherapy efficacy via macrophage-mediated T cell elimination

Jiali Yu[1,2,17], Michael D. Green[2,3,4,17] ✉, Shasha Li[1,2,5], Yilun Sun[3,6], Sara N. Journey[7], Jae Eun Choi[8,9], Syed Monem Rizvi[10], Angel Qin[11], Jessica J. Waninger[7,9], Xueting Lang[1,2], Zoey Chopra[7], Issam El Naqa[3,12], Jiajia Zhou[1,2], Yingjie Bian[1,2], Long Jiang[2,3], Alangoya Tezel[7], Jeremy Skvarce[7], Rohan K. Achar[7,13], Merna Sitto[3], Benjamin S. Rosen[3], Fengyun Su[8,9], Sathiya P. Narayanan[8,9], Xuhong Cao[8,9,14], Shuang Wei[1,2], Wojciech Szeliga[1,2], Linda Vatan[1,2], Charles Mayo[3], Meredith A. Morgan[3], Caitlin A. Schonewolf[3], Kyle Cuneo[3], Ilona Kryczek[1,2], Vincent T. Ma[11], Christopher D. Lao[11], Theodore S. Lawrence[3], Nithya Ramnath[4,11], Fei Wen[10], Arul M. Chinnaiyan[8,9,14], Marcin Cieslik[5,8,9], Ajjai Alva[2,11] and Weiping Zou[1,2,8,15,16] ✉

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The liver is an immune privileged site

The human liver processes about 1.5 L of blood every minute including antigens from harmless dietary products.

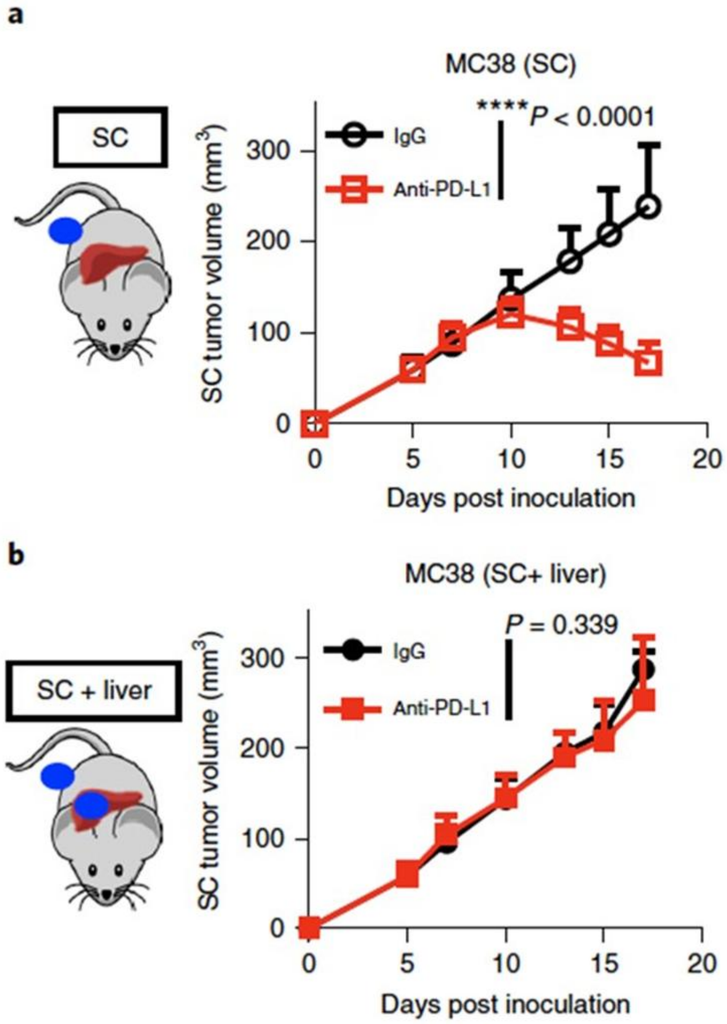
Tight immune regulation in the liver is facilitated by immunosuppressive cells

This immune tolerance may explain why the liver is relatively tolerant to allotransplant compared to other solid organ and may facilitate persistent infections by pathogens like hepatitis B and C.

Possible Mechanisms

- Ineffective immune synapses resulting in T cell anergy
- Induction of regulatory T cells
- Elimination of effector T cells

Liver metastases diminish immunotherapy efficacy systemically in patients and preclinical models



Yu J, Liver metastasis restrains immunotherapy efficacy via macrophage-mediated T cell elimination. Nat Med. 2021 Jan;27(1):152-164.

