



A Response to Immunotherapy in Microsatellite Stable Colorectal Cancer

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Society for Immunotherapy of Cancer

#SITC2019

Disclosures

- None

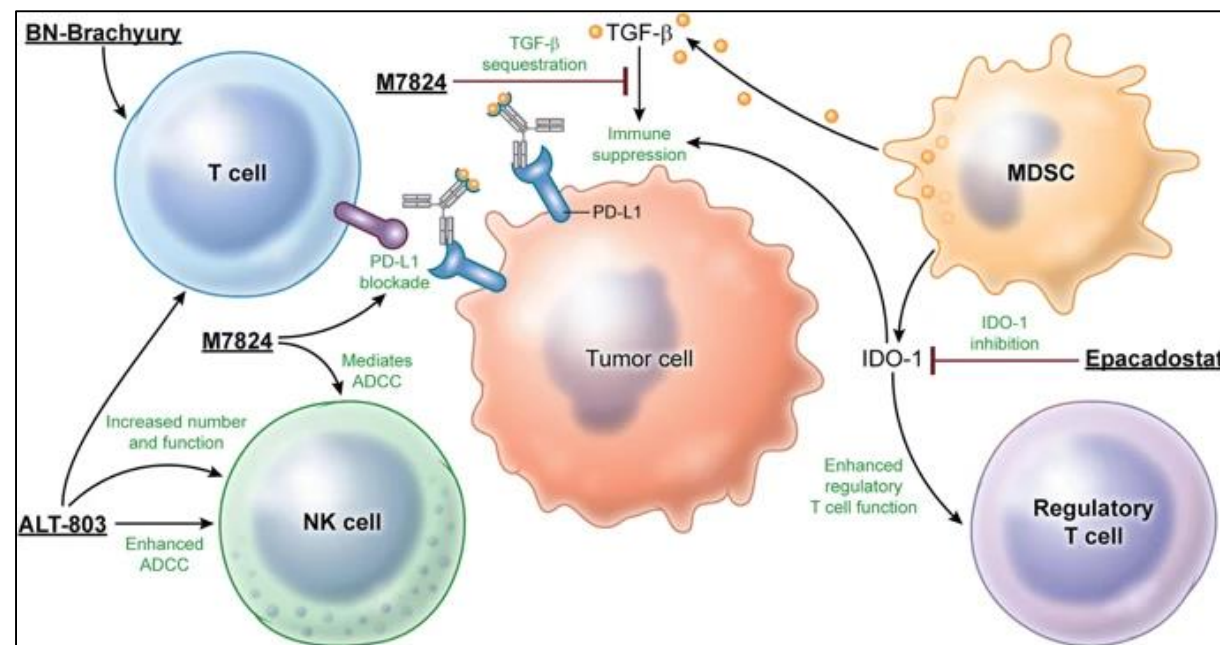
NCI Immunotherapy Fellowship 2018-2019

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- Mentors: James L. Gulley M.D., Ph.D., F.A.C.P. and Ravi Madan, M.D.



• QuEST1 (Quick Efficacy Seeking Trial)

- Castration resistant prostate cancer (CRPC)
- Adaptive design trial to rapidly interrogate safety and efficacy of combination immunotherapy in CRPC
- Three CRPC treatment arms
 - **BN-Brachyury vaccine + Bintrafusp alfa**
 - BN-Brachyury + Bintrafusp alfa + **N-803**
 - BN-Brachyury + Bintrafusp alfa + N-803 + **Epacadostat**
- Immune correlatives
 - PBMC Analyses
 - Immunophenotype
 - Antigen specific T cells
 - T cell clonality
 - Serum cytokines
 - Soluble factors
- Dose finding safety arm (solid tumors)
 - **Bintrafusp alfa + N-803**



Redman JM, Steinberg SM, Gulley JL. J Immunother Cancer 6:91, 2018

Immunotherapy for Metastatic Colorectal Cancer

- **DNA Mismatch Repair *deficient* (MSI-H)**
 - FDA approvals for Pembrolizumab, Nivolumab +/- Ipilimumab
 - ORR = 26-57%
- **DNA Mismatch Repair *proficient***
 - Minimal activity
 - Anti-PD-1/PD-L1: 0%
 - Anti-CTLA +/- anti- PD-1: 2-5%

Le et al. NEJM. 2015
Overman et al. J Clin Oncol. 2016
Chung et al. J Clin Oncol. 2010
Topalian et al. NEJM. 2012
Brahmer et al. NEJM. 2012

