SITC 2019
Gaylord National Hotel & Convention Center Nov. 6-10
NATIONAL HARBOR, MARYLAND

Novel Approaches and Rational RT-Drug Combinations:

A Phase I Study of TGF-β trap (M7824) and NHS-IL12 (M9241) Alone and in Combination with multi-site Stereotactic Body Radiation Therapy (SBRT) for Metastatic Non-Prostate Genitourinary Malignancies

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Financial Relationships

- Advisory Board – Jounce Therapeutics

Acknowledgements

NATIONAL CANCER INSTITUTE
Center for Cancer Research

Genitourinary Malignancies Branch (GMB)
- **James L. Gulley MD PhD**
- **Andrea B. Apolo, MD (PI)**

Merck KGaA
Darmstadt, Germany

Research Partners / CRADA
- Merck KGaA, Darmstadt, Germany/GSK

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Society for Immunotherapy of Cancer

2017-2018 SITC-NCI Immunotherapy Fellowship

- SITC co-sponsored fellowship made possible in part by a grant from **EMD Serono**

Background/Overview

- Immune checkpoint blockade (ICB) targeting the PD-1/PD-L1 pathway has transformed prognosis for a subset of pts with non-prostate GU malignancies

- Several indications for anti-PD-1 /PD-L1 agents in non-prostate GU cancers, currently:
  - 5 approvals in 2nd–line metastatic/advanced urothelial carcinoma (mUC)
  - 2 approvals in 1st –line mUC (cisplatin-ineligible)
  - 1 approval in 2nd –line metastatic renal cell carcinoma (mRCC)

- Anti-PD-1/PD-L1 monotherapy insufficient for the majority of pts and ORR remains modest ~15-25%

- IO combination regimens have emerged as an attractive option
  - Ipi+Nivo, TKI+IO, chemo+IO, ADC+IO
  - Options after progression on anti-PD-1/PD-L1 is a rapidly growing area of clinical need
  - **Less progress with PD-1/PD-L1 + novel IO combinations**

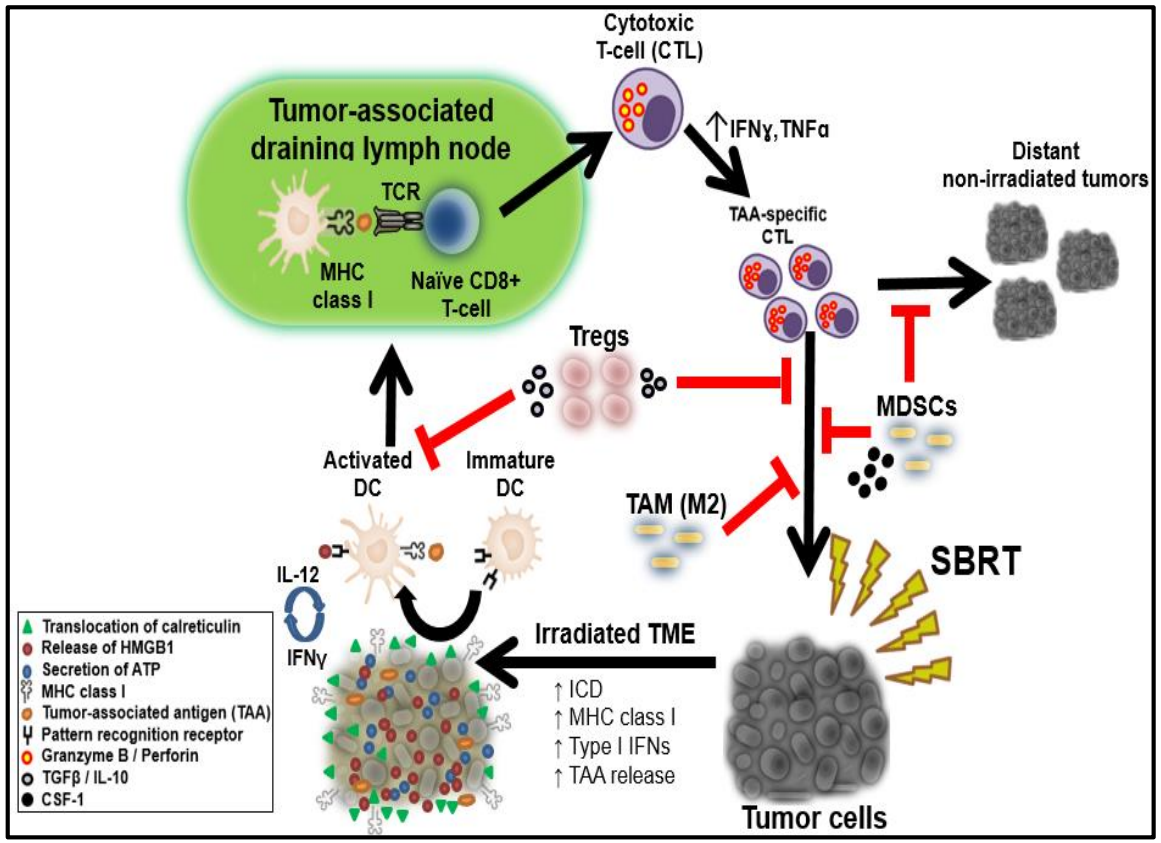
SBRT + IO – a nascent partnership

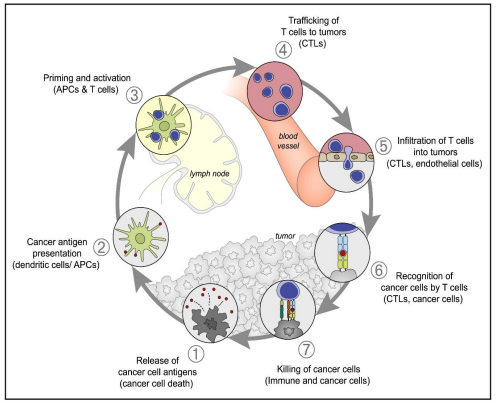
- Expanding clinical indications for SBRT in the metastatic setting
  - SBRT has potential to meaningfully extend PFS/OS in patients with limited metastatic disease[1-3]

