

Immunological correlates of long-term survival in melanoma patients

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Presenter Disclosure Information

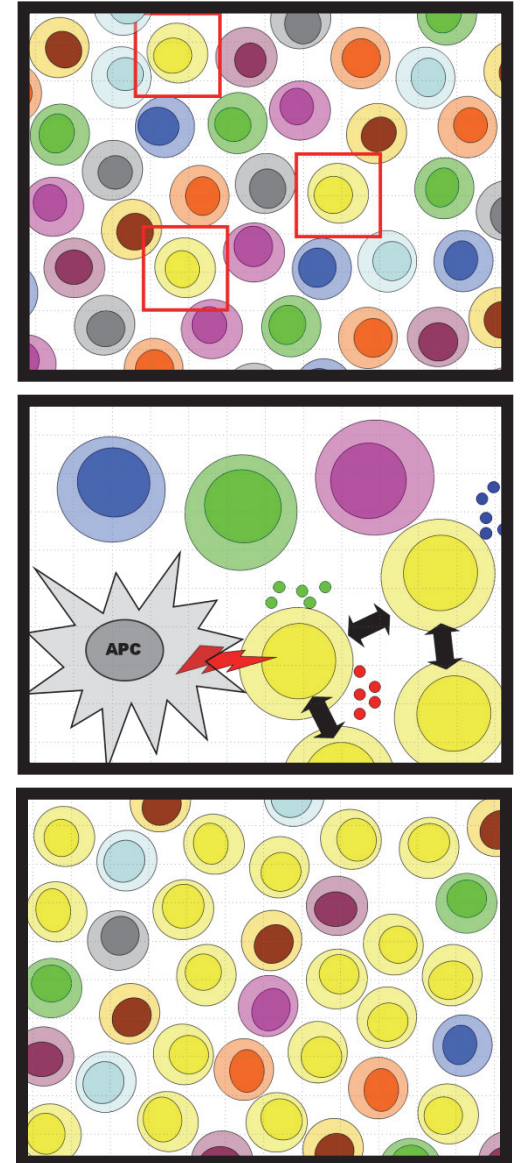
Graham Pawelec

The following relationships exist related to this presentation:

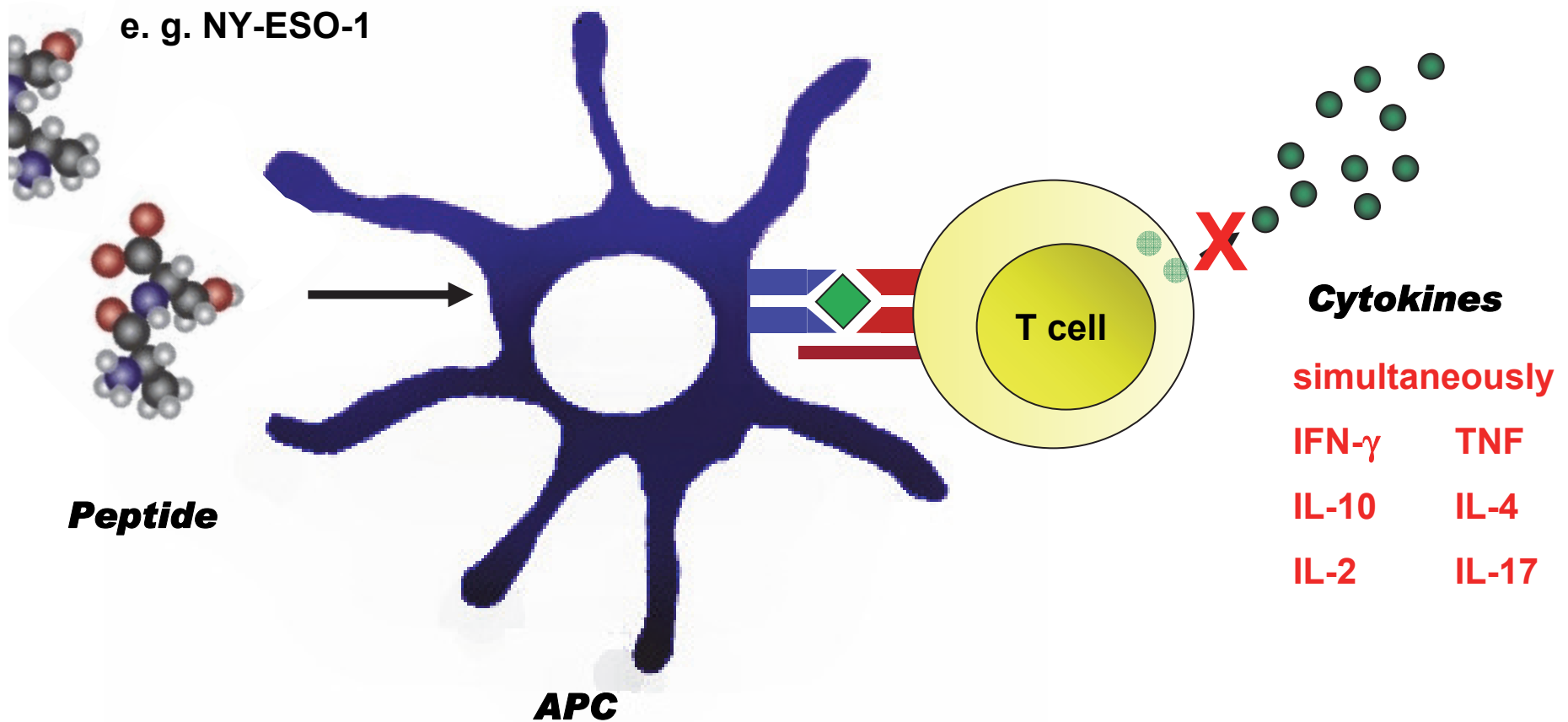
No Relationships to Disclose

Detection of antigen-reactive T-cells

- PBMC/PBL collected from stage IV melanoma patients, cryopreserved
- Day 0: Stimulate cells in vitro with selected candidate target antigens (overlapping peptides, PepMix)
- Day 4: IL-2 added to cultures
- Day 12: Restimulate with CFSE-stained autologous PBMCs/PBLs as APC, and PepMixes in the presence of Brefeldin A



Assay readout: intracellular cytokine staining (ICS)



Response defined as Pro-inflammatory: IFN- γ , TNF, IL-2, IL-17
Anti-inflammatory: IL-4, IL-10

