Immuno-Oncology in colorectal cancer:

What has been tried?

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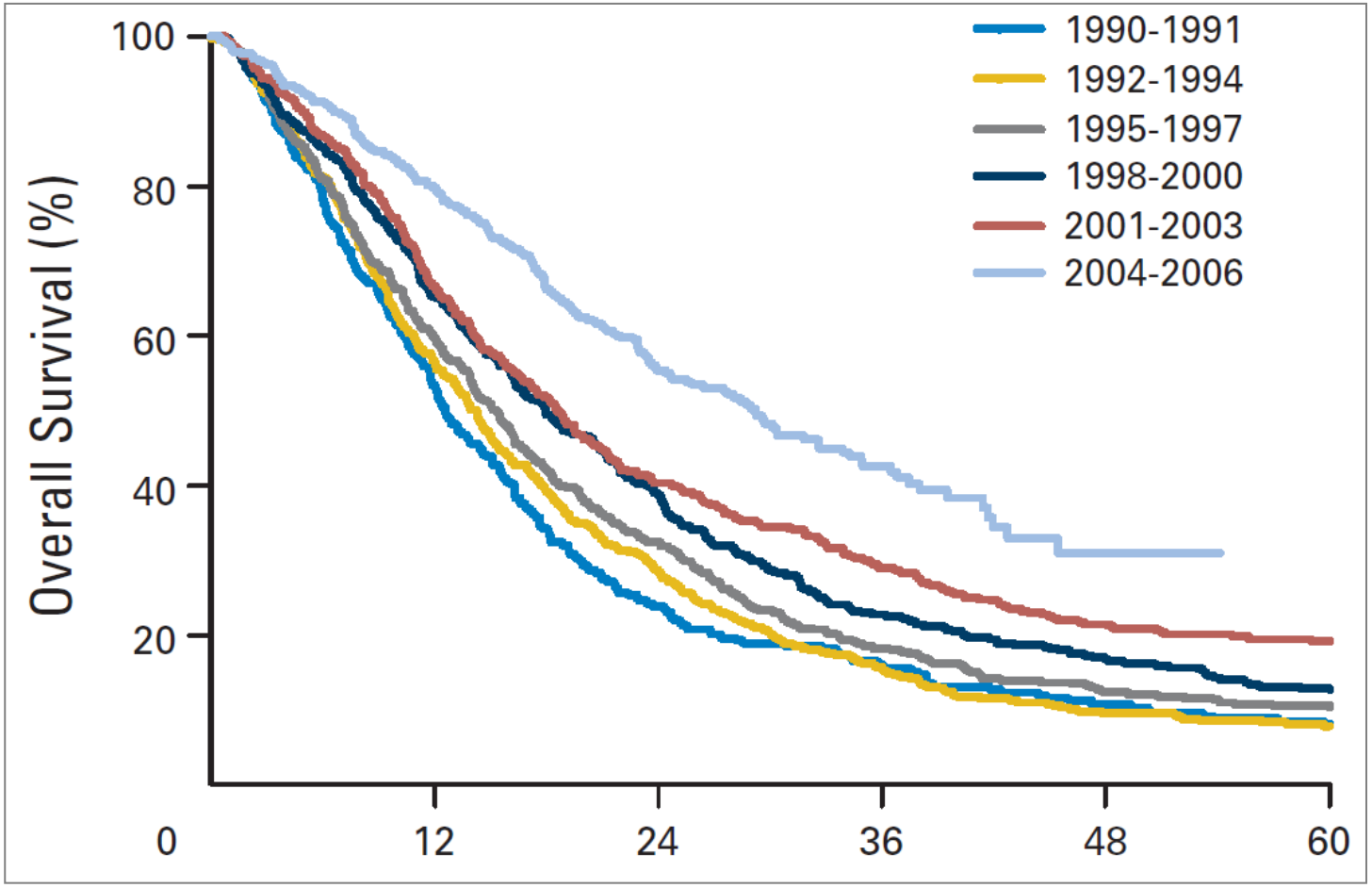
Potential conflicts of interest

- Travel support, activities as speaker and research support from

  Roche, sanofi-aventis, Bayer, Merck Serono

Survival with MCRC: Improvement over the last years



Kopetz S, et al. J Clin Oncol 27:3677-83, 2009

clinical practice guidelines

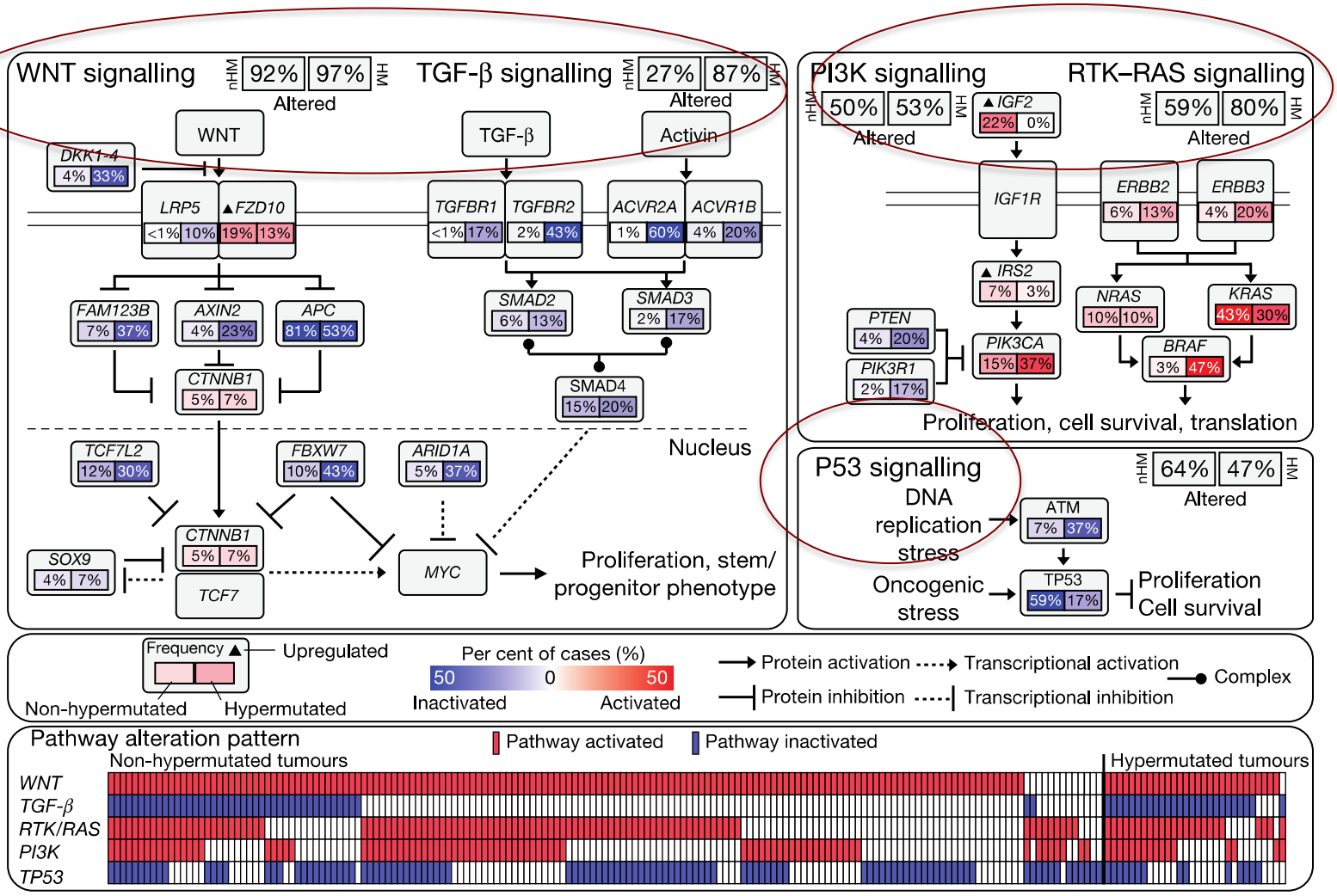
Annals of Oncology 25 (Supplement 3): iii1–iii9, 2014
doi:10.1093/annonc/mdu260

Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

E. Van Cutsem[1], A. Cervantes[2], B. Nordlinger[3] & D. Arnold[4], on behalf of the ESMO Guidelines Working Group*

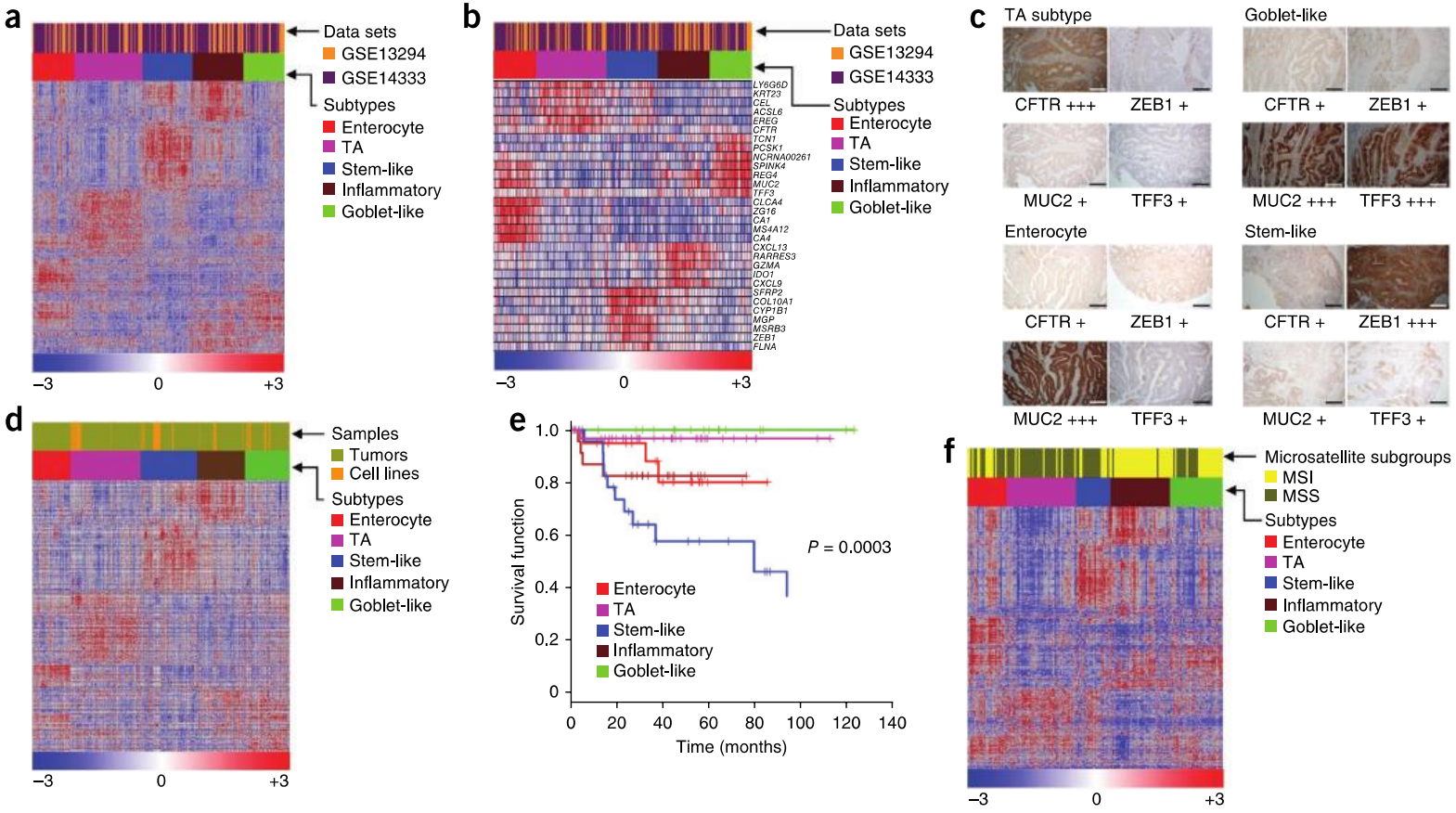
- **Improving treatment** efficacy - and **selecting the best** treatment (chemo/TT) for the individual patient
- Using the **„chance for cure“** – by **resection** of metastases (and other **local ablative** treatments)
- Using the **„continuum of care“** with optimizing treatment at different lines, incl. supportive care

Colon Cancer: How many diseases...?



Human Cancer Genome Atlas, Nature 2012

A colorectal cancer classification system that associates cellular phenotype and responses to therapy



Sadanandam et al., Nature Medicine, 19 (5) 2013

Combination chemotherapies with cytokines: Phase II trial

VOLUME 23 · NUMBER 35 · DECEMBER 10 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Chemo-Immunotherapy of Metastatic Colorectal Carcinoma With Gemcitabine Plus FOLFOX 4 Followed by Subcutaneous Granulocyte Macrophage Colony-Stimulating Factor and Interleukin-2 Induces Strong Immunologic and Antitumor Activity in Metastatic Colon Cancer Patients

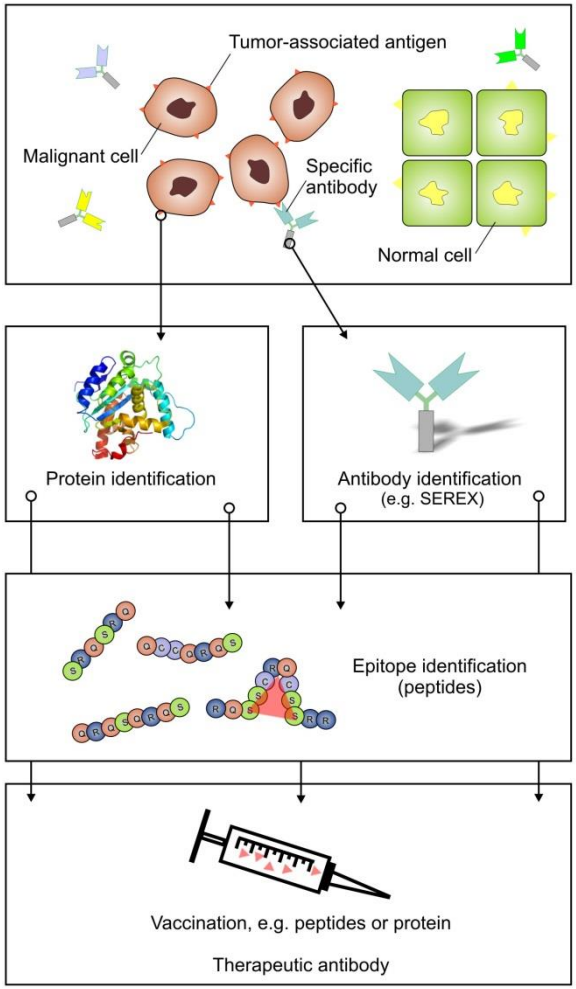
Pierpaolo Correale, Maria Grazia Cusi, Kwong Yok Tsang, Maria Teresa Del Vecchio, Stefania Marsili, Marco La Placa, Chiara Intrivici, Angelo Aquino, Lucia Micheli, Cristina Nencini, Francesco Ferrari, Giorgio Giorgi, Enzo Bonmassar, and Guido Francini

Gemcitabine + FOLFOX-4 followed by GM-CSF and low-dose IL-2 in mCRC pts.

- **29 pts.**, 21 with previous treatment; 19 with CLM.
- **Very high ORR (69%) and disease control rates (96%)**
- Median **time to progression: 12.5 months**.
- Immunologic study of PBMCs: enhanced proliferative response to colon carcinoma antigen and a signal reduction in suppressive T regs (CD4+CD25T-reg+)
- Cytofluorimetric study of the PBMCs of five HLA-A(★)02.01+ pts. with ORR showed an increased frequency of cytolytic T lymphocyte precursors specific for known CEA- and TS-derived epitopes.

Correale et al., J Clin Oncol 2005; 23(35): 1741-52

Vaccination strategies



Halama et al. J Oncology 2010

Clinical and immunologic responses to active specific cancer vaccines

- To 2005**: 32** phase I/II studies; **527** patients with advanced or metastatic CRC
- broad variety of substances (e.g., autologous tumor cells, peptide vaccine, dendritic cells, idiotypic antibody, and virus-based vaccine).
- Pooled analysis: **ORR 0.9%** for advanced/metastatic CRC
- **Disease stabilization rate: 8.3%**
- Humoral immune responses: 59%, and cellular responses in 44% of the cases.

Nagorsen et al., Clin Cancer Res. 2006; 12(10):3064-9.

Phase I/II Combined Chemoimmunotherapy with Carcinoembryonic Antigen–Derived HLA-A2–Restricted CAP-1 Peptide and Irinotecan, 5-Fluorouracil, and Leucovorin in Patients with Primary Metastatic Colorectal Cancer

Martin R. Weihrauch,[1,2] Sascha Ansén,[1,2] Elke Jurkiewicz,[4] Caroline Geisen,[4] Zhinan Xia,[1,2] Karen S. Anderson,[1,2,3] Edith Gracien,[8] Manuel Schmidt,[6] Burghardt Wittig,[6,7] Volker Diehl,[4] Juergen Wolf,[4] Heribert Bohlen,[5] and Lee M. Nadler[1,2,3]

- HLA-A2–positive pts., with elevated serum CEA
- 3# of **5FU/irinotecan and vaccinations with CEA-derived CAP-1 peptide** with different adjuvants

  [CAP-1/GM-CSF/interleukin-2, CAP-1/dSLIM/IL-2, CAP-1/IL-2].
- After chemotherapy: weekly vaccinations until PD
- **17** included; 12 completed 3 cycles: 5 CR, 1 PR, 5 SD, 6 PD
- 8 pts. (47%) showed elevation of CAP-1–specific CTLs.
- ***None* of the adjuvants** provided superiority in eliciting CAP-1–specific immune responses.

Weihrauch et al., Clin Cancer Res 2005

Cancer Immunology, Immunotherapy
November 2011, Volume 60, Issue 11, pp 1565-1575

Date: 17 Jun 2011

Comprehensive immunological analyses of colorectal cancer patients in the phase I/II study of quickly matured dendritic cell vaccine pulsed with carcinoembryonic antigen peptide

Mitsuru Sakakibara, Tatsuya Kanto, Michiyo Hayakawa, Shoko Kuroda, Hideki Miyatake, Ichiyo Itose, Masanori Miyazaki, Naruyasu Kakita, Koyo Higashitani, Tokuhiro Matsubara, ... show all 14

CIMT
Cancer Immunotherapy

- CEA peptide-loaded DC generated with OK432 (Streptococcuspyogenes preparation), prostanoid, and interferon-α (OPA-DC).
  8 evaluable pts: 1 with stable disease
  In the SD patient, NK cell frequency and cytolytic activity were increased and frequency of CEA-specific cytotoxic T cells (CTLs) increased stepwise with repetitive vaccinations.

