NY-ESO-1 specific responses in patients with advanced prostate cancer treated with ipilimumab

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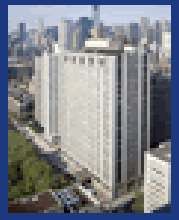


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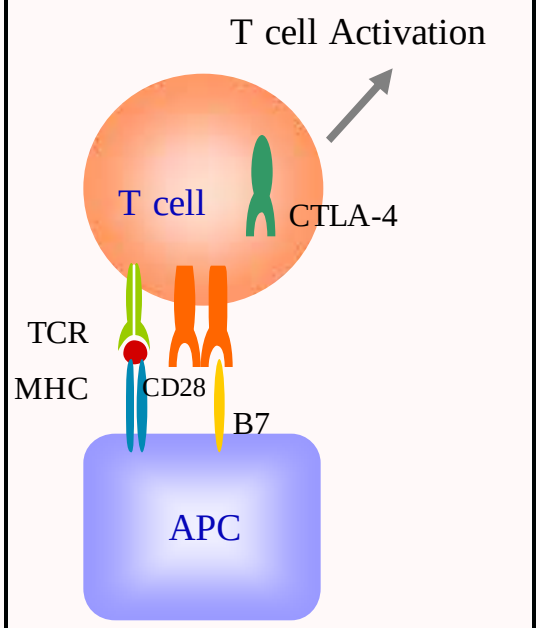
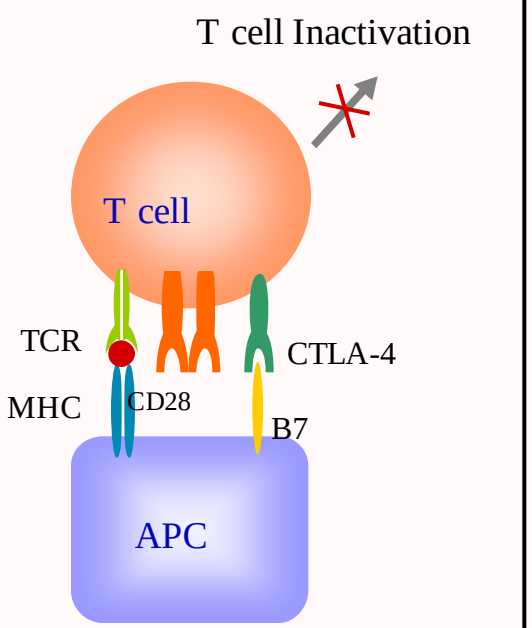
B7-CD28 signals and CTLA-4 blocking

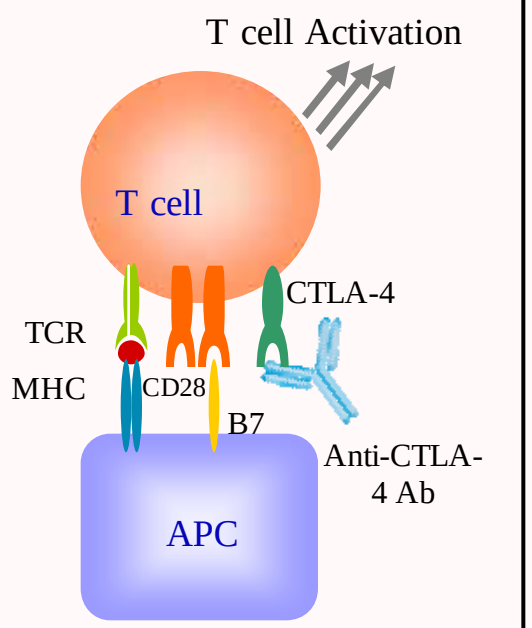
1. Co-stimulation via CD28 ligation transduces T cell activating signals



2. CTLA-4 ligation on activated T cells down-regulates T cell responses



3. Blocking CTLA-4 ligation enhances T cell responses



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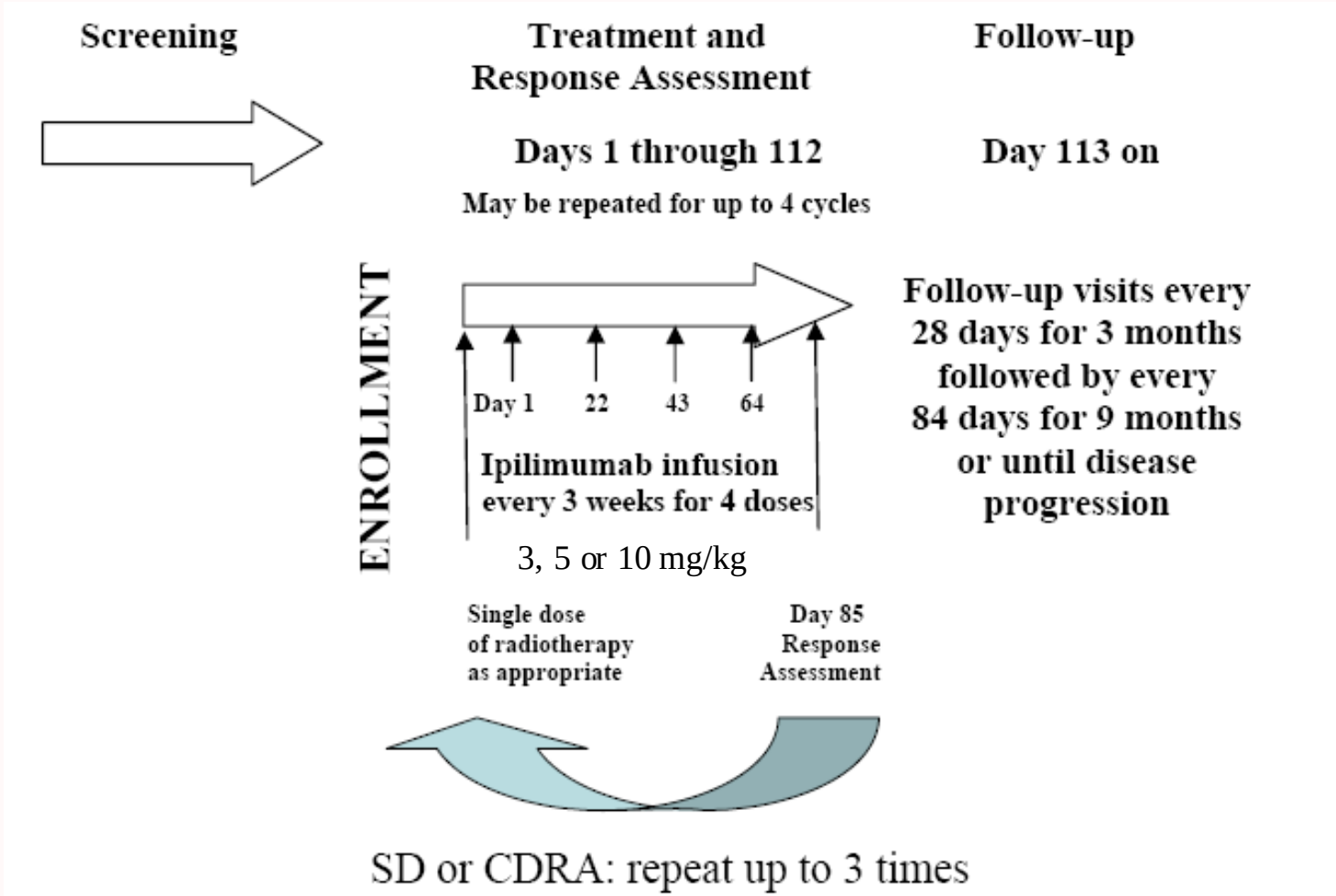
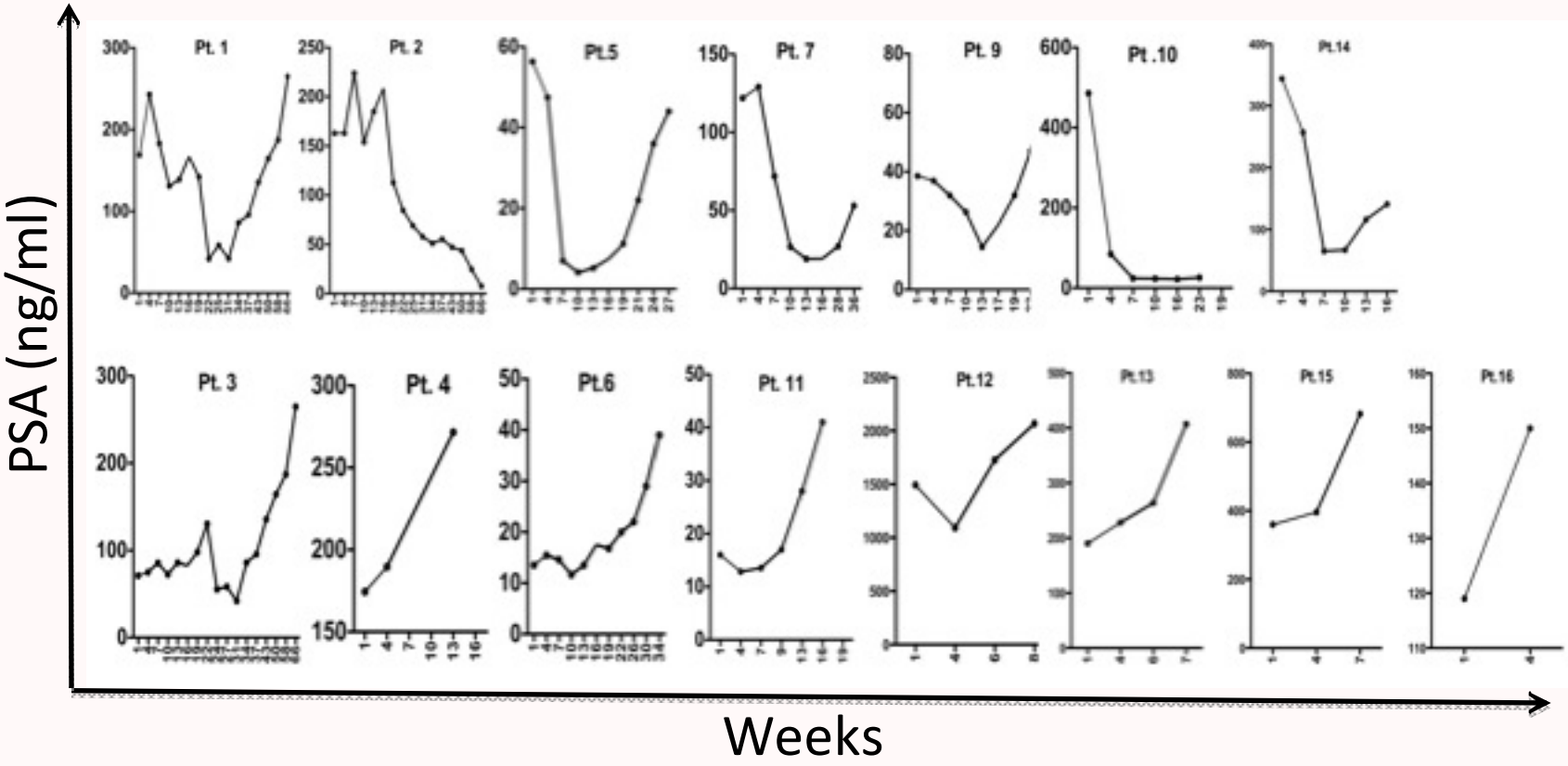
RT+ ipilimumab protocol MDX-010-21 : Time and events schema