Pilot RNA vaccination trial (Garbe & Weide, Dermatology, Tübingen)

Responses to tumor antigens post-vaccination

Pat. ID	Stage at start	Survival (month)	NY- ESO-1	Survivin	MAGE- A3	Melan-A	NY-ESO-1 Expression	Pre Vacc response
#10	IV M1c	5		pro	pro			
#14	IIIc	5						
#9	IIIb	8			pro		x	
#3	IIIb	10	anti					
#12	IV M1c	17		pro	pro	pro		
#2	IV M1a	19			pro			
#4	IV M1c	21	pro					
#11	IV M1c	23	pro		pro		x	
#7	IV M1c	24						
#1	IV M1a	>25	pro	pro	pro		x	x
#6	IV M1c	>31						
#5	IV M1a	>32	pro + anti		pro + anti		x	x

Pilot trial, ipilimumab, (Garbe & Weide, Dermatology, Tübingen)

					Responses to						
	Age	sex	CMV	Substage at onset	NY- ESO-1	Melan- A	MAGE- A3	Survivin	Survival in stage IV	Response CTLA4	
GFI	53	f	neg	M1c	pro				> 7 years (NED)	CR	
UST	41	m	pos	M1c			pro		> 3 years (NED)	MR	(finally tumorfree after surgery, chemotherapy)
HKR	63	f	neg	M1c	pro	pro			> 5 years (NED)	SD	(finally tumorfree after surgery)
WH A	66	m	pos	M1c	pro + anti		pro		> 3 years (NED)	CR	
HSE	70	m	neg	M1c	pro + anti				> 3 years (NED)	MR	(finally tumorfree after surgery)

Long-term survivors: Retrospective - Good Clinical outcome

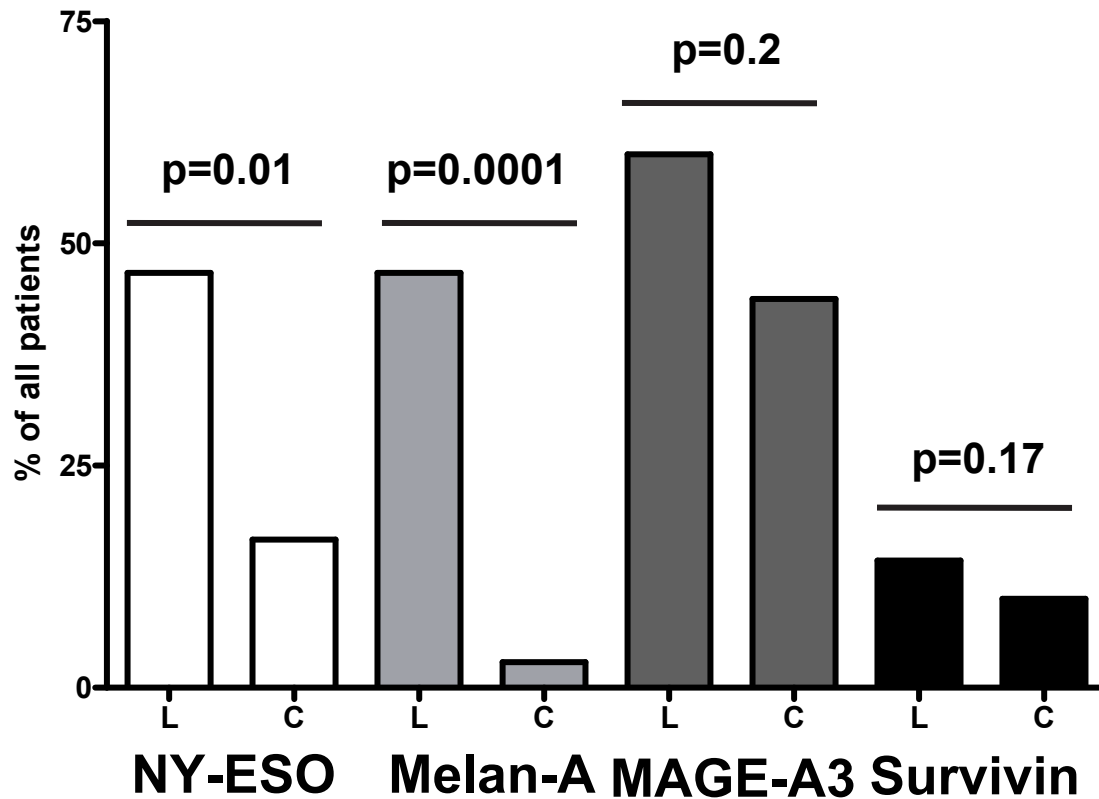


Usual patients:



No control for the LTS, more the mean situation in melanoma patients

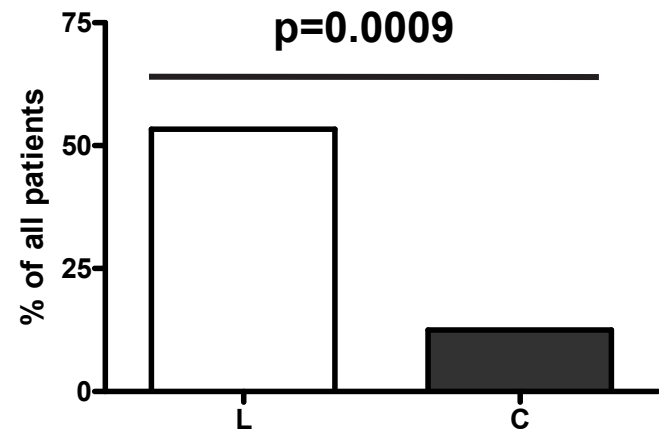
Percentages of patients with TAA-specific T-cells in each group



L = Long-term survivors n=15

C = Control patients n=48 for NY-ESO and MAGE-A3, 35 for Melan-A and 30 for Survivin (Zelba, 2010) H

Fraction of patients with T-cells against >1 TAA:



Slide 8

H9

maybe you should delete this slide. the control patients are actually the prospective samples.
so we see the same (but with more patients) on slide 10 and 12! you can show the right graph...

