Immunotherapie voor longkanker

J. Vansteenkiste

Respiratory Oncology Unit
Dept. Pulmonology
Univ. Hospital Leuven
Leuven Lung Cancer Group

Respiratory Oncology Unit
Univ. Hospital Leuven
Leuven Lung Cancer Group
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Lung cancer immunotherapy

- **Introduction: immunotherapy**
- **Lung cancer vaccination**
- **Lung cancer immunomodulation**
- **Conclusion**

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Cancer immunotherapy > a bit of history…

- Exploit capacity of the immune system to recognize and destroy tumours
- 1890s: Coley's toxins, first cancer treatment vaccine derived from dead bacteria
- Immunotherapies offer the promise of prolonging survival with limited toxicity
  - Limited success of immunotherapies in initial clinical trials in solid tumours
  - Renewed interest with ipilimumab for melanoma and sipuleucel-T for prostate cancer

Dr William Coley: pioneer of cancer immunotherapy

Thomas et al, Lancet Oncol 13:e301–e310, 2012

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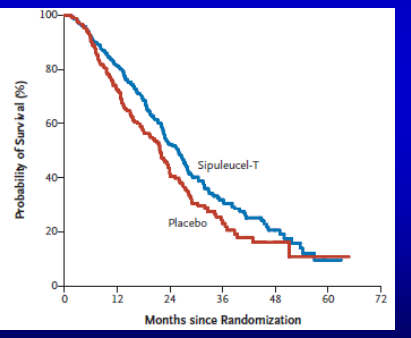
Lung cancer immunotherapy > what?

Cancer immunotherapy: any interaction with the immune system to treat cancer

Active: priming of the immune system		Passive: delivery of compounds that may use immune system	
Antigen-specific	Non-antigen-specific	Monoclonal antibodies	Adoptive cell transfer
-> AG -specific antibodies & cytotixic T cells	-> enhancement of immune system · cytokines · checkpoint inhibitors	· cetuximab · trastuzumab · …	· T cells · CARs · ….
Cancer vaccination therapy	Cancer immunomodulation therapy	Targeted antibodies immunotherapy	Cellular immunotherapy

Lung cancer immunotherapy > for which patients?

- Immunotherapies traditionally considered more appropriate for low burden disease (e.g. early – locally advanced NSCLC)
- Recent positive findings in advanced tumours as well
  - Ipilimumab immunomodulaton for advanced melanoma[1]
  - Sipuleucel-T dendritic cell vaccine for metastatic hormone-refr. prostate cancer[2]



Hodi et al, N Engl J Med 363:711–23, 2010
Kantoff et al, N Engl J Med 363:411–422, 2010

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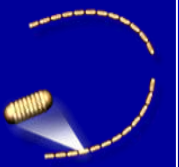
Lung cancer vaccination
> components

Antigen(s) + **Adjuvants**

- tumour cells
  - autologous
  - allogeneic

- peptides
- full proteins
- gangliosides



- DNA

- chemical — Phospholipids, aluminium, ...
- biological — TGF-β blockade, ...
- viral vectors

- dendritic cells

- liposomes

Lung cancer vaccination
> NSCLC ongoing ph3 trials

Setting	Phase 3
Early stage Post surgery	MAGE-A3 ASCI *MAGRIT* target 2270 recruited
Loc. adv. stage Post chemorad	Tecemotide (L-BLP25) *START* target 1300 reported ASCO 13
Advanced	Belagenpumatucel-L *STOP* target 700 reported ESMO 13
	rEGF target 1000 ongoing
In combo with chemo	TG4010 *TIME* target 1000 ongoing
	Racotumomab (1E10) target 1082 ongoing

N ~ 8,000

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- compound
- ph2 data
- ph3 development / data
- predictive biomarker?

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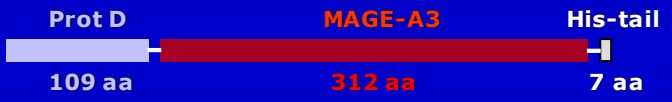
Lung cancer vaccination
> *compound*: MAGE-A3 ASCI

- Antigen
  - MAGE-A3 protein, not expressed in normal cells, expressed in 35% of early stage NSCLC*



- Adjuvant
  - GSK proprietary adjuvant system (AS02B)
  - in oil-in water emulsion
- Administration
  - i.m. / q3w x5 –> q3m x8 (27 months in total)

* Sienel et al, Eur J Cardiothorac Surg 25: 131-134, 2004

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Lung cancer vaccination
> *ph2*: randomised MAGE-A3 trial

