Implications of Microsatellite Instability (MSI) for Treatment

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Disclosures

- Consulting:
  - Merrimack, BMS, Roche, Karyopharm
- Research Funding:
  - Roche, Merck, Celgene, Medimmune, BMS, Amgen

Guidelines and FDA Indications

Testing for Microsatellite Instability (NCCN)

- The panel recommends universal MMR or MSI testing for all patients with a personal history of colon or rectal cancer to identify individuals with Lynch syndrome, **to inform use of immunotherapy in patients with metastatic disease,** and to inform decisions for patients with stage II disease.

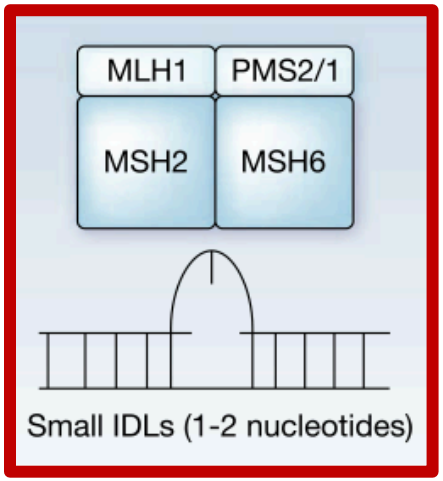
Treatment Recommendations

- **<u>FDA label for Pembrolizumab:</u>**
  - "For the treatment of adult and pediatric patients **with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient**"
    - **"solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options"**
    - **"colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan"**

- **<u>NCCN:</u>**
  - **Recommends nivolumab or prembrolizumab as treatment options in patients with metastatic MMR-deficient colorectal cancer in second- or third-line therapy.**

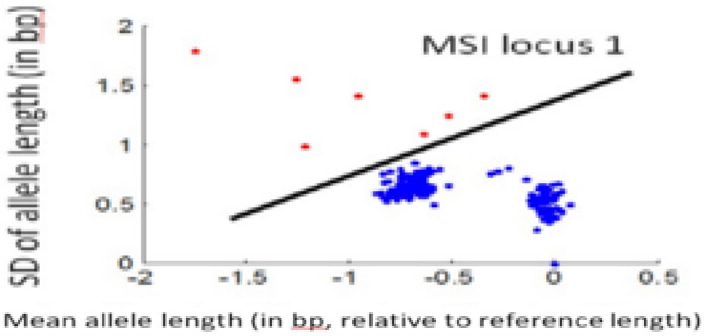
NCCN update 11/23/2016; FDA label 5/23/2017