- The strategy of combining radiation and immunotherapy to enhance local and systemic antitumor immune responses is intriguing yet largely unproven in the clinic
  - substantial preclinical rationale for synergy of RT+IO exists
  - growing arena of clinical investigation suggests that SBRT is immunomodulatory and may synergize with IO[4-6]

Gomez DR et al. *J Clin Oncol* 2019[1]
Palma DA et al. *Lancet Oncol* 2019[2]
Bauml JM et al. *JAMA Oncol* 2019[3]
Luke JJ et al. *J Clin Oncol* 2018[4]
Formenti SC et al. *Nat Med* 2018[5]
Theelen WSME et al. *JAMA Oncol* 2019[6]

SBRT and the interplay with the cancer-immunity cycle





increasingly recognized that therapeutic efficacy of of SBRT is *in part* mediated by anti-tumor immune responses in addition to DNA damage/DSBs

Key Immunomodulatory Effects of SBRT

1) **Induction of Immunogenic Cell Death (ICD)**
   - ICD hallmarks – CRT, HMGB1, ATP
   - cGAS-STING pathway activation

2) **Release/Exposure of tumor-associated (neo)antigens**
   - **Cross-presentation** → antigen-specific CTL

3) **Immunogenic Modulation**
   - Alters target(tumor) cell immunophenotype (**PD-L1**)
   - Enhances antigen presentation

4) **Modulation of the immune TME**
   - Chemokines/cytokines (**IFNs**, **TGF-β**)
   - Alteration of stroma/endothelium
   - Trafficking → immune access into TME

Demaria S, Golden EB, Formenti SC. *JAMA Oncol* 2015
Marciscano AE et al. *Int J Radiat Oncol Biol Phys* 2019
Chen DS and Mellman I. *Immunity* 2013

Hypothesis

The combination of multi-site SBRT + NHS-IL12 (M9241) + anti-PD-L1/TGF-β trap (M7824) is safe and improves clinical outcomes for patients w/ metastatic non-prostate GU cancers

To boost response rates in non-responders and treatment-refractory pts, rational immune-intensification combinations should :

- Reverse immunosuppression – both intrinsic to TME and txt-induced (adaptive resistance)
- Enhance immunogenicity
- Exploit potential synergies w/ MOA that are complementary / non-redundant

Trial Synopsis

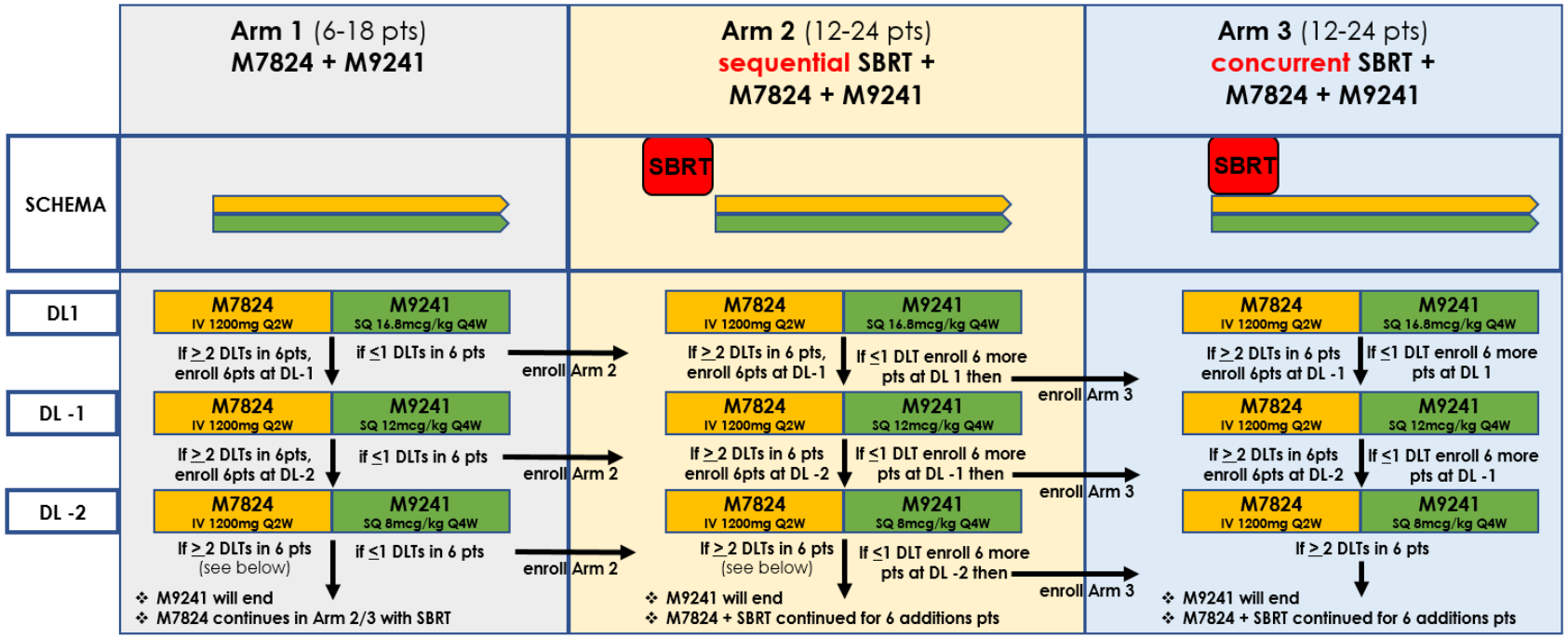
Eligibility: metastatic non-prostate genitourinary cancer w/ new or progressive disease

- at least one site suitable for irradiation (up to 4 sites permitted)
- at least one site of measurable disease (non-irradiated)

Objective: safety + RP2D of M7824 + M9241 alone OR in combination with multi-site SBRT that is sequential or concurrent

Design: open-label non-randomized three-stage phase I trial w/ sequential enrollment of each arm

- Flat dose of M7824*
- Fixed dose of multi-site SBRT → 8Gy x 3 to ≤ 4 metastatic sites
- De-escalating dose M9241 if DLTs (potential to continue as M7824+SBRT doublet)



Robust immune correlatives

Peripheral immune modulation

- Immune subsets/PBMC
- Chemokine/cytokine analysis
- T-cell clonality / TCR repertoire
- CTCs and extracellular vesicles (EVs)

Intratumoral / TME immune status

- Multiplex IHC (CD8/CD4/FoxP3/PD-L1)
- RNA-Seq
- Baseline TMB

Response rate in non-irradiated lesions

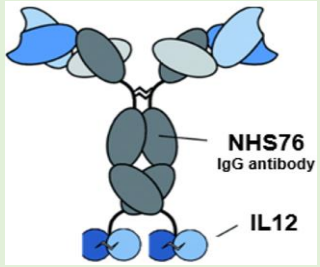
- Metabolic response w/ 18-F FDG PET

Leveraging Rational RT+IO Combinations

Stereotactic Body Radiation Therapy (SBRT)

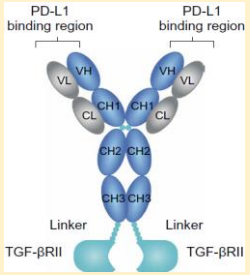
- Precision image-guided high-dose radiotherapy delivered over 1-5 sessions
- Tumoricidal effects predominantly driven by **DNA damage → dsDNA breaks**
- Increasing recognition of immunomodulatory effects → can promote or restrain
- Induces IFN signaling, upregulation of **PD-L1** and activation of **TGF-β**

NHS-IL12 (M9241) – a DNA-damage localizing immunocytokine

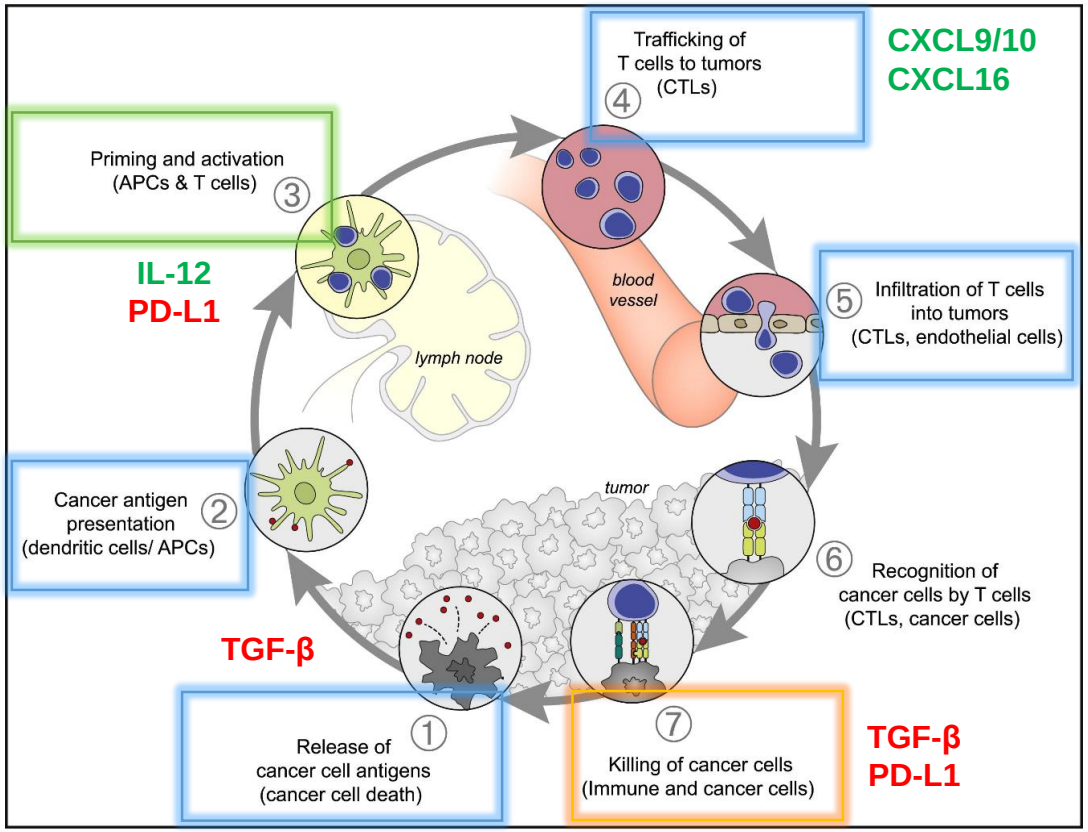


- IL-12 plays a central role in both T and NK-cell-mediated inflammatory responses
- Two IL-12 heterodimers fused to H-chain of NHS76
- NHS76 is a fully human IgG1 antibody with affinity for both ssDNA and **dsDNA breaks** (tumor-necrosis targeting)
- **DNA damage localizing properties of NHS76 allow selective delivery IL-12**

