

Adoptive Cell Therapy with Tumor Infiltrating Lymphocytes and Intermediate dose IL-2 for Metastatic Melanoma

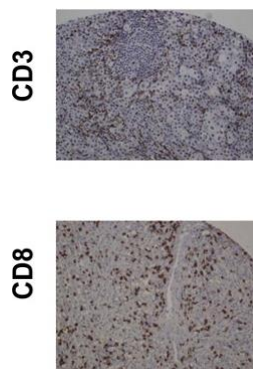
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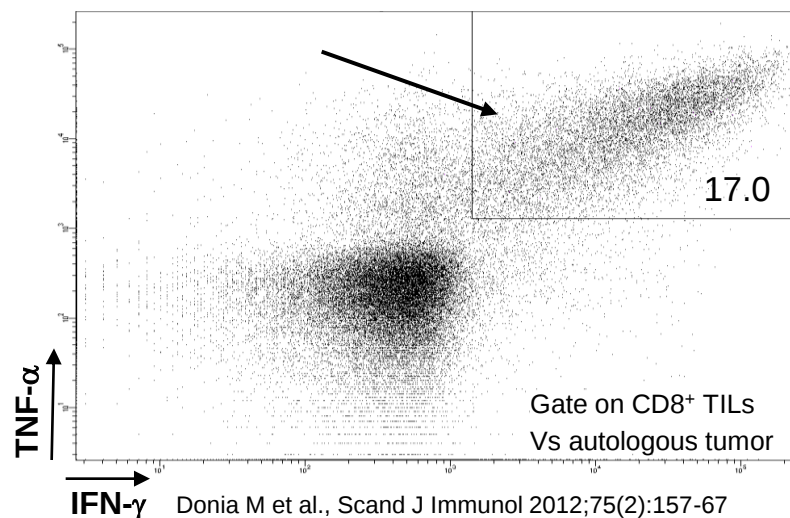
Tumor Infiltrating Lymphocytes - TILs

T cells infiltrate melanomas



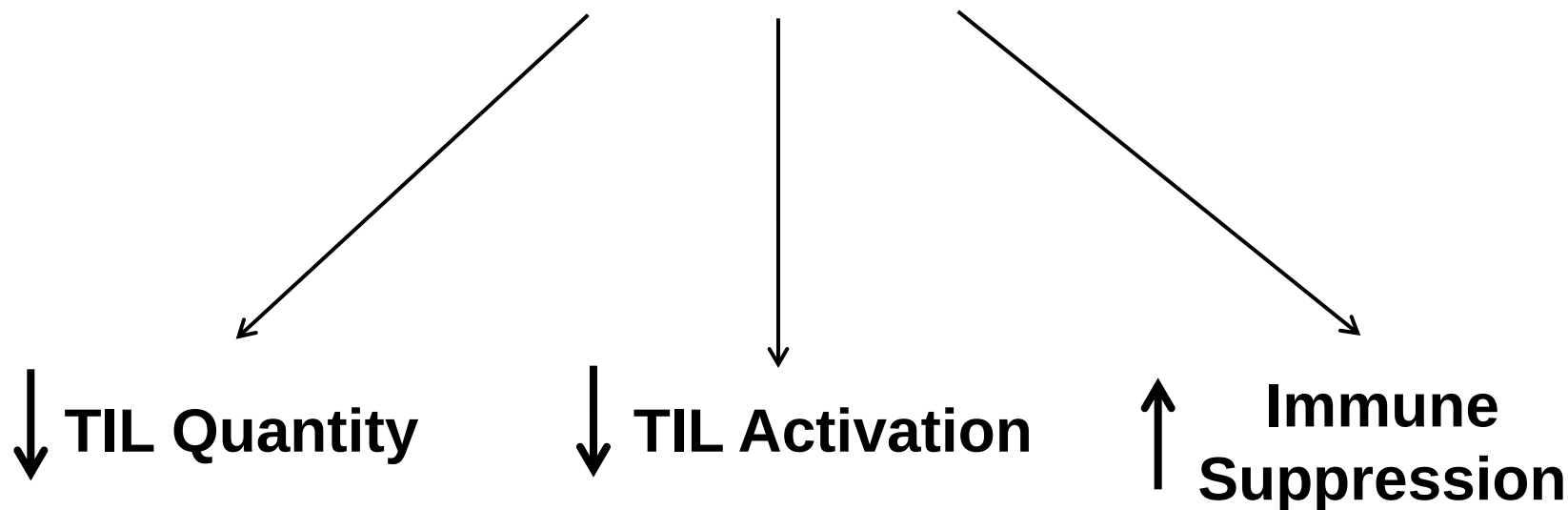
Erdag G et al., Cancer Res 2012;72(5):1070-80

