Synopsis

TITLE OF STUDY
An open-label, randomised, Phase II study to investigate the efficacy and safety of ALECSAT treatment as an add-on therapy to radiotherapy and temozolomide in patients with newly diagnosed glioblastoma

INVESTIGATORS

- Principal Investigator, Dr. Katja Werlenius, Göteborg
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- Principal Investigator, Dr. Sara Kinhult, Lund

STUDY SITES

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PUBLICATIONS
In process

STUDY PERIOD	**DEVELOPMENT PHASE**
29th Marts 2016 to 24th February 2020 (Database lock 14 -Nov 2019)	Phase II

OBJECTIVES:

Primary Objective:

- To obtain preliminary but not conclusive evidence by analysing progression-free survival (PFS) in patients receiving autologous lymphoid effector cells specific against tumour cells (ALECSAT) as add-on therapy to radiotherapy and temozolomide (TMZ) (this combination is hereafter entitled standard of care, SOC) versus patients receiving SOC only.

Secondary Objectives:

a) To compare overall survival (OS) between patients who received ALECSAT as an add-on therapy to SOC versus patients who received SOC only.

b) To compare OS rate at 12 and 24 months between patients who received ALECSAT as an add-on therapy to SOC versus patients who received SOC only.

METHODOLOGY

This is a randomised, open-label, multi-centre, Phase II study in patients with newly diagnosed glioblastoma.

Up to 60 patients with newly diagnosed glioblastoma will be enrolled in the study in a 1:2 allocation (SOC vs ALECSAT + SOC).

Patients recruited into this study will receive either:

- ALECSAT as an adjunct therapy to SOC for newly diagnosed glioblastoma (first line therapy: Stupp regimen), followed by second line therapy at the Investigator's discretion, or
- SOC for newly diagnosed glioblastoma (first line therapy: Stupp regimen, followed by second line therapy at the Investigator's discretion).

Patients will be screened (Week -4 - 0) and will enter the study within six weeks of their glioblastoma resection. Eligible patients will be randomised to either ALECSAT treatment as an add-on therapy to SOC, or SOC only.

Patients will continue to complete the treatment phase. All patients will complete the radiotherapy phase of the Stupp regimen (radiotherapy ideally five days per week combined with daily TMZ for approximately six weeks (Weeks 1-6). Patients who terminate radiotherapy or TMZ treatment early for any reason will be allowed to remain in the study.

Patients will begin adjuvant TMZ treatment four to five weeks after completion of radiotherapy. Typically, six cycles of TMZ will be given (daily for five days every 28 days).

Alongside TMZ treatment, patients randomised to the ALECSAT treatment arm will receive three doses of ALECSAT at four-week intervals during the loading phase of the study (Weeks 8-16). Following the loading phase, patients will enter the maintenance phase. Patients in the ALECSAT treatment arm will receive further ALECSAT administrations during the maintenance phase at 12-week intervals except for the first maintenance dose, which is given after approximately 16 weeks have elapsed since the loading phase. The maintenance phase of ALECSAT administrations will continue for patients in the ALECSAT treatment arm until death or until a patient discontinuation criterion is observed or until closure of the study (24 months after recruitment has closed). After termination of the study, patients treated with ALECSAT will be offered to continue ALECSAT treatment in a compassionate use program.

Patients randomised to the control arm (Stupp treatment only followed by second line treatment at the discretion of the Investigator) will follow the same study plan and undergo the same study procedures as patients in the ALECSAT treatment arm (with the exception of blood donations for ALECSAT production, ALECSAT administrations and vital signs). After termination of the study, patients treated in the SOC arm will continue treatment as judged by the investigator.

The final analysis will be carried out when 47 events (investigator assessed progression or death by any cause) have been observed. Twenty-four months after recruitment to the study has closed, treatment and data collection for any patients still alive will end and the study will close. Any data collected for patients still alive after the point of final analysis (47 events) until study closure (24 months after recruitment has closed) will be analysed and included as an addendum to the final report.

There will be an independent Data Safety Monitoring Board (DSMB) performing annual review of all collected safety data.