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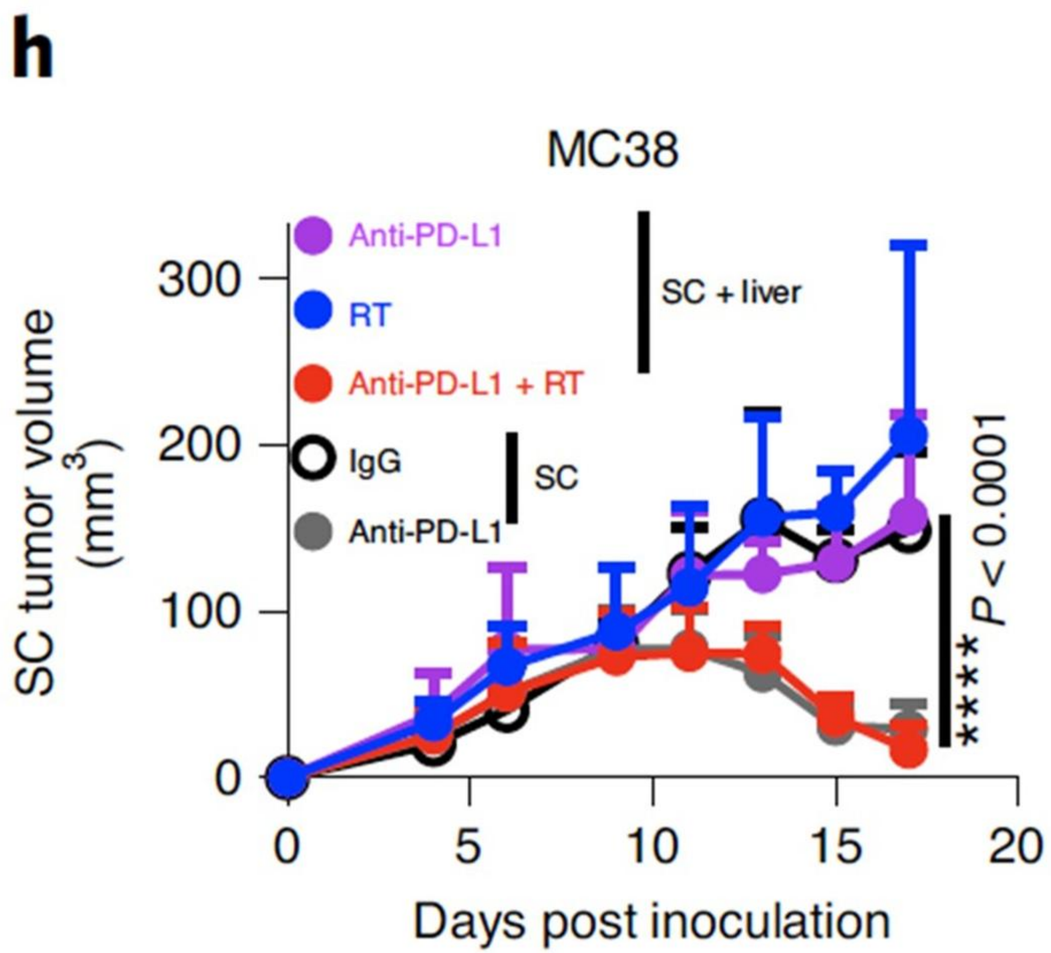
Liver-directed radiotherapy eliminates immunosuppressive hepatic macrophages, increases hepatic T cell survival and reduces hepatic siphoning of T-cells



Yu J, Liver metastasis restrains immunotherapy efficacy via macrophage-mediated T cell elimination. Nat Med. 2021 Jan;27(1):152-164.

