

# TREATMENT OF HIGH-GRADE GLIOMA WITH SITIMAGENE CERADENOVEC GENE THERAPY: UPDATE OF PHASE III RESULTS

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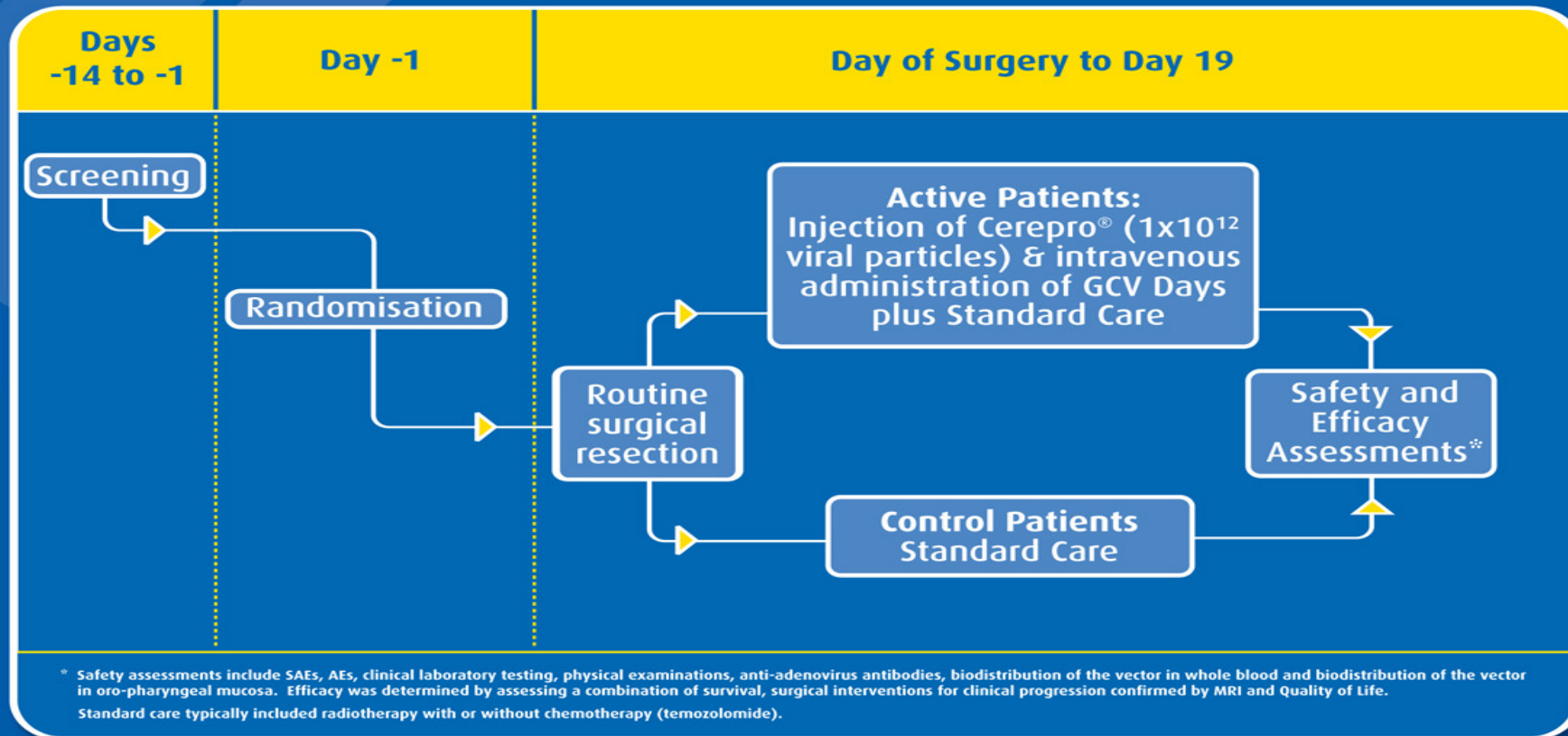
# ASPECT Study design

- Phase III, controlled, randomized, parallel group, multicentre study
- 40 sites in Europe and Israel
- Patients with operable primary high-grade glioblastoma
- 251 patients in 2 study arms:
  - Active group: one-time treatment with Cerepro<sup>®</sup> followed by intravenous GCV as an adjunct to standard therapy
  - Control group: standard therapy alone with no gene therapy or GCV
- Standard care included RT with/without CT (TMZ)
- Randomization in a 1:1 ratio

CT= chemotherapy; GCV=ganciclovir;  
RT=radiotherapy; TMZ=temozolomide.

