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Supported by an Independent Educational Grant from BAYER

IMMUNOTHERAPY IN MCRC

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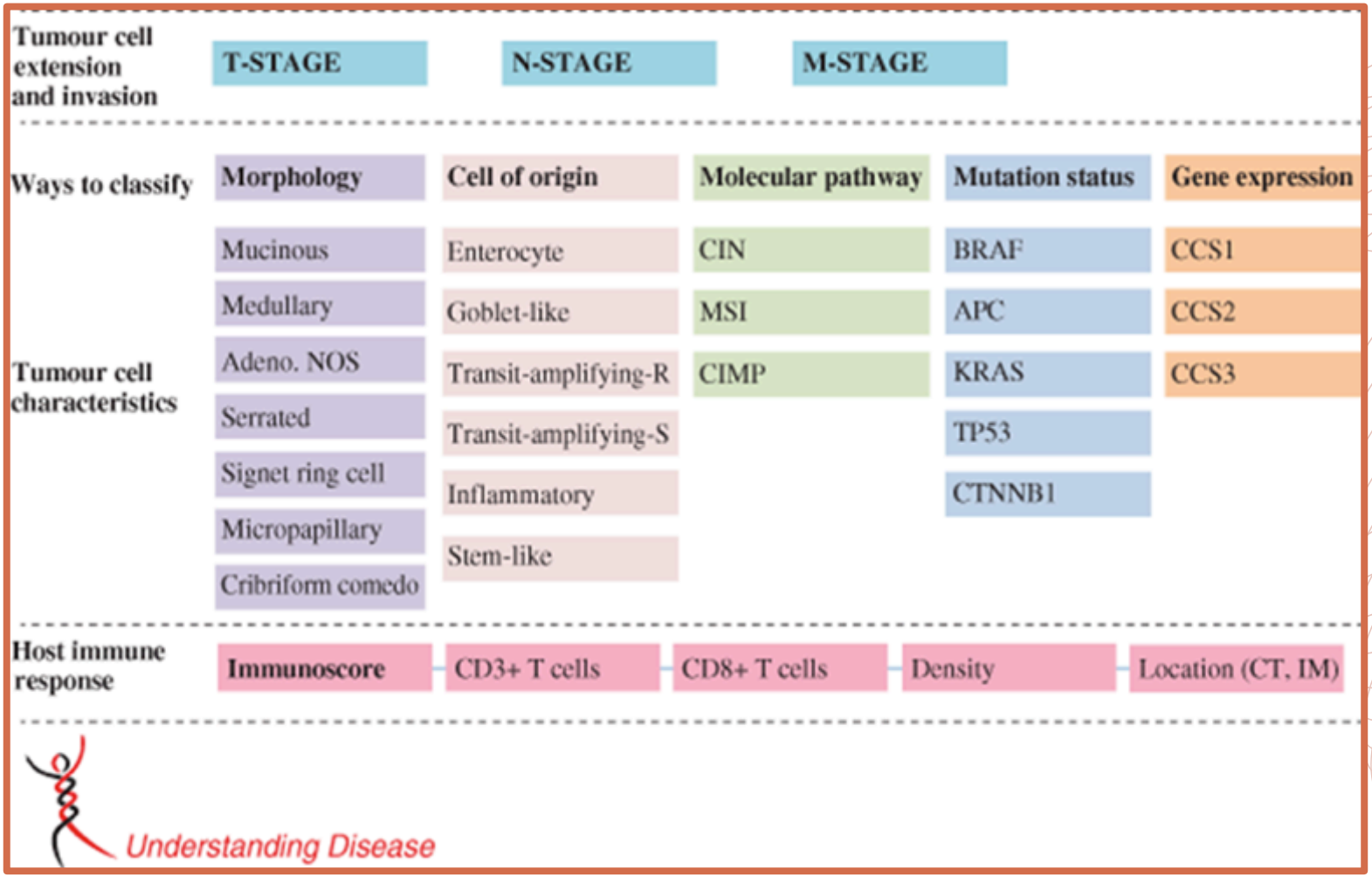
MEDICAL UNIVERSITY OF VIENNA

IMMUNOLOGY AND CRC

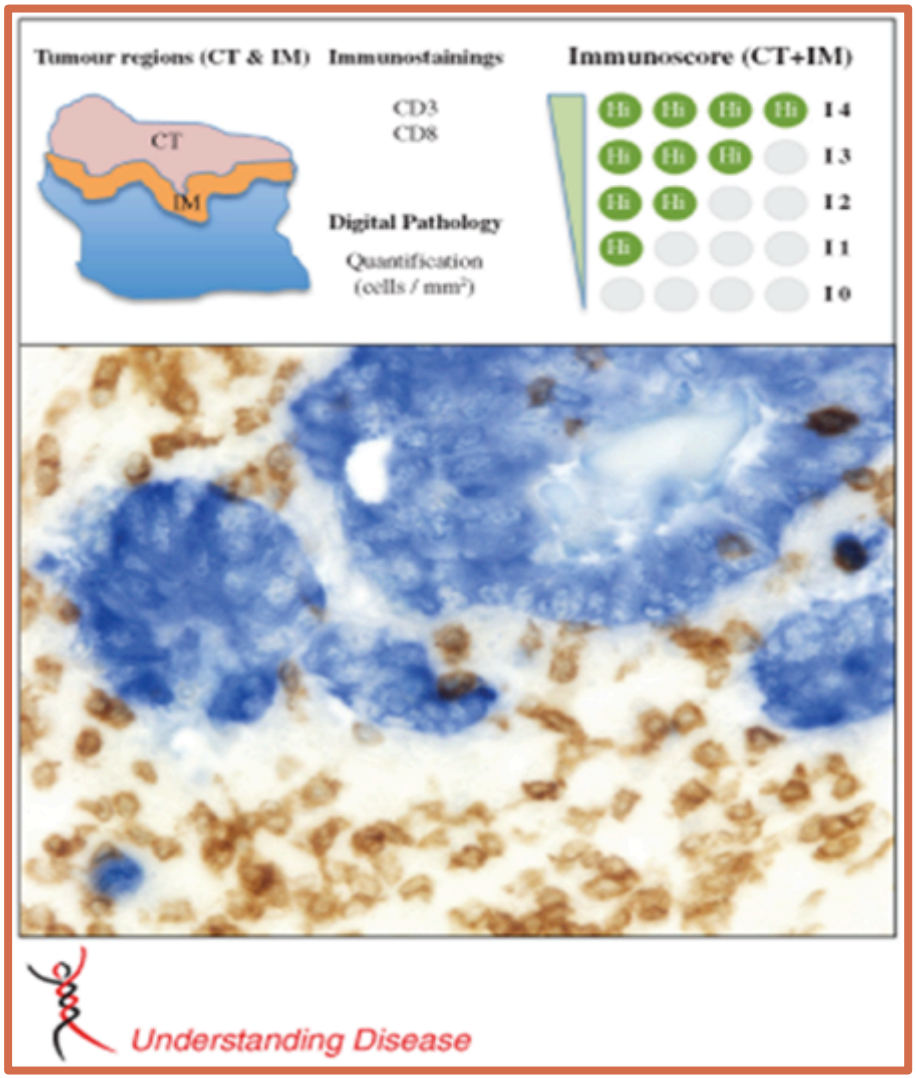
- **In diagnosis**
  - Predictive marker
  - Prognostic marker

- **In treatment**
  - Passive immunotherapy (monoclonal antibodies)
  - Active immunotherapy (immunization)