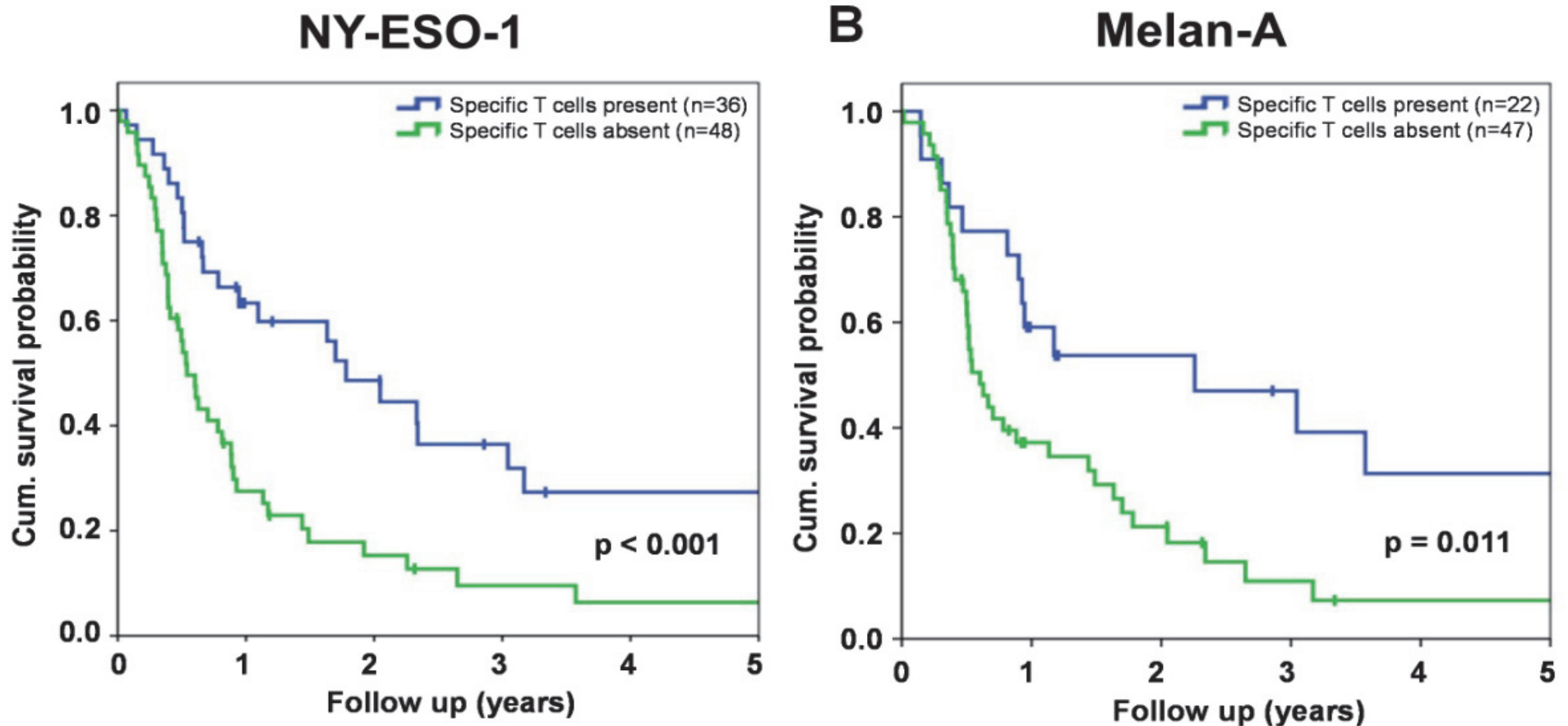
Henning, 5/1/2011

Summary retrospective and prospective analyses

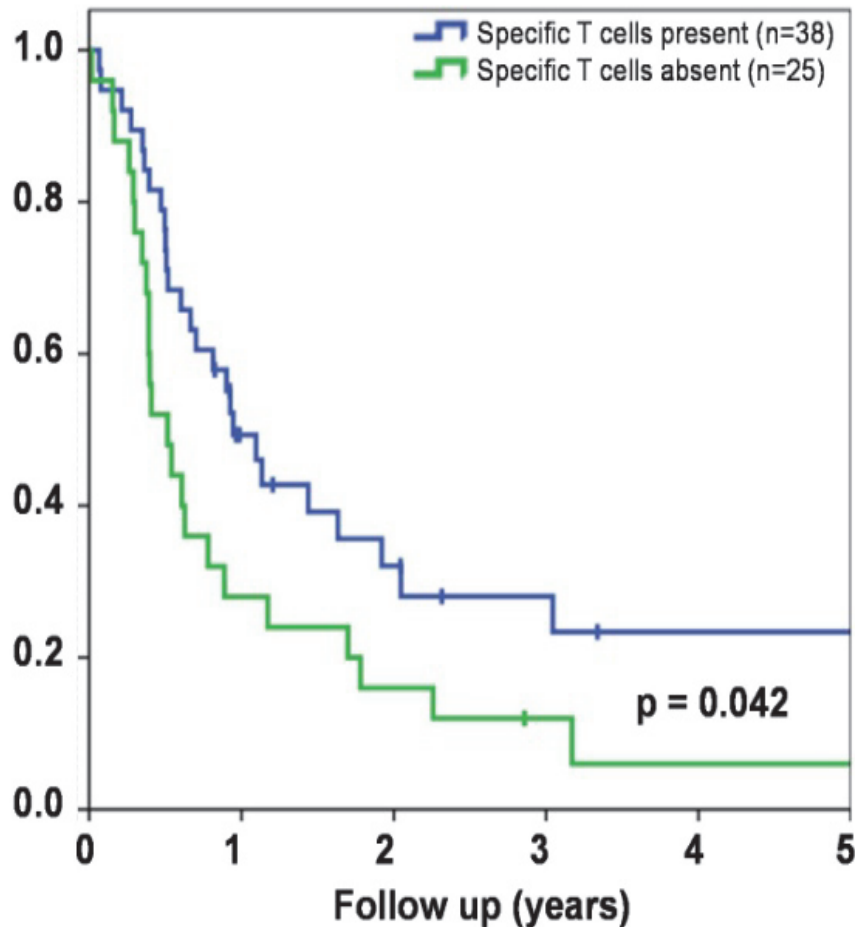
				Responses to				
		Age	Male	NY-ESO-1	Melan A	MAGE A3	Survivin	Influenza
Retrospective Long term survivors	n=26	57	64%	62%	48%	68%	13%	100%
Prospective good (>18 months survival)	n=19	50	57%	63%	47%	69%	27%	100%
Prospective middle (6-18 months survival)	n=24	58	79%	38%	26%	63%	19%	100%
Prospective bad (<6 months survival)	n=23	49	67%	13%	17%	42%	0%	100%

