MAGRIT
A double-blind, randomised, placebo-controlled phase III study to assess the efficacy of recMAGE-A3 / AS15 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive non-small cell lung cancer (NSCLC)

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Presented by Johan F. Vansteenkiste

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Disclosures

- Research funding at University Hospitals KU Leuven: AstraZeneca, Amgen
- Advisory functions: GlaxoSmithKline Biologicals, Merck-Serono, Novartis, BMS
- Speaker bureau: Eli-Lilly

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Background

- MAGE-A3 is a tumour-specific antigen
  - No expression in normal cells (except testis and placenta)
- The antigen is expressed in several tumour types, including NSCLC
- MAGE-A3 Cancer Immunotherapeutic (MAGE-A3 CI) is delivered as a recombinant protein, combined with immunostimulants

- Room for improvement of overall survival (OS) after complete resection of early-stage NSCLC
  - No new adjuvant strategies since IALT trial in 2004 [1]
  - LACE meta-analysis: 5-year OS after surgery 44%, increased to 49% with adjuvant cisplatin-based chemotherapy (HR 0.89, 95% CI 0.82-0.96) [2]
  - Tolerability of adjuvant cisplatin-based chemotherapy (CT) suboptimal

HR – hazard ratio; CI – confidence interval

1 International IALT collaborative group, *N Engl J Med* 2004

2 Pignon *et al, J Clin Oncol* 2008

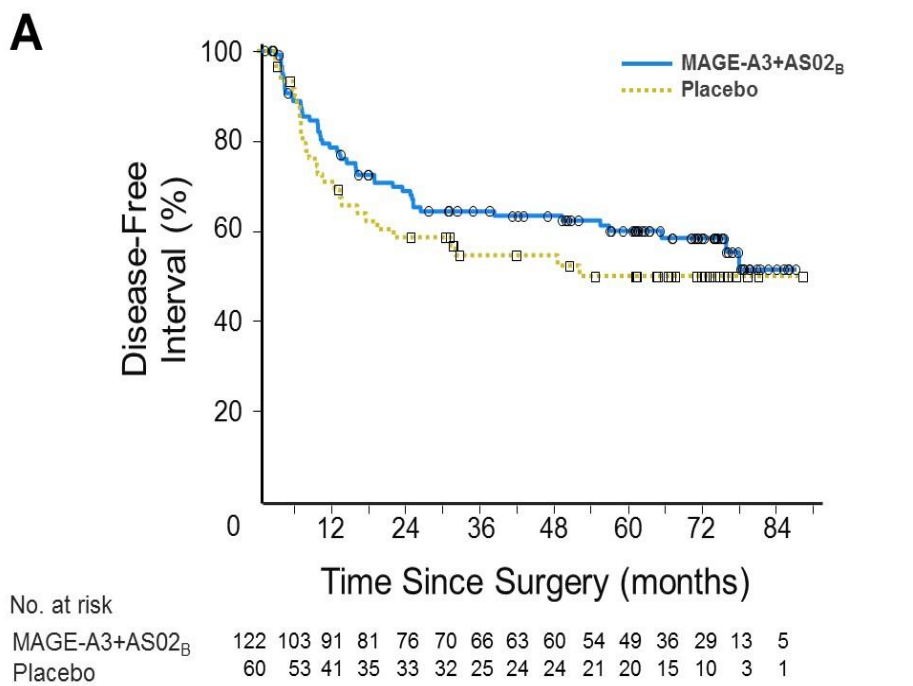
Trial Rationale

- MAGE-A3 CI
  - Activity in metastatic melanoma [1]
  - Double-blind, placebo-controlled, phase II trial in 182 completely resected MAGE-A3+ stage IB-II NSCLC [2]
    - 25% reduction in the relative risk of lung cancer recurrence with MAGE-A3 CI (HR 0.75, 95% CI 0.46-1.23)
    - Very well tolerated
  - Predictive gene signature (GS) [3]
    - Discovered in metastatic melanoma
    - Reproduced in early stage NSCLC

1.Kruit et *al, J Clin Oncol* 2013
2.Vansteenkiste *et al, J Clin Oncol* 2013
3.Ulloa-Montoya *et al, J Clin Oncol* 2013