dMMR Testing



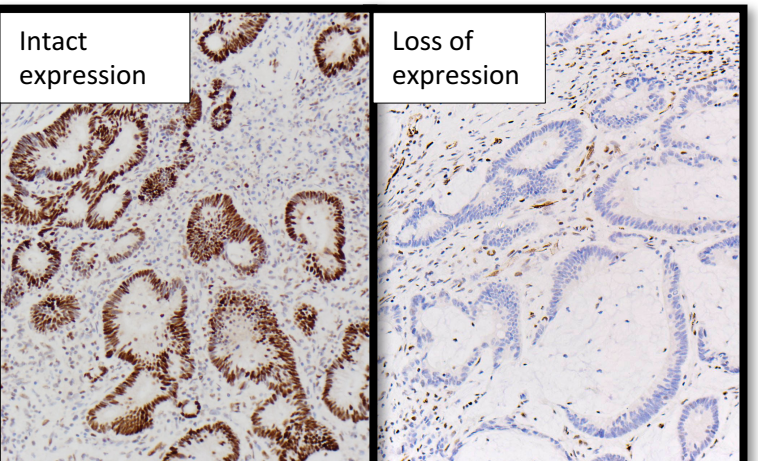
Next-generation Sequencing

Foundation Medicine:
variance at 114 MSI loci



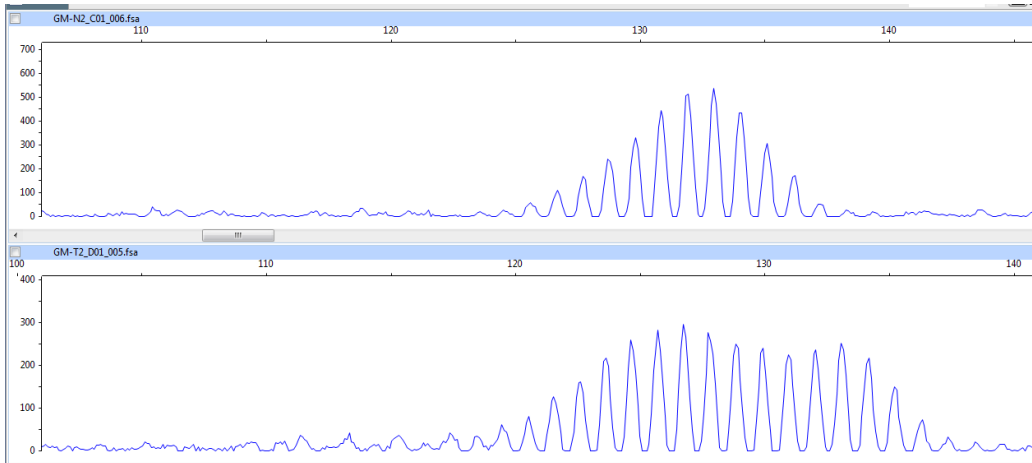
Immunohisto-chemistry

Complete loss of expression in one of the MMR proteins = MSI-high



Polymerase Chain Reaction

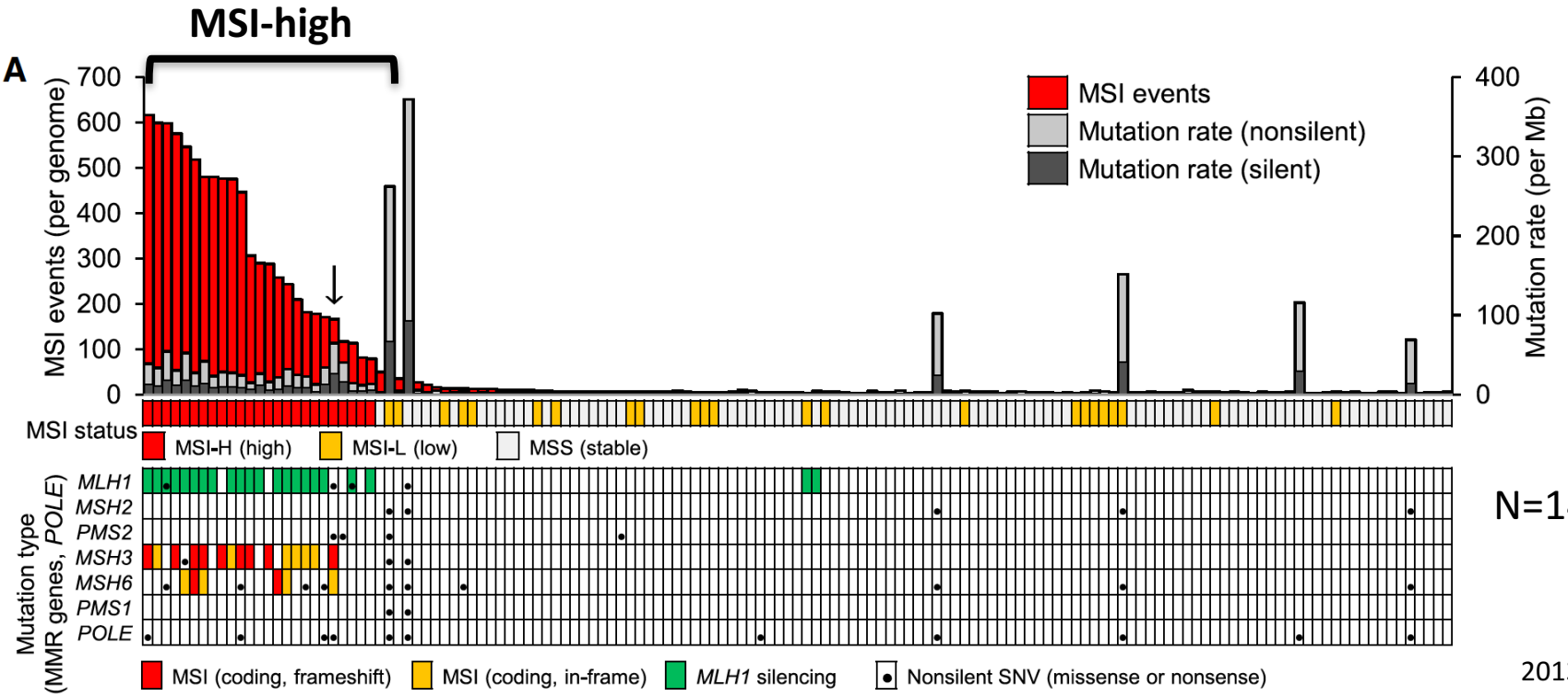
Panel of 5 or more microsatellites with allelic shift in 2 (>30%) or more markers = MSI-high



dMMR or MSI-H CRC

Stage	MSI-H
II	22%
III	12%
IV	4%

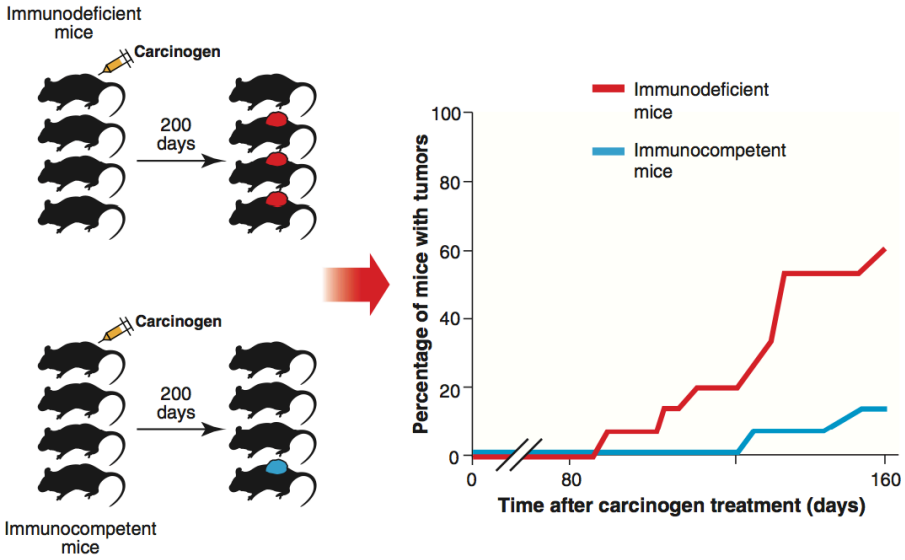
- Inherited mutations in MMR (HNPCC or Lynch). **≈1/3**
- Sporadic loss of MMR by MLH-1 methylation or biallelic somatic genomic alteration. **≈2/3**



N=141

2013 Kim et al. Cell

Tumor Rejection and Neoantigens



Tumor Antigens:

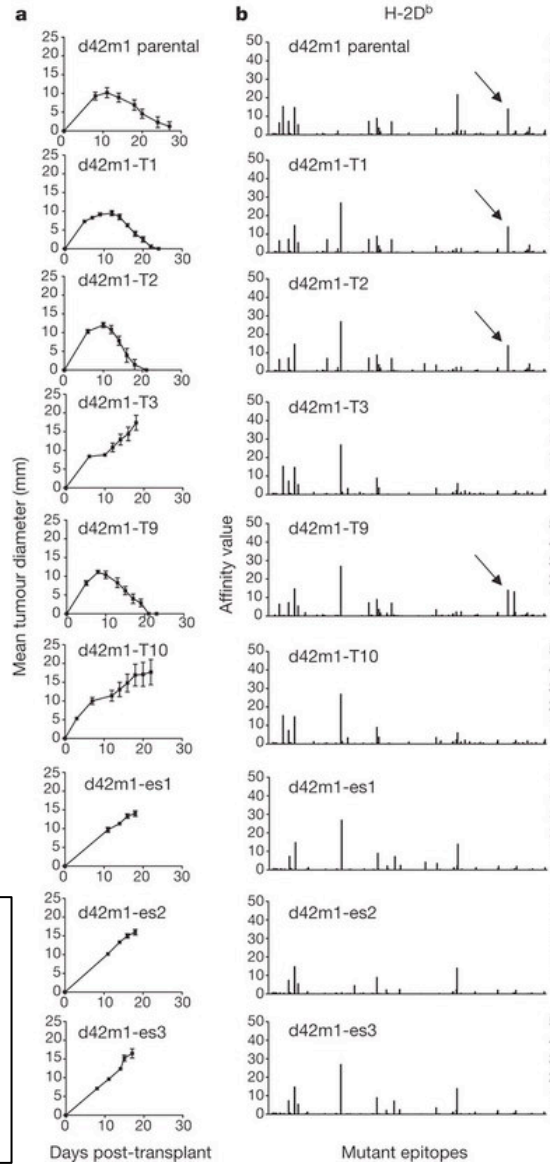
Differentiation (melanocyte differentiation antigens…)

Overexpressed (HER-2…)

Viral (HPV proteins…)

Cancer/testis (MAGE, NY-ESO-1…)

Mutational (p53…)



Immunogenic methylcholantherene-induced sarcoma cell lines from Rag2-/- mice demonstrate ≈20% tumor rate in naïve wildtype mice