CLASSIFICATION OF COLORECTAL CANCER



IMMUNOSCORE DEFINITION AND METHODOLOGY

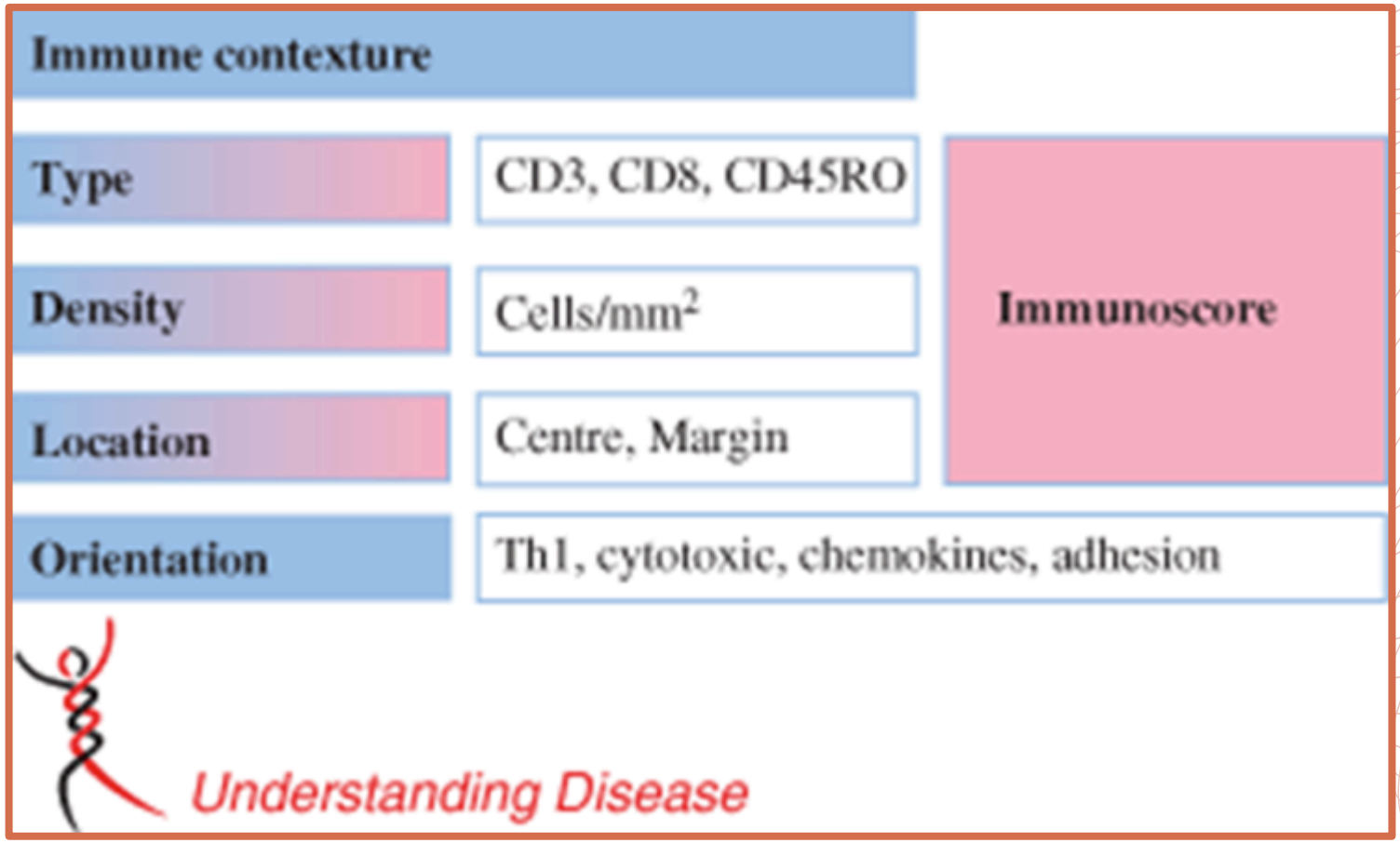


Immunoscore by staining CD3 and CD8 positive cells in the CT and IM of rectal cancer

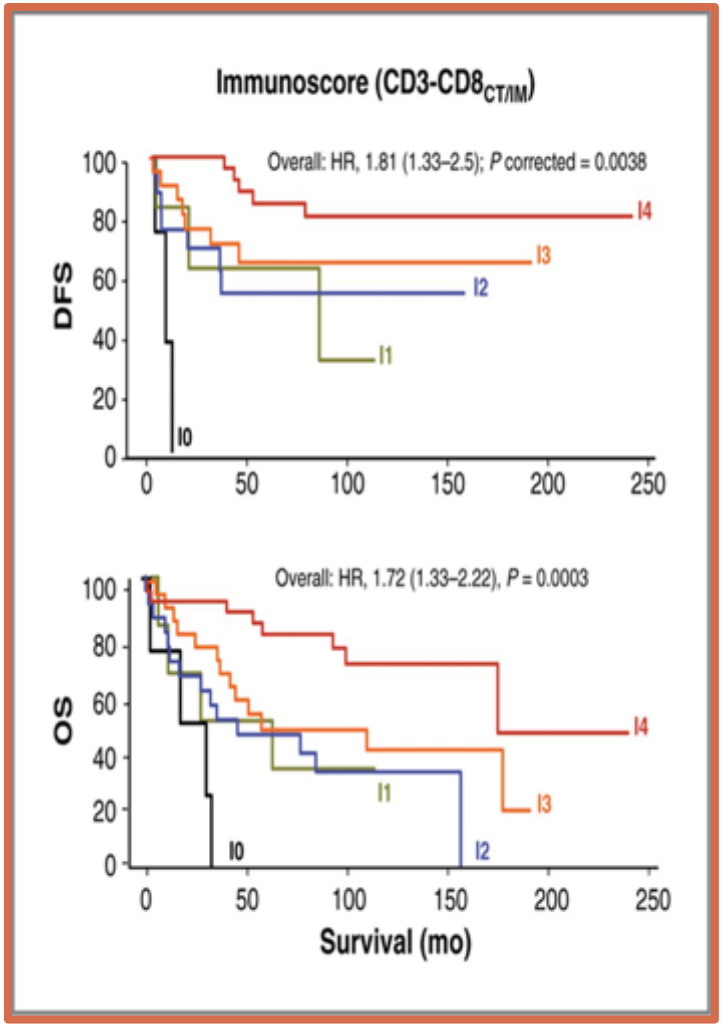
Immunohistochemistry of a colorectal tumour stained for CD3 + T cells (brown)

Anitei M et al. Clin Cancer Res 2014;20:1891-1899

CORRESPONDENCE BETWEEN THE IMMUNE CONTEXTURE AND THE IMMUNOSCORE



CORRELATION BETWEEN IMMUNOSCORE AND DFS, OS IN RECTAL CANCER



Anitei M et al. Clin Cancer Res 2014;20:1891-1899

IMMUNOLOGY AND CRC

- In diagnosis
  - Predictive marker
  - Prognostic marker

- **In treatment**
  - **Passive immunotherapy (monoclonal antibodies)**
  - **Active immunotherapy (immunization)**

IMMUNOTHERAPY FOR COLORECTAL CANCER

Current immunotherapies for colorectal cancer (CRC) fall into 7 broad categories

- Monoclonal antibodies (MAbs)
- Checkpoint inhibitors and immune modulators
- Cancer vaccines
- Adoptive cell therapy
- Dendritic cell therapies
- Oncolytic virus therapy
- Cytokines
- Adjuvant immunotherapies

Although proven successful in other types of cancer, immunotherapies are still in early-phase clinical testing (phase I and II) for CRC

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Oh D.Y, et al. JNCCN. 2015;13(8):970-978

MABS AS IMMUNOTHERAPY: ANTI-EGFR ANTIBODIES

Cetuximab has activity in mCRC[1]

- As monotherapy in the second- and third-line settings
- In combination with cytotoxic chemotherapy in any line
- Limited or no activity with EGFR-targeted therapies in patients with KRAS mutations[1,2]
- Acts through multiple mechanisms (cell growth inhibition, apoptosis but also ADCC)[3]

Panitumumab has similar antitumour activity to cetuximab in CRC but does not trigger ADCC[1-3]

A phase I study demonstrated clinical activity of **SYM004** in patients with WT *KRAS* mCRC, resistant to anti-EGFR mAbs[4,5]

- Among 17 patients treated at the higher dose level of 18 mg/kg, 1 (7%) patient experienced PR and 11 (73%) patients had SD[3]
- Median PFS was 3.3 months (95% CI 2.6, 5.1)

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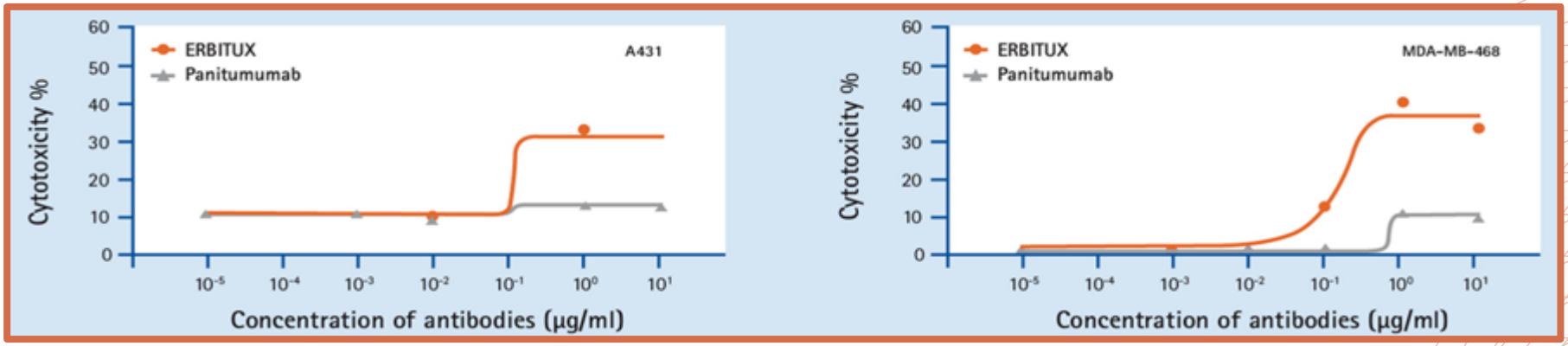
1. Woo J, et al. Cancer. 2013;119:1941–50; 2. Liang RF, et al. Drug Des Devel Ther. 2015;9:4471–8; Oh D.Y, et al. JNCCN. 2015;13(8):970-978. 4. Argiles G, et al. J Clin Oncol. 2014;32(Suppl 5):Abstr 3551; 5. Dienstmann R, et al. J Clin Oncol. 2013;31(Suppl):Abstr 3551.

DOES HUMORAL RESPONSE CONTRIBUTE TO MAB EFFICACY IN MCRC?

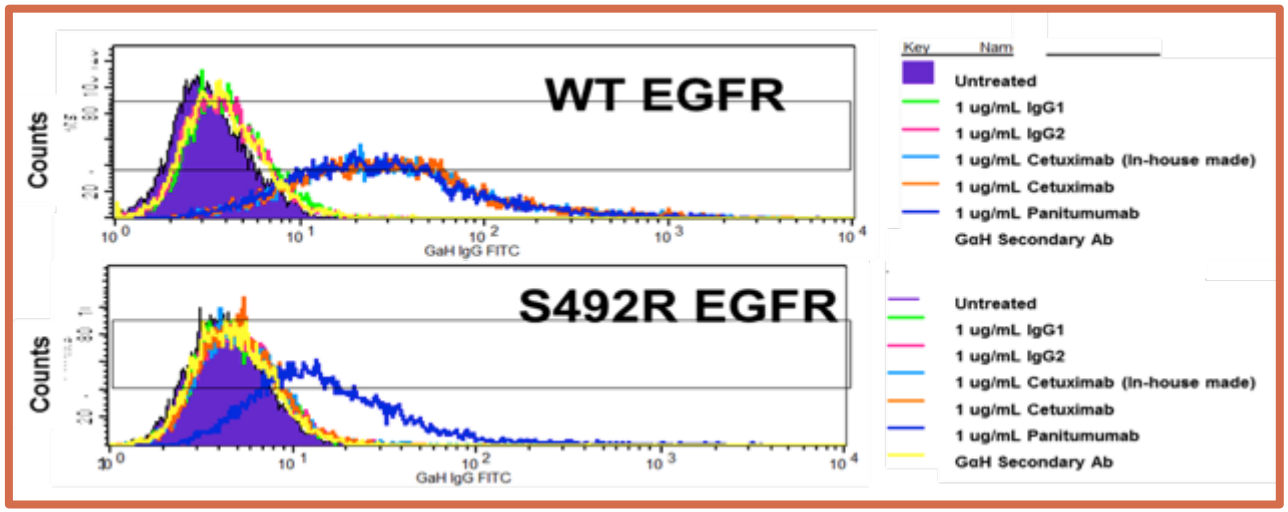


- Cetuximab is an IgG1 antibody and therefore attracts immune cells, which attack the tumor cell on which Cetuximab binds and kills them

- ADCC is not mediated by antibodies of IgG2 subtypes like panitumumab

Stroh C, et al. AACR 2010 (Abstract No. LB-316)

ACQUIRED MUTATION EGFR S492R IN THE IMMUNE-EPITOPE FOR CETUXIMAB LEADS TO ITS RESISTANCE



ACQUIRED MUTATION EGFR S492R IN THE IMMUNE-EPITOPE FOR CETUXIMAB LEADS TO ITS RESISTANCE

Treatment	WT	Mutant	Frequency of S492R Mutation	95% CI	P Value
Cetuximab	239	46	16.1%	12.1-20.9%	P<0.0001
Panitumunab	258	3	1.1%	0.2-3.3%	

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MABS AS IMMUNOTHERAPY: ONGOING TRIALS (1)

Several MAbs are currently being tested in phase I/II clinical trials:

Agent (Company)	Description	Phase	Indication	CT.gov identifier
RO5520985 (Hoffmann-La Roche)	Bispecific anti-ANG-2/ anti-VEGF-A antibody	II	Untreated mCRC	NCT02141295
Sym004 (EMD Sorono)	Anti-EGFR antibody	II	mCRC	NCT02083653
IMMU-132 (Immunomedics)	Antibody-drug conjugate targeting Trop-2	I/II	Epithelial cancers	NCT01631552
IMMU-130 (Immunomedics)	Antibody-drug conjugate targeting CEACAM5	I/II	mCRC	NCT01605318

mCRC, metastatic colorectal cancer. 1. Clinicaltrials.gov

MABS AS IMMUNOTHERAPY: ONGOING TRIALS (2)

