What's Next for Cancer Immunotherapy?

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Disclosures

- University of Wisconsin School of Medicine and Public Health - Employer
- Scientific Advisory Board Member
  - Seneca Therapeutics
  - Archeus Technologies Inc.
- Ownership Interest
  - Seneca Therapeutics
  - Archeus Technologies Inc.
- Patents held through the Wisconsin Alumni Research Foundation
  - NM600 for targeted radionuclide delivery and immunomodulation
  - Bacterial membrane nanoparticle to enhance the in situ vaccine effect of radiation
  - Brachytherapy catheter for intratumoral injection
- I will be discussing non-FDA approved indications during my presentation.

Summary of FDA-approved immunotherapies

Mechanism	FDA-approved therapies	Disease indication (year of approval)
Anti-CTLA4	Ipilimumab	•Melanoma (2011) •Renal cell carcinoma (2018) •MSI-H or dMMR colorectal cancer (2018) •Hepatocellular carcinoma (2020)
Anti-PD1	Nivolumab	•Melanoma (2014) •Non-small cell lung cancer (2015) •Renal cell carcinoma (2015) •Hodgkin lymphoma (2016) •Squamous cell of the head and neck (2016) •Urothelial carcinoma (2017) •MSI-H or dMMR colorectal cancer (2017) •Hepatocellular carcinoma (2017) •Small cell lung cancer (2018)
	Cemiplimab	•Cutaneous squamous cell carcinoma (2018)
	Pembrolizumab	•Melanoma (2014) •Non-small cell lung cancer (2015) •Head and neck squamous cell carcinoma (2015) •Hodgkin lymphoma (2017) •Urothelial carcinoma (2017) •MSI-H cancer (2017) •Gastric cancer (2017) •Cervical cancer (2018) •Primary mediastinal large B-cell lymphoma (2018) •Merkel cell carcinoma (2018) •Renal cell carcinoma (2019) •Esophageal cancer (2019) •Hepatocellular carcinoma (2019) •Endometrial carcinoma (2019)
Anti-PD-L1	Atezolizumab	•Urothelial cancer (2016) •Non-small cell lung cancer (2016) •Triple-negative breast cancer (2018) •Small cell lung cancer (2019)
	Avelumab	•Merkel cell carcinoma (2017) •Urothelial cell carcinoma (2017) •Renal cell carcinoma (2019)
	Durvalumab	•Urothelial cell carcinoma (2017) •Non-small cell carcinoma (2018) •Small cell lung cancer (2020)
CAR-T cell therapy	Axicabtagene ciloleucel	•Large B-cell lymphoma (2017)
	Tisagenledeucel	•B-cell precursor acute lymphoblastic leukemia (2017) •Large B-cell lymphoma (2018)
Cytokine modulation	Interferon	Interferon Alfa-2B: •Hairy cell leukemia (1986) •AIDS-related Kaposi's sarcoma (1988) •Melanoma (1995) •Follicular lymphoma (1997)
	Interleukin	Interleukin-2: •Renal cell carcinoma (1992) •Melanoma (1998)
Dendritic cell vaccine	Sipuleucel-T	•Prostate cancer (2010)
Oncolytic viruses	Talimogene laherparepvec	•Melanoma (2015)

Murciano-Goroff et al. Cell Research 2019

Anticipated and necessary advancements in cancer immunotherapy

- Expanding clinical indications for existing immunotherapies
- Development of additional clinically effective immunotherapies
- Clinical testing of immunotherapy combinations
- Integration of immunotherapies with localized therapies
- Integration of immunotherapies with other systemic therapies
- Novel strategies for systemic and/or tumor immunomodulation
- Development of companion imaging and strategies for personalized immunotherapy
- Advancement of clinical correlative assays for immunotherapy
- Expanding access to cancer immunotherapy globally

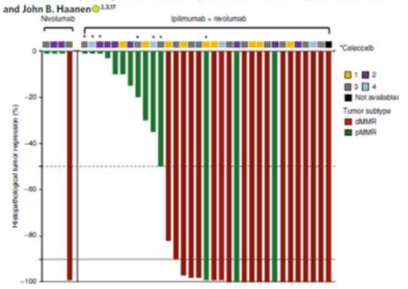
Expanding clinical indications for existing immunotherapies

