elcc

Geneva, Switzerland
26-29 MARCH 2014

EUROPEAN LUNG CANCER CONFERENCE

New targets and vaccines

J. Vansteenkiste

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Leuven Lung Cancer Group

Disclosure

- Consultant: GSK-BIO, Merck-Serono
- Speaker: Eli-Lilly
- Research funding: Astra Zeneca

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Lung cancer immunotherapy

- **Introduction: immunotherapy**
- **Lung cancer vaccination for locoregional NSCLC**
- **Lung cancer vaccination for advanced NSCLC**
- **Conclusion**

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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

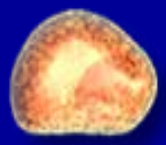
Passive: delivery of compounds that may use immune system

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**

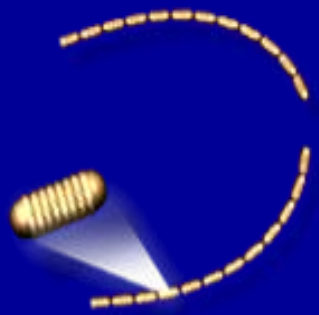
Lung cancer vaccination
> components

Antigen(s) + **Adjuvants**

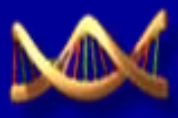
- tumour cells
  - autologous
  - allogeneic



- peptides
- full proteins
- gangliosides



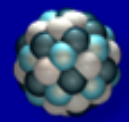
- DNA



- 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 *MAGRIT* target 2270 recruited
Loc. adv. stage Post chemorad	L-BLP25 *START* target 1300 reported ASCO 13
Advanced In combo with chemo	Belagenpumatucel-L *STOP* target 700 reported ESMO 13
	rEGF target 1000 ongoing
	TG4010 *TIME* target 1000 ongoing
	1E10 target 1082 ongoing

N ~ 8,000

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Lung cancer immunotherapy

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

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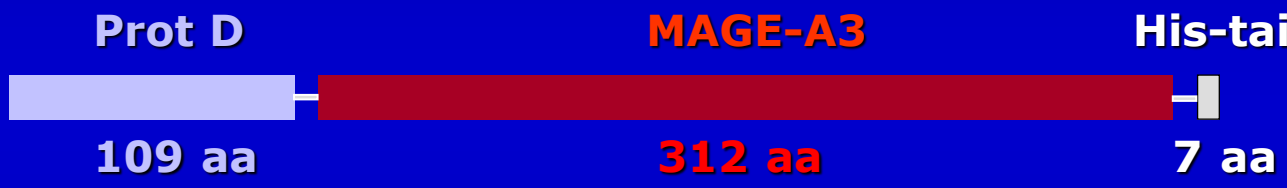
Lung cancer vaccination
> *compound*: MAGE-A3 ASCI

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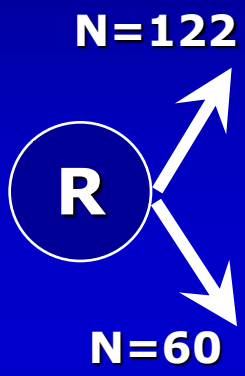
Lung cancer vaccination
> *ph2*: randomised MAGE-A3 trial

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



MAGE-A3 ASCI 300 µg i.m.
q3w x5 -> q3m x8 (27 m total)

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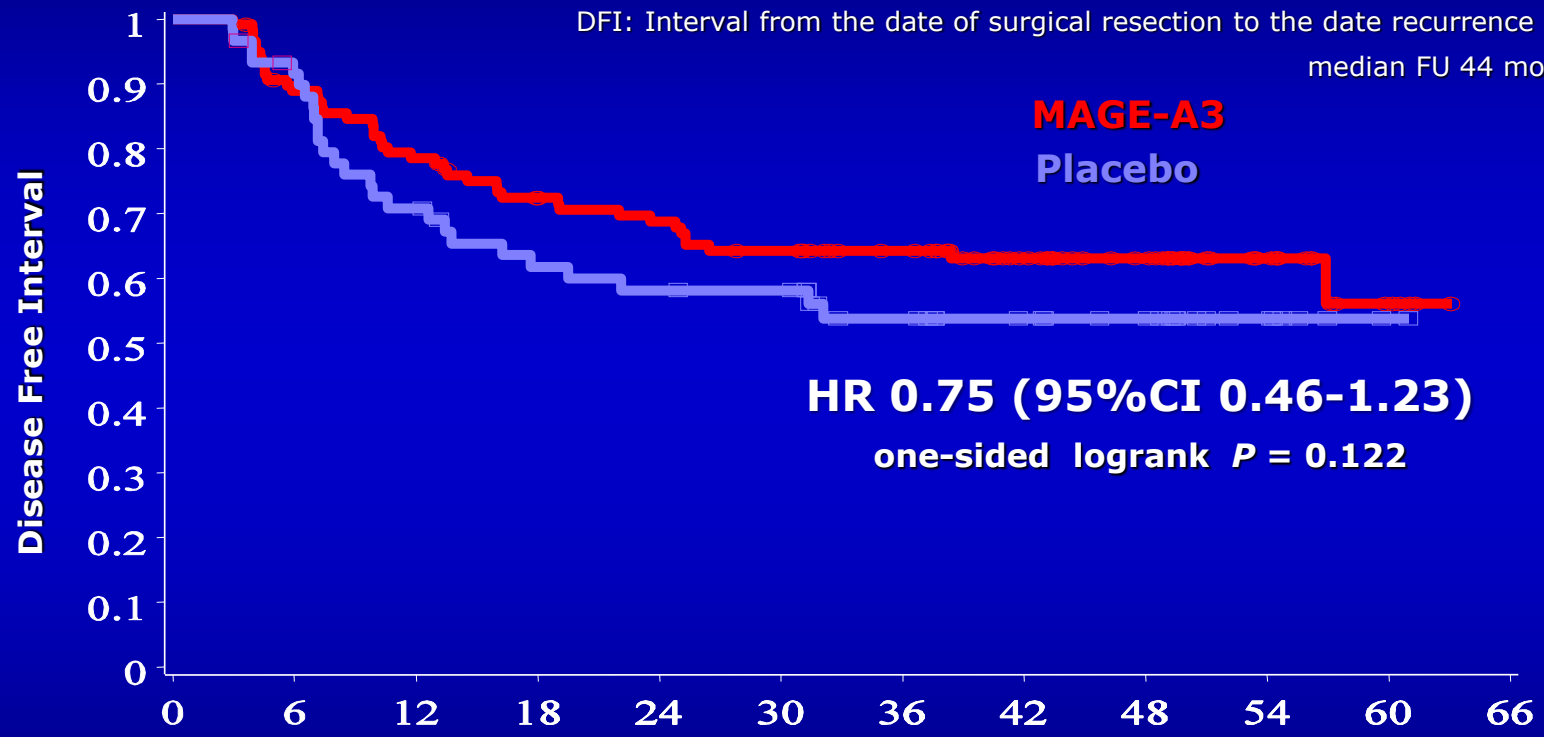
Lung cancer vaccination
> *ph2*: MAGE-A3 disease-free interval



Number at risk

MAGE-A3	122	103	91	81	76	70	62	47	35	16	5
Placebo	60	53	41	34	32	31	23	18	15	7	1

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

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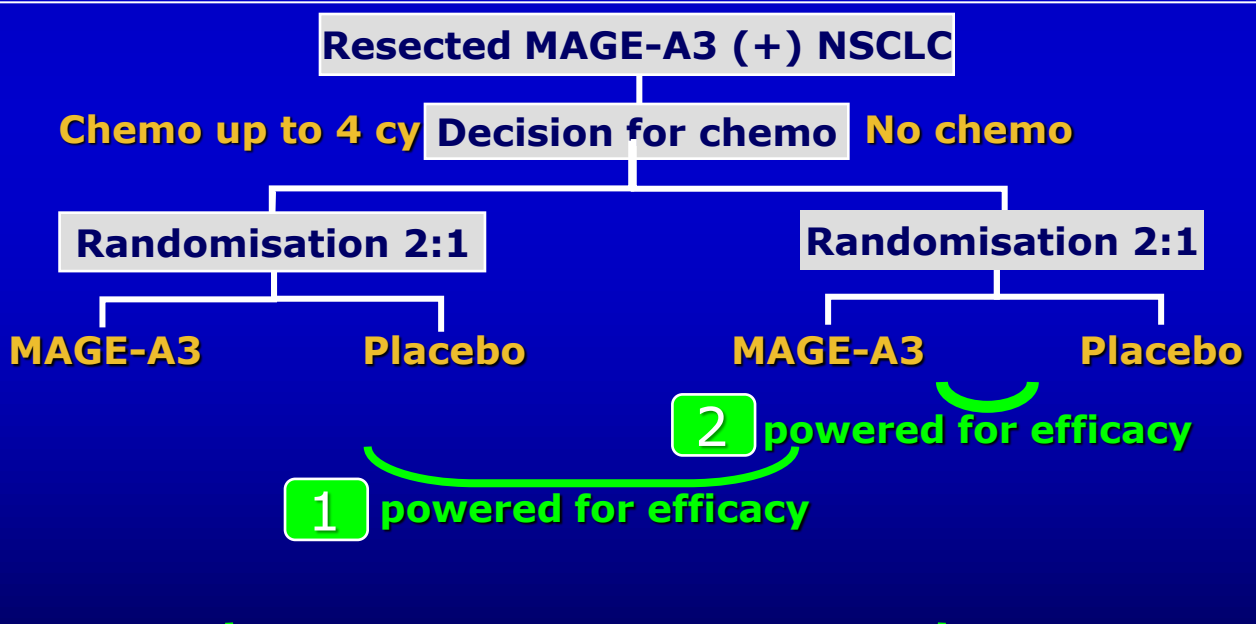
Lung cancer vaccination
> *ph3:* MAGE-A3 MAGRIT trial

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



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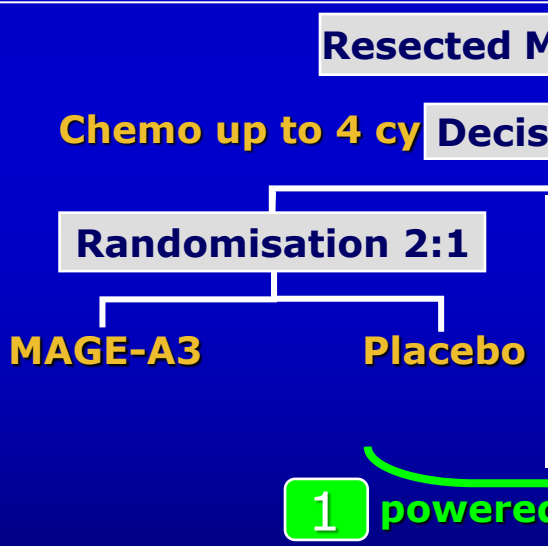

Issued: Thursday 20 March 2014, London UK

Investigational MAGE-A3 antigen-specific cancer immunotherapeutic does not meet first co-primary endpoints in MAGRIT, a phase III non-small cell lung cancer clinical trial

1 powered for efficacy

3 powered for prospective evaluation of gene signature analysis

Clinicaltrials.gov NCT00480025

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MAGE-A3 vaccination
> *biomarker*

#7501

Gene expression signature is strongly associated with clinical efficacy of MAGE-A3 Antigen-Specific Cancer Immunotherapeutic (ASCI) as adjuvant therapy in resected stage IB/II non-small cell lung cancer (NSCLC)

J. Vansteenkiste[1], M. Zielinski[2], J. Dahabreh[3], A. Linder[4], F. Lehmann[5], O. Gruselle[5], P. Therasse[5], J. Louahed[5] and V.G. Brichard[5]

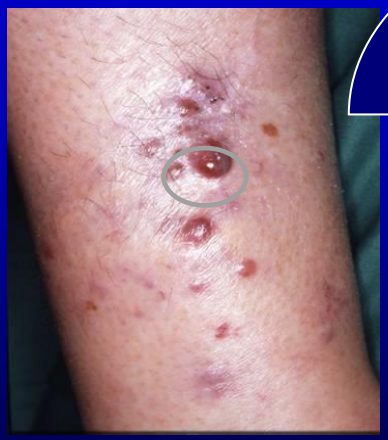
[1]Respiratory Oncology Unit/Pneumology, Leuven, Belgium, [2]Szpital Chorob Pluc, Zakopane, Poland, [3]Medical Centre, Athens, Greece, [4]LungenKlinik, Hemer, Germany, [5]GlaxoSmithKline Biologicals, Rixensart, Belgium.

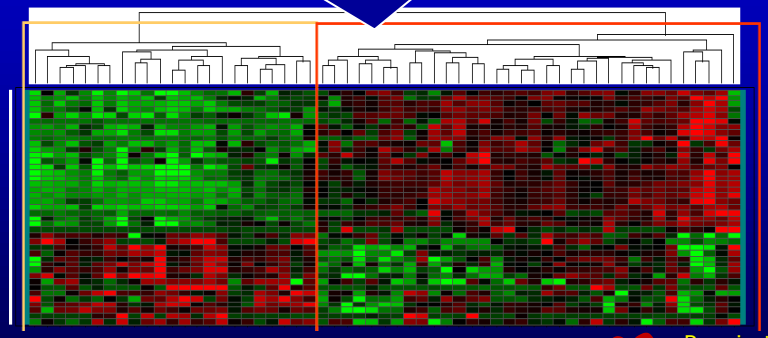
ASCO | Annual '08 Meeting

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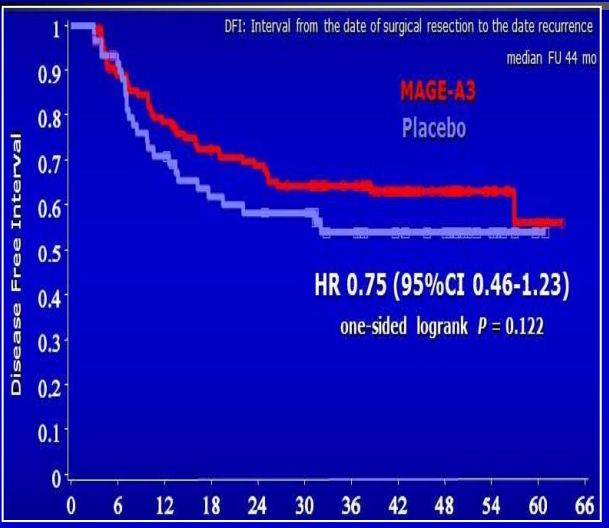
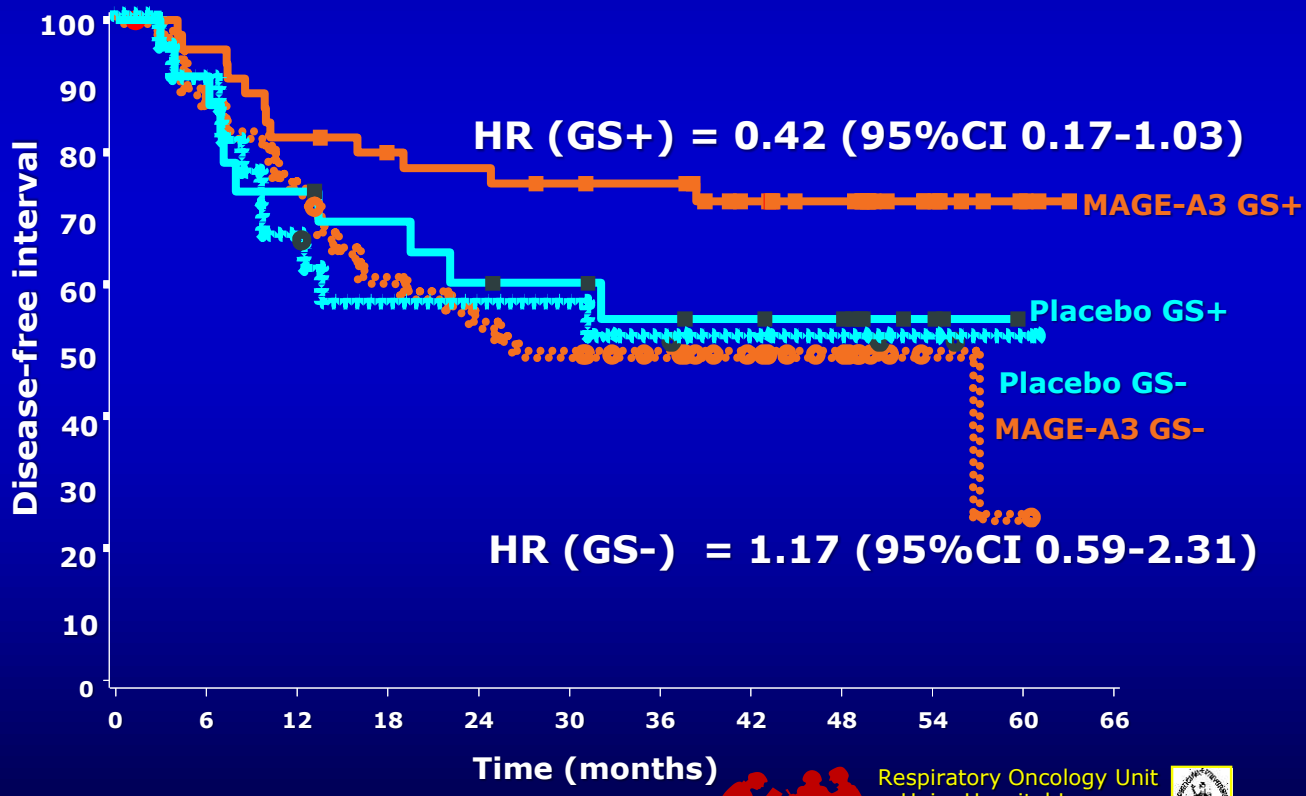
MAGE-A3 vaccination
> *biomarker?* randomised ph2 NSCLC





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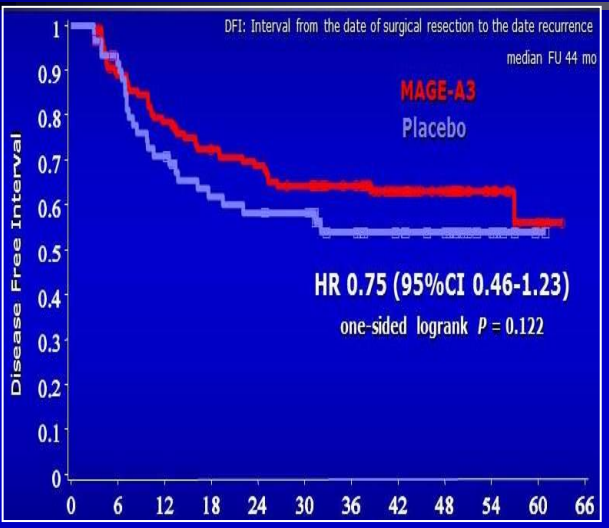

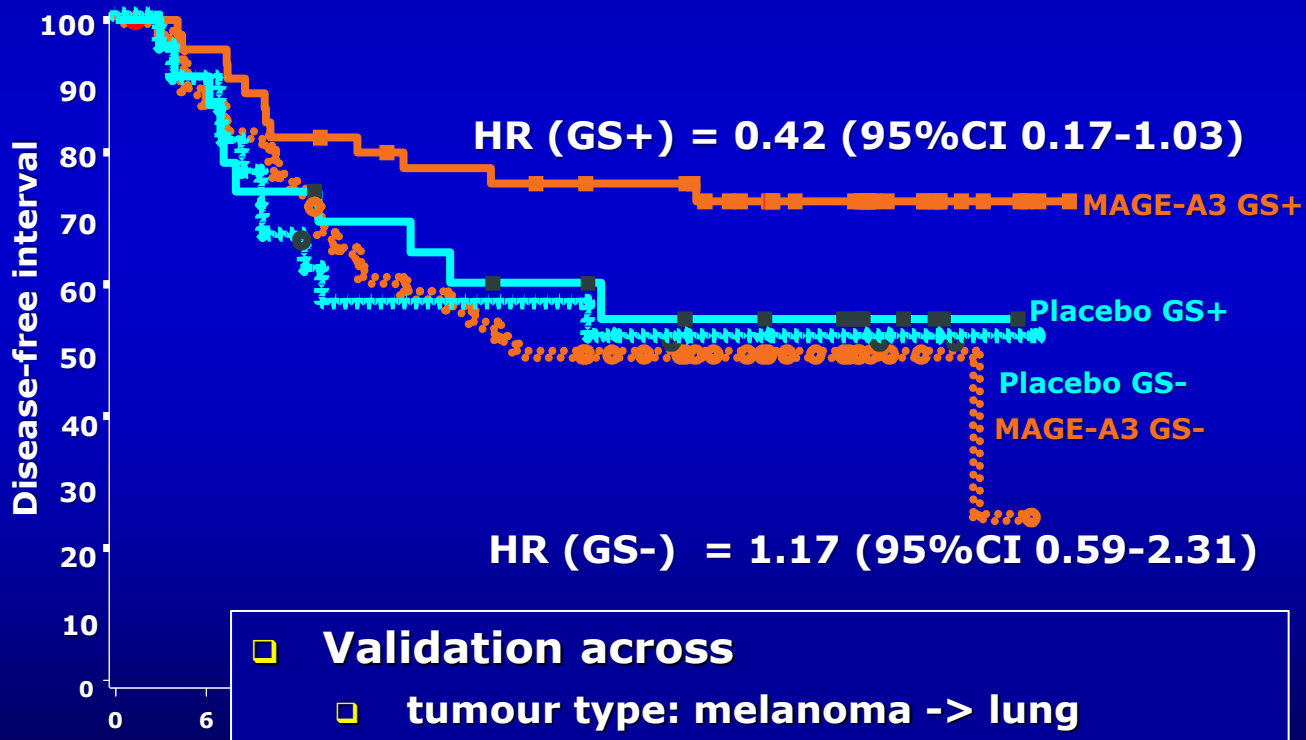

- **Validation across**
  - **tumour type: melanoma -> lung**
  - **stage: advanced -> early**
- **Further validation in ph3**