Trial Rationale

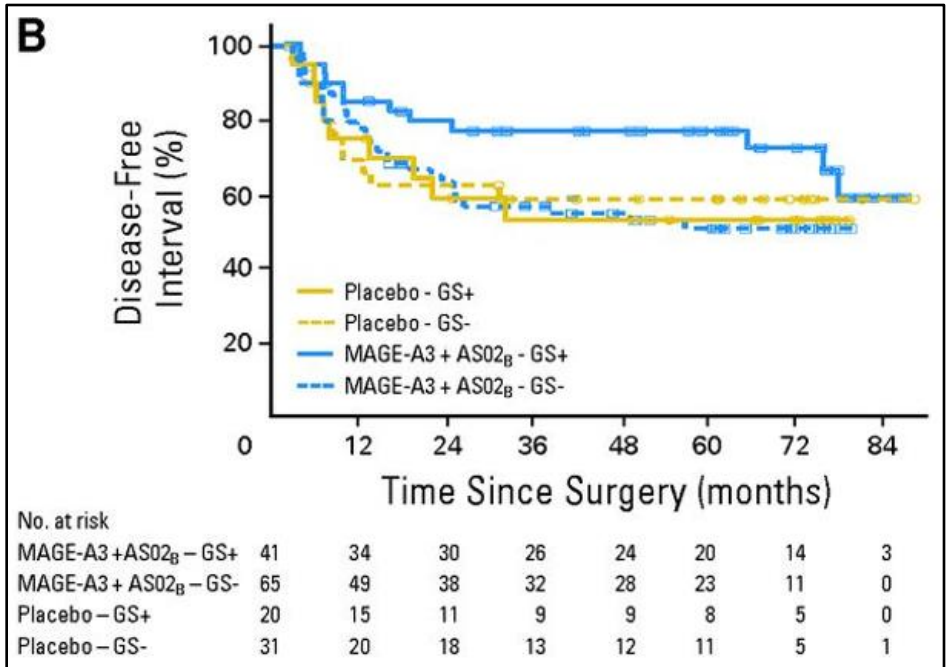
Overall Population



HR = 0.78 (95% CI 0.49-1.24)
p = 0.295

Vansteenkiste *et al, J Clin Oncol* 2013;31:2396–403

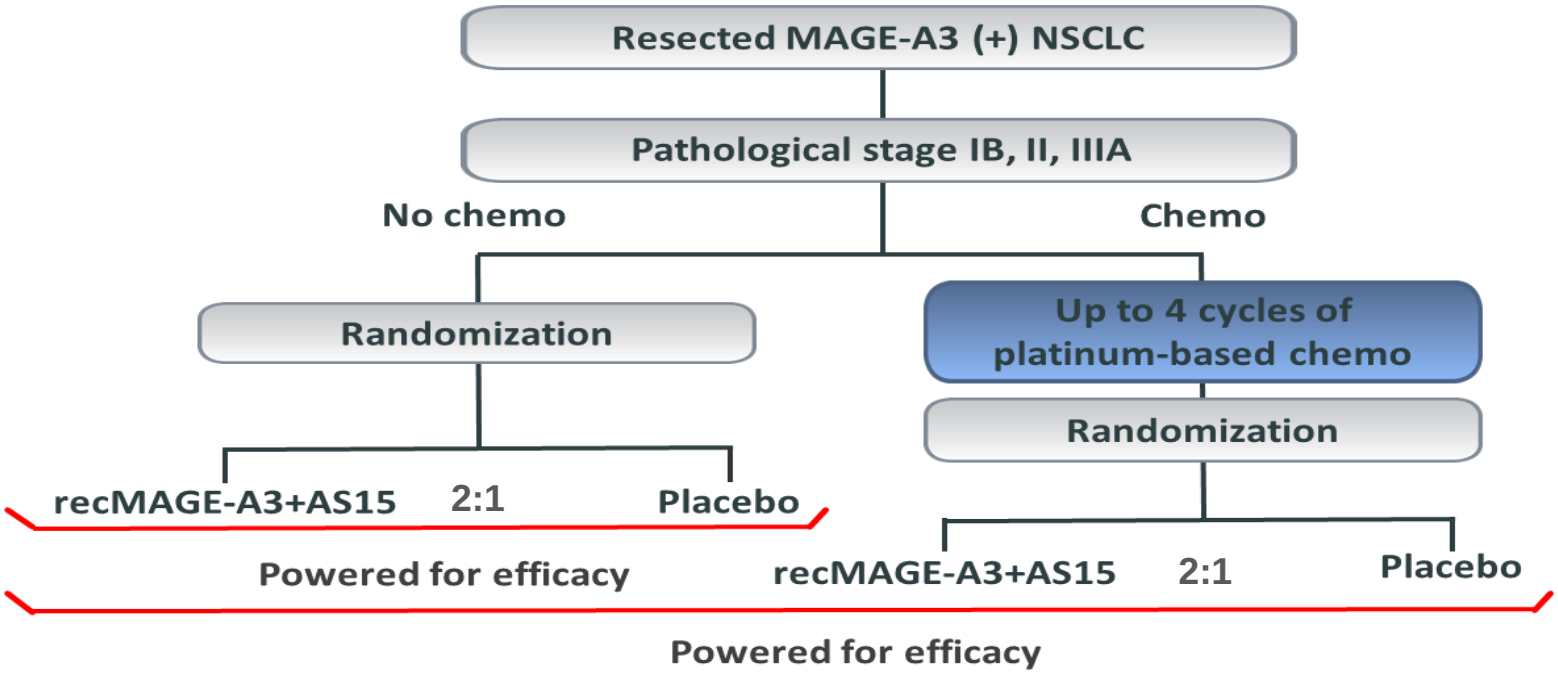
Gene Signature Positive Population



HR= 0.42 (95% CI 0.17-1.03) in the GS+ population
p = 0.06

Ulloa-Montoya et al, *J Clin Oncol* 2013;31:2388–95

MAGRIT: Phase III Study - MAGE-A3 as Adjuvant Non-Small Cell LunG CanceR ImmunoTherapy



13 administrations over 27 months - 2,312 patients randomized (screened >13,000 patients)

Stratification factor: chemotherapy (CT)/no-CT

Minimization factors: nb of CT cycles (1-2 *vs* 3-4), stage of disease (IB *vs* II *vs* IIIA), type of lymph-node sampling (radical *vs* sampling), PS (0,1 *vs* 2), smoking status (never *vs* past *vs* current)

MAGRIT: Study Endpoints and Statistical Considerations

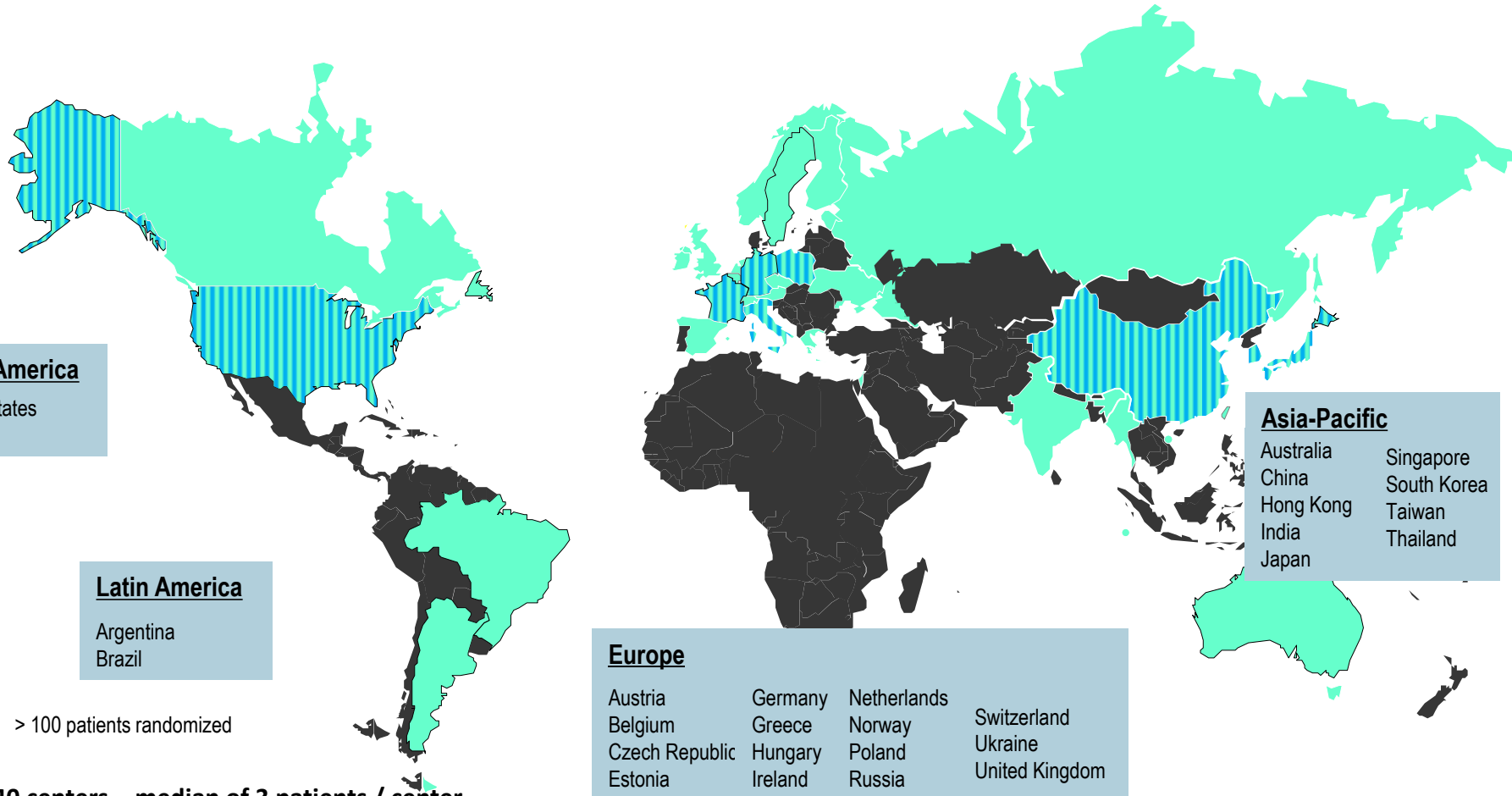
- Primary endpoints

Objective	Nb of Events	2-Sided alpha Global 0.05	2-Sided alpha Interim analysis at 75% events	Power	Target HR
DFS Overall	881	0.02	0.0001	90%	0.78
DFS No-CT	441	0.0256	-	80%	0.74
DFS GS+	171	0.01	-	80%	0.58

- Secondary endpoints
  - OS, Lung cancer specific survival, Immunogenicity, Safety, Health-related Quality of Life
- One interim analysis:
  - *"Study may continue as pre-specified boundary not met and no safety concerns"*

MADRID 2014 ESMO congress

MAGRIT: Global Trial (NCT00480025)



North America
United States
Canada

Latin America
Argentina
Brazil

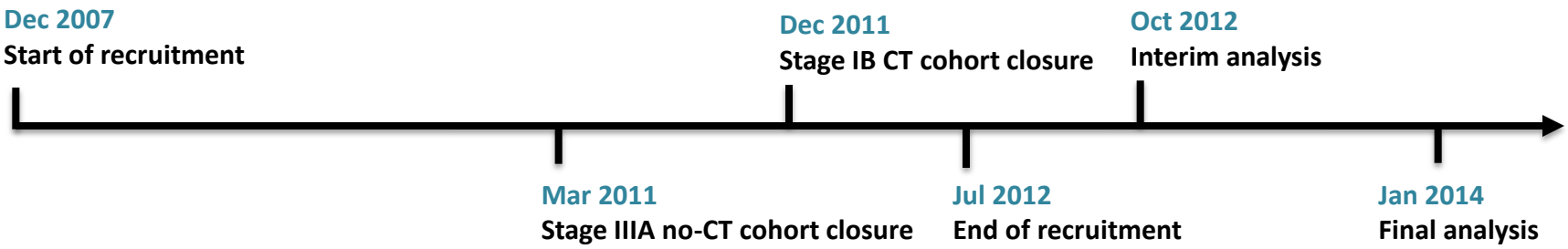
Asia-Pacific
Australia
China
Hong Kong
India
Japan
Singapore
South Korea
Taiwan
Thailand