Sakakibara et al., Cancer Immunology Immunotherapy 2011 (60),11: 1565-75

A Randomized Phase II Study of Immunization With Dendritic Cells Modified With Poxvectors Encoding CEA and MUC1 Compared With the Same Poxvectors Plus GM-CSF for Resected Metastatic Colorectal Cancer

- **DCs** modified with poxvectors encoding CEA and MUC1 **(PANVAC)** or **PANVAC/GM-CSF**
- After CLM resection and perioperative chemotherapy; n = 74 also compared with that of an unvaccinated, contemporary group
- Recurrence-free survival at 2 y was **similar** (47% and 55% for DC/PANVAC and PANVAC/GM-CSF, respectively)
- As a group, vaccinated patients had **superior OS** compared with the contemporary **unvaccinated** group.

Morse et al., Ann Surg Oncol 2013; 258 (6): 1579-87

Cancer Immunology, Immunotherapy
January 2009, Volume 58, Issue 1, pp 61-69

Date: 17 May 2008

Efficiency of adjuvant active specific immunization with Newcastle disease virus modified tumor cells in colorectal cancer patients following resection of liver metastases: results of a prospective randomized trial

T. Schulze, W. Kemmner, J. Weitz, K.-D. Wernecke, V. Schirrmacher, P. M. Schlag

CIMT
Cancer Immunotherapy

- Patients after CLM resection: **randomised** to the vaccination (6 doses of Newcastle disease virus infected autologous tumour cell **vaccine or control**.
- 50 pts available for analysis.
- In the total patient group (colorectal cancer), **no differences** in PFS and secondary endpoints.
- Subgroup: significant advantage for vaccinated *colon* cancer patients in the intention-to-treat analysis.

Schulze et al., Cancer Immunology Immunotherapy 2009 (58),1: 61-9

CALGB trial 89903 after CLM resection

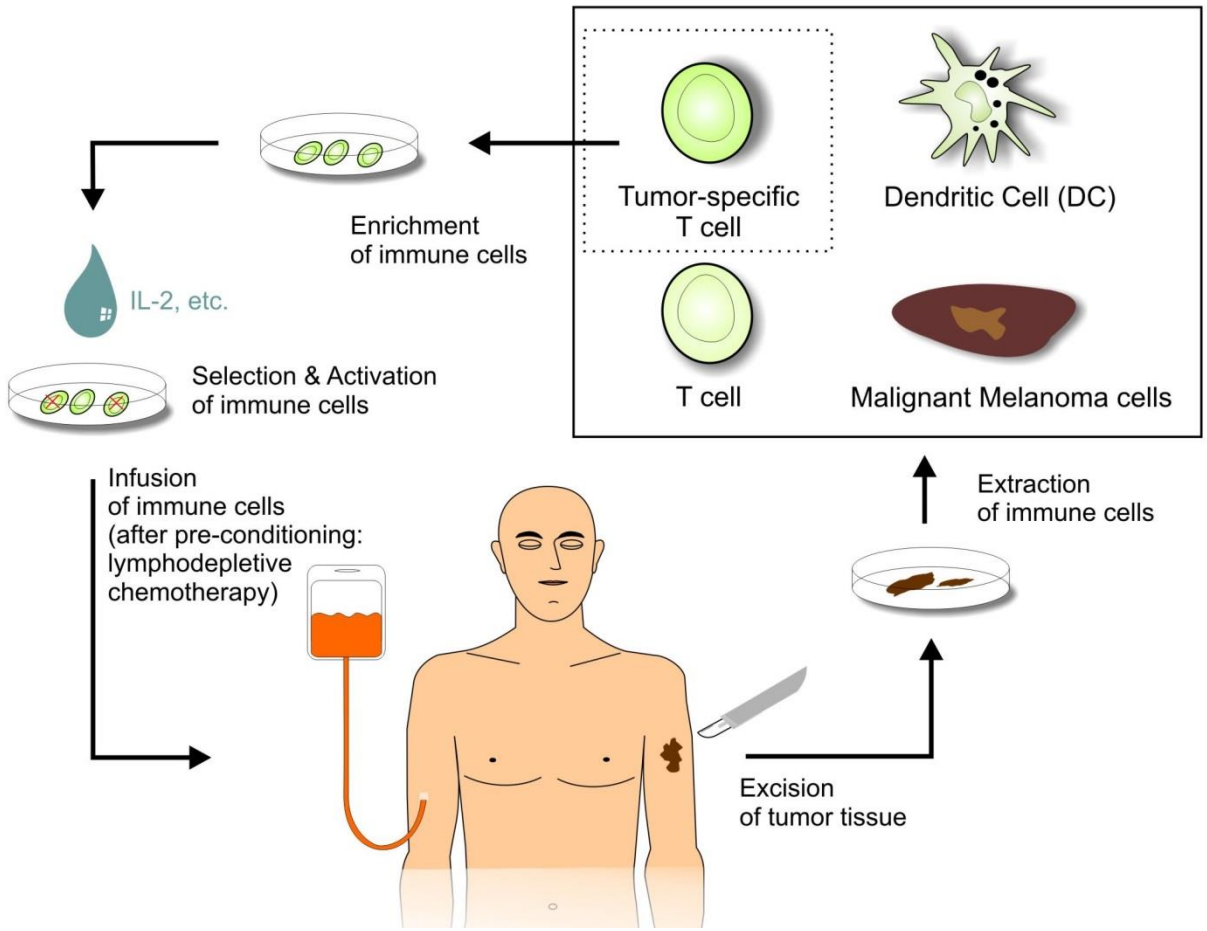
- 6-12 weeks post: **4 # of CeaVac** and human milk fat globule **(TriAb)** (both are co-expressed in more than 90% of CRC)
- Monthly treatments for 2 years, then 6/yr. for 3 yrs.
- **49 pts** evaluable for the primary endpoint.
- Patients with RFS / OS @ 2 yrs.: **39% and 94%**
- **„...**did **not improve** 2-year recurrence-free survival when **compared with the expected** value of 40% reported for hepatic resection alone.

Posner et al., Ann Surg Oncol 2011, 254(4): 931-9

Vaccination strategies in CRC: Summary

- Mainly adjuvant treatment with vaccines shows some efficacy
- No large trials available
- In advanced disease: (very) limited effects

Adoptive T cell transfer



Halama et al. J Oncology 2010

Adjuvant, Adoptive Immunotherapy With Tumor Infiltrating Lymphocytes Plus Interleukin-2 After Radical Hepatic Resection for Colorectal Liver Metastases: 5-Year Analysis

ANDREA GARDINI, MD,[1]* GIORGIO ERCOLANI, MD,[1] ANGELA RICCOBON, BSc,[2] MATTEO RAVAIOLI, MD,[1] LAURA RIDOLFI, MD,[2] EMANUELA FLAMINI, BSc,[2] RUGGERO RIDOLFI, MD,[2] GIAN LUCA GRAZI, MD,[1] ANTONINO CAVALLARI, MD,[1] AND DINO AMADORI, MD[2]

[1]*Department of Surgery and Transplantation, University of Bologna, Bologna, Italy*
[2]*Department of Medical Oncology, Pierantoni Hospital, Forlì, Italy*

Background and Objectives: Conventional chemotherapy has not proven effective in improving long-term results of surgery for liver metastases from colorectal cancer. We assessed the usefulness of immunotherapy with tumor infiltrating lymphocytes (TIL) plus Interleukin-2 (IL-2) as adjuvant treatment.

Methods: Between 1995 and 1998, 47 patients were enrolled onto a prospective protocol; 25 entered the treatment group (A) and 22 entered the control group (B). All patients had undergone radical liver resection. TIL obtained from surgical specimens from group A patients were cultured and activated in vitro with IL-2, then reinfused into the patients with IL-2. We investigated pre- and post-IL-2 stimulation expression of T cell receptor (TCR) ζ- and ε-chains, $p56^{lck}$, Fas, and Fas-L by TIL immunostaining.

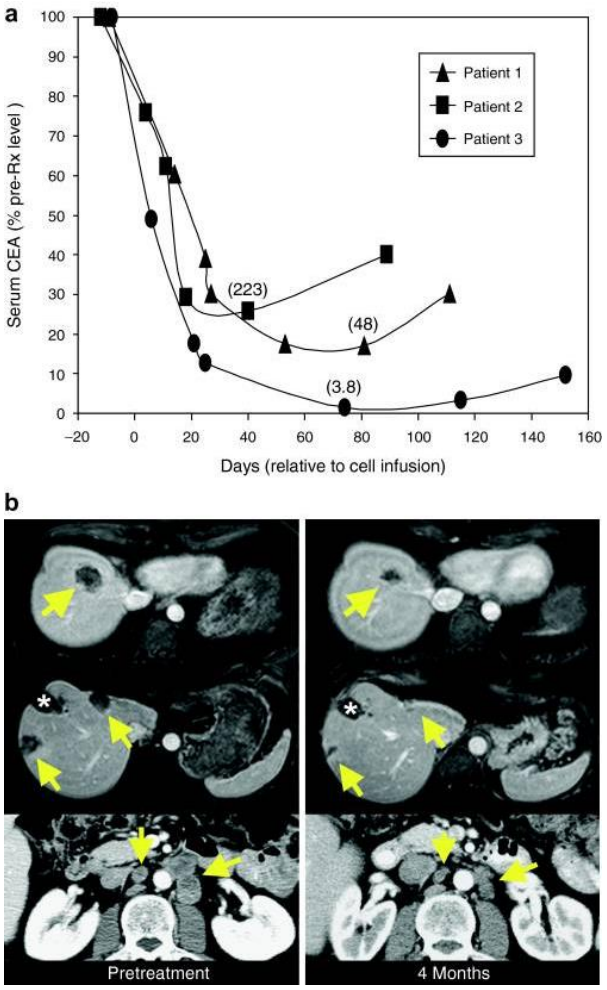
Results: Fourteen patients from group A (56%) received immunotherapy; 14 from group B (60%) underwent conventional chemotherapy, and the remaining 19 patients did not receive any treatment. No significant differences between the two groups were found in the actuarial and disease-free survival (DSF) rates after 1, 3, and 5 years. After IL-2 exposure, TCR ζ-chain expression significantly increased ($P = 0.001$); An increase in TCR ε-chain expression ($P = 0.04$), and $p56^{lck}$ ($P = 0.03$) was detected; TCR ε-chain expression was significantly increased in disease-free patients compared to those who relapsed ($P = 0.04$). Fas-L expression was correlated with the TCR ε-chain and $p56^{lck}$ levels ($P = 0.05$).

