ESMO 2012

Poster discussion: Immunotherapy lung cancer

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Disclosure

Thank to the presenters for a selection of their slides.

J. Vansteenkiste is holder of the Amgen Chair in Supportive Cancer Care at the Leuven University (research funding)

J. Vansteenkiste is holder of the Eli-Lilly Chair in Respiratory Oncology at the Leuven University (research funding)

J. Vansteenkiste is holder of the Astra Zeneca Chair in Personalised Lung Cancer Care at the Leuven University (research funding)

Lung cancer immunotherapy

Interact with the immune system to treat cancer

"Supportive" non-specific enhancement of innate immune system

- **poor history (BCG, IL, IFN, C. parvum, thymosin,...)**

Immuno-modulation

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Lung cancer immunotherapy

Interact with the immune system to treat cancer

"Supportive"	"Active"
non-specific enhancement of innate immune system	specific priming of immune system -> antibodies and/or cyto-toxic T cellls
• poor history (BCG, IL, IFN, C. parvum, thymosin,...)	• tumour antigen specific • whole tumour cells
Immuno-modulation	**Cancer vaccination**

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Lung cancer immunotherapy

Interact with the immune system to treat cancer

"Supportive"	"Active"
non-specific enhancement of innate immune system	specific priming of immune system -> antibodies and/or cyto-toxic T cellls
• poor history (BCG, IL, IFN, C. parvum, thymosin,...)	• tumour antigen specific • whole tumour cells
Immuno-modulation	Cancer vaccination

- better targets
- better adjuvants
- better trials

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Lung cancer immunotherapy

- **Immunomodulation**

1237PD Gettinger et al.

Clinical activity and safety of anti-programmed death-1 (PD-1) (BMS-936558/MDX-1106/ONO-4538) in patients (pts) with advanced non-small cell lung cancer (NSCLC)

- **Therapeutic vaccination**

1238PD Macias et al.

Active specific immunotherapy with Racotumomab in the treatment of advanced non-small cell lung cancer (NSCLC)

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Lung cancer immunotherapy
> conditions for a successful strategy

Phase	Question	
Preclinical	Specificity?	• Tumour specific or not?
	Expression?	• Broadly expressed? Sufficient level? Conserved in metastatic cells?
MOA	Immunogenic?	• Effective humoral and cellular response?
Phase I-II	Clinical effects?	• Cancer sensitive to immune killing?
		• Tolerabilty?
		• Possible predictive biomarker?
Phase III	Patient benefit?	• Outcome (OS preferred)? • Tolerability (~QoL)? • Predictive biomarker confirmed?

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Lung cancer immunomodulation > overview

- "Disappointing historical experience": levamisole, BCG, IL, IFN, C. parvum, thymosin,...
- PF-3512676 (Promune): 2 negative large ph3 studies
- Talactoferrin alpha

LBA34 | FORTIS-M, A Randomized, Double-blind, Placebo-controlled Phase 3 Study of Oral Talactoferrin alfa with Best Supportive Care in Patients with Advanced Non-Small Cell Lung Cancer following Two or More Prior Regimens- by The FORTIS-M Study Group

Session Info: Proffered Papers, NSCLC metastatic, II
Day/Date: Monday, October 1, 2012
Session Time: 11:00 AM - 12:30 PM
Room: Hall A

- Ipilimumab (anti CTLA4 MoAb)
- BMS-936558 / BMS-936559 (anti PD-1 / PD-L1 Moab)

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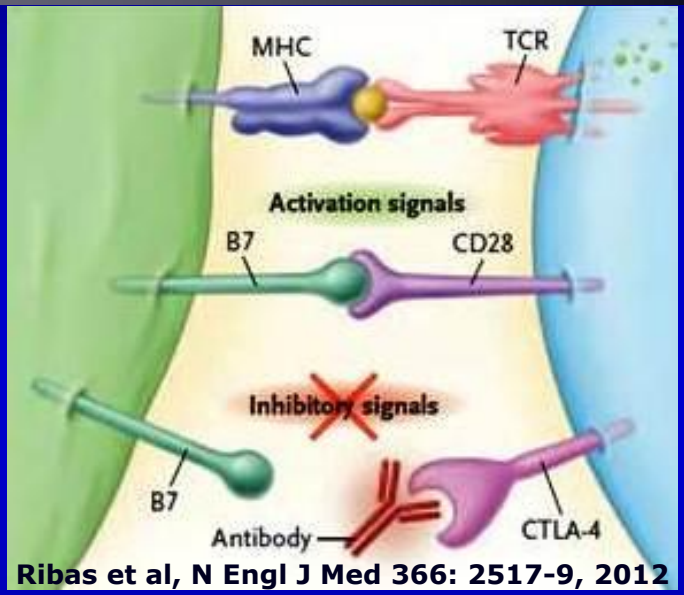
Lung cancer immunomodulation > ipilimumab

- Human MoAb inhibiting cytotoxic T lymphocyte antigen 4 (CTLA-4)
- -> promotes signalling to CD28 and stimulation of T cell response
- -> may block suppressive signal from regulatory T cells, and promote autoimmunity



Ribas et al, N Engl J Med 366: 2517-9, 2012

- Approved for advanced melanoma
- Promising ph2 R data in advanced NSCLC
- Some patients experience major autoimmune toxicity

Lynch et al, J Clin Oncol 30:2046-2055, 2012

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Lung cancer immunomodulation > ipilimumab