Resected NSCLC
- **p-stage IB / II**
- **complete resection**
- **MAGE-A3 rt PCR +**
- **PS 0-1**

R

N=122 → **MAGE-A3 ASCI 300 µg i.m. q3w x5 -> q3m x8 (27 m total)**

N=60 → **Placebo same schedule**

Stratified by:
- stage: IB vs. II
- histology: squamous vs. non-squamous
- LN procedure: limited vs. dissection

Primary endpoint: disease-free interval

Vansteenkiste et al, J Clin Oncol 31: 2396-2403, 2013

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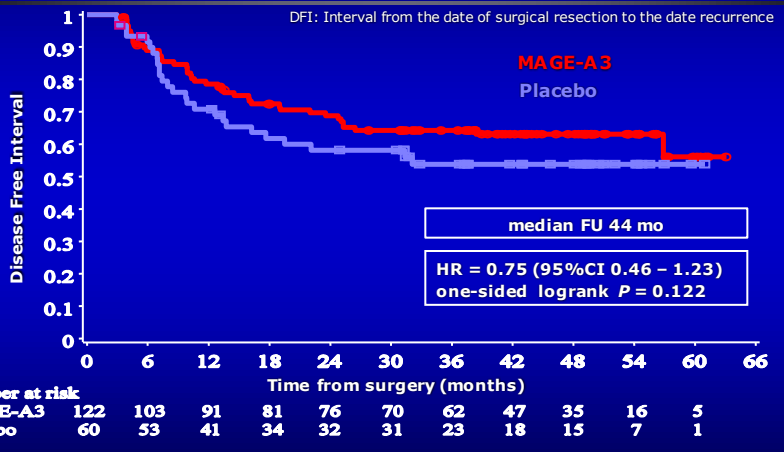
Lung cancer vaccination
> *ph2*: MAGE-A3 disease-free interval



Vansteenkiste et al, ASCO 2007 *and* J Clin Oncol 31:2396-2403, 2013

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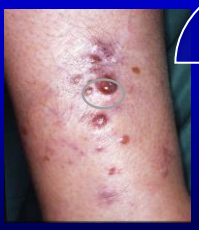
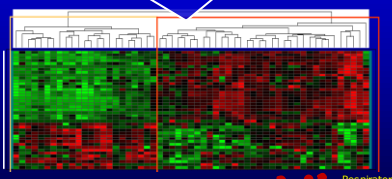
MAGE-A3 vaccination
> *biomarker?* experience in melanoma

- Gene profiling as optional exploratory research
- Tumor biopsies taken prior to MAGE-A3 immunization
- Affymetrix platform : HG-U133. Plus 2.0 gene chips

prediction of clinical benefit?





Louahed et al, EORTC-NCI-AACR 2009 *and*
Ulloa-Montoya et al, J Clin Oncol 31: 2388-2395, 2013

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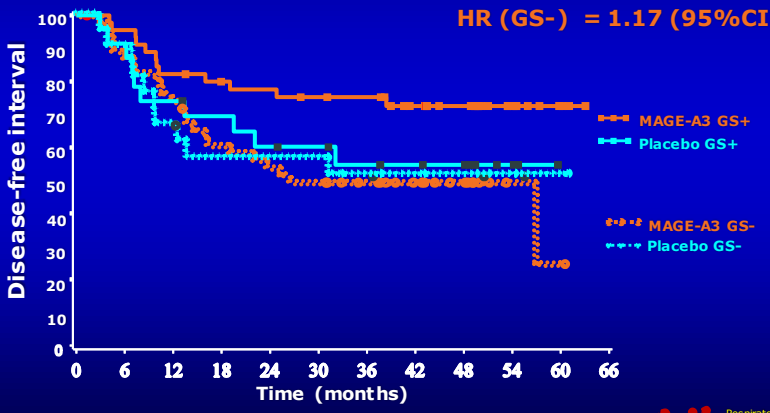
MAGE-A3 vaccination
> *biomarker?* randomised ph2 NSCLC

HR (GS+) = 0.42 (95%CI 0.17-1.03)
HR (GS-) = 1.17 (95%CI 0.59-2.31)