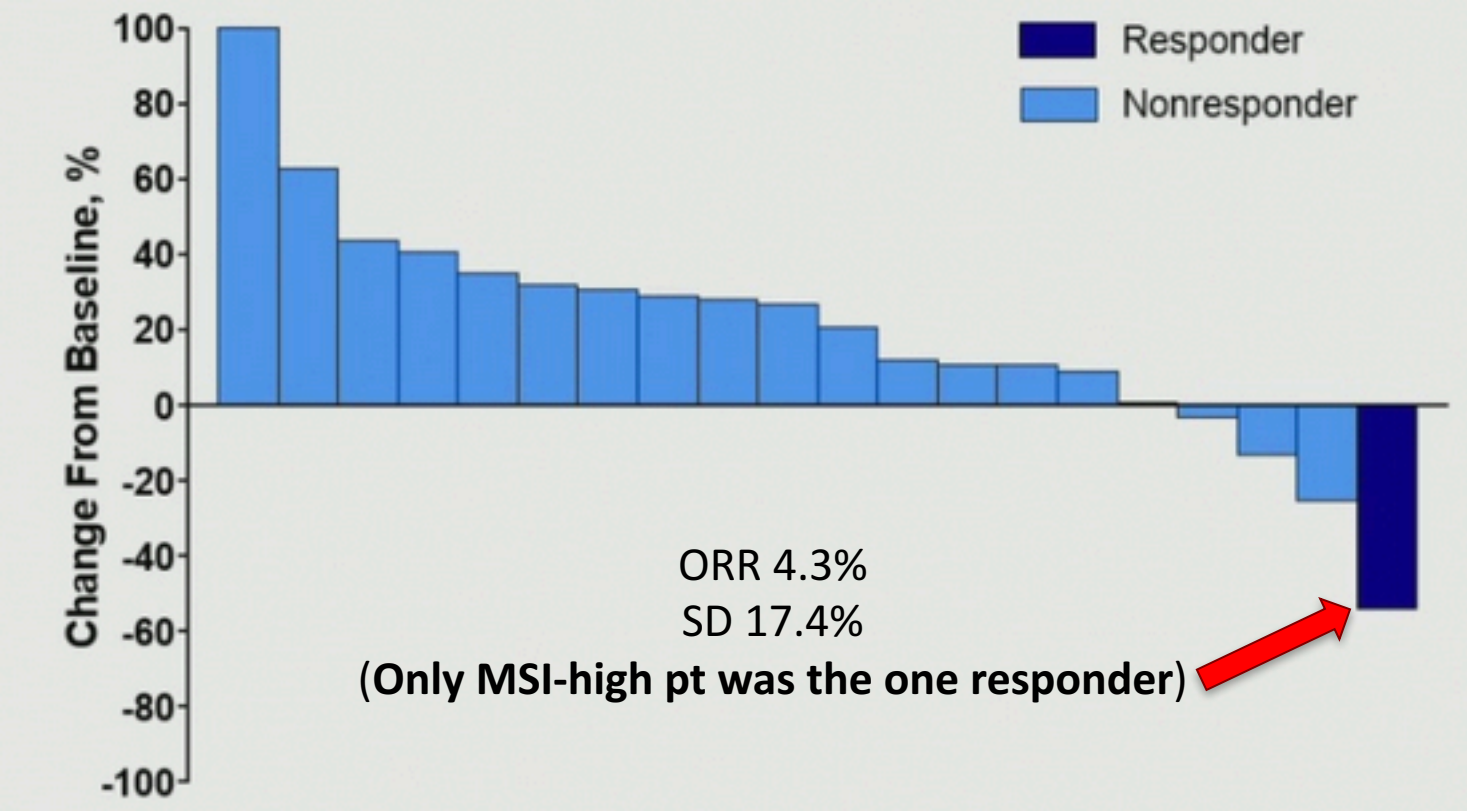
Spectirn β-2 R913L mutation predicted and cloned from TIL

Matsushita A et al. Nature (2012); 482 (7385); 400-4

KEYNOTE-028 for PDL1+ CRC

- Pembrolizumab 10mg/kg IV q2wks
- PD-L1+: “membranous PD-L1 expression in ≥1% of cells in tumor and stroma”