PSA changes after CTLA-4 blockade



Pt. W/ BR (7/15)

Pt. W/O BR (8/15)

The median time-to PSA-progression was 3.4 months (0.6 to 23.2+ months). Median follow-up 10.6 months.

BR=biochemical response

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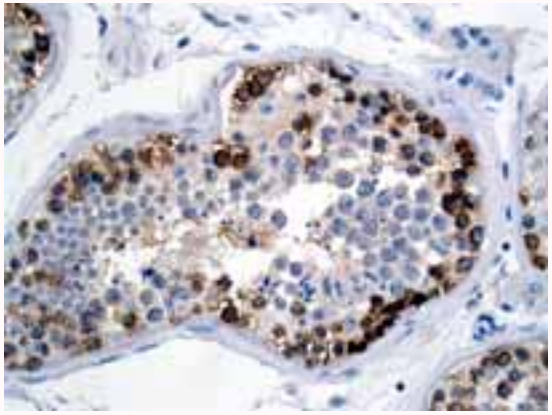
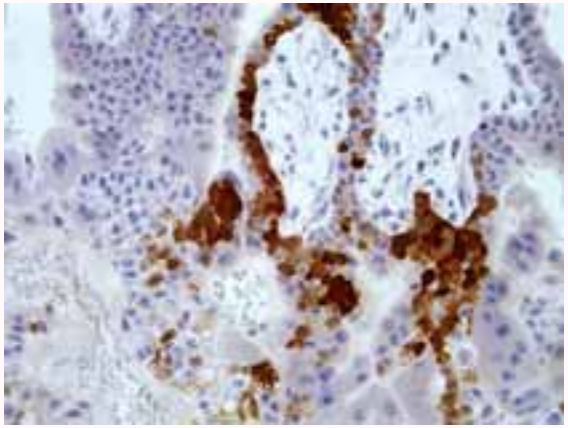
NY-ESO-1 expression on testis and cancer by IHC

