ESMO IMMUNO-ONCOLOGY
VIRTUAL CONGRESS

A PHASE I CLINICAL TRIAL ON INTRATUMORAL ADMINISTRATION OF IPILIMUMAB PLUS NIVOLUMAB FOLLOWED BY INTRACAVITARY ADMINISTRATION OF NIVOLUMAB IN PATIENTS WITH RECURRENT GLIOBLASTOMA

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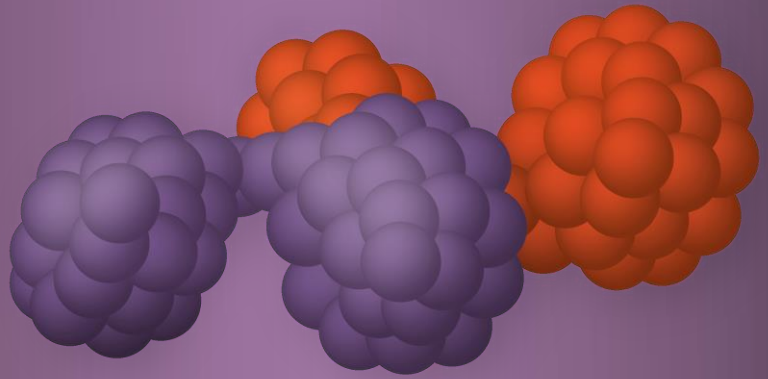

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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DISCLOSURE INFORMATION

Grants and non-financial support: Amgen, Merck Sharp & Dohme

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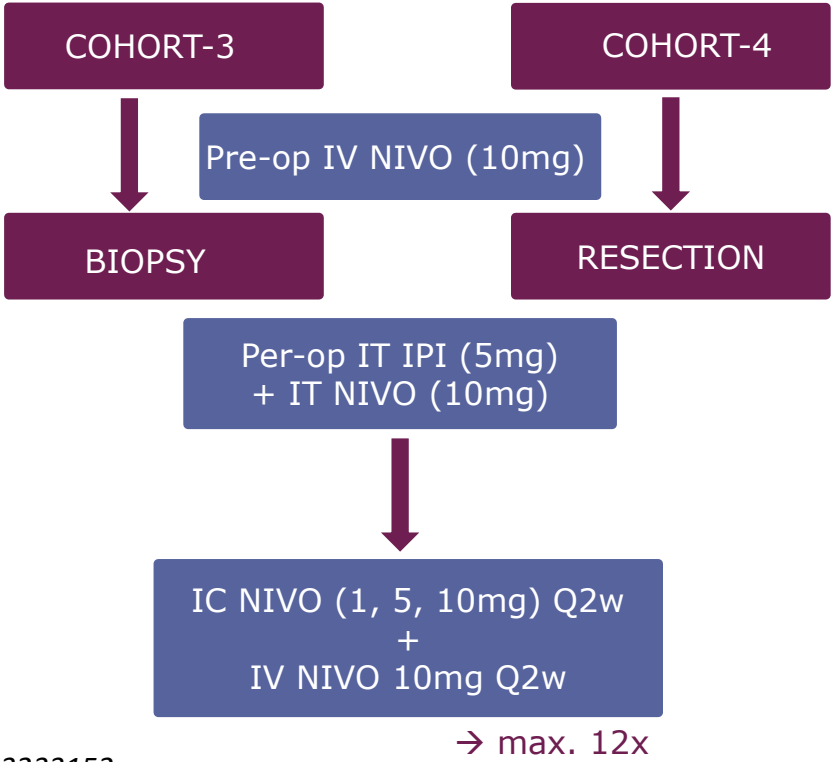
BACKGROUND & TRIAL DESIGN

- Intravenous (IV) administration of anti-PD-1 and anti-CTLA-4 monoclonal antibodies has low activity in patients with recurrent glioblastoma (rGB)
- Intratumoral (IT) and intracavitary (IC) administration of ipilimumab (IPI) and nivolumab (NIVO) is under evaluation in the **GlITIpNi** phase I clinical trial
- Feasible and safe in cohort-1 and -2 (Duerinck J, Schwarze JK et al, JITC 2021)

- **GlITIpNi** is a single-center, open-label phase I clinical trial.
- **Primary objectives:** safety (grading by CTCAEv5.0) and feasibility
- **Secondary objectives:** tumor response (iRANO), PFS, OS, tumor and CSF analysis (IHC, gene expression, cfDNA)