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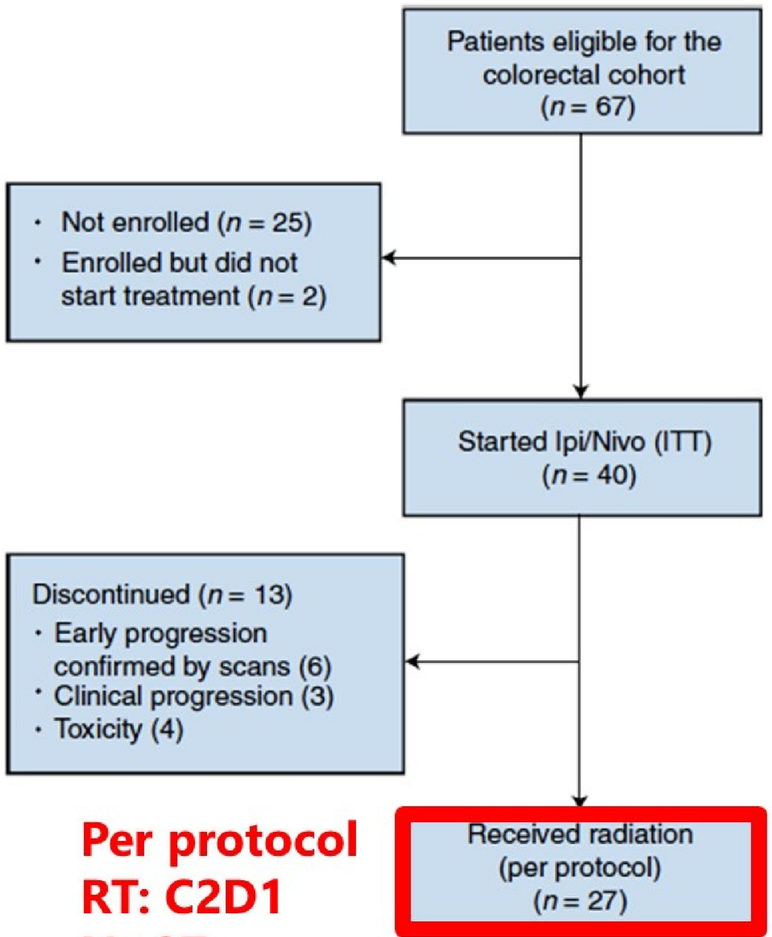
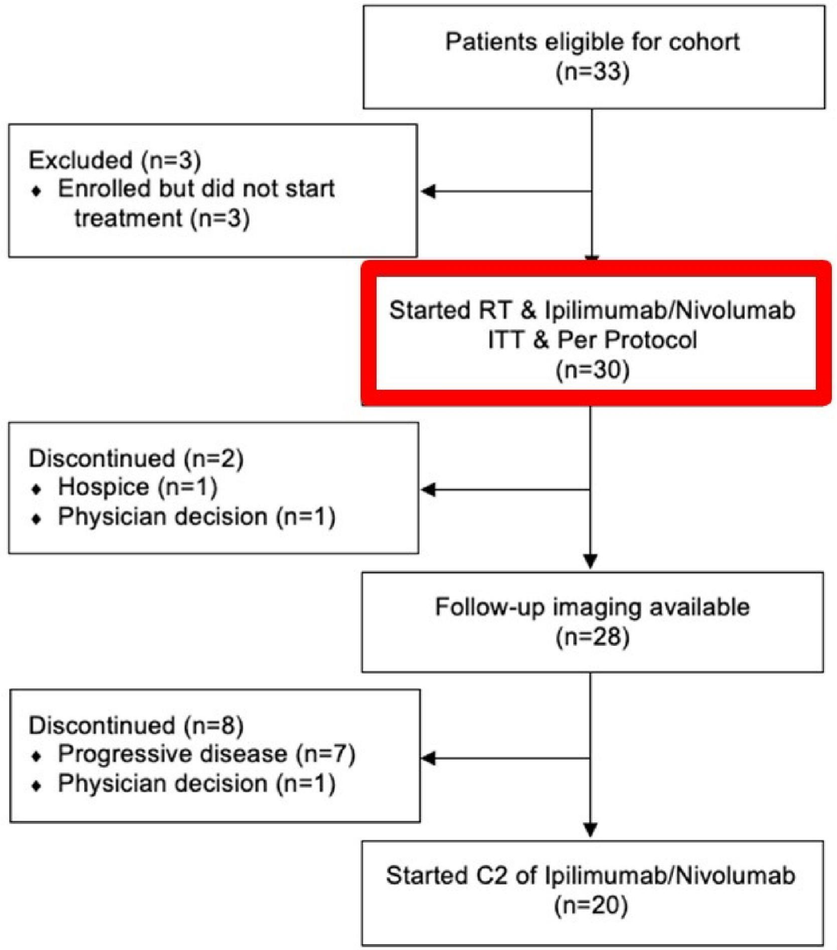
Liver metastases: combined 17-021+20-256

17-021



Per protocol
RT: C2D1
N=27

20-256



ITT/Per protocol
RT: C1D1
N=30

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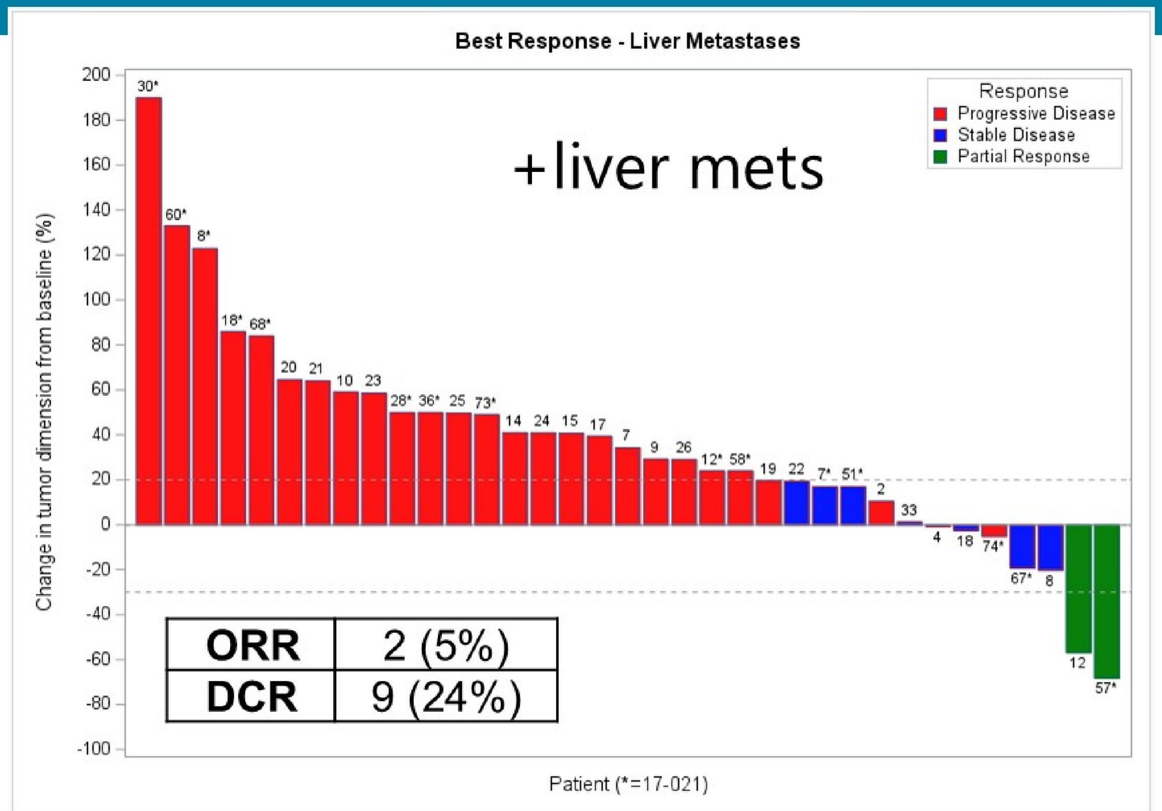
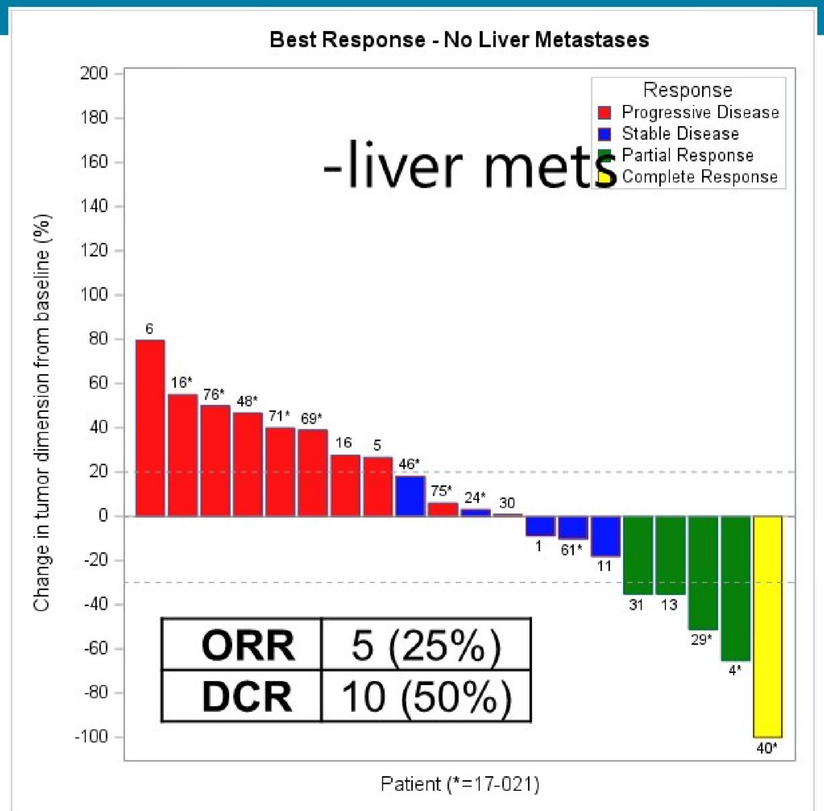
Patients without liver metastases have higher rates of response and disease control