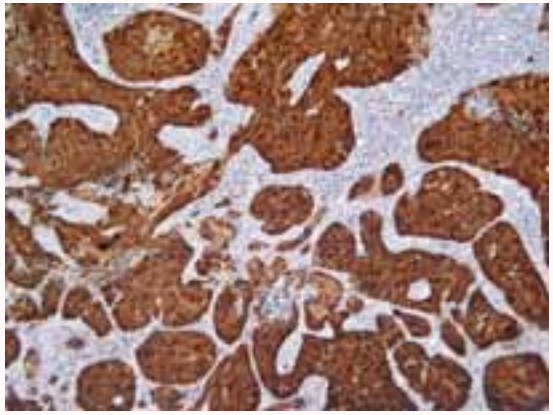
Testis



Placenta



Lung Cancer



- **Expression in adult normal tissue is restricted to testis or/and placenta.**
- **Gene expression is detected in a fraction of tumors.**
- **Expression of NY-ESO-1 genes is associated with advanced disease and poor outcome.**
- **Spontaneous humoral or T cell immunity in cancer patients, with a high frequency in patients with advanced NY-ESO-1-expressing tumors.**

Courtesy of Achim Junbluth
Ludwig Institute of Cancer Research, New York Branch

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Correlation of NY-ESO-1 antibody with clinical course following anti-CTLA-4 treatment

In collaboration with Sacha Gnjatic, Jedd Wolchok, MSKCC/Ludwig Center and with
Ruth Halaban and Mario Sznol, Yale University - Melanoma sera

Patients with NY-ESO-1 antibodies at any time point during study

Response	# patients Status at wk24 (%)
CR	6 (5.1%)
PR	14 (12.0%)
SD	25 (21.4%)
Clinical Benefit	**45** (38.5%)
No Clinical Benefit	**72** (61.5%)
Total	117 (100%)

According to Immune-related response criteria:

CR: Complete Response
PR: Partial Response
SD: Stable Disease
POD: Progression of Disease (includes MR: mixed response)
DOD: Dead of Disease

