15-18 April 2015, Geneva, Switzerland

Organisers

Partners

Is there any room left for vaccines in lung cancer?

Johan Vansteenkiste

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

Disclosure

- **Research funding at University Hospitals KU Leuven:**
  AstraZeneca, Amgen

- **Advisory functions:**
  GlaxoSmithKline, Merck-Serono, Novartis, BMS, MSD

- **Speaker bureau:**
  Eli-Lilly, Boehringer-Ingelheim

Lung cancer vaccination

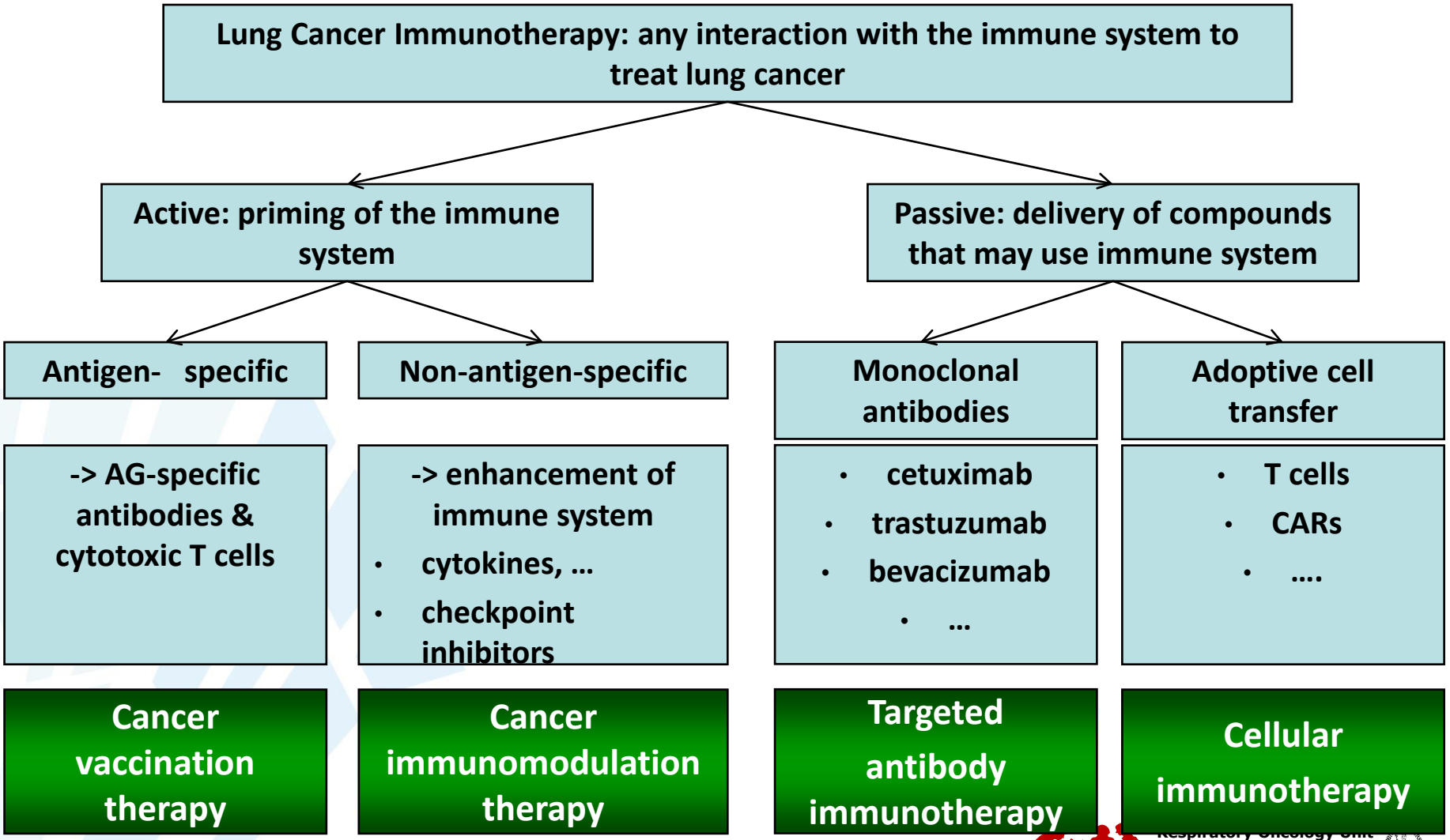
- Introduction: lung cancer immunotherapy

- Lung cancer vaccination
  - reports 2013
  - reports 2014

- Conclusion and outlook

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

Lung cancer immunotherapy

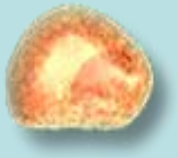


Univ. Hospital Leuven
Leuven Lung Cancer Group
http://www.LLCG.be

Lung cancer vaccination
> components

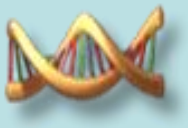
Antigen(s)

- tumour cells
  - autologous
  - allogeneic



- peptides
- full proteins
- gangliosides

- DNA



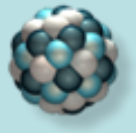
+

Adjuvants

- chemical — Phospholipids, aluminium, …
- biological — TGF-β blockade, …

- viral vectors

- dendritic cells



- liposomes

Lung cancer vaccination
> ph3 trials

Setting	Phase 3
Early stage Post surgery	MAGE-A3 ASCI *MAGRIT* target 2270 reported ESMO 2014
Loc. adv. stage Post chemorad	Tecemotide (L-BLP25) *START* target 1300 reported ASCO 13
Advanced In combo with chemo	Belagenpumatucel-L *STOP* target 700 reported ESMO 13
	rEGF target 1000 recruited
	TG4010 *TIME* target 1000 reported ESMO 2014 / ELCC 2015 -> continuation
	Racotumomab (1E10) target 1082 ongoing

N ~ 8,000

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

Lung cancer vaccination

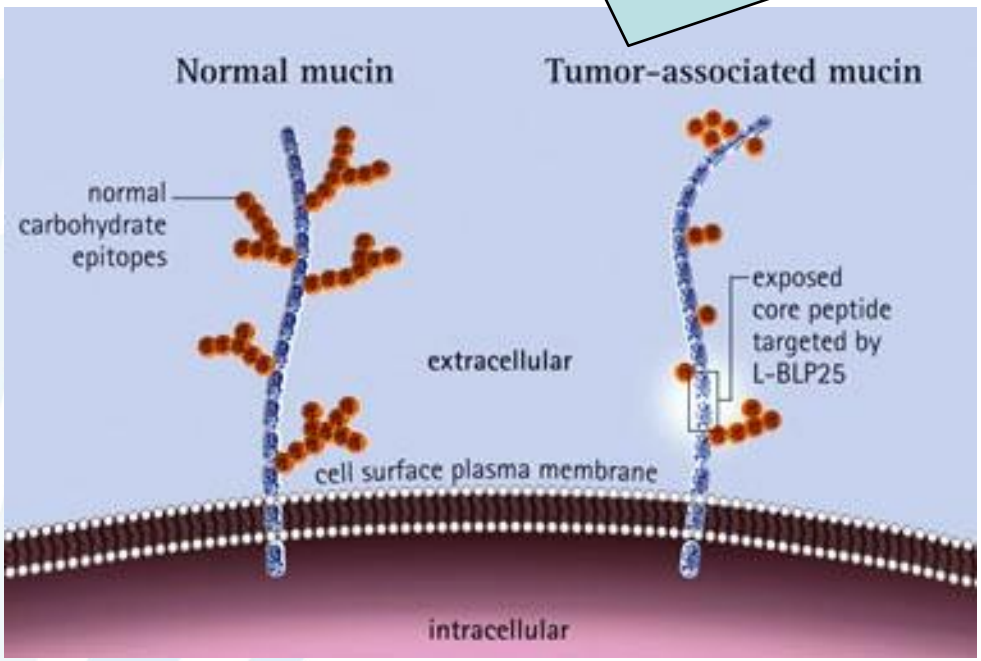
- **Introduction: lung cancer immunotherapy**
- **Lung cancer vaccination**
  - **reports 2013**
  - **reports 2014**
- **Conclusion and outlook**