	Patients ipilimumab-only arm (N=131)	
	Grade 3-4 (N)	Grade 3-4 (%)
Any	60	45.8
Drug-related	30	22.9
Hepatic	5	3.8
Immune-related	19	14.5
(skin, intestinal, endocrine)	*2*	*1.5*

- Besides corticosteroids, 4 patients received infliximab (anti–TNF) for diarrhea /colitis grade 3+
- Residual colitis in 4, residual endocrine AEs requiring hormone-replacement in 8
- 14 deaths related to the study drugs, 7 immune-related AEs

Hodi et al, N Engl J Med 363:711–23, 2010

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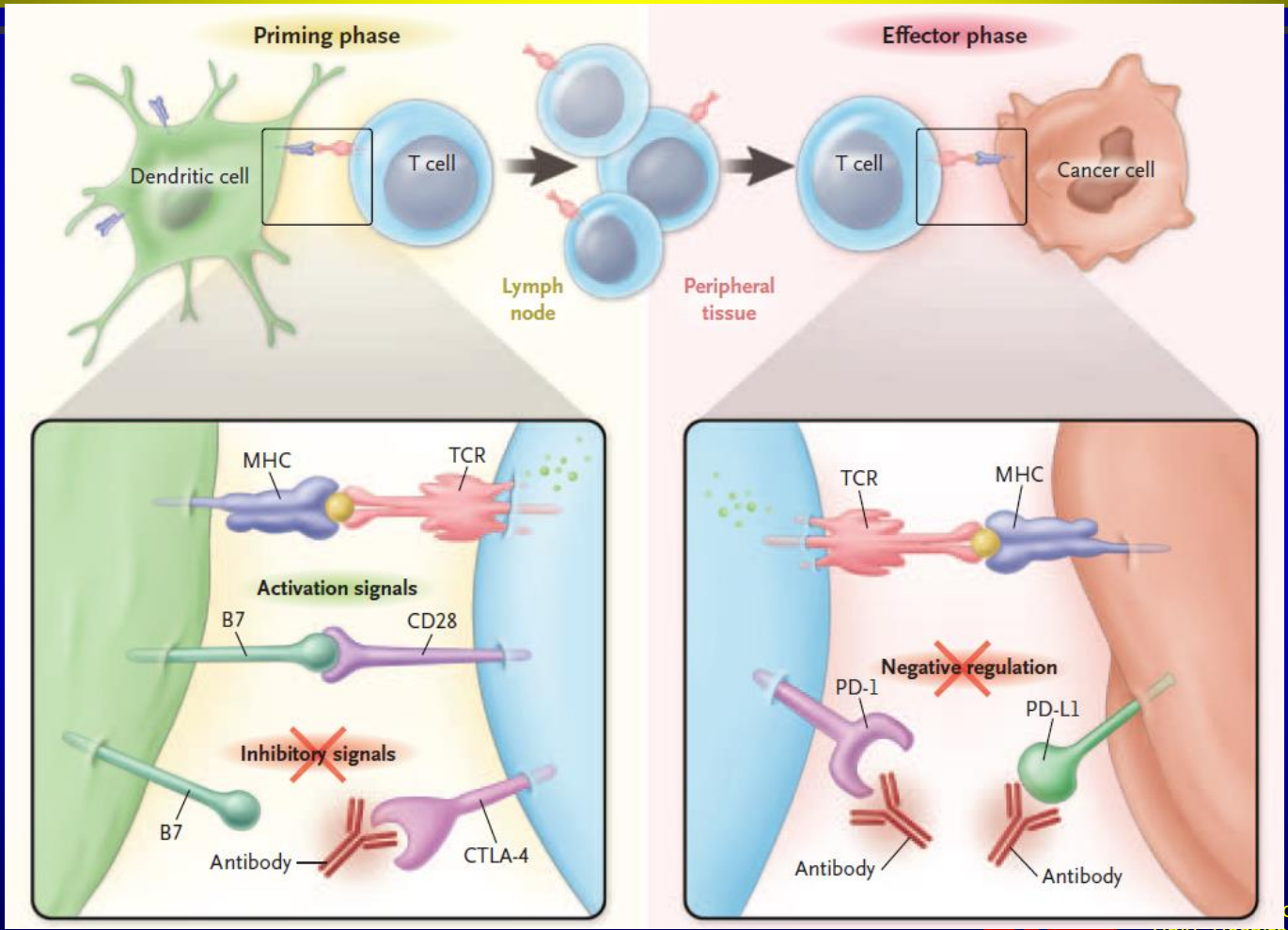
Lung cancer immunomodulation
> anti PD-1 and PD-L1



Ribas et al, N Engl J Med 366: 2517-2519, 2012

Lung cancer immunomodulation
> anti-PD-1: large ph1 study

	"Efficacy population"	Total
Melanoma	94	104
NSCLC	76	122
Renal	33	34

	Anti-PD1
All therapy related AEs	70%
G3/4 therapy related AEs	14%
pulmonary	1%
diarrhea	1%
auto-immune*	<1%
Discontinued for related AE	5%
Grade 5 (pulmonary)	N=3