Conclusions: Our data suggest that we are still a long way from being able to propose TIL + IL-2 treatment as an effective adjuvant therapy. However, the results confirm that the biological indicators examined could play an important role in modulating immunitary response against tumor cells.

J. Surg. Oncol. 2004;87:46–52.

KEY WORDS: TIL; liver metastases; adoptive immunotherapy; colorectal cancer

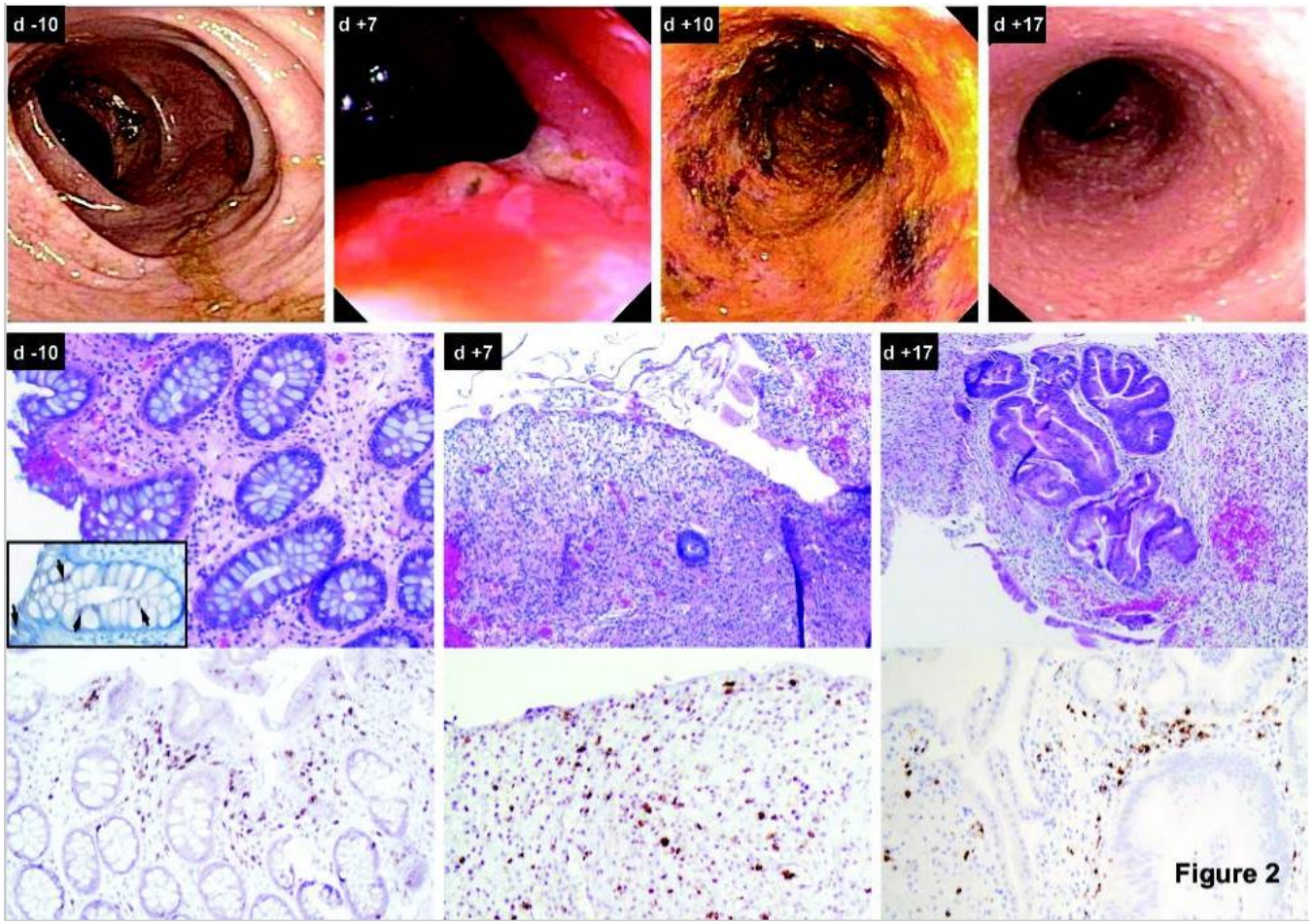
“T cells targeting carcinoembryonic antigen can mediate regression of mCRC….



Cancer-related responses to treatment. (**a**) Carcinoembryonic antigen (CEA) protein levels in sequential serum samples from each patient. Levels are expressed as the percent of the pretreatment concentrations, and values in parentheses are the lowest concentrations achieved in each patient in µg/l. (**b**) Computed tomography scans for patient 3 prior to treatment and 4 months post-treatment. Arrows represent locations of colorectal cancer metastases, and the asterisk indicates a liver defect at a site of liver metastasis previously treated with radiofrequency ablation (RFA). Top and middle rows: patient 3 liver. Bottom row: patient 3 paraaortic lymph nodes.

Parkhurst et al. Mol Therapy 2011

“…. but induce severe transient colitis.”



Parkhurst et al. Mol Therapy 2011

“T cells targeting carcinoembryonic antigen can mediate regression of mCRC….but induce severe transient colitis

„This report represents the first example of objective regression of metastatic colorectal cancer mediated by adoptive T cell transfer **and illustrates the successful use of a TCR**, raised in human leukocyte antigen (HLA) transgenic mice, against a human tumor associated antigen.

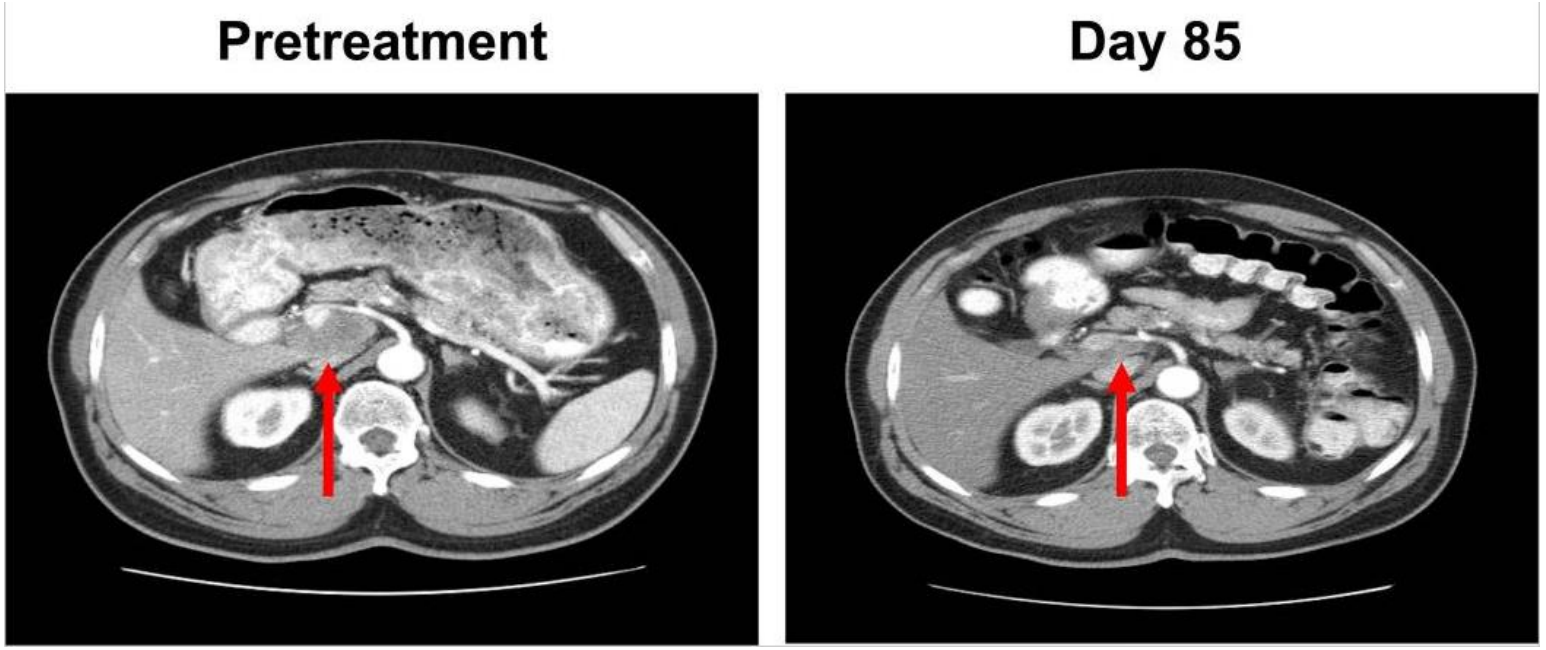
It also **emphasizes the destructive power of small numbers of highly avid T cells and the limitations of using CEA** as a target for cancer immunotherapy.“

Cell mediated immune (CMI) induction with ETBX-011

- Phase 1/2 **single agent trial ETBX-011** for mCRC
- every 3 wks for 3 immunizations.
- Patients **refractory to prior** therapies
- well-tolerated (at all doses)
- Specific anti-CEA immune responses were observed in the majority of patients and median OS: 11 months.
- **48% of patients still survived at 12 month** follow-up and **28% at 18 months** following treatments.
- A single agent randomized multicenter Phase 2b trial initiated to further evaluate the clinical effectiveness.