Clinical Trials.gov: NCT03233152

BASELINE CHARACTERISTICS & TREATMENT DISPOSITION

Baseline characteristics		COHORT 3 N (%) (N = 16)	COHORT 4 N (%) (N = 16)
Age (in years)	Median (range)	56 (38-74)	57 (42-77)
Sex	Male	11 (69)	12 (75)
	Female	5 (31)	4 (25)
ECOG PS	0	7 (44)	6 (38)
	1	5 (31)	7 (42)
	2	4 (25)	3 (20)
Primary histopathologic diagnosis	Glioblastoma (WHO grade IV)	12 (75)	14 (87)
	Anaplastic glioma (WHO grade III)	3 (19)	2 (13)
	Low-grade glioma (WHO grade II)	1 (6)	0 (0)
IDH1/2 mutation status	Mutant	3 (19)	0 (0)
	Wild-type	2 (12)	10 (62)
	Unknown	11 (69)	6 (38)
MGMT promotor methylation status	Methylated	2 (12)	3 (20)
	Unmethylated	1 (6)	3 (20)
	Unknown	13 (76)	10 (62)
1p/19q codeletion	Yes	1 (6)	0 (0)
	No	3 (19)	0 (0)
	Unknown	12 (75)	16 (100)
Prior surgical intervention	Resection	15 (94)	15 (94)
	Biopsy	1 (6)	1 (6)
Prior therapy at primary diagnosis	Surgery + concomitant RT/TMZ + adjuvant TMZ	10 (63)	16 (100)
	Surgery + chemotherapy only	1 (6)	0 (0)
	Surgery + STUPP + additional cycles of TMZ	2 (12)	0 (0)
	Surgery + sequential radiotherapy and/or chemotherapy (TMZ and other)	2 (12)	0 (0)
	Surgery + STUPP + additional chemotherapy other than TMZ	1 (6)	0 (0)
Prior therapy for recurrent disease	Surgery only	4 (25)	6 (40)
	Surgery + chemotherapy	2 (12)	3 (20)

RT: radiotherapy; TMZ: temozolomide

Treatment Disposition						
Cohort	Dose Level IC NIVO	N° enrolled patients	N° administrations IC NIVO	N° administrations IV NIVO	Stop due to PD	Stop due to tox
C3-01	1 mg	4	7.5 (3-12)	7.5 (3-12)		
C3-02	5 mg	6	4.5 (1-11)	4.5 (1-11)	n=10	n=4
C3-03	10 mg	6	3 (1-6)	3 (1-6)		
C4-01	1 mg	3	8 (4-8)	8 (4-8)		
C4-02	5 mg	4	4.5 (1-12)	4.5 (1-12)	n=6	n=7
C4-03	10 mg	9	3 (2-12)	3 (2-12)		

SAFETY

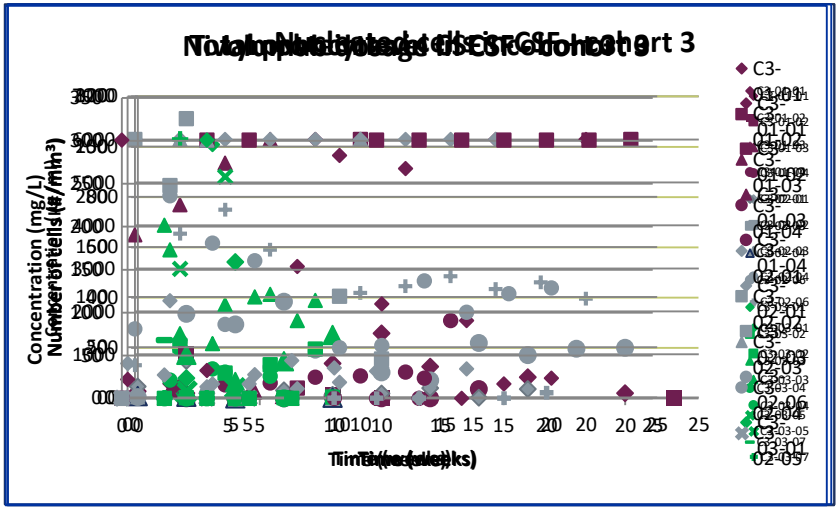
- No grade 4 or 5 AE
- No dose limiting toxicities
- Post-op need for corticosteroids in 1 pt (C3)