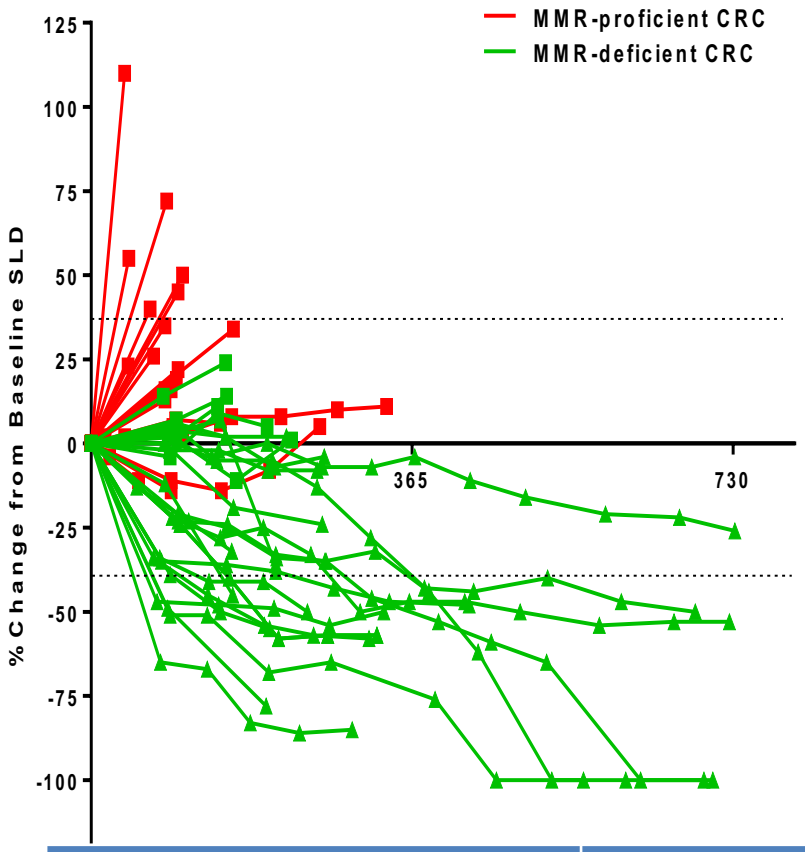
33/137 (24.1%) PD-L1+ with 23 enrolled

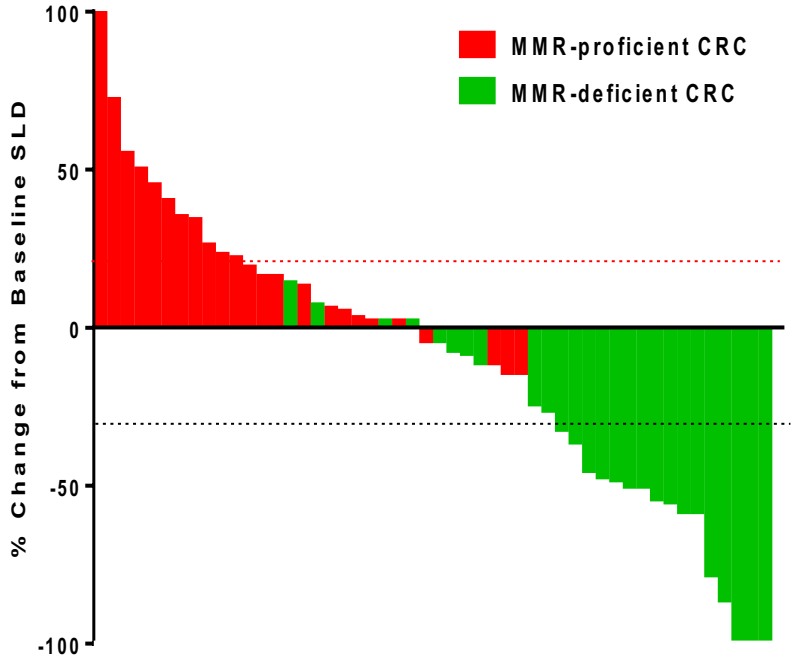


O’Neil et al. ESMO 2015

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

The NEW ENGLAND JOURNAL *of* MEDICINE





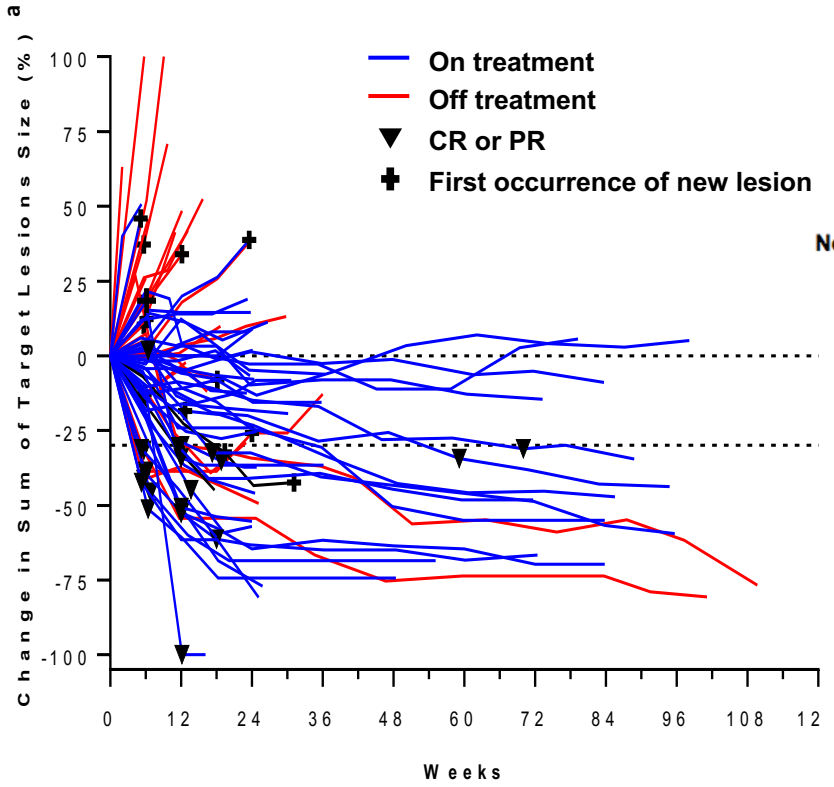
	MMR-deficient CRC, N=28	MMR-proficient CRC, N=25
Response Rate	**57%**	0%
Disease Control Rate	**89%**	16%