ARTICLES

nature medicine

Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers

Myriam Chalabi, Lorenzo F. Fanchi, Krijn K. Dijkstra, José G. Van den Berg, Arend G. Aalbers, Karolina Sikorska, Marta Lopez-Yurda, Cecile Grootscholten, Geerard L. Beets, Petur Snaebjornsson, Monique Maas, Marjolijn Mertz, Vivien Veninga, Gergana Bounova, Annegien Broeks, Regina G. Beets-Tan, Thomas R. de Wijkerslooth, Anja U. van Lent, Hendrik A. Marsman, Elvira Nuijten, Niels F. Kok, Maria Kuiper, Wieke H. Verbeek, Marleen Kok, Monique E. Van Leerdam, Ton N. Schumacher, Emile E. Voest and John B. Haanen



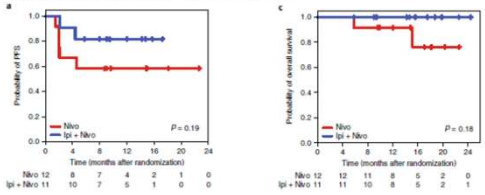
nature medicine

LETTERS

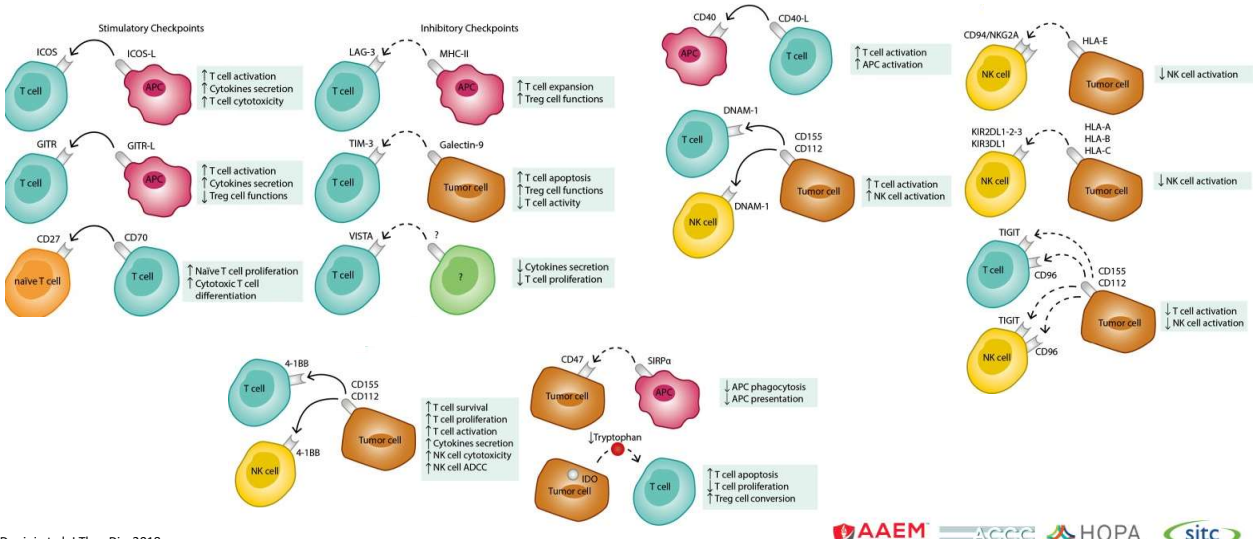
Corrected: Author Correction; Publisher Correction

Neoadjuvant immune checkpoint blockade in high-risk resectable melanoma

Rodabe N. Amaria, Sangeetha M. Reddy, Hussein A. Tawbi, Michael A. Davies, Merrick I. Ross, Isabella C. Glitza, Janice N. Cormier, Carol Lewis, Wen-Jen Hwu, Ehab Hanna, Adi Diab, Michael K. Wong, Richard Royal, Neil Gross, Randal Weber, Stephen Y. Lai, Richard Ehlers, Jorge Blando, Denái R. Milton, Scott Woodman, Robin Kageyama, Daniel K. Wells, Patrick Hwu, Sapna P. Patel, Anthony Lucci, Amy Hessel, Jeffrey E. Lee, Jeffrey Gershenwald, Lauren Simpson, Elizabeth M. Burton, Liberty Posada, Lauren Haydu, Linghua Wang, Shaojun Zhang, Alexander J. Lazar, Courtney W. Hudgens, Vancheswaran Gopalakrishnan, Alexandre Reuben, Miles C. Andrews, Christine N. Spencer, Victor Prieto, Padmanee Sharma, James Allison, Michael T. Tetzlaff and Jennifer A. Wargo

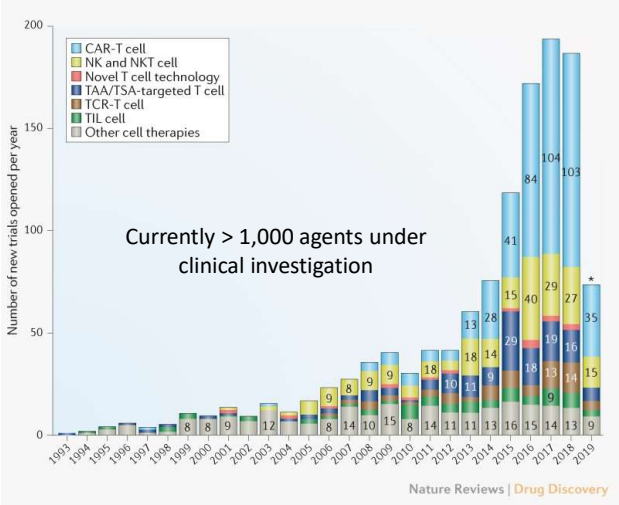


Development of additional clinically effective immunotherapies: Immune checkpoint blockade



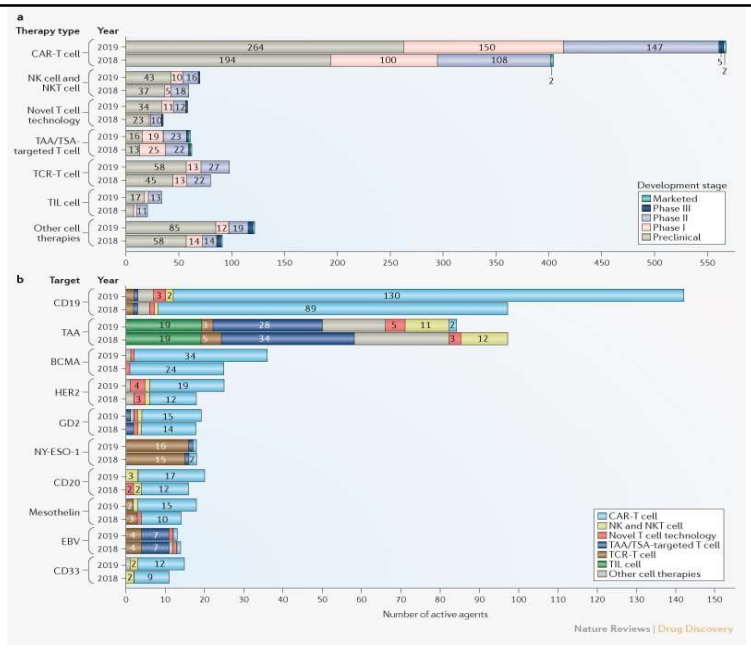
Donini et al. J Thor Dis, 2018

Development of additional clinically effective immunotherapies: Cell Therapies



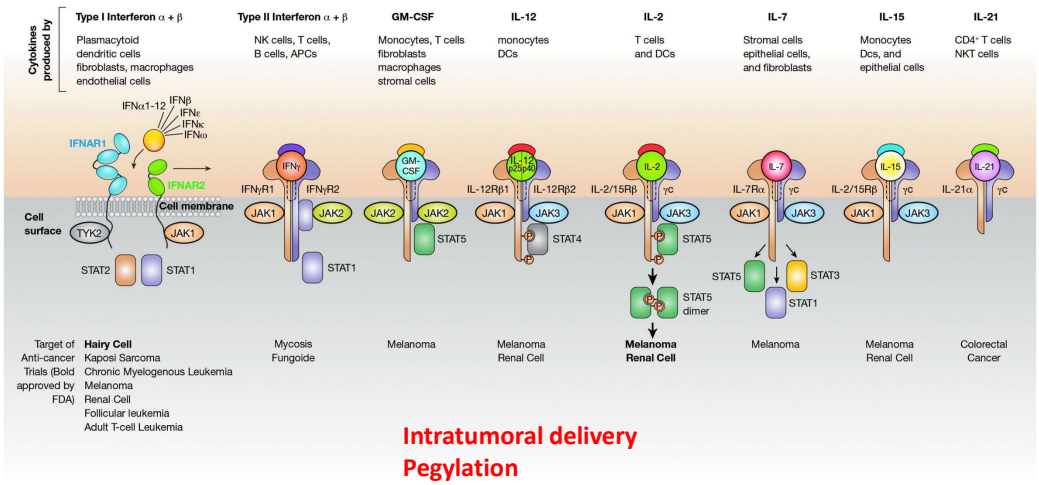
Yu et al. Nat Rev Drug Disc, 2019

Development of additional clinically effective immunotherapies: Cell Therapies



Yu et al. Nat Rev Drug Disc, 2019

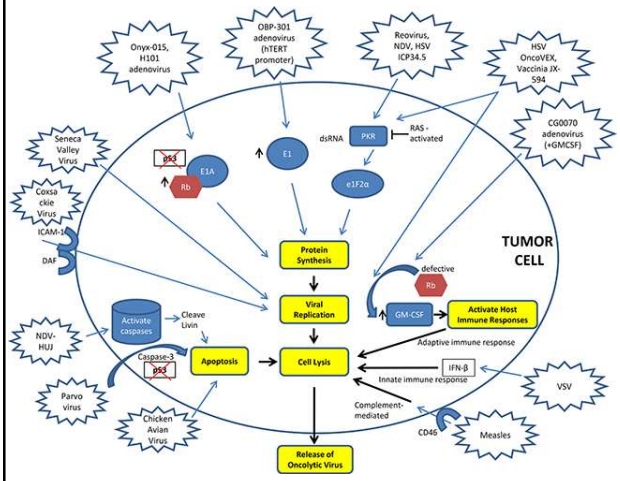
Development of additional clinically effective immunotherapies: Cytokines/Chemokines