Agent (Company)	Description	Phase	Indication	CT.gov identifier
Ensituximab (Precision Biologics)	Antibody against a MUC5AC-related antigen	I/II	Recurrent, locally advanced CRC after standard therapy	NCT01040000
Bavituximab	Anti-immune-suppressing molecule antibody	I	Rectal cancer	NCT01634685
MORAb-066 (Morphotek)	Anti-tissue factor (TF) antibody	I	TF-expressing CRC and other cancers	NCT01761240
Anti-MIF antibody (Baxalta US)	Targets macrophage migration inhibitory factor	I	CRC	NCT01765790
MGD007 (MacroGenics)	Dual-affinity re-targeting (DART) protein targeting A33 antigen	I	mCRC	NCT02248805

mCRC, metastatic colorectal cancer. Clinicaltrials.gov

CHECKPOINT INHIBITORS AND IMMUNE MODULATORS

- These agents are blocking antibodies to inhibitory cell-surface molecules, e.g. CTLA4 and PD-1/ programmed death ligand 1 (PD-l1), which restrain the priming and effector phases of the adaptive T-cell immune response.[1]

- CTLA4 blocking antibodies and antibodies blocking thevPD-1/PD-L1 axis have been assessed in CRC.[1]

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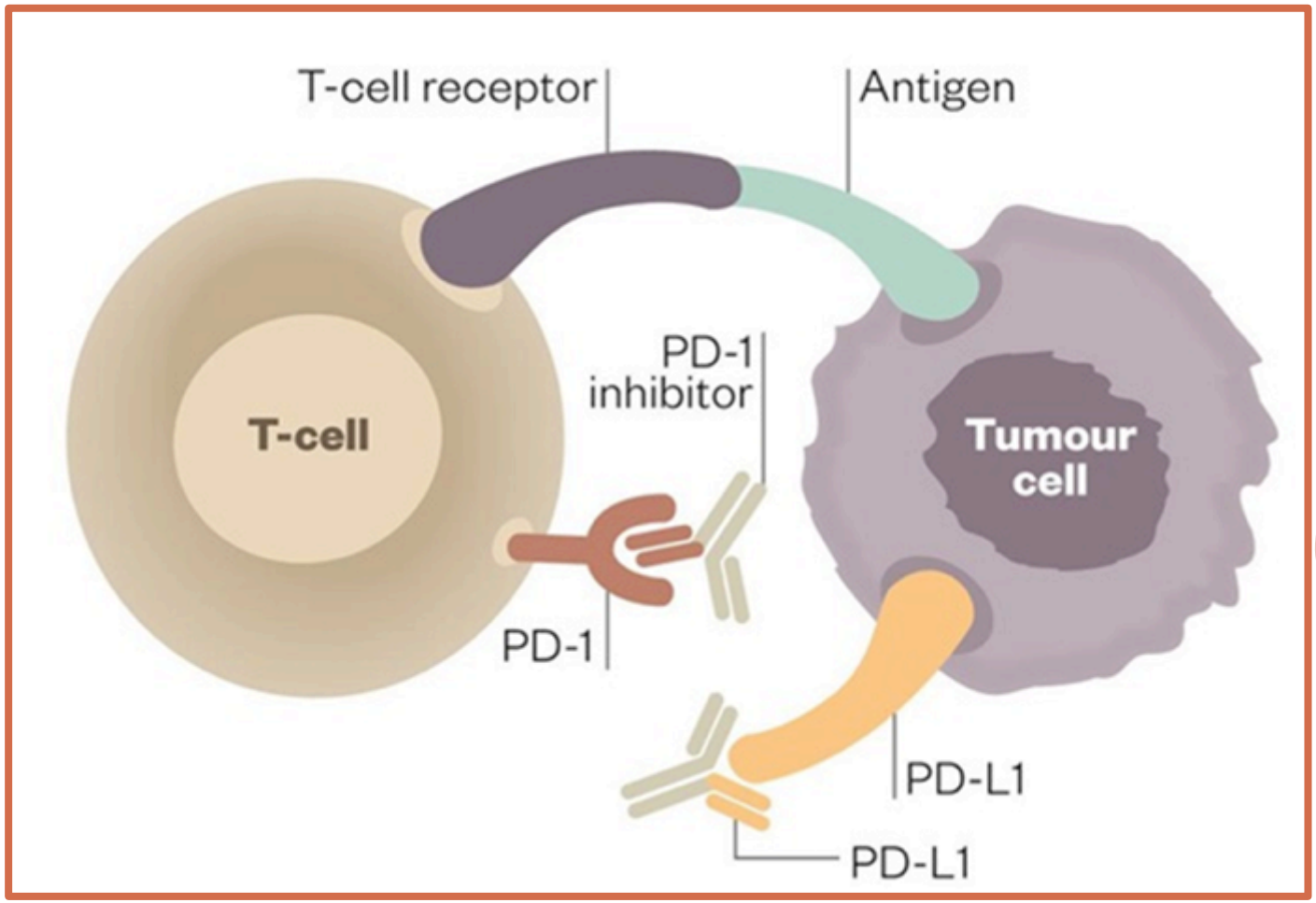
Oh D.Y, et al. JNCCN. 2015;13(8):970-978

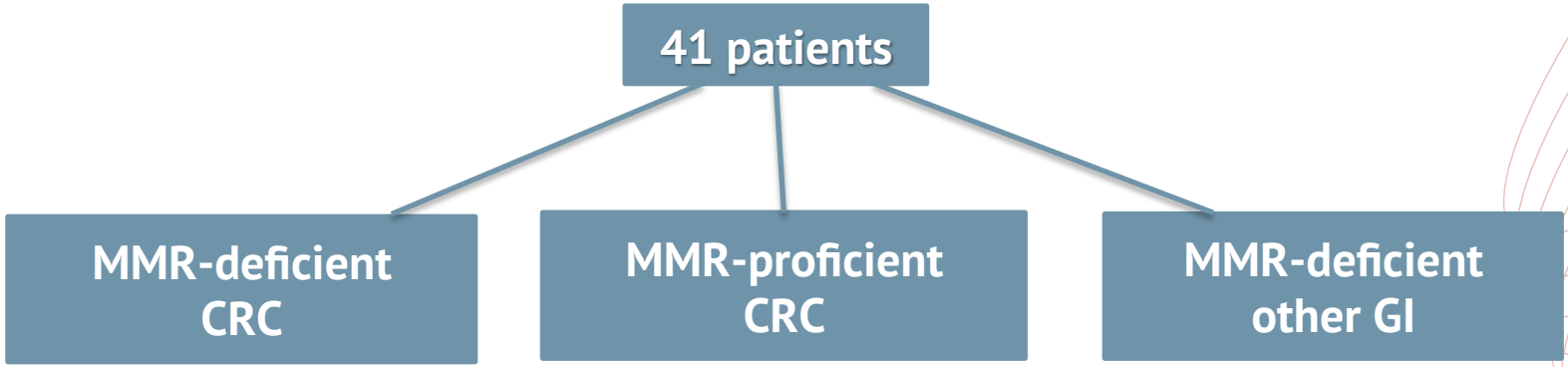
CHECKPOINT INHIBITORS AND MCRC



ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.