# ASPECT Study Design

A Controlled, Randomised, Parallel Group, Multicentre Study of the Efficacy and Safety of Herpes Simplex Virus-Thymidine Kinase Gene Therapy (Cerepro<sup>®</sup>), with Subsequent Ganciclovir, for the Treatment of Patients with Operable High-grade Glioma



Cerepro<sup>®</sup> – sitimagene ceradenovec

GCV – Ganciclovir

ASPECT – Ark Study Proving the Efficacy of Cerepro<sup>®</sup> Treatment

# 904 Study endpoints

## Primary endpoint:

- To determine if Cerepro<sup>®</sup> / GCV is superior to standard care for the treatment of operable primary glioblastoma based on **time to re-intervention or death**\*

## Secondary endpoint:

- To determine if Cerepro<sup>®</sup> / GCV is superior to standard care for the treatment of operable primary glioblastoma based on **all-cause mortality**

\* NOTE: (re-intervention is defined as any kind of treatment [surgery, chemotherapy or radiotherapy] given to prolong survival after tumour recurrence)

# Study assessments

## Efficacy assessments

- Time to Re-intervention or death
- Survival
- Measurements of tumour by MRI
- Quality of life evaluations
- Karnofsky score

## Safety assessments

- CNS SAEs & AEs
- Laboratory
- ECG
- Vital signs

AE=adverse event; MRI=magnetic resonance imaging;  
SAE=serious adverse event.

# Analyses of the trial

## Intent-to-treat (ITT) population

- All randomized patients who have a GBM (as confirmed by histology –central review)

## Safety population

- All randomized patients

# Results

## Recruitment October 2005 to April 2007

- Countries: Germany, France, Belgium, UK, Poland, Finland, Czech Republic, Hungary, Israel – 40 centres
- 251 patients randomized
- 236 ITT (8 metastatic tumour, 1 died before operation, 1 bilateral tumour, 1 withdrew consent, 4 not HGG)
- 29 patients have not reached primary endpoint (18 Active & 11 Control)
- 56 (24%) patients remain alive (31 Active & 25 Control)