17-021+20-256	Total	+Liver Mets	-Liver Mets	p-value
Number	57	37	20	
CR	1 (2%)	0 (0%)	1 (5%)	0.1477
PR	6 (11%)	2 (5%)	4 (20%)	
SD	12 (21%)	7 (19%)	5 (25%)	
PD	36 (63%)	26 (70%)	10 (50%)	
NE	2 (4%)	2 (5%)	0 (0%)	
ORR	7 (12%)	2 (5%)	5 (25%)	0.0837
DCR	19 (33%)	9 (24%)	10 (50%)	0.0770

Koenig JL, et al. ASTRO 2023.

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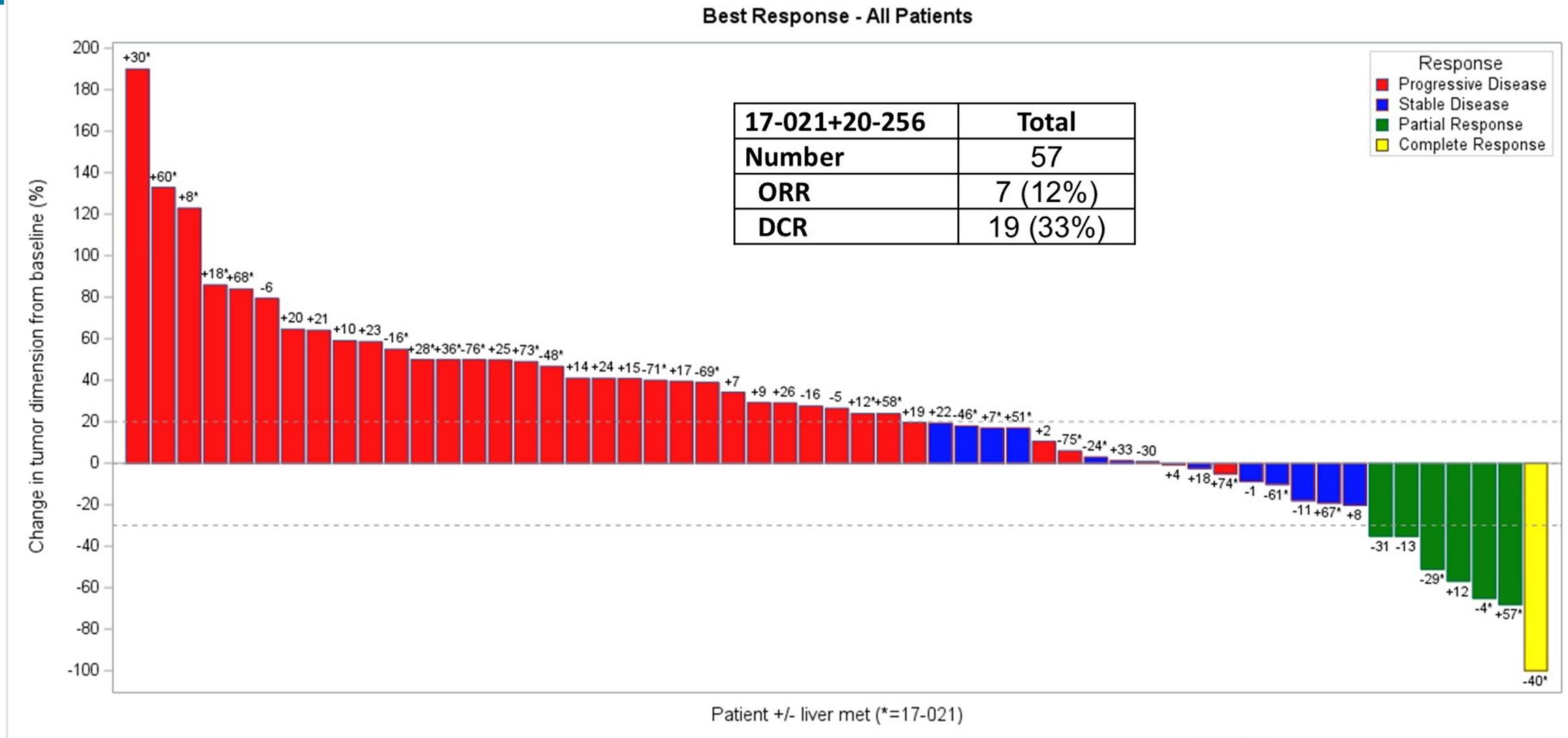
Best out-of-field response with combined data