(Zelba 2011)

Significant association between survival of unresectable stage IV patients and the presence of T cells responding to NY-ESO-1 or Melan-A peptides

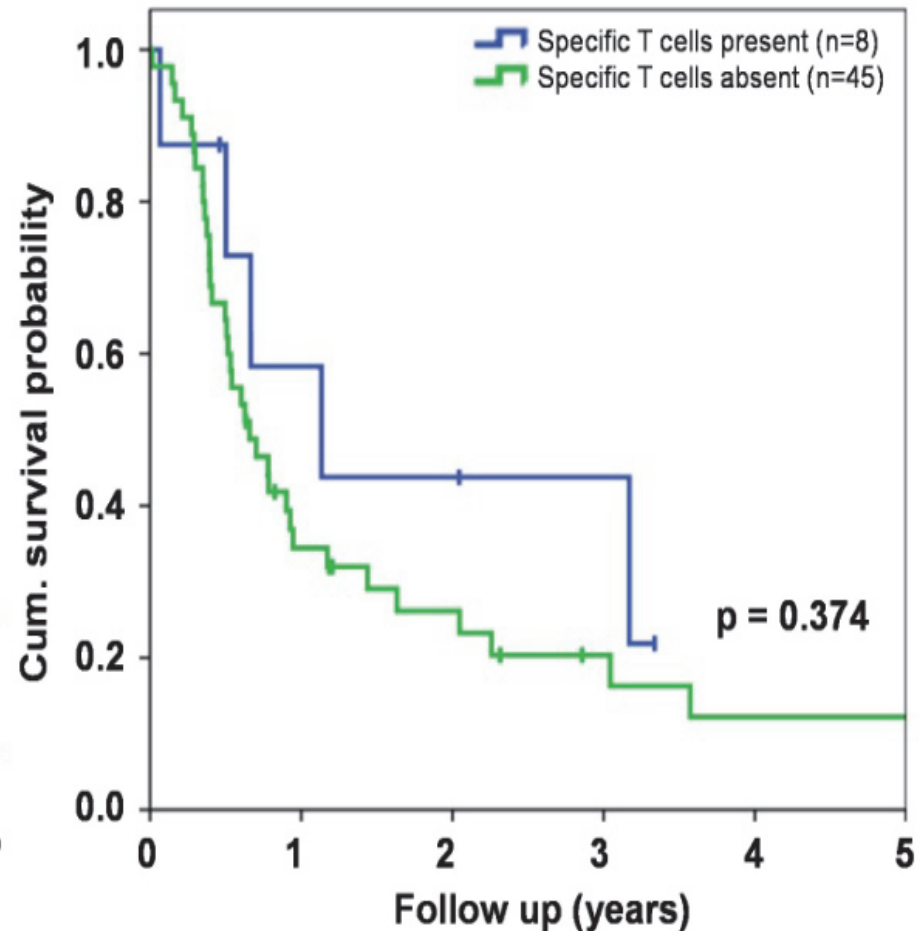


Mage-3