# Baseline characteristics

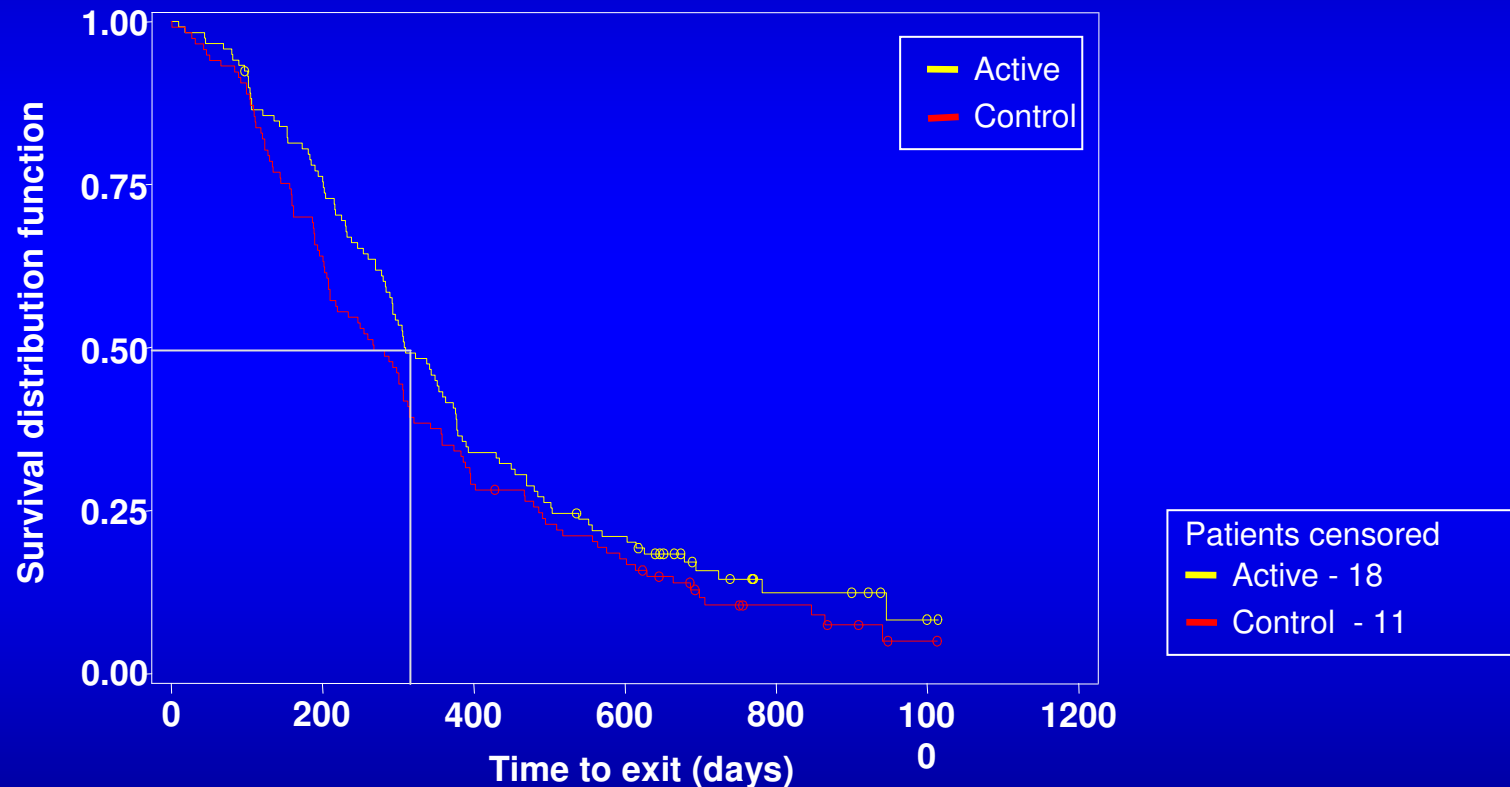
ITT	n	Age	Gender (M : F)	Karnofsky score		GBM
				≤70	>70	
<b>Cerepro®</b>	119	55.8	70 : 49	18 (15%)	101 (85%)	112
<b>Standard care</b>	117	55.1	76 : 41	11 (10%)	106 (90%)	111

**Groups well balanced for important prognostic factors**

# Statistical Analyses

1. KM plots
2. Survival analysis
3. MGMT introduced as a baseline covariate

# Kaplan-Meier – Primary endpoint (Time to re-intervention or death)



# Time to Primary Endpoint (ITT):

Standard Cox analysis per Statistical plan (intended TMZ.)  
All Base-line covariates March 2009

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	HR	95% CI	p-value
Cerepro compared with 'standard care' treatment group			
<b>Primary endpoint</b>	<b>1.43</b>	<b>(1.06-1.93)</b>	<b>0.02</b>

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# Temozolomide use (ITT)

Parameter	Active Group Stratified for Temozolomide Use				Control Group Stratified for Temozolomide Use			
	Yes (n=51)	No (n=32)	Unknown (n=36)	Overall (N=119)	Yes (n=51)	No (n=28)	Unknown (n=38)	Overall (N=117)
<b>Actual Temozolomide Use</b>								
Yes	39 (76.5)	7 (21.9)	12 (33.3)	58 (48.7)	39 (76.5)	11 (39.3)	26 (68.4)	76 (65.0)
No	12 (23.5)	25 (78.1)	24 (66.7)	61 (51.3)	12 (23.5)	17 (60.7)	12 (31.6)	41 (35.0)

Data source: 904 CSR Table 11.2

The non-randomized use of TMZ **required** (Regulators) additional analyses for Actual TMZ use (Time-dependent analysis)

# Time to Primary Endpoint (ITT)

Time dependent analysis (Actual TMZ use prior to Day 56 & Karnofsky Score at Day 19) March 2009