17-021+20-256	Total
Number	57
ORR	7 (12%)
DCR	19 (33%)

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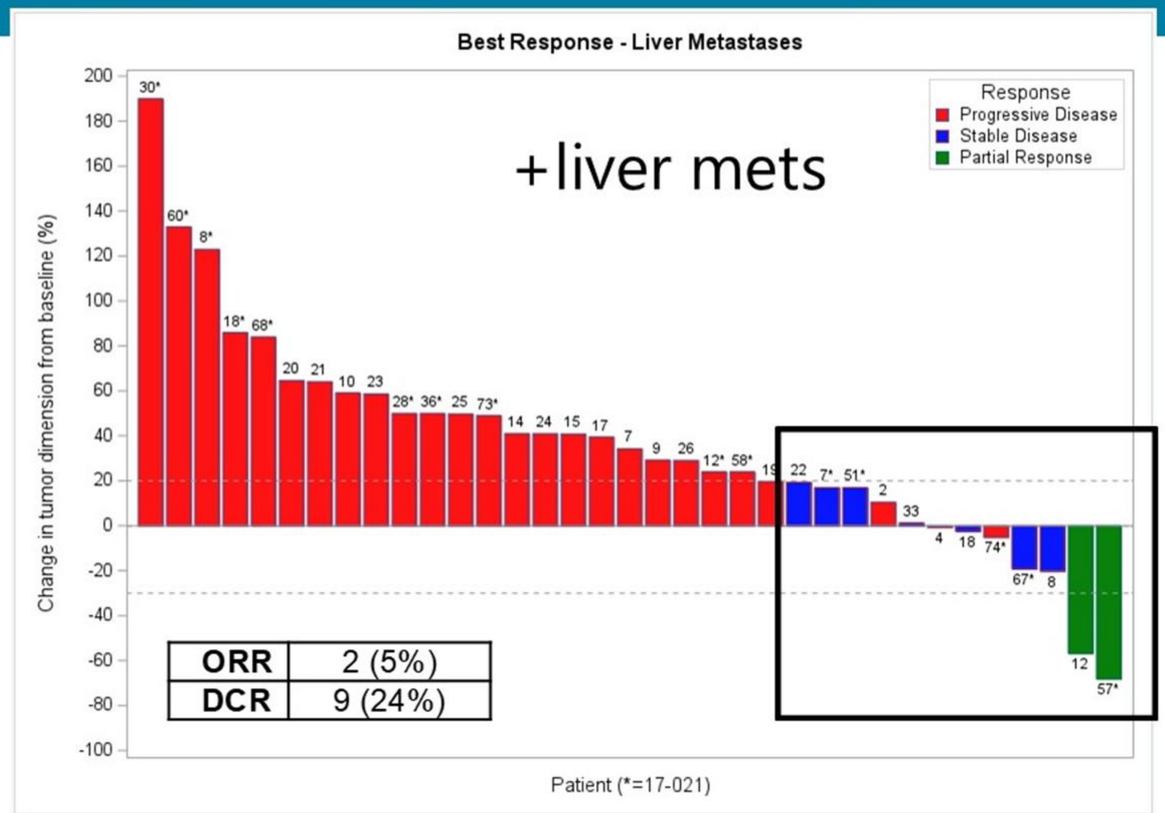
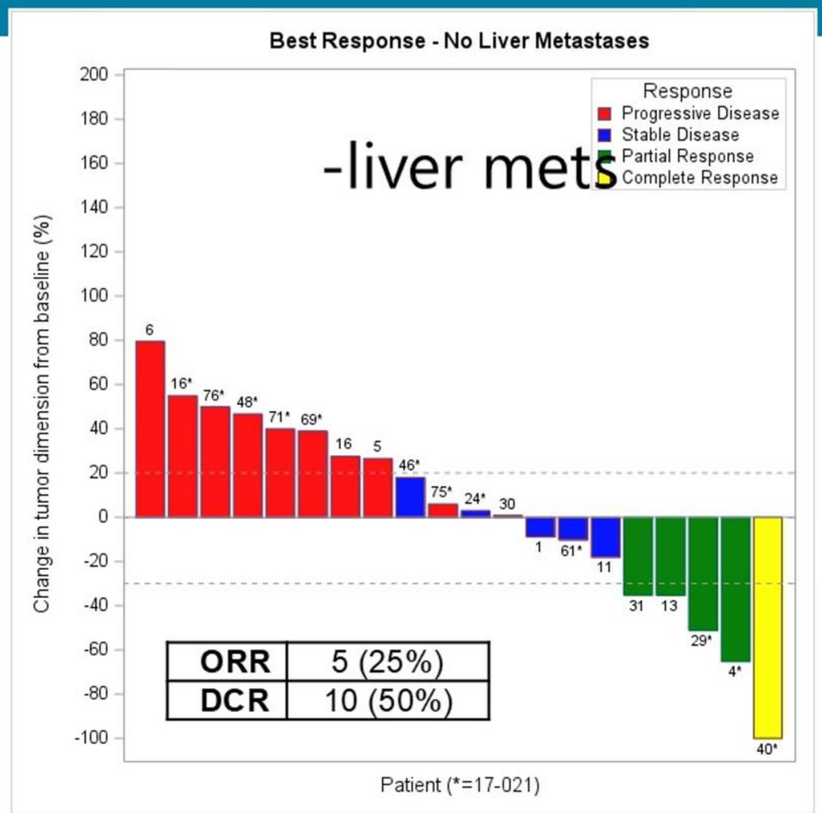
MASS GENERAL CANCER CENTER