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

> 100 patients randomized

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

MAGRIT: Study Flow



Screened	MAGE-A3 Valid test	MAGE-A3 (+) n (%)	Randomized	Treated
13,849	12,820	4,210 (33%)	2,312	2,272

Main protocol amendment: addition of DFS in Gene Signature positive (GS+) patients as co-primary endpoint

MAGRIT: Main Inclusion Criteria

- Pathologically proven stage IB, II or IIIA NSCLC (TNM version 6.0)
- Completely resected (R0) - Anatomical resection (at least lobectomy or sleeve lobectomy)
- MAGE-A3-positive primary tumor (RT-PCR tested on formalin-fixed paraffin embedded (FFPE) tissue)
- Performance status (PS) 0, 1 or 2
- Adequate bone-marrow reserve, renal function and hepatic function
- No auto-immune disease

MAGRIT: Baseline Characteristics (1)

	MAGE-A3 CI N = 1,515	Placebo N = 757	Total N = 2,272
Median age (range) in years	63 (34-90)	63 (35-87)	63 (34-90)
Male	1,145 (76%)	578 (76%)	1,723 (76%)
Region			
Europe	882 (58%)	416 (55%)	1,298 (57%)
East Asian (China, HK, Japan, Singapore, S Korea, Taiwan)	333 (22%)	182 (24%)	515 (23%)
North America	240 (16%)	132 (17%)	372 (16%)
ROW (Argentina, Australia, Brazil, India and Thailand)	60 (4%)	27 (4%)	87 (4%)
PS			
0-1	1,487 (98%)	740 (98%)	2,227 (98%)
Never smoker	99 (7%)	49 (7%)	148 (7%)
Prior adjuvant chemo	785 (52%)	391 (52%)	1,176 (52%)
3-4 cycles	*714 (91%)*	*358 (92%)*	*1,072 (91%)*

MAGRIT: Baseline Characteristics (2)

	MAGE-A3 CI N = 1,515	Placebo N = 757	Total N = 2,272
Histopathology			
Squamous cell carcinoma	779 (51%)	401 (53%)	1,180 (52%)
Non-squamous cell carcinoma	736 (49%)	356 (47%)	1,092 (48%)
Pathological stage (TNM 6)			
IB	712 (47%)	347 (46%)	1,059 (47%)
II	546 (36%)	275 (36%)	821 (36%)
IIIA	254 (17%)	133 (18%)	387 (17%)
Other – Ineligible	3 (<1%)	2 (<1%)	5 (<1%)
Type of surgery			
Lobectomy / bilobectomy / sleeve resection	1,298 (86%)	644 (85%)	1,942 (85%)
Pneumonectomy	216 (14%)	113 (15%)	349 (15%)
Type of lymph node procedure			
Limited	800 (53%)	402 (53%)	1,202 (53%)
Radical	712 (47%)	355 (47%)	1067 (47%)

MAGRIT: Common Adverse Events (≥ 10%)

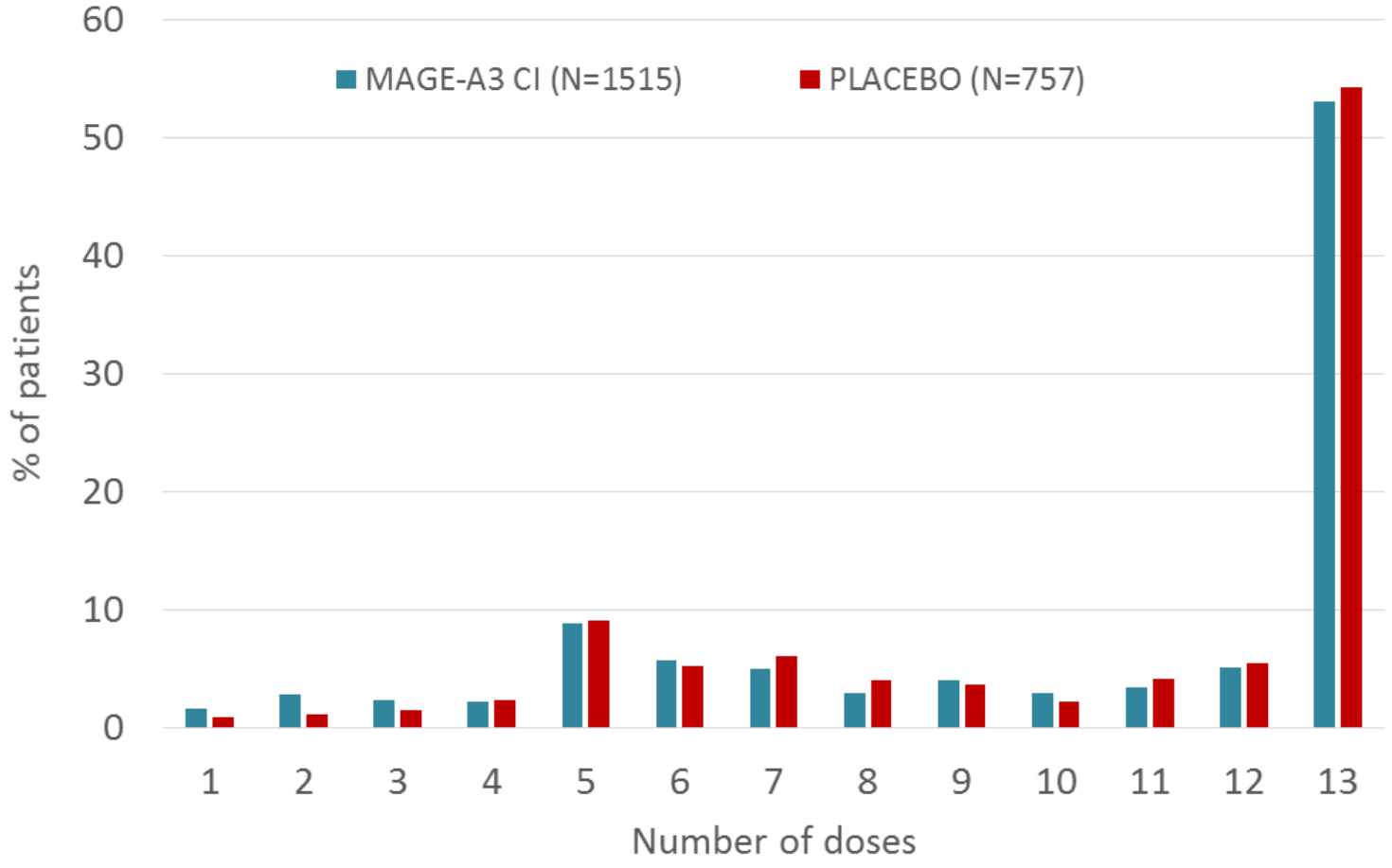
(within 31 days of administration)