Garbitsch et al., J Clin Oncol 32:5s, 2014 (suppl; abstr 3093)

„Durable Cancer Regression Off-Treatment and Effective Reinduction Therapy with an anti-PD-1 moAb“



Response of metastatic colorectal cancer to anti-PD-1 therapy. CT scan showing partial regression of a representative lymph node metastasis in a patient with CRC after receiving a single dose of anti-PD-1.

Lipson et al., Clin Cancer Res. Jan 15, 2013; 19(2): 462–468

Immunomodulation: Summary

- Results from 19 patients with mCRC in 3 trials
- Only in few responses to immunomodulation have been observed
- Similar findings across different immunomodulatory approaches (PD-1, PD-L1, etc.)

Currently ongoing

Phase 2 study of programmed death-1 antibody **(anti-PD-1, MK-3475**) in patients **with microsatellite unstable (MSI)** tumors.

Dung T. Le, J Clin Oncol 32:5s, 2014 (suppl; abstr TPS3128)

A phase 1/2 study to evaluate the safety and tolerability of **MEDI4736, an anti–PD-L1 antibody, in combination with tremelimumab** in patients with advanced solid tumors.

Margaret Callahan, J Clin Oncol 32:5s, 2014 (suppl; abstr TPS3120)

A pilot trial of a combination of **therapeutic vaccines** (GI-4000 and GI-6207) as adjunctive therapy with first-line therapy **with bevacizumab plus either FOLFOX or FOLFIRI** in patients with newly diagnosed Ras-mutant or WT metastatic CRC.

John Marshall, J Clin Oncol 30, 2012 (suppl; abstr TPS3638)

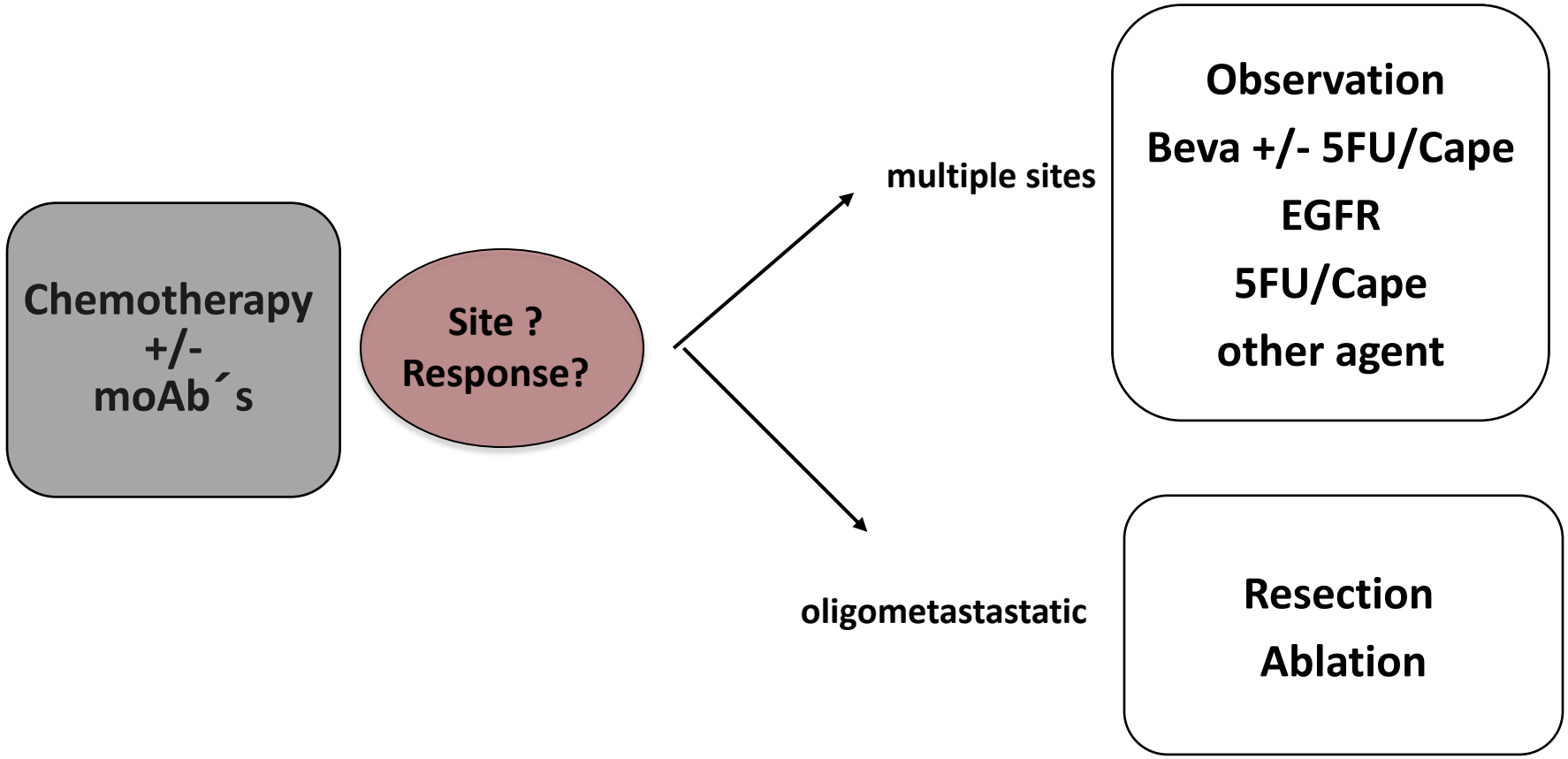
Where is the best place to develop immunotherapies in CRC?

- Adjuvant treatment UICC II/III?
- Additive after liver mets resection?
- Upfront, in indolent disease?
- In refractory patients?
- As „maintenance“, after induction treatment and/or ablation?