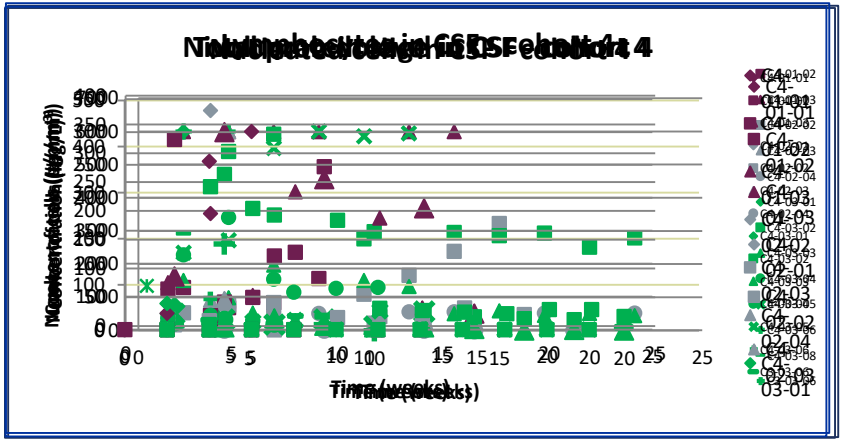
CTCAE type of AE	All AE (N=32)	Grade 1	Grade 2	Grade 3	Grade 4
Fatigue	26 (81%)	13	11	2	0
Headache	17 (53%)	12	4	1	0
Confusion	10 (31%)	7	3	0	0
Dysphasia	9 (28%)	5	4	0	0
Fever	9 (28%)	9	0	0	0
Nausea	9 (28%)	7	2	0	0
Hypertension	7 (22%)	3	3	1	0
Asthenia	7 (22%)	3	3	1	0
Seizures	5 (16%)	3	1	1	0
Pruritus	3 (9%)	2	1	0	0
Cerebral edema	3 (9%)	1	0	2	0
Subcutaneous CSF collection	2 (6%)	1	1	0	0
Wound excretion	2 (6%)	1	0	1	0
CSF infection	2 (6%)	0	0	2	0
Liver enzyme elevation	2 (6%)	2	0	0	0
Swelling craniotomy scar	2 (6%)	0	2	0	0
Infection ommaya catheter	2 (6%)	0	0	2	0
Dermatitis	2 (6%)	2	0	0	0
Chills	1 (3%)	0	1	0	0
CSF leakage at ressection site	1 (3%)	0	1	0	0
Hyperthyroidism	1 (3%)	0	1	0	0
Infusion-related reaction	1 (3%)	1	0	0	0
Irritation surgical wound	1 (3%)	1	0	0	0
Post-operative pain	1 (3%)	1	0	0	0
Psoriasis	1 (3%)	0	1	0	0

CEREBROSPINAL FLUID ANALYSIS

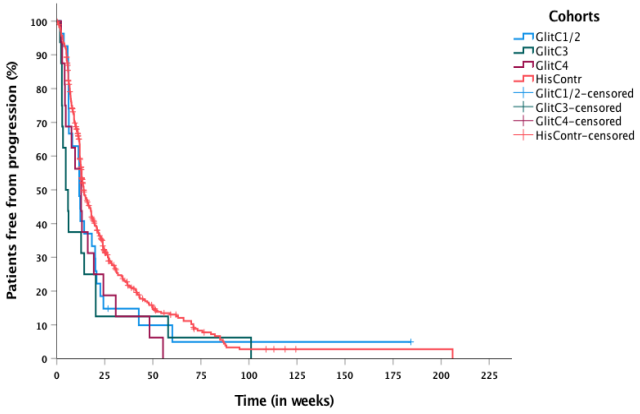
	Cohort	Number of patients	Number of samples	Above upper limit of detection
Elevated protein levels	C3	15 (94%)	58/62 (94%)	21 (34%)
	C4	13 (81%)	55/56 (98%)	10 (18%)
Elevated nucleated cell count	C3	12 (75%)	44/63 (70%)	
	C4	15 (94%)	51/63 (81%)	
Elevated lymphocytic cell count	C3	10 (63%)	37/37 (100%)	
	C4	14 (88%)	41/43 (95%)	