Pembrolizumab, 10mg/KG, every other week

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DEMOGRAPHIC AND BASELINE CHARACTERISTICS OF PATIENTS

Table 1. Demographic and Baseline Characteristics of the Patients.*

Characteristic	Mismatch Repair–Deficient Colorectal Cancer (N=11)	Mismatch Repair–Proficient Colorectal Cancer (N=21)	Mismatch Repair–Deficient Noncolorectal Cancer (N=9)	P Value†
Median age (range) — yr	46 (24–65)	61 (32–79)	57 (34–92)	0.02
Sex — no. (%)				0.72
Female	5 (45)	8 (38)	4 (44)	
Male	6 (55)	13 (62)	5 (56)	
Race — no. (%)‡				0.66
White	8 (73)	17 (81)	8 (89)	
Black	1 (9)	3 (14)	0	
Other	2 (18)	1 (5)	1 (11)	
ECOG performance status — no. (%)§				0.07
0	0	6 (29)	2 (22)	
1	11 (100)	15 (71)	7 (78)	
Cancer type — no. (%)				>0.99
Colon	9 (82)	18 (86)	0	
Rectal	2 (18)	3 (14)	0	
Ampullary or cholangiocarcinoma	0	NA	4 (44)	
Endometrial	0	NA	2 (22)	
Small bowel	0	NA	2 (22)	
Gastric	0	NA	1 (11)	
Histologic grade — no. (%)				0.20
Well or moderately differentiated	7 (64)	18 (86)	4 (44)	
Poorly differentiated	4 (36)	3 (14)	3 (33)	
Other	0	0	2 (22)	
Stage IV cancer — no. (%)	11(100)	21 (100)	9 (100)	>0.99
Liver metastases — no. (%)	6 (55)	11 (52)	6 (67)	>0.99
Median time since initial diagnosis (range) — mo	31 (6–95)	58 (27–192)	23 (2–105)	0.07
Previous therapies — no. (%)				0.89
1	0	0	1 (11)	
2	3 (27)	4 (19)	5 (56)	
3	3 (27)	5 (24)	1 (11)	
>4	5 (45)	12 (57)	2 (22)	
Detected germline mutation or known Lynch syndrome — no. (%)				<0.001
Yes	9 (82)	0	4 (44)	
No	2 (18)	21 (100)	4 (44)	
Unknown	0	0	1 (11)	
BRAF wild type — no. (%)				0.64
Yes	8 (73)	11 (52)	4 (44)	
No	0	1 (5)	0	
Unknown	3 (27)	9 (43)	5 (56)	
KRAS wild type — no. (%)				0.72
Yes	6 (55)	13 (62)	4 (44)	
No	5 (45)	8 (38)	1 (11)	
Unknown	0	0	4 (44)	

* NA denotes not applicable.
† P values are for the comparison between the cohort with mismatch repair–deficient colorectal cancer and the cohort with mismatch repair–proficient colorectal cancer.
‡ Race was self-reported.
§ Eastern Cooperative Oncology Group (ECOG) performance status is a measure of a patient's ability to perform activities of daily living; values range from 0 to 5, with higher scores indicating greater impairment.

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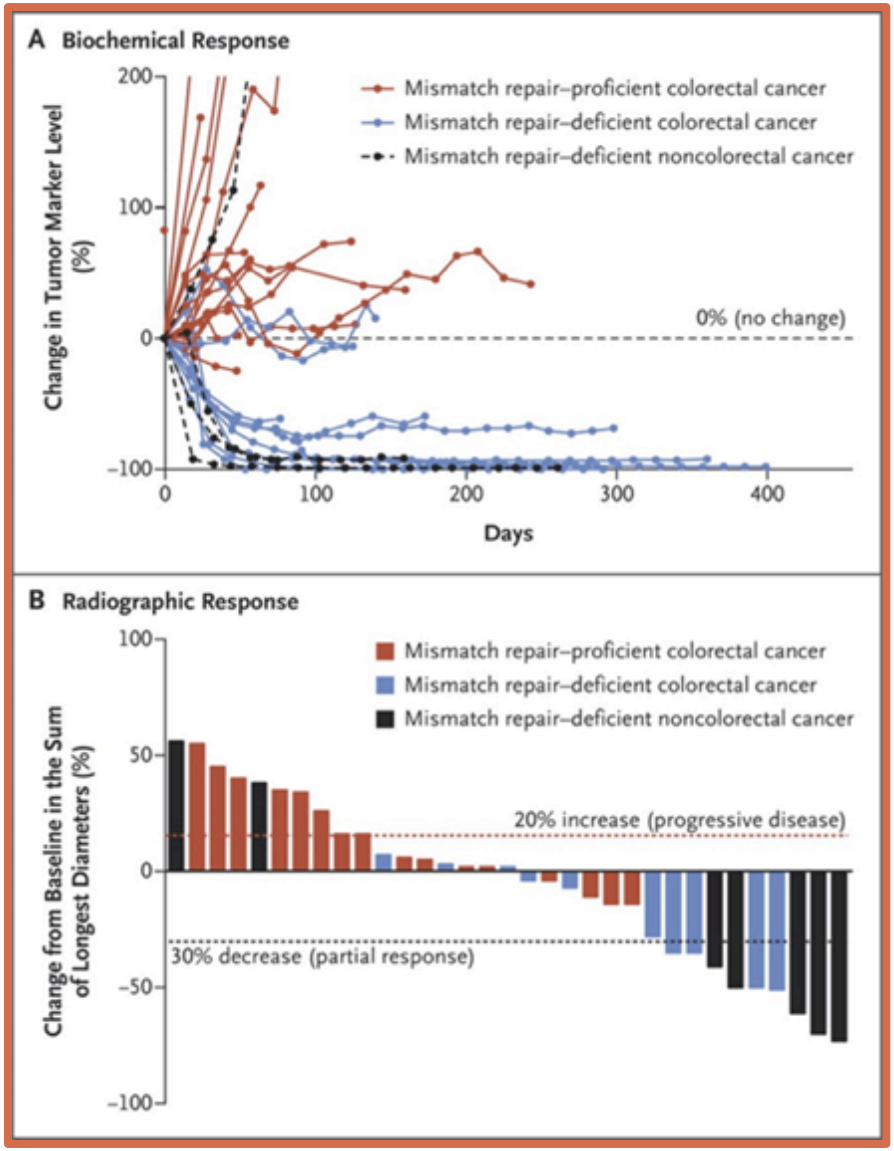
Le DT et al. N Engl J Med 2015;372:2509-2520.

CLINICAL RESPONSES TO PEMBROLIZUMAB TREATMENT



Le DT et al. N Engl J Med 2015;372:2509-2520.

OBJECTIVE RESPONSES ACCORDING TO RECIST CRITERIA

Table 2. Objective Responses According to RECIST Criteria.

Type of Response	Mismatch Repair–Deficient Colorectal Cancer (N=10)	Mismatch Repair–Proficient Colorectal Cancer (N=18)	Mismatch Repair–Deficient Noncolorectal Cancer (N=7)
Complete response — no. (%)	0	0	1 (14)*
Partial response — no. (%)	4 (40)	0	4 (57)†
Stable disease at week 12 — no. (%)	5 (50)	2 (11)	0
Progressive disease — no. (%)	1 (10)	11 (61)	2 (29)
Could not be evaluated — no. (%)‡	0	5 (28)	0
Objective response rate (95% CI) — %	40 (12–74)	0 (0–19)	71 (29–96)
Disease control rate (95% CI) — %§	90 (55–100)	11 (1–35)	71 (29–96)
Median duration of response — wk	Not reached	NA¶	Not reached
Median time to response (range) — wk	28 (13–35)	NA¶	12 (10–13)

* The patient had a partial response at 12 weeks, which then became a complete response at 20 weeks.
† One patient had a partial response at 12 weeks.
‡ Patients could not be evaluated if they did not undergo a scan at 12 weeks because of clinical progression.
§ The rate of disease control was defined as the percentage of patients who had a complete response, partial response, or stable disease for 12 weeks or more.
¶ The median time to response was not applicable (NA) because no responses were observed among patients with mismatch repair–proficient colorectal cancer.