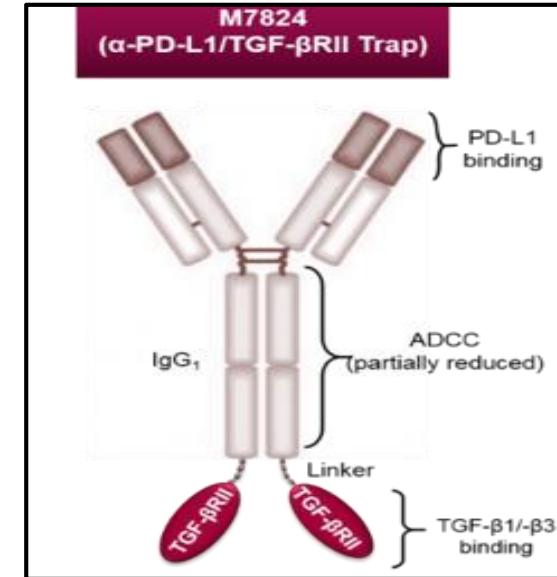
Case History

42 year male with microsatellite stable rectal cancer

- Diagnosed with T3N1 NRAS mutant rectal adenocarcinoma in 2015
 - Neoadjuvant capecitabine plus radiotherapy
 - Status post abdominoperineal resection
 - 12 cycles of adjuvant FOLFOX (completed June 2016)
- Multifocal, bilateral recurrence in lung 2017
 - Status post wedge resection and radiotherapy
- Recurrence in lumbar vertebrae 2018
 - Status post radiotherapy to L1, L3
- Enrolled (April 2018) on NCT03384316:
 - Recombinant Ad5 (CEA/MUC1/Brachyury) Based Immunotherapy Vaccine
 - Progressive disease September 2018
- Enrolled (November 2018) on NCT03493945:
 - **QuEST1 trial**, Arm 1.1
 - **Bintrafusp alfa** (M7824) 1,200 mg IV q2weeks + **N-803** 15 mcg/kg SC q2weeks.

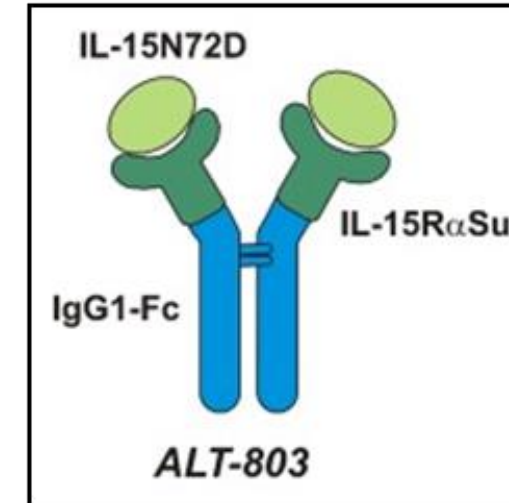
Bintrafusp alfa (M7824)

- Bifunctional fusion protein
 - IgG1 anti-PD-L1 monoclonal antibody
 - TGF β receptor type 2 'TGF β trap'
 - Orphan drug status for biliary tract cancer