	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%)	-

MAGRIT: Overview of Adverse Events

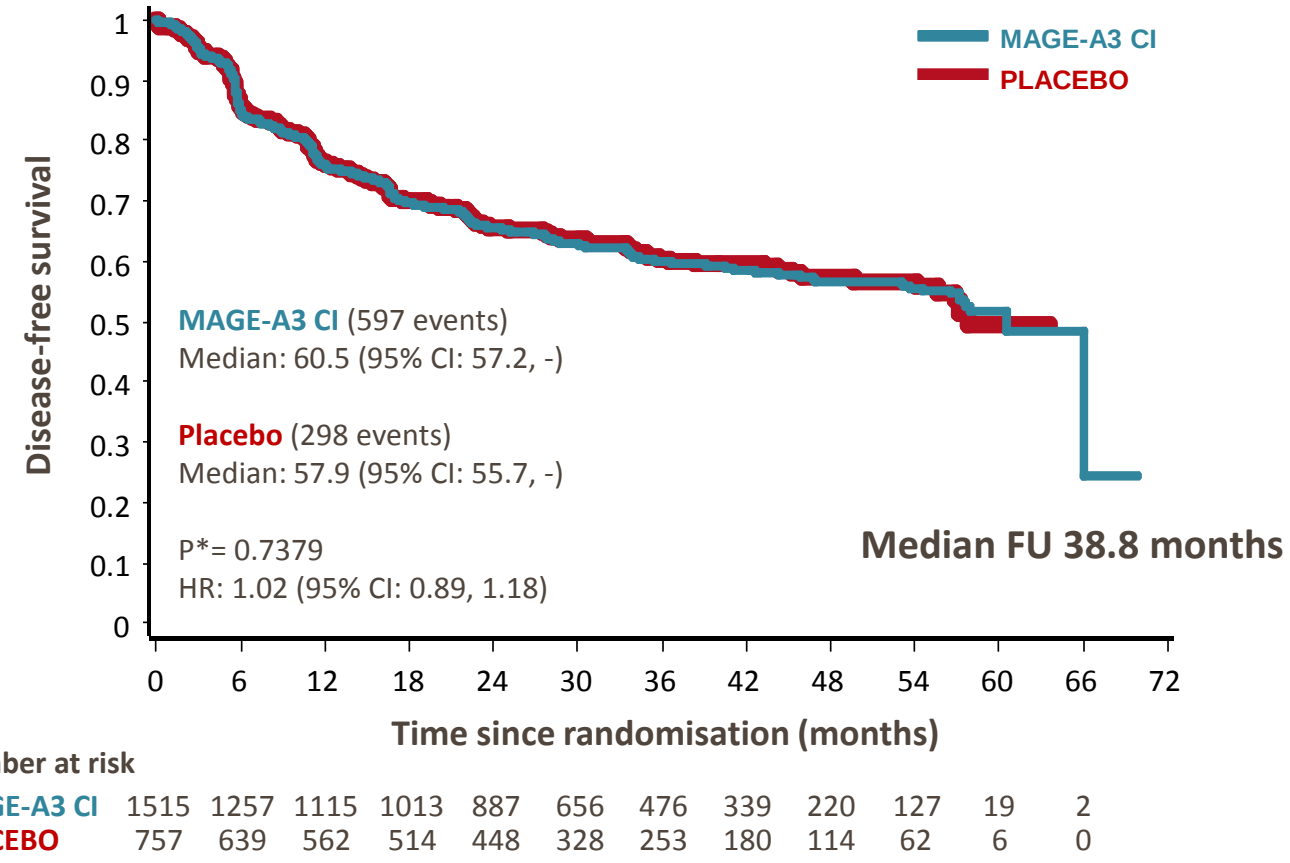
	MAGE-A3 CI N = 1,515	Placebo N = 757
Any AE (within 31 days of administration)	1,369 (90%)	556 (73%)
Treatment related AE	1,213 (80%)	191 (25%)
AE grade ≥ 3 (within 31 days of administration)	246 (16%)	122 (16%)
Treatment related AE grade ≥ 3	41 (3%)	10 (1%)
Serious AE (SAE)	330 (22%)	164 (22%)
Treatment related SAE	29 (2%)	8 (1%)
AE leading to treatment withdrawal	120 (8%)	54 (7%)
Treatment related AE leading to treatment withdrawal	53 (4%)	11 (1%)
AE leading to death	30 (2%)	17 (2%)
Treatment related AE leading to death	-	1 (<1%)
Potential Immune Mediated Disorders (pIMD)	31 (2%)	14 (2%)
Treatment related pIMD	15 (<1%)	7 (<1%)