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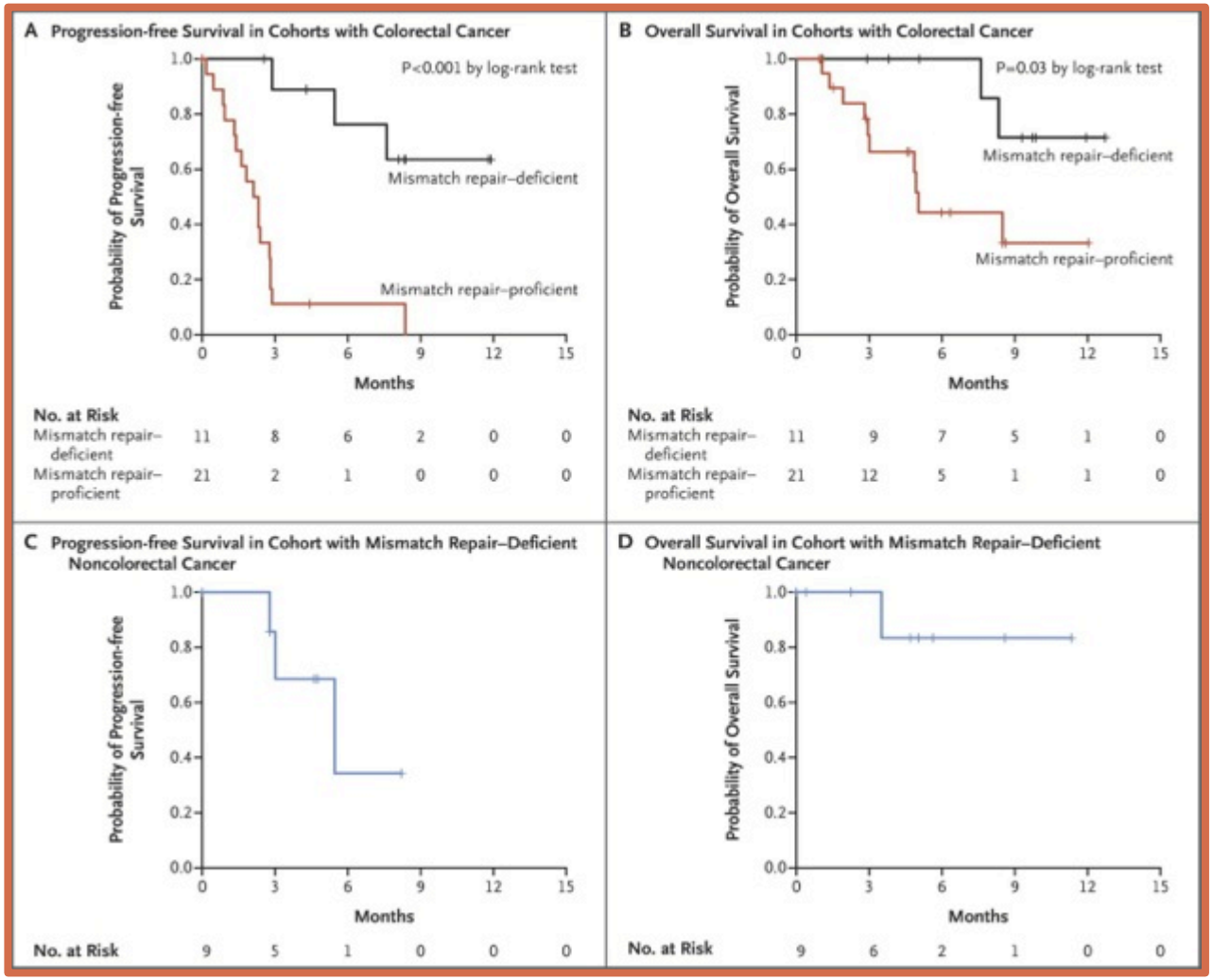
Le DT et al. N Engl J Med 2015;372:2509-2520.

CLINICAL BENEFIT OF PEMBROLIZUMAB TREATMENT ACCORDING TO MISMATCH-REPAIR STATUS

Progression Free Survival



Overall Survival

Le DT et al. N Engl J Med 2015;372:2509-2520.

ADVERSE EVENTS.

Table 3. Adverse Events.*

Event	All Grades	Grade 3 or 4
	no. of patients (%)	
Any	40 (98)	17 (41)
Blood or lymphatic		
Anemia	8 (20)	7 (17)
Lymphopenia	8 (20)	8 (20)
Sinus tachycardia	4 (10)	0
Dermatologic		
Dry skin	5 (12)	0
Rash or pruritus	10 (24)	0
Thyroiditis, hypothyroidism, or hypophysitis	4 (10)	0
Gastrointestinal		
Abdominal pain	10 (24)	0
Anorexia	4 (10)	0
Constipation	8 (20)	0
Diarrhea	10 (24)	2 (5)
Dry mouth	5 (12)	0
Nausea	5 (12)	0
Bowel obstruction	3 (7)	3 (7)
Hepatobiliary		
Elevated alanine aminotransferase	3 (7)	2 (5)
Pancreatitis†	6 (15)	0
Metabolism and nutrition		
Hypoalbuminemia	4 (10)	4 (10)
Hyponatremia	3 (7)	3 (7)
Musculoskeletal		
Arthralgia	7 (17)	0
Myalgia	6 (15)	0
Nervous system		
Dizziness	4 (10)	0
Headache	7 (17)	0
Insomnia	3 (7)	0
Respiratory‡		
Allergic rhinitis	12 (29)	0
Cough	4 (10)	0
Dyspnea	6 (15)	0
Upper respiratory infection	3 (7)	0
Cold intolerance	6 (15)	0
Edema	4 (10)	0
Fatigue	13 (32)	0
Fever	5 (12)	0
Pain	14 (34)	0

* Included are adverse events occurring in more than 5% of patients. A total of 41 patients were included in the analysis.
† All cases of pancreatitis were asymptomatic.
‡ One case of pneumonitis occurred (2%).

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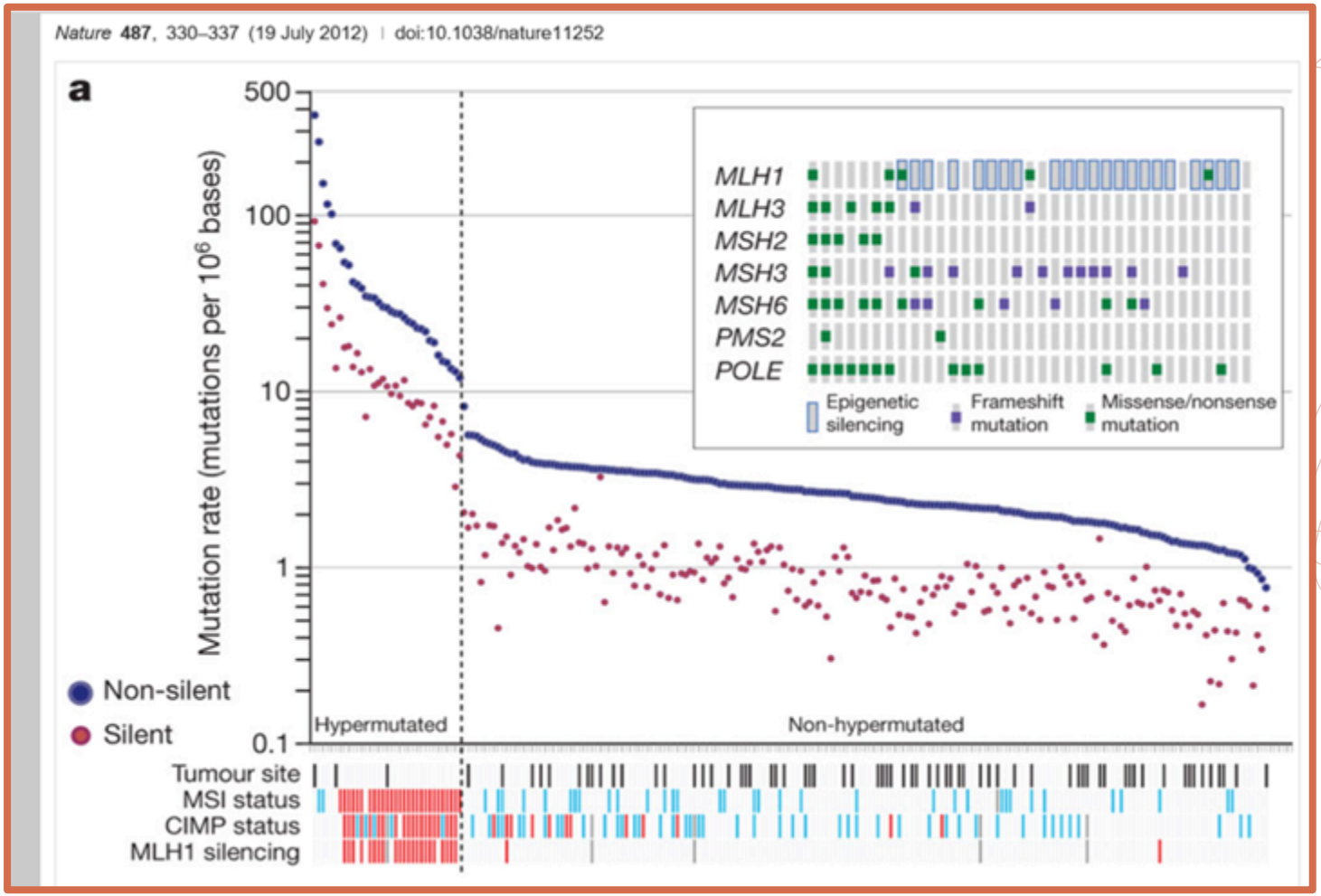
HYPERMUTATED CRCS ARE PRONE TO BENEFIT FROM IMMUNOTHERAPY