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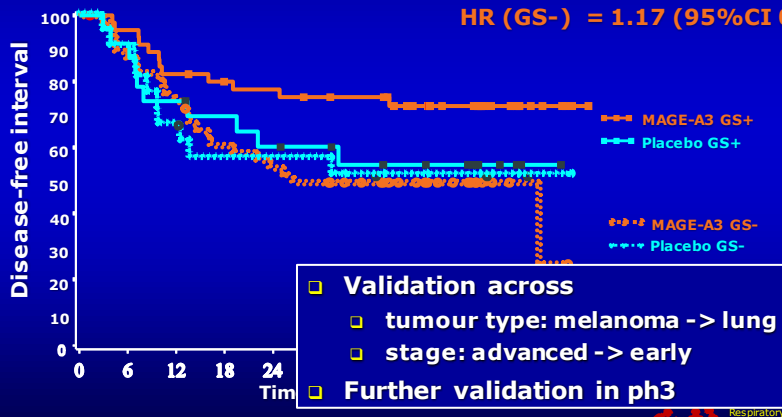

- Validation across
  - tumour type: melanoma -> lung
  - stage: advanced -> early
- Further validation in ph3

Louahed et al, EORTC-NCI-AACR 2009 *and*
Ulloa-Montoya et al, J Clin Oncol 31: 2388-2395, 2013

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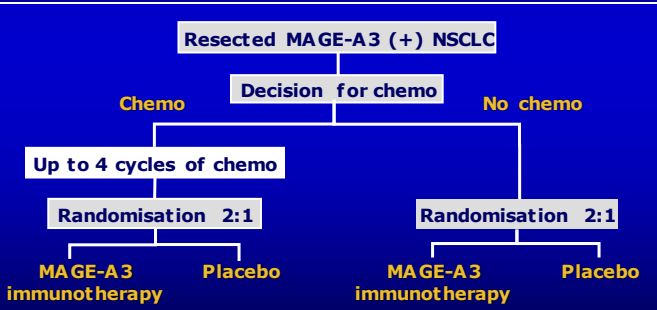
Lung cancer vaccination
> *ph3:* MAGE-A3 MAGRIT trial

MAGE-A3 as Adjuvant Non-Small Cell LunG CanceR ImmunoTherapy

- worldwide multicenter, randomized, double-blind, placebo-controlled ph III trial
- expected N=10,000 screened -> N=2270 patients randomized
- primary endpoint: disease-free survival



Clinicaltrials.gov NCT00480025

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Lung cancer vaccination
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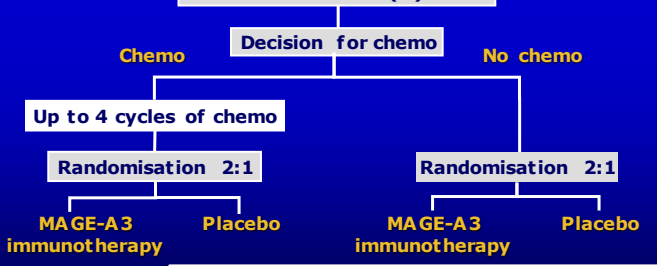
Dec 2011: end of recruitment



©clinicaltrials.gov NCT00480025

Prospective validation of biomarker = co-primary endpoint

Lung cancer vaccination
> NSCLC ongoing ph3 trials

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- compound
- ph2 data
- ph3 development
- predictive biomarker?

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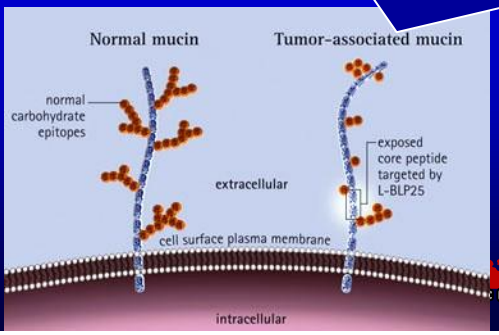
Lung cancer vaccination
> *antigen:* MUC1 protein

- Overexpressed by most cancers including NSCLC
- Loss of polarity of expression: entire cell surface
- N-terminal ectodomain aberrantly glycosylated
- high MUC1 levels associated with poor prognosis *



* Agrawal et al, Mol Med Today 4:397–403, 1998

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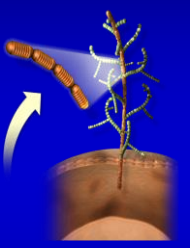
Lung cancer vaccination
> *compound*: tecemotide (L-BLP-25)

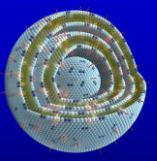
- Antigen: tandem repeat peptide of MUC1



STAPPAHGVTSAPDTRPAPGSTAPP-Lys(PAL)G

25 aa lipopeptide (BLP-25)

- Adjuvant
  - monophosphoryl lipid A
  - in liposomal formulation



- Administration
  - s.c. / qw x8 –> q6w until PD

Lung cancer vaccination
> *ph3*: tecemotide START trial

Stage III
- disease control after chemoradiotherapy (concurr. or sequential)
- no brain mets
- no immune disease