Bintrafusp alfa "TGF-β trap" (M7824) a bifunctional fusion protein simultaneously blocking PD-L1 and TGF-β



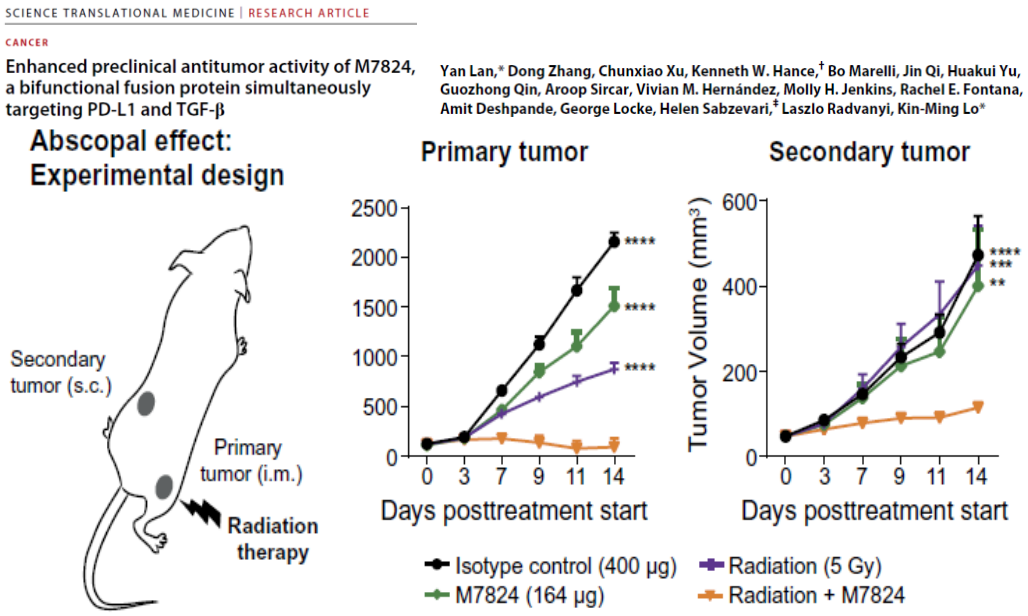
- Fully human PD-L1 (IgG1) monoclonal antibody
- TGF-β neutralizing trap moiety → TGF-βRII fused to CH3-C terminus of FCγ1 domain of IgG via flexible linker
- **First-in-class bifunctional protein targeting TWO immune-inhibitory pathways**



Strauss J et al. *Clin Cancer Res* 2019[1]
Lan Y et al. *Sci Transl Med* 2018[2]
Strauss J et al. *Clin Cancer Res* 2018[5]
Chen DS and Mellman I. *Immunity* 2013[4]

SBRT may synergize with dual blockade of PD-L1 and TGF-β

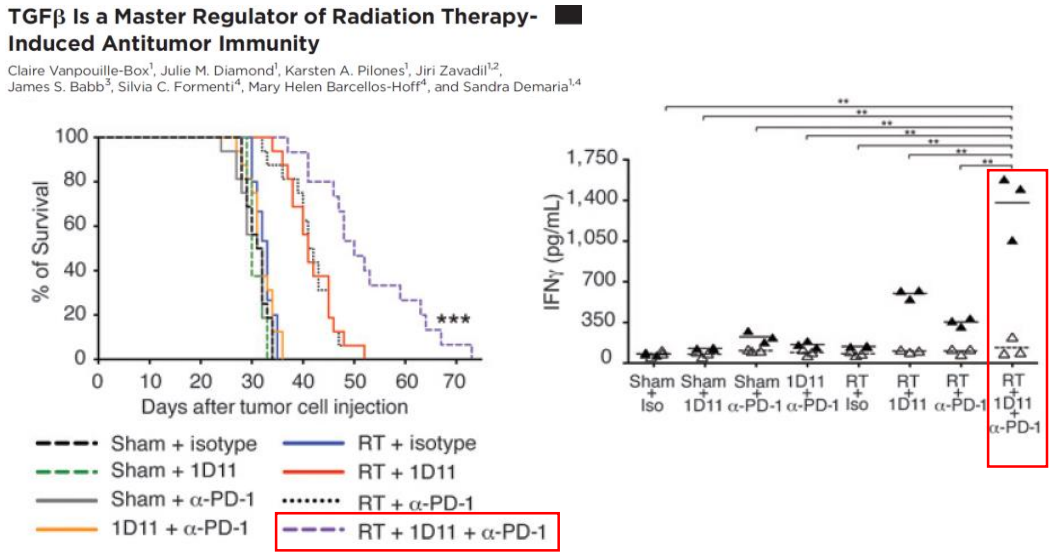
Abscopal responses are a rare clinical event yet increasingly observed in setting of ICB



Preclinical models suggest that addition of RT + M7824 boosts abscopal responses relative to monotherapy

- SBRT promotes TGF-β activation
- SBRT upregulates PD-L1 via IFNɣ-driven adaptive resistance

Addition of PD-1/PD-L1 axis blockade may augment responses to SBRT+TGF-β blockade