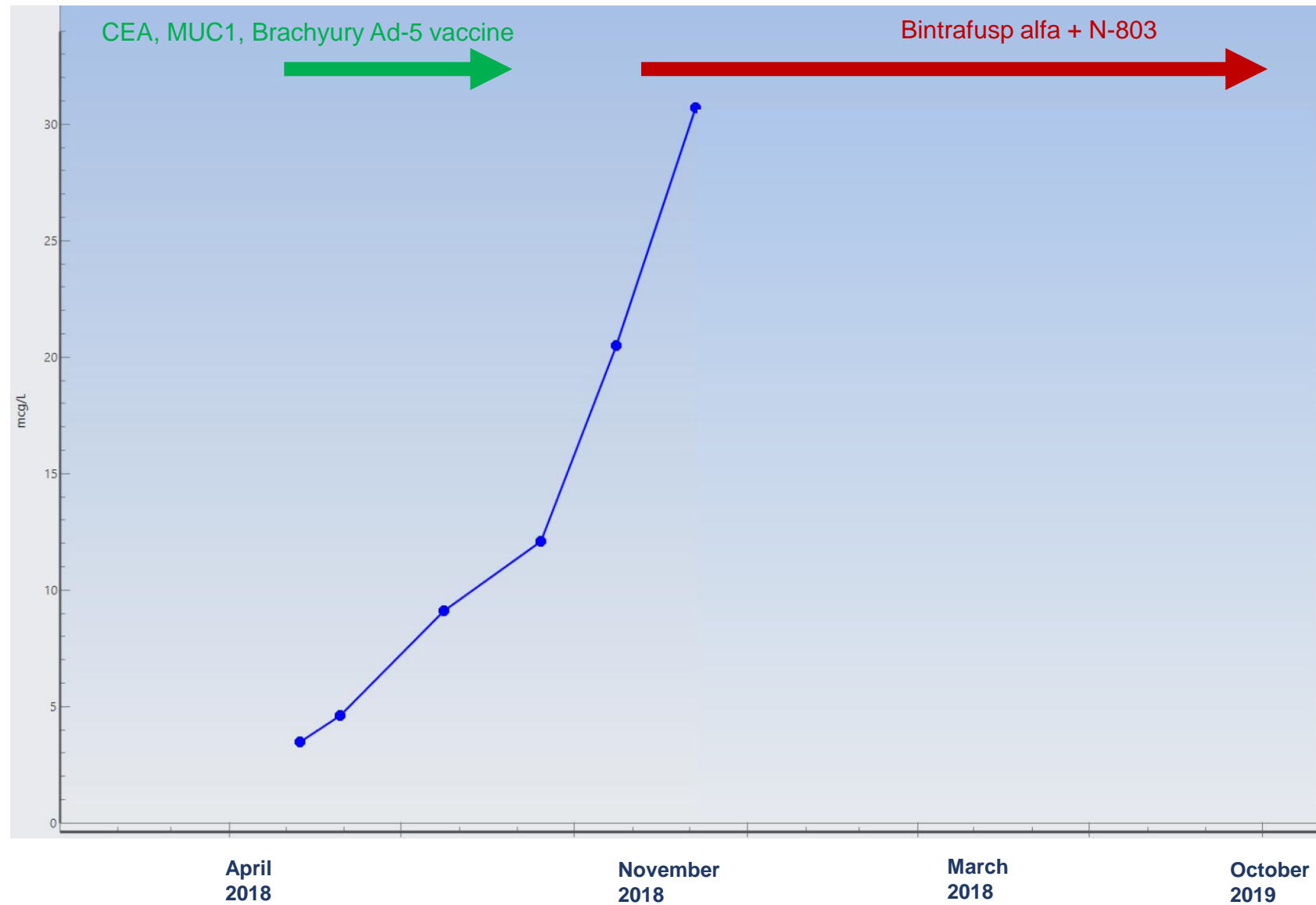


N-803 (ALT-803)

- Interleukin-15 superagonist complex
- Expands and activates effector T cells and NK cells



Changes in Serum CEA



10/23/2018

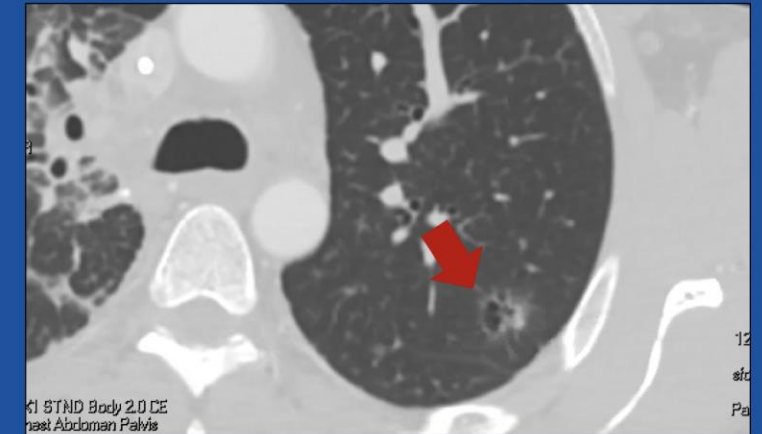
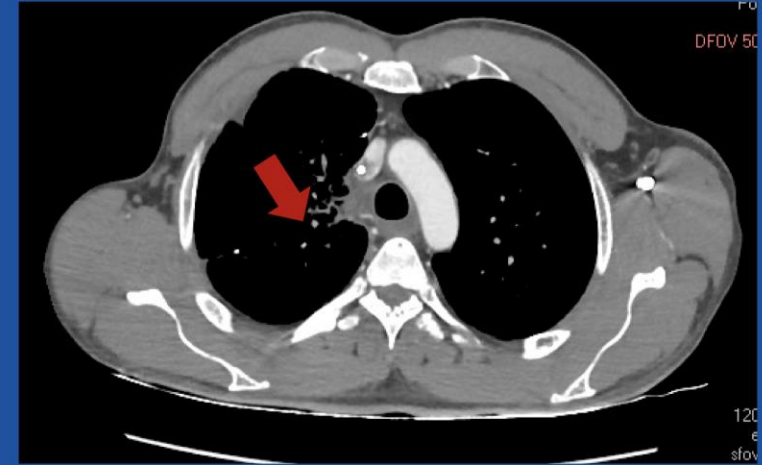