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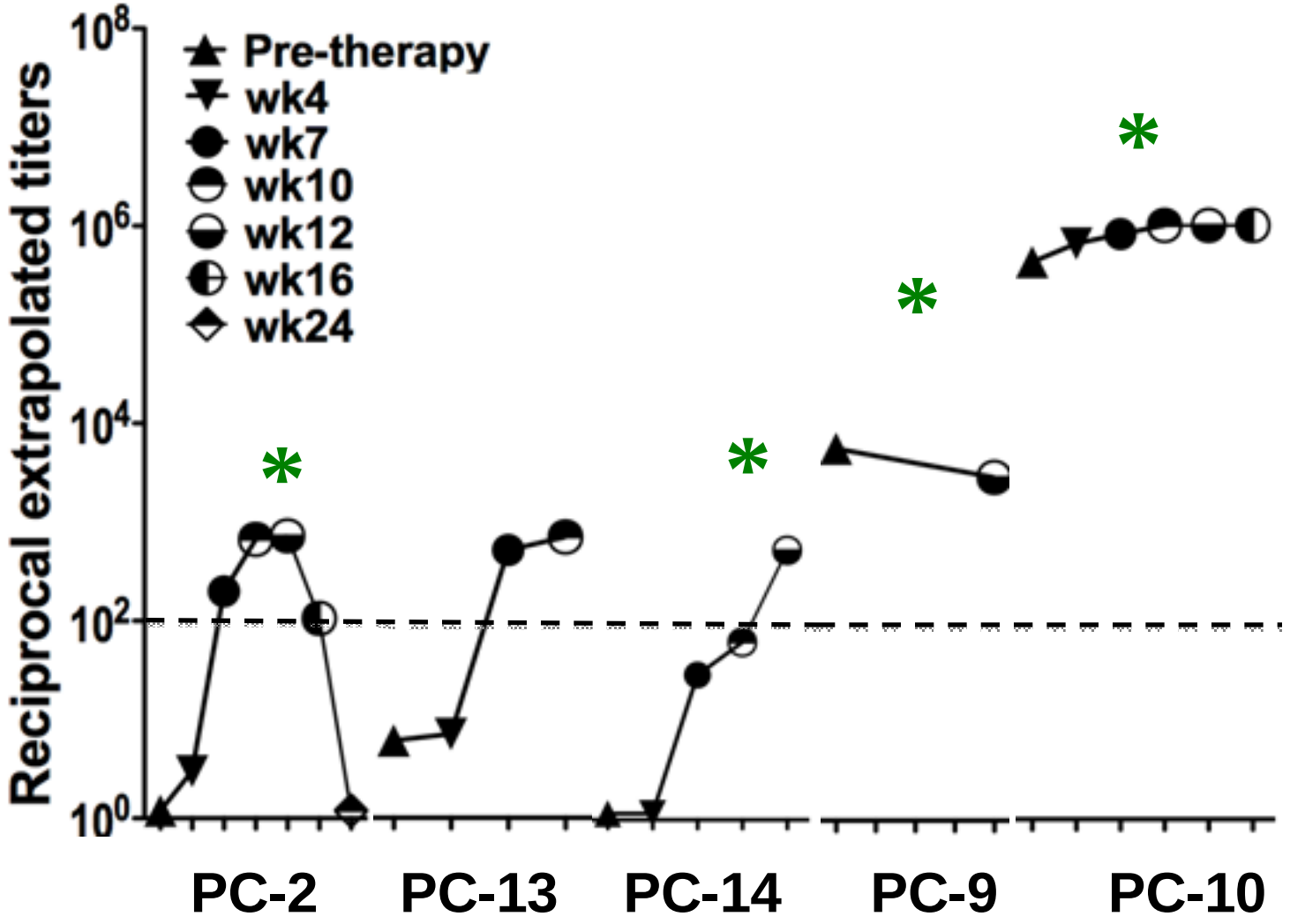
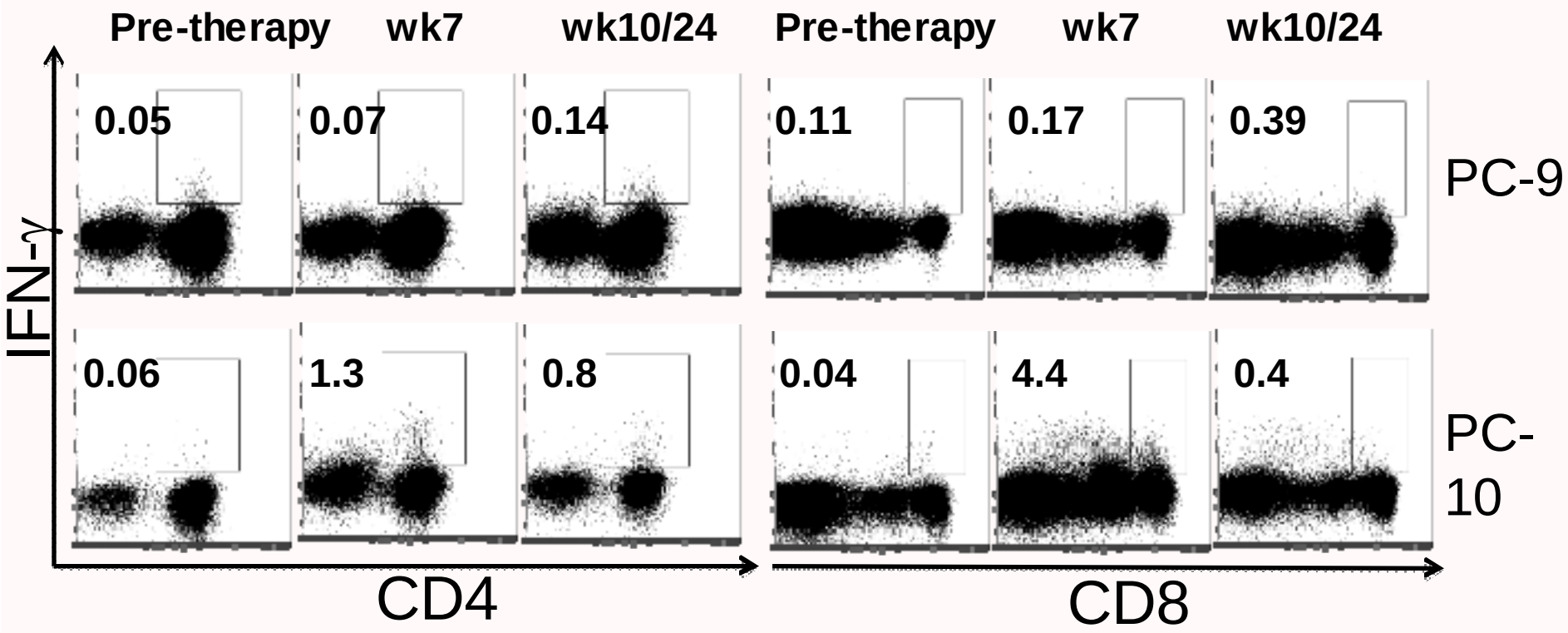
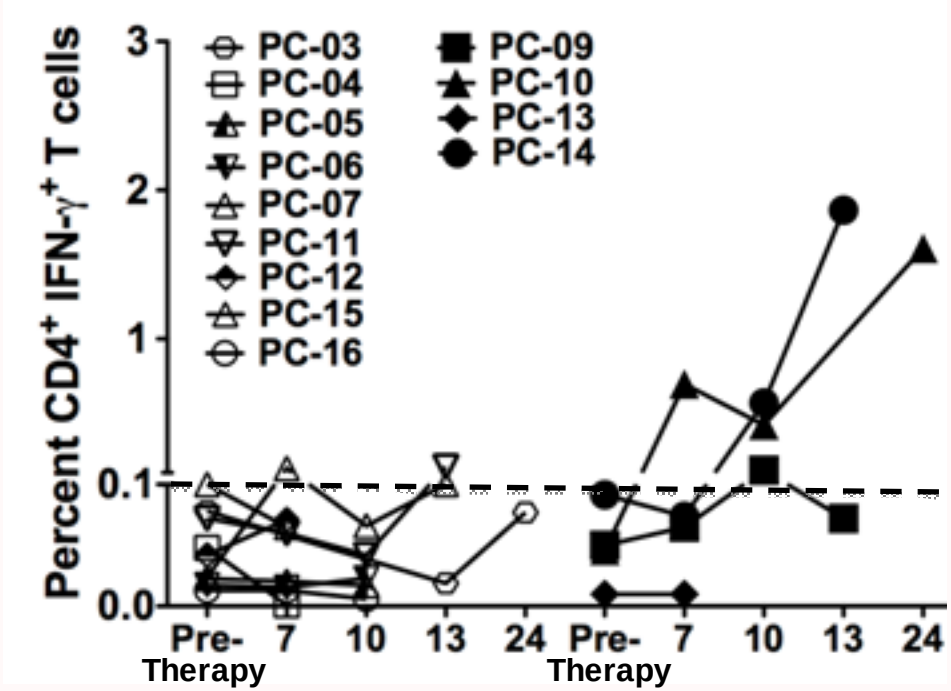
Changes in NY-ESO-1 antibody titers following ipilimumab therapy.