MAGRIT: Drug Delivery



N – number of patients

MAGRIT: Disease-Free Survival in the Overall Population

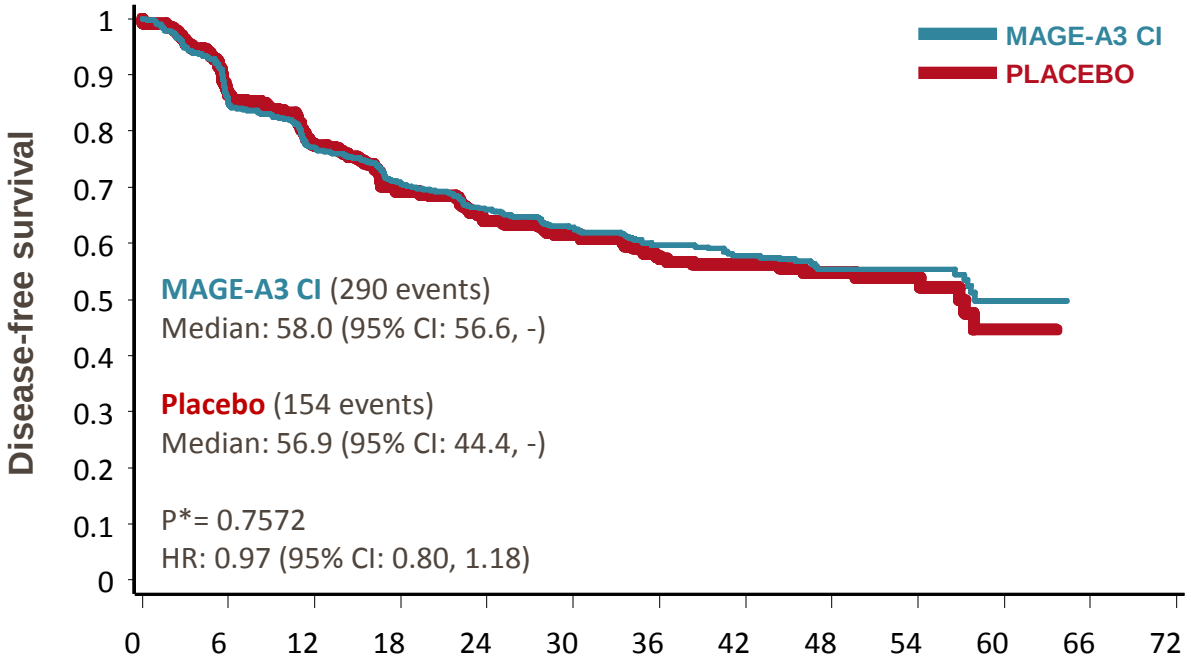


Number at risk

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.

