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THE FUTURE OF IMMUNOTHERAPY IN COLORECTAL CANCER

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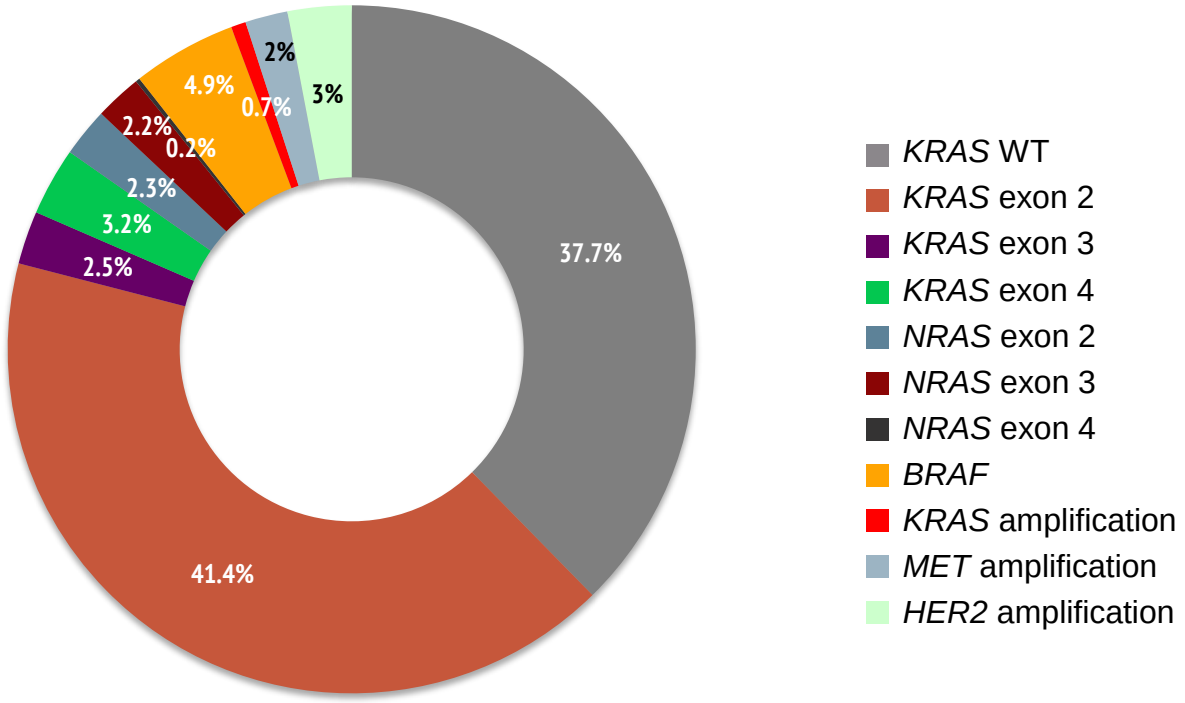
INTRODUCTION

- Colorectal cancer (CRC) is a heterogeneous disease
- Most CRCs are tested for the presence of *RAS* and *BRAF* mutations, serving as prognostic or predictive biomarkers



Misale S, et al. Cancer Discov 2014;4:1269–80

BRAF, rapidly accelerated fibrosarcoma isoform B; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten RAS oncogene homolog; MET, mesenchymal-epithelial transition; NRAS, neuroblastoma RAS oncogene homolog; RAS, rat sarcoma; WT, wild type

MICROSATELLITE INSTABILITY

- In the era of immune therapy all CRC patients should be tested for microsatellite instability (MSI) regardless of family history
  - By immunohistochemistry staining for mismatch repair proteins
  - Or by MSI-PCR
  - Or by next-generation sequencing, which allows for assessment of more microsatellite loci than MSI-PCR

CRC, colorectal cancer; MSI, microsatellite instability; PCR, polymerase chain reaction

MSI TUMOURS

- Characterised by lymphocyte infiltration
- Good prognosis, specifically in early stages
- Because of good prognosis, frequency of MSI-H is different in different stages