NUMBER OF SUBJECTS PLANNED AND ANALYZED

Planned:

Up to 60 patients will be enrolled and the final analysis will be carried out when 47 events (investigator assessed progression or death by any cause) have been observed.

Analyzed:

61 subjects were enrolled and the results were analyzed after 47 events with a cut-off date 14th Nov 2019.
21 in the SOC arm and 40 in the ALECSAT /SOC arm

INCLUSION/EXCLUSION CRITERIA:

Inclusion:

1. Male or female patients, aged between 18 and 70.
2. Histologically confirmed, newly diagnosed glioblastoma, including gliosarcoma.
3. Eligible for combined radiotherapy and TMZ treatment (Stupp treatment).
4. Patients with complete or partial tumour resection. For patients with limited tumour volume, biopsy is acceptable.
5. WHO Performance status 0-2.
6. Body weight ≥ 40 kg (males), ≥ 50 kg (females).
7. Able and willing to provide written informed consent and comply with the study protocol and study procedures.
8. Women of child-bearing potential must have a negative pregnancy test at screening and agree to use acceptable methods of contraception during the study.

Exclusion:

1. Prior treatment for brain tumours at study entry.
2. Prior treatment with temozolomide at study entry
3. Females who are pregnant, planning to become pregnant or breastfeeding
4. Positive tests for anti- human immunodeficiency virus (HIV)-1/2; HBsAg, anti-HBc, anti-HCV or being positive in a Treponema Pallidum test (syphilis).
5. Patients who may have been exposed to high risk contagious virus within a reasonable time prior to enrolment should be excluded, unless the patient has been tested negative. e.g. by travelling in areas of the world with known high risk of infection or known epidemics, (in particular but not limited to West Nile virus (in season), Dengue fever, Zika or Ebola when outbreaks are recognized)
6. Patients from high incidence areas for Human T-Lymphotropic Virus (HTLV-1) virus or who has a parent or spouse from a high incidence area must be excluded unless tested negative for HTLV-1 virus.
7. Known allergy to study medication.
8. Any condition or illness that, in the opinion of the Investigator or medical monitor, would compromise patient safety or interfere with the evaluation of the safety of the investigational drug.
9. Any concurrent illness that may worsen or cause complications in connection with blood donation, for example uncontrolled epilepsy, cardiovascular, cerebrovascular or respiratory disease.
10. Use of immunosuppressant drugs with the exception of steroids.
11. Blood transfusion within 48 hours prior to the donation of blood for ALECSAT production.
12. Low haemoglobin count in the opinion of the Investigator.
13. Lymphocyte count $<0.3 \times 10^9$/litre.
14. Receiving any other experimental treatment, including compassionate use programs and other interventional clinical studies for glioblastoma, within 30 days prior to inclusion, at the moment of inclusion or during active treatment within the assigned group.

TMZ contraindication.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Product name: ALECSAT
Dose: 1 x 10^7 - 1 x 10^9 cells suspended in 20 ml plasmalyte solution

Pharmaceutical form: Suspension for injection
Route of administration: Intravenous

Patients randomized to ALECSAT treatment will also receive the SOC treatment

SOC TREATMENT:

The SOC therapy for newly diagnosed glioblastoma is the Stupp regimen. The Stupp treatment includes a combination of external radiotherapy (daily fractions of 2 Gy per fraction ideally five days per week up to a total dose of 60 Gy) and TMZ (75 mg/m^2) daily for approximately six weeks. Patients who terminate radiotherapy or TMZ treatment early for any reason will be allowed to remain in the study.

Patients then begin adjuvant TMZ treatment four to five weeks after completion of radiotherapy. Typically, six cycles of TMZ will be given (daily for five days every 28 days). TMZ will be administered orally at a dose of 150 mg/m^2 per day for the first treatment cycle. The dose of TMZ will increase to 200 mg/m^2 per day in the subsequent treatment cycles, in the absence of haematological toxicity. No other first line treatment is allowed.

Patients may also receive any second line/salvage therapy, at the discretion of the Investigator as per institutional routine.