MAGRIT: Disease-Free Survival in the No-CT Population

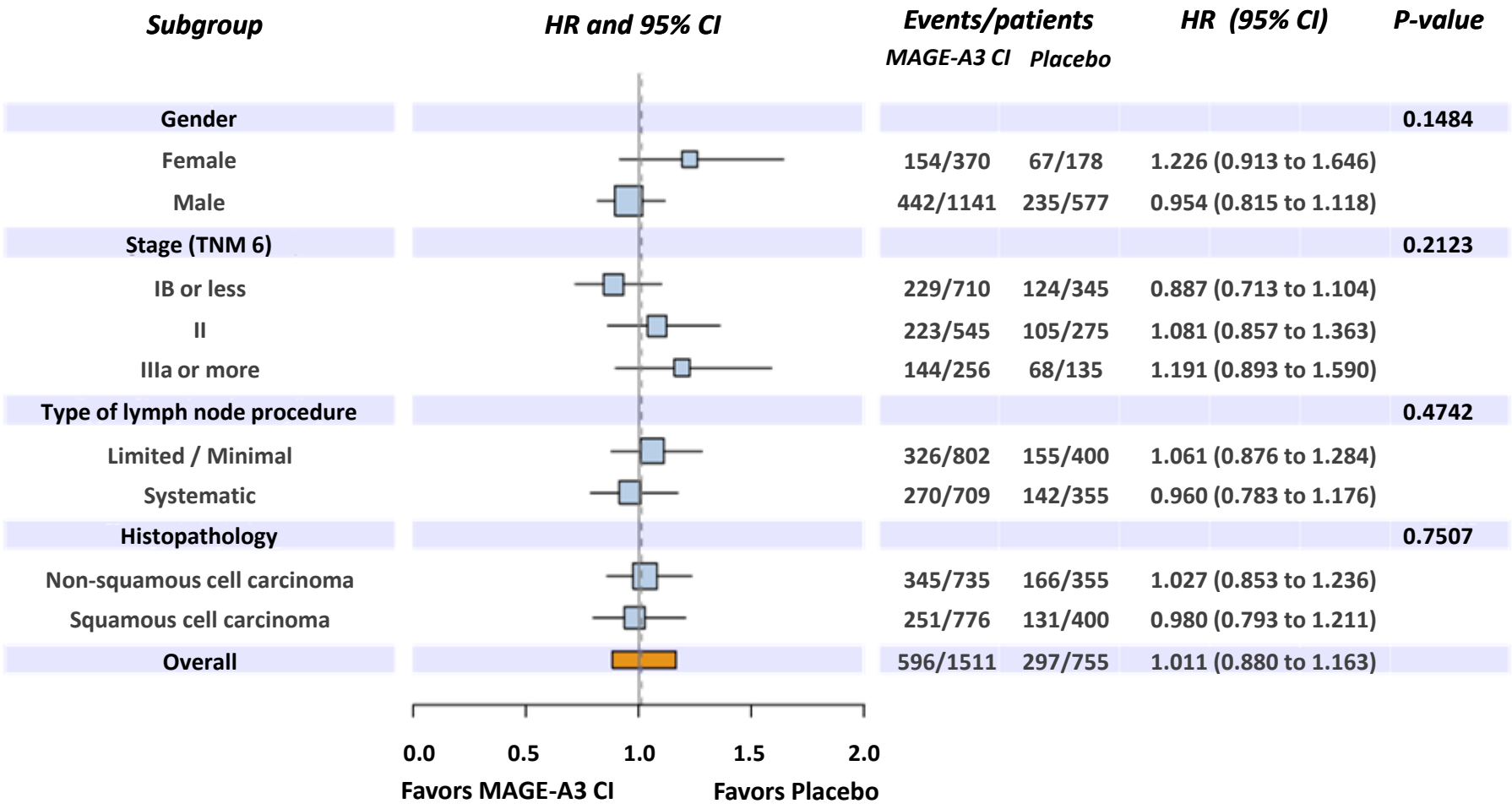


Number at risk

MAGE-A3 CI	731	604	541	492	440	324	243	176	113	66	11
PLACEBO	365	310	275	245	214	152	123	92	59	32	3

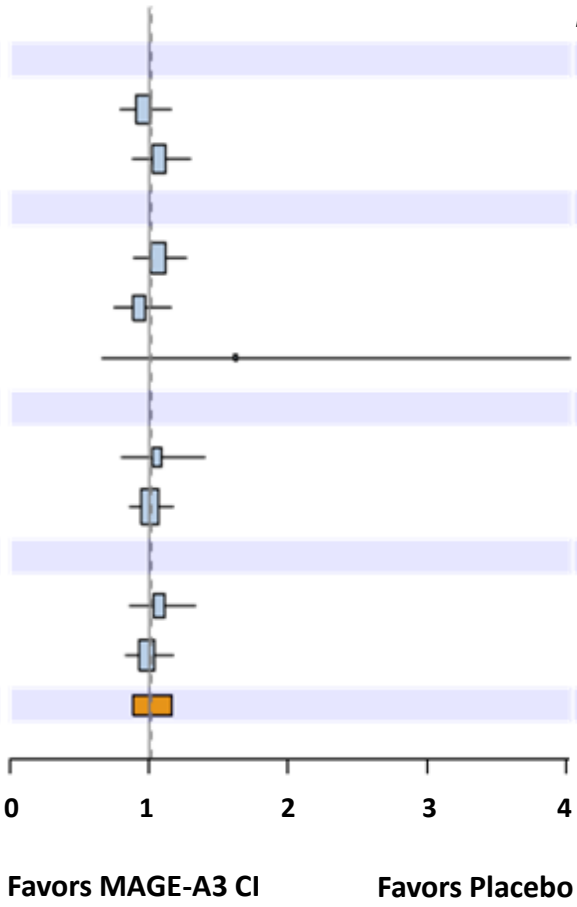
*Likelihood ratio test from cox regression model stratified by CT and adjusted for baseline variables used as minimization factors

MAGRIT: Disease-Free Survival by Key Covariates (1)