* colitis, hepatitis, hypophysitis, thyroiditis

Topalian et al, N Engl J Med 366: 2443-2454, 2012

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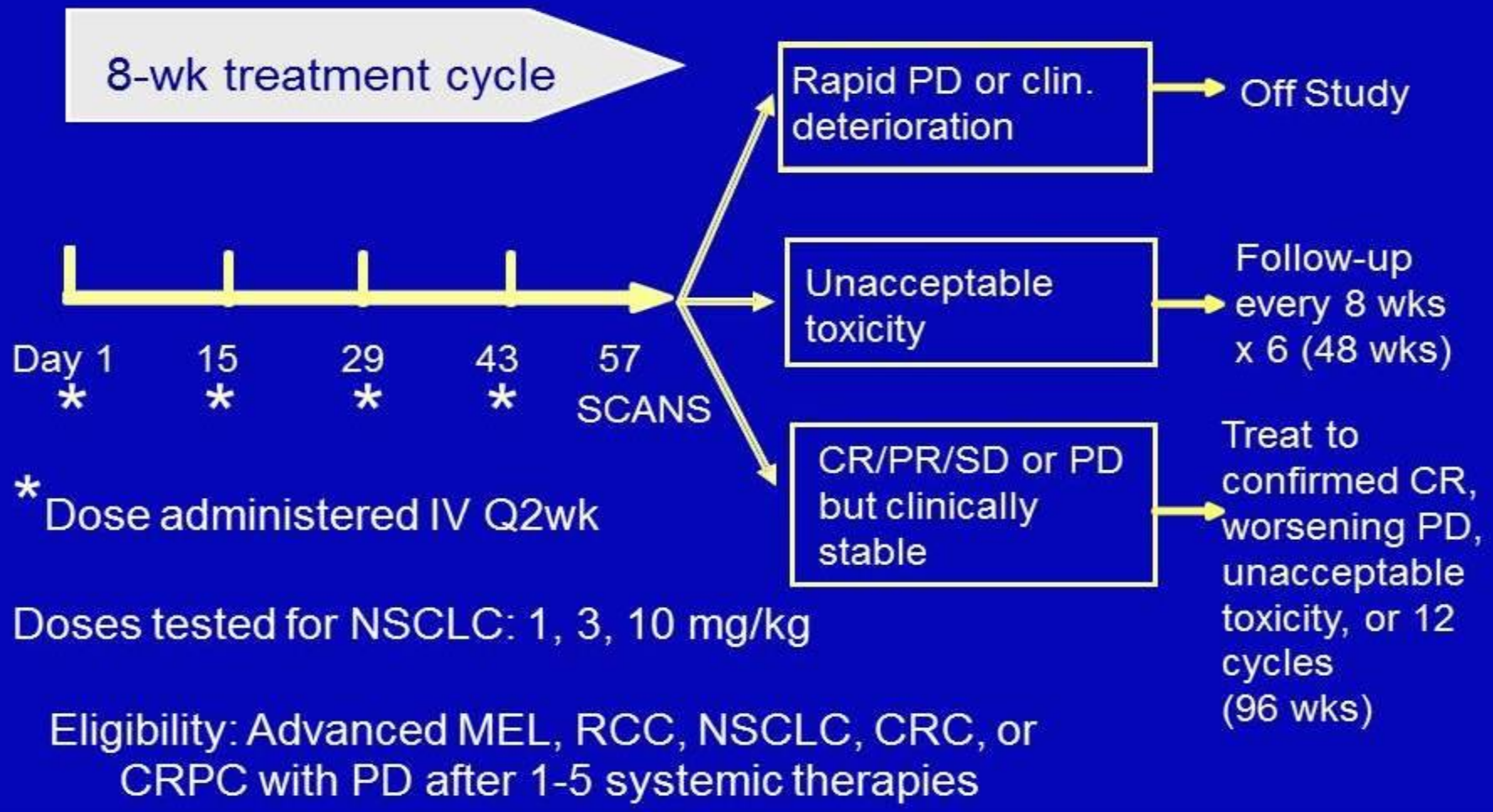
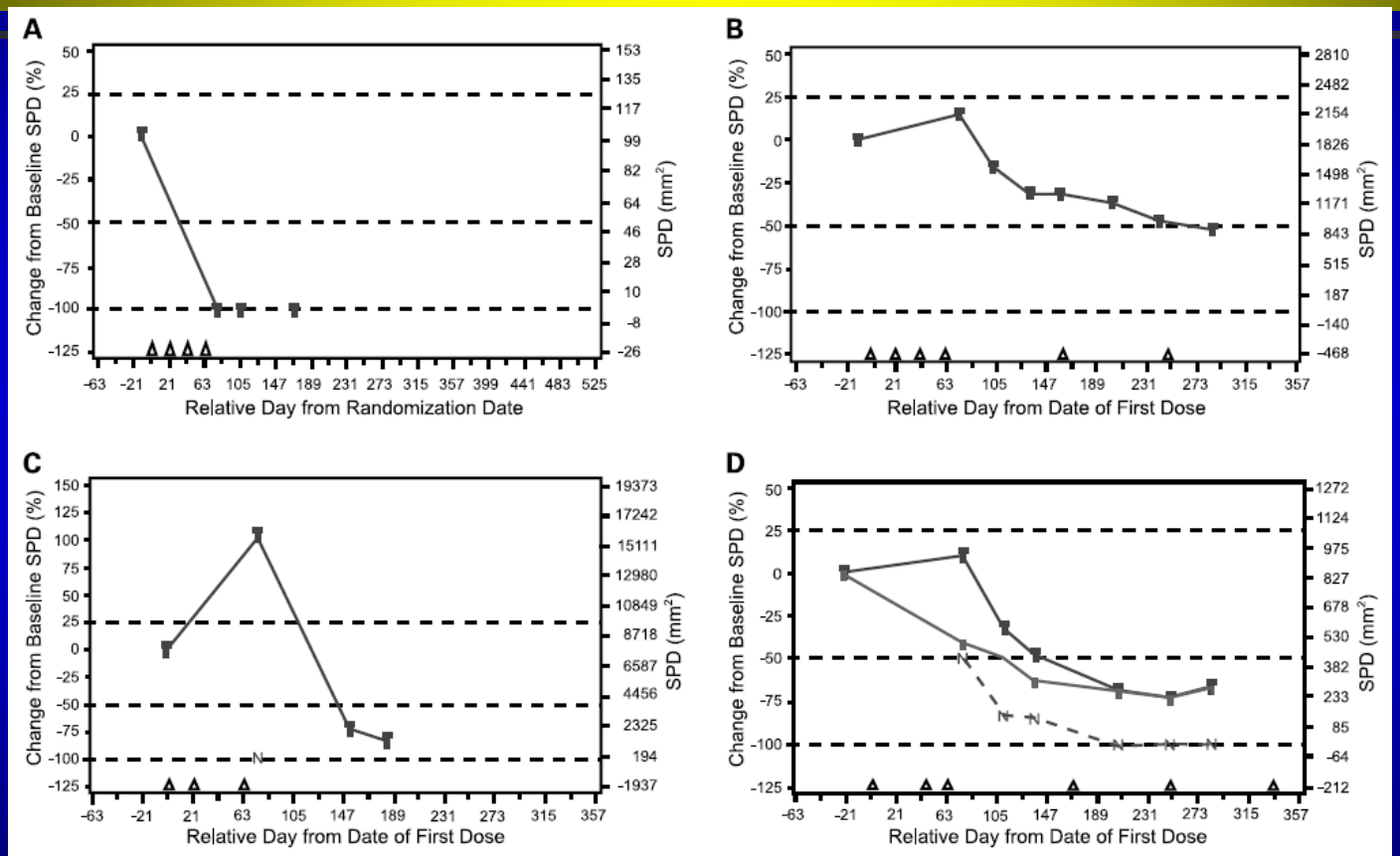
Lung cancer immunomodulation
> anti-PD-1, abstract 1237, Gettinger et al.