	Frequency Analysis		
	Stage II	Stage III	Stage IV*
MSI-H	22% (86/395)	12% (104/859)	3.5%

- The poor prognosis of stage IV patients cannot be attributed to *BRAF* mutations alone, but appears to be driven by enhanced tumour immune escape

*Koopman M, et al. Br J Cancer 2009;100(2):266–73
BRAF, rapidly accelerated fibrosarcoma isoform B; MSI-H, microsatellite instability high

MSI TUMOURS

- MSI-H tumours generate highly immunogenic frameshift peptide antigens, which can be recognized by tumour-infiltrating T-cells

WHERE IT ALL STARTED: PEMBROLIZUMAB

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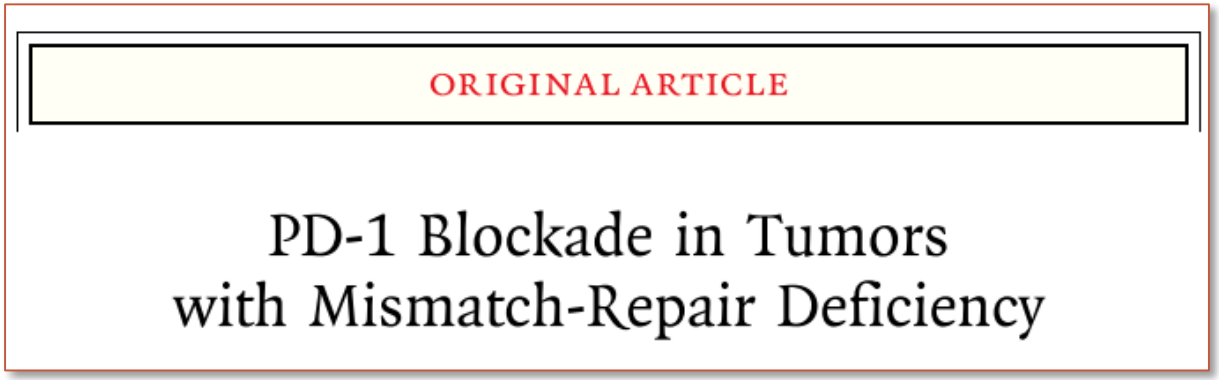
ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

Type of response	MSI CRC (n=10)	MSS CRC (n=18)
Complete Response	0%	0%
Partial Response	40%	0%
Objective Response Rate	40%	0%
Disease Control Rate	90%	11%

Le D, et al. N Eng J Med 2015;372(26):2509–20
CRC, colorectal cancer; MSI, microsatellite instability; MSS, microsatellite stability; PD-1, programmed cell death protein-1