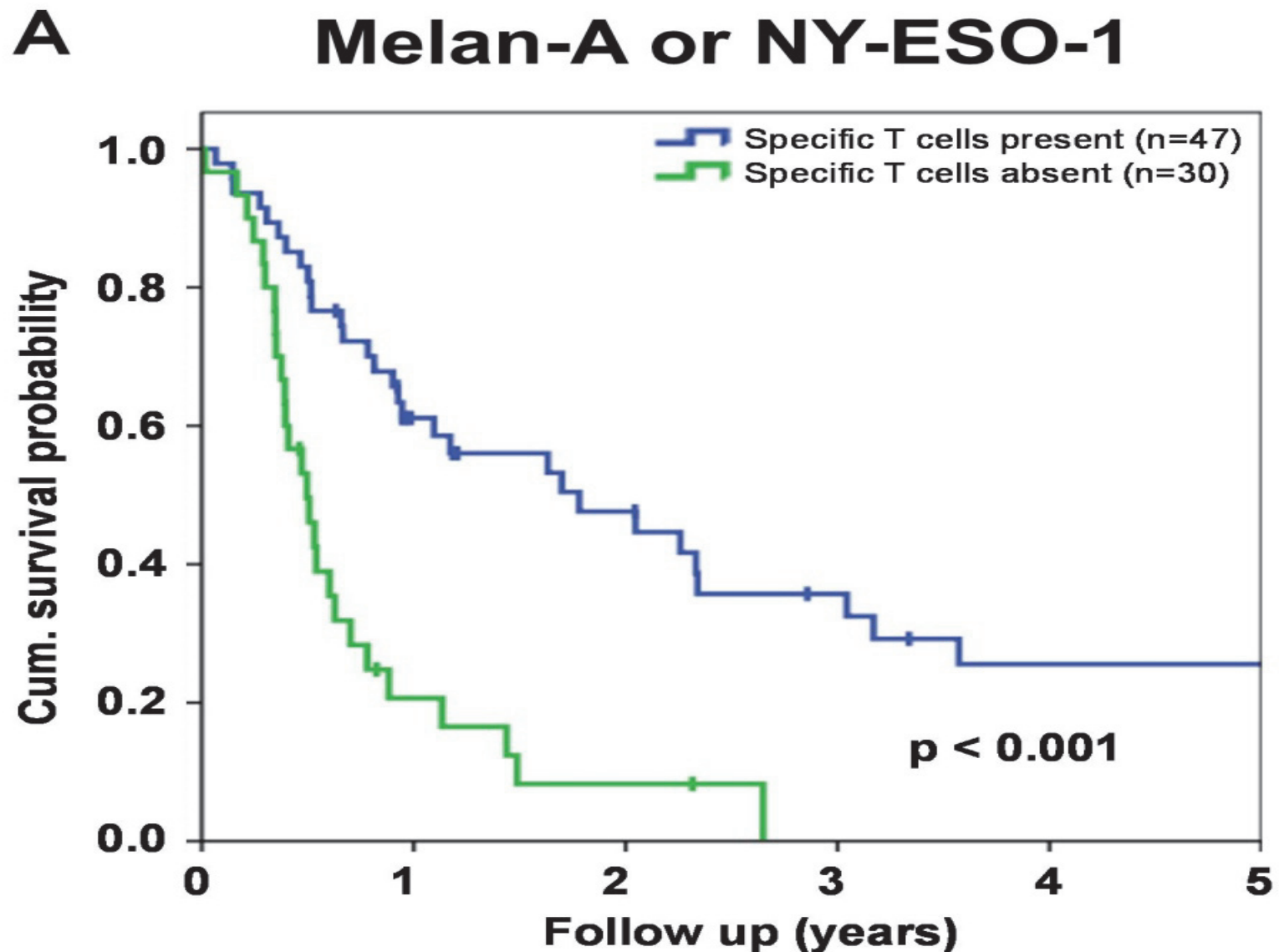
D

Survivin



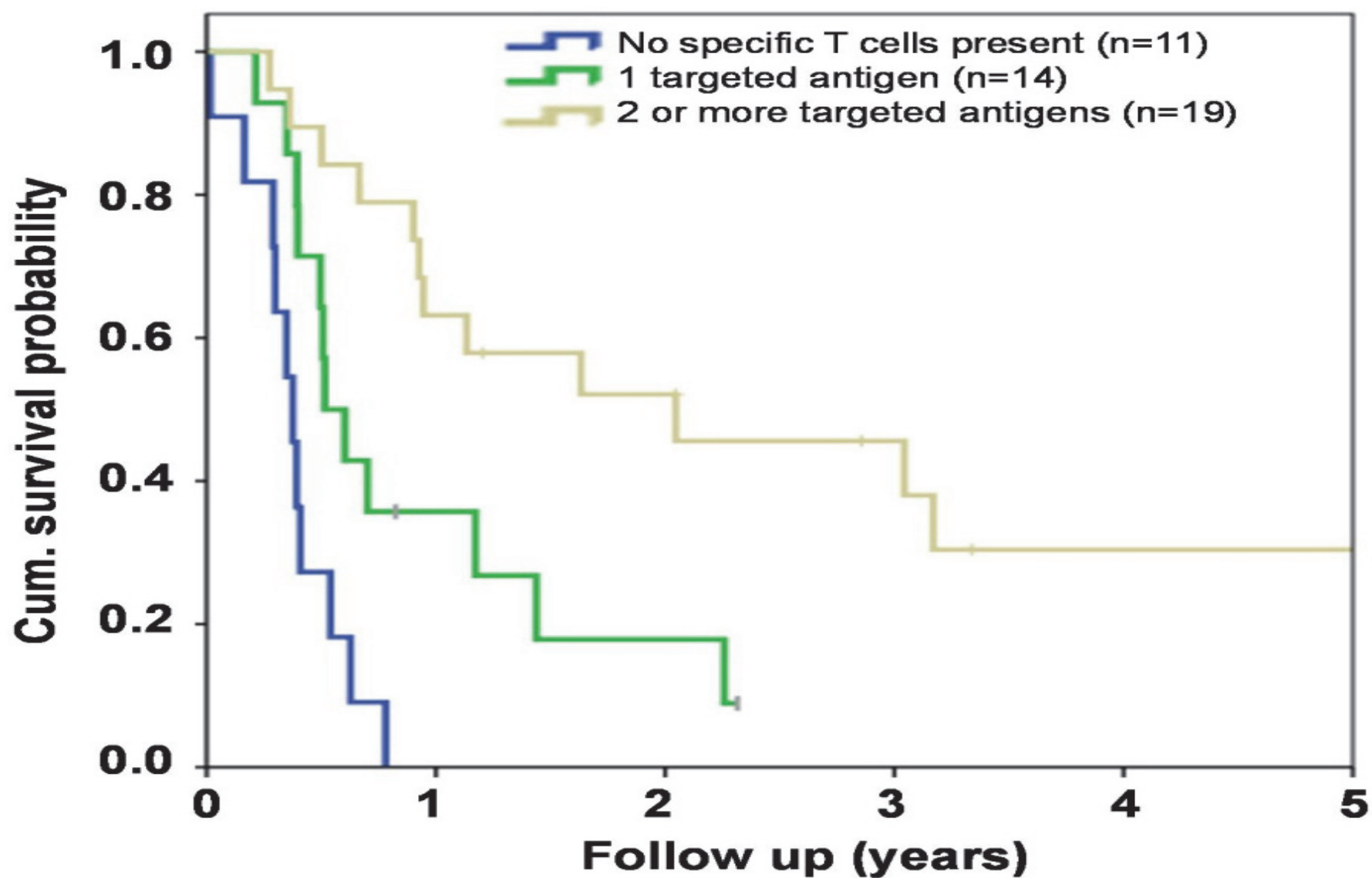
But no significant association between survival of unresectable stage IV patients and the presence of T cells responding to MAGE-A3 or survivin