Lung cancer immunotherapy
> patterns of response



➢ **all patterns associated with favourable survival**

Wolchok et al, Clin Canc Res 15:7412, 2009

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Lung cancer immunomodulation
> anti-PD-1, abstract 1237, Gettinger et al.

BMS-936558-Related Adverse Events

Drug-Related Adverse Event	All Grades		Grades 3-4	
	Tot Pop[a,b,c]	NSCLC	Tot Pop	NSCLC[d]
	No. (%) of Patients, All Doses			
Any adverse event	220 (72)	84 (66)	45 (15)	11 (9)
Fatigue	78 (26)	7 (6)	5 (2)	2 (2)
Rash	41(14)	6 (5)	—	—
Diarrhea	36 (12)	9 (7)	3 (1)	1 (1)
Pruritus	31 (10)	9 (7)	1 (0.3)	—
Nausea	24 (8)	9 (7)	1 (0.3)	—
Appetite ↓	24 (8)	12 (9)	—	—
Hemoglobin ↓	18 (6)	10 (8)	1 (0.3)	—
Pyrexia	16 (5)	4 (3)	—	—

Lung cancer immunomodulation
> anti-PD-1, abstract 1237, Gettinger et al.

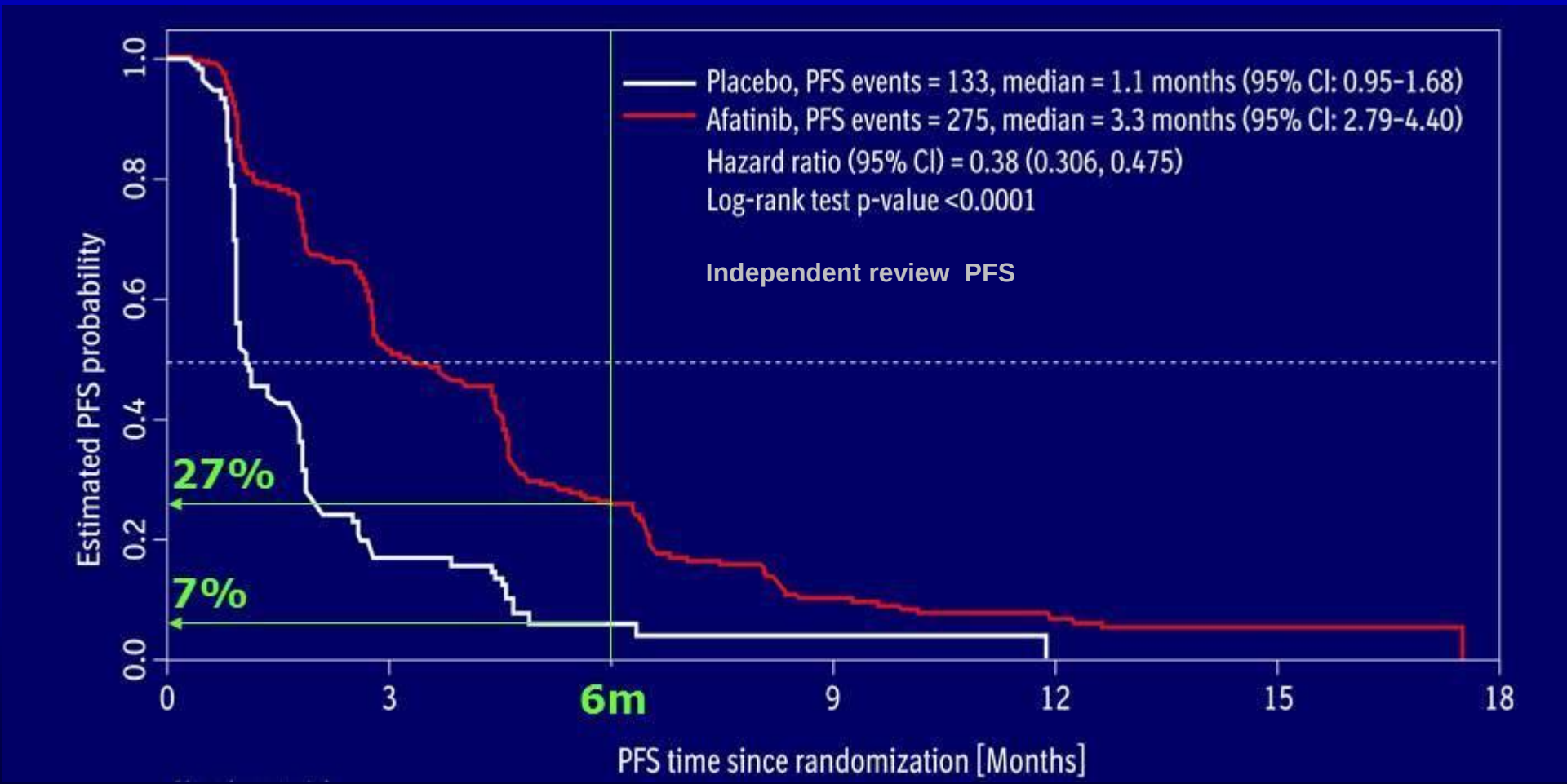
Clinical Activity of BMS-936558 in NSCLC Patients