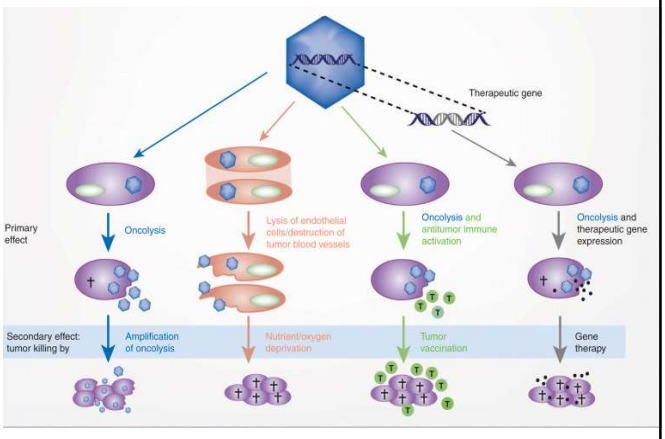


Intratumoral delivery
Pegylation
Fusion proteins

Conlon et al. J Interferon and Cytokine Res, 2019

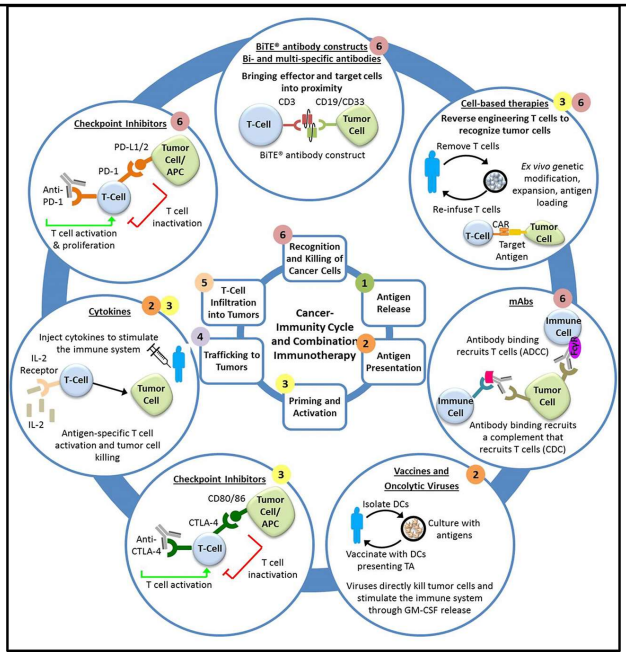
Development of additional clinically effective immunotherapies: Oncolytic Viruses





Fountzilas et al. Oncotarget 2017
Ungerechts et al. Mol Ther 2016

Clinical testing of immunotherapy combinations



Morrissey et al Clin Trans Sci 2016

Integration of immunotherapies with localized therapies

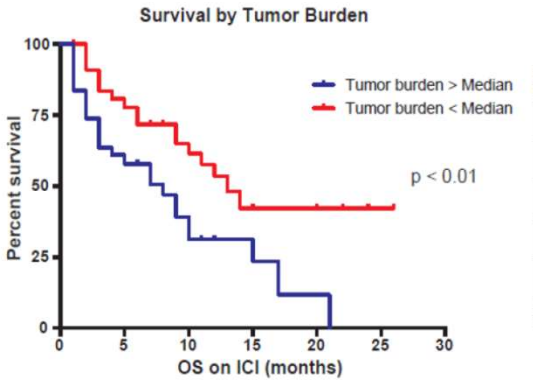


Fig. 3B. Patients whose TB was lower than the median showed improved OS.

Sridharan et al. Oral Oncology 2018.