DURATION OF TREATMENT

Dosing schedule: Loading phase (Weeks 8-16) - approximately three doses administered at approximately four-week intervals. Maintenance phase (from Week 18) - dose administered 12-week intervals except for the first maintenance dose which is given after approximately 16 weeks have elapsed since the loading phase until death or until a patient discontinuation criterion is observed or until closure of the study (24 months after last patient first visit (LPFV)).

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

SOC TREATMENT:

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Patients then begin adjuvant TMZ treatment four to five weeks after completion of radiotherapy. Typically, six cycles of TMZ will be given (daily for five days every 28 days). TMZ will be administered orally at a dose of 150 mg/m^2 per day for the first treatment cycle. The dose of TMZ will increase to 200 mg/m^2 per day in the subsequent treatment cycles, in the absence of haematological toxicity. No other first line treatment is allowed.

Patients may also receive any second line/salvage therapy, at the discretion of the Investigator as per institutional routine.

CRITERIA FOR EVALUATION – EFFICACY

Primary Endpoint:

- PFS is measured as the time from surgical resection to the date of investigator assessed progressive disease (PD) or death by any cause. PD will be declared based on MRI scans, clinical status, and corticosteroid usage according to the Revised Assessment for Neuro-Oncology (RANO) criteria.

Secondary Endpoints:

a) OS time is measured from time of surgical resection until death for any reason.

b) Proportion of patients alive at 12 and 24 months after randomization (1-year and 2-year OS).

CRITERIA FOR EVALUATION – PHARMACOKINETICS

Not applicable for this study.

CRITERIA FOR EVALUATION – SAFETY

Safety Objectives

- To assess the safety of ALECSAT treatment.

Safety Endpoints

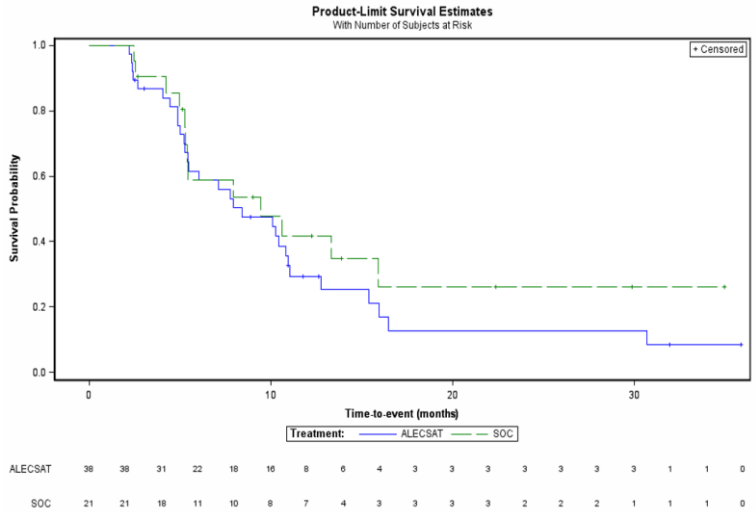
- Adverse events and pregnancies
- Safety laboratory parameters
- Immune system status

DEMOGRAPHY OF STUDY POPULATION

	SOC (N=21)	ALECSAT+SOC (N=40)
Age (yr)		
Mean (SD)	59.9 (7.3)	55.2 (9.0)
Median	62.0	55.5
Gender (%)		
Male	57.1	60.0
Female	42.9	40.0
WHO performance n, (%)		
0	10 (47.6)	19 (47.5)
1	10 (47.6)	19 (47.5)
2	1 (4.8)	2 (5.0)
Multifocal disease; n (%)		
Yes	0.0	2.5
No	21 (100.0)	40 (97.5)
Extend of surgery; n (%)		
Biopsy only	3 (14.3)	2 (5.0)
Complete	10 (47.6)	17 (42.5)
Partial	8 (38.1)	21 (52.5)
Time from radiological diagnosis to start radiotherapy (Days)		
Mean (SD)	41.4 (13.3)	41.5 (11.6)
Median (95% CI)	38.0 (35.4 - 47.5)	41.0 (37.5 - 44.9)
Time from resection to start radiotherapy (Days)		
Mean (SD)	34.4 (6.2)	32.5 (5.5)
Median (95% CI)	35.0 (31.6 - 37.2)	31.0 (30.7 - 34.2)
Steroid therapy at baseline n, (%)		
No	11 (52.4)	28 (70.0)
Yes	10 (47.6)	12 (30.0)
Mean dose (Betamethasone, mg)	0.3	0.2