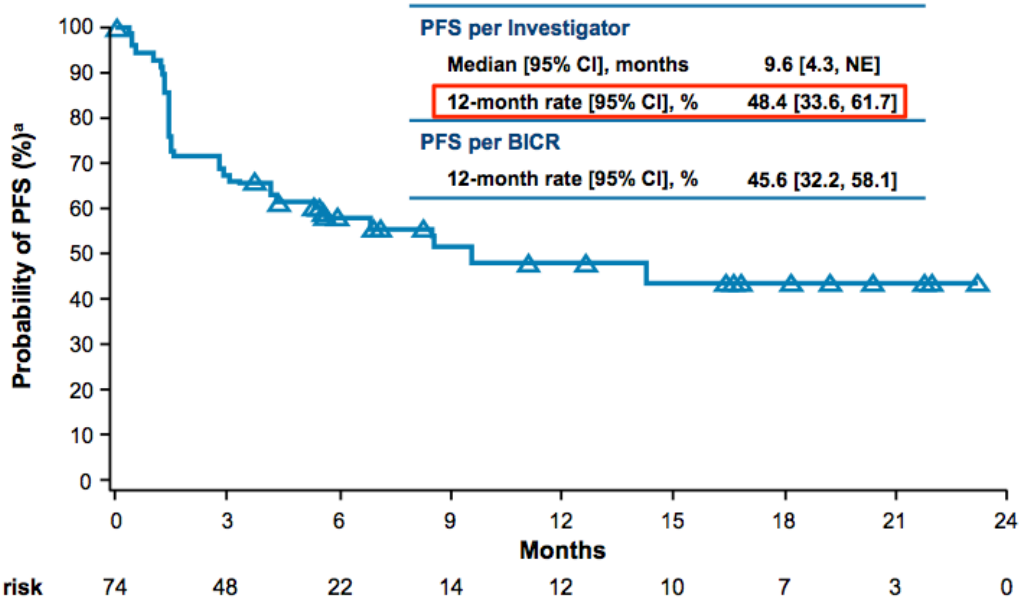
Le DT, et al. NEJM 2015 and *ASCO 2016*

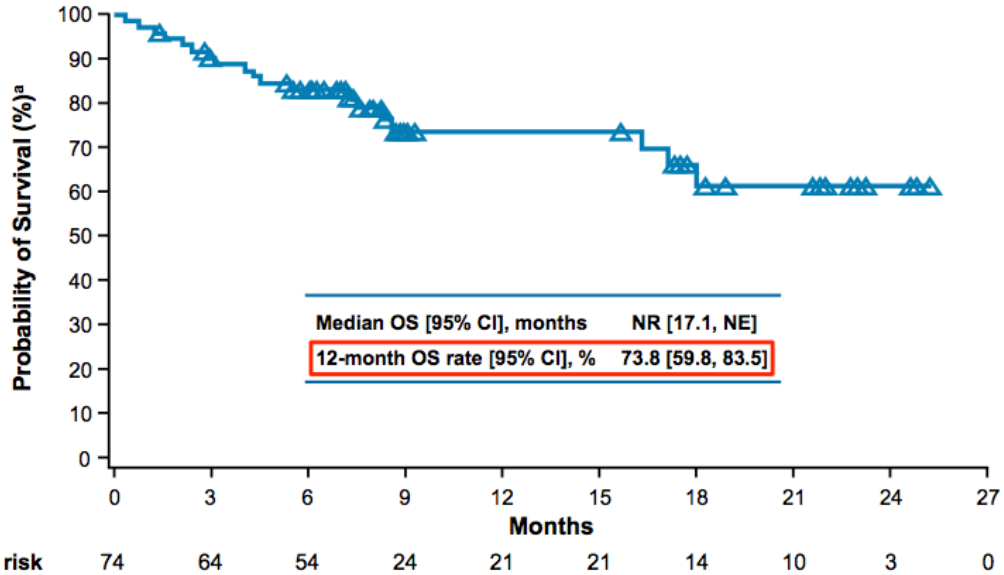
dMMR CRC: Nivolumab Monotherapy

RR 31%
SD 39%
PD 24%

Disease Control ≥12weeks in 69%

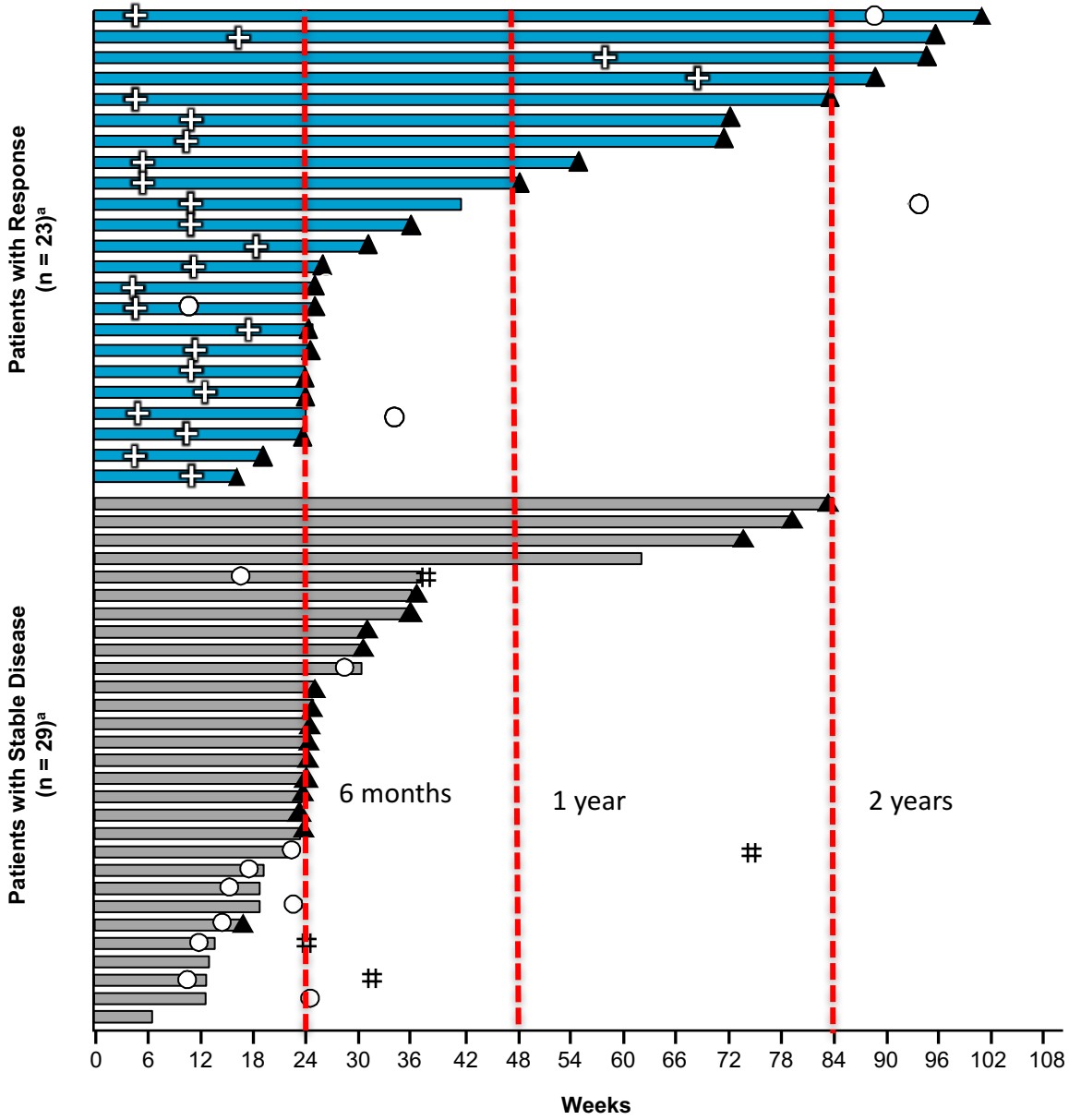






Overman et al. Lancet Oncology 2017 in press

Characterization of Response and Stable Disease

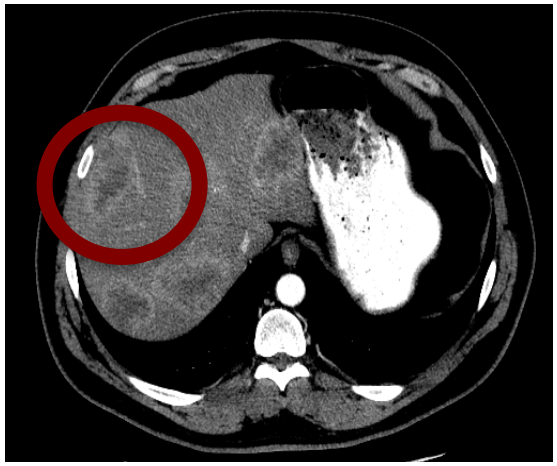


Investigator Assessed

- Median TTR: 2.8 months
- Median DOR: not reached
- 83% (19/23) responses ongoing

▲ Censored
○ Last dose when patient off treatment
✛ First response
Death

DOR, duration of response; TTR, time to response. [a] Investigator assessed dMMR/MSI-H by local laboratory.