Optimization of the treatment flow

„Induction treatment“

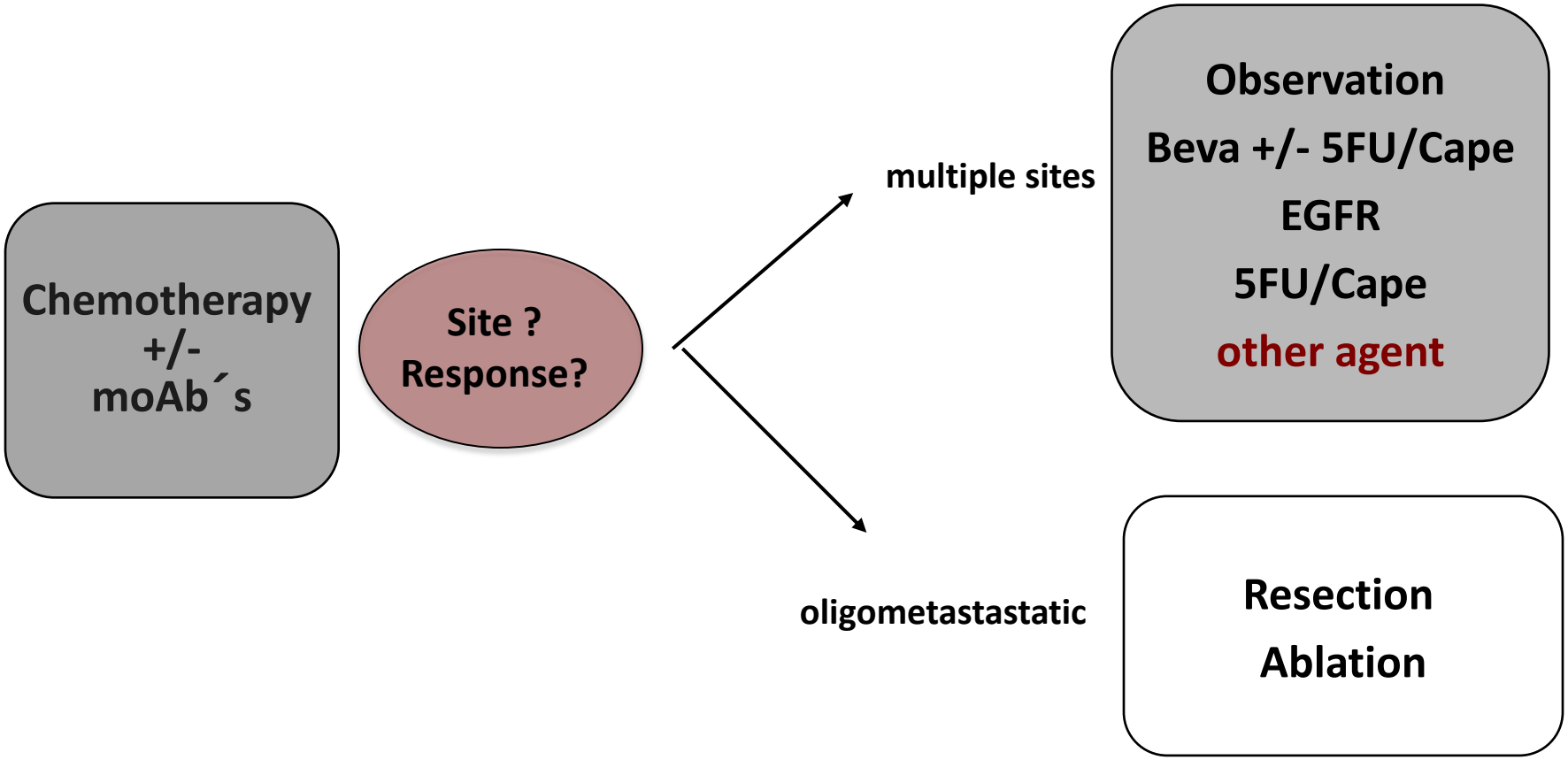
„Maintenance treatment



Optimization of the treatment flow

„Induction treatment“

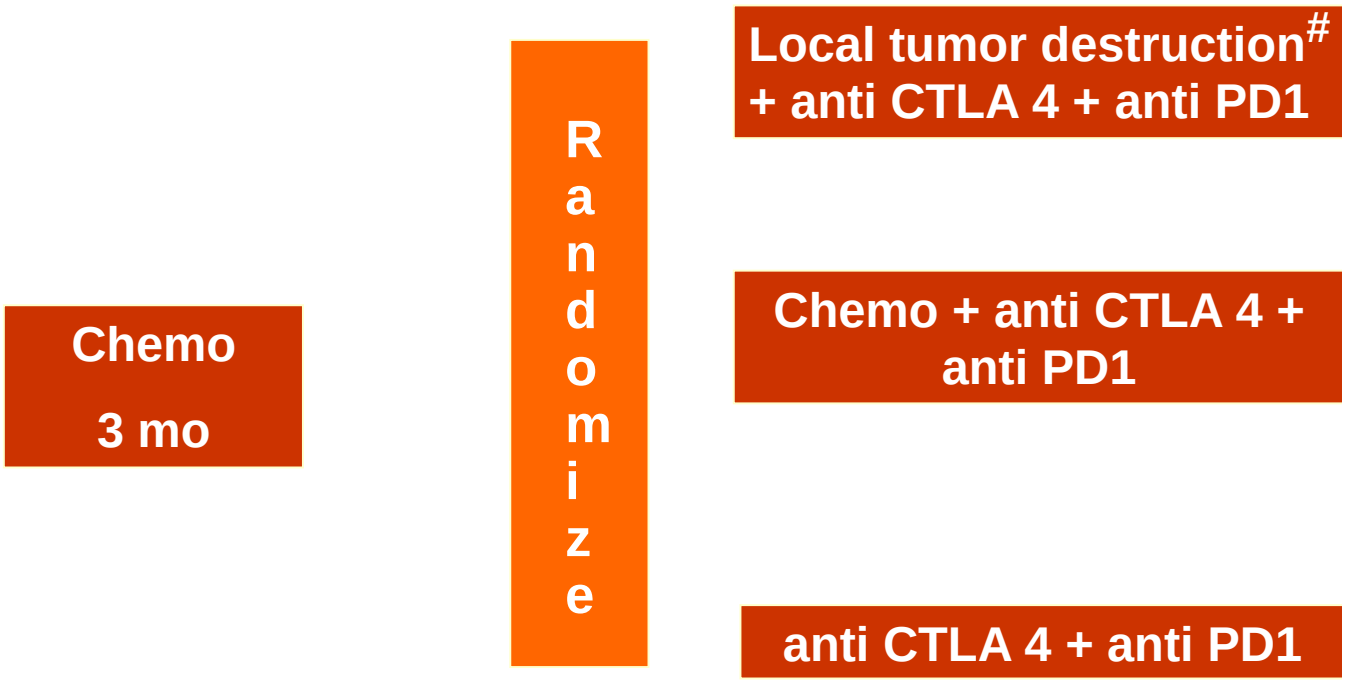
„Maintenance treatment



Draft: CLOCC2 trial

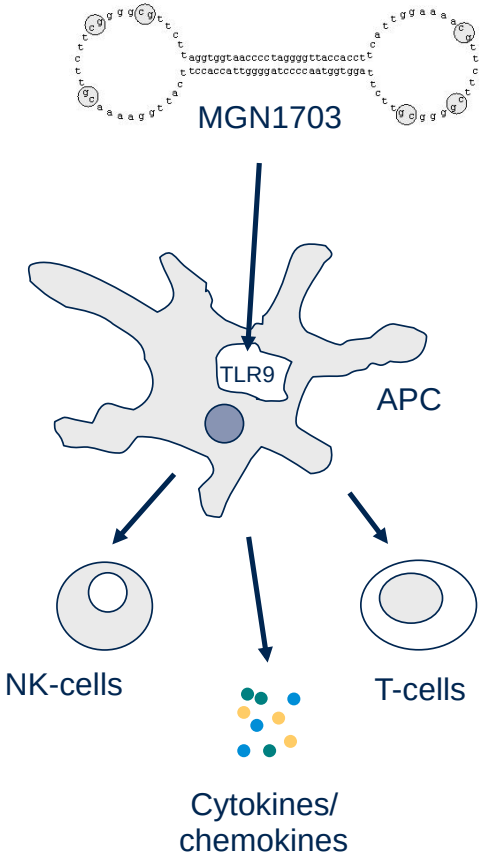
EORTC
European Organization for Research and Treatment of Cancer

Study design



MGN1703: A DNA Immunomodulator

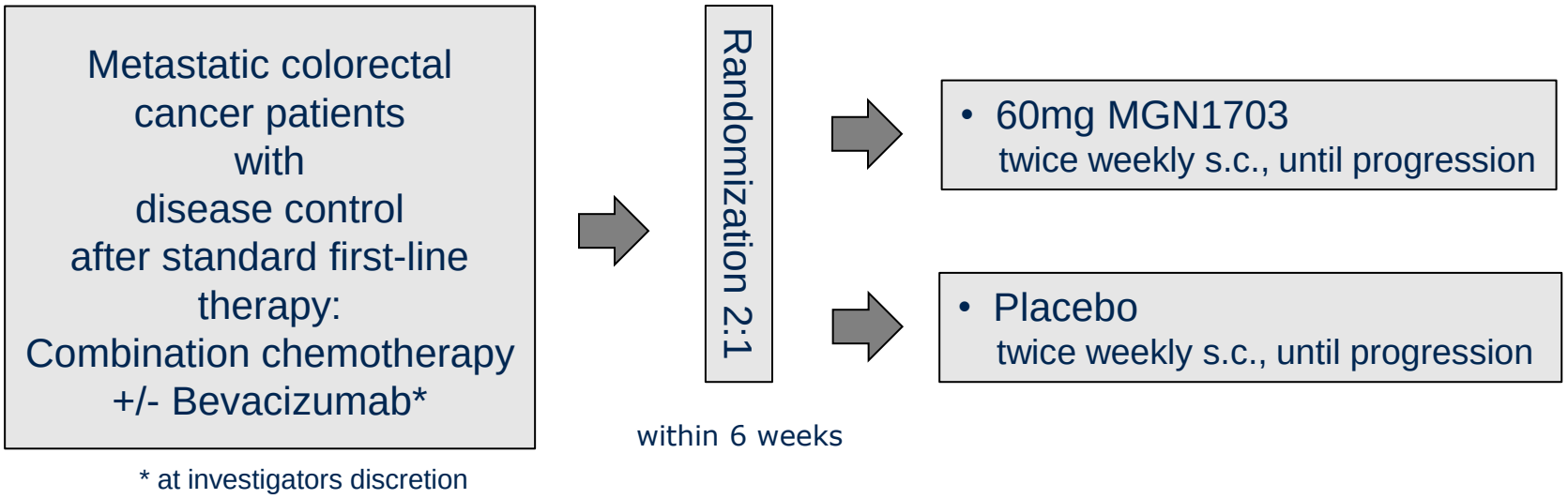
- Non-coding DNA molecule with CG-motifs
- Linear, double-stranded, covalently-closed, dumbbell-shaped immunomodulator
- TLR9 agonist
- Broad activation of innate & adaptive immune system
  - Antigen presenting cells (pDCs, B-cells)
  - Subsequent activation of various pathways (like CTL, NK-cells, ADCC)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

Arnold et al., Ann Oncol Supppl 2012 (oral ESMO 2012); in press: J Cancer Res Clin Oncol 2014

STUDY DESIGN



* at investigators discretion

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)

Arnold et al., Ann Oncol Suppl (ESMO, oral presentation) 2012

MGN1703 versus Placebo as „Maintenance“in 1L mCRC

Primary and secondary endpoints

Progression free survival (PFS)

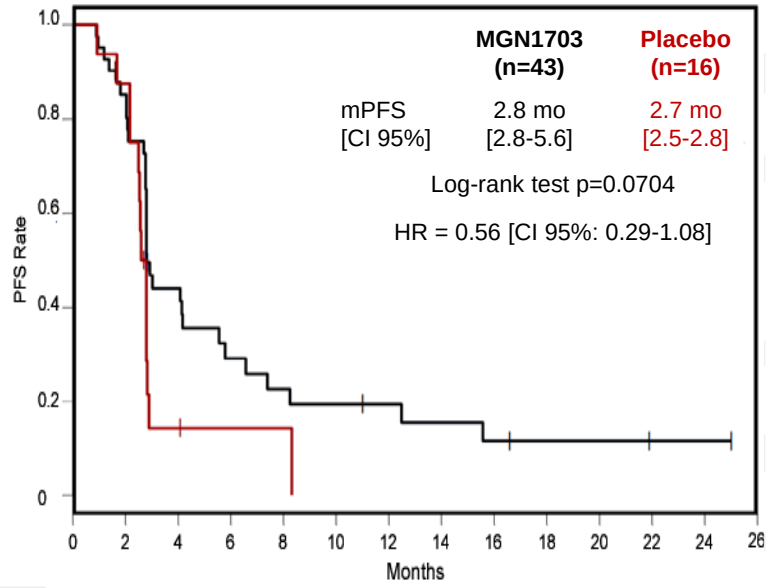


Figure 2: Primary endpoint - PFS on maintenance from start of MGN1703 or placebo. Abbreviations: HR, hazard ratio; CI, confidence interval.