MSI TUMOURS

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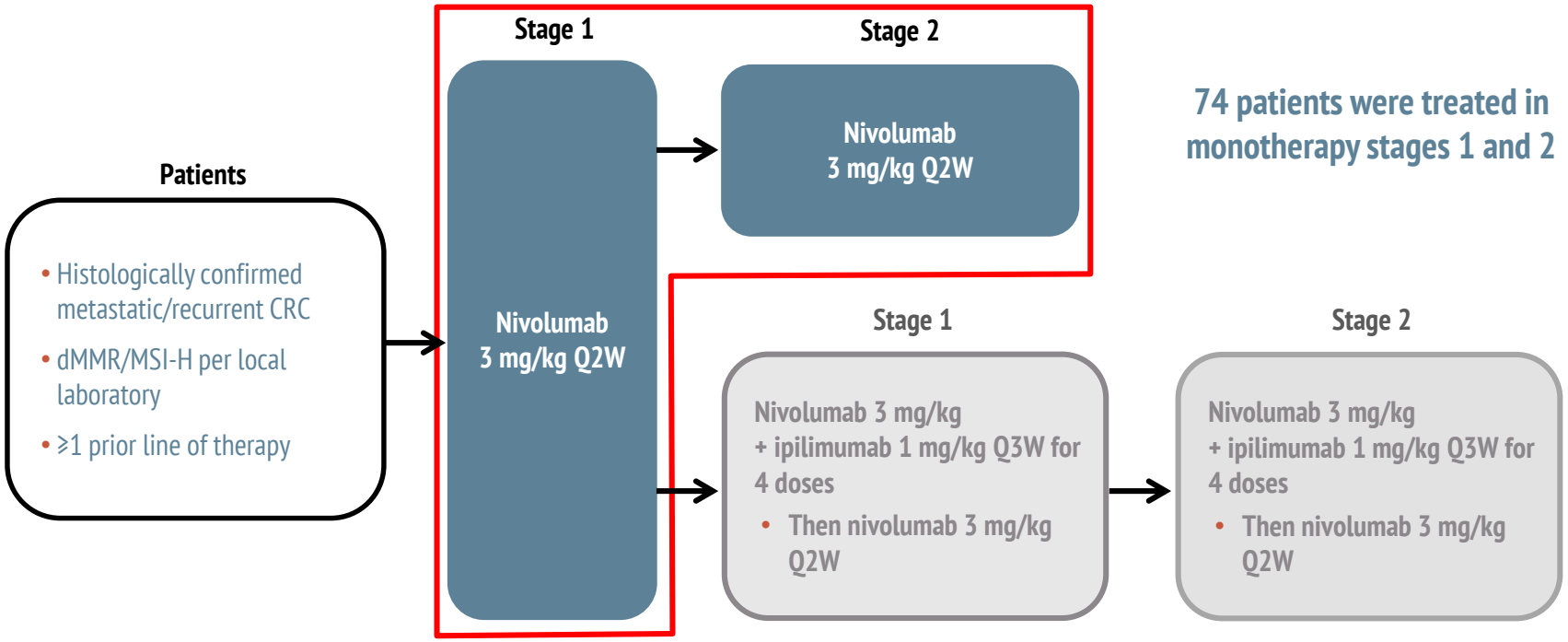
- Data for nivolumab, another anti-PD-1 monoclonal antibody, later confirmed pembrolizumab activity
- Both pembrolizumab and nivolumab are good options for MSI-H metastatic CRC
- Sometimes responses are very durable, with patients responding for more than 2 years, including some patients with complete responses
- Anti-PD-1 therapy should be standard of care for dMMR CRC

Overman M, et al. Lancet Oncol 2017; 18(9):1182–91
CRC, colorectal cancer; dMMR, deficient mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability high; PD-1, programmed cell death protein-1

NIVOLUMAB IN PATIENTS WITH METASTATIC DNA MISMATCH REPAIR-DEFICIENT OR MSI-H CRC (CHECKMATE 142): AN OPEN-LABEL, MULTICENTRE, PHASE 2 STUDY



74 patients were treated in monotherapy stages 1 and 2

Overman M, et al. Lancet Oncol 2017;18(9):1182–91

CRC, colorectal cancer; dMMR, deficient mismatch repair; MSI-H, microsatellite instability high; Q2W, once every 2 weeks; Q3W, once every 3 weeks

NIVOLUMAB IN PATIENTS WITH METASTATIC DNA MISMATCH REPAIR-DEFICIENT OR MSI-H CRC (CHECKMATE 142): AN OPEN-LABEL, MULTICENTRE, PHASE 2 STUDY

EFFICACY RESULTS

Type of response	dMMR/MSI-H per local laboratory (n=74)
	BICR
ORR, n (%)	24 (32)
95% CI	22-44
Best overall response, n (%)	
CR	2 (3.6)
PR	22 (30)
SD	25 (34)
PD	21 (28)
Unable to determine	4 (5)
Disease control for ⩾ 12 weeks, n (%)	46 (62.2)

Overman M, et al. Lancet Oncol 2017; 18(9):1182–91

BICR, blinded independent central review; CI, confidence interval; CR, complete response; dMMR, deficient mismatch repair; MSI-H, microsatellite instability high; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