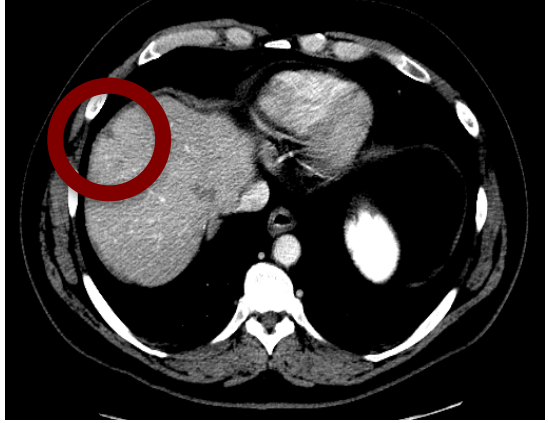


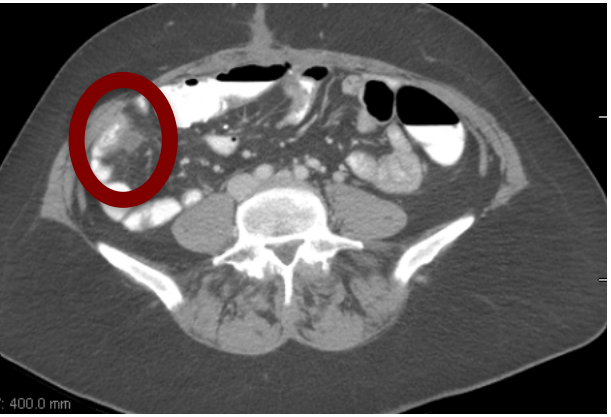
6/12/2014

Nivolumab 1yr 5m

Lynch syndrome
BRAF wt

11/22/2015



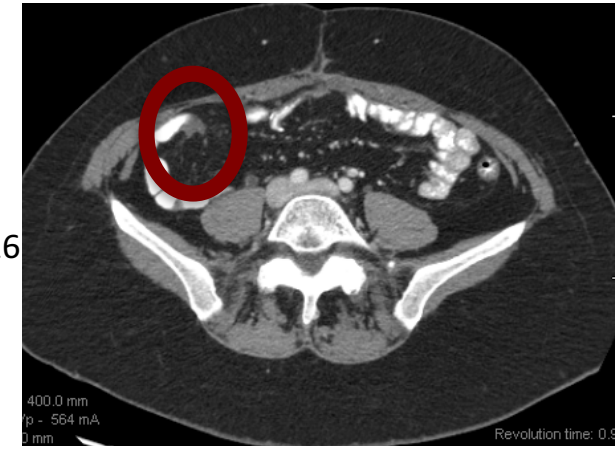


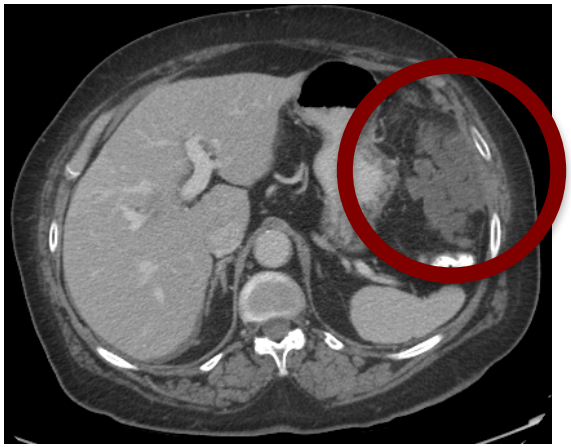
11/11/2014

Nivolumab 2yr 1m

Lynch syndrome
MLH1 germline
BRAF wt

12/30/2016



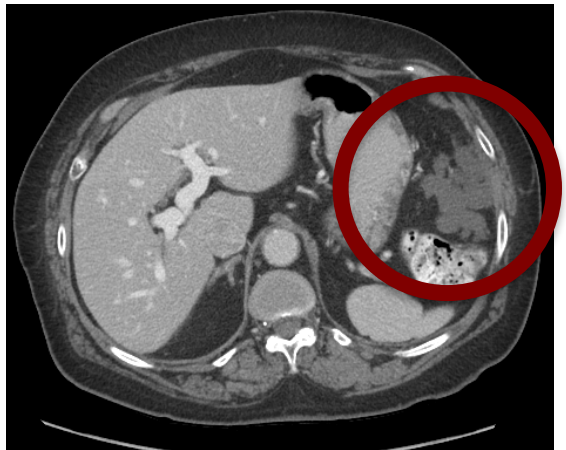


12/8/2015

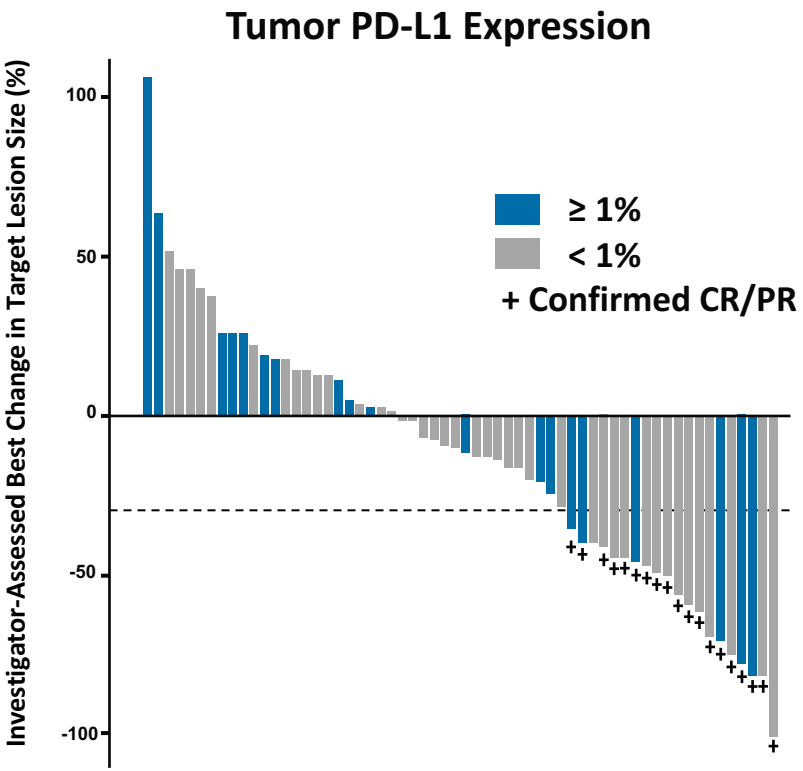
Nivolumab 1yr 2m

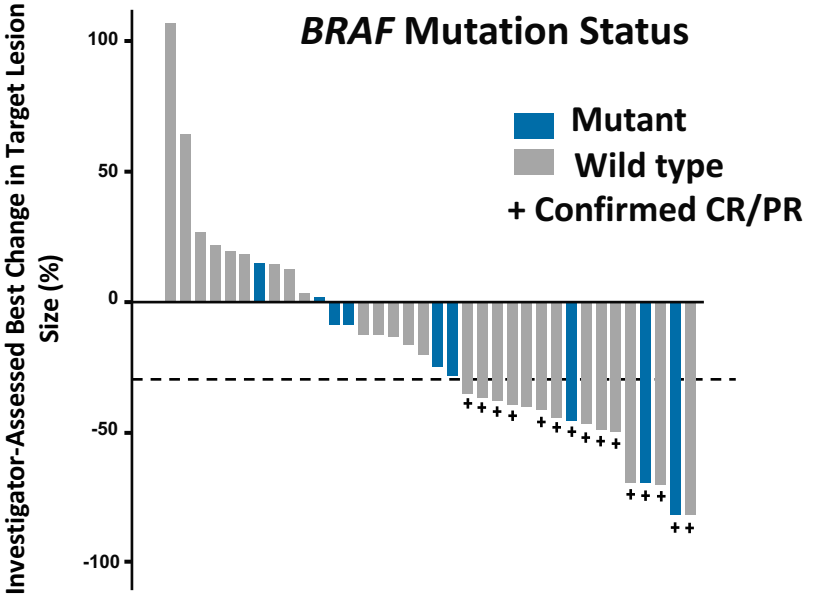
MLH1/PMS2 loss
BRAF V600E

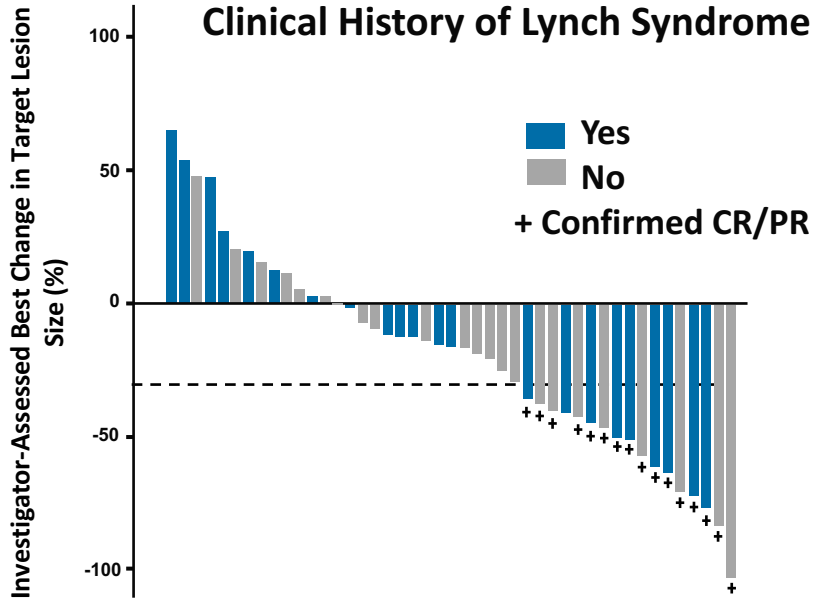
2/28/2017



Reduction in Target Lesions Regardless of PD-L1 Expression, BRAF or Lynch History