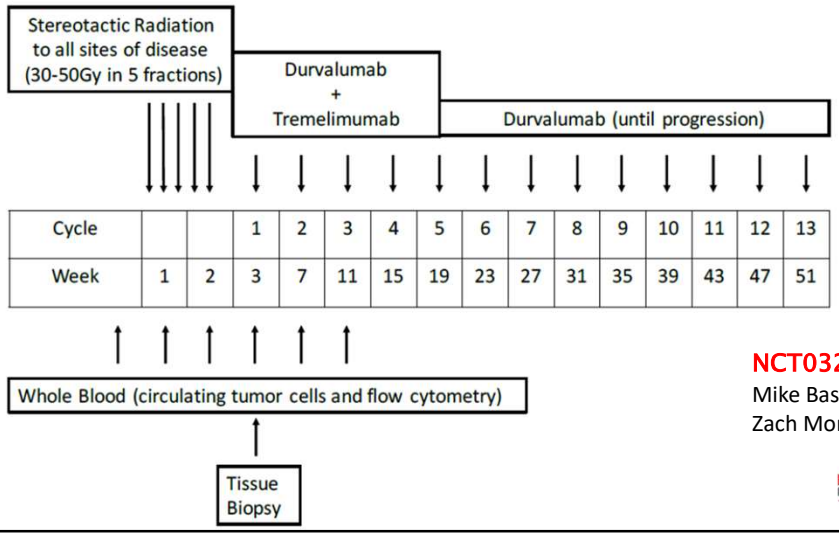
eTable 3. Association Between Baseline Sum of Target Lesion Diameters and 5-Year Survival in All Patients Receiving Nivolumab (N = 270)[a]

Sum of Target Lesion Diameters (mm)	5-Year Survivors	All Other Patients	*P* value
Melanoma Median (IQR) Range	n = 30 75 (48-134) 22-374	n = 77 111 (69-189) 10-377	.0427
RCC Median (IQR) Range	n = 9 98 (89-110) 42-236	n = 25 139 (88-191) 43-615	.0542
NSCLC Median (IQR) Range	n = 16 83 (62.5-117) 11-291	n = 113 95 (59-147) 10-292	.5084
All 3 tumor types Median (IQR) Range	n = 55 88 (52-116) 11-374	n = 215 109 (65-165) 10-615	.0244

[a]Analysis is based on *t* tests for comparing the 2 subsets of baseline sum of target lesion diameters.
IQR indicates interquartile range.

Topalian et al. JAMA Oncol 2019.

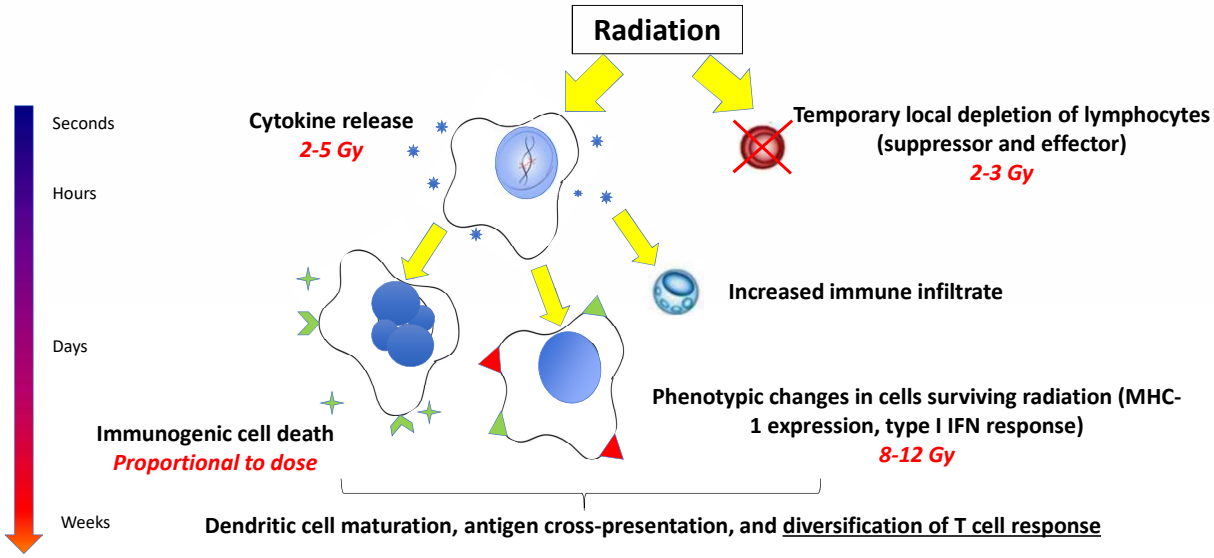
Phase Ib Study of Stereotactic Body Radiotherapy (SBRT) in Oligometastatic Non-small Lung Cancer (NSCLC) With Dual Immune Checkpoint Inhibition (NCT03275597)