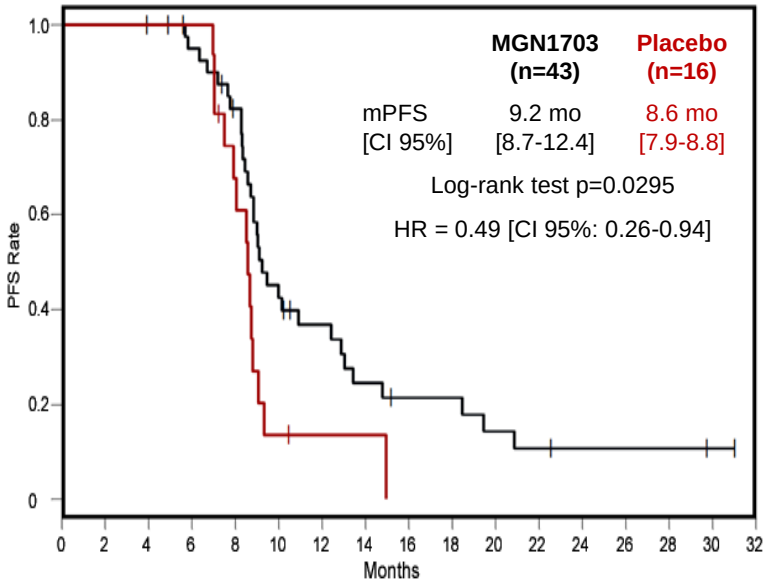


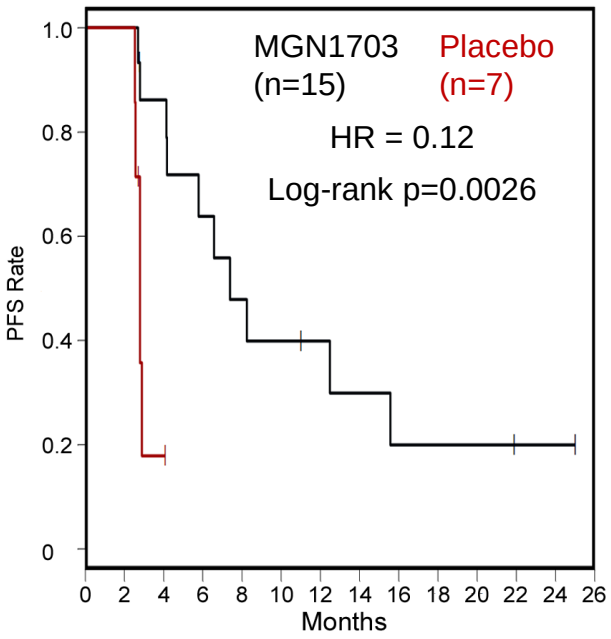
Figure 3: Secondary endpoint - PFS from start of induction chemotherapy. Abbreviations: HR, hazard ratio; CI, confidence interval.

Arnold et al., Ann Oncol Suppl (ESMO, oral presentation) 2012
Schmoll et al., J Cancer Res Clin Oncol 2014