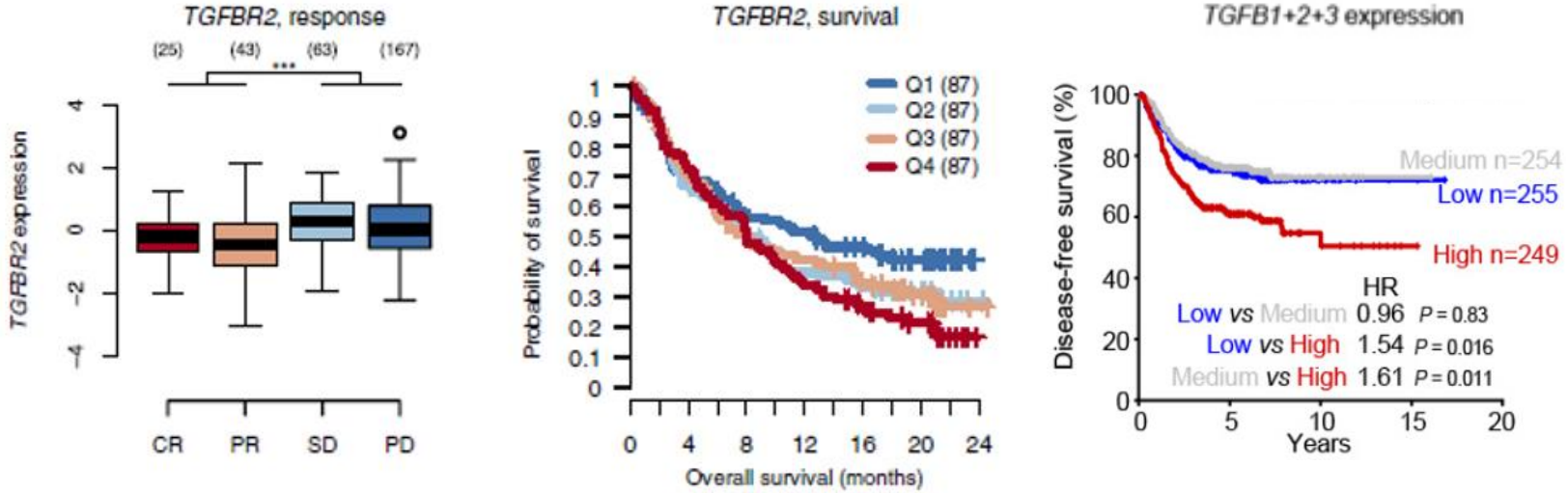


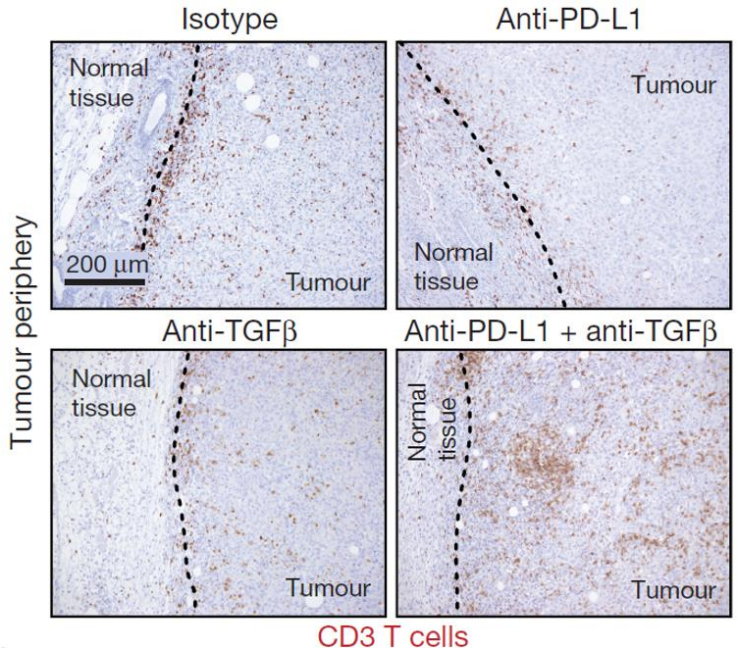
- Preclinical 4T1 model suggests PD-1 blockade in mice treated with RT+TGF-β blockade improves tumor rejection and survival → Ag-specific CD8+ T-cell-dependent mechanism (4T1, AH1A5 pep stim)
- reduced TCR signaling in circulating PD-1+ T-cells may underlie immune resistance signature and absence of abscopal response in a ph I/II of MBC pts treated with SBRT + TGF-β blockade (fresolimumab)

Lan Y et al. *Sci Transl Med* 2018[1]
Strauss J et al. *Clin Cancer Res* 2018[2]
Vanpouille-Box C et al. Clin Cancer Res 2015[3]
Formenti SC et al. *Clin Cancer Res* 2018[4]
Formenti SC et al. *J Immunother Cancer* 2018[5]

TGF-β axis is a dominant mechanism of immune exclusion

- TGF-β signaling has been associated with lack of response to anti-PD-L1 monotherapy[1-2]
  - TGF-β is a pleotropic cytokine with potent immunosuppressive activity in the TME
  - T-cell exclusion phenotype / reduced T-cell tumor infiltration
  - TGF-β gene expression adversely correlates with clinical outcomes in mUC patients treated with atezolizumab (anti-PD-L1)[1]