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

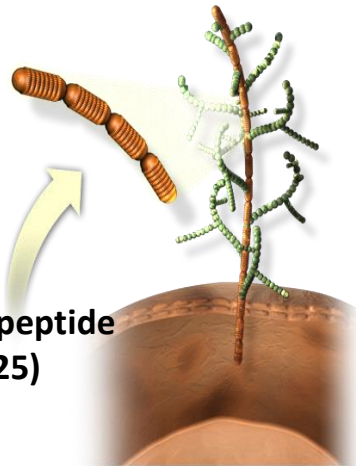
Lung cancer vaccination

> 2013 MUC1 vaccination in stage III NSCLC

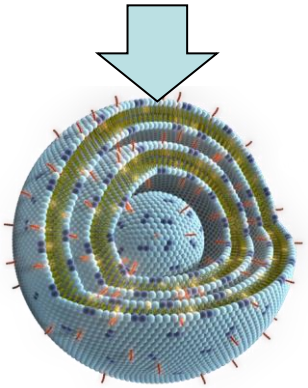
- Overexpressed by most cancers including NSCLC
- Loss of polarity of expression: entire cell surface
- N-terminal ectodomain aberrantly glycosylated
- high MUC1 levels associated with poor prognosis *



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



25 aa lipopeptide (BLP-25)



with adjuvant monophosphoryl lipid A in liposomal formulation

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

Lung cancer vaccination
> ph3 Tecemotide (L-BLP25) trial

START-trial

Stage III NSCLC

- **controlled after chemo-radiotherapy (conc / seq)**
- **no brain mets**
- **non immune disease**

N=880

R

N=440

Tecemotide 1000 µg s.c.
qw (x8) -> q6w
+ BSC

+ priming cyclophosphamide 300 mg/m2

Placebo same schedule
+ BSC

Stratified: stage : IIIA – IIIB
response: PR – SD
RT: concurrent – sequential
region

Primary endpoint: OS

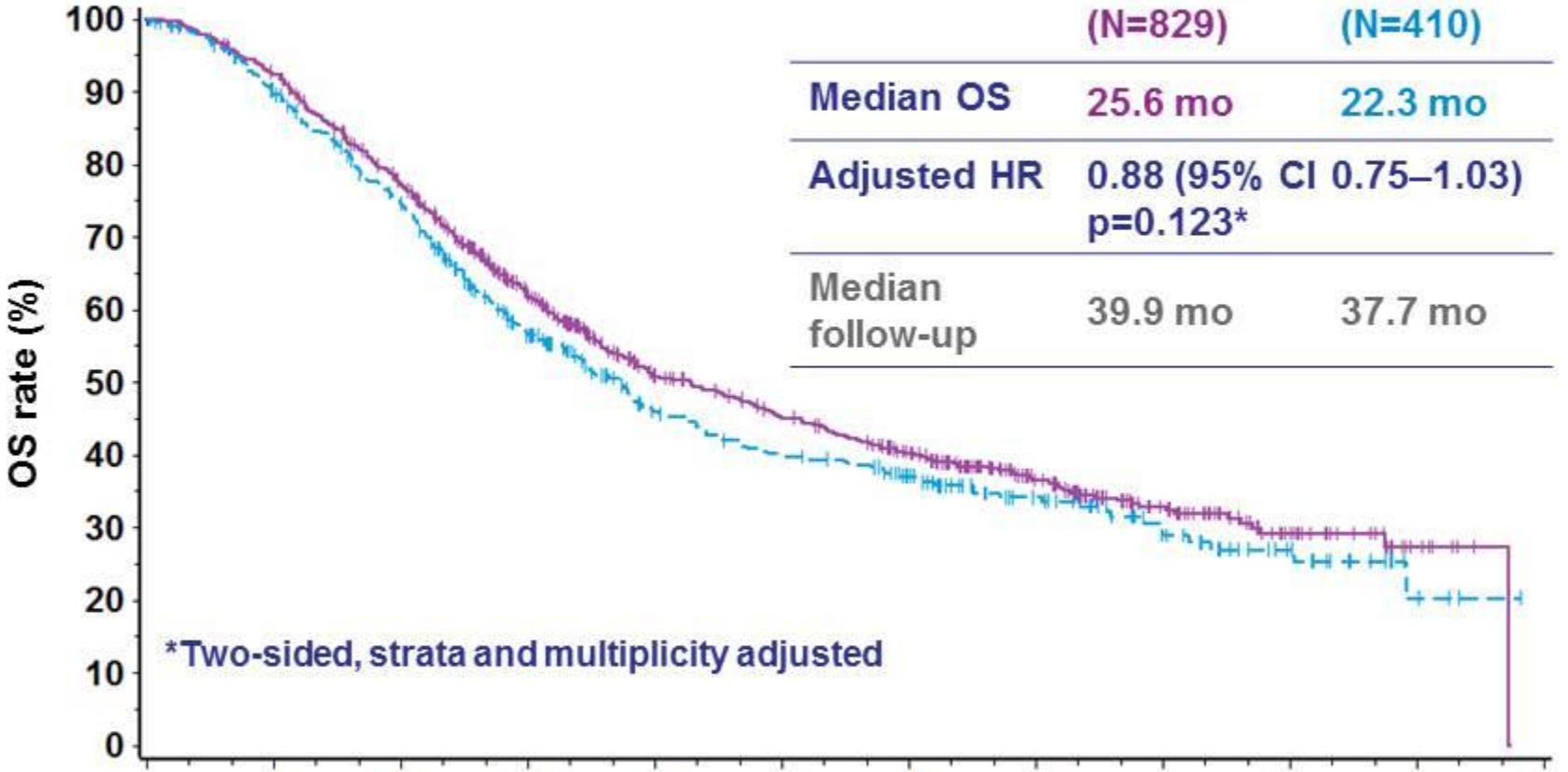
Other endpoints: TTP, safety, symptoms

Butts et al, ASCO 2013 *and* Lancet Oncol 15:59-68, 2014

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

Primary endpoint: Overall survival

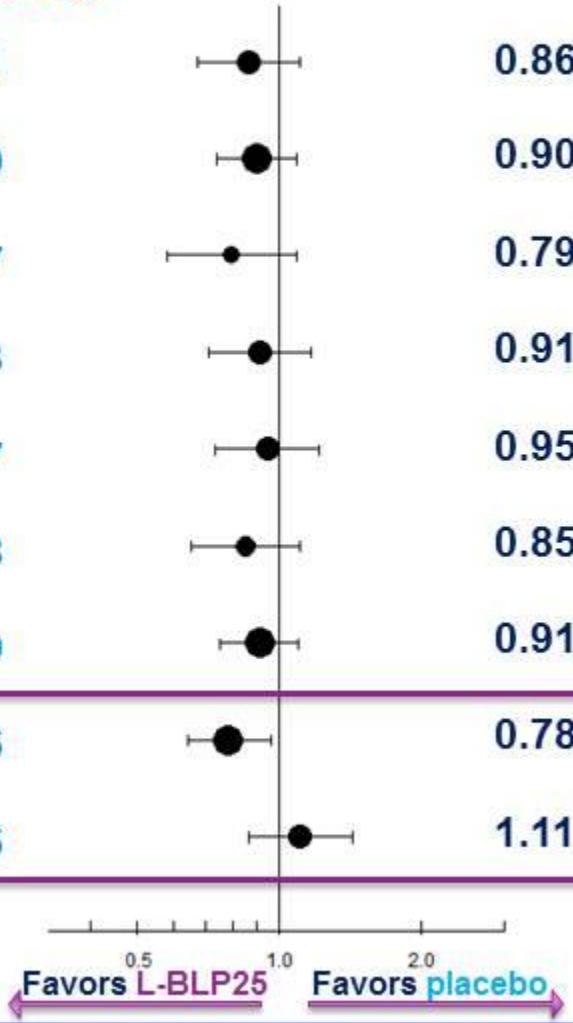
	L-BLP25 (N=829)	Placebo (N=410)
Median OS	25.6 mo	22.3 mo
Adjusted HR	0.88 (95% CI 0.75–1.03) p=0.123*	
Median follow-up	39.9 mo	37.7 mo