DURABLE CLINICAL BENEFIT WITH NIVOLUMAB PLUS IPILIMUMAB IN DNA MISMATCH REPAIR-DEFICIENT / MSI-H METASTATIC CRC

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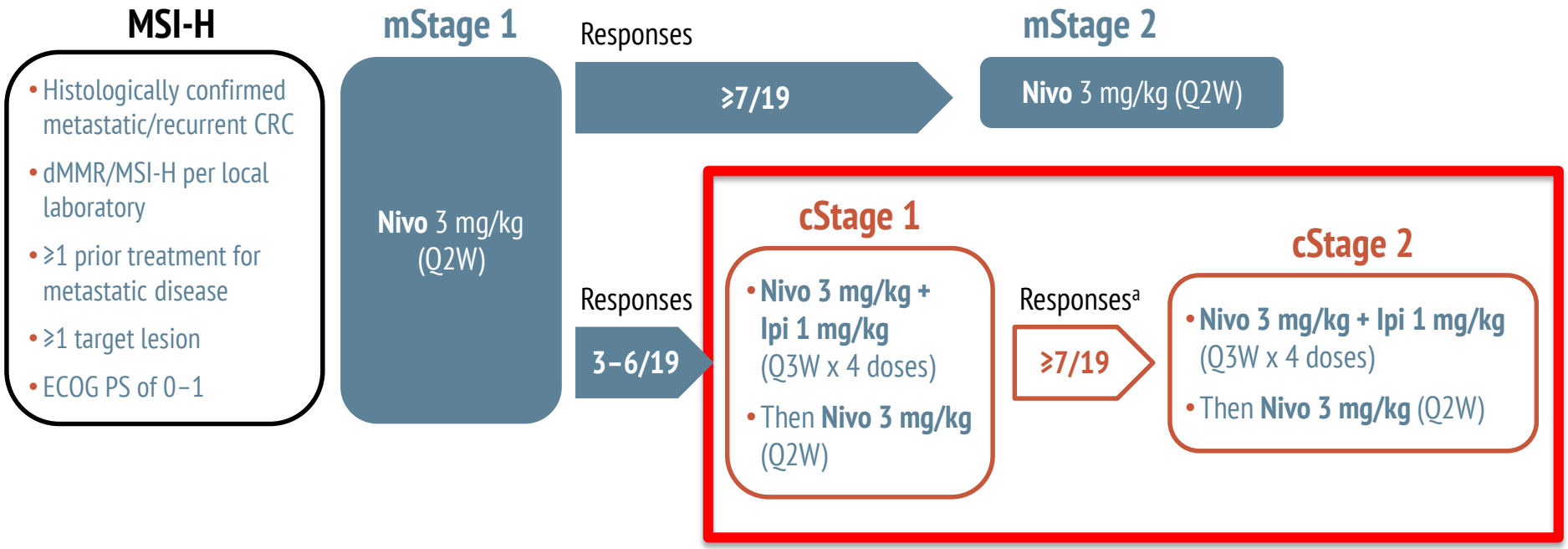
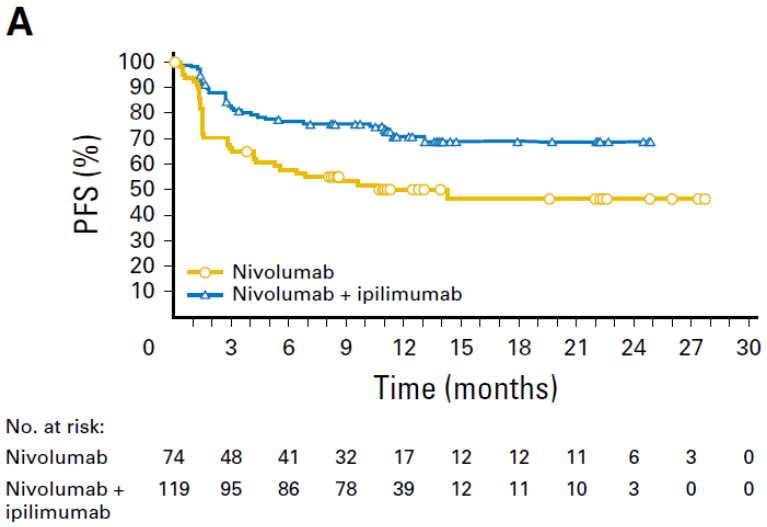