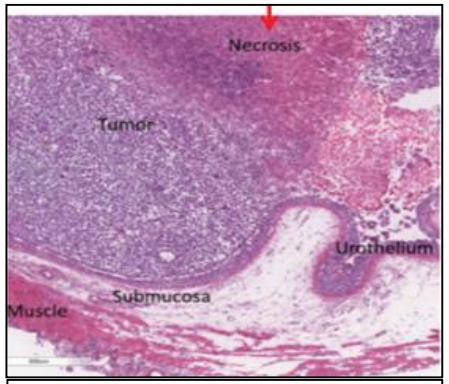


Mariathasan S et al *Nature* 2018
Tauriello DVF et al *Nature* 2018

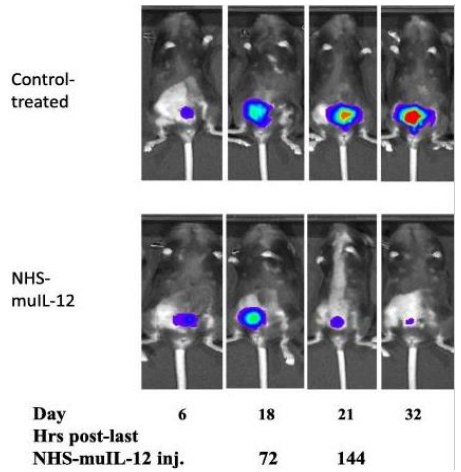
NHS-IL12 incites preclinical abscopal responses + innate / adaptive immunity

A DNA-damage localizing "tumor-targeted" immunocytokine

IL-12 → potent anti-tumor immunocytokine limited by systemic toxicity
- Central role in NK, NKT and T-cell inflammatory responses
- DCs produce IL-12 upon stimulation→ ↑ Ag presentation + CTL activation
- Effective anti-PD-1 therapy may depend on a DC "licensing"[1]
  - intratumoral cross talk **CD8 T-cell / IFNɣ ↔ DC / IL-12**
- Immunogenic reprogramming of TME (myeloid compartment)[2,7]



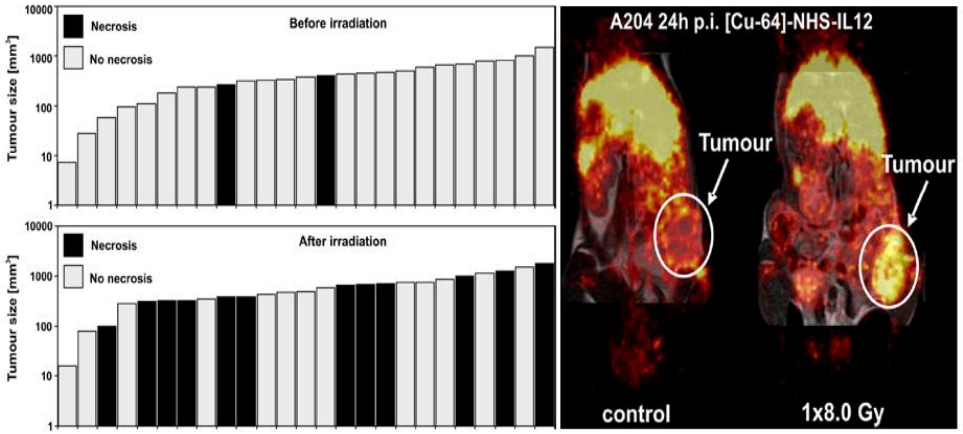
Intravesical MB49 tumors exhibit high levels of necrosis



First-in-human study @ NCI/CCR → **safe** w/encouraging bioactivity[2]
- Increased systemic IFNɣ secretion (as well as IL-10, CXCL10)
- Increased intratumoral TIL density and TCR diversity
- Many expanded tumor-associated clones also detected in periphery
- **Modest single-agent activity, excellent rationale for combination**

SBRT augments NHS-IL12 activity via complementary MOA
- M9241 targets areas of tumor necrosis by binding histones on free DNA fragments
- Precision tumor-targeting with SBRT can introduce DNA damage/DSBs which may facilitate intratumoral localization of NHS-IL12