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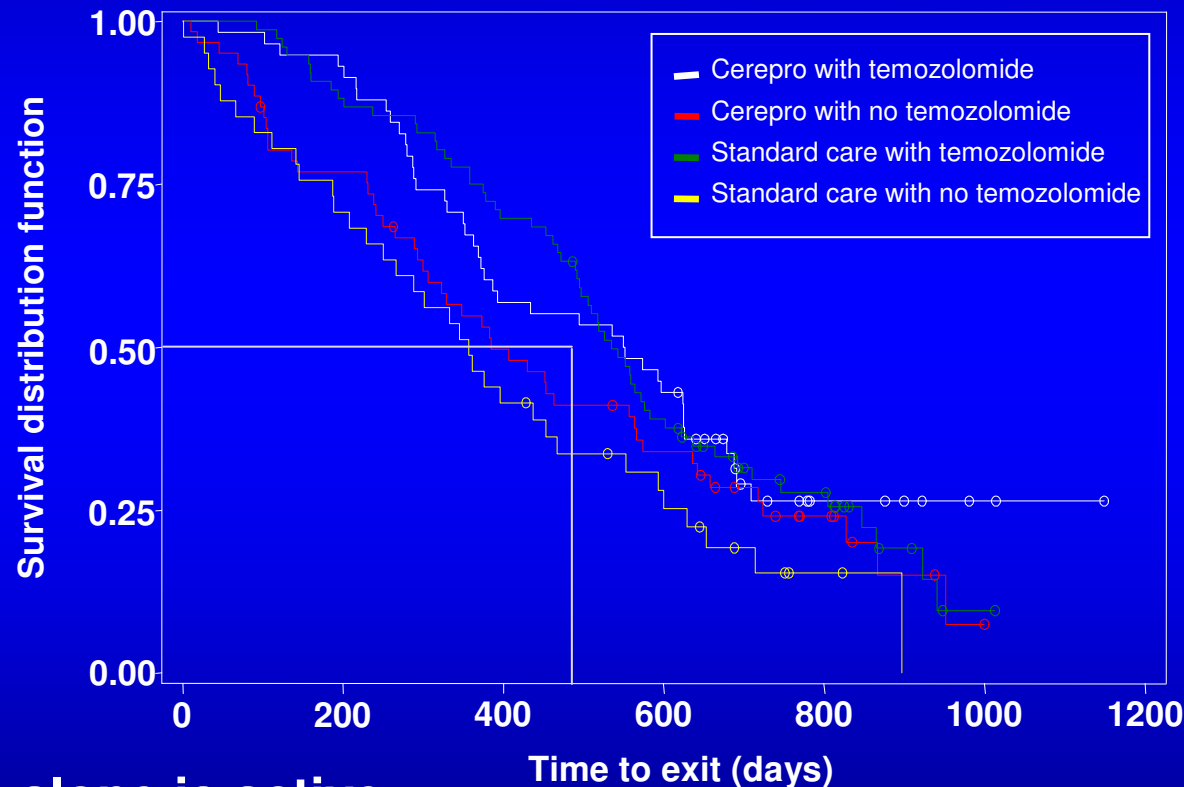
	HR	95% CI	p-value
Cerepro group compared with 'standard care' treatment group			
<b>Primary Endpoint</b>	<b>1.41</b>	<b>(1.05, 1.89)</b>	<b>0.022</b>

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Cerepro group - 48.6% received TMZ  
'Standard care' group - 65.0% received TMZ

Hazard ratios, and p-values for for both primary endpoint are calculated using a time dependent covariate analysis using temozolomide as a time dependent covariate with D19 KPS. Baseline covariates are age and treatment.

# Kaplan–Meier time to all-cause mortality: by actual temozolomide use



\*Cerepro alone is active

\*\*Cerepro in combination with TMZ – **27% of patients alive at > 3 years**

# Time to All Cause Mortality (ITT):

Time dependent analysis (Actual TMZ use prior to Day 56 & Karnofsky Score at Day 19) March 2009

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	HR	95% CI	p-value
Cerepro group compared with 'standard care' treatment group			
<b>Secondary Endpoint</b>	<b>1.29</b>	<b>(0.94, 1.77)</b>	<b>0.11‡</b>

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Cerepro group - 48.6% received TMZ  
'Standard care' group - 65.0% received TMZ