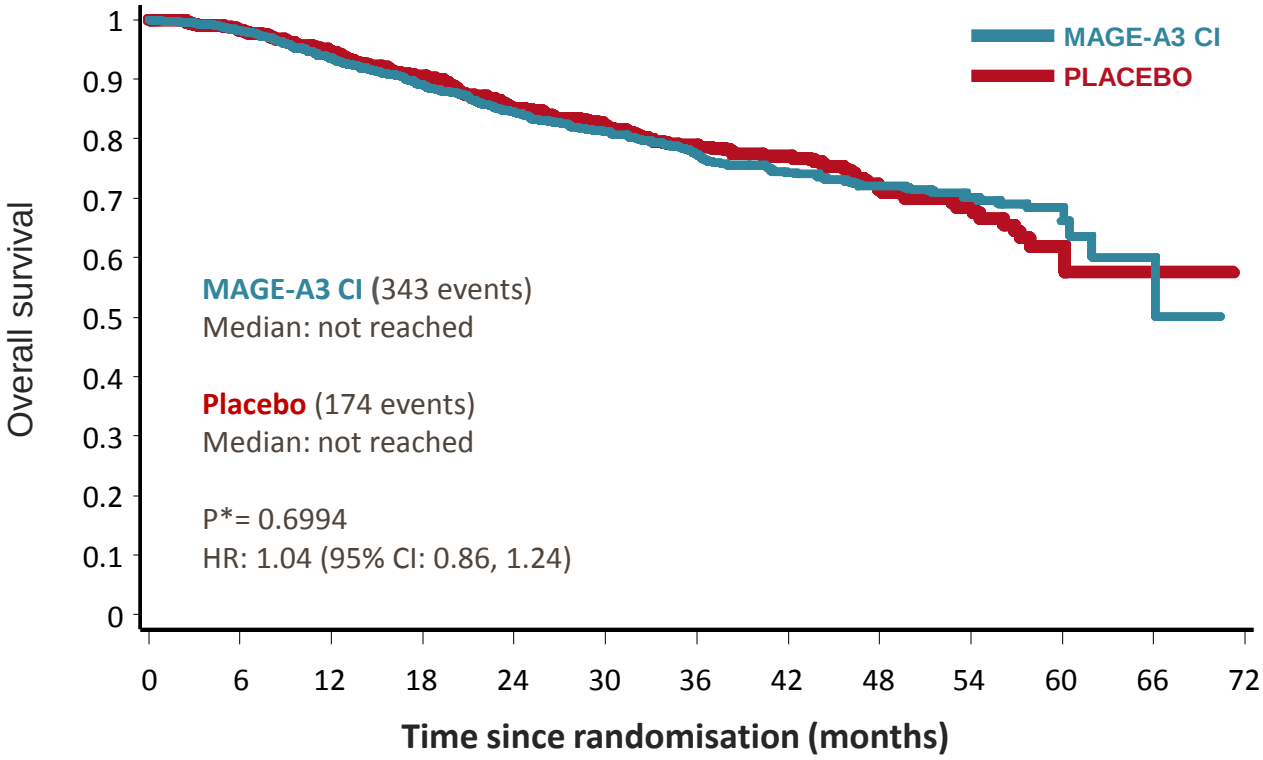


MAGRIT: Disease-Free Survival by Key Covariates (2)

Subgroup	HR and 95% CI	Events/patients MAGE-A3 CI	Events/patients Placebo	HR (95% CI)	P-value
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 quantitative 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)	



MAGRIT: Overall Survival in the Overall Population



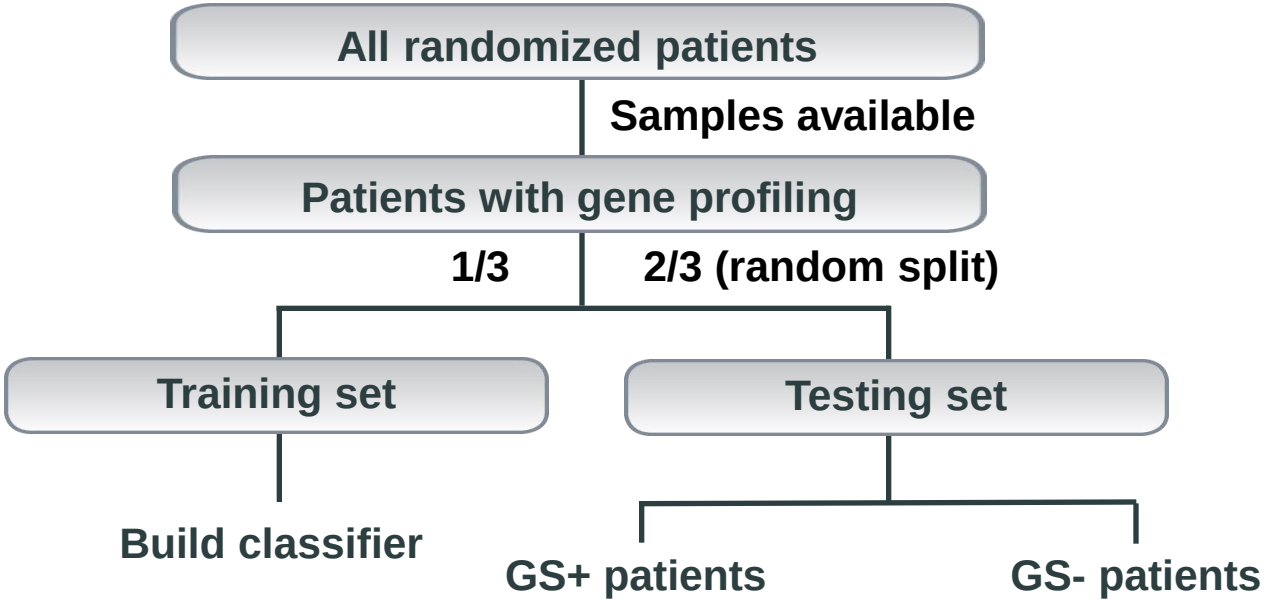
Number at risk

MAGE-A3 CI	1515	1459	1370	1273	1101	827	607	421	275	159	31	6
PLACEBO	757	731	693	654	570	427	330	235	145	78	14	5

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

MAGRIT: Search for the Predictive Gene Signature

- Design



- The intent of the training set was to search for a predictive tumor gene expression signature
- Due to the total absence of treatment effect in the training set, it was not feasible to assess the 3rd co-primary endpoint

Freidlin and Simon, *Clin Cancer Res* 2005

MAGRIT: Conclusions (1)

- 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
- MAGE-A3 CI generally well tolerated, adverse events mainly grade 1-2
  - No detectable increase in immune-mediated disorders
- No predictive GS could be identified

MAGRIT: Conclusions (2)

- 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

- Largest prospective study dataset on global contemporary approach to early stage NSCLC
  - Expected 5-year OS above 50% in both arms

MAGRIT: Acknowledgements

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- The authors would like to thank
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  - note: writing and coordination support was provided by XPE Pharma & Science and CromSource (on behalf of GlaxoSmithKline Biologicals SA)