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

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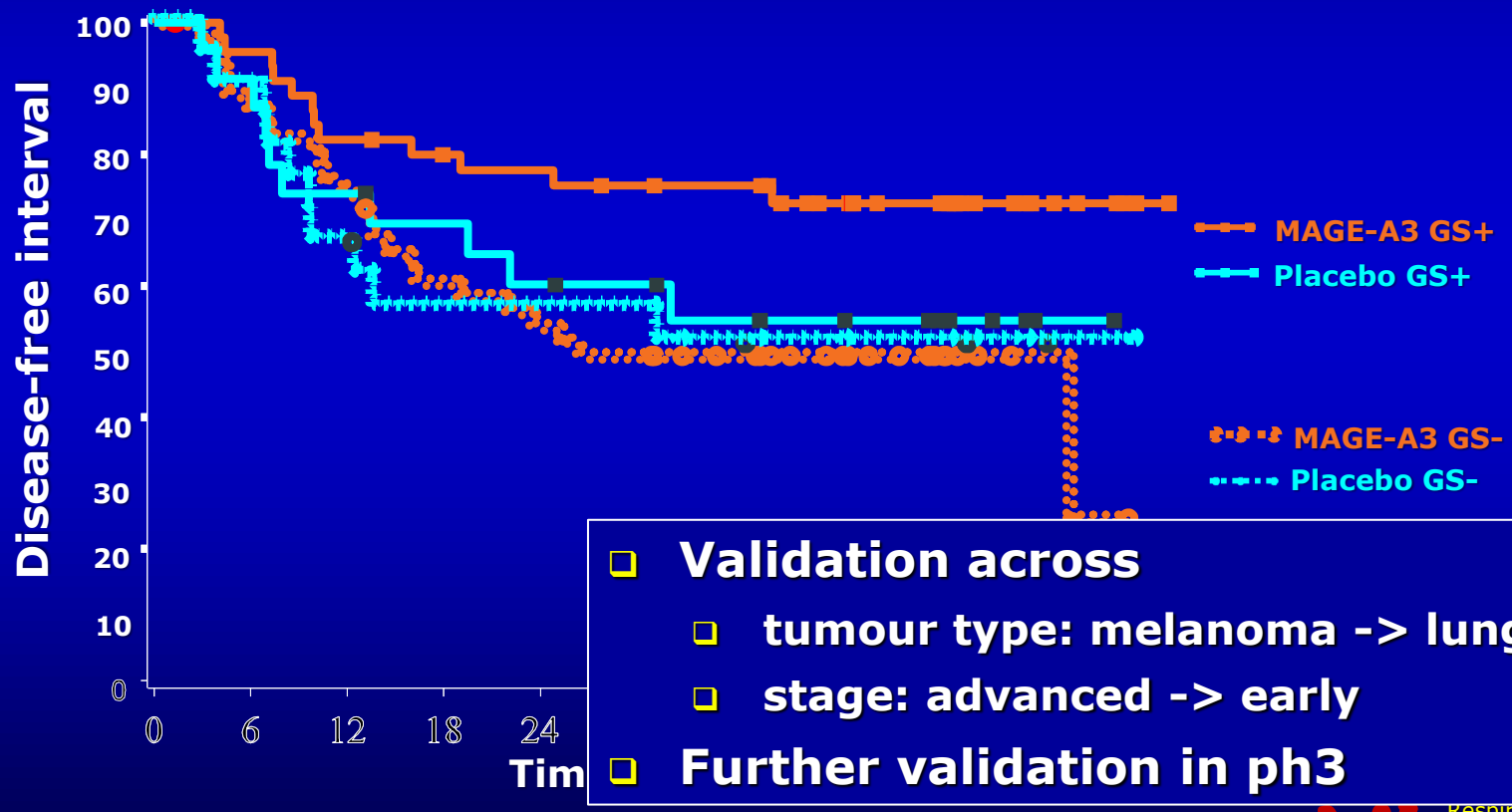

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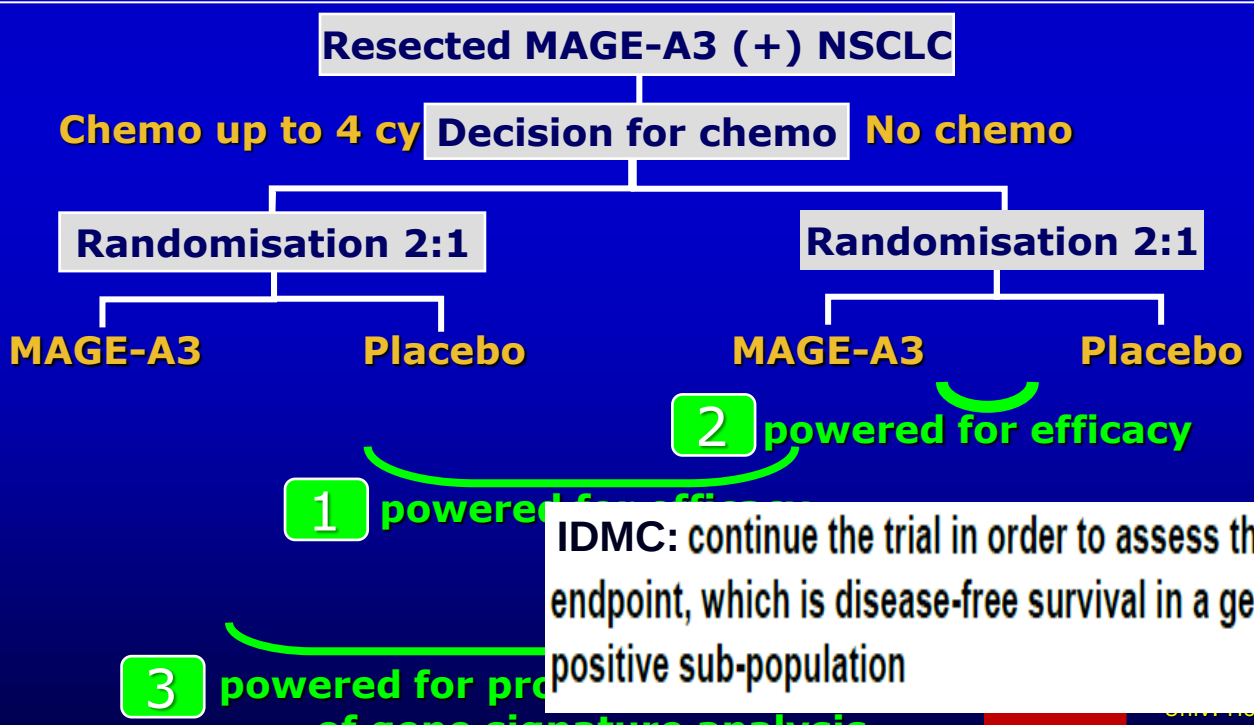

IDMC: continue the trial in order to assess the third co-primary endpoint, which is disease-free survival in a gene signature positive sub-population

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

- trial continues
- investigators and study team remain totally blinded to the data
- independent (academic) team: gene signature training set and validation set analysis

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Lung cancer vaccination
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- compound
- ph2 data
- ph3 development
- predictive biomarker?