‡ ~ 24% of patients still alive

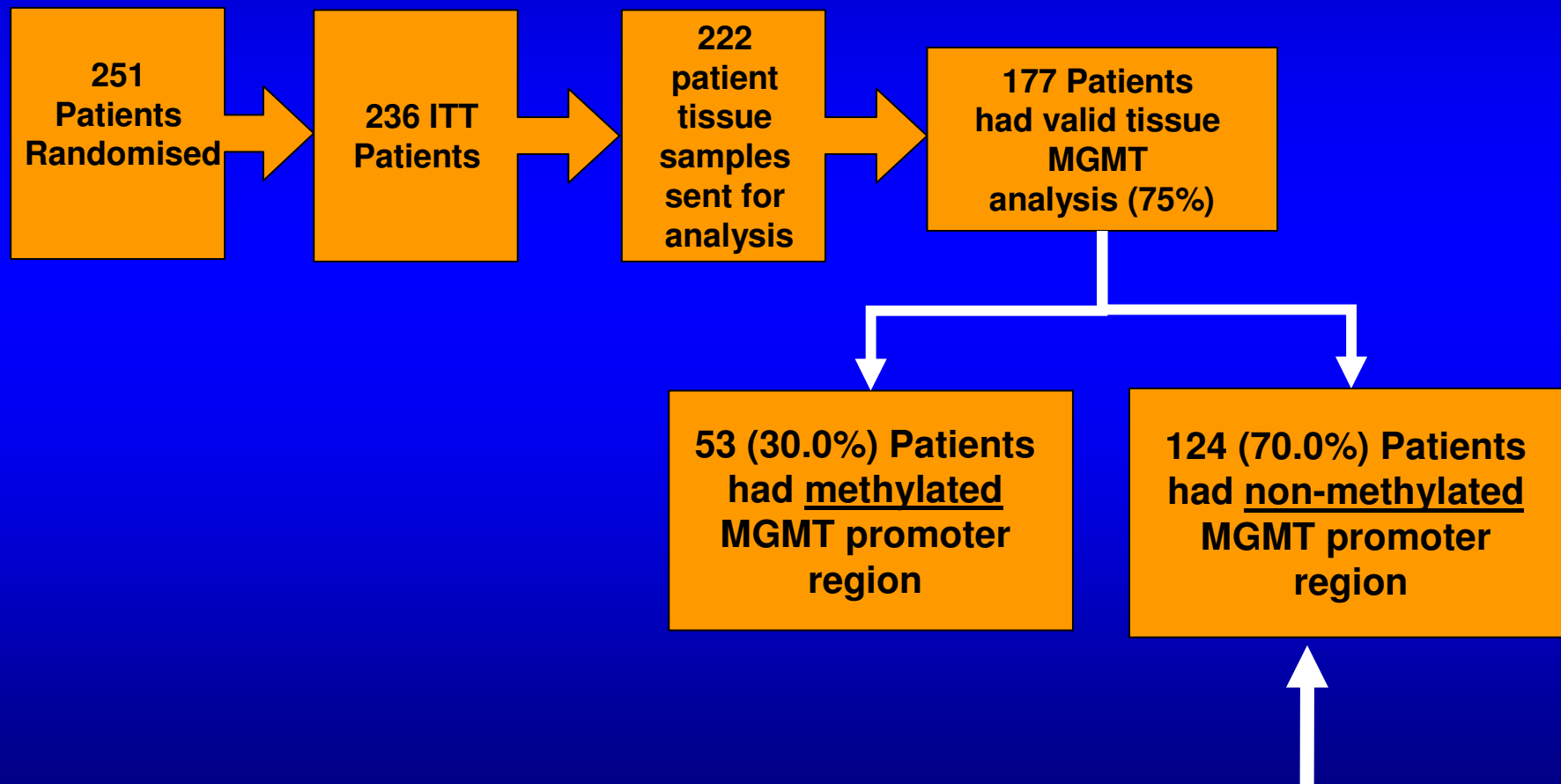
Hazard ratios, and p-values for for both primary endpoint are calculated using a time dependent covariate analysis using temozolomide as a time dependent covariate with D19 KPS. Baseline covariates are age and treatment.