R

N=880 → **Tecemotide 1000 µg s.c. qw (x8) -> q6w + BSC**

N=440 → **Placebo same schedule + BSC**

Stratified stage: IIIA *vs.* IIIB
response: SD *vs.* OR
RT: concurrent *vs.* sequential
region

priming cyclophosphamide 300 mg/m2

Primary endpoint: overall survival
Other endpoints: safety, TTP, symptoms

Butts et al, ASCO 2013

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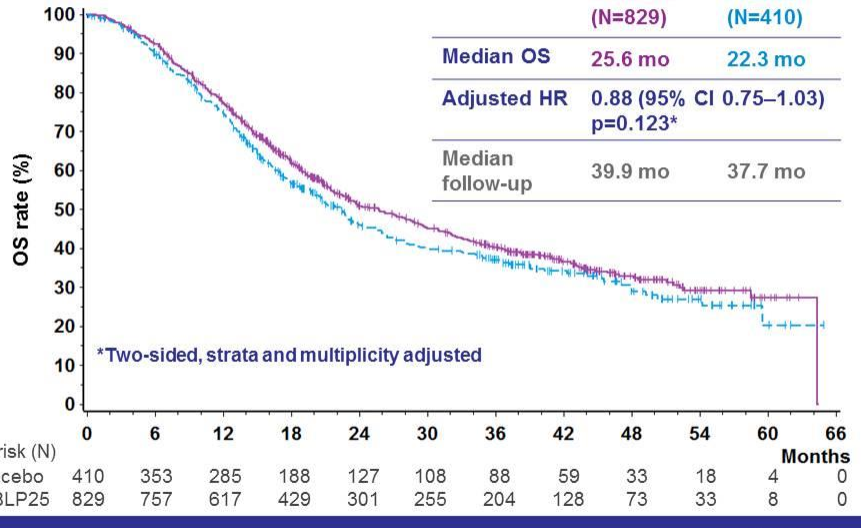
Primary endpoint: Overall survival

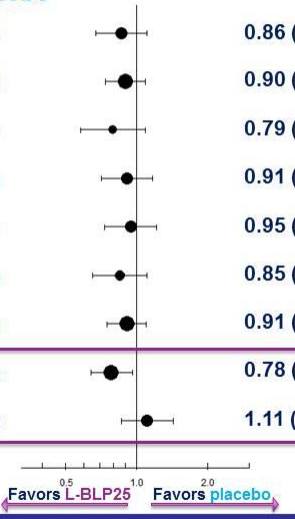


	L-BLP25 (N=829)	Placebo (N=410)
Median OS	25.6 mo	22.3 mo
Adjusted HR	0.88 (95% CI 0.75–1.03) p=0.123*	
Median follow-up	39.9 mo	37.7 mo

At risk (N)												
Placebo	410	353	285	188	127	108	88	59	33	18	4	0
L-BLP25	829	757	617	429	301	255	204	128	73	33	8	0

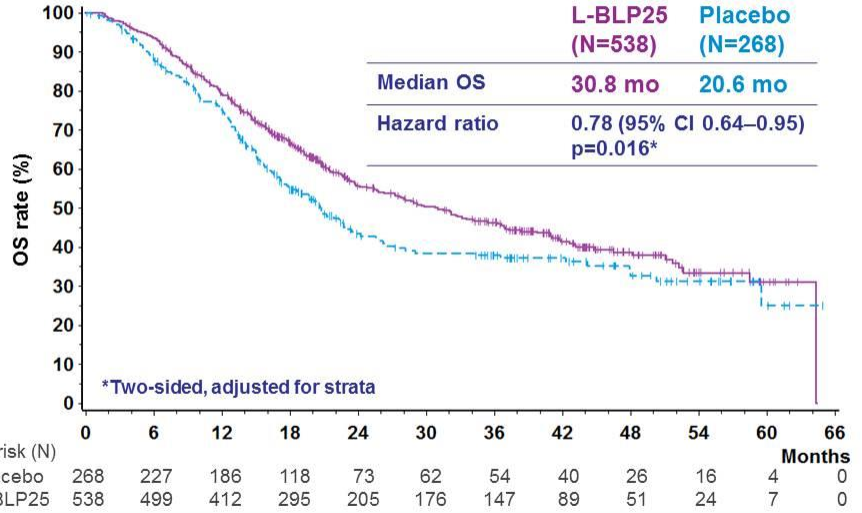
OS: Subgroup analyses by randomization strata

		Median OS (months) L-BLP25 vs. Placebo	HR* (95% CI)
Stage	Stage IIIA (N=487)	27.6 vs. 23.1	0.86 (0.67, 1.11)
	Stage IIIB (N=752)	23.7 vs. 20.9	0.90 (0.74, 1.09)
Region	NA and Aus. (N=321)	34.1 vs. 21.7	0.79 (0.58, 1.09)
	W. Europe (N=475)	24.2 vs. 22.3	0.91 (0.71, 1.17)
	Rest of world (N=443)	21.8 vs. 22.7	0.95 (0.73, 1.22)
Response to chemo/ RT	Stable disease (N=396)	20.4 vs. 17.8	0.85 (0.65, 1.11)
	Obj. response (N=843)	27.8 vs. 23.9	0.91 (0.75, 1.10)
Chemo/ RT type	Concurrent (N=806)	30.8 vs. 20.6	0.78 (0.64, 0.96)
	Sequential (N=433)	19.4 vs. 24.6	1.11 (0.86, 1.43)



*Not adjusted for strata

Overall survival: Concurrent chemo/RT



	L-BLP25 (N=538)	Placebo (N=268)
Median OS	30.8 mo	20.6 mo
Hazard ratio	0.78 (95% CI 0.64–0.95) p=0.016*	

At risk (N)												
Placebo	268	227	186	118	73	62	54	40	26	16	4	0
L-BLP25	538	499	412	295	205	176	147	89	51	24	7	0

Lung cancer vaccination
> *ph3*: tecemotide safety

Injection site reactions	L-BLP25 (N=1,024)	Placebo (N=477)
Any	176 (17.3)	56 (11.9)
Any Grade 3/4	0 (0)	0 (0)
Flu-like symptoms	**L-BLP25 (N=1,024)**	**Placebo (N=477)**
Any	391 (38.2)	158 (33.1)
Any Grade 3/4	15 (1.5)	8 (1.7)
Cough	338 (33.0)	133 (27.9)
Dyspnea	238 (23.2)	112 (23.5)

Grade 3/4 AE preferred term	L-BLP25 N=1,024 n (%)	Placebo N=477 n (%)
Adrenal insufficiency	1 (0.1)	0
Guillain-Barre syndrome	1 (0.1)	0
Hemolytic anemia	0	1 (0.2)
Temporal arteritis	0	1 (0.2)
Any Grade 3/4	2 (0.2)	2 (0.4)

- **Excellent safety: mostly grade 1-2 local or flu-like reactions**
- **No increase in severe immune-related AEs**
- **No increase in (symptoms of) RT pneumonitis**

Butts et al, ASCO 2013

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Lung cancer vaccination
> *biomarker?* START exploratory analysis

- **Analysis of plasma samples**
- **HLA type**

HLA subgroup	N	Overall survival, months (Tecemotide vs Placebo)		Hazard ratio (95% CI)	P-value
Primary analysis population (mITT)	1239	25.6	22.3	0.88 (0.75–1.03)	0.123
HLA-A02 positive	586	25.8	22.7	0.89 (0.71–1.11)	0.301
HLA-DRB4 positive	557	28.0	22.3	0.85 (0.67–1.08)	0.179
HLA-B08 negative	976	26.3	22.8	0.91 (0.76–1.08)	0.276

Mitchell et al, WCLC 2013

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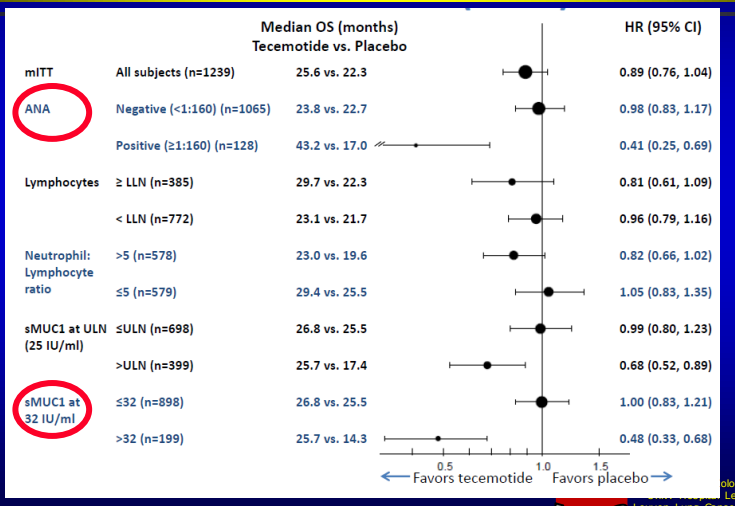

Mitchell et al, WCLC 2013

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Lung cancer immunomodulation

- "Disappointing historical experience": levamisole, BCG, IL, IFN, C. parvum, thymosin,...
- PF-3512676 (Promune): TLR stimulation – NEGATIVE
- Talactoferrin alpha: gut-associated lymphoid tissue - NEGATIVE
- Ipilimumab (anti-CTLA4 MAb)
- Anti-PD1 and anti-PD-L1 MAb

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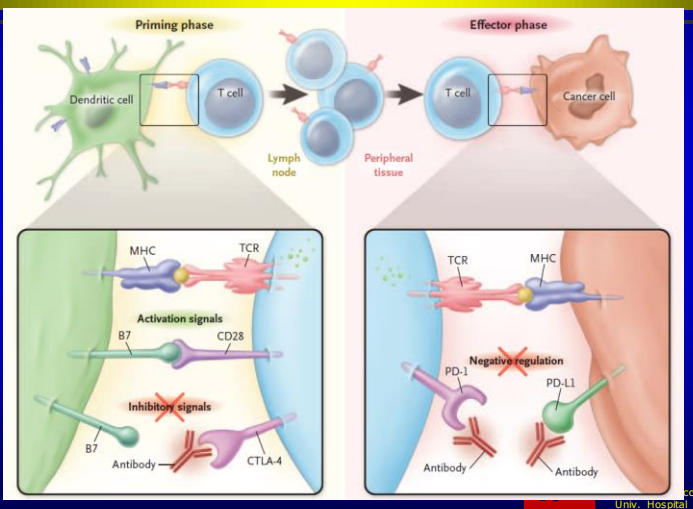
Lung cancer immunomodulation > priming and effector phase



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

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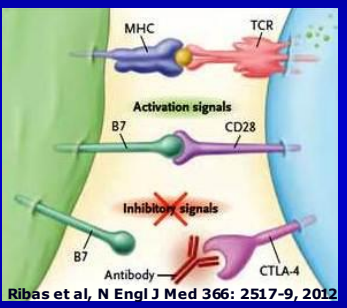
Lung cancer immunomodulation > *compound*: ipilimumab

- Human MAb inhibiting cytotoxic T lymphocyte antigen 4 (CTLA-4)
  - promotes signaling to CD28 and stimulation of T cell response *(priming phase)*
  - may block suppressive signal from regulatory T cells, and promote autoimmunity



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

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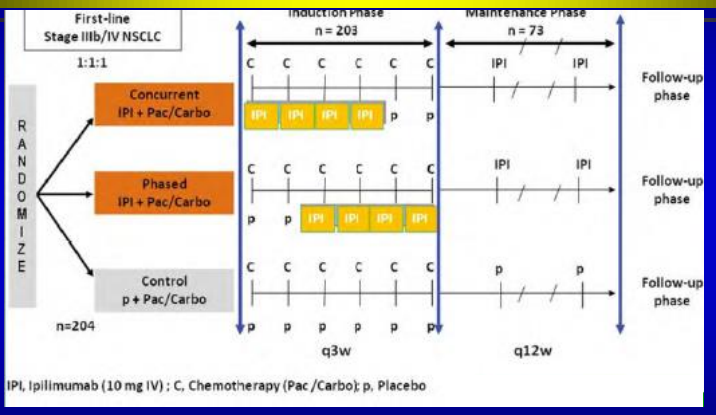
Lung cancer immunomodulation > *ph2*: ipilimumab



- Primary endpoint: immune-related PFS

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

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Lung cancer immunomodulation > *ph2*: ipilimumab safety

- **Safety**
  - "generally well tolerated"
  - grade 3-4 immune-related AEs
    - 15% phased ipilimumab / 20% concurrent ipilimumab / 6% control
- **Similar to major toxicity in melanoma study ***
  - colitis: besides corticosteroids, 4 pts received infliximab (anti–TNF) for diarrhea / colitis grade 3+; residual colitis in 4 pts
  - residual endocrine AEs requiring hormone-replacement in 8 pts
  - 14 deaths related to the study drugs, 7 to immune-related AEs

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

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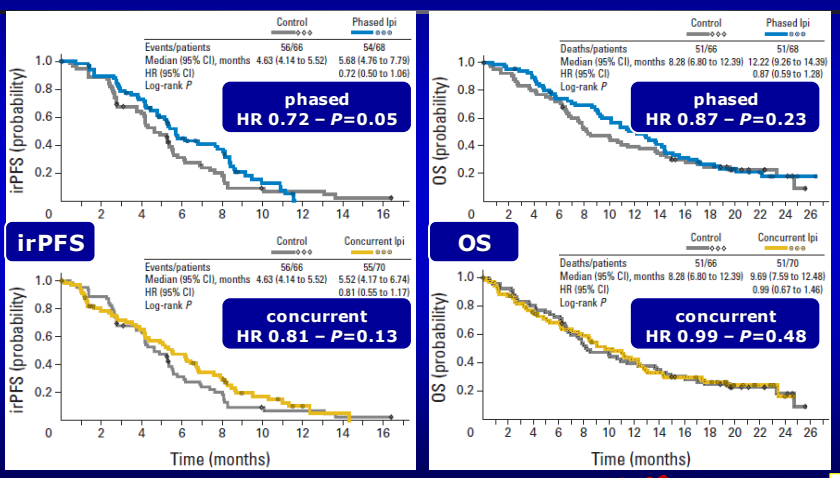
Lung cancer immunomodulation > *ph2*: ipilimumab efficicay



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

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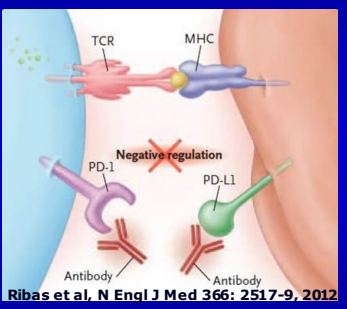
Lung cancer immunomodulation > ipilimumab development

Trial	Treatment arms	N_{rand}	Study population	Primary endpoint	Other endpoints
Phase III randomised placebo-controlled NCT01285609	Carbo-paclitaxel + phased ipilimumab or placebo -> maintenance ipilimumab or placebo	920	Stage IV or recurrent squamous NSCLC	OS	WHO-modified PFS, ORR
Phase III randomised placebo-controlled NCT01450761	Platinum-etoposide + phased ipilimumab or placebo -> maintenance ipilimumab or placebo	1100	Advanced SCLC	OS	Immune-related PFS, WHO-modified PFS, ORR, duration of response
Planned ETOP phase II randomised placebo-controlled	Concurrent chemotherapy -> maintencance ipilimumab or placebo	260	Stage I-III SCLC	OS	PFS, RECIST response, time-to-relapse, toxicity, translational research

Lung cancer immunomodulation > *compounds*: anti-PD-1 / anti-PD-L1

- Human MAb blocking programmed death 1 (PD-1) inhibitory receptor on activated T-cells or its ligand
  - promotes attack of tumour cells by activated T cells *(effector phase)*
  - may block function of regulatory T cells, and promote autoimmunity



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

"The race for the antibody"

- anti-PD-1: BMS-936558/Nivolumab, CT-011, MK-3475
- anti-PD-L1: BMS-936559, MedI-4736, MDPL-3280A

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Lung cancer immunomodulation
> *compounds*: anti-PD-1 / anti-PD-L1

- BMS-936558 (Nivolumab): human IgG4 anti-PD-1 (BMS)
  - at least 1 prior treatment (54% ≥3 prior treatments)
  - response rate (all pts): 17%
  - median duration of response: 74 wks
- MPDL3280A: human IgG1 anti-PD-L1 (Genentech)
  - at least 1 prior treatment (55% ≥3 prior treatments)
  - response rate (all pts): 23%
  - median duration of response: >45 wks (ongoing, median NR)
- MK-3475: humanized IgG4 anti-PD-1 (Merck MSD)
  - 2 prior treatments
  - response rate (all pts): 24%
  - median duration of response: >60 wks (ongoing, median NR)

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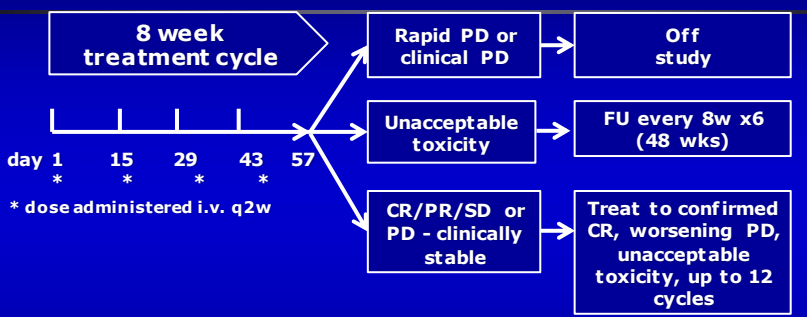
Cancer immunomodulation
> *large ph1*: anti-PD-1