NCT03275597

Mike Bassetti, Ticiana Leal, Andrew Baschnagel, Zach Morris, Josh Lang, and others

Radiation may overcome mechanisms of tumor immune escape



In situ vaccine = personalized immuno-oncology

Destroy cancer cells in a way that enables them to function as a potent, personalized immune stimulus and source of antigenicity for tumor-specific adaptive T cell immunity

The in situ vaccine effect, while very rare with radiation alone, may be clinically meaningful when combined with immune checkpoint blockade

FULL TEXT JAMA Oncology

Original Investigation

July 11, 2019

Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non–Small Cell Lung

Theelen WSME[1], Peulen HMU[2,3], Lalezari F[4], van der Noort V[5], de Vries JF[5], Aerts JGJV[6], Dumoulin DW[6], Bahce I[7], Niemeijer AN[7], de Langen AJ[1], Monkhorst K[8], Baas P[1].

- 76 pts NSCLC randomized to pembro or pembro + 8 Gy x 3
- **ORR at 12 wks = 18% vs 36% (P = .07)**
- Median PFS 1.9 mos vs 6.6 mos (P = .19)
- Median OS 7.6 mos vs 15.9 mos (P = .16)
- Largest benefit in patients with PD-L1–negative tumors
- No increase in treatment-related toxic effects

Table. Response to Treatment

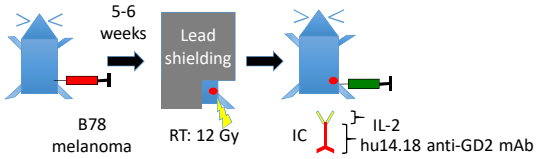
Response	Experimental Arm, No./Total No. (%) (n = 36)[a]	Control Arm, No./Total No. (%) (n = 40)[b]
Best overall response, No.		
Complete response	3	1
Partial response	14	8
Stable disease	9	10
Progressive disease	10	21
Objective response rate at 12 wk		
Overall[c]	13/36 (36)	7/40 (18)
PD-L1 TPS, %		
0	4/18 (22)	1/25 (4)
1-49	3/8 (38)	3/8 (38)
≥50	6/10 (60)	3/5 (60)
Disease control rate at 12 wk[d]	23/36 (64)	16/40 (40)

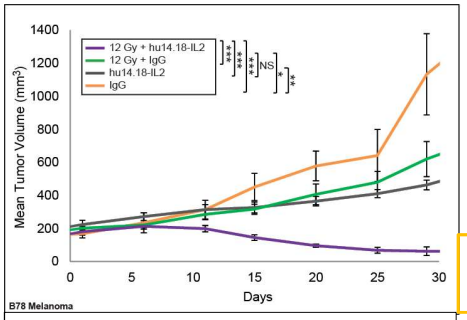
Abbreviations: PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

[a] Patients who received pembrolizumab therapy after stereotactic body radiotherapy.

[b] Patients who received pembrolizumab therapy alone.

Enhancing the *in situ* vaccination effect of external beam radiation with combinatorial local therapies





71% DF with T cell memory

Requires:
- Tumor GD2 antigen
- Host T cells
- Host Fcγ receptor and FasL

IT-hu14.18-IL2 With Radiation, Nivolumab and Ipilimumab for Melanoma (NCT03958383)

- Patients with metastatic melanoma with injectable site of disease
- Phase I study
  - A. Dose escalation IT-hu14.18-IL2 daily x 3
  - B. Radiation + IT-hu14.18-IL2
  - C. Radiation + IT-hu14.18-IL2 + anti-PD1
  - D. Radiation + IT-hu14.18-IL2 + anti-PD1 + anti-CTLA4

Study Chair and PIs: Paul Sondel, Mark Albertini, Zachary Morris

Morris *et al*. Cancer Res, 2016

Enhancing the *in situ* vaccination effect of external beam radiation with combinatorial therapies

Phase II Study of Bempegaldesleukin (NKTR-214) Together with Palliative Radiation and anti-PD-1 Checkpoint Blockade in Patients with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC)

Schematic of Study Design:

Screen patients with biopsy-proven **recurrent/metastatic head and neck squamous cell** carcinoma who are taking or will be starting anti-PD-1 therapy and have a need for palliative radiation.