SBRT enhances tumor necrosis on MR imaging and intratumoral uptake of NHS-IL12



Garris CS et al. *Immunity* 2018[1]
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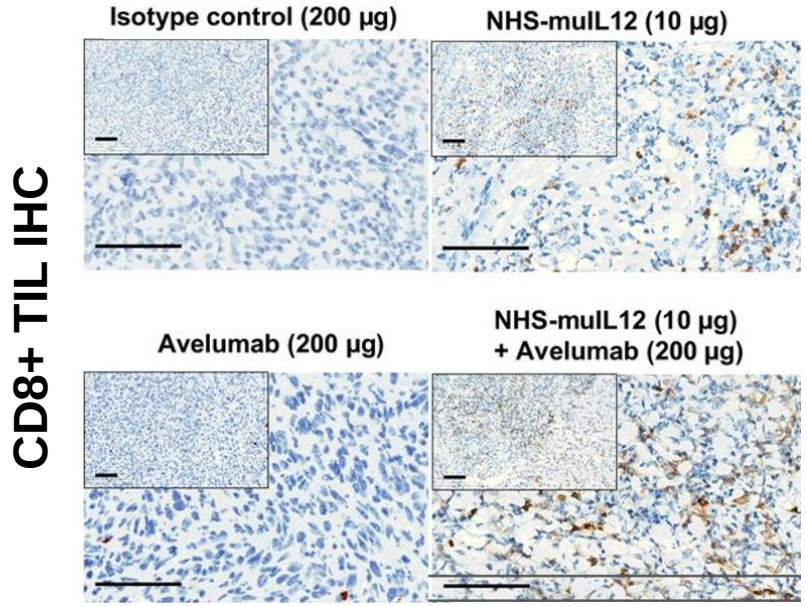
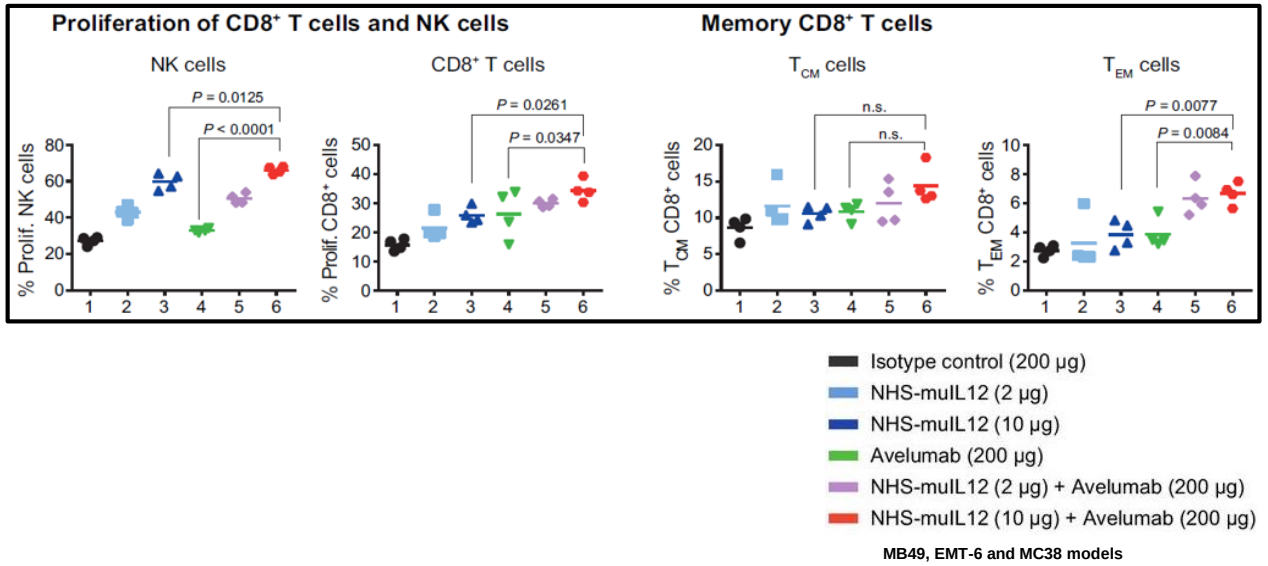
Fallon JK et al. Oncotarget. 2017[3]
Morillon YM 2nd et al. J Immunother Cancer. 2019[4]
Eckert F et al. *Cancer Immunol Immunother* 2016[5]
Eckert F et al. *Oncoimmunology* 2016[6]
Mills BN et al. *Cell Rep*. 2019[7]

M7824 + M9241 are complementary

Preclinical models suggest NHS-IL12 + M7824 (and NHS-IL12+avelumab) enhance anti-tumor efficacy via innate (NK cell) and adaptive (T-cell) immune-based mechanisms





MB49, EMT-6 and MC38 models

- Clinical evaluation of NHS-IL12 + avelumab currently underway – phase Ib open-label, dose-finding trial in pts with metastatic solid tumors (NCT02994953)
- Reassuring safety signal and manageable side effect profile from M7824, M9241 monotherapy studies (NCT02517398, NCT01417546) and ongoing M7824 + avelumab study → **optimism that M7824 + M9241 will be safe w/ potential for enhanced clinical benefit?**

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Courtesy of Gulley and Strauss/ GMB and LTIB

Summary

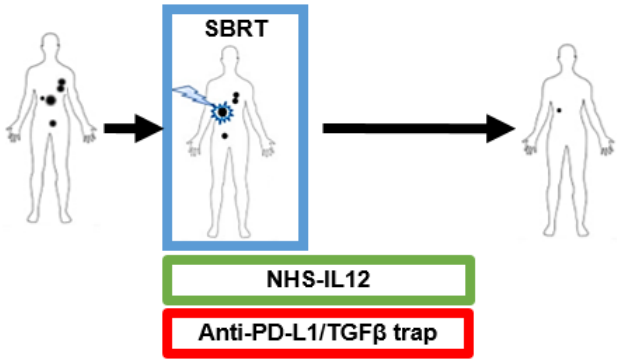
- Phase I of M7824 + M9241 +/- Multi-Site SBRT (sequential vs concurrent) in non-prostate GU malignancies
    - 3-arm sequential design w/ robust immune correlatives
        - Establish M7824+M9241 safety and PD/PK optimization
        - Explore Timing of SBRT (sequential vs. concurrent)
        - Early signal to inform rational phase II design (if Arm 2/3 both safe)

- Complementary MOA
    - SBRT increases IFNɣ production as well PD-L1 expression, TGF-β activation (M7824)
    - Cross-presentation critical aspect of RT-driven adaptive immunity (DC/IL-12 role may be important missing link)
    - Multi-site SBRT can help 'guide' NHS-IL12 to several tumor sites

- Disease-specific rationale
    - TGF-β immune exclusion predominant in urothelial cancers (M7824)
    - urothelial tumors exhibit high degree of necrosis (M9241)

Overcome Immunosuppression

- **Targeting dual immune-inhibitory axes (PD-L1 and TGF-β) can circumvent immune suppression / evasion in the tumor microenvironment**
- **SBRT can upregulate PD-L1 and activate TGF-β**



Enhance Immunogenicity

- **Hypofractionated 'non-ablative' SBRT is immunogenic and may potentiate abscopal responses via synergy with M7284/M9241**
- **Intratumoral targeting of NHS-IL12 can enhance innate and adaptive immunity**

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  - substantial preclinical rationale for synergy of RT+IO exists
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- RT+IO combos are a potential gamechanger → we are in the nascency of this complex partnership
  - many open questions / controversies and unlikely to be uniformly "correct" answers
  - mechanisms of synergy / determinants of response remain incompletely defined
  - optimal application of SBRT (**timing**, **dose**, **target**) is unknown