# MGMT Analyses

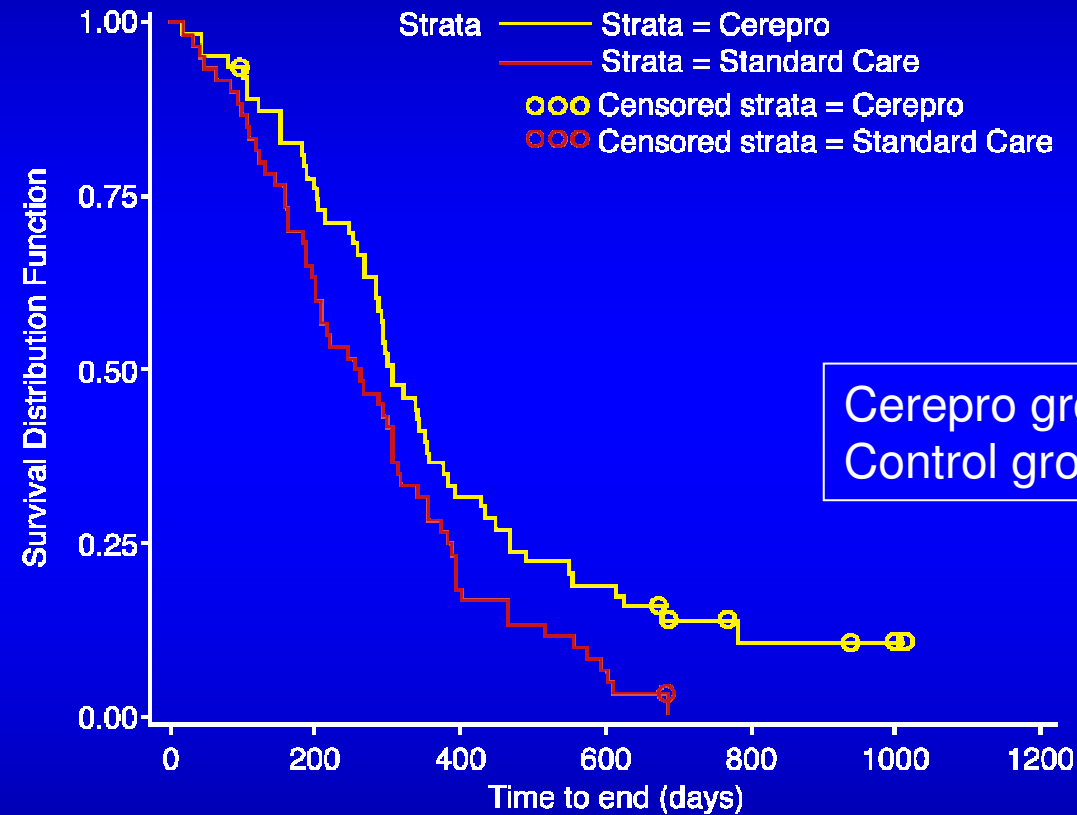
- The non-randomized use of TMZ created a statistical challenge.
- By analysing data from non-methylated MGMT promotor patients the effect of Cerepro is delineated (TMZ expected to be less effective)
- The majority of patients harbor unmethylated MGMT (~70%)
- MGMT analysis conducted by Oncomethylome Sciences B.V.

MGMT - O<sup>6</sup> –methylguanine-DNA methyltransferase promoter

# Tumor MGMT Analyses



# Time to Primary Endpoint : non-methylated MGMT promoter



Time to Re-intervention or Death (March 2009 update)  
for Non MGMT Responders: Intent-To-Treat Population

Cerepro group combined with TMZ - 63%  
'Standard care' group combined with TMZ - 80%

# Time to Primary Endpoint

Time dependent analysis (Actual TMZ D56  
& Karnofsky Score at D19) & MGMT status, March 2009