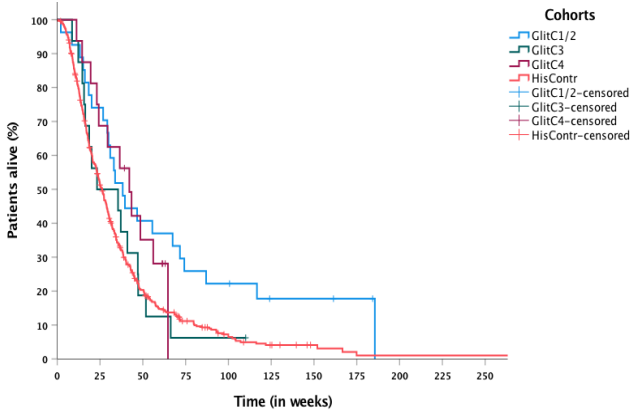
	Measured on N samples	Samples with measurable conc	Samples with conc below detection threshold
Free IPI conc	28	2/28 (7%)	26/28 (93%)
Free NIVO conc	132	40/132 (30%)	92/132 (70%)





SURVIVAL





Median PFS

- C3: 4.7 weeks (95% CI 1.4 – 8.1)
- C4: 12.7 weeks (95% CI 6.6 – 18.8)

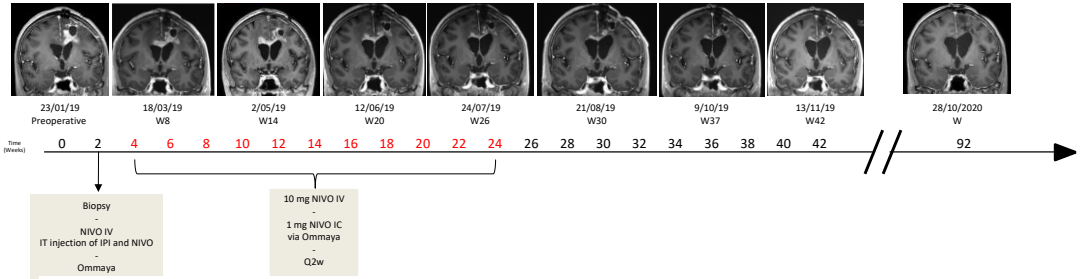
Median OS

- C3: 23.3 weeks (95% CI 0.0 – 53.5)
- C4: 42.1 weeks (95% CI 30.0 – 54.3)

Six-month OS rate

- C3: 50% (95% CI 25.5 – 74.5)
- C4: 68.8% (95% CI 46.1 – 91.5)

60y F, *de novo* glioblastoma, IDH1wt, MGMT-promotor unmethylated,
PD following concomitant RT/TMZ and 4 adjuvant cycles of TMZ



CONCLUSION

- Intracerebral administration of ipilimumab and nivolumab followed by repetitive intrathecal administration of nivolumab in patients with recurrent glioblastoma (rGB) in combination with low dose IV nivolumab is feasible & safe
- Further tissue & CSF analysis ongoing

Ongoing

- Additional cohorts investigating escalating doses of intrathecally administered ipilimumab
- Additional cohorts investigating intracerebral administration of autologous myeloid dendritic cells (BDCA-1+ / BDCA-3+)

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Acknowledgments

Patients & their caregivers

Research staff & co-authors

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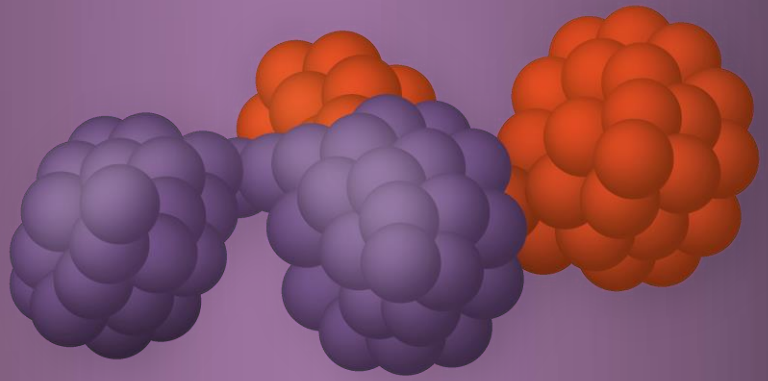
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