Survival of patients possessing T cells responding to NY-ESO-1 and/or Melan-A



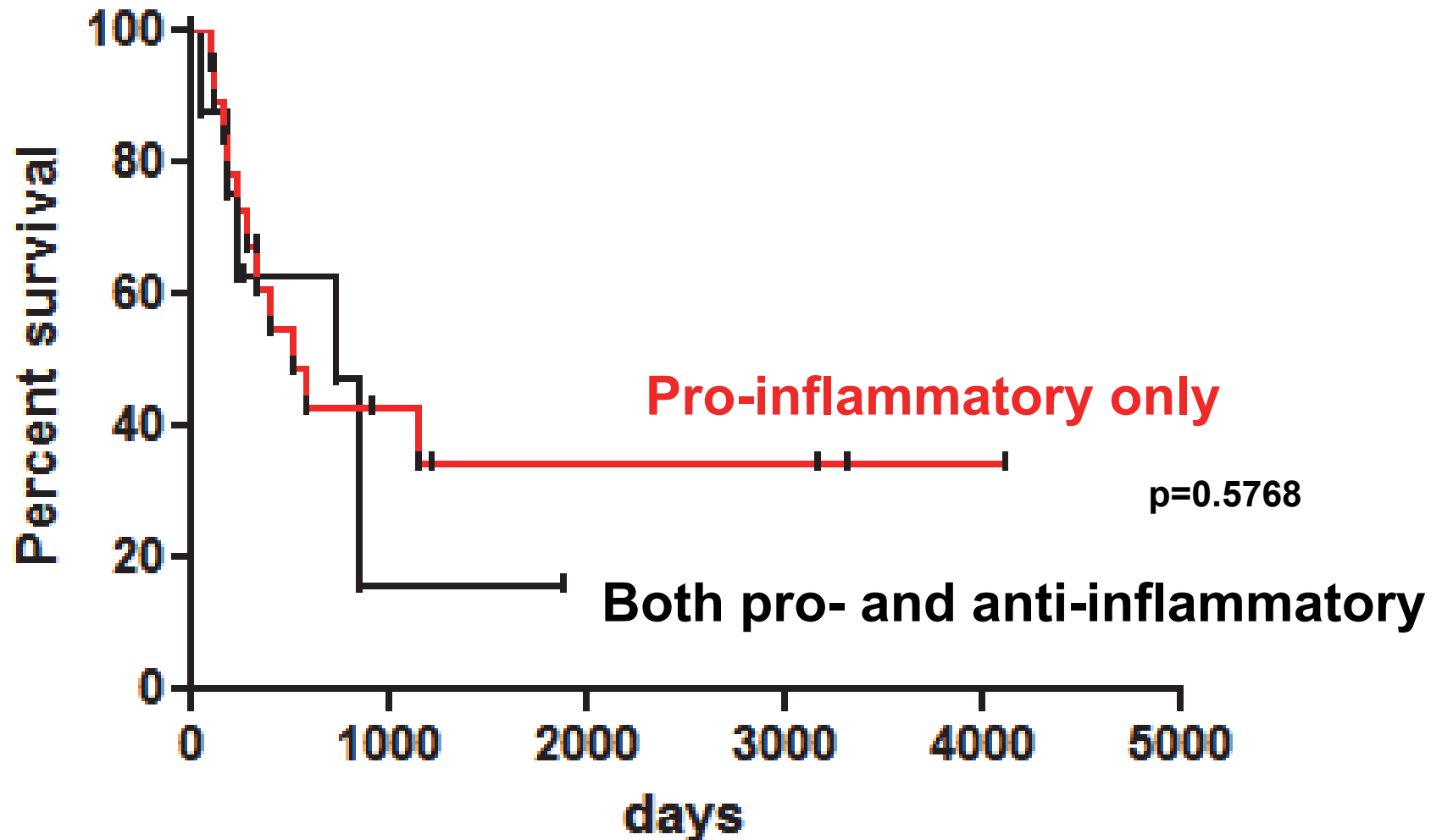
B

Number of targets



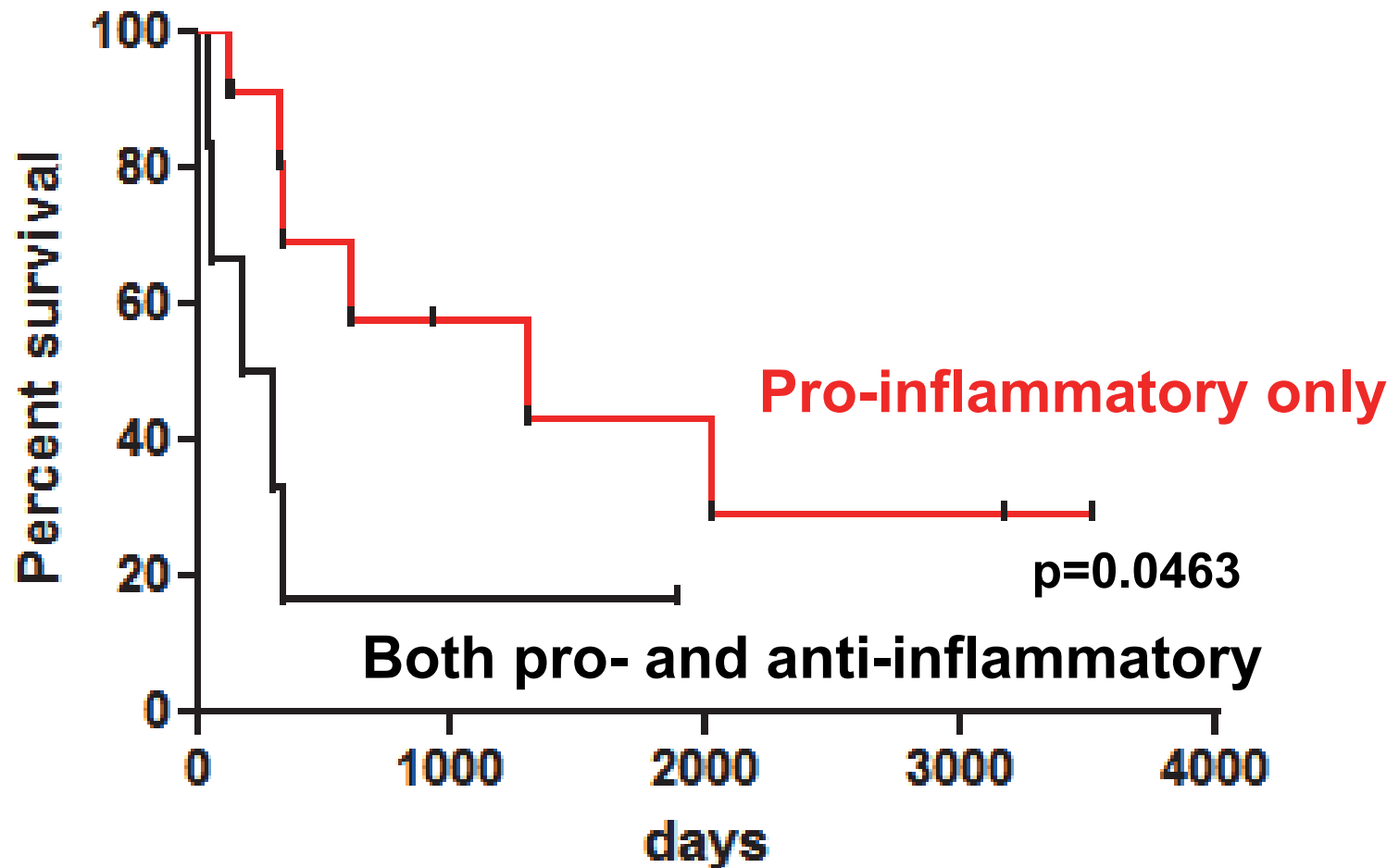
Survival according to type of response

NY-ESO-1

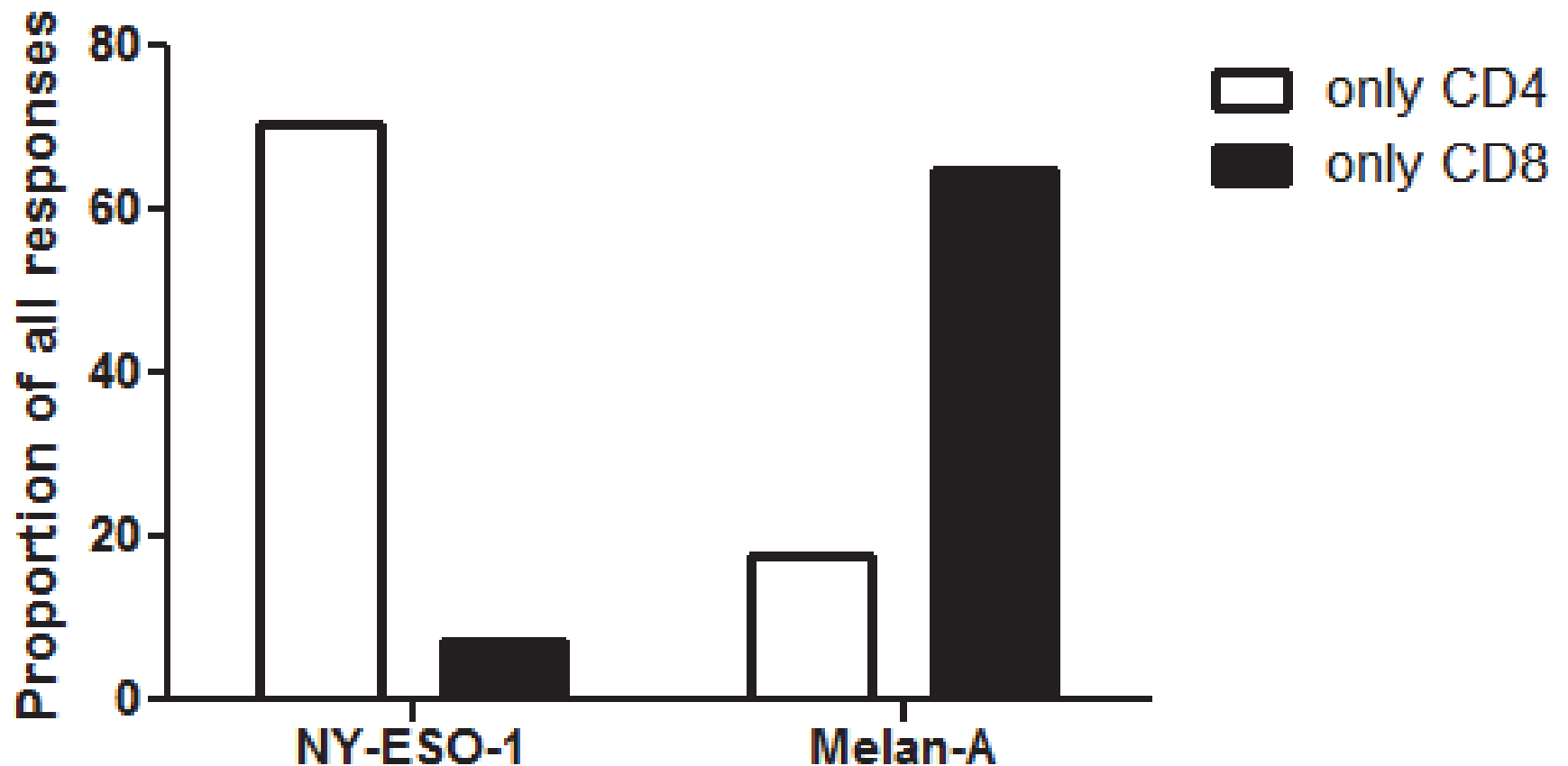


Survival according to type of response

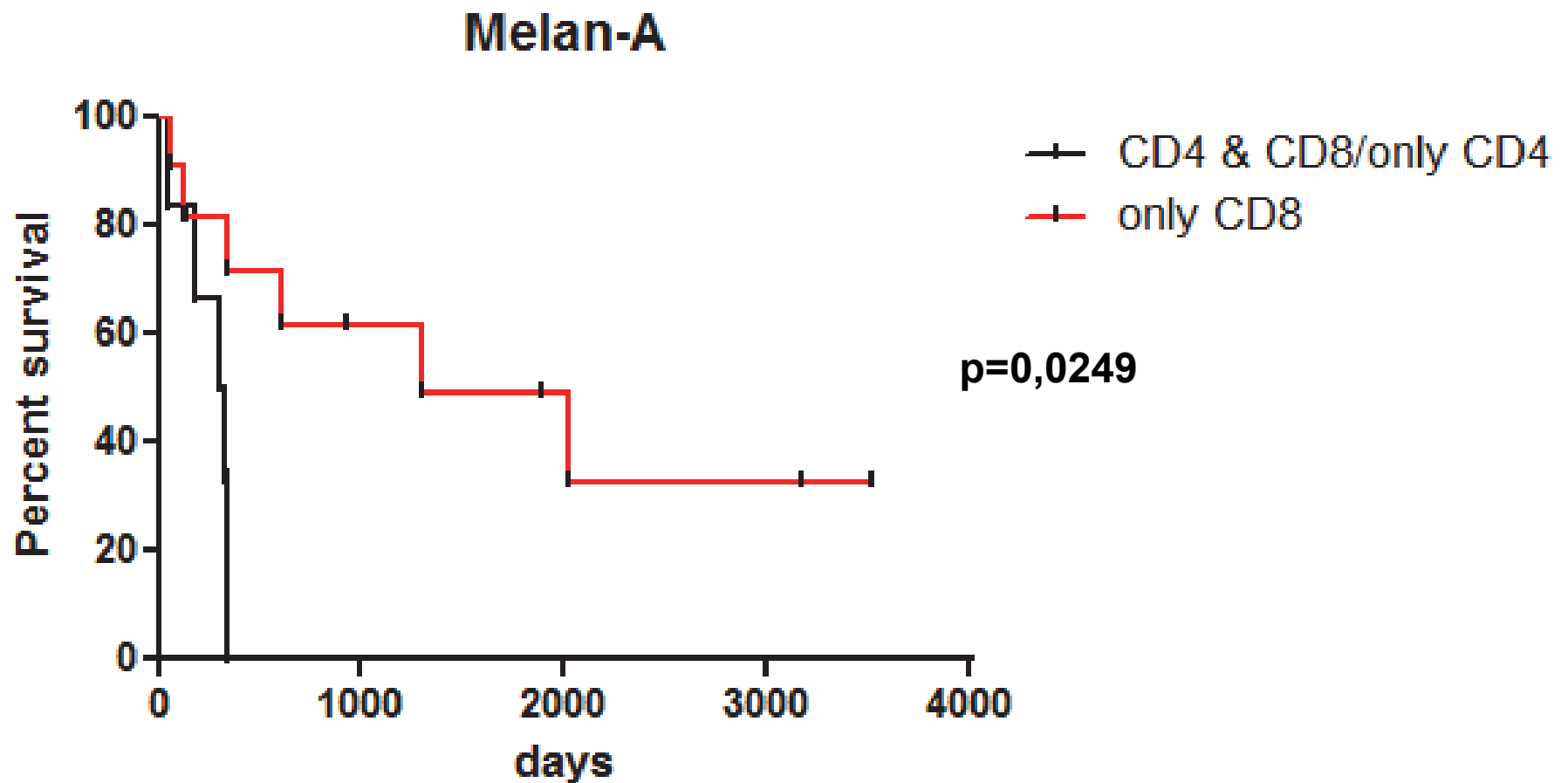