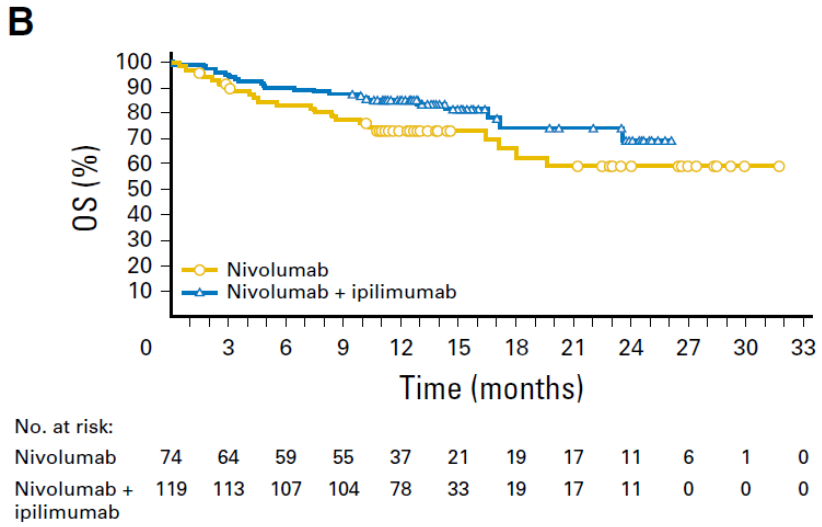
Overman M, et al. J Clin Oncol 2018; 36(8):773–9

CRC, colorectal cancer; dMMR, deficient mismatch repair; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MSI-H, microsatellite instability high; ipi, ipilimumab; nivo, nivolumab; Q2W, once every 2 weeks; Q3W, once every 3 weeks

DURABLE CLINICAL BENEFIT WITH NIVOLUMAB PLUS IPILIMUMAB IN DNA MISMATCH REPAIR-DEFICIENT / MSI-H METASTATIC CRC

EFFICACY RESULTS





ORR, Best Overall Response, and DCR per Investigator Assessment

Response	No. (%)	95% CI
ORR	65 (55)	45.2 to 63.8
Best overall response		
Complete response	4 (3)	
Partial response	61 (51)	
Stable disease	37 (31)	
Progressive disease	14 (12)	
Not determined	3 (3)	
Disease control for ≥12 weeks	95 (80)	71.5 to 86.6

Overman M, et al. J Clin Oncol 2018; 36(8):773–9

CI, confidence interval; DCR, disease control rate; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

MSI COLON CANCER TREATED WITH ANTI-PD-1

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- Biomarkers for response to anti-PD-1 therapy
  - PD-L1 expression: No
  - *BRAF* mutation: No
  - History of Lynch syndrome: No

Overman M, et al. Lancet Oncol 2017;18(9):1182–91

BRAF, rapidly accelerated fibrosarcoma isoform B; MSI, microsatellite instability; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1

NTRK FUSIONS IN MSI-H COLON CANCER

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- Of the MSI-H patients, 1 out of 3 have NTRK fusions, which can be targeted with entrectinib or larotrectinib

Pietrantonio et al. Ann Oncol 2018
MSI-H, microsatellite instability high; NTRK, neurotrophic tyrosine kinase

WHAT ABOUT MICRO SATELLITE STABLE (MSS) COLON CANCER?