EFFICACY RESULTS

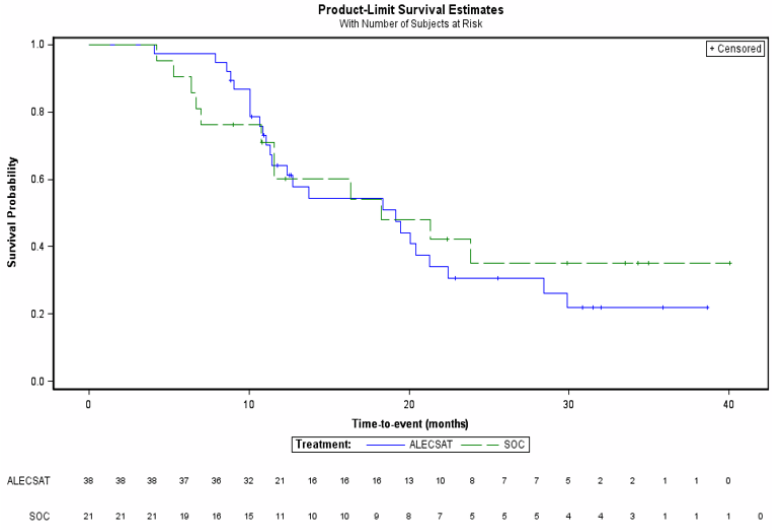
Progression free survival from randomisation to event (Per Protocol)



	SOC	SOC+ALECSAT	Estimate	P value	Method
	N=21	N=38			
Median time (months) (95% CI)	9.46 (5.26, 15.90)	8.41 (5.26, 10.94)			
Median time (months) (90% CI)	9.46 (5.29, 15.90)	8.41 (5.45, 10.81)			
Number of events observed	13	30			
Event rate (%)	61.9	78.9			
Number of censored patients (%)	8 (38.1)	8 (21.1)			
Hazard ratio (SOC+ALECSAT/SOC) (95% CI)			1.36 (0.71, 2.62)	0.349	Log-rank test
Hazard ratio (SOC+ALECSAT/SOC) (90% CI)			1.36 (0.79, 2.36)	0.349	Log-rank test
12-month probability of PFS (%, 95% CI)	41.7 (20.7, 64.5)	29.4 (15.6, 45.6)			
24-month probability of PFS (%, 95% CI)	26.1 (7.6, 50.6)	12.6 (3.0, 27.6)			

Study ID: CV-006, Program name: programs/T_2_1.sas, Run date: 13DEC19
FAS: Full analysis set. PP: Per protocol
PFS: Progression Free Survival. OS: Overall survival
Median time is derived from Kaplan Meier curve using time from random. to event.
PFS is measured as time to first date of either investigator assessed progressive disease (PD) or death by any cause.
Censored patients with event: 01-1013 (SOC), 02-1007 (SOC+ALECSAT), 03-1003 (SOC), 03-1010(SOC), 03-1011 (SOC+ALECSAT). All due to second line treatment prior event. Rest censored patients due to no event. Censoring date set to 14Nov2019 (database lock).
Log rank test was used with time dependent stratification representing the actual treatment.
One-sided 10% significance level is used, i.e. reported two-sided p-value must be below 0.2 to obtain statistical significance.
Random. = randomisation. EOS=end of study.