Melan-A



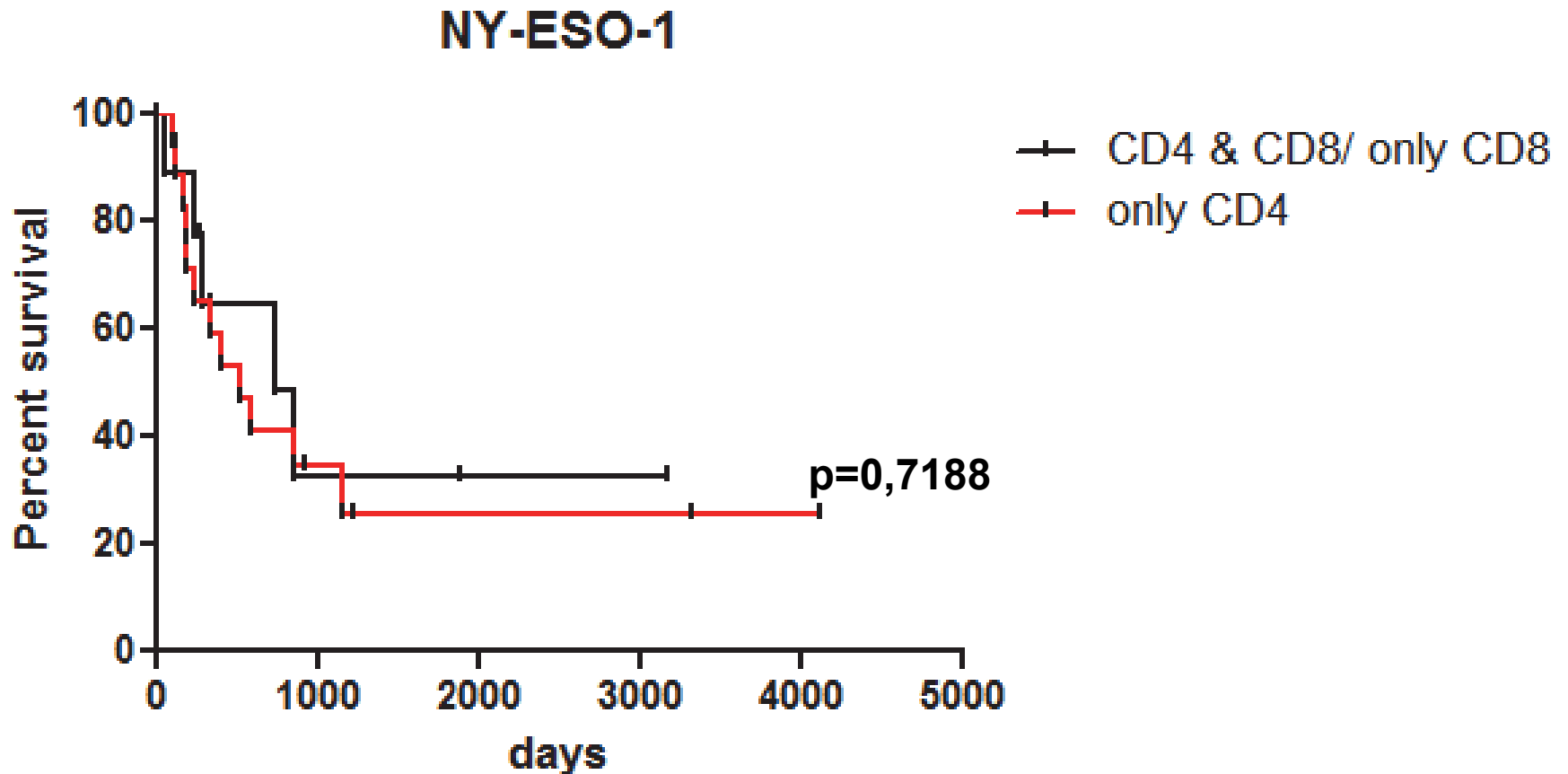
Preponderance of CD4 and CD8 responses to NY-ESO-1 and Melan-A differs



Only CD8 cell reactivity to Melan-A correlates with survival



Both CD4 and CD8 reactivity to NY-ESO-1 correlate equally well with survival



Conclusions

Prospective studies show that an unopposed pro-inflammatory CD4 or CD8 T cell response to NY-ESO-1 is associated with long-term survival in stage IV melanoma

Only CD8 T cell responses to Melan-A are associated with extended survival

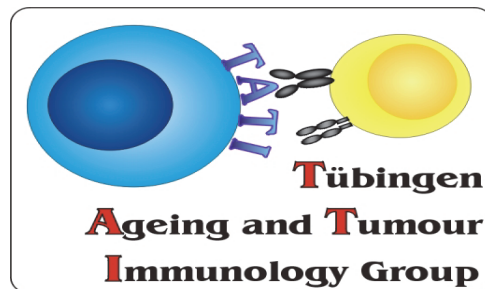
No associations with survival are seen for any responses to MAGE-A3 or survivin

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