TILs have the potential to recognize multiple targets on tumor cells

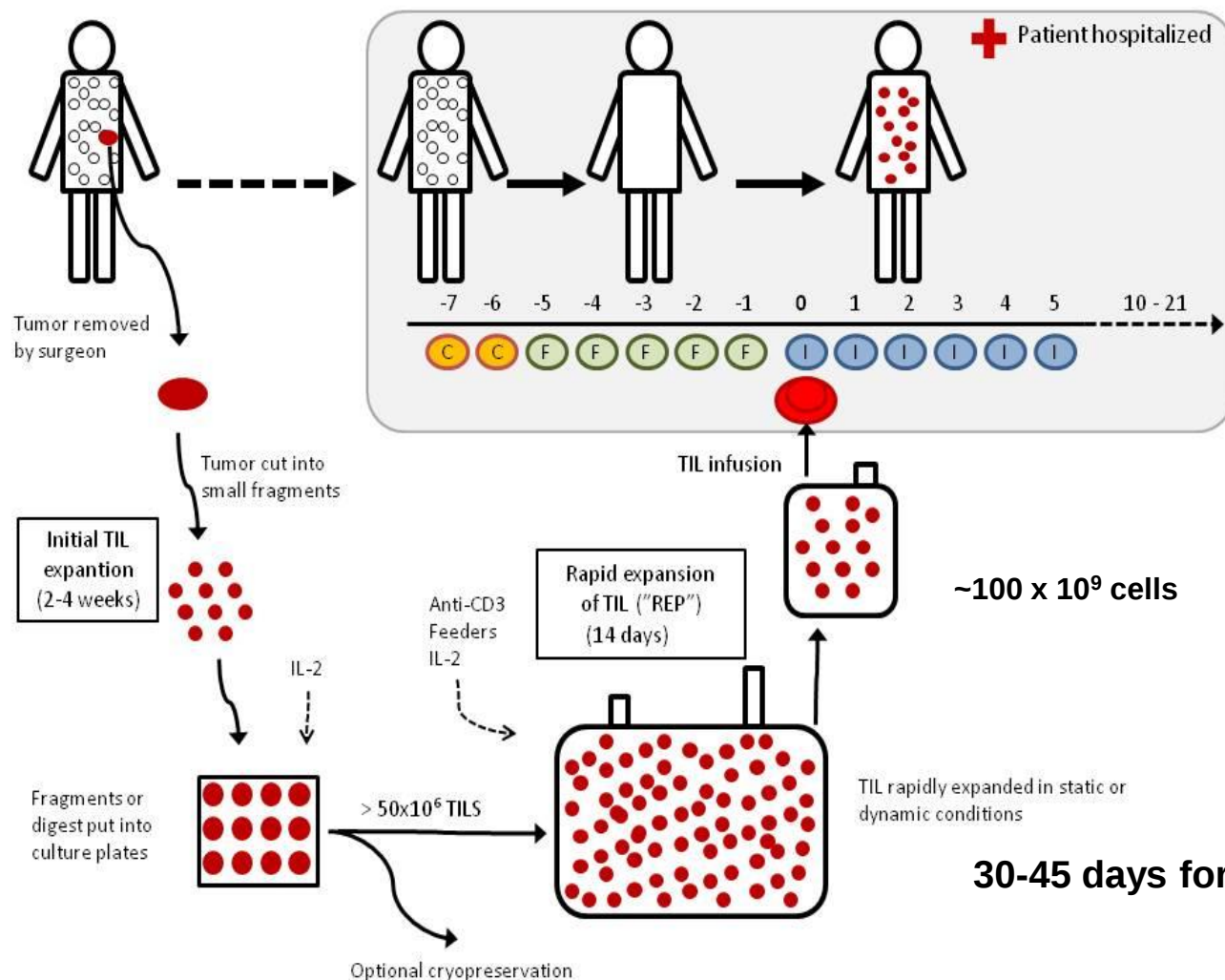


Tumor Infiltrating Lymphocytes - TILs

Tumors continue to grow

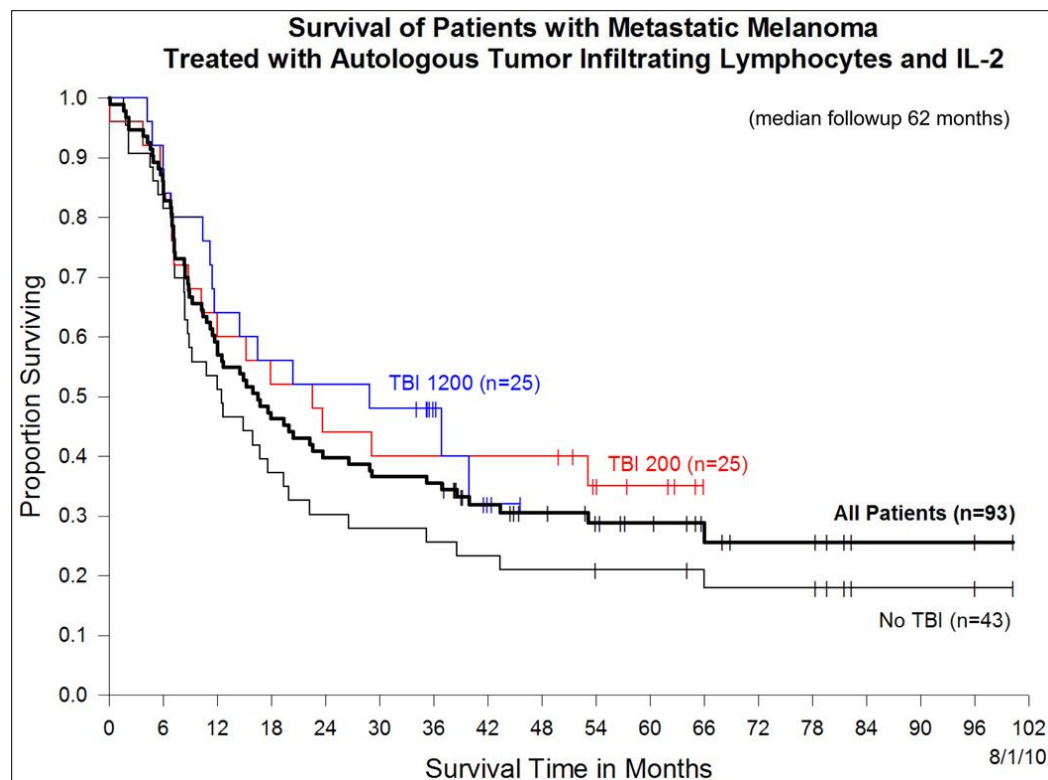


Adoptive T-cell Therapy with TILs



Adoptive T-cell Therapy - NCI, USA

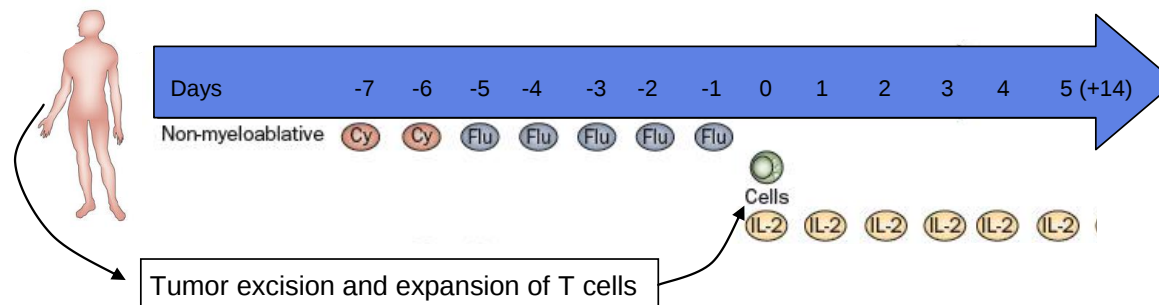
- **Response rates**
~ 50-70%
- **> 20%**
long term survivors



20 CR: 3-year survival 100% and 5-year survival 93%

Study Design

- 25 patients with progressive treatment-refractory metastatic melanoma
- 3-step treatment: HD chemotherapy, TIL infusion, IL-2
 - Young TILs
 - Wave bioreactor
 - Intermediate dose IL-2 (Decrescendo-regimen*)
 - 18 MIU/m² over 6 h, 12 h and 24 h
 - 4.5 MIU/m² over 24 h for 3 days



Objectives

- **Primary objective**
 - To evaluate tolerability and feasibility
- **Secondary objectives**
 - Immune response
 - Clinical response (RECIST 1.0)
 - Overall survival (OS), progression free survival (PFS)



Eligibility Criteria

- ≥ 18 years with treatment-refractory progressive metastatic melanoma
- ECOG PS 0-1
- Measurable disease according to RECIST 1.0
- Adequate hematologic, hepatic, cardiac and renal function
- No active brain metastases
 - eligible if lesions were treated and stable ≥ 4 weeks
- No history of severe chronic autoimmune disease or chronic infection (e.g. HIV, Hepatitis B or C)
- Life expectancy > 3 months
- No toxicity from prior treatments
- Surgically resectable metastasis