Pop	Dose (mg/kg)	Pts n	ORR n (%)	Median DOR months (95%CI) [Individual pt response]	SD ≥24 wk n (%)	PFSR at 24 wk (%)
ALL NSCLC	1-10	122	20 (16)	NE Range:1.9+ to 30.8+	11 (9)	33
NSCLC	1	31	1 (6)	NE [11.0+]	3 (10)	25
	3	33	9 (27)	NE [2.3 +, 3.7+, 5.5+, 6.7+, 9.2+, 9.4+, 13.3+, 15.8, 30.8+]	3 (9)	44
	10	58	10 (17)	9.8 (4.2 – NE) [1.9+, 1.9+, 3.7, 4.2, 5.6+, 6.7, 7.4+, 9.8, 13.0+, 18.5 +]	5 (9)	31

- ORR was assessed using modified RECIST v1.0
- 6 NSCLC patients showed a non-conventional pattern of response and were not classified as responders by the conventional RECIST

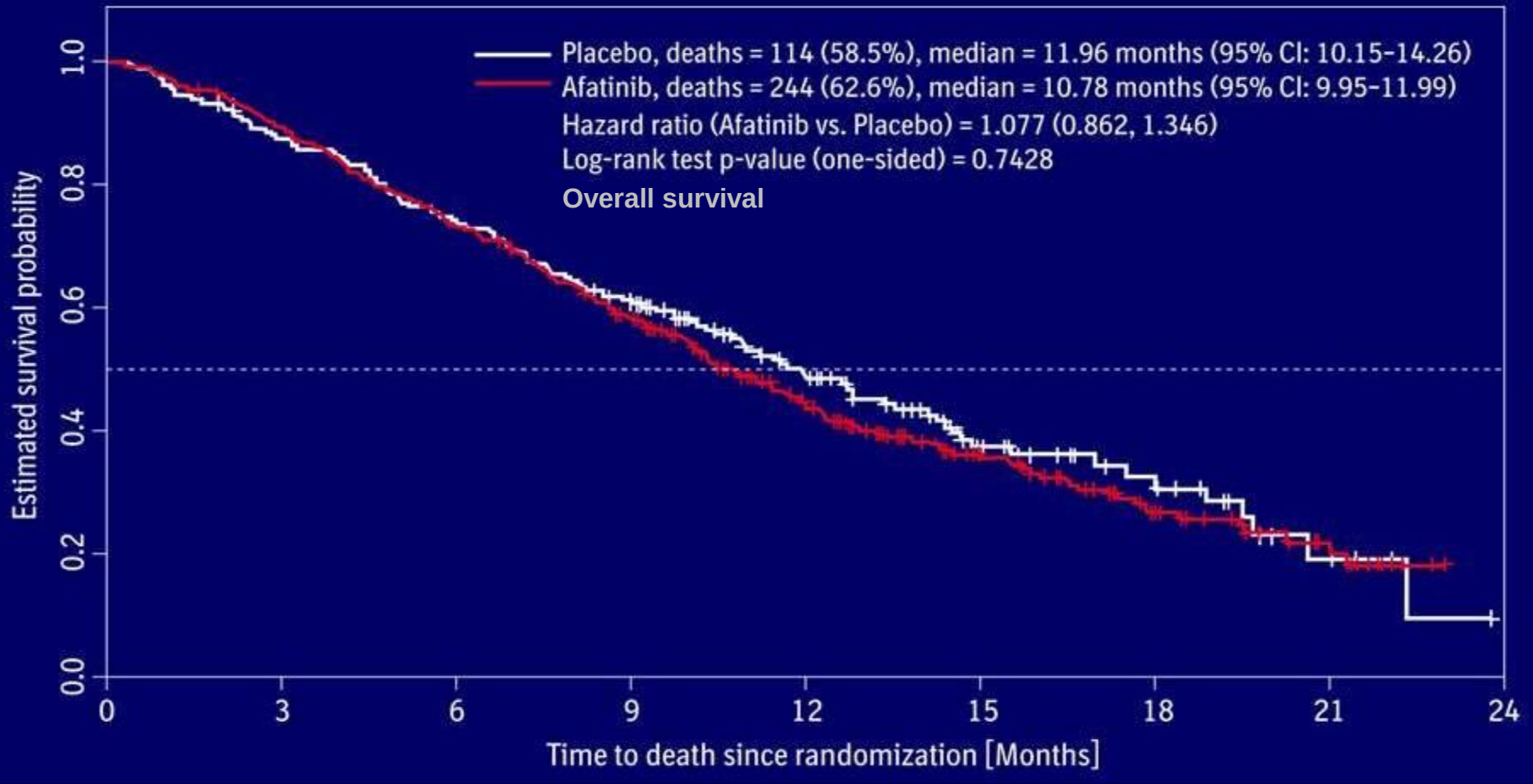
Pretreated advanced NSCLC

- **ESMO 2010: PFS afatinib vs. placebo (Miller et al.)**



Pretreated advanced NSCLC

- **ESMO 2010: OS afatinib vs. placebo (Miller et al.)**



Lung cancer immunomodulation
> anti-PD-1: large ph1 study

Phase	Question		
Preclinical	Specificity?	• Not AG directed, but better than ipilimumab	±
	Expression?	• Yes	√
MOA	Immunogenic?	• Effective humoral and cellular response?	±
Phase I-II	Clinical effects?	• Cancer sensitive to immune killing?	√
		• Tolerabilty?	±
		• Possible predictive biomarker?	√
Phase III	Patient benefit?	• Outcome (OS preferred)? • Tolerability (~QoL)? • Predictive biomarker confirmed?	?

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Lung cancer vaccination
> overview

Setting	Phase III	Class	Phase II data
Post surgery	MAGE-A3 recruited – target 2270 (MAGRIT)	MAGE-A3 full protein	RCT vs. placebo
Post chemoradio	BLP25 recruited – enrolled 1476 (START)	MUC1-peptide	RCT vs. BSC
Advanced	Lucanix recruited – target 700	allogeneic tumor cells	open label dose compar
	rEGF ongoing – target 230/1000	EGF full protein	RCT vs. BSC
	TG4010 ongoing – target 1000	MUC1-peptide	RCT vs. BSC
	1E10 ongoing – target 1082	anti-idiotype ab	RCT vs. standard care

>7500 patients

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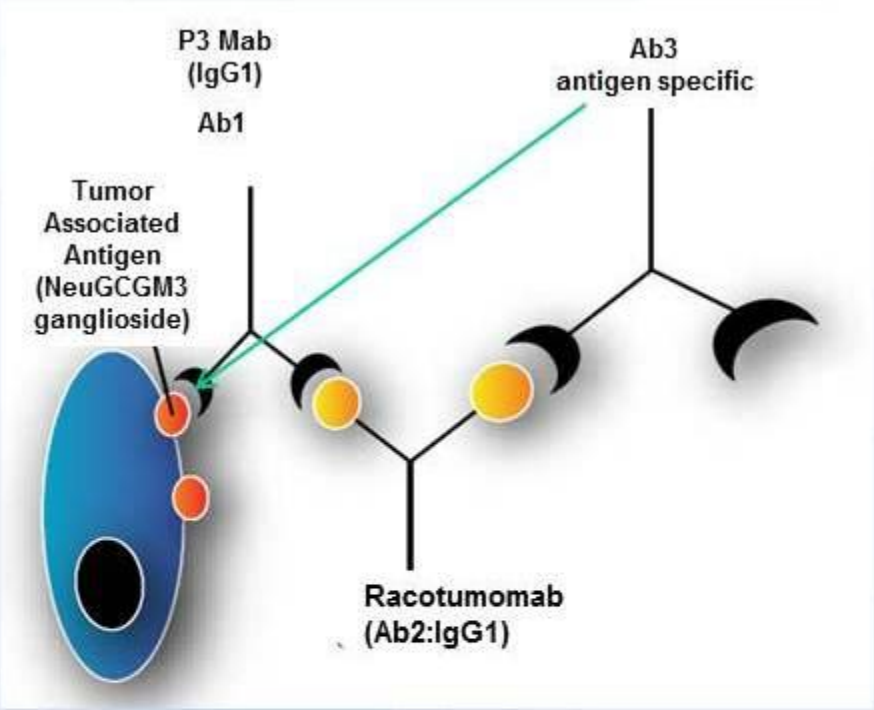
Lung cancer vaccination
> racotumomab, abstract 1238, Macias et al.



Target expression:

NeuGc GM3 is a tumor specific antigen, expressed in melanoma, breast cancer, lung cancer and several neuroectodermal pediatric tumors .

Mechanism of Action: Racotumomab induces a specific Ab3 (IgM and IgG) and cellular response against NeuGcGM3.

Lung cancer vaccination
> racotumomab, abstract 1238, Macias et al.

Phase II/III, multicentric, randomized, double blind and placebo- controlled.

176 patients with:
NSCLC Stages IIIB/IV
After completion of standard first line chemotherapy (CT) and
Response: PR, CR, SD.

Randomization
1:1

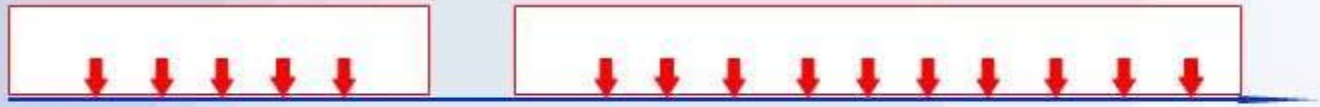
- **Placebo**
- **Racotumomab**

Two stages in the trial:

Stage 1- 15 immunizations during a period of one year.

Stage 2- Follow up for all patients. Blind was opened and monthly re-immunizations continued only for patients receiving racotumomab. Vaccination continued beyond progression (no second line therapy) until worsening PS or unacceptable toxicity.

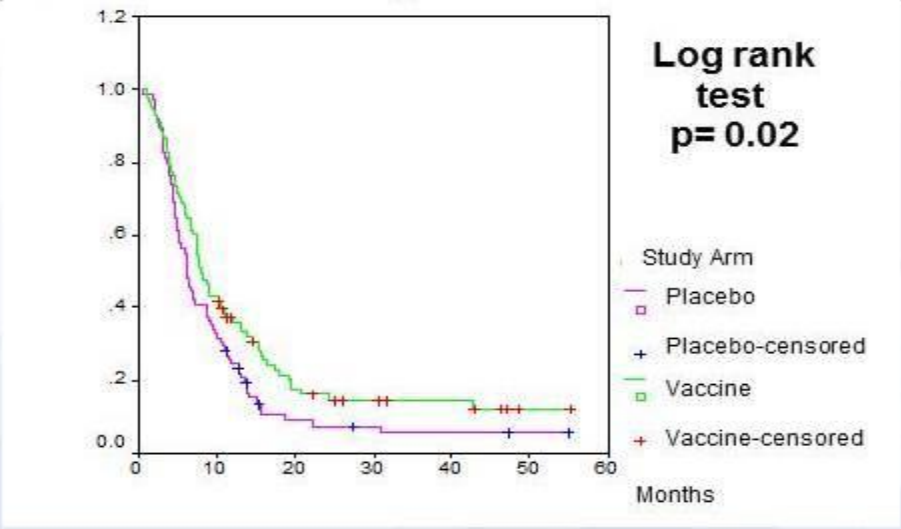
Vaccination Schedule:

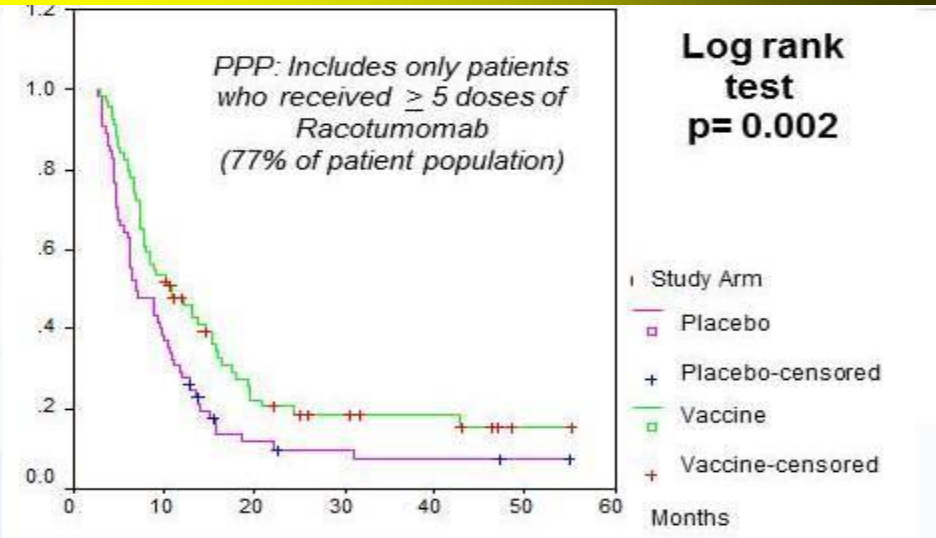


Induction Period
5 doses every 14 days

Maintenance Period
10 doses every 28 days (1 year of treatment)

Lung cancer vaccination
> racotumomab, abstract 1238, Macias et al.





OS (ITT)		
Arm	**Mean**	**Median**
Racotumomab (n= 88) Events: 73	15.7	8.3
Placebo (n= 85) Events: 77	10.6	6.3

OS (PPP)		
Arm	**Mean**	**Median**
Racotumomab (n= 69) Events: 54	18.9	10.9
Placebo (n= 65) Events: 58	11.4	6.9

OS Rate	6 m	12 m	18 m	24 m
Racotumomab	68	38	23	17
Placebo	55	24	11	7

OS Rate	6 m	12 m	18 m	24 m
Racotumomab	83	48	29	22
Placebo	63	28	13	8

Lung cancer vaccination
> anti-ganglioside in SCLC: ph3 (SILVA)