11/20/18

- began
Bintrafusp alfa +
N-803



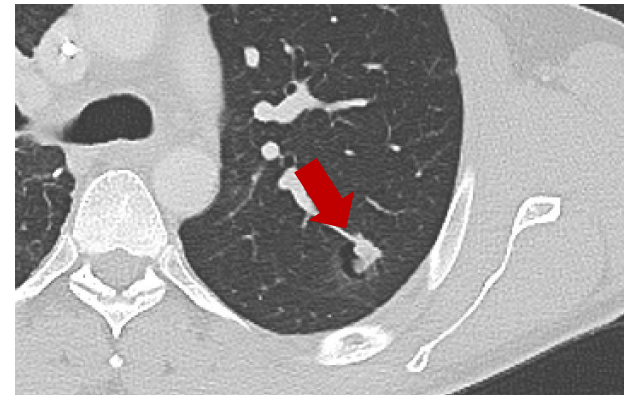
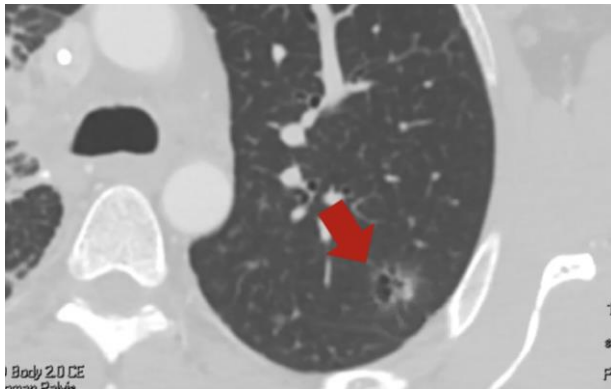
1/15/2019



Case Update as of 10/10/2019

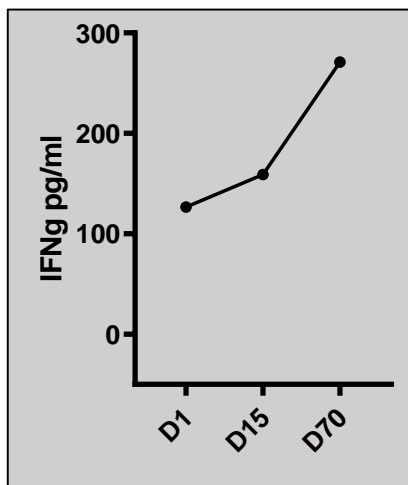
43 year male with microsatellite stable rectal adenocarcinoma metastatic to lung and bone

- 10+ months on treatment
 - Bintrafusp alfa + N-803 every 2 weeks
- 9+ month confirmed partial response as of 9/23/19 imaging
 - Regrowth of tumor in LUL cavitory nodule
 - Radiotherapy planned



Select Immune Correlates

Serum IFN- γ



Expansion of Multifunctional Ag-specific T cells
(Post vs Pre M7824 + N-803)

+	++		Brachyury		MUC1		CEA	
3x pre	10x pre	Day (vs Pre)	CD4	CD8	CD4	CD8	CD4	CD8
Or if no pre, >100 post	Or if no pre, >1000 post	D15	+	+	+	+		+
		D71	+			+		
		D154	++	++	+	++	+	

- Multi-functional antigen-specific T-cells to CEA, MUC1, brachyury were transiently detectable after treatment on the CEA, MUC1, brachyury Ad-5 vaccine clinical trial
- These cells were undetectable/decreased pre-treatment with Bintrafusp alfa + N-803
- These cells reappeared after treatment with Bintrafusp alfa + N-803

Summary

- Confirmed, durable partial response observed in a MSS metastatic rectal adenocarcinoma patient receiving Bintrafusp alfa (anti-PD-L1/ TGF β Trap) + N-803 (IL-15 agonist)
- Associated with detectable serum IFN- γ pre-treatment, followed by increase on treatment
 - IFN- γ as a biomarker candidate
- Response associated with prior, consecutive treatment with CEA, MUC1, brachyury Ad-5 vaccine
- Reappearance of CEA-, MUC1-, and brachyury-specific T cells after Bintrafusp alfa + N-803 treatment
- Bintrafusp alfa + N-803 + CEA, MUC1, brachyury Ad-5 vaccine combination is of therapeutic interest in microsatellite stable/mismatch repair proficient colorectal cancer

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