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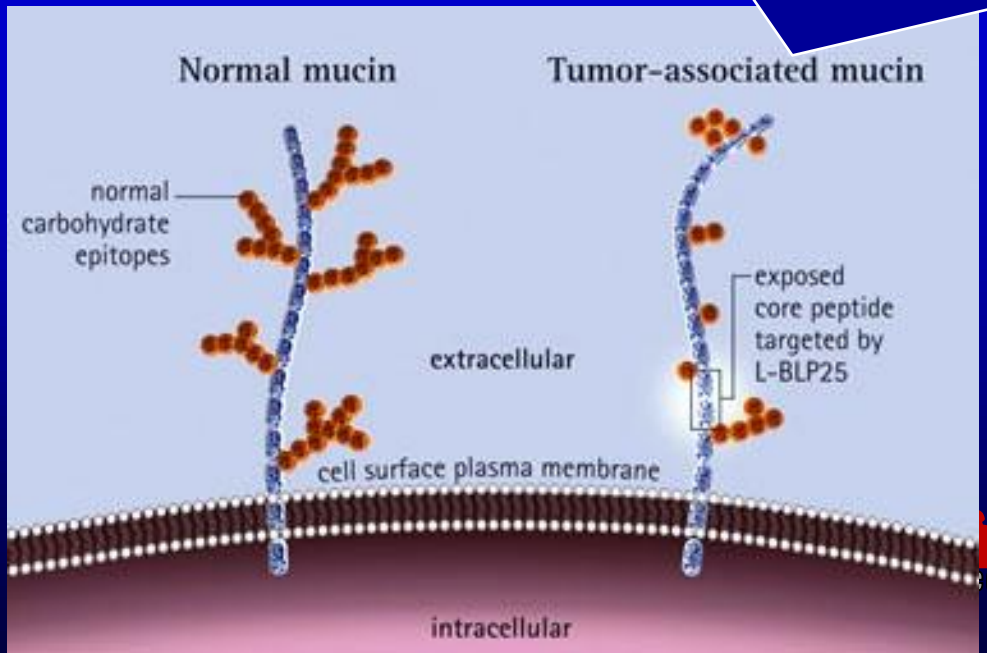
Lung cancer vaccination
> *antigen:* MUC1 protein

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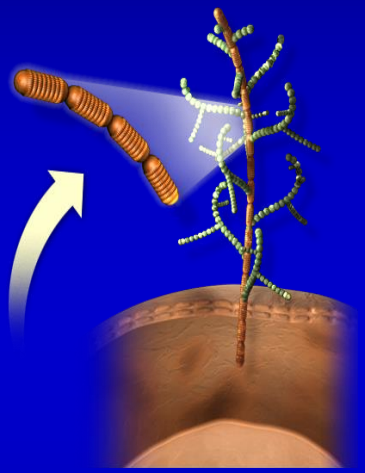
Lung cancer vaccination
> *compound*: tecemotide (L-BLP-25)

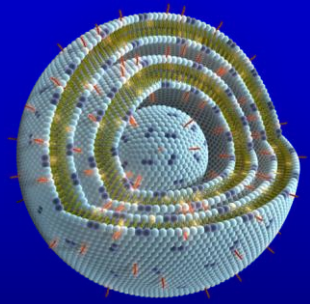
- **Antigen: tandem repeat peptide of MUC1**



S T A P P A H G V T S A P D T R P A P G S T A P P - 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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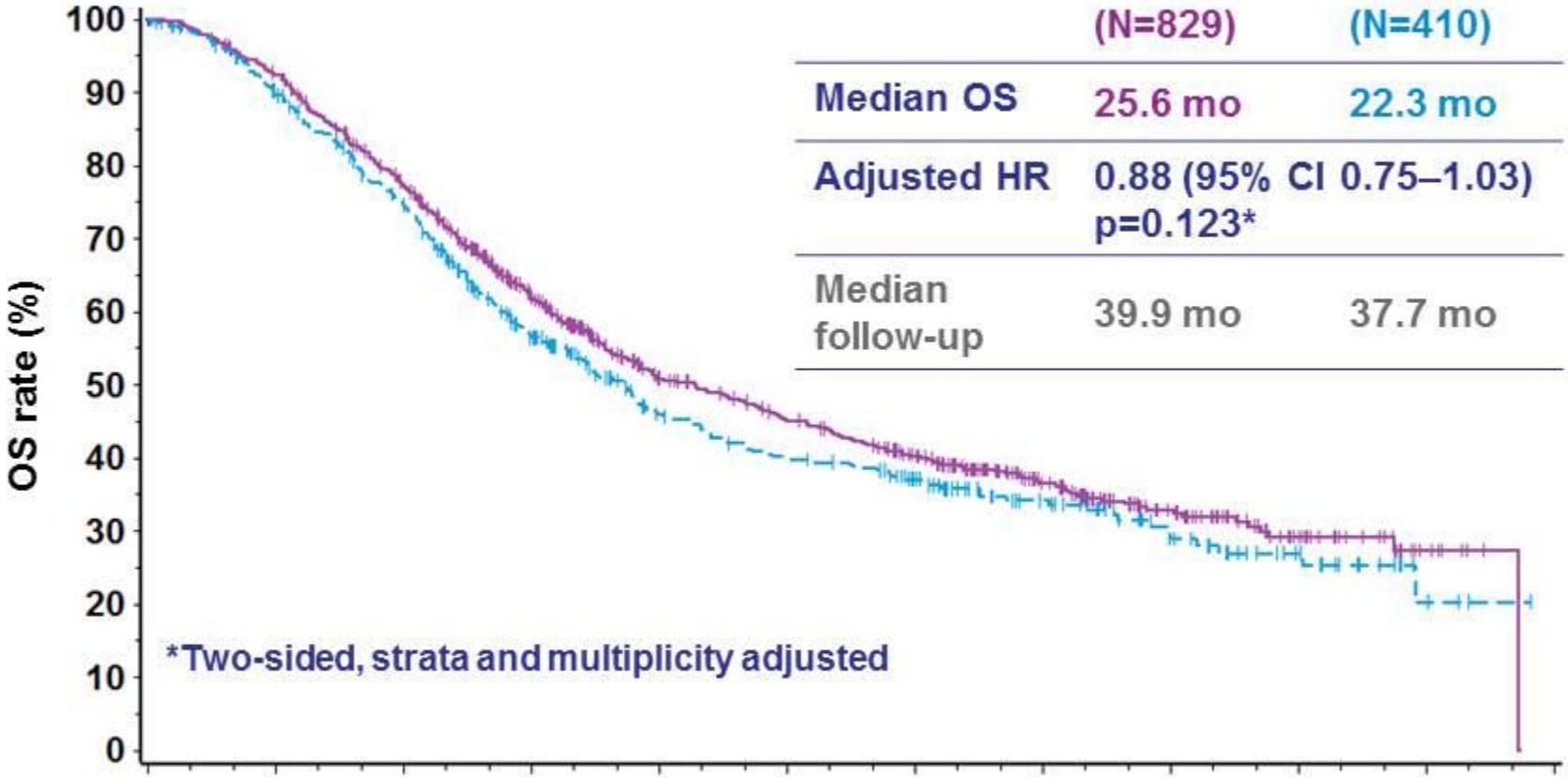
Primary endpoint: Overall survival