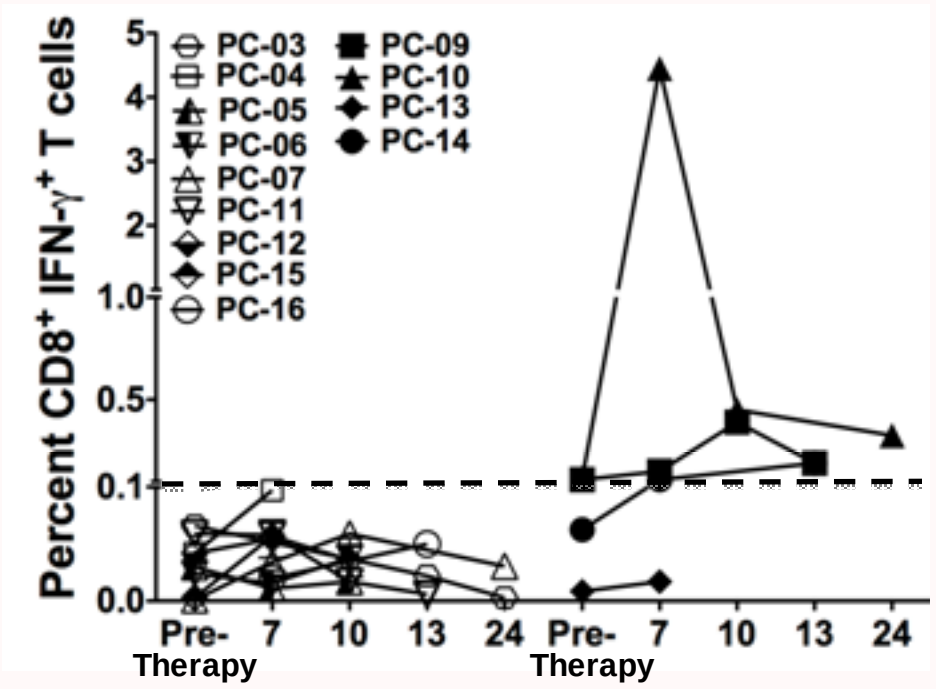
NY-ESO-1 specific CD4+ and CD8+ T cell responses