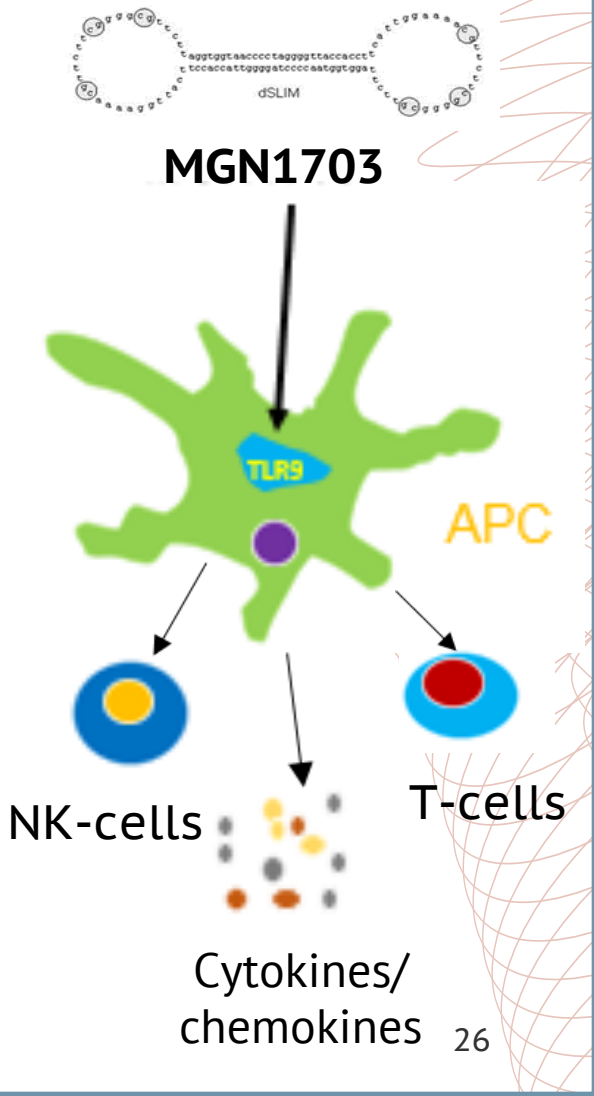
IMMUNOLOGY AND CRC

- **In diagnosis**
  - Predictive marker
  - Prognostic marker

- **In treatment**
  - Passive immunotherapy (monoclonal antibodies)
  - **Active immunotherapy (immunization)**

MGN1703: IS A COVALENTLY CLOSED DUMBBELL-SHAPED DNA MOLECULE ACTING AS A POTENT TLR-9 AGONIST

- Non-coding DNA molecule with CG-motifs
- Linear, double-stranded, covalently-closed, dumbbell-shaped immunomodulator
- TLR9 agonist
- Broad activation of innate & adaptive immune system
  - Antigen presenting cells (pDCs, B-cells)
  - Subsequent activation of various pathways (like CTL, NK-cells, ADCC)
- Phase 1 Study with metastatic solid tumor patients (i.e. mCRC, metastatic lung cancer)
- Phase 2: Good safety profile and first signs of a potential clinical effect



Abbreviations - TLR-9: toll-like receptor 9; APC: antigen presenting cells; pDC: plasmacytoid dendritic cells; NK-Cells: natural killer cells; CTL: cytotoxic T-lymphocytes; ADCC: antibody-dependent cell-mediated cytotoxicity;

STUDY DESIGN

Primary endpoint:

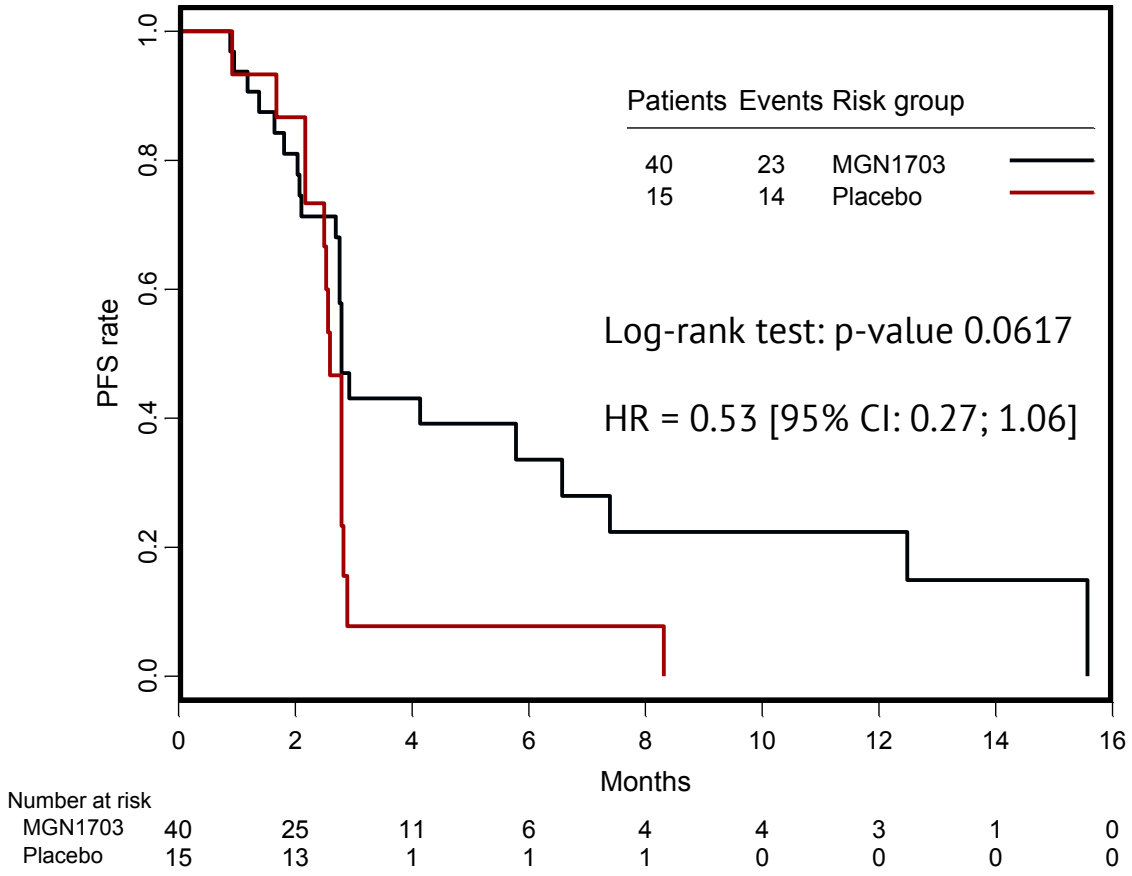
- PFS from randomization

Secondary endpoints:

- PFS from induction therapy
- Overall survival, Overall response rates
- Safety (CTCAE v4.0)
- Pharmacodynamics
- Biomarker (incl. immunologic response)
- QoL (QLQ-C30 and -CR29)

PRIMARY ENDPOINT: PFS OF MAINTENANCE

Intent-to-treat (ITT) population



	Months [95% CI]	
PFS	**MGN1703**	**Placebo**
Median PFS	**2.8** [2.8; 6.6]	**2.6** [2.5; 2.8]
25% quartile	2.1 [1.6; 2.8]	2.2 [1.7; 2.6]
75% quartile	7.4 [2.9; 15.6]	2.8 [2.6; 2.9]

ESMO 2012. Abbreviations: HR, Hazard ratio; CI, Confidence interval

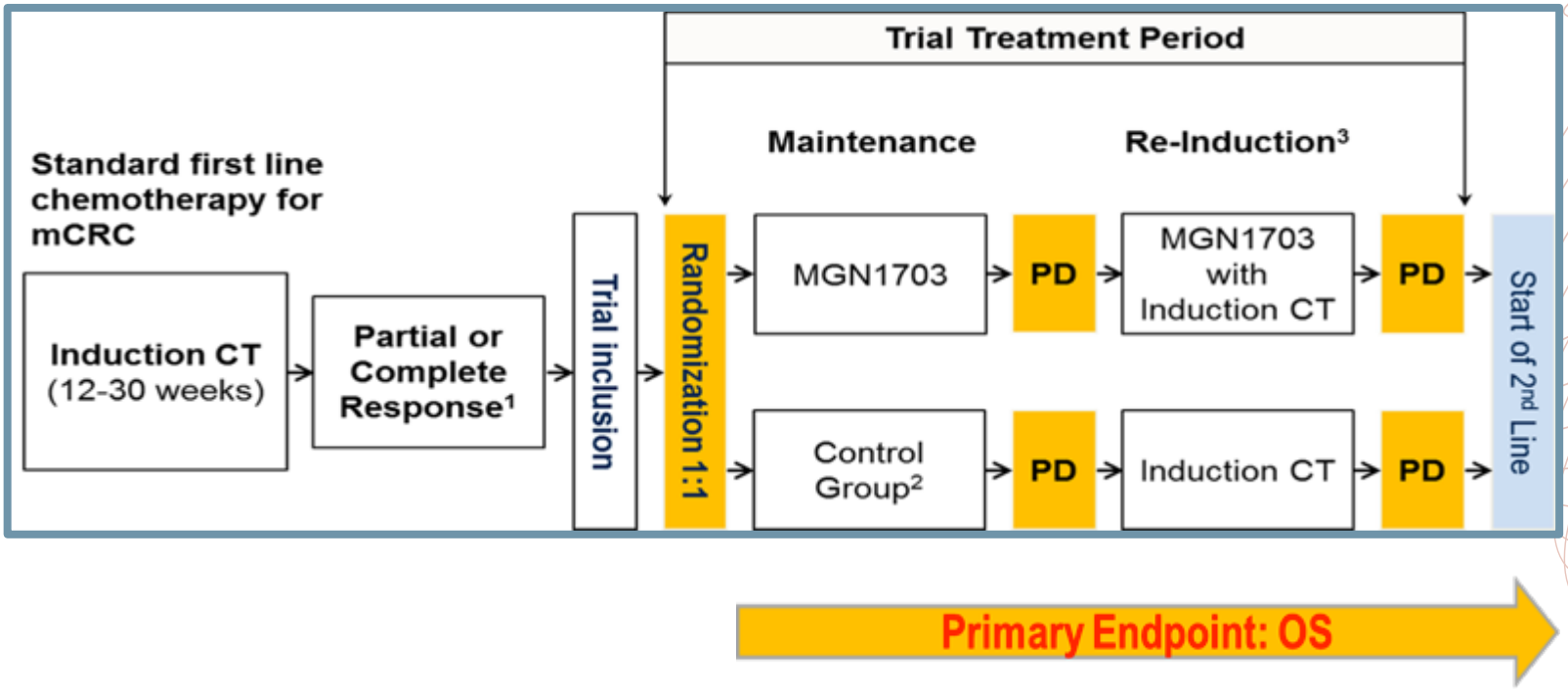
RESULTS – ADVERSE EVENTS (1/2)

Grade 3 & 4 Toxicities

Event	MGN1703, n=40		Placebo, n=15	
Grade / No. of events (patients)	3	4	3	4
Hypertension	4 (2)	---	---	---
Hypertension worsening	1 (1)	---	----	---
Ileus	1 (1)	2 (2)	---	---
Paralytic ileus	1 (1)	---	---	---
Sepsis	---	1 (1)	---	---
Pain	---	---	1 (1)	---
Sensory polyneuropathy	1 (1)	---	---	---
Papular exanthema	---	---	1 (1)	---
Nausea / Vomiting	1 (1)	---	---	---

IMPALA: STUDY DESIGN

A prospective randomized Phase III Study:
MGN1703 is a potent TLR-9 agonist, with a safe profile, which activates the immunsystem



COMBINATION IMMUNOTHERAPY: ONGOING STUDIES

Treatment (Company)	Strategy	Phase	Indication	CT.gov identifier
Imprime PGG® + cetuximab vs cetuximab (Biothera)	Cancer vaccine (neutrophil-activating beta-glucan polymer) + anti-EGFR mAb	III (PRIMUS)	Recurrent or progressive KRAS wild type CRC	NCT01309126
MEDI6469 ± tremelimumab and/or MEDI4736 (MedImmune)	Anti-OX40 agonist antibody ± anti CTLA4 antibody and/or anti-PD-L1 antibody	I/II	Advanced solid tumours	NCT02205333
Nivolumab ± ipilimumab (Bristol-Myers Squibb)	Anti-PD-1 antibody ± anti-CTLA-4 antibody	I/II (CheckMate 142)	Recurrent MSI-positive mCRC	NCT02060188
Urelumab ± nivolumab (Bristol-Myers Squibb)	Anti-4-1BB/CD137 antibody ± anti-PD-1 antibody	I/II	Solid tumours	NCT02253992

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Clinicaltrials.gov

CONCLUSIONS

- Immunotherapies in the treatment of advanced colorectal cancer have been introduced into clinical routine 10 years ago
- They provide an effective tool for inducing treatment response and prolonging survival
- Acquired mutations occur frequently during the development of anti-EGFR resistance
- Novel active immunostimulation seems to be a promising approach for control of disease
- MSI might represent a novel biomarker for anti-PD-(L)1 treatment in GI cancer
- Clinical trials are urged for implementation of the Immunoscore, liquid biopsies and active immuno-therapies into routine clinical use

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THE HEART OF MEDICAL EDUCATION

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