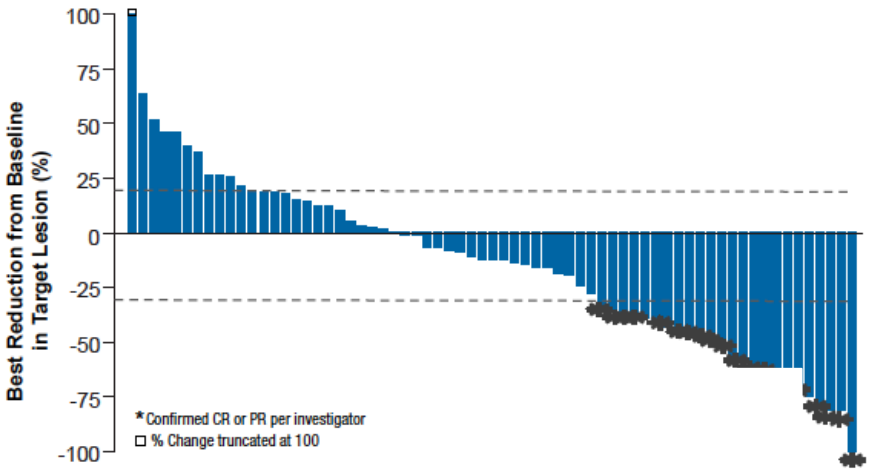






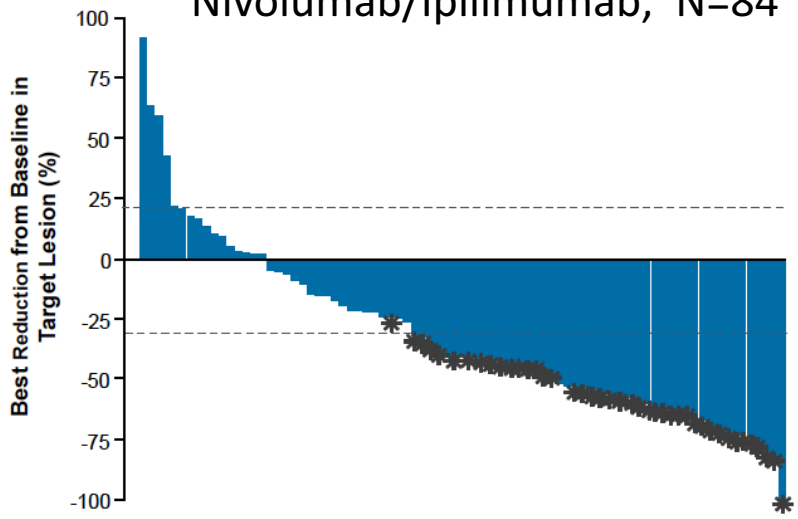
dMMR CRC Nivolumab vs. Nivolumab/Ipilimumab: Checkmate 142