Clinical Response

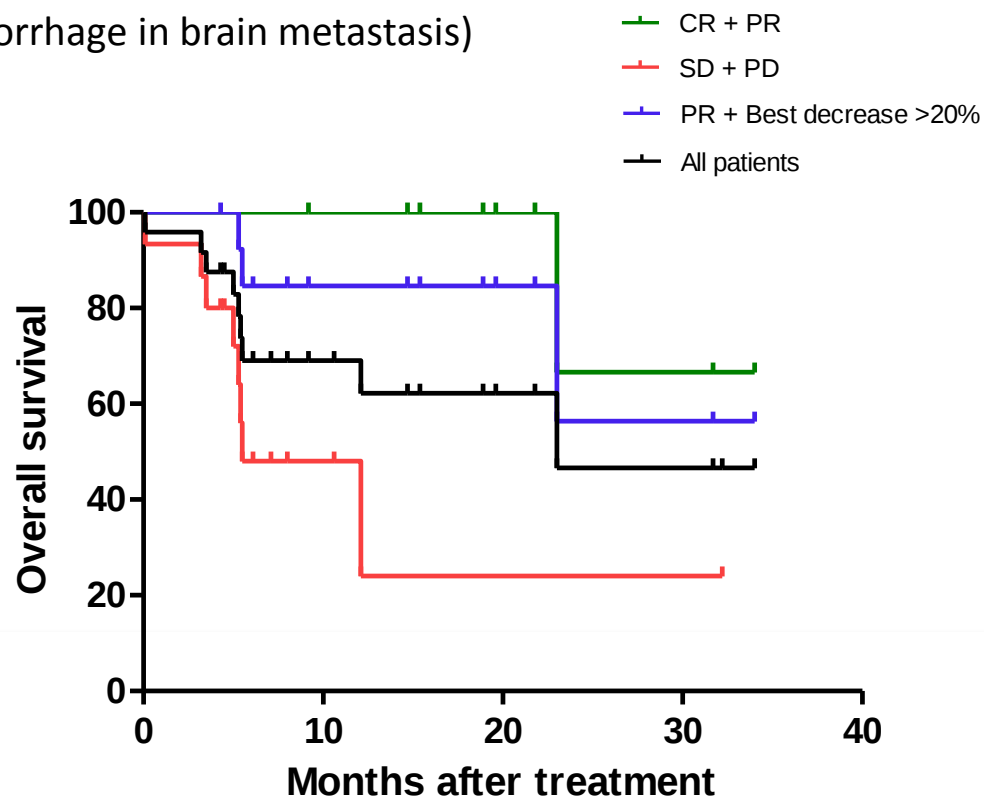
- **25 patients treated**

- 96 % success rate for TIL-production
- 1 patient dead during IL-2 (CNS haemorrhage in brain metastasis)
- 2 patients evaluation pending

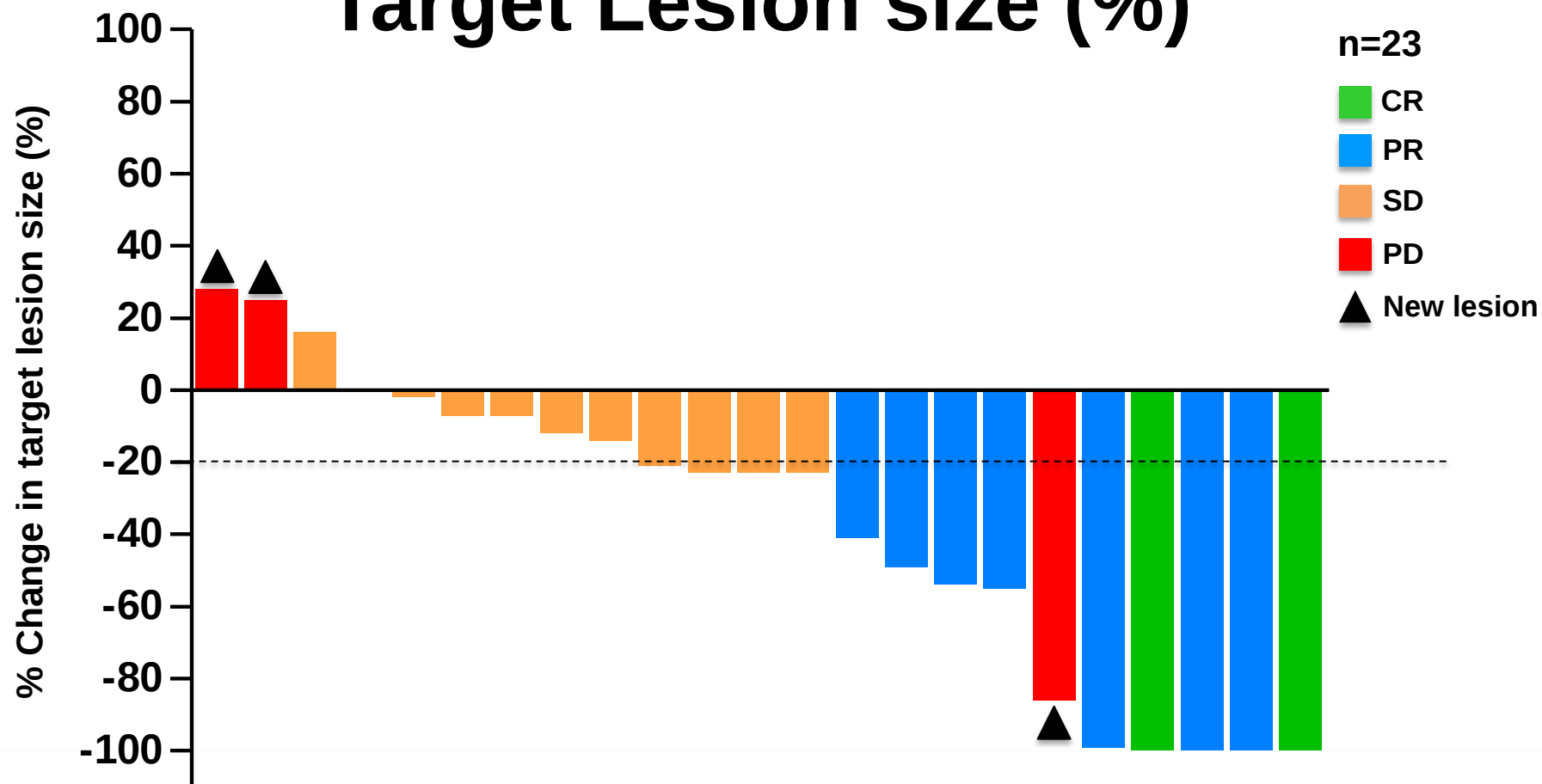
- **22 patients evaluated**

- **2 CR** (+33, +16 months)
- **7 PR** (+31 (NED), 12, +23 (NED), 12, +14, 8, +6 months)
- **10 SD** (4-6 months)
- **3 PD**

NED = No evidence of disease

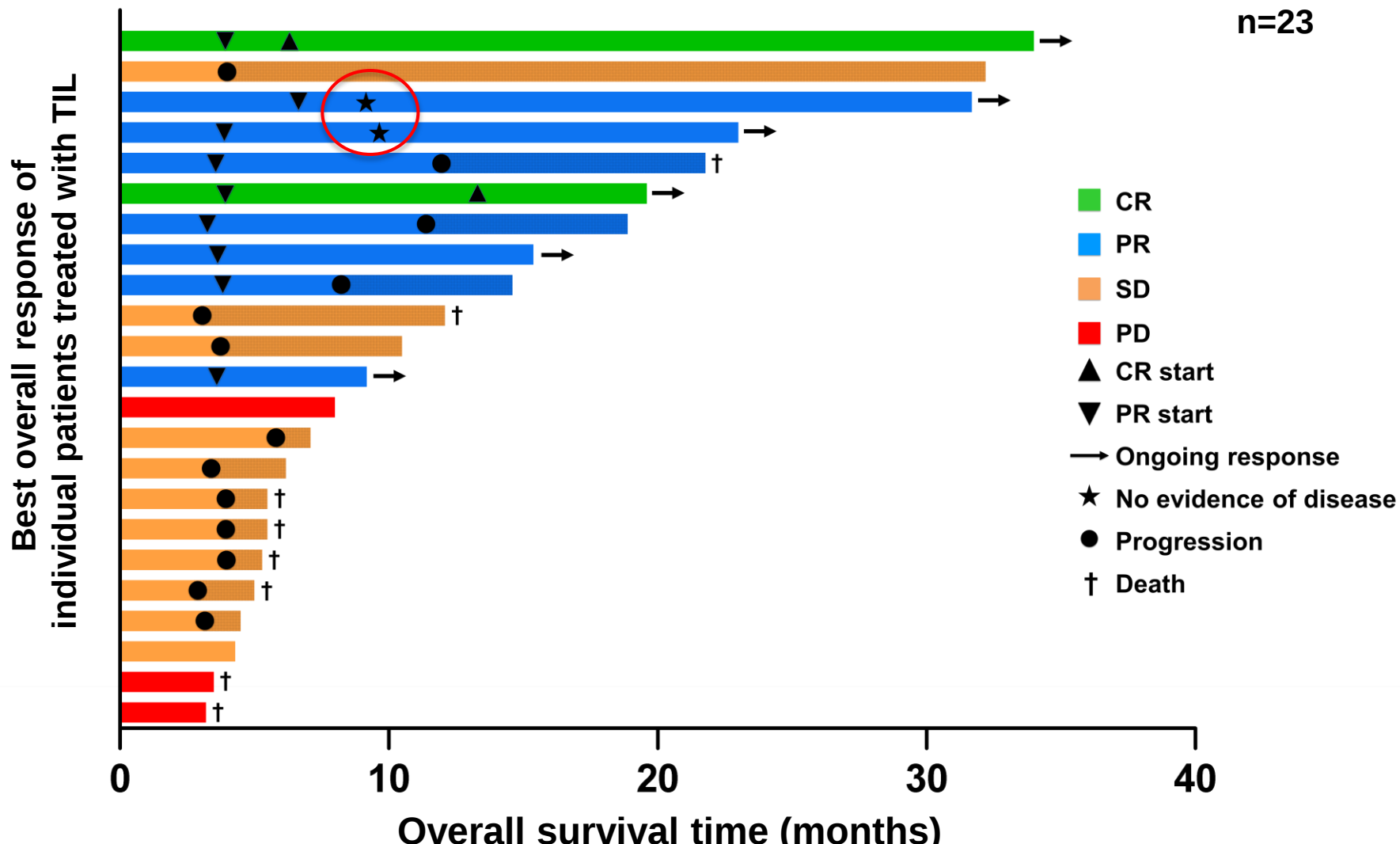


Best Change from Baseline in Target Lesion size (%)



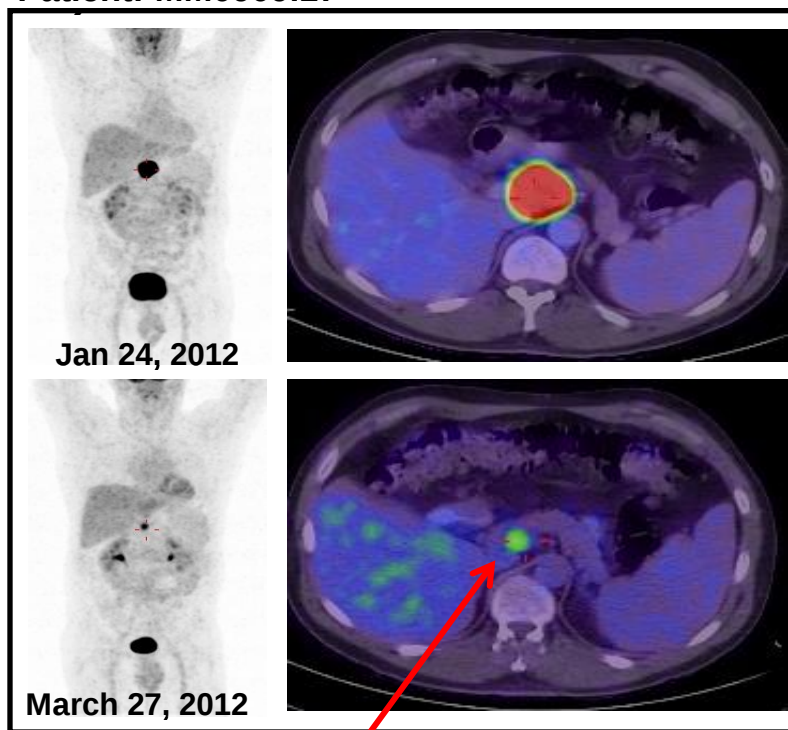
Partial response patients with 100% change have non-target lesions present

Best Overall Response



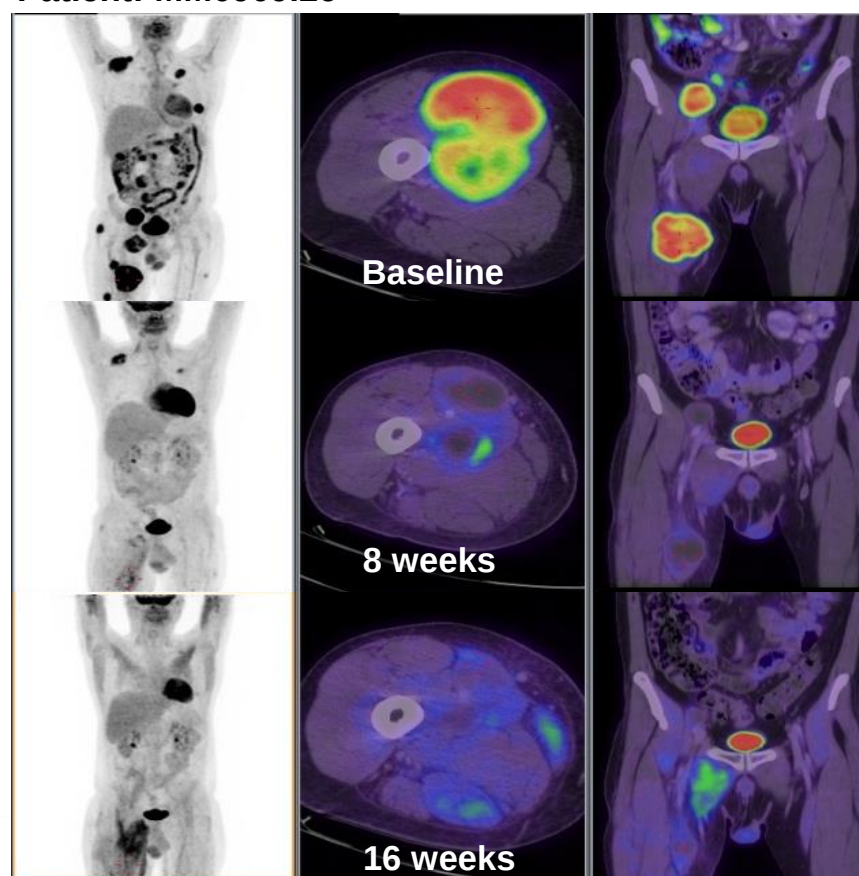
Clinical Response

Patient: MM0909.17



Surgically removed September 2012
PR/PMR (NED): +29 months

Patient: MM0909.26



CR/CMR obtained after 13 months
 (+16 months)



Toxicity

- **Intensive chemotherapy**

- Bone marrow suppression
- Electrolyte derangement
- Nausea, diarrhoea

- **T-cells**

- Fever, chills, dyspnoea

- **IL-2**

- Fever, capillary leak syndrome, fluid retention, hypotension, electrolyte derangement, nausea

All patients (n=22)	
Time in hospital (days)	20 (16;39)
RBC transfusion (n)	5 (1;25)
Platelet transfusion (n)	7 (3;17)
Neutrophils < 0,5 (days)	8 (4;12)
IL-2 dose (MIE)	112 (50;135)
% IL-2 of planned dose	93 (60;100)

Median (range)

All patients experience temporary grade III-IV events

Baseline Patient Characteristics

	Responders (n=9)	Non-Responders (n=13)	P-value
Age (years)*	56 (40;68)	50 (25;63)	0,23
Sex (n, % male)**	4 (44)	4 (31)	0,66
Primary tumor origin (% skin)**	8 (89)	9 (69)	0,36
AJCC Stage (% M1c)**	7 (78)	12 (92)	0,54
BRAF status (% wt)**	5 (56)	5 (38)	0,67
Tumor burden (cm)*	9.7 (1.7;34.2)	13.7 (9.1;26.4)	0,26
LDH level (% above normal)**	5 (56)	8 (62)	0,66
Metastatic sites (n)*	2 (1;6)	4 (1;7)	0,31
Previous treatments (n)*	2 (1;4)	2 (2;4)	0,57
Prior response to IL-2**	2 (22)	3 (23)	1,00
Prior response to Ipilimumab**	1 (11)	1 (8)	1,00

*) Median, (range), Mann-Whitney test

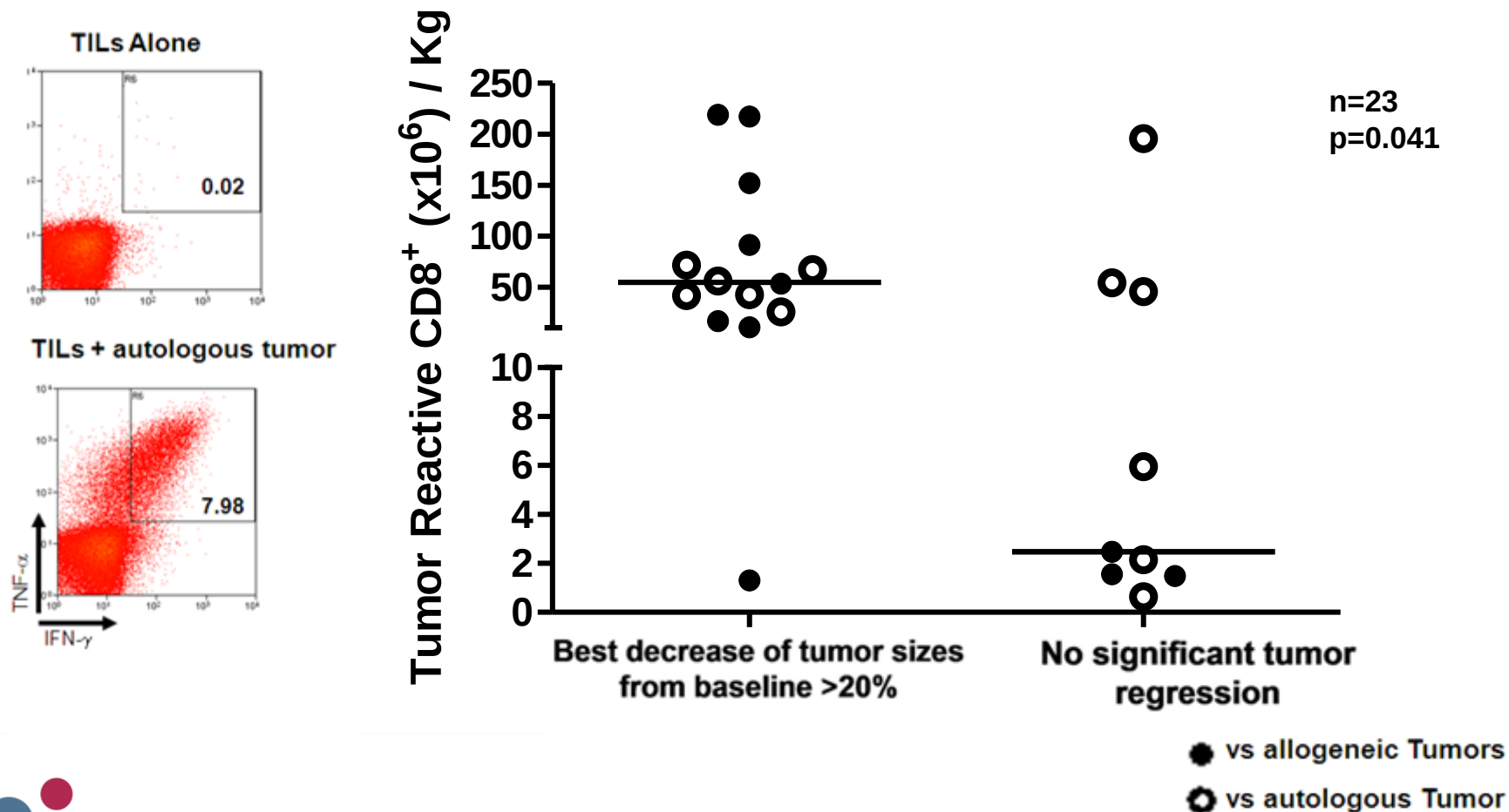
***) n (%), Fisher's Exact test

TIL Characteristics

	Responders (n=9)	Non-Responders (n=13)	P-value
TIL culture generation (days)	24 (16;34)	20 (13;36)	0,27
TILs cryo before REP (n,%)	4 (44)	6 (46)	1,00
Fold expansion during REP	5860 (4100;7125)	4454 (2856;9975)	0,19
Infused Cells			
Total ($\times 10^9$)	117 (68;143)	98 (62;200)	0,23
CD8 %	53 (6;92)	48 (8;93)	0,68
CD4 %	47 (5;91)	35 (4;93)	0,86
$\gamma\delta$ %	0.2 (0;11)	1.0 (0;51)	0,06
CD8 ($\times 10^9$)	62 (7;122)	32 (6;172)	0,26

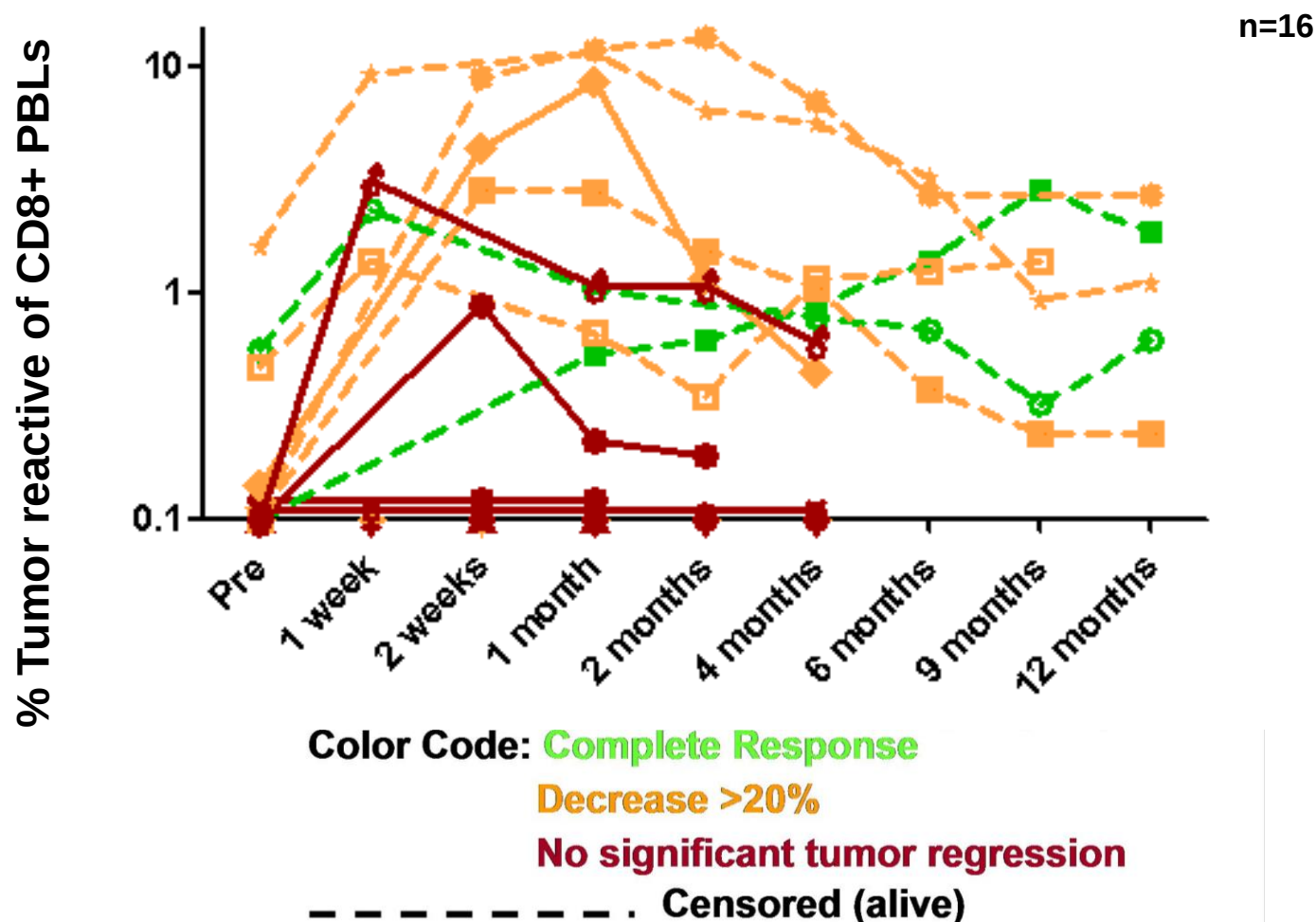
Median, (range), Mann-Whitney test

Anticancer Responses of Infusion Products



TILs are co-cultured with autologous melanoma cell lines or HLA-semimatched allogeneic melanoma cell lines, and tumor reactivity was evaluated by assessing the amount of CD8⁺ T cells co-expressing TNF- α and IFN- γ

Anticancer Responses in Peripheral Blood



Conclusions

- Adoptive cell therapy using lymphodepleting high-dose chemotherapy and IL-2 is feasible and safe to use at a European cancer centre.
- Toxicity is manageable in a normal department of oncology.
- Complete and long-lasting response can be obtained using intermediate dose IL-2.
- Complete responses can develop slowly over months.
- Clinical response correlates to tumour reactivity in T-cell infusion product and to induction of peripheral tumour-reactive T cells.



Next steps for TIL based ACT at CCIT

- **Randomized phase III trial**
 - Generate robust efficacy data
 - Approval of TIL therapy as standard treatment

(Collaborators: J. Haanen, Netherlands Cancer Institute, R. Hawkins, University of Manchester)

- **Combination therapies**
 - BRAF inhibitor
 - Interferon- α



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