NY-ESO-1 specific CD4+ and CD8+ T cell responses were induced after CTLA-4 blockade



CD4+ T-cell



CD8+ T-cell

Patients PC-1 and -2 are not included because they lacked baseline PBMCs for analysis.

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NY-ESO-1 antibody and T cell responses

Pt.ID	PSA response	Time-to-PSA progression (mos)	Spontanous NY-ESO-1 Ab response	NY-ESO-1 Ab response	NY-ESO-1 CD4 T-cell response	NY-ESO-1 CD8 T-cell response	Polyfunctional CD4 and/or CD8 T-cell response
PC-1	+	7.9	-	-	-	-	-
PC-2	+	23.2+	-	+	+	-	++
PC-3	-	4.1	-	-	-	-	-
PC-4	-	3.4	-	-	-	-	-
PC-5	+	2.9	-	-	-	-	
PC-6	-	3.5	-	-	-	-	-
PC-7	+	8.5	-	-	+	-	-
PC-9	+	3.9	+	+	+	+	++
PC-10	+	9.8	++	++	++	++	++
PC-11	-	2.7	-	-	+	-	-
PC-12	-	1.4	-	-	-	-	-
PC-13	-	1.7	-	+	-	-	-
PC-14	+	2.7	-	+	++	+	++
PC-15	-	1.4	-	-	-	-	-
PC-16	-	0.6	±	-	-	-	-

-	<0	<0	<0.1	<0.1	<0.1
±	0~100	0~100			
+	100~1000	100~1000	0.1~0.5	0.1~0.5	0.1~0.5
++	>1000	>1000	>0.5	>0.5	>0.5

Four patterns of humoral and cellular immune responses to NY-ESO-1

Category	NY-ESO-1 Ab		CD4 T cells		CD8 T cells		Biochemical Response	Patients
	Pre	Post	Pre	Post	Pre	Post		
I	-	-	-	-	-	-	-	PC-3, PC-4,PC-6, PC-12, PC-15
	-	-	-	-	-	-	+	PC-5
II	-	-	-	+	-	-	+	PC-7
	-	-	-	+	-	-	-	PC-11
III	±	-	-	-	+	-	-	PC-16
	-	+	-	-	-	-	-	PC-13
	-	+	-	+	-	+	+	PC-14
IV	+	+	+	+	+	+	+	PC-9, PC-10

Patients PC-1 and -2 are not included because they lacked baseline PBMCs for analysis.

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Conclusions:

- NY-ESO-1 antibody responses can be detected in a subset of metastatic prostate cancer patients before immunotherapy

- CTLA-4 blockade enhanced NY-ESO-1 some pre-existing antibody responses and also induced de novo responses in some patients

- Seropositive patients also had CD4+ and CD8+ T cell responses augmented after ipilimumab treatment

- The prognostic importance of NY-ESO-1 immunity in response to CTLA-4 blockade will be prospectively assessed in an upcoming phase III trial

Further Questions

- What is the functional impact of anti-CTLA-4 therapy on NY-ESO-1 specific T cells?
- Which specific T cell populations are affected by CTLA-4 blockade?
- Why do some NY-ESO-1 seropositive patients (eg, PC-13) not respond to CTLA-4 blockade?
- Is NY-ESO-1 serostatus a general biomarker for responsiveness to immunotherapy or does the response to this specific antigen have a therapeutic impact?

Acknowledgement



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Patient demographics (n=15)