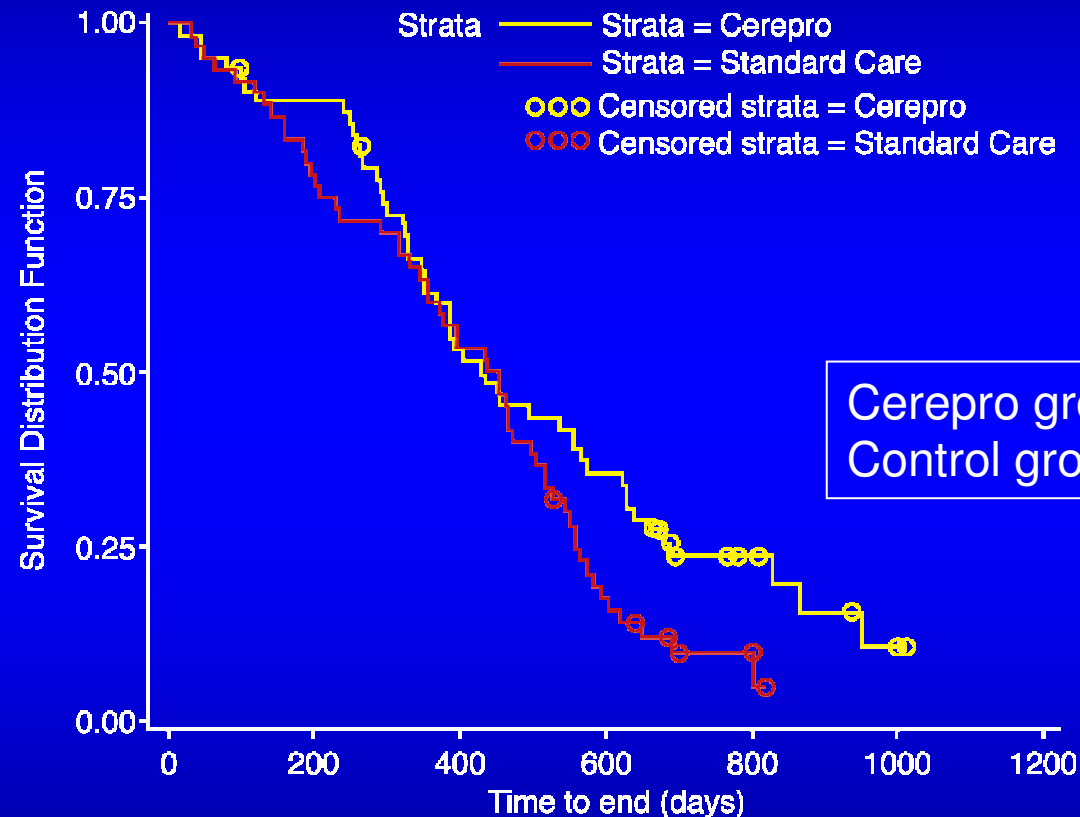
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	HR	95% CI	p-value
Cerepro group compared with 'standard care' treatment group			
<b>All MGMT assessed pts</b>	<b>1.68</b>	<b>(1.21, 2.32)</b>	<b>0.0017</b>
<b>Non-Methylated promoter pts</b>	<b>1.58</b>	<b>(1.05, 2.38)</b>	<b>0.027</b>

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Hazard ratios, and p-values for for both primary endpoint are calculated using a time dependent covariate analysis using temozolomide as a time dependent covariate with D19 KPS. Baseline covariates are age, MGMT and treatment.

# Time to all-cause mortality: non-methylated MGMT promoter



Time to Death (March 2009 update) for Non MGMT Responders:  
Intent-To-Treat Population

Cerepro group combined with TMZ - 63%  
'Standard care' group combined with TMZ - 80%

# Time to All Cause Mortality (ITT): Time dependent analysis (Actual Temo. D56 & Karnofsky Score at D19) & MGMT status, March 2009

	HR	95% CI	p-value
Cerepro group compared with 'standard care' treatment group			
<b>All MGMT assessed pts</b>	<b>1.43</b>	<b>(1.01, 2.02)</b>	<b>0.043</b>
<b>Non-Methylated promoter pts</b>	<b>1.51</b>	<b>(0.98 - 2.33)</b>	<b>0.059</b>

Hazard ratios, and p-values for both endpoints are calculated using a time dependent covariate analysis using temozolomide as a time dependent covariate with D19 KPS. Baseline covariates are age, MGMT and treatment.

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Safety data

# Focal Brain Injury AEs (904)

CNS AEs	Cerepro® (%)					Standard Care (%)				
	0-5 (N=124)	6-19 (N=124)	20-56 (N=124)	>56 days		0-5 (N=126)	6-19 (N=126)	20-56 (N=126)	>56 days	
	-	-	-	+TMZ (N=58)	-TMZ (N=66)	-	-	-	+TMZ (N=76)	-TMZ (N=50)
Seizures	6	10	3	34	14	5	2	2	39	12
Hemiparesis	12	2	3	19	18	6	<1	0	20	14
Aphasia	9	2	0	5	12	5	2	<1	13	12
Cerebral haematoma & haemorrhage	2	0	0	0	0	2	<1	0	1	0
Brain Abscess	0	0	<1	2	0	<1	0	0	0	0
Operative haemorrhage	2	0	0	0	0	0	0	0	0	0
Traumatic brain injury	<1	0	0	0	0	0	0	0	0	0

AEs – Adverse events

CNS=central nervous system.