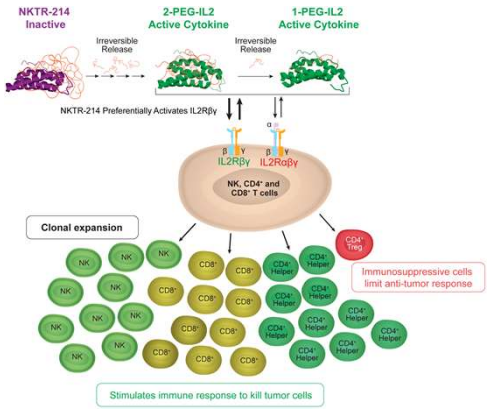
Cycle 1
Anti-PD-1* and NKTR-214

⇩

Cycle 2 Day -3 to -7
Complete palliative radiation therapy

⇩

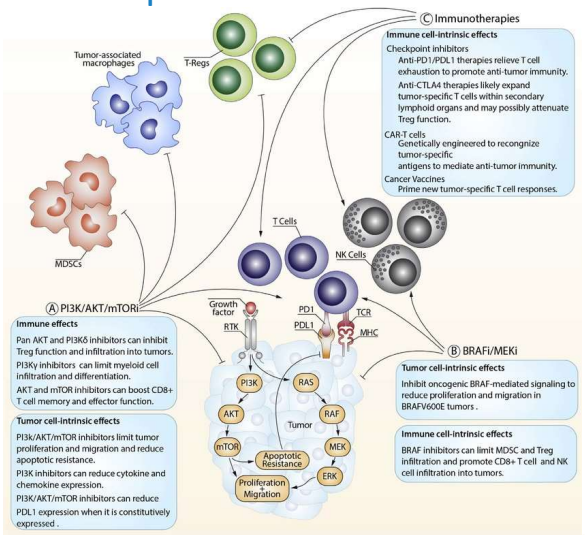
Cycle 2+
Anti-PD-1* and NTRK-214



Study Chairs: Zach Morris and Paul Harari **Study PIs**: Adam Burr and Justine Bruce

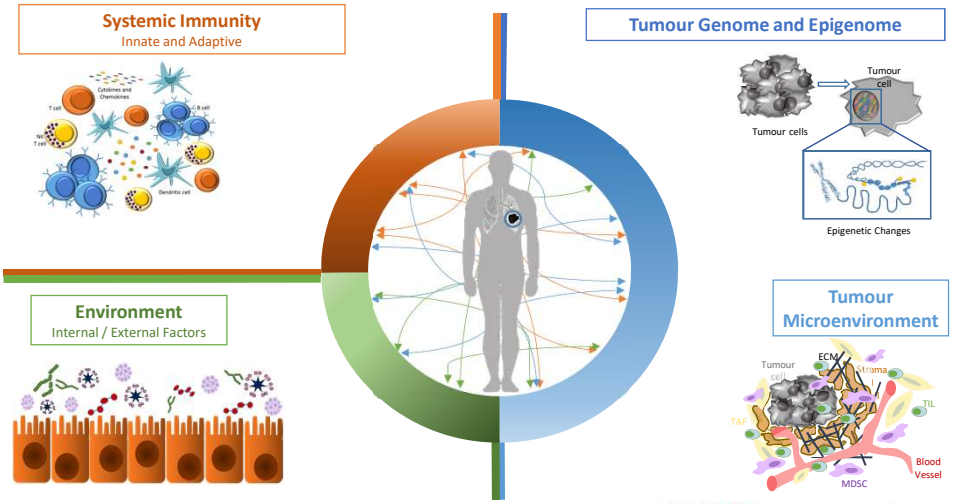
Integration of immunotherapies with other systemic therapies

- Chemotherapeutics
- Tyrosine kinase inhibitors/signaling blockade
- Anti-angiogenesis agents
- Therapies targeting tumor metabolism



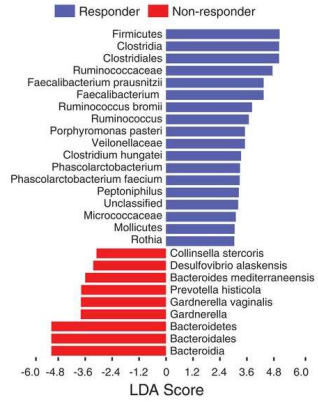
O'Donnell et al. Sem Cancer Bio 2017

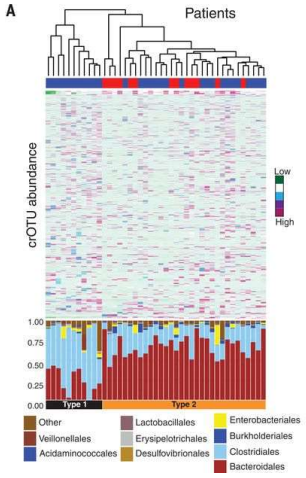
Novel strategies for systemic and/or tumor immunomodulation