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

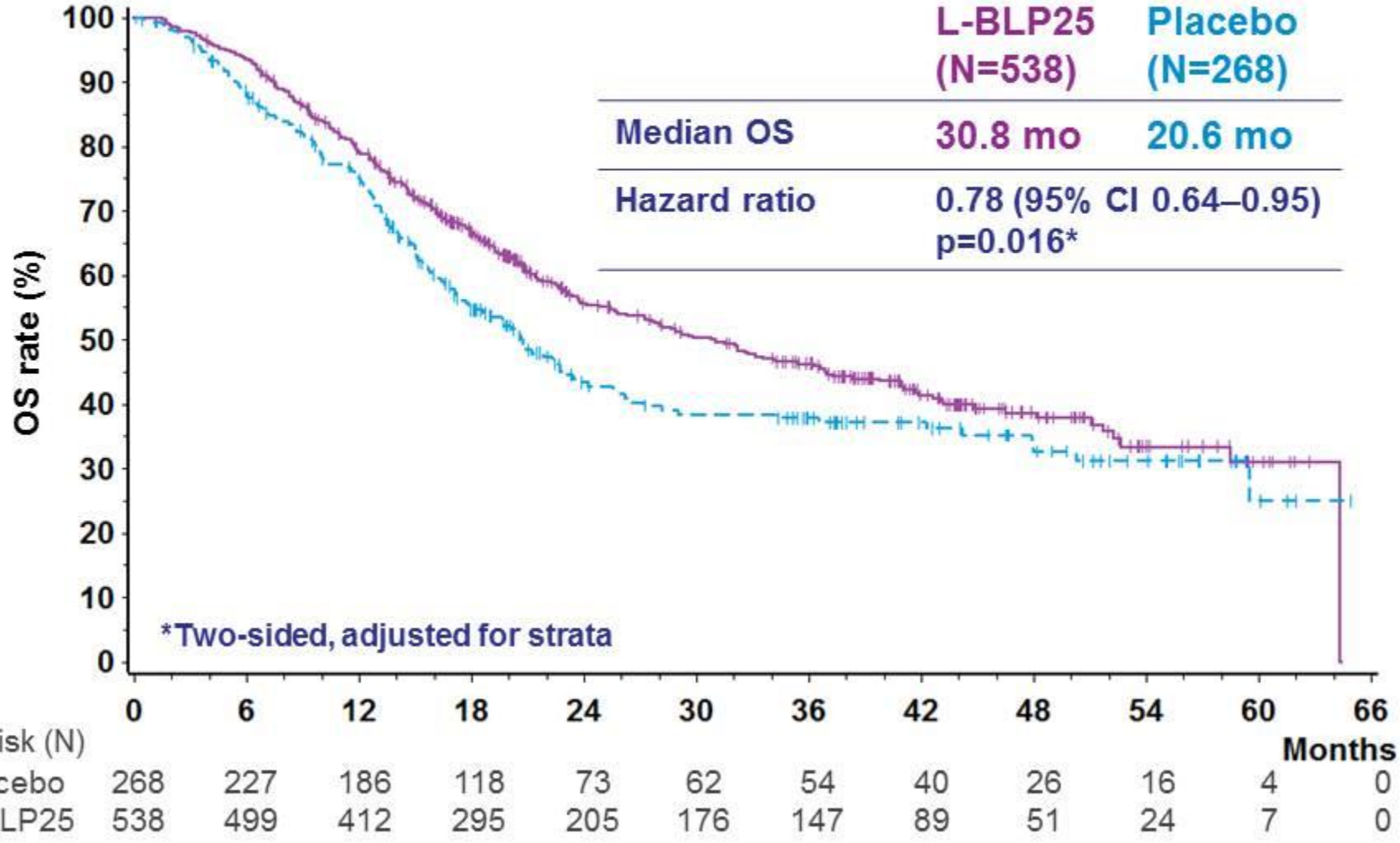
OS: Subgroup analyses by randomization strata

		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)												
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 *and* Lancet Oncol 15:59-68, 2014

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

Lung cancer vaccination
> ph3 Tecemotide program

- **Findings of START1 to be confirmed in global START2 trial in patients with concurrent chemoradiotherapy only**
- **Analysis of Japanese trial unfavourable**

September 12, 2014

Sponsor Discontinues Clinical Development Program of Tecemotide as a Monotherapy in Stage III Non-Small Cell Lung Cancer

"While the data from the exploratory subgroup analysis in the START trial[1] generated a reasonable hypothesis to warrant additional study, the results of the recent trial in Japanese patients decreased the probability of current studies to reach their goals. Therefore, we have decided to discontinue the development of tecemotide as a monotherapy in NSCLC in order to refocus our efforts on other promising candidates in our pipeline, like our anti-PD-L1 antibody MSB0010718C.

Lung cancer vaccination

> 2013 Belagenpumatucel-L in stage III/IV NSCLC

- **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**

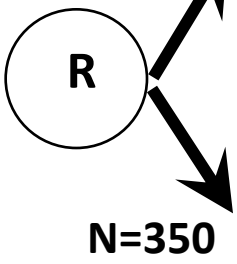
Respiratory Oncology Unit
Univ. Hospital Leuven
Leuven Lung Cancer Group
http://www.LLCG.be

Lung cancer vaccination
> ph3 belagenpumatucel-L trial

STOP-trial

Stage III/IV NSCLC

- **controlled after 1st line**
- **PS 0-2**
- **brain mets allowed**
- **non immune disease**