Limited SCLC
- CR/PR after CT-RT
- Karnofsky >60%
- PPD skin test <3

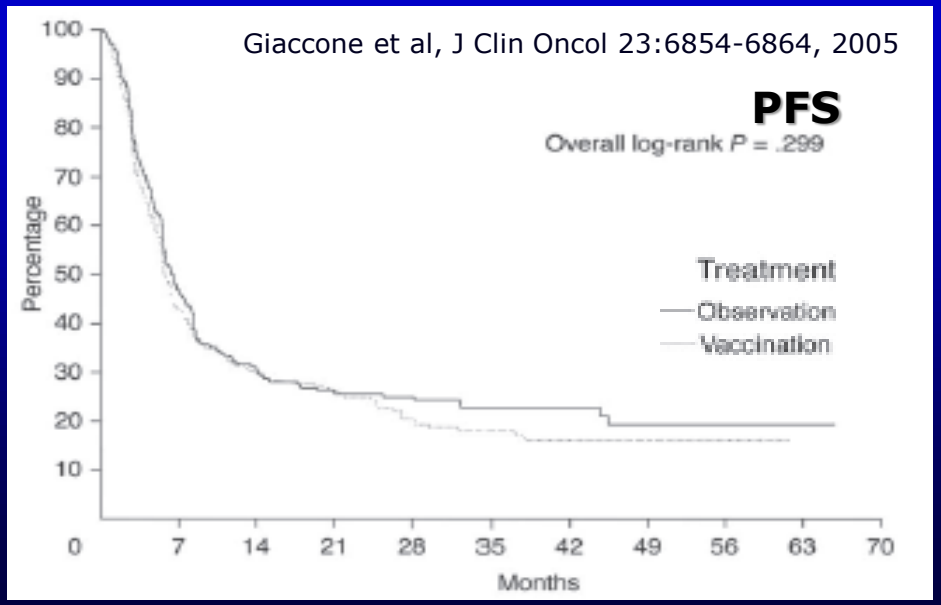
N=258

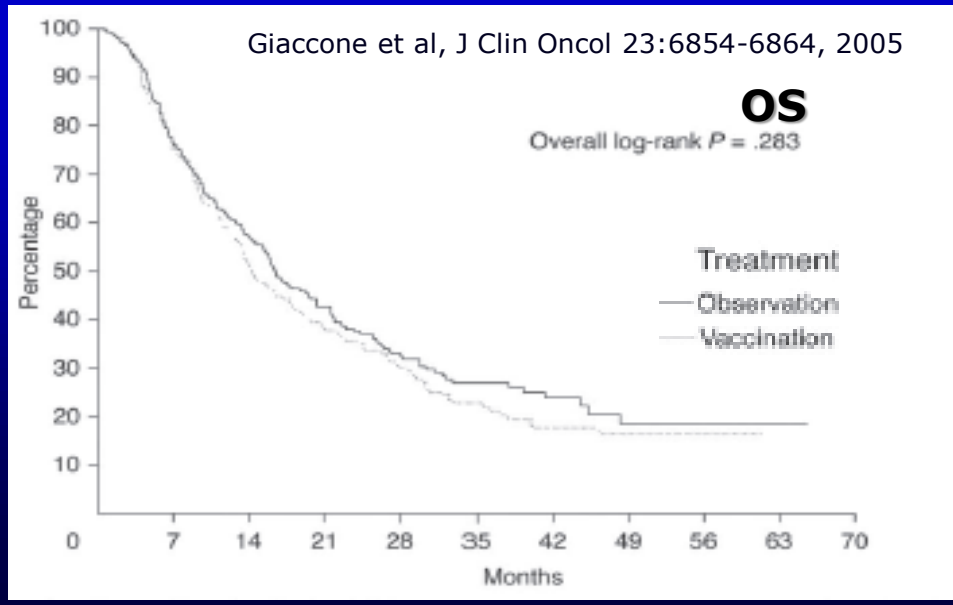
R

N=257

BEC2/BCG 2.5 mg
weeks 0, 2, 4, 6 and 10

Placebo
weeks 0, 2, 4, 6 and 10





Lung cancer vaccination
> 1E10 early clinical trial program

Tumor	Phase	Status	No. of Patients
Breast	I/II	Completed	19
	II	Ongoing	80
Melanoma	I	Completed	22
SCLC	I	Completed	9
	II	Ongoing	80
NSCLC	I	Completed	20
	II	ESMO 2012	176
MCRC	II	Completed	40

BREAST : De Leon et al, Cancer Immunol Immunother 55:443-450, 2006
SCLC: Neninger et al, Cancer Biol Ther 6:145-150, 2007
MELANOMA: Osorio et al, Cancer Biol Ther 7:488-495, 2008
NSCLC: Hernandez et al, J Immunol 15:3735-3744, 2011

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Lung cancer vaccination
> 1E10 [racotumomab]

Phase	Question		
Preclinical	Specificity?	• Gangliosides differently expressed in tumours • GM3 expression largely limited to cancer	√
	Expression?	• Yes	√
MOA	Immunogenic?	• Effective humoral and cellular response?	±
Phase I-II	Clinical effects?	• Cancer sensitive to immune killing?	√
		• Tolerabilty?	√
		• Possible predictive biomarker?	?
Phase III	Patient benefit?	• Outcome (OS preferred)? • Tolerability (~QoL)? • Predictive biomarker confirmed?	?

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Lung cancer immunotherapy > conclusion

- Lung cancer has important immunosuppressive environment
  - historical results with non-specific agents disappointing
- Recent immunomodulation strategies are better targeted, but do have toxicity
- Recent vaccination strategies include well defined antigens with strong adjuvants, have little toxicity
- Nothing proven, but exciting ph3 development

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