Patients without liver metastases have higher rates of response and disease control





7/9 patients with liver mets with SD or PR received liver-directed RT. Patients 7 and 67 (17-021) had small volume liver disease (6mm/17mm and 23mm lesions, respectively).

Koenig JL, et al. ASTRO 2023.

17-021+20-256	Total	+Liver Mets	-Liver Mets	p-value
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PD	36 (63%)	26 (70%)	10 (50%)	
NE	2 (4%)	2 (5%)	0 (0%)	
ORR	7 (12%)	2 (5%)	5 (25%)	0.0837
DCR	19 (33%)	9 (24%)	10 (50%)	0.0770

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Cox models for overall survival

Variable	Univariable HR (95% CI)	p-value	Multivariable HR	p-value	Multivariable HR	p-value
Liver metastases	2.62 (1.23-5.61)	**0.0126**	2.99	**0.0056**		
ECOG PS	1.55 (0.75-3.21)	0.2380	1.76	0.1302	1.44	0.4234
Trial 20-256	0.76 (0.40-1.46)	0.4129	0.63	0.2043	0.69	0.3831
Prior lines of systemic therapy	1.02 (0.89-1.18)	0.7442	0.99	0.8406	0.93	0.4270
Liver-directed RT (n=37, pts w/ liver mets)	0.39 (0.17-0.92)	**0.0306**			0.40	**0.0420**

Koenig JL, et al. ASTRO 2023.

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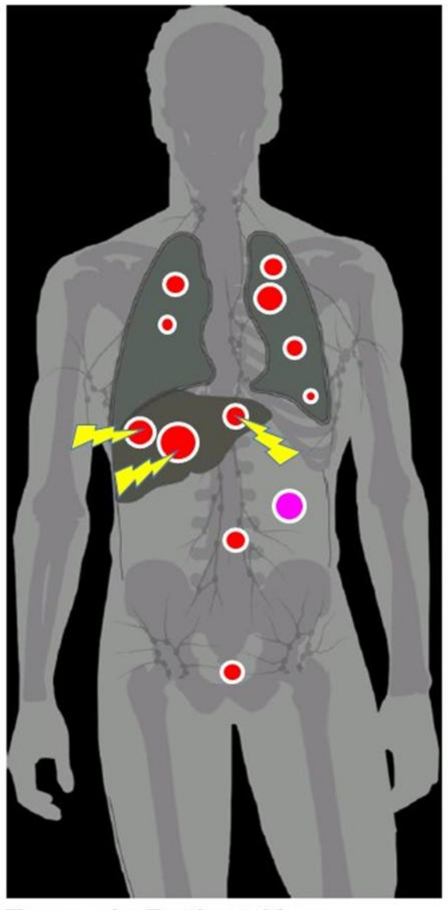
NRG CR2314-RadIO