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- Most patients with metastatic CRC have MSS disease
- Response to anti-PD-1 therapy in MSS patients is 0%, alone or in combination with 2 different checkpoint inhibitors[1]
- MEK inhibition plus anti-PD-L1 therapy showed promising preclinical activity in MSS CRC
  - MEK inhibition has shown to enhance T-cell infiltration due to increased tumour antigen expression and presentation
  - Phase I data showed a promising 20% RR[2]
  - Unfortunately the phase III data (COTEZO trial combining cobimetinib with atezolizumab) were negative[3]

1. Le D, et al. N Eng J Med 2015;372(26):2509–20; 2. Bendell JC. WCGIC 2016; 3. Bendell JC. WCGIC 2018 (LBA-004)
CRC, colorectal cancer; MEK, mitogen-activated protein kinase kinase; MSS, microsatellite stability; PD-1, programmed cell death ligand-1; PD-L1, programmed cell death ligand-1; RR, response rate

HOW TO TREAT MSS COLON CANCER WITH IMMUNOTHERAPY THEN: WHY DOESN'T IT RESPOND TO IMMUNOTHERAPY?

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- One of the reasons is the lower mutational load of MSS tumours compared with MSI-H tumours
  - But mutational load is not so low that it explains the 0% response to immunotherapy
  - Studies further suggest that there is no relationship between mutational load and T-cell infiltration in MSS

- What about PD-L1 expression in MSS versus MSI tumours?
  - PD-L1+ is not a predictor of benefit from pembrolizumab in mCRC

- What about immune cell content?
  - More T-cell infiltration in MSI versus MSS tumours

Morse M. Presented at ASCO 2018: Challenges with colorectal cancer with proficient mismatch repair
mCRC, metastatic colorectal cancer; MSI, microsatellite instability; MSI-H, microsatellite instability high; MSS, microsatellite stability; PD-L1, programmed cell death ligand-1

WHAT ABOUT THE ROLE OF WNT SIGNALLING?

- Wnt signalling plays an important role in CRC
- Wnt signalling is inversely correlated with T-cell infiltration
- Question is whether we can target Wnt signalling
  - Therapeutic targeting of Wnt signalling is difficult due to high pathway complexity and its role in tissue homeostasis
  - Several trials are ongoing, including one study evaluating a porcupine inhibitor in combination with pembrolizumab

Morse M. Presented at ASCO 2018: Challenges with colorectal cancer with proficient mismatch repair CRC, colorectal cancer; Wnt, homologous wingless and Int-1

ANOTHER STRATEGY: MODULATING CYTOKINES

- MSI tumours express higher levels of cytokines than MSS tumours
- Systemic administration of cytokines is associated with considerable toxicity
- Injecting an agent that causes inflammation in the tumour as a strategy to increase the immunogenicity of the tumour microenvironment
  - The oncolytic virus T-VEC can activate anti-tumour immunity by triggering immune responses following release of pro-inflammatory cytokines[1]
  - An ongoing trial is currently evaluating T-VEC in patients with CRC and liver metastases[2]

1. Fountzilas C. Oncotarget 2017 May 31;8(60):102617-102639; 2. Clinicaltrials.gov: NCT03256344
CRC, colorectal cancer; MSI, microsatellite instability; MSS, microsatellite stability; T-VEC, talimogene laherparepvec