All over survival (Per Protocol)



	SOC	SOC+ALECSAT	Estimate	P value	Method
	N=21	N=38			
Median time (months) (95% CI)	18.27 (10.78, NA)	19.19 (11.30, 22.44)			
Median time (months) (90% CI)	18.27 (11.60, NA)	19.19 (11.43, 21.29)			
Number of events observed	12	25			
Event rate (%)	57.1	65.8			
Number of censored patients (%)	9 (42.9)	13 (34.2)			
Hazard ratio (SOC+ALECSAT/SOC) (95% CI)			1.16 (0.58, 2.32)	0.671	Log-rank test
Hazard ratio (SOC+ALECSAT/SOC) (90% CI)			1.16 (0.65, 2.07)	0.671	Log-rank test
12-month probability of OS (%, 95% CI)	60.2 (38.3, 80.1)	64.3 (48.1, 78.9)			
12-months odds ratio (SOC+ALECSAT/SOC)			1.06 (0.35, 3.17)	0.917	Logistic reg.
24-month probability of OS (%, 95% CI)	35.1 (14.8, 58.7)	30.6 (15.9, 47.7)			
24-months odds ratio (SOC+ALECSAT/SOC)			1.15 (0.39, 3.39)	0.800	Logistic reg.

Study ID: CV-006, Program name: programs/T_3_1.sas, Run date: 13DEC19
FAS: Full analysis set. PP: Per protocol
PFS: Progression Free Survival. OS: Overall survival
Median time is derived from Kaplan Meier curve using time from random. to event.
Event is measured as the time from randomisation to death
Censored patients did not have an event. Censoring date set to 14Nov2019 (database lock).
Log rank test was used with time dependent stratification representing the actual treatment.
One-sided 10% significance level is used, i.e. reported two-sided p-value must be below 0.2 to obtain statistical significance.
Random.=randomisation. Reg.=regression. EOS=end of study.

PHARMACOKINETIC RESULTS

Not applicable for this study

SAFETY RESULTS

	SOC (N=21)			SOC+ALECSAT (N=40)			Total (N=61)		
	n	(%)	E	n	(%)	E	n	(%)	E
All adverse event	21	(100.0)	445	40	(100.0)	1042	61	(100.0)	1487
AE >= grade 3	17	(81.0)	76	37	(92.5)	152	54	(88.5)	228
AE life-threatening	4	(19.0)	5	7	(17.5)	13	11	(18.0)	18
AE leading to death	12	(57.1)	12	24	(60.0)	24	36	(59.0)	36
AE related to ALECSAT	0	(0)	0	23	(57.5)	201	23	(37.7)	201
AE related to standard of care	21	(100.0)	213	40	(100.0)	477	61	(100.0)	690
AE leading to discontinued treatment	11	(52.4)	35	22	(55.0)	33	33	(54.1)	68
Serious adverse event	15	(71.4)	30	30	(75.0)	65	45	(73.8)	95
SAEs related to ALECSAT	0	(0)	0	9	(22.5)	12	9	(14.8)	12
SAEs related to SOC	4	(19.0)	7	8	(20.0)	11	12	(19.7)	18

Study ID: CV-006, Program name: programs/T_AE_summary.sas, Run date: 02DEC19
n = Number of subjects in treatment group having the adverse event. Subjects can be counted in more than one PT group.
% = Percentage of randomized subjects in treatment group having the adverse event.
E = Number of adverse events. Adverse events can be counted in only one PT group.
SAF: Safety analysis population, SOC: Standard of care, PT: Preferred term.
Related: the relationship between AE and the treatment is certain, probable or possible

CONCLUSION

- No statistically significant difference between the SOC+ ALECSAT group compared to the SOC group for the primary and secondary endpoints.
- A review on the immunomodulatory effect of cytostatic temozolomide on the lymphocytes could potentially negatively have an impact on the effect of ALECSAT (Karachi A et al, 2018)
- The results were consistent for the Per Protocol analyses (and all explorative analyses)
- There were no imbalances in baseline characteristics, demographics or laboratory parameters (lymphocyte and leukocyte count) of importance for the GBM prognosis that could explain the seemingly lack of ALECSAT effect on disease progression/overall survival

- Based on the provided data, the DSMB did not consider any safety issues as a barrier for further development of ALECSAT. There were no specific mitigations of AEs required for future trials.
- The trial CV006 is being closed down due to efficacy data and not safety concerns.