Patient No.	Age	KPS	Gleason score	Mets			Prior therapy					Baseline PSA	Cohort	No. of doses
				LN	Bone	Other	Surgery	RT	Hormonal	Chemo	Immuno			
PC-1	62	90	6		x		x		x	x	x	197	3+RT	7
PC-2	63	90	6	x	x	ST	x	x	x			163	10	6
PC-3	62	80	9		x	ST		x	x	x		71	10+RT	4
PC-4	60	80	9	x	x			x	x			174	10+RT	2
PC-5	57	90	9		x	ST	x		x	x		56	10+RT	4
PC-6	65	90	9		x		x		x		x	14	10 exp	2
PC-7	64	90	9		x				x			122	10 exp	2
PC-9	74	80	8	x	x		x		x			39	10 exp	4
PC-10	61	80	9		x	Adrenal			x	x		486	10+RT	3
PC-11	58	90	9	x			x	x	x	x		16	10+RT	3
PC-12	78	80	9	x				x	x	x		1493	10	1
PC-13	63	90	9	x	x		x		x	x		190	10+RT	2
PC-14	53	80	7	x	x		x	x	x			345	10+RT	1
PC-15	66	80	7	x	x		x	x	x	x		360	10+RT	2
PC-16	50		8	x	x		x	x	x	x		119	10+RT	1
PC-I	60	100	9	x			x	x	x	x		20	10	3
PC-II	75	90	9	x			x		x			12	10	4
PC-III	57	90	9	x	x				x			9	5	4
PC-IV	78	90	8			PB	x	x	x			7	3	2
PC-V	70	90	7	x			x	x	x			63	3	4
PC-VI	73	90	7	x	x			x		x		114	3	3
PC-VII	62	90	9		x		x	x				13	3	2

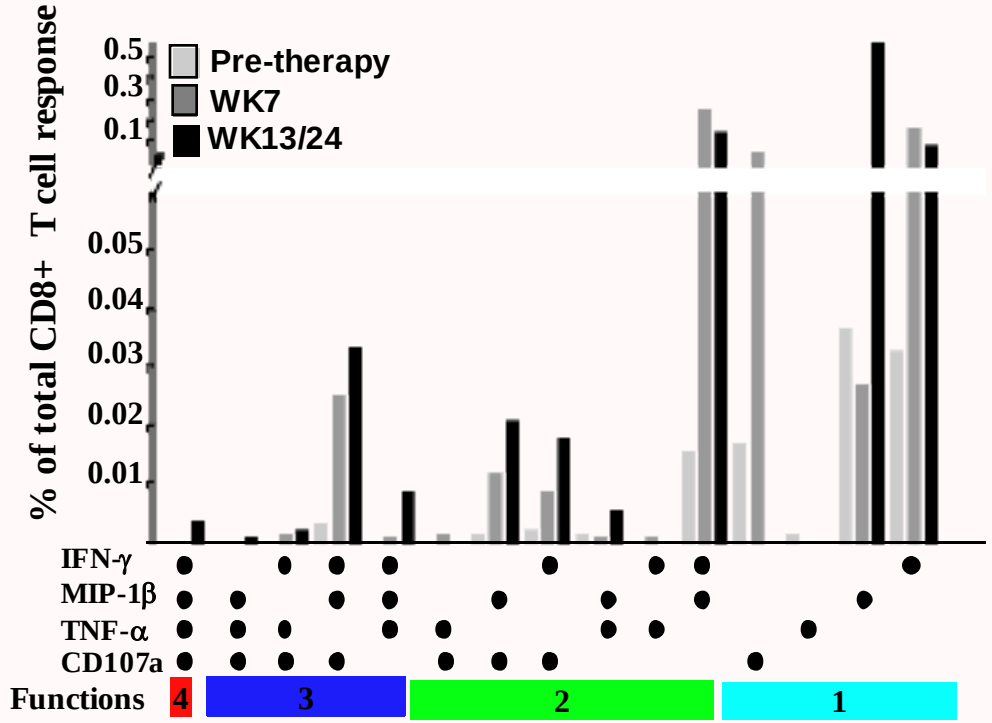
Patient demographics (n=15)

Age, years	
Median	62
Range	50-78
Karnofsky performance status	
Median	90
Range	80-90
Prostate-specific antigen, ng/ml	
Median	163
Range	14-1,493
Extent of disease	
Bone metastases	15 (100%)
Lymph node metastases	11 (73%)
Visceral/soft tissue metastases	6 (40%)
Local therapy	
Prostatectomy	3 (20%)
Prostatectomy + EBRT	5 (33%)
EBRT/Brachythrapy	4 (27%)
No definitive local therapy	3 (20%)
Hormone therapy	
Primary therapy only	1 (7%)
Second-line therapy	2 (13%)
≥3 therapies	12 (90%)
Chemotherapy	
Any chemotherapy	10 (67%)
Taxane-based chemotherapy	8 (53%)
Radiation therapy (for metastatic disease)	6 (40%)

EBRT, external beam radiation therapy

CTLA-4 blockade induced polyfunctional CD8 T cell responses.

A.



B.