ANOTHER STRATEGY: MAKE THE T-CELLS RECOGNIZE THE TUMOUR

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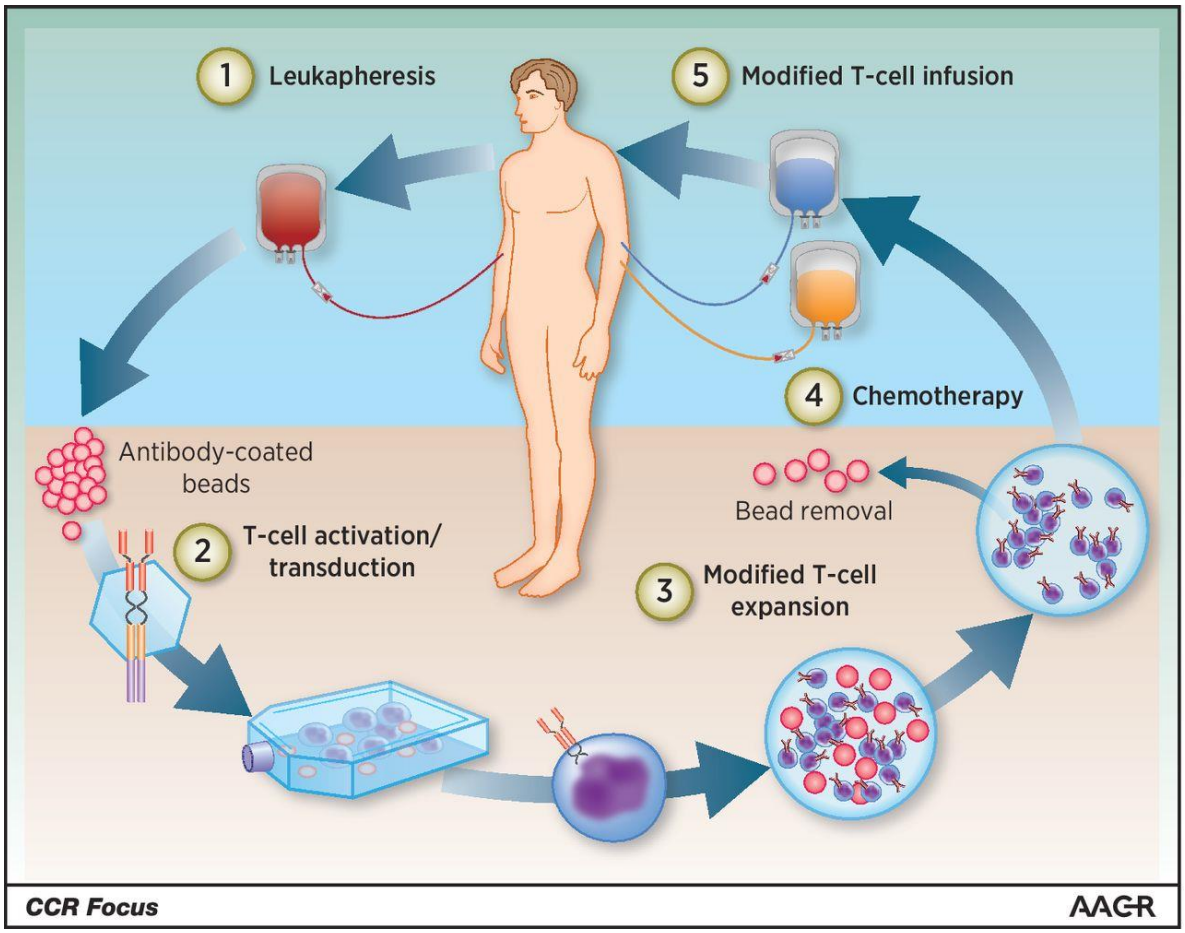
OVERVIEW OF CAR T-CELL THERAPY IN THE CLINIC



Maus and June. Clin Cancer Res 2016;22:1875–84
CAR, chimeric antigen receptor

ANOTHER STRATEGY: MODULATION OF MYELOID-DERIVED SUPPRESSOR CELLS (MDSCs)

- MDSCs possess strong immunosuppressive activities
- MDSCs interact with other immune cell types including **T- cells, dendritic cells, macrophages** and **natural killer cells** to regulate their functions

- Not easy to deplete MDSCs
  - HDAC inhibition alters the function of MDSCs
    - Phase II trial of HDAC inhibitor in combination with anti-PD-1 is ongoing
  - Data suggest that bevacizumab also depletes MDSCs
    - Number of trials of bevacizumab in combination with checkpoint inhibition are ongoing

Morse M. Presented at ASCO 2018: Challenges with colorectal cancer with proficient mismatch repair
HDAC, histone deacetylase; MDSCs, myeloid-derived suppressor cells; PD-1, programmed cell death protein-1

CONCLUSIONS

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- Immunotherapy works fantastically in most MSI-H patients, so all CRC patients should be tested for MSI

- Many strategies are currently being explored to make immunotherapy work in MSS patients as well

CRC, colorectal cancer; MSI, microsatellite instability; MSS, microsatellite stability; MSI-H, microsatellite instability high

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