NRG CR2314: Ph III Dual CPB and ablative liver SBRT for MSS CRC
PI: Parikh
NCI GISC approved 2024



Example Patient Key:
Red spots = multi-organ mets
Purple spot = primary colon ca.
Lightning = RT to all liver mets

MSS mCRC with multi-organ metastases (must include 1-3 liver metastases)

- Previously treated with 5-FU, Oxaliplatin, and Irinotecan and/or intolerant/unable to receive these meds
- MSS (by IHC, PCR, or NGS)
- No curative surgical/ablative options
- No prior Y90
- No symptomatic carcinomatosis, ascites requiring paracentesis, or history of partial small bowel obstruction
- No portal hypertension
- Between 1-3 liver lesions, all of which must be amenable to ablative RT
- ≥700 cc liver (approximately 1/3 of liver) uninvolved by metastases*
- At least 1 extrahepatic metastasis measuring ≥1 cm outside RT field (RECIST Target)

Key: MSS = Microsatellite stable; mCRC = metastatic colorectal cancer; mets = metastases; IHC = Immunohistochemistry; RT = Radiation Therapy
***Automatic eligibility** Automatically eligible if metastatic disease is confined to one liver lobe. Otherwise, central review is required for bilobar disease to confirm feasibility of ablative RT for the first 3 patients at a site or if not credentialed for RT1112

Randomized 1:1

Cycle 1
- Nivolumab
- Ipilimumab
- **RT to all liver lesions**: up to 50-54 Gy in 5-6 fractions (RT prescription dose reduced based on Allowed Mean Liver Dose)

→ **Cycles 2-4**
- Nivolumab
- Ipilimumab

→ **Cycles 5 + (up to a year)**
- Nivolumab

Nivolumab dose= 240 mg q2 (d1, 15, 29)
Ipilimumab= 1 mg/kg q 6 weeks (d1)

IO continued until PD, intolerance, unacceptable AE(s), or withdrawal

If PD, but clinically well and tolerating IO, pt can consent to treatment beyond PD and continue until further PD

→ Lonsurf/Bevacizumab or Fruquitinib

Phase II co-primary endpoint assessment Safety Failure Rate/Objective Response Rate to occur on first 50 patients randomized to RT+IO arm, with all Phase II patients contributing to the Phase III portion (1º endpoint OS, n=278)

CT scans & CEA = baseline, after every 2 cycles, FU q3m x 3 years

Archival tumor (FFPE) will be requested for exploratory genomic and molecular profiling testing post-hoc. Prospective collection of peripheral blood at several time points in the experimental arm (and control arm at similar time points) corresponding to baseline, post-RT, post completion of ipilimumab, at 6 months, 9 months and 12 months will be done.

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Conclusions

- Site-specific metastases may have an unrealized impact on efficacy to immunotherapy
- Radiotherapy may be one option to reprogram the immunosuppressive microenvironment
- This will be formally evaluated in an upcoming NRG trial

Acknowledgements

MGH Cancer Center

Aparna Parikh, MD
David Ting, MD, PhD
Arnav Mehta, MD, PhD
Nir Hacohen, PhD

Ryan Corcoran, MD, PhD
David Ryan, MD
Eunice Kwak, MD, PhD
Lawrence Blaszkowsky, MD
Jeffrey Clark, MD
Lipika Goyal, MD
Jill Allen, MD
Ryan Nipp, MD
Bruce Giantonio, MD
Sam Klempner, MD
Colin Weekes, MD, PhD

Motaz Qadan, MD, PhD
Carlos Fernandez-del Castillo, MD
Keith Lillemoe, MD
Cristina Ferrone, MD

MGH GI Radiation Oncology

Lorraine Drapek, DNP
Jennifer Wo, MD
Christie Eyler, MD, PhD
Hannah Roberts, MD
Julie Koenig, MD
Tarin Norkum
Leilana Ly
Dan Duda, PhD
John Wolfgang, PhD