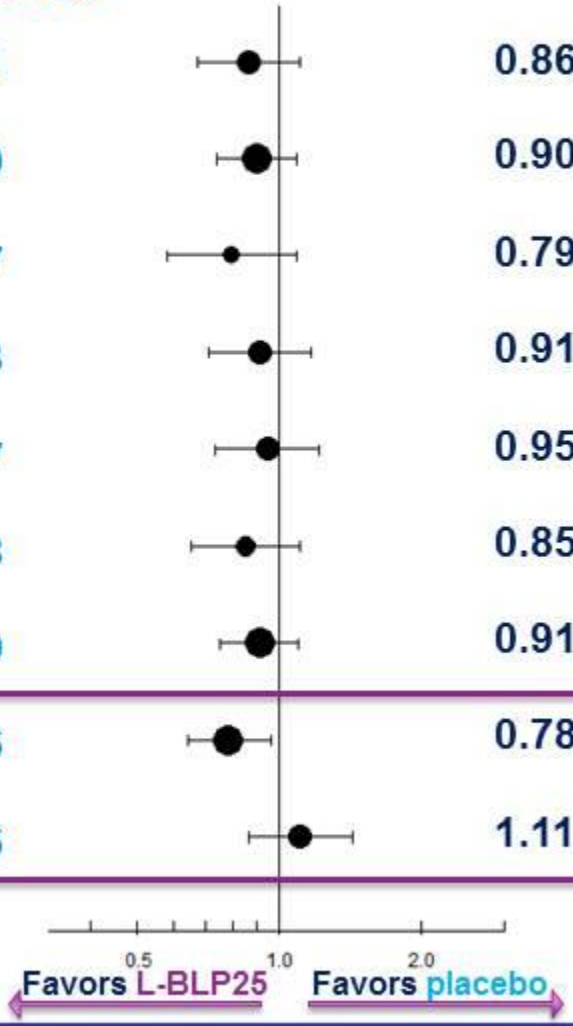
	L-BLP25 (N=829)	Placebo (N=410)
Median OS	25.6 mo	22.3 mo
Adjusted HR	0.88 (95% CI 0.75–1.03) p=0.123*	
Median follow-up	39.9 mo	37.7 mo



At risk (N)												
	0	6	12	18	24	30	36	42	48	54	60	66
												Months
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

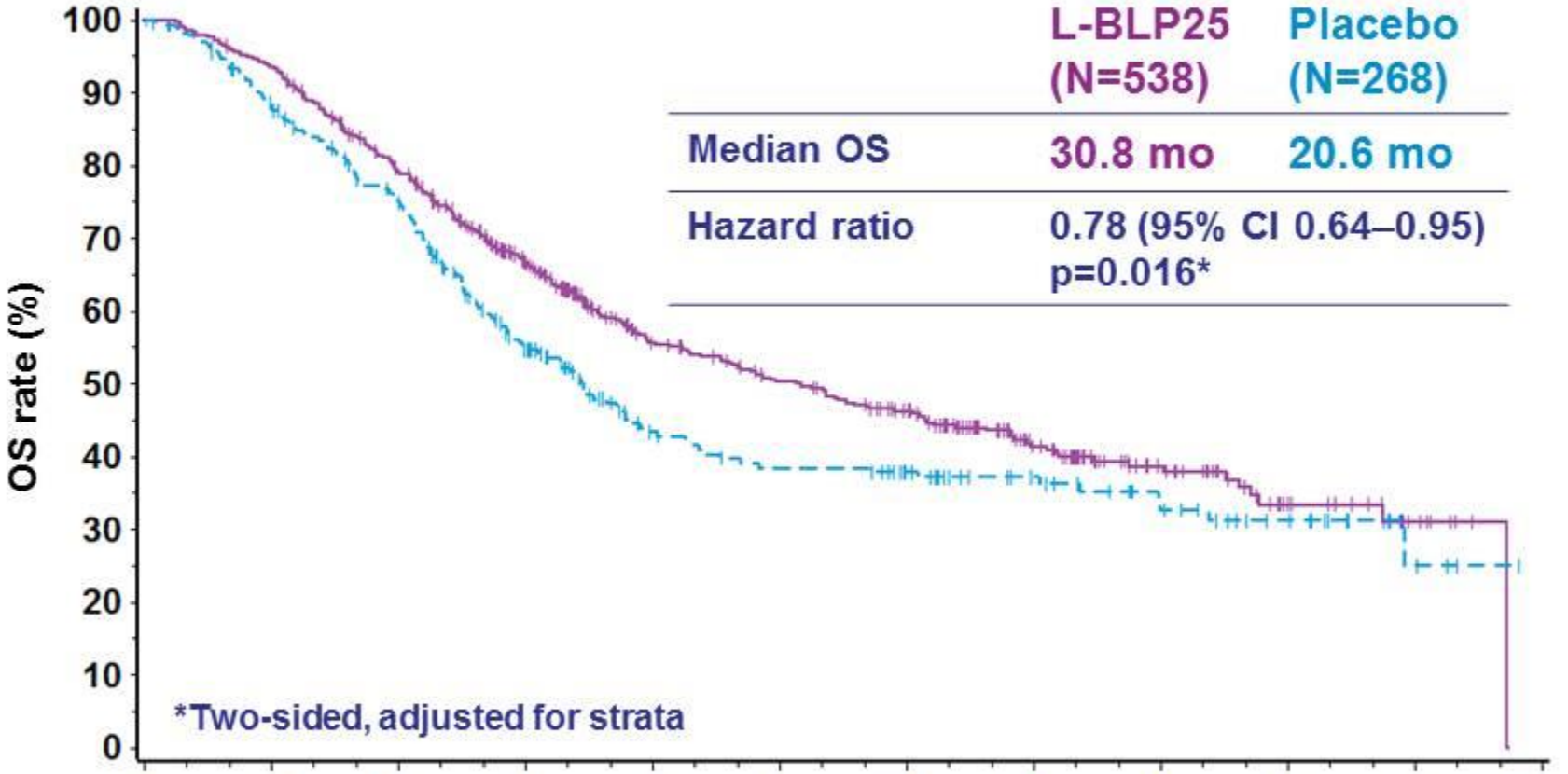
		Median OS (months) L-BLP25 vs. Placebo	HR* (95% CI)
Stage	Stage IIIA (N=487)	27.6 vs. 23.1	0.86 (0.67, 1.11)
	Stage IIIB (N=752)	23.7 vs. 20.9	0.90 (0.74, 1.09)
Region	NA and Aus. (N=321)	34.1 vs. 21.7	0.79 (0.58, 1.09)
	W. Europe (N=475)	24.2 vs. 22.3	0.91 (0.71, 1.17)
	Rest of world (N=443)	21.8 vs. 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)												
	0	6	12	18	24	30	36	42	48	54	60	66
												Months
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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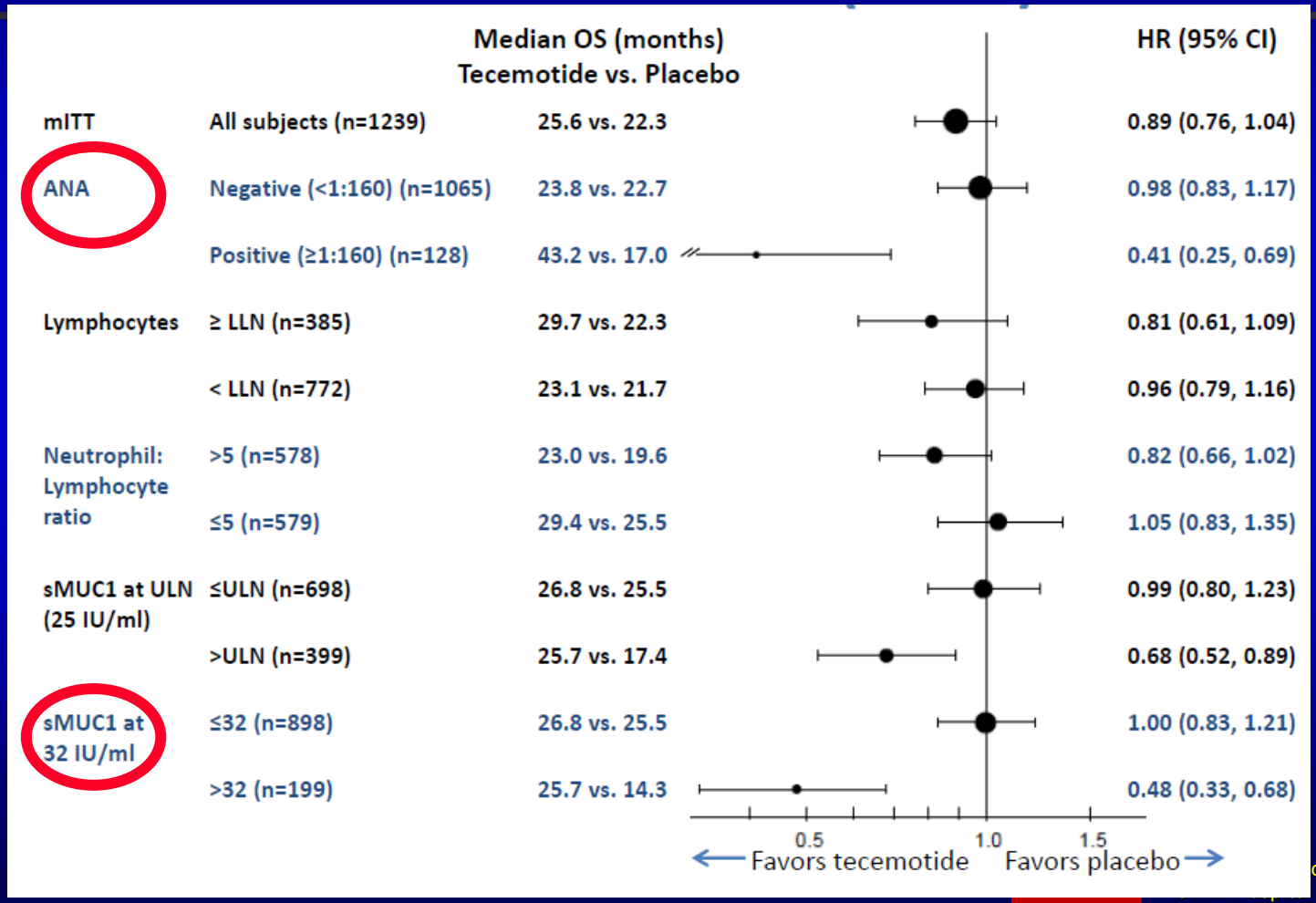

