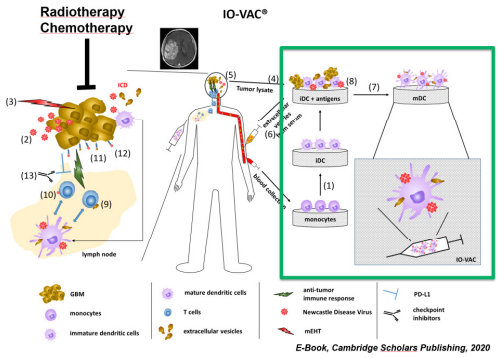
IOZK | NEW PERSPECTIVES IN CANCER THERAPY

Synergy between TMZ and individualized multimodal immunotherapy to improve overall survival of IDH1 wild-type MGMT promoter-unmethylated GBM patients

Stefaan W Van Gool, Jennifer Makalowski , Michael Bitar, Peter Van de Vliet, Volker Schirrmacher , Wilfried Stuecker
Immun-Onkologische Zentrum Köln, www.iozk.de
In press in Genes & Immunity

Introduction. The prognosis of IDH1 wild-type MGMT promotor-unmethylated GBM patients remains poor. Addition of Temozolomide (TMZ) to local treatment shifted the median Overall Survival (OS) from 11.8 to 12.6 months (Stupp et al. 2009). We retrospectively analysed the value of individualized multimodal immunotherapy (IMI) to improve OS in these patients. IMI consists of 1/ Immunogenic cell death (ICD) immunotherapy during 5 consecutive days: combined bolus injections of Newcastle Disease Virus (NDV) and sessions of modulated electrohyperthermia (mEHT); 2/ **IO-Vac®** dendritic cell vaccines (see below); 3/ Modulatory immunotherapy personalized for each patient; 4/ complementary medicines.

The principle of Individualized Multimodal Immunotherapy. During a vaccination cycle, immature dendritic cells (DCs) are differentiated *ex vivo* out of adherent peripheral blood monocytes in the presence of 800 U/ml IL-4 and 1000 U/ml GM-CSF. DCs are loaded on day 5 with autologous tumor antigens, obtained via tumor lysate or obtained from serum containing tumor-derived antigenic extracellular microvesicles and apoptotic bodies, induced via 5 daily **immunogenic cell death immunotherapies**. DC maturation is induced with NDV (10^5 infectious particles per 10^6 DCs) and a cytokine cocktail (1000 U/ml IL-6, 1100 U/ml TNF-a and 1900 U/ml IL-1b). **Active specific immunotherapy**: an intradermal injection of autologous loaded mature DCs is administrated on day 8, combined with an extra ICD immunotherapy. Two full vaccination cycles are administered with three weeks interval. **Modulatory immunotherapy** is defined for each patient. ***IO-VAC® is an approved medicinal product by the German authorities (DE_NW_04_MIA_2015_0033, DE_NW_04_MIA_2020_0017).***

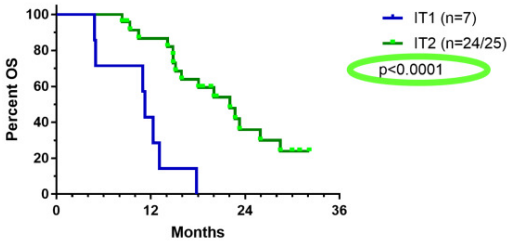


E-Book, Cambridge Scholars Publishing, 2020

	Group-1			Group-2		
	Clinical data					
	P25	**Median**	**P75**	**P25**	**Median**	**P75**
Age	36	49	69	41.5	46	57.5
KPI	50	70	95	70	90	100
	R0	**R1**	**ND**	**R0**	**R1**	**ND**
Surgery	1	4	2	10	8	7
Laboratory data						
	Low	**Normal**	**High**	**Low**	**Normal**	**High**
Hemoglobin		7		3	21	1
White Blood cells	1	5	1	2	19	4
Platelets	4	3		5	20	
T cells	2	4		13	12	
B cells	6			22	2	1
NK cells	3	3		15	10	
NK cell function	5		1	13	8	2
CD4 IFNg	1	4		1	19	2
CD4 IL4	1	5		2	13	8
	CCC-	**CCC+PDL1-**	**CCC+PDL1+**	**CCC-**	**CCC+PDL1-**	**CCC+PDL1+**
CCC	2	2	1	9	9	5
Treatment data						
	P25	**Median**	**P75**	**P25**	**Median**	**P75**
IO-Vac®	1	2	2	1	2	2
Total DCs	11600000	15400000	38300000	7200000	24000000	36450000
Total NDV injections	6	15	24	24	42	47
Total mEHT sessions	4	11	24	17	39	46

Patients. All adults who met the selection criteria (primary GBM, first line treatment, adults 18-75y, IDH1wt, MGMT promoter-unmethylated) and were treated between 06/2015 and 06/2021 were selected. Thirty-two patients (12f, 20m) had a median age of 47y (range 18-69) and a KPI of 70 (50-100). Extent of resection was complete (11), <complete (12) or not documented (ND, 9). Seven patients were treated with surgery/radio(chemo)therapy and subsequent **IO-Vac®** and maintenance ICD therapy (Group-1) without maintenance TMZ (TMZm refused by the patient because of the MGMT promoter methylation status); 25 patients were treated with radiochemotherapy followed by TMZm plus ICD therapy (days 8 to 12) during each TMZm course, and subsequent **IO-Vac®** and maintenance ICD therapy (Group-2). Age, KPI, extent of resection, general immune variable, and circulating cancer cells (CCC) were not different amongst both groups. The number of **IO-Vac®** treatments between both groups was equal. Group-2 received more ICD therapies.

IT1: Local therapy -> immunotherapy: **n = 7**
IT2: Surgery -> radiochemotherapy -> TMZm+ICD -> