

First-in-human phase I study of the DNA repair inhibitor DT01 in combination with radiotherapy in patients with skin metastases from melanoma

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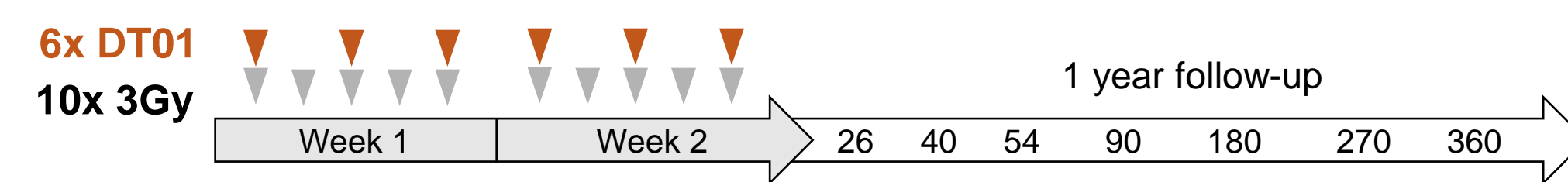
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Funding: This work is supported by the grant Agence Nationale pour la Recherche (ANR-10-BIOT-006) and DNA Therapeutics

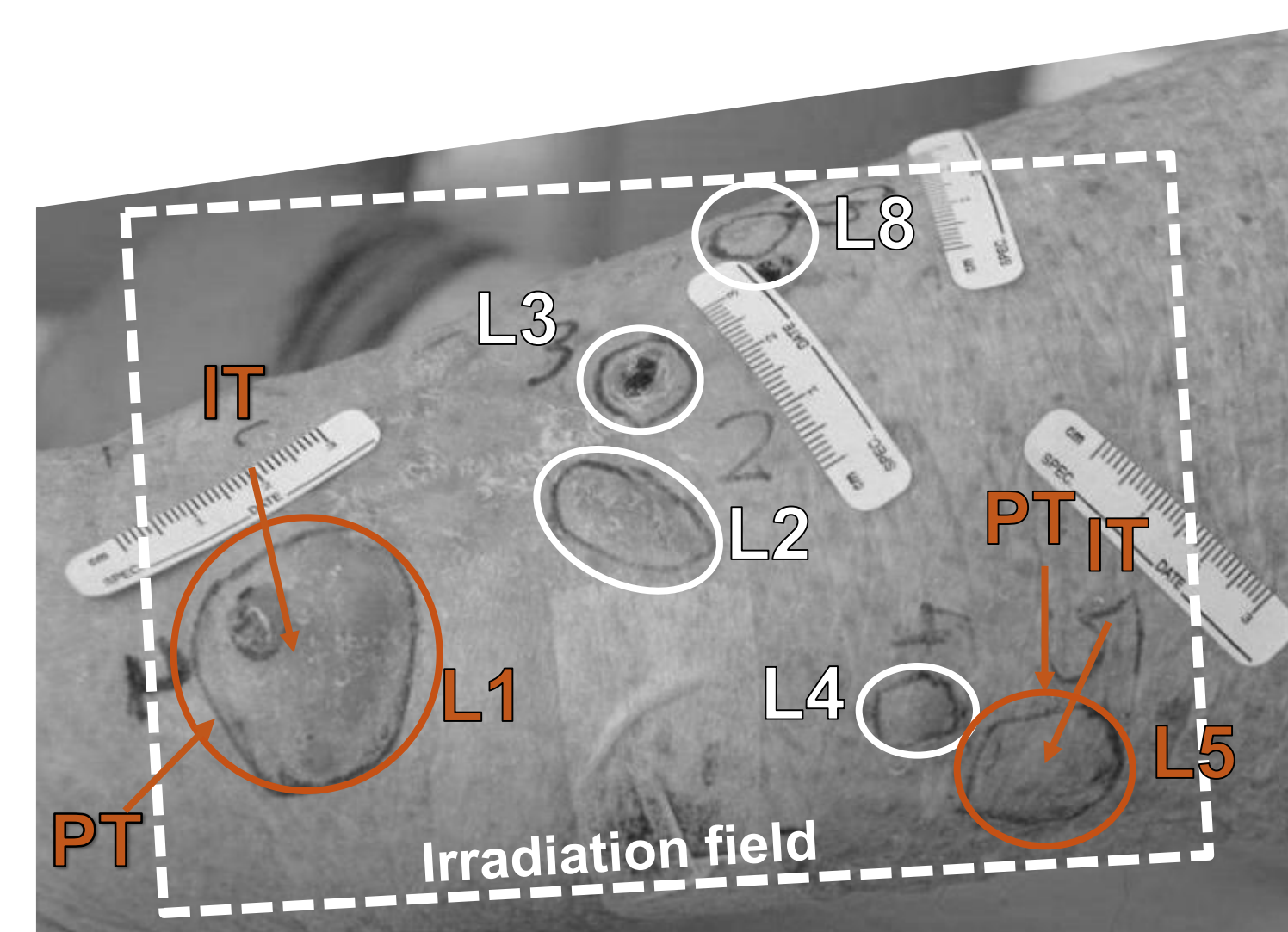
Background

- Melanoma is known to be resistant to palliative radiotherapy (RT).
- DNA damage repair is an important mechanism of resistance to RT.
- DT01** is a double stranded **DNA oligonucleotide** mimicking a "false" double strand breaks which lures and traps DNA repair proteins [1].
- DT01 displayed antitumor activity in combination with RT in several tumor types including melanoma without additional toxicity in **preclinical models** [2].
- We evaluated in a **first-in-human phase I trial** the combination of intratumoral (IT) and peritumoral (PT) injections of **DT01** with **RT** in patients with **skin metastases of melanoma**.

Administration scheme



All target lesions were irradiated (10x3 Gy over 2 weeks), including 2 lesions injected with DT01



Disease characteristics

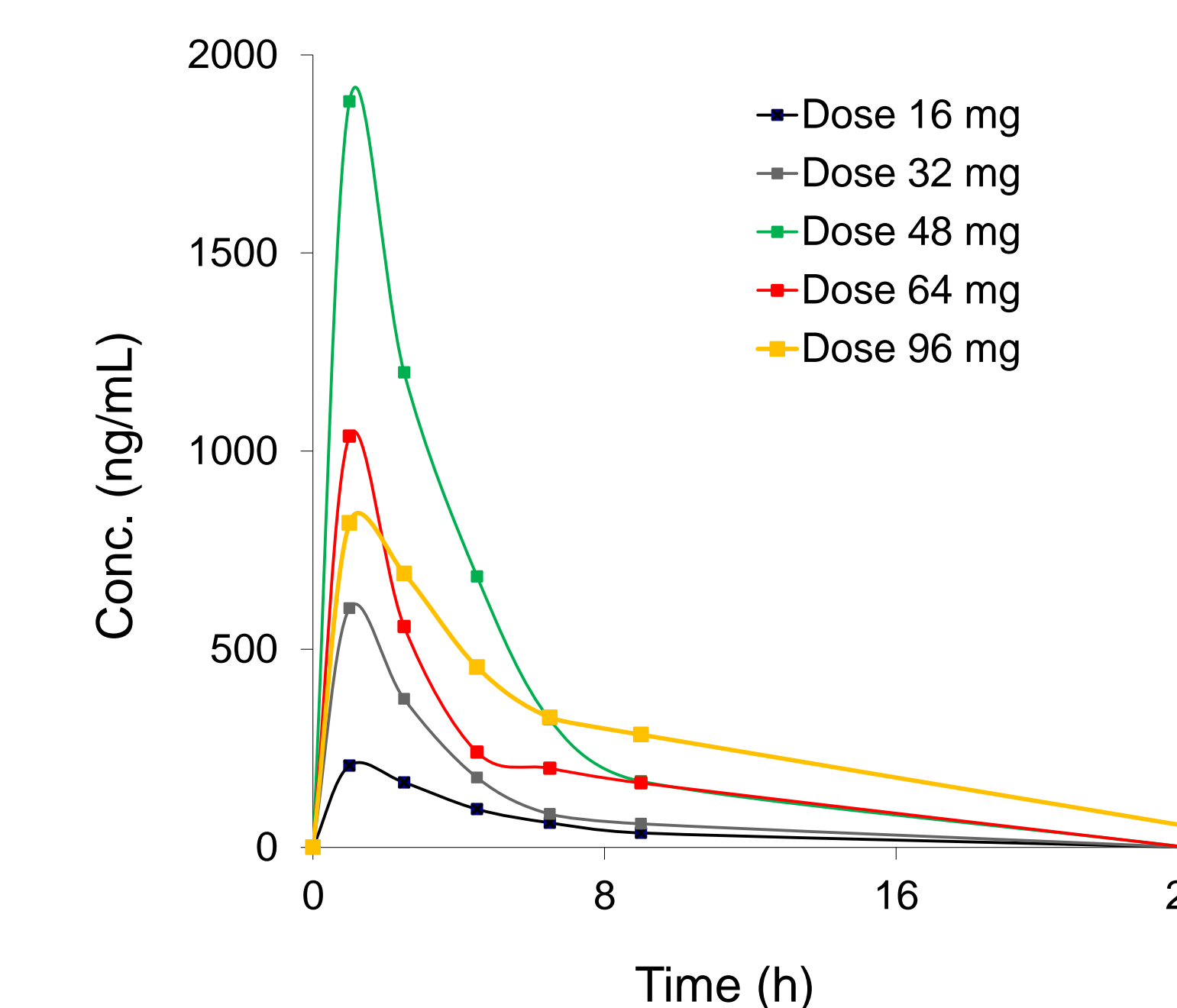
Characteristics	All patients (n=23)
Time from diagnosis, years	
Median	1.7
Range	0.3-18.4
Melanoma stage at inclusion, n (%)	
III	16 (70%)
IV	7 (30%)
Site of metastases, n (%)	
Leg	17 (74%)
Arm	1 (4%)
Chest	1 (4%)
Head	4 (17%)
No. of treated lesions, n	
DT01-injected	45
DT01-non-injected	40
Total	85

American Joint Committee on Cancer (AJCC) classification was used for melanoma staging

Safety

Only reversible grade 1 or 2 local reactions were observed
No DLTs were reported
The MTD was not reached

Pharmacokinetics

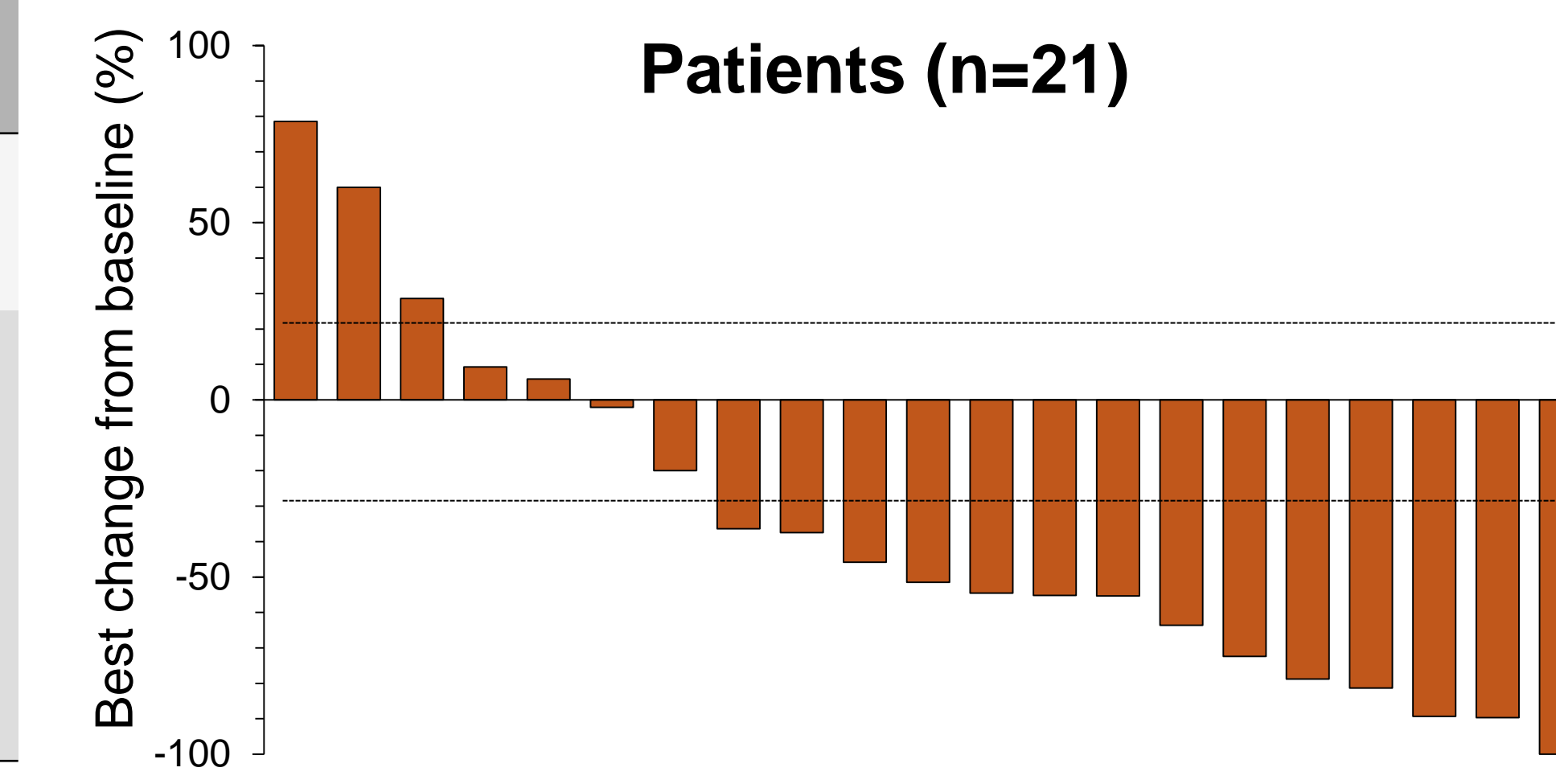


- No dose-dependent exposure was observed
- AUC:** 0.6 to 7.8 $\mu\text{g}\cdot\text{h}/\text{mL}$ (median: 2.6 $\mu\text{g}\cdot\text{h}/\text{mL}$)
- Half-life:** 5 hrs

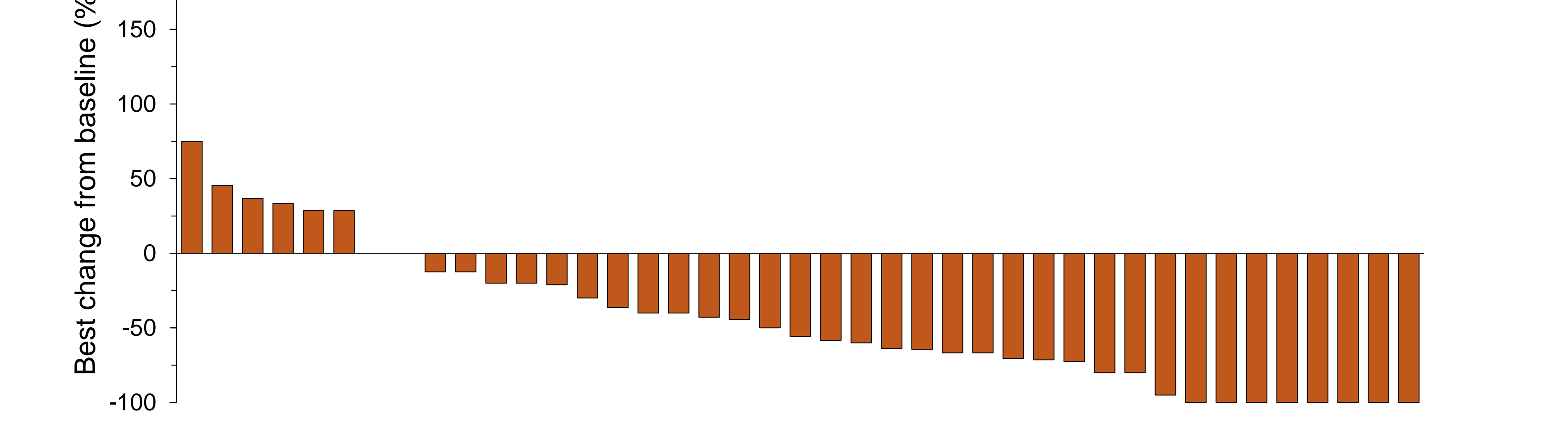
Best overall response

	PR	CR	ORR
Patients (n=21)	62%	5%	67%
Lesions (n=76)			
All	29%	30%	59%
DT01 Injected	49%	19%	68%
DT01-non-injected	6%	43%	49%

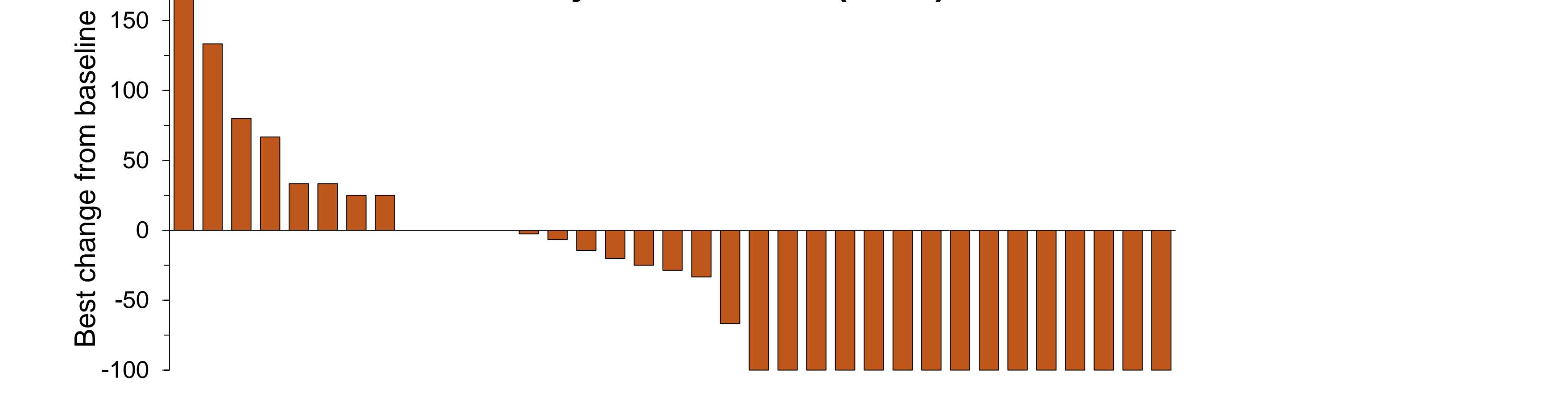
Based on RECIST 1.1 criteria. PR: Partial response; CR: Complete response; ORR: overall response rate.



DT01-injected lesions (n=41)



DT01-non-injected lesions (n=35)



	AUC < 2.6 $\mu\text{g}\cdot\text{h}/\text{mL}$		AUC > 2.6 $\mu\text{g}\cdot\text{h}/\text{mL}$		p-value
	No. of patients	ORR	No. of patients	ORR	
DT01-non-injected lesions	7	29%	6	71%	0.032
DT01-injected lesions	8	56%	8	80%	0.283
All lesions	8	42%	8	81%	0.010

Patient and Methods

Objectives

- Safety and tolerability of DT01
- Pharmacokinetics (PK)
- Preliminary antitumor activity

Patient selection

- Patient with histologically confirmed **skin metastases from melanoma** not eligible for immediate surgery
- ECOG performance status of 0 or 1
- No prior RT
- Adequate organ and hematopoietic functions

Study design

Open label, non-randomized, multi-center, 3+3 dose escalation design
Dose levels: 16, 32, 48, 64 and 96 mg total dose
Expansion (96 mg): IT+PT versus PT only

References

- Quanz M, Chassoux D, Berthault N, Agrario C, Sun JS, Dutreix M. Hyperactivation of DNA-PK by double-strand break mimicking molecules disorganizes DNA damage response. *PLoS One* 2009; 4(7): e6298
- Biau J, Devun F, Jdey W, et al. A preclinical study combining the DNA repair inhibitor D bait with radiotherapy for the treatment of melanoma. *Neoplasia* 2014; 16(10): 835-44.

Results

Patient characteristics

Characteristics	All patients (n=23)
Gender, n (%)	
Male	11 (48%)
Female	12 (52%)
Age, years	
Median	72
Range	40 - 85
ECOG performance status	
0	17 (74%)
1	6 (26%)

ECOG: Eastern Cooperative Oncology Group performance status

- 23 patients received the full course of treatment and were eligible for safety and PK assessment
- 21 patients were eligible for efficacy assessment, for a total of 76 lesions
- Median follow-up was 180 days [26-360]

Conclusions

IT and PT DT01 in combination with RT is **safe** in patients with skin metastases of melanoma and **provides antitumor activity**. **ORR correlated with AUC** in DT01-non-injected lesions which can be possibly explained by a **systemic distribution** of the drug.

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