Mitchell et al, WCLC 2013

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- predictive biomarker?

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Univ. Hospital Leuven
Leuven Lung Cancer Group
http://www.LLCG.be

Lung cancer vaccination
> *compound*: belagenpumatucel-L

- Antigen of whole tumour cells
  - based on cocktail of 4 different NSCLC cell lines
  - processed to cell suspension
  - cryopreserved
- Adjuvans
  - lowering of TGF-β2 activity by TGF-β2 antisense gene modification -> increase immunogenicity
- Administration
  - vaccinate i.d. every month up to 16 times

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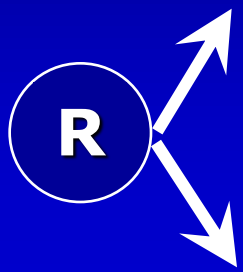
Lung cancer vaccination
> *ph3*: belagenpumatucel-L

STOP trial

Stage III/IV NSCLC

- **disease control after first-line therapy**
- **PS 0-2**
- **brain mets allowed**



Lucanix i.d.
- **qm (18 m), at 21 and 24 m**

Placebo same schedule

Stratified by:
- stage: IIIA-IIIB-IV
- response: CR-PR-SD
- therapy: CT or CTRT

Primary endpoint: overall survival

Other endpoints: PFS, RR, QoL, CNS metastases, safety

Giaccone et al, ESMO 2013

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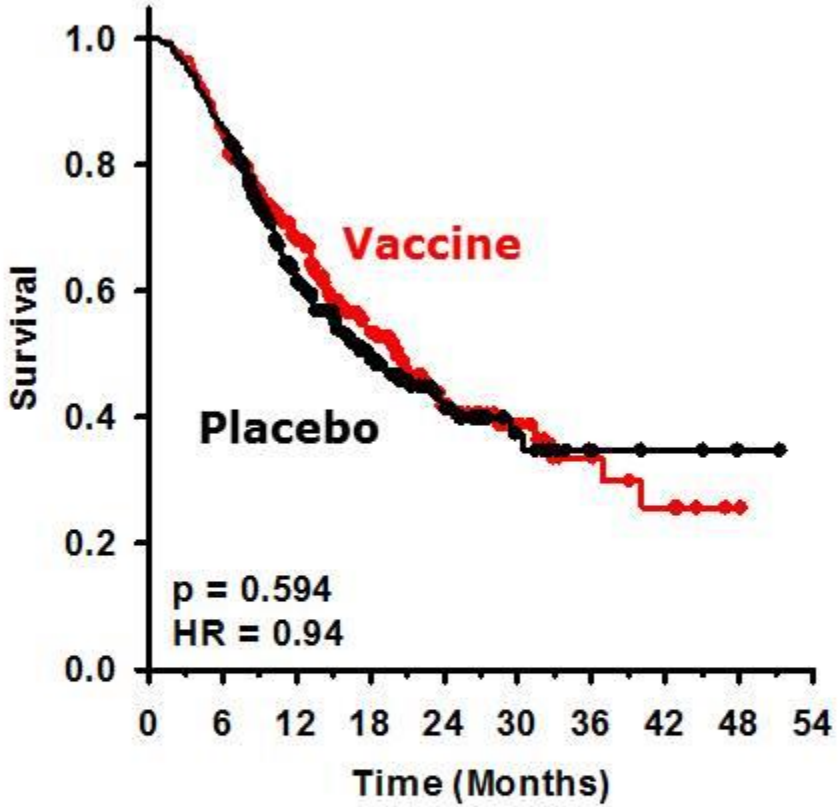
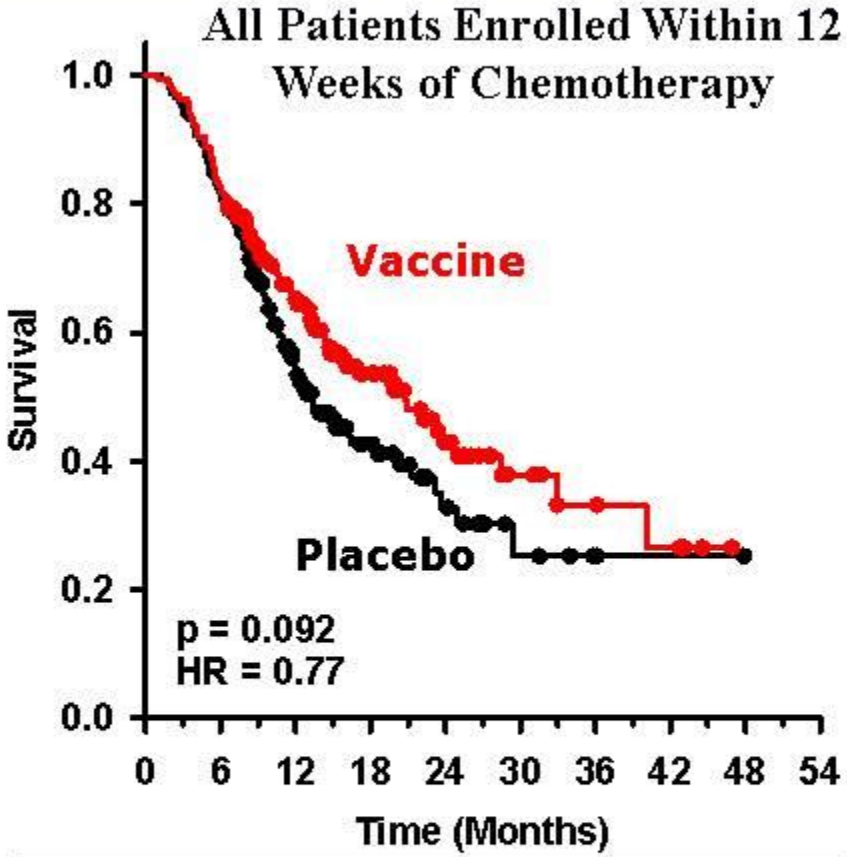
ITT Overall Survival