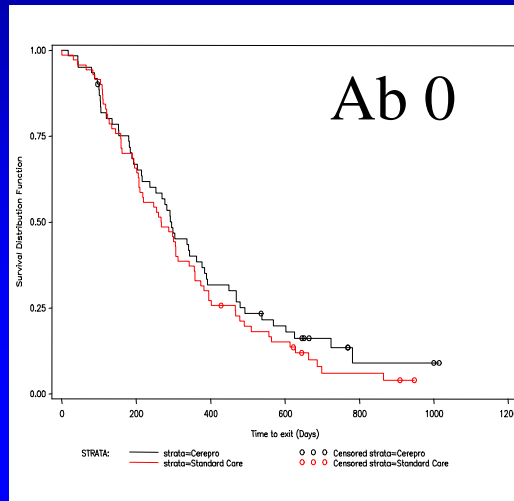
# Other Surgical, Local inflammatory AEs (904)

CNS AEs	Cerepro® (%)					Standard Care (%)				
	0-5 (N=124)	6-19 (N=124)	20-56 (N=124)	>56 days		0-5 (N=126)	6-19 (N=126)	20-56 (N=126)	>56 days	
	-	-	-	+TMZ (N=58)	-TMZ (N=66)	-	-	-	+TMZ (N=76)	-TMZ (N=50)
Brain oedema	5	2	2	3	5	3	0	0	13	2
Hydrocephalus	0	0	<1	9	5	0	<1	<1	4	0
Hyponatraemia (low blood sodium)	<1	7	<1	0	3	2	0	3	5	0
Intracranial pressure increased	0	<1	0	0	0	0	<1	0	0	0
Cognitive disorder	0	<1	<1	0	3	0	0	0	4	0
Decreased consciousness	<1	0	0	0	0	0	0	0	0	0

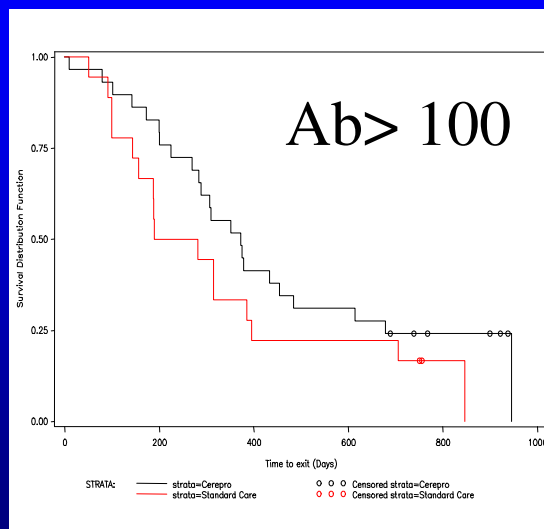
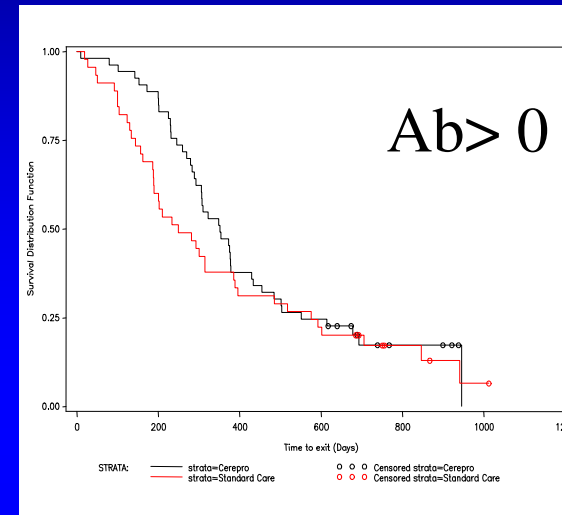
AEs – Adverse events

CNS=central nervous system.

# K-M of primary endpoint by antibody levels



-Cerepro  
-Standard care



Antibody level (n)	Hazard Ratio (95% CI)	P-value vs Standard care
0 (131)	1.29 (.86, 1.93)	0.221
>0 (98)	1.55 (.98, 2.45)	0.063
>100 (47)	2.17 (1.01, 4.64)	0.047

# Summary

1. Cerepro<sup>®</sup> gave a statistically significant effect in the primary endpoint (p=0.0017)
2. Cerepro<sup>®</sup> effect on 1<sup>°</sup> and 2<sup>°</sup> endpoints is similar in both MGMT methylated and non-methylated pts
  - Cerepro beneficial in all patients
3. Safety profile as expected for local therapy in the patient population
4. The role of an immune component is yet to be determined.

Q & A