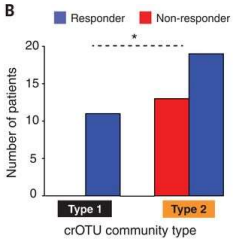


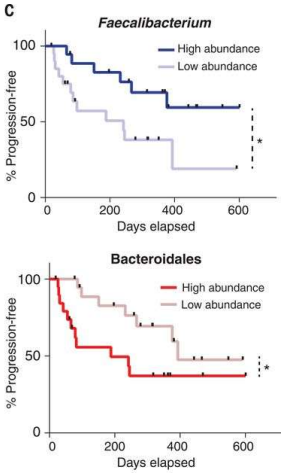
Cogdill, Andrews, Wargo - *British Journal of Cancer* 2017

Novel strategies for systemic and/or tumor immunomodulation – Tumor Microbiome



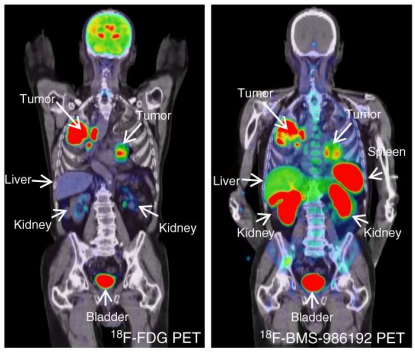


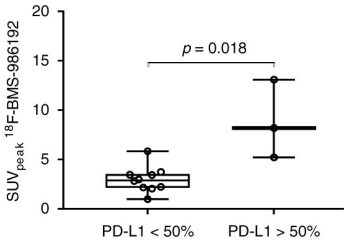


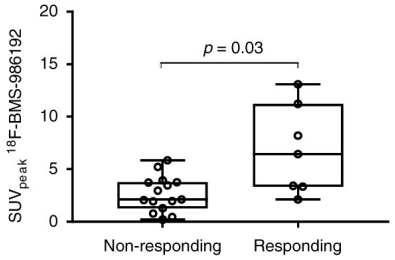


Gopalakrishnan et al Science 2018

Development of companion imaging and strategies for personalized immunotherapy

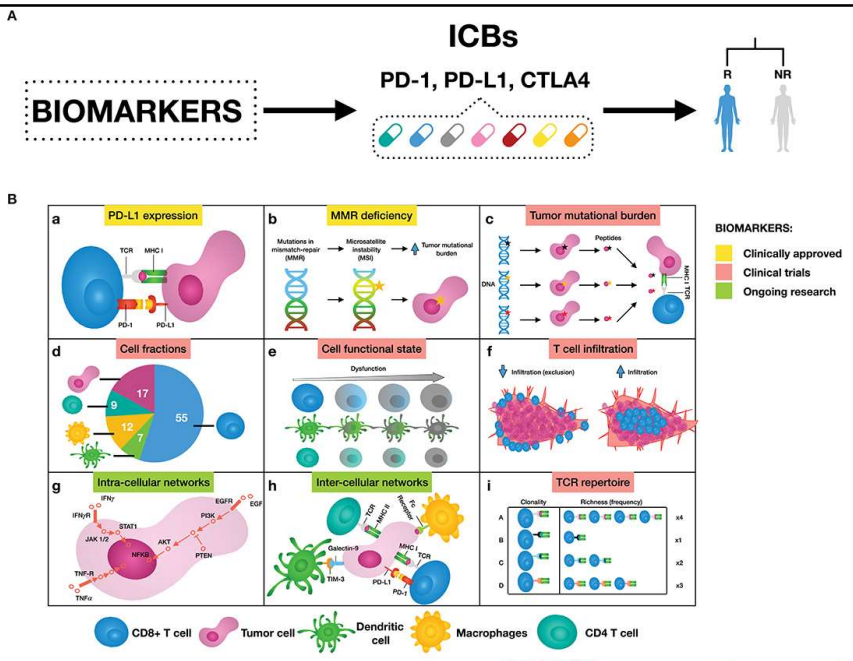






Niemeijer et al. Nat Comm 2018

Advancement of clinical correlative assays for immunotherapy



Lapuente-Santana et al. Front Oncol 2020

Expanding access to cancer immunotherapy globally

- Cancer is the second leading cause of death globally
  - Estimated 10 million deaths annually
  - Globally, about 1 in 6 deaths is due to cancer
- Approximately 70% of deaths from cancer occur in low- and middle-income countries
- More than 90% of high-income countries reported treatment services are available compared to less than 30% of low-income countries

WHO https://www.who.int/news-room/fact-sheets/detail/cancer

Questions and Discussion