Gomez DR et al. *J Clin Oncol* 2019[1]
Palma DA et al. *Lancet Oncol* 2019[2]
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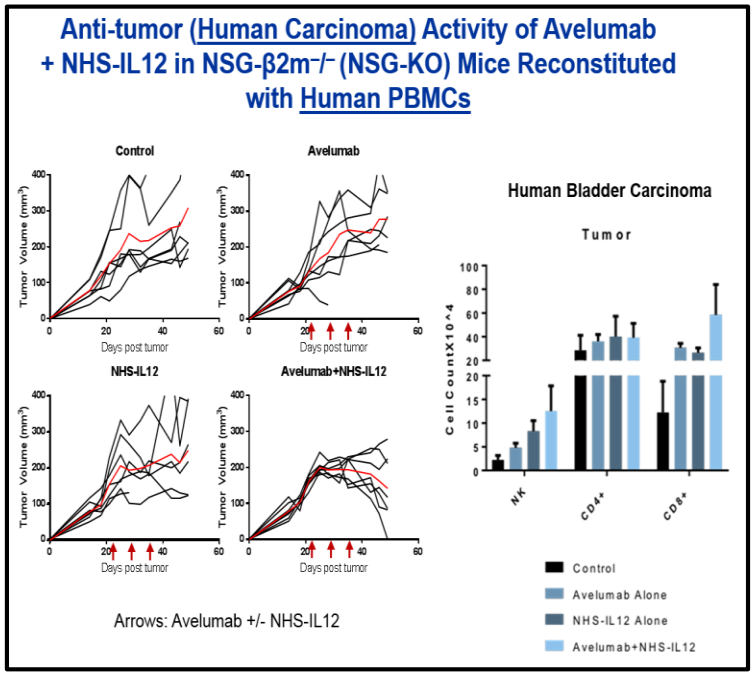

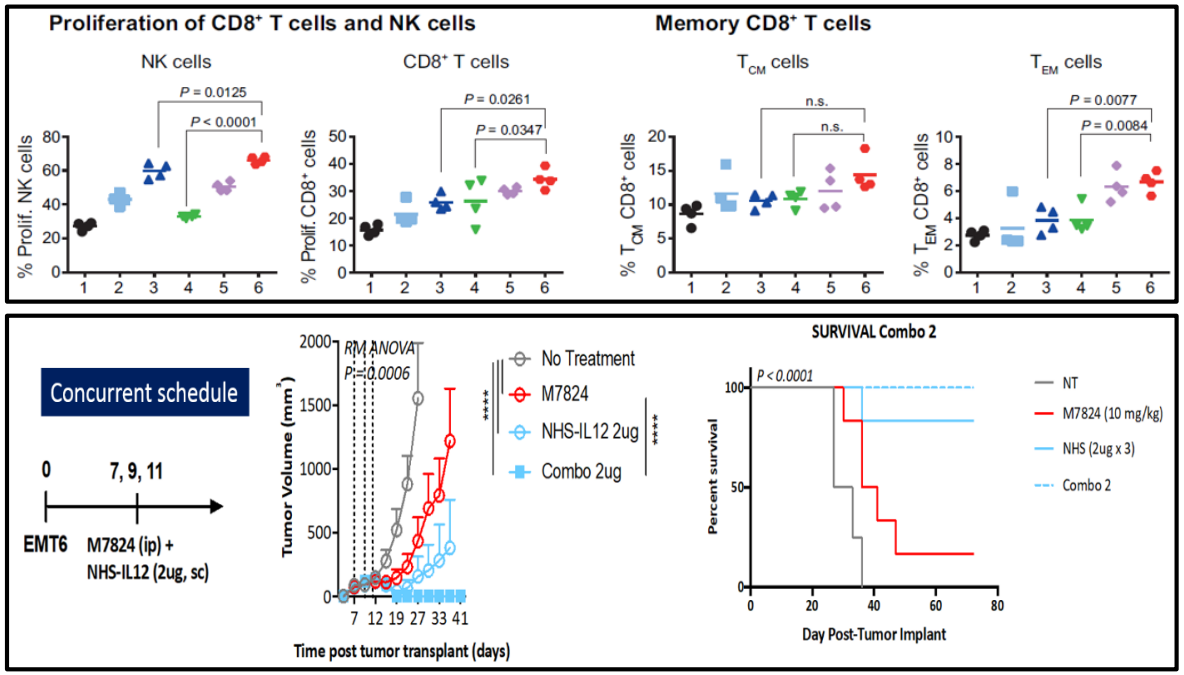

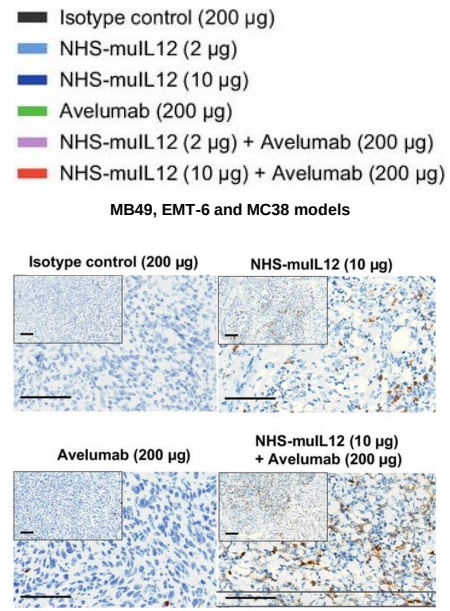

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