Cohort	Median Survival	N	Percent Censored
Vaccine	20.3	270	53%
Control	17.8	262	52%
Difference	2.5		

Slide courtesy: Giaccone et al, ESMO 2013

Survival of Patients Enrolled within 12 Weeks

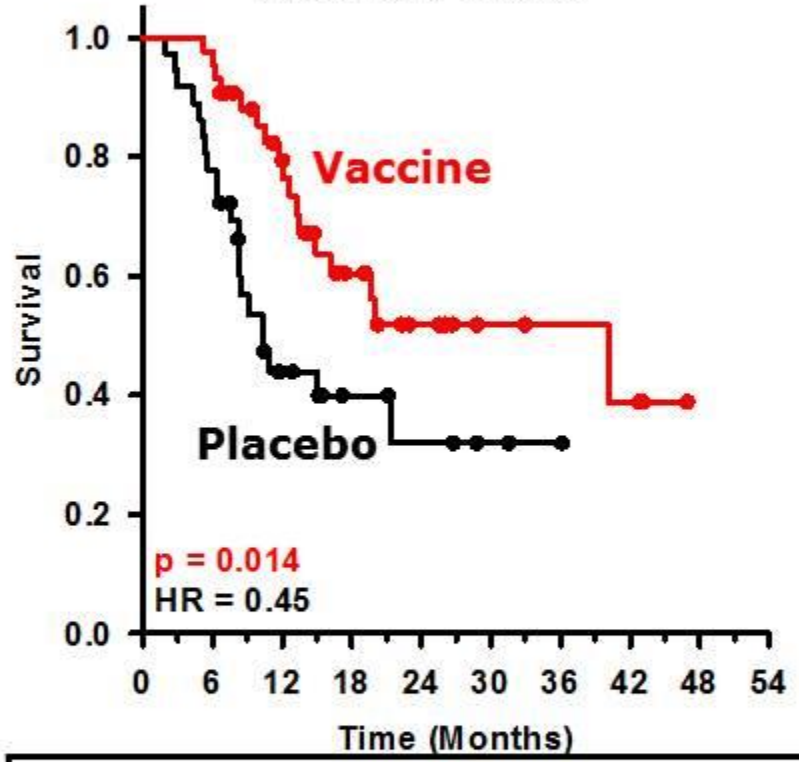


Cohort	Median Survival	N	Percent Censored
Lucanix	20.7	169	53%
Control	13.3	149	46%
Difference	7.4		

Cox regression showed significance for time elapsed from chemotherapy

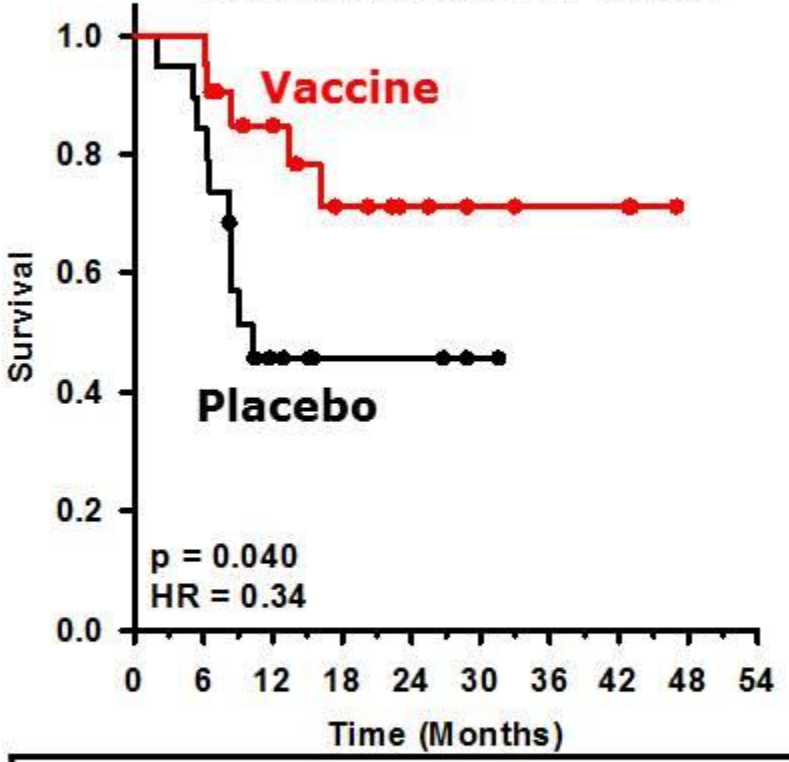
Radiation Therapy and Survival in IIIB/IV

Patients With Prior Radiation Enrolled within 12 Weeks



Cohort	Median Survival	N	Percent Censored
Vaccine	40.1	43	60%
Control	10.3	36	42%
Difference	**29.8**		

Patients With Concurrent Radiation Enrolled within 12 Weeks



Cohort	Median Survival	N	Percent Censored
Vaccine	NR	21	76%
Control	10.3	19	47%
Difference	ND		

Slide courtesy: Giaccone et al, ESMO 2013

Lung cancer immunotherapy

- Introduction: immunotherapy
- Lung cancer vaccination for locoregional NSCLC
- Lung cancer vaccination for advanced NSCLC
- Conclusion

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Lung cancer vaccination > conclusion

- Recent cancer vaccination studies
  - Better defined antigens and adjuvants
  - Low toxicity defines a unique treatment opportunity
- Strong ph3 data from recent ph3 study with L-BLP-25 vaccine
  - 10 month improvement in median OS after concurrent chemoradiotherapy for stage III NSCLC
- Ph3 data with belagenpumatucel-L in advanced NSCLC were less convincing – similar trend for RT interaction
- Data of largest ph3 study therapeutic study in NSCLC – postoperative MAGE-A3 vaccine – awaited
  - suggestion of strong predictive biomarker from phase 2R studies

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Thank you for your kind attention

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