MGN 1703 as maintenance: Exploratory Subgroups

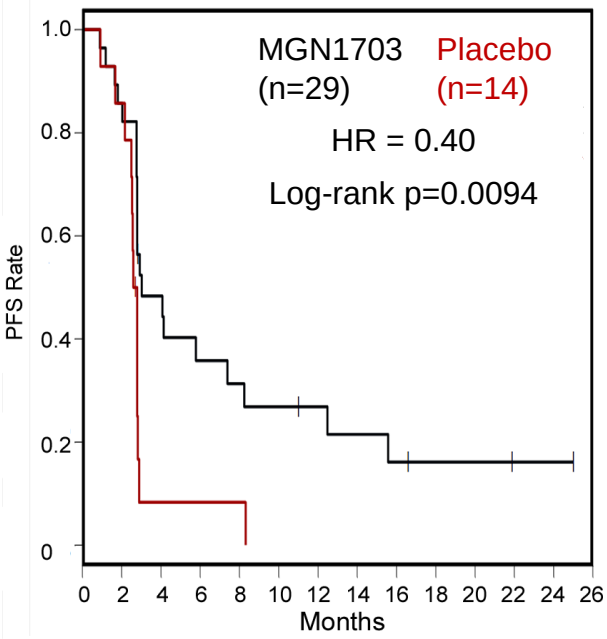
A

Patients with normal CEA



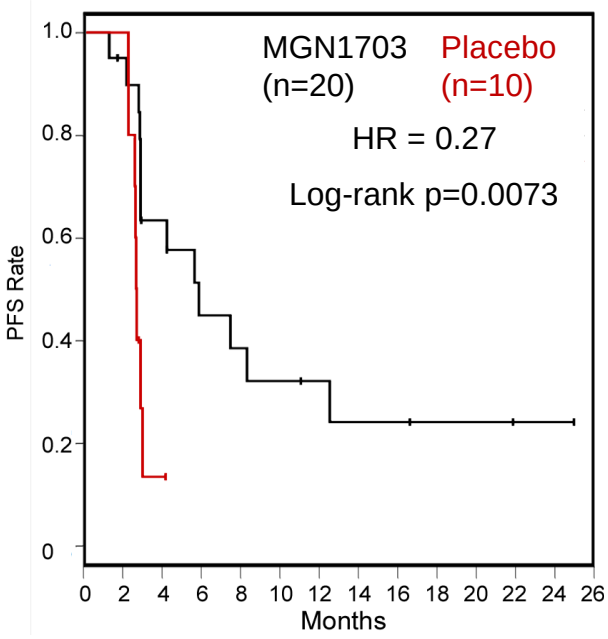
B

Patients with CR/PR after induction therapy



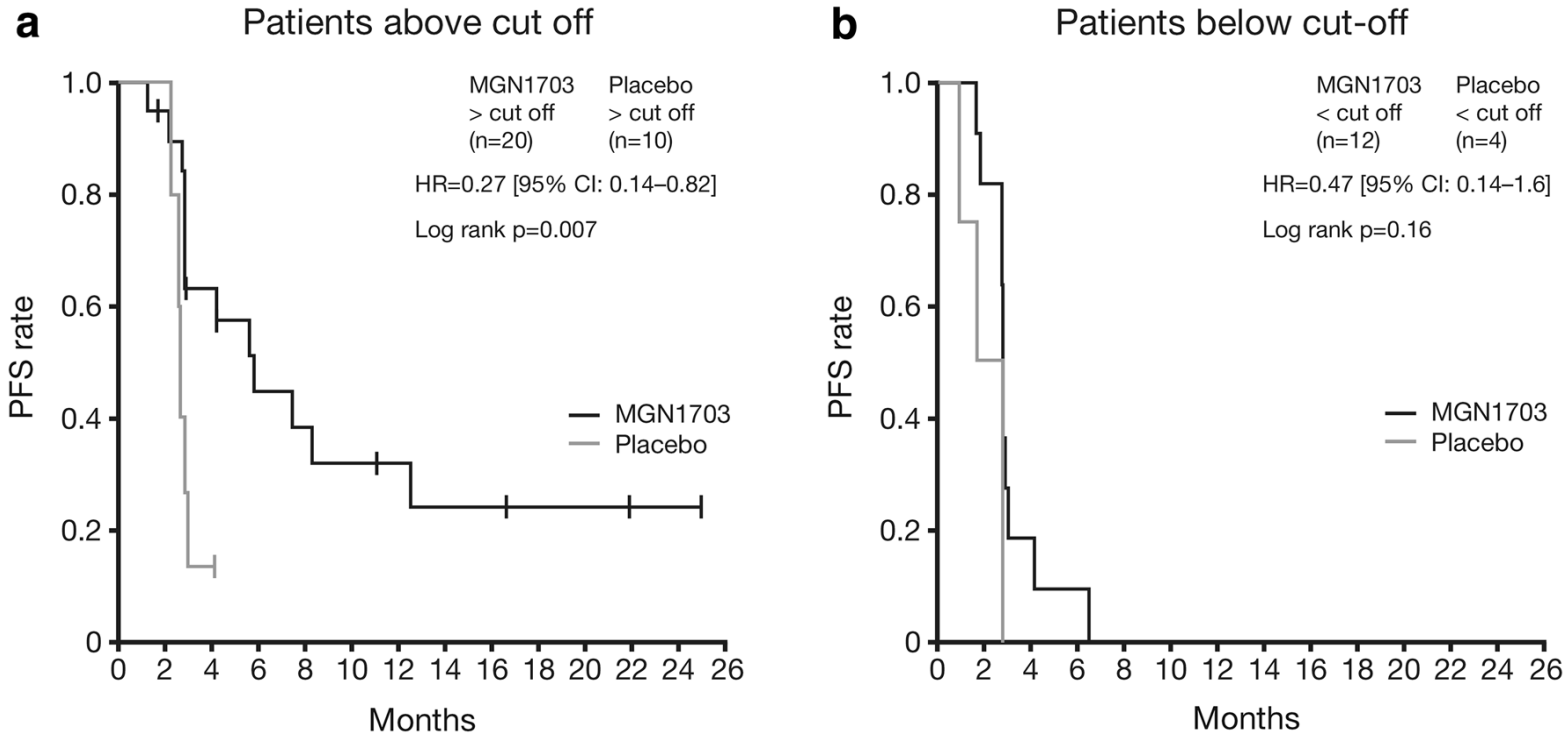
C

Patients above aNKT cut-off



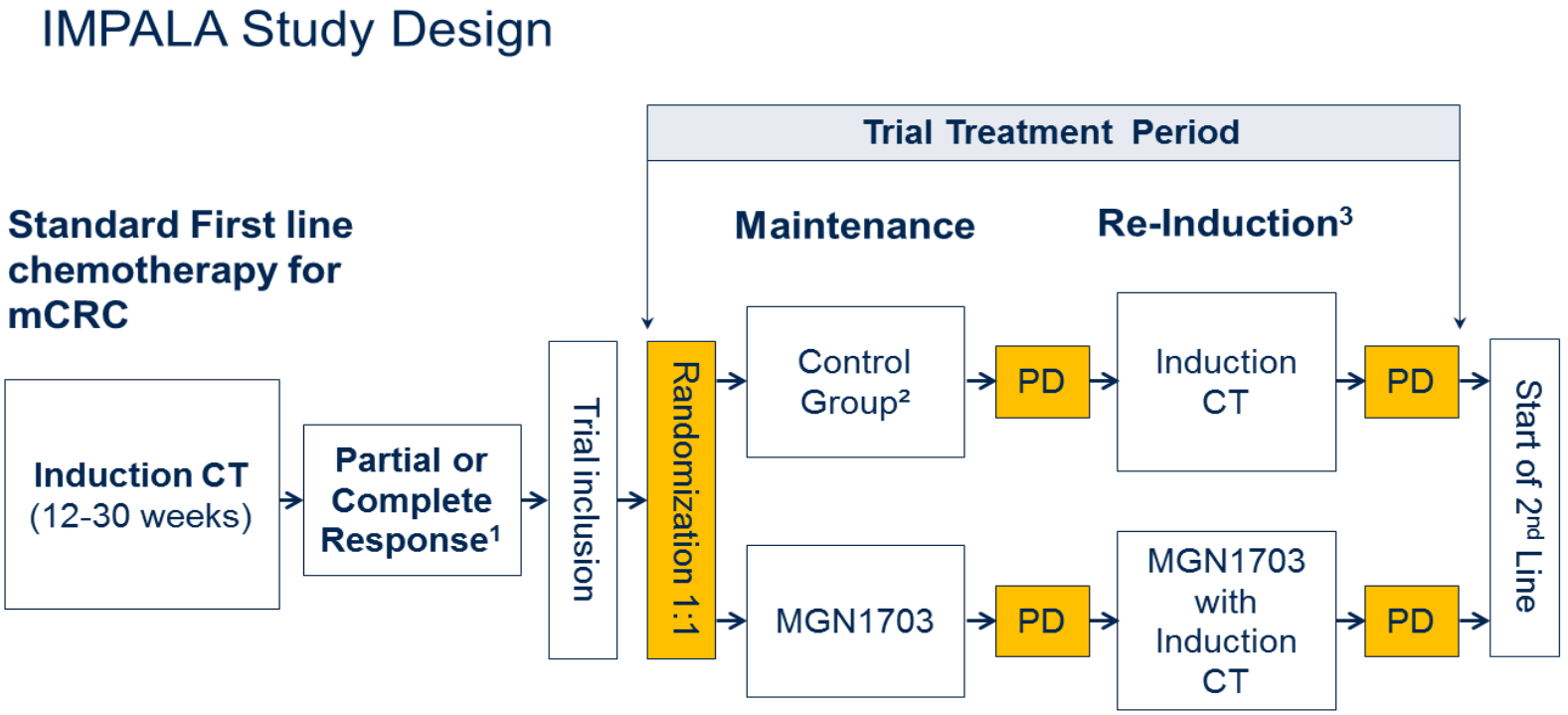
Scheithauer et al., Ann Oncol Suppl. (ESMO congress) 2014

MGN 1703 as maintenance: Exploratory Subgroup NKT cells



Schmoll, Wittig, Arnold et al., J Cancer Res Clin Oncol 2014

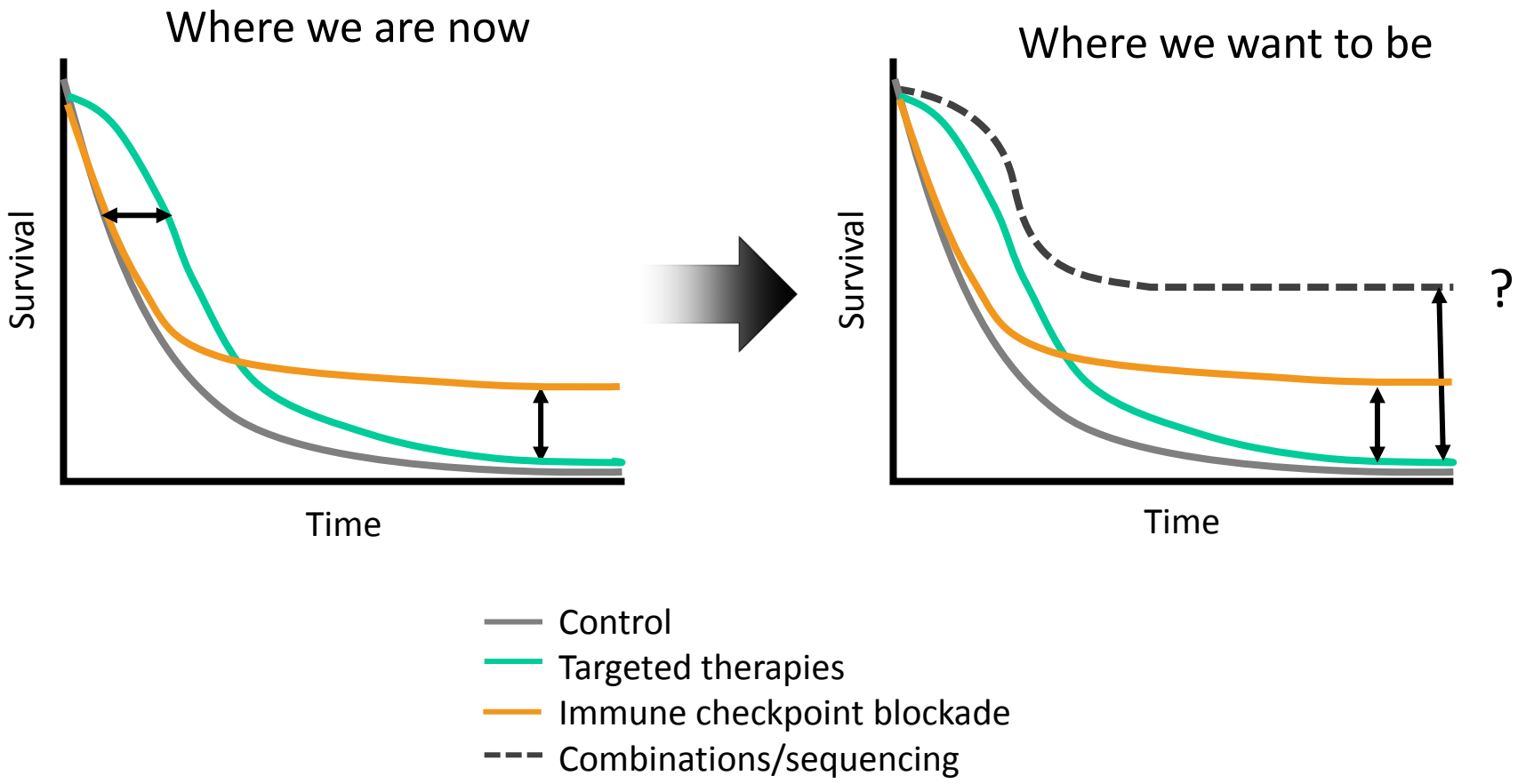
IMPALA: International phase III trial
Planned: N=540



1. RECIST 1.1. Responses are assessed locally. No need of response confirmation or independent review
2. Control Group patients may either continue induction therapy or halt some of the agents or interrupt all therapies
3. Re-introduction of prior induction therapy mandated whenever feasible in all patients of the MGN1703 arm and in those of the control group who reduced treatment intensity during maintenance

PI: Dirk Arnold, DE & David Cunningham, UK

The future in mCRC? Combination Immuntherapy with Targeted Therapy?



Adapted from Ribas A, presented at WCM, 2013; Ribas A, et al. Clin Cancer Res 2012;18:336–341; Drake CG. Ann Oncol 2012;23(suppl 8):viii41–viii46