Nivolumab, N=77

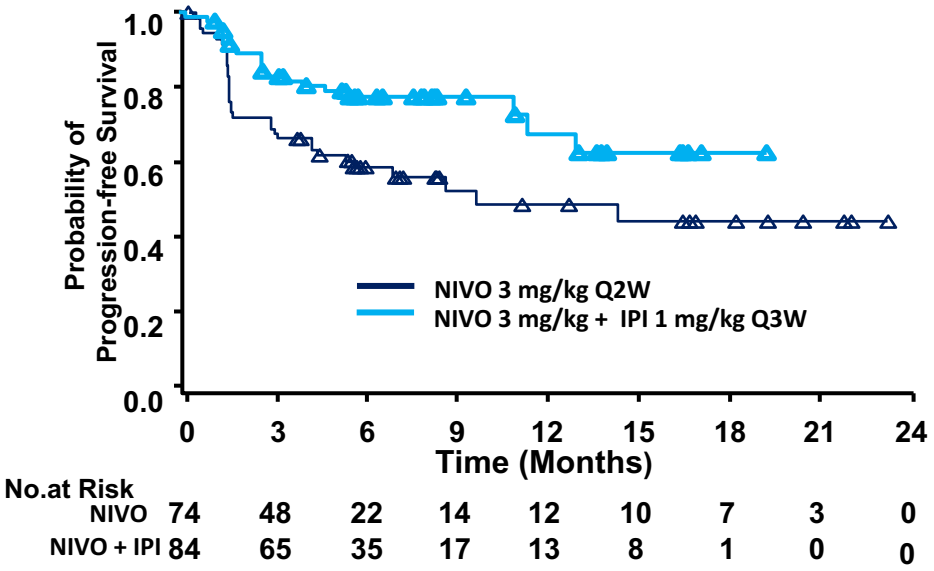


ORR 31%
≥12wk DCR 69%
12m PFS 48%

Nivolumab/Ipilimumab, N=84



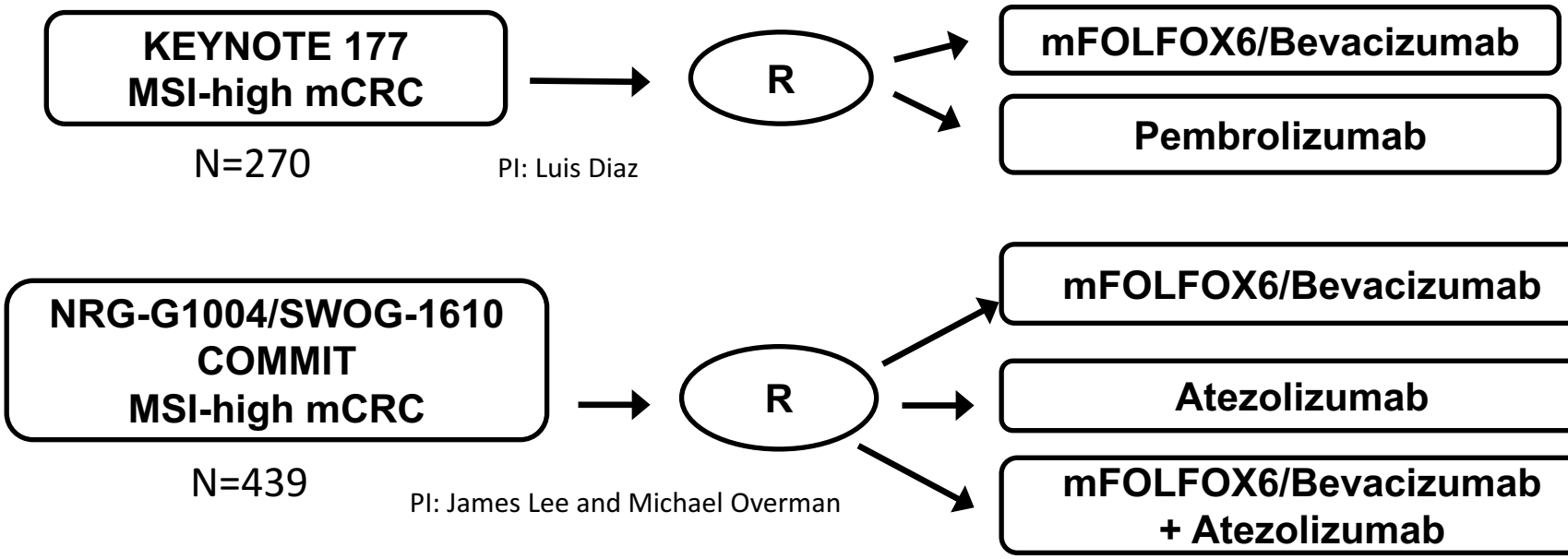
ORR 55%
≥12wk DCR 79%
12m PFS 77%



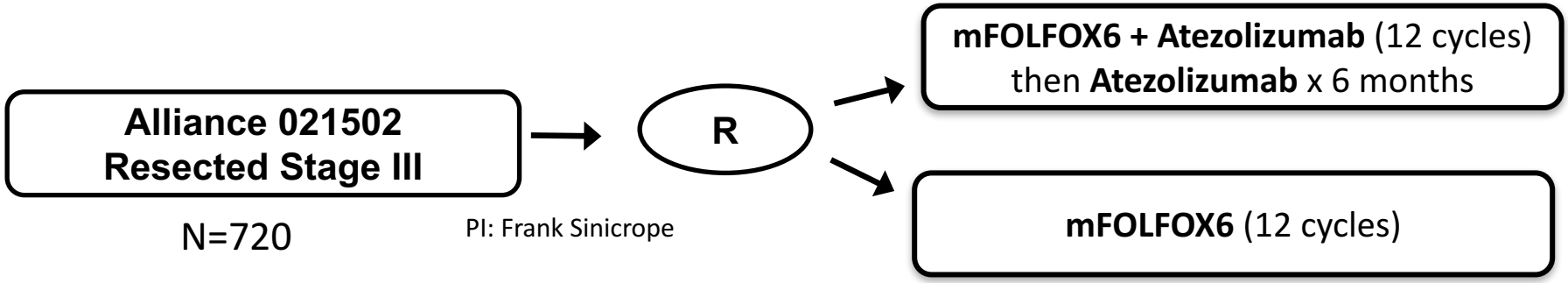
Overman Lancet Onc 2017 in press
Andre et al. ASCO 2017 a3531

MSI-h/dMMR Phase III CRC Trials

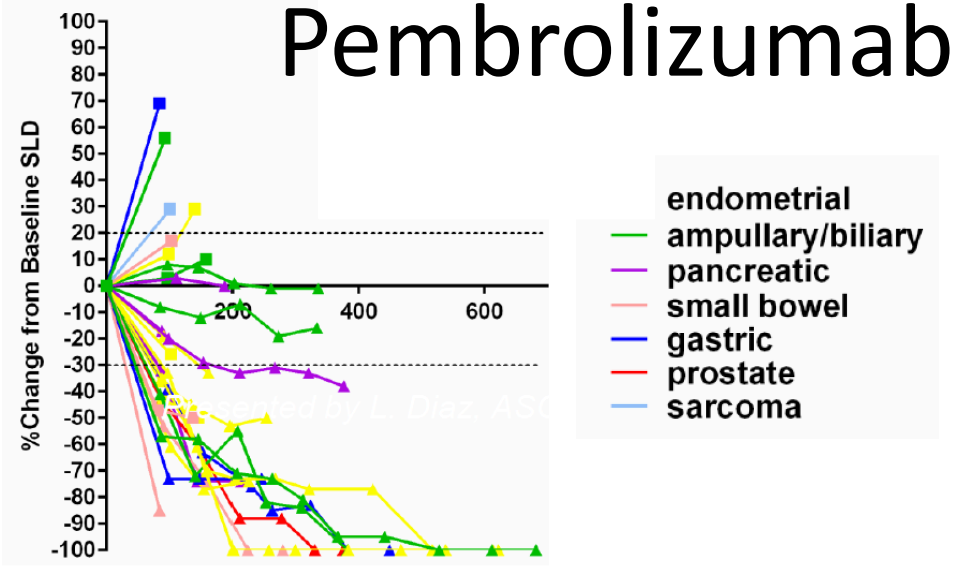
Frontline Metastatic



Stage III Adjuvant



Pembrolizumab: non-CRC



	N	Objective response rate n (%)	95% CI
CRC	90	32 (36%)	(26%, 46%)
Non-CRC	59	27 (46%)	(33%, 59%)
Endometrial cancer	14	5 (36%)	(13%, 65%)
Biliary cancer	11	3 (27%)	(6%, 61%)
Gastric or GE junction cancer	9	5 (56%)	(21%, 86%)
Pancreatic cancer	6	5 (83%)	(36%, 100%)
Small intestinal cancer	8	3 (38%)	(9%, 76%)
Breast cancer	2	PR, PR	
Prostate cancer	2	PR, SD	
Bladder cancer	1	NE	
Esophageal cancer	1	PR	
Sarcoma	1	PD	
Thyroid cancer	1	NE	
Retroperitoneal adenocarcinoma	1	PR	
Small cell lung cancer	1	CR	
Renal cell cancer	1	PD	

Rate of dMMR

Cancer type (n=7,817)	MSI-high rate
Uterine	39/277 (14.1%)
Small bowel	6/70 (8.6%)
Prostate	11/178 (6.2%)
CRC	42/1185 (3.5%)
CUP	22/815 (2.7%)
Hepatobiliary	9/389 (2.3%)
Gastroesophageal	6/400 (1.5%)
Neuroendocrine	1/431 (0.2%)
Pancreatic	1/459 (0.2%)
NSCLC	5/2112 (0.2%)
Breast	2/1459 (0.1%)
Anal SCC	0/42 (0%)

Hall et al ASCO 2016 and GI ASCO 2016 and Lee et al ASCO 2016, Pembrolizumab FDA label

Conclusions

- Standard of Care for ≥2nd line metastatic dMMR CRC is now anti-PD1 therapy
  - NCCN recommends either Pembrolizumab or Nivolumab
    - Pembrolizumab is FDA approved for dMMR CRC after fluoropyrimidine/oxaliplatin/irinotecan
  - Test all patients with metastatic CRC for dMMR
  - Phase III Trials for adjuvant and front-line metastatic dMMR CRC are ongoing

- Standard of Care for ≥2nd line metastatic dMMR cancers is now anti-PD1 therapy
  - Pembrolizumab is FDA approved for dMMR cancers
  - Testing methodology not specified by FDA label

- Predictive Factors
  - PD-L1 expression is not a predictive factor for MSS or MSI-high CRC
  - Improved understanding of dMMR intrinsic resistance is needed
  - dMMR is the best predictive marker we have for anti-PD1 therapy!