Belagenpumatucel-L i.d.
qm (18 m), at 21 and 24 m

Placebo same schedule

Stratified: stage : IIIA – IIIB – IV
response: PR – SD
therapy: CT – CTRT

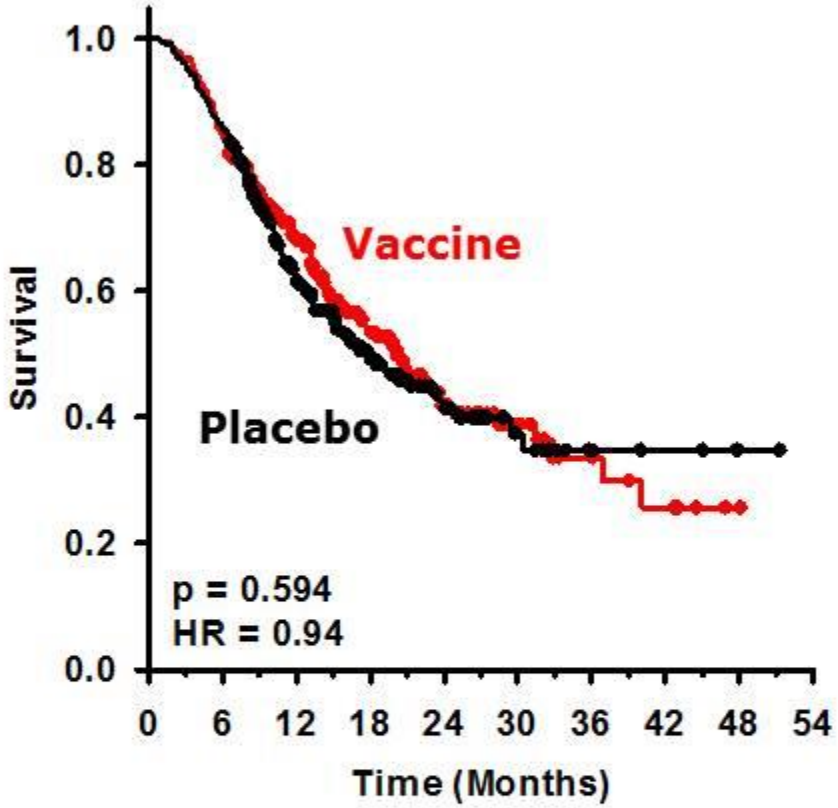
Primary endpoint: OS

Other endpoints: PFS, RR, safety, QoL

Giaccone et al, ESMO 2013

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

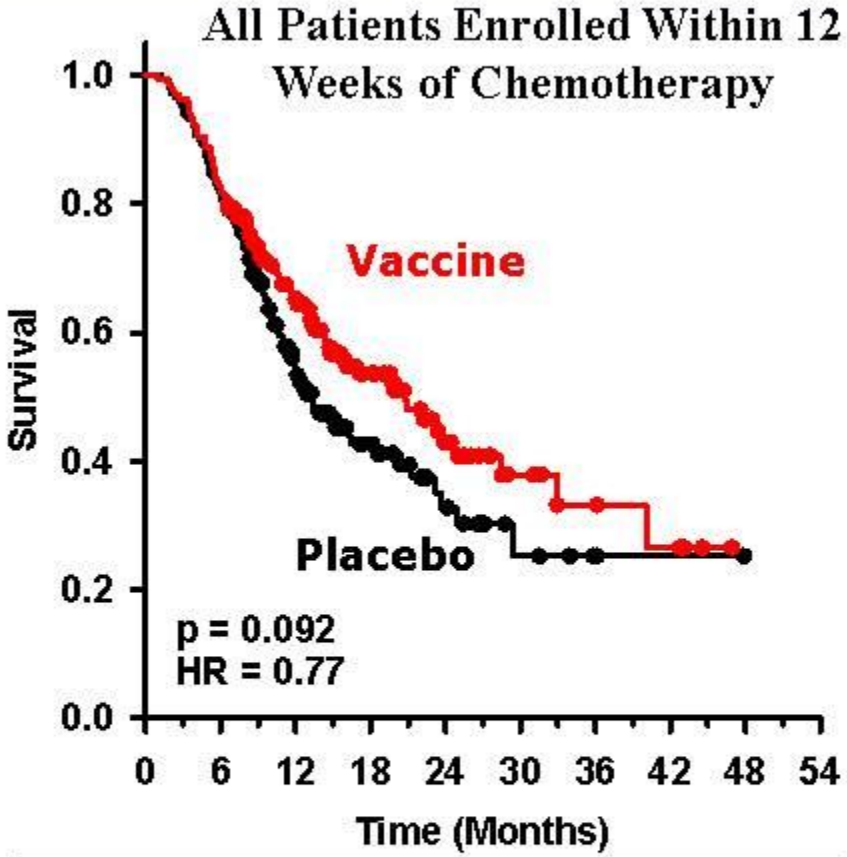
ITT Overall Survival



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

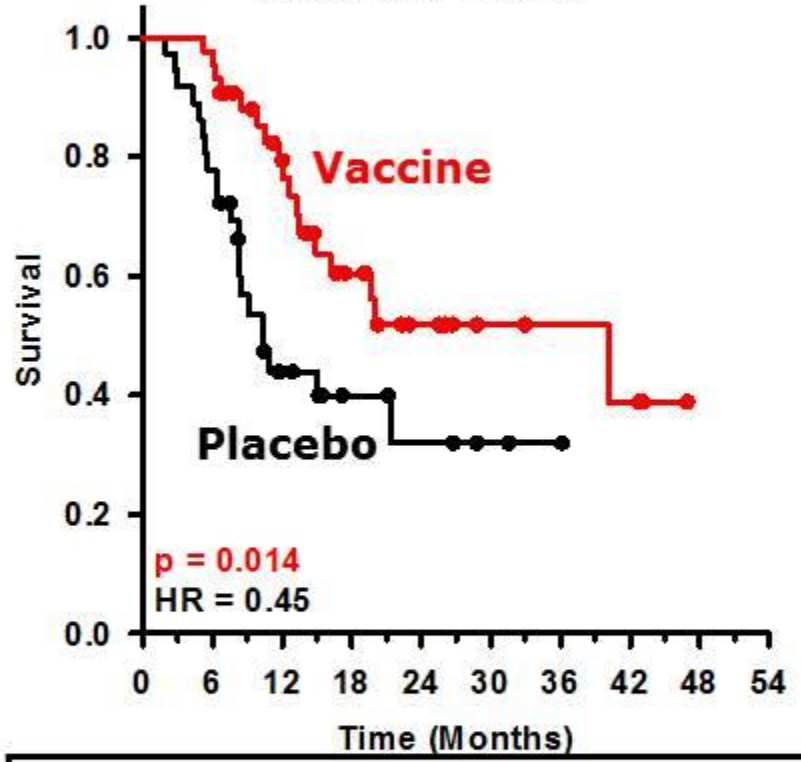


Cohort	Median Survival	N	Percent Censored
Lucanix	20.7	169	53%
Control	13.3	149	46%
Difference	7.4		

Cox regression showed significance for time elapsed from chemotherapy

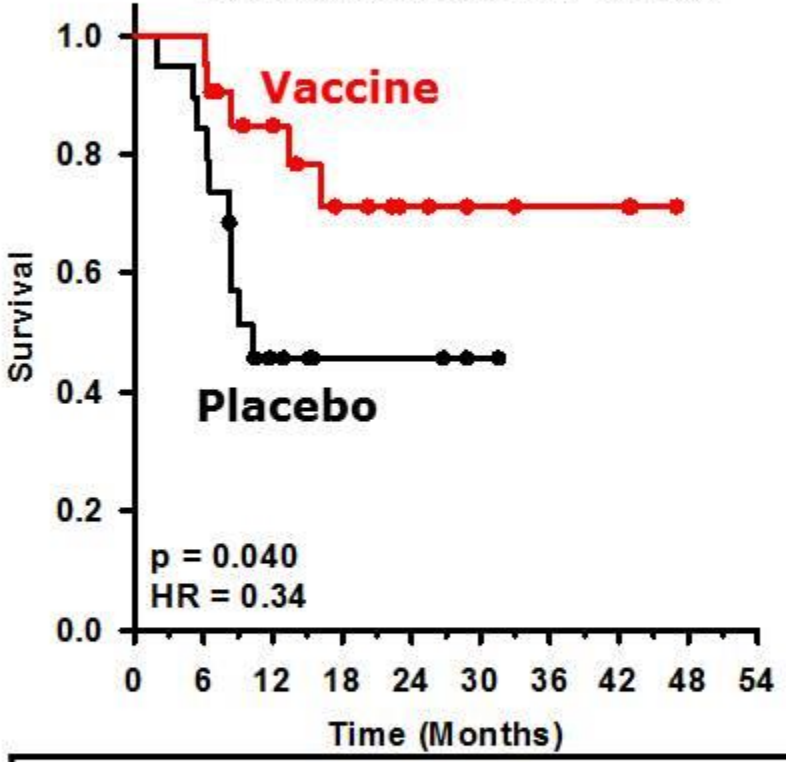
Radiation Therapy and Survival in IIIB/IV

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 vaccination

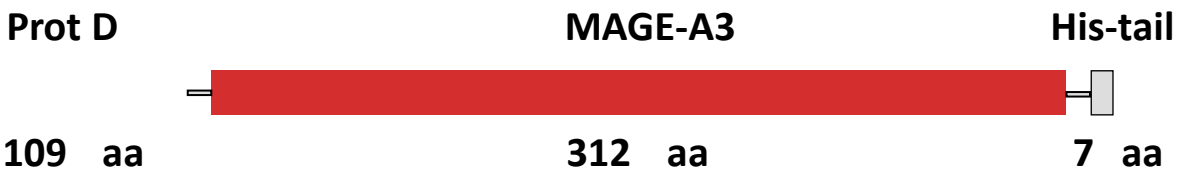
- **Introduction: lung cancer immunotherapy**
- **Lung cancer vaccination**
  - **reports 2013**
  - **reports 2014**
- **Conclusion and outlook**

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

Lung cancer vaccination

> 2014 MAGE-A3 CI in stage IB/II/IIIA NSCLC

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



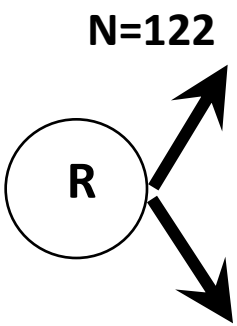
- **Adjuvant**
  - **Proprietary adjuvant system (AS02B)**
  - **in oil-in water emulsion**
- **Administration**
  - **i.m. / q3w x5 –> q3m x8 (27 months in total)**

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

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

Lung cancer vaccination
> ph2 randomised MAGE-A3 CI 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 (27m total)

Placebo same schedule

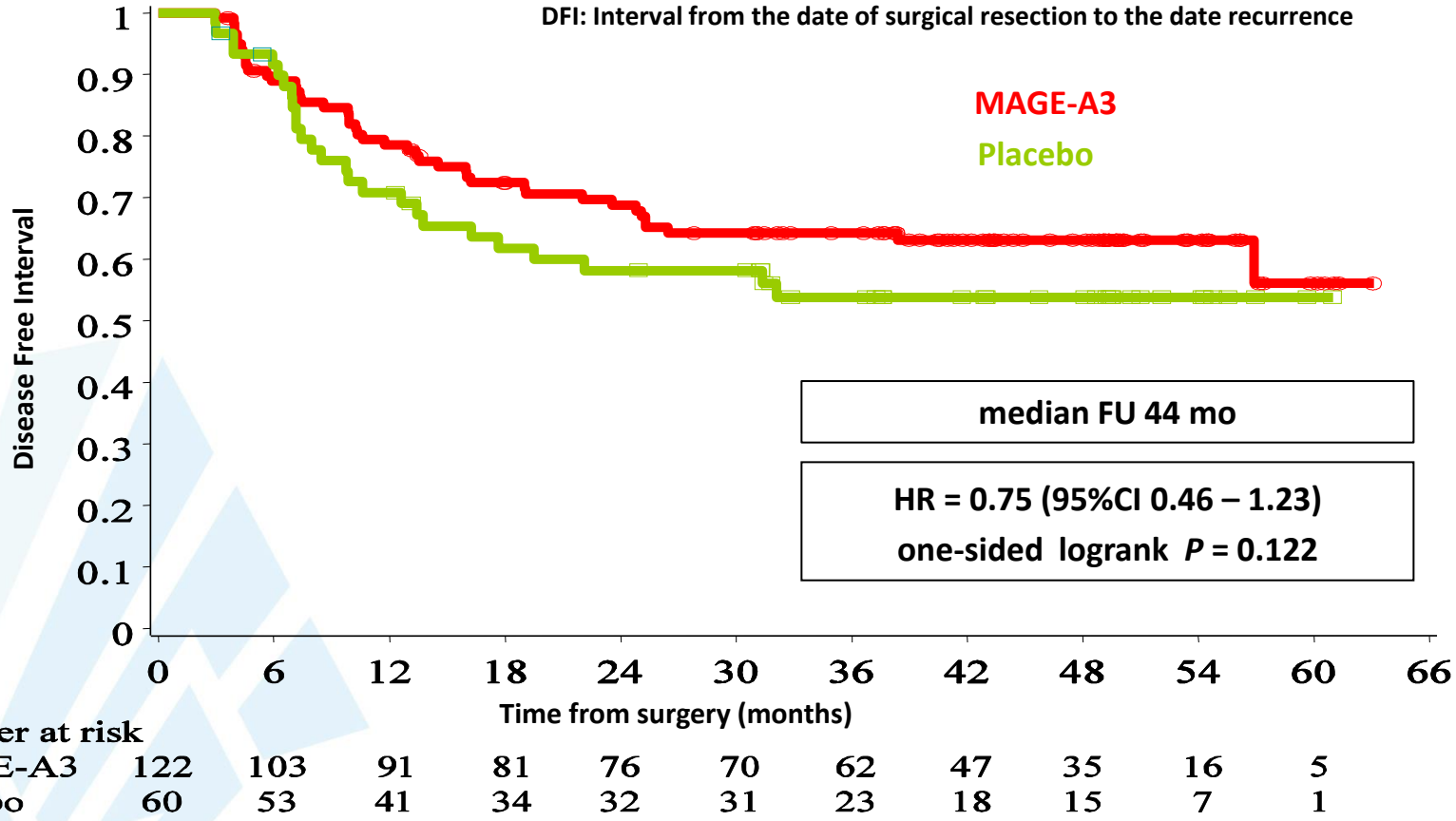
Stratified: stage : IB – II
histology: squam – nonsquam
LN procedure: sampling – radical

Primary endpoint: disease-free interval

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

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

Lung cancer vaccination
> ph2 randomised MAGE-A3 CI trial



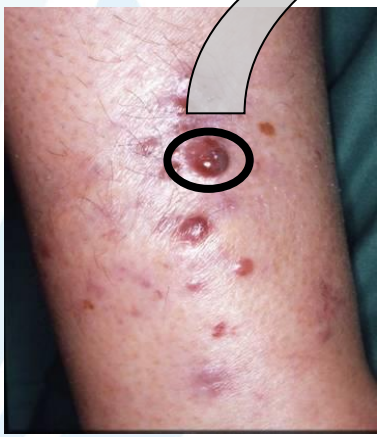
Vansteenkiste et al, ASCO 2007 *and* J Clin Oncol 31:2396-2403, 2013

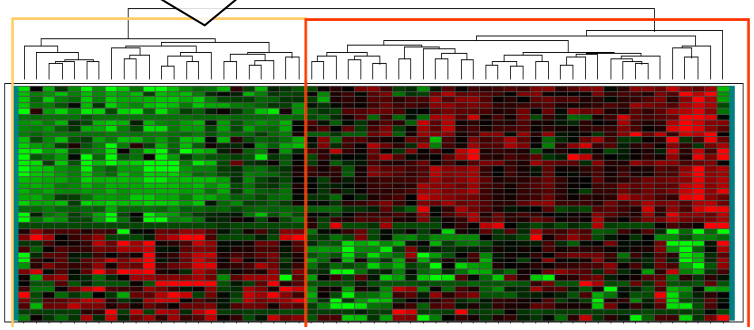
Respiratory Oncology Unit
Univ. Hospital Leuven
Leuven Lung Cancer Group
http://www.LLCG.be

MAGE-A3 vaccination
> biomarker experience from melanoma

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

prediction of clinical benefit?

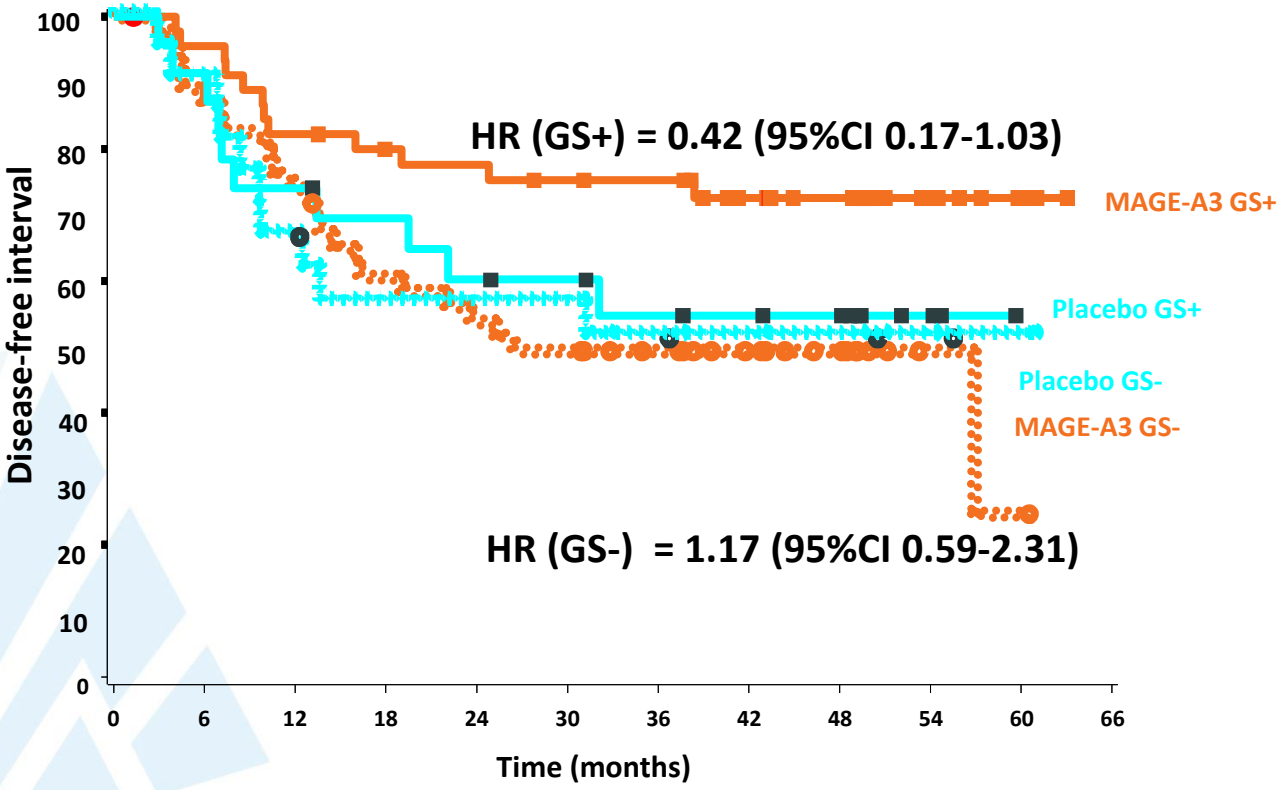




Louahed et al, EORTC-NCI-AACR 2009 *and*
Ulloa-Montoya et al, J Clin Oncol 31: 2388-2395, 2013

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

Lung cancer vaccination
> ph2 randomised MAGE-A3 CI trial



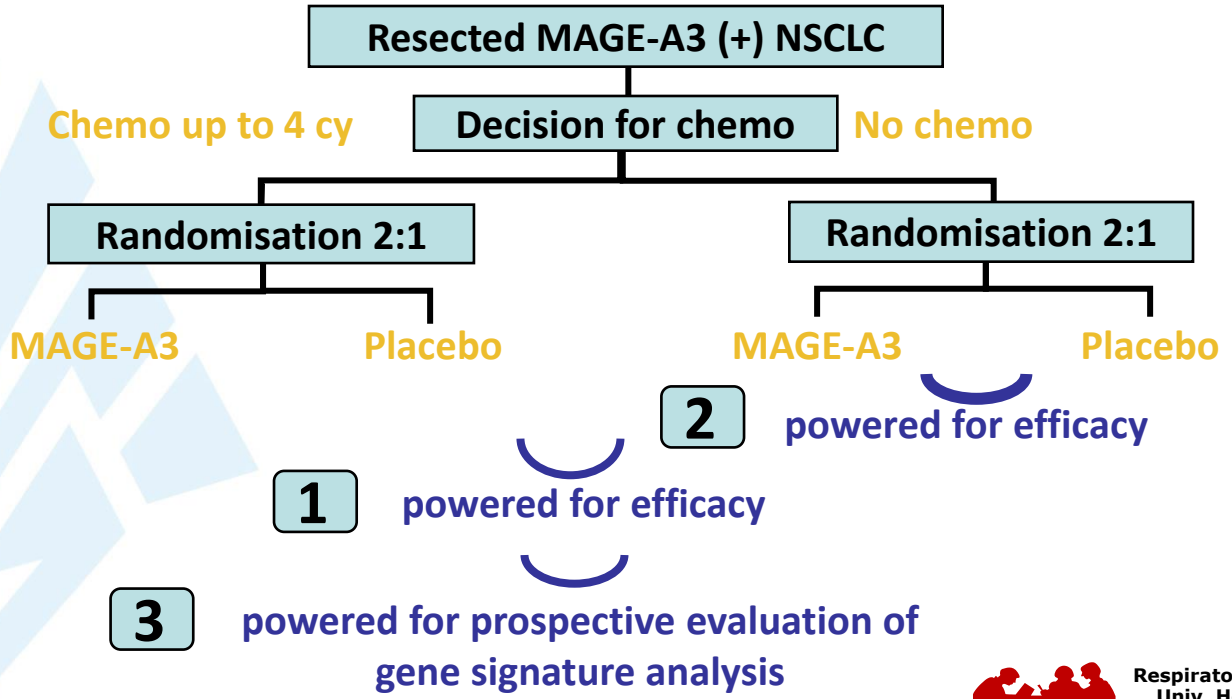
Louahed et al, EORTC-NCI-AACR 2009 *and*
Ulloa-Montoya et al, J Clin Oncol 31: 2388-2395, 2013

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

Lung cancer vaccination
> MAGRIT: ph3 randomised MAGE-A3 CI 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**

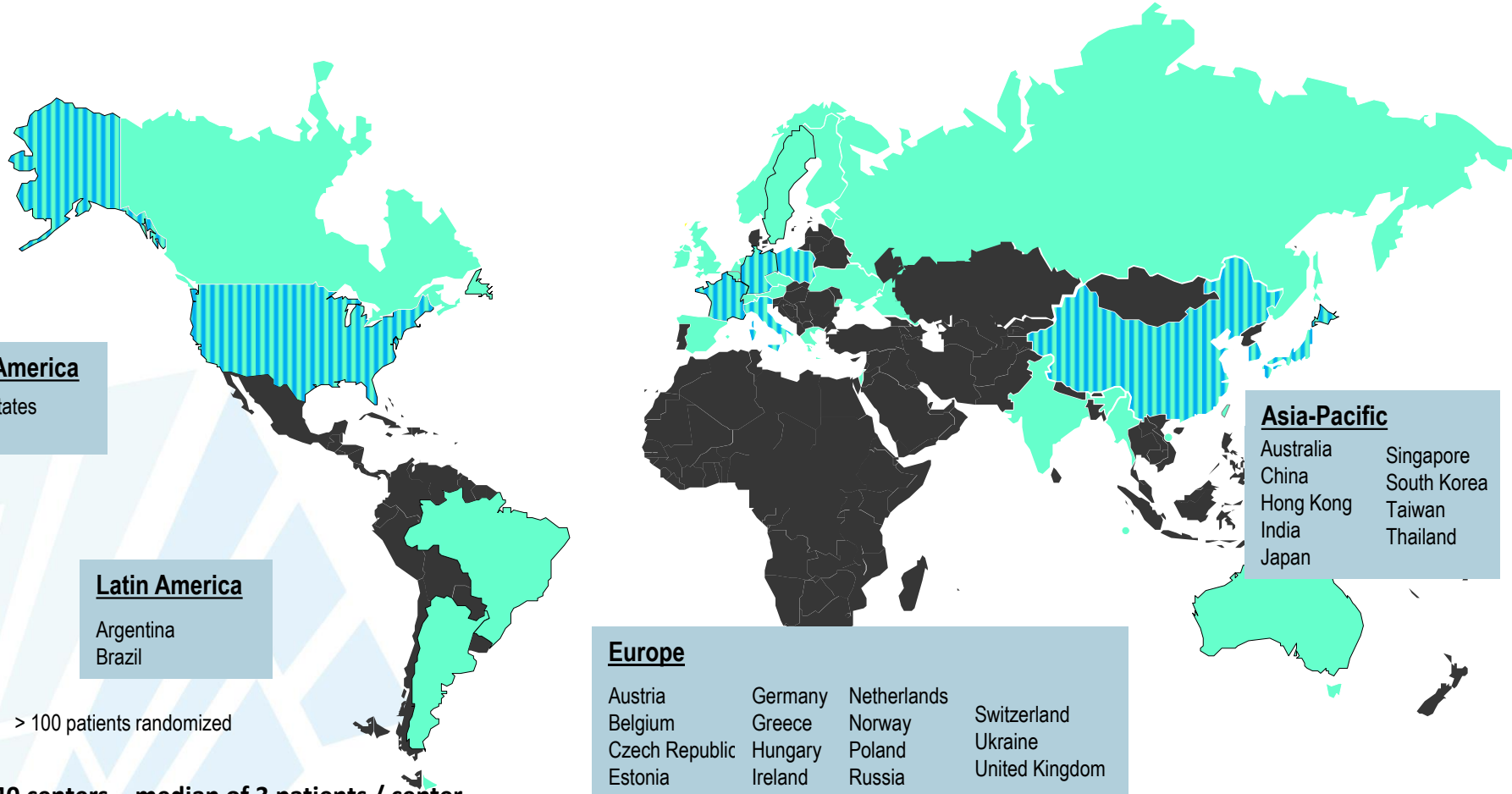


Clinicaltrials.gov NCT00480025

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

Lung cancer vaccination

> MAGRIT: ph3 randomised MAGE-A3 CI trial



North America

United States
Canada

Latin America

Argentina
Brazil

> 100 patients randomized

Asia-Pacific

Australia
China
Hong Kong
India
Japan
Singapore
South Korea
Taiwan
Thailand

Europe

Austria
Belgium
Czech Republic
Estonia
Finland
France
Germany
Greece
Hungary
Ireland
Israel
Italy
Netherlands
Norway
Poland
Russia
Spain
Sweden
Switzerland
Ukraine
United Kingdom

440 centers - median of 3 patients / center (ranging from 1 to 50 patients / center)

Clinicaltrials.gov NCT00480025

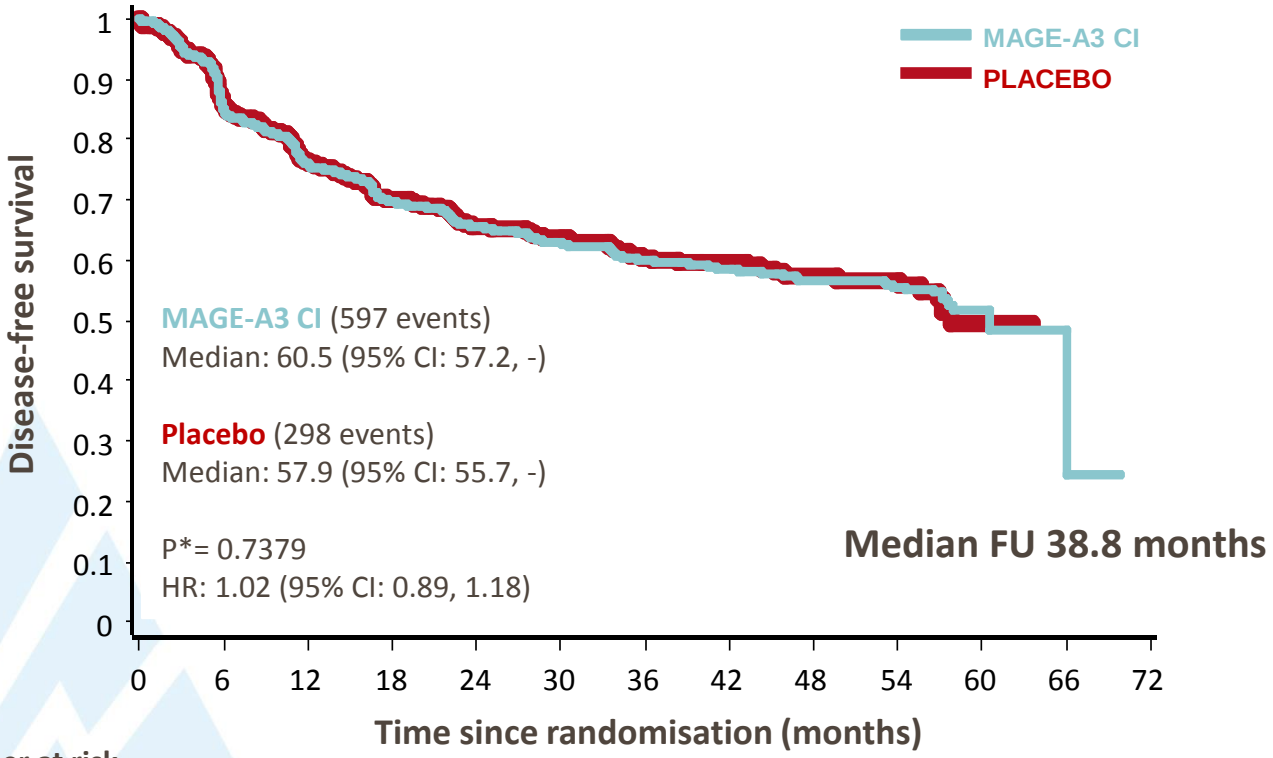
Respiratory Oncology Unit
Univ. Hospital Leuven
Leuven Lung Cancer Group
http://www.LLCG.be

Lung cancer vaccination
> MAGRIT: common adverse events (>10%)

	Any Grade		Grade ≥ 3	
	MAGE-A3 CI N = 1,515	Placebo N = 757	MAGE-A3 CI N = 1,515	Placebo N = 757
Pyrexia	530 (35%)	38 (5%)	3 (<1%)	-
Injection site pain	477 (31%)	35 (5%)	-	-
Injection site reaction	273 (18%)	14 (2%)	-	-
Fatigue	244 (16%)	50 (7%)	7 (<1%)	1 (<1%)
Pain	237 (16%)	13 (2%)	1 (<1%)	-
Influenza like illness	198 (13%)	23 (3%)	-	-
Myalgia	183 (12%)	20 (3%)	3 (<1%)	-

Lung cancer vaccination

> MAGRIT: disease-free survival in overall population



Number at risk

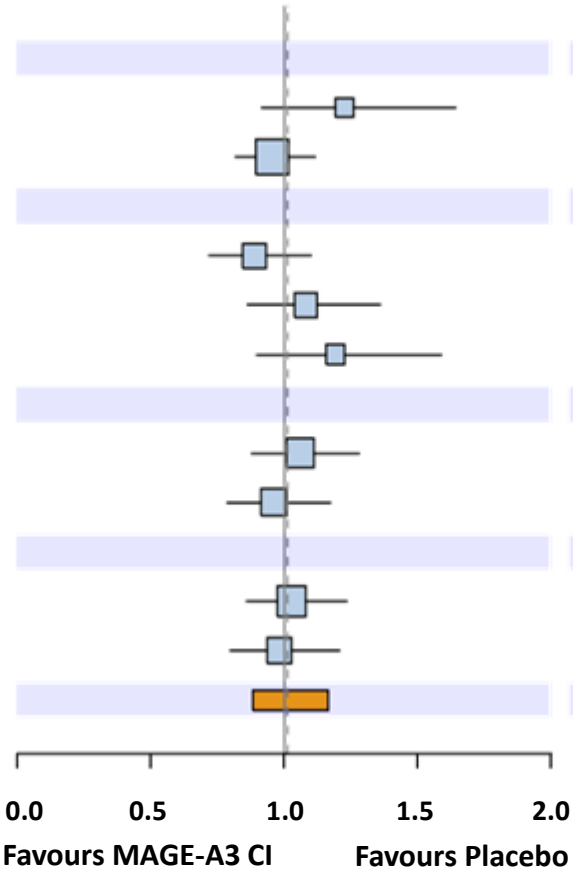
MAGE-A3 CI	1515	1257	1115	1013	887	656	476	339	220	127	19	2
PLACEBO	757	639	562	514	448	328	253	180	114	62	6	0

*Likelihood ratio test from cox regression model stratified by CT and adjusted for baseline variables used as minimization factors.

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

Lung cancer vaccination

> MAGRIT: disease-free survival by key covariates (1)



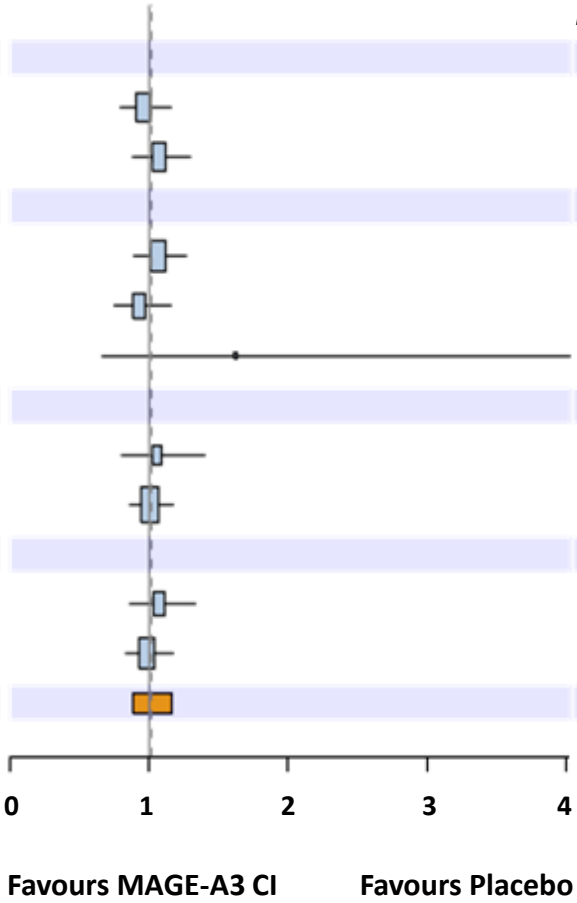
Subgroup	Events/patients MAGE-A3 CI	Events/patients Placebo	HR (95% CI)	P-value
Gender				**0.1484**
Female	154/370	67/178	1.226 (0.913 to 1.646)	
Male	442/1141	235/577	0.954 (0.815 to 1.118)	
Stage (TNM 6)				**0.2123**
IB or less	229/710	124/345	0.887 (0.713 to 1.104)	
II	223/545	105/275	1.081 (0.857 to 1.363)	
IIIa or more	144/256	68/135	1.191 (0.893 to 1.590)	
Type of lymph node procedure				**0.4742**
Limited / Minimal	326/802	155/400	1.061 (0.876 to 1.284)	
Systematic	270/709	142/355	0.960 (0.783 to 1.176)	
Histopathology				**0.7507**
Non-squamous cell carcinoma	345/735	166/355	1.027 (0.853 to 1.236)	
Squamous cell carcinoma	251/776	131/400	0.980 (0.793 to 1.211)	
Overall	596/1511	297/755	1.011 (0.880 to 1.163)	

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

Lung cancer vaccination

> MAGRIT: disease-free survival by key covariates (2)

Subgroup	*HR and 95% CI*	*Events/patients*		*HR (95% CI)*	*P-value*
		MAGE-A3 CI	*Placebo*		
Chemotherapy					**0.4365**
No-CT		289/727	153/363	0.955 (0.785 to 1.162)	
CT		307/784	144/392	1.067 (0.876 to 1.301)	
Performance status					**0.6521**
0		349/863	172/440	1.058 (0.882 to 1.270)	
1		232/620	118/298	0.928 (0.744 to 1.158)	
2		15/28	7/17	1.621 (0.652 to 4.030)	
Region					**0.7686**
Asian		133/332	72/182	1.055 (0.792 to 1.405)	
Non-Asian		463/1179	225/573	1.001 (0.854 to 1.174)	
MAGE-A3 quant expression					**0.5669**
Less than 10		226/528	113/277	1.068 (0.852 to 1.399)	
10 or above		370/983	184/478	0.982 (0.822 to 1.172)	
Overall		596/1511	297/755	1.011 (0.880 to 1.163)	



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

Lung cancer vaccination
> MAGRIT: conclusions

- **Largest therapeutic trial in NSCLC**
  - **First one to investigate immunotherapy in adjuvant setting of early stage NSCLC**

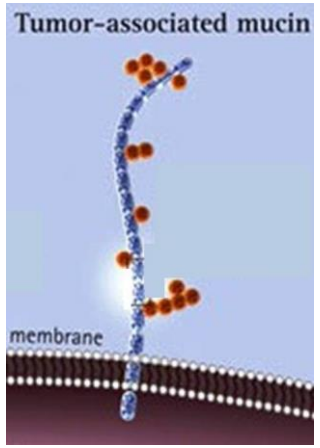
- **Adjuvant MAGE-A3 CI did not increase DFS compared to placebo in the overall population nor in patients without adjuvant chemotherapy**
  - **No benefit observed in any subset analysis**

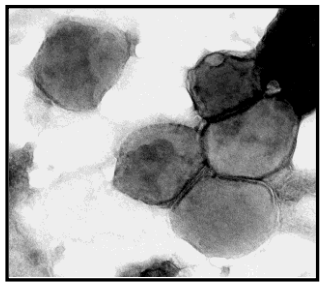
- **Promising strategy of adjuvant vaccination formally tested -> clear answer**
  - **Appropriate setting, design and power**
  - **Therapeutic vaccination with current technology does not work in lung cancer**

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

Lung cancer vaccination
> TG4010 MUC1 vaccine

- **Antigen**
  - **MUC1 full protein**
- **Adjuvant**
  - **recombinant viral vector (attenuated strain of vaccinia virus) expressing both the tumor-associated antigen MUC1 and interleukin-2**
- **Administration**
  - **s.c. / qw x6 –> q3w until PD**
- **Phase 2B-3 RCT**



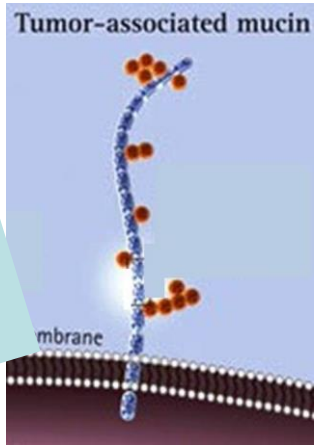


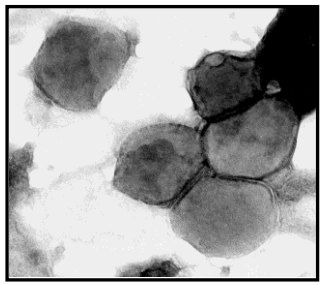
Respiratory Oncology Unit
Univ. Hospital Leuven
Leuven Lung Cancer Group
http://www.LLCG.be

Lung cancer vaccination
> TG4010 MUC1 vaccine

- **Antigen**
  - **MUC1 full protein**
- **Adjuvant**
  - **recombinant viral vector (at**
    vaccinia virus) exp
    associat
- **Ad**
  - **–> q3w until PD**
- **Phase 2B-3 RCT**

Thursday, 16 April 2015, 16:30-17:45
Room V
Poster Discussion 2 – Advanced NSCLC





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

Lung cancer vaccination

- **Introduction: lung cancer immunotherapy**
- **Lung cancer vaccination**
  - **reports 2013**
  - **reports 2014**
- **Conclusion and outlook**

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

Lung cancer vaccination
> ph3 trials

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

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

Lung cancer immunotherapy
> conclusion

- **Lung cancer: strong immunosuppressive environment and disappoining historical immunotherapy results**

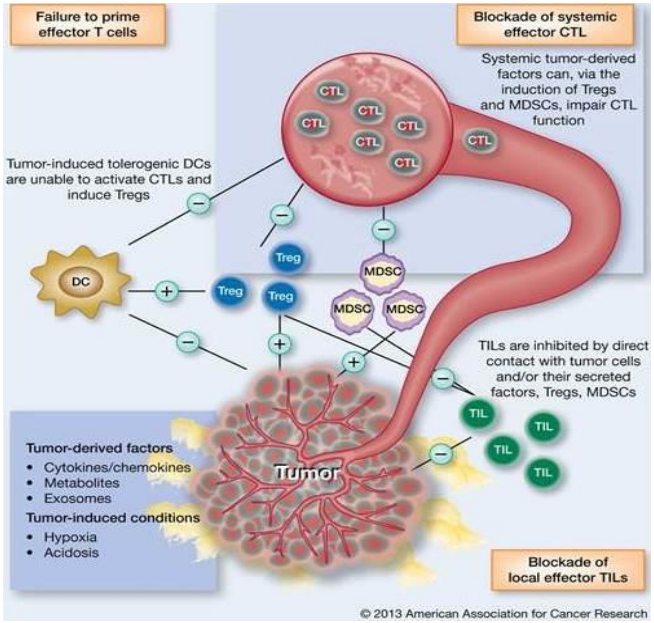
- **Recent cancer vaccination studies**
  - **Better defined antigens and adjuvants**
  - **Low toxicity defines a unique treatment opportunity**
  - **Strong ph3 data from recent ph3 study with L-BLP-25 vaccine**
    - **10 months improvement in median OS after concurrent chemoradiotherapy for stage III NSCLC**

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

Lung cancer immunotherapy
> conclusion

- **MAGRIT : largest therapeutic trial ever done in lung cancer**
  - **Appropriate vaccination setting: eliminate minimal remaining tumour cells after surgery**
  - **Appropriate power and design (N=2272)**
  - ➢ **Therapeutic vaccination with current technologies does not work in lung cancer**

- **Better understanding of mechanisms needed**
  - **MAGE-A3 CI does result in AG-specific antibodies and cytotoxic cells**
  - **Effective soldiers, but do they act in the battle field?**
  - **Outlook**
    - **Combination of vaccination and checkpoint inhibition ?**
    - **mRNA based vaccines?**



Aerts et al, Cancer Res 2013;73:2381-2388

Thank you for your kind attention

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