Patients

- Heavily pretreated advanced melanoma, RCC, NSCLC, CRPC, CRC (PD after 1–5 systemic therapies)
- Some melanoma/RCC patients had prior immunotherapy (64% - 59%)

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

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

	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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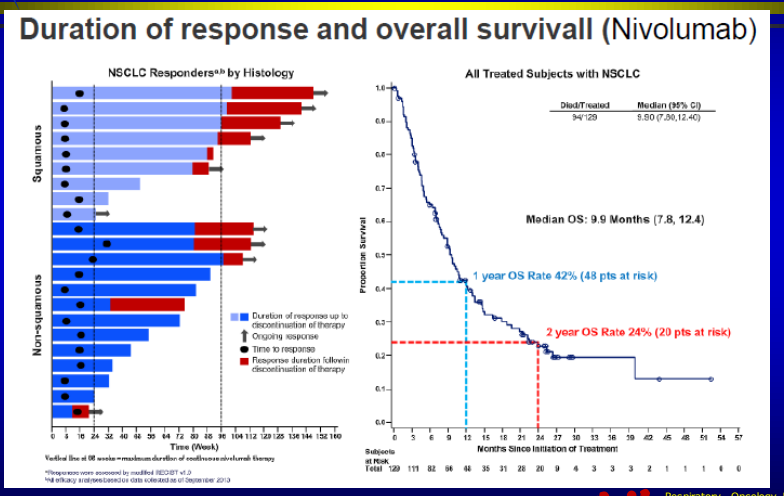
Lung cancer immunomodulation
> *large ph1*: anti-PD-1 in NSCLC



Brahmer et al, ASCO 2013 and WCLC 2013 update

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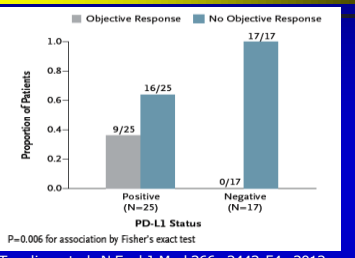
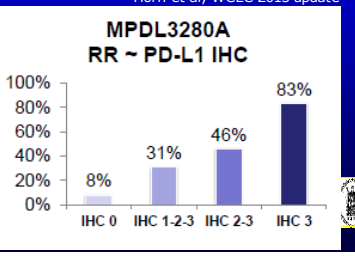
Lung cancer immunomodulation > *biomarker?* PD-L1 IHC

- For all
  - PD-L1 expression appears to be strongly correlated with response rate
  - but long-lasting responses also seen PD-L1 negative tumours
  - responses regardless of histology, smoking, *EGFR/KRAS* mutation status



Topalian et al, N Engl J Med 366: 2443-54, 2012

Horn et al, WCLC 2013 update



Lung cancer immunomodulation > PD-1 PD-L1 development

Trial	Treatment arms	N	Study population	Primary endpoint	Other endpoints
Phase III randomised open label *CheckMate017* NCT01642004	Nivolumab vs. docetaxel	264	Squamous cell NSCLC recurrent or progressing during/after platinum-based chemotherapy for stage IIIB/IV	ORR, OS	PFS, clinical benefit, duration of OR, time to OR
Phase III randomised open label *CheckMate057* NCT01673867	Nivolumab vs. docetaxel	574	Non-squamous cell NSCLC recurrent or progressing during/after platinum-based chemotherapy for stage IIIB/IV	OS	ORR, PFS, clinical benefit
Phase II/III randomised open label *POPLAR* NCT01903993	MPDL3280A vs. docetaxel	180	Advanced recurrent NSCLC with FFPE specimen for PD-L1 staining	OS	ORR, PFS, safety, patient reported outcomes
Phase II/III randomised open label NCT01905657	MK-3475 low vs. MK-3475 high vs. docetaxel	920	Squamous cell NSCLC progressing after platinum-containing chemotherapy	OS	PFS, safety, ORR, response duration

Lung cancer immunotherapy

- Introduction: immunotherapy
- Lung cancer vaccination
- Lung cancer immunomodulation
- Conclusion

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Lung cancer immunotherapy > conclusion

- Lung cancer
  - Strong immunosuppressive environment
  - Historical results (non-specific agents) disappointing
- Recent cancer vaccination studies
  - Better defined antigens and adjuvants
  - Low toxicity defines a unique treatment opportunity
  - Strong ph3 data from recent study with BLP-25
- Recent cancer immunomodulation studies
  - Better understanding of dendritic cell biology
  - Important toxicity may occur in some patients
  - Strong ph1 data with anti-PD-1/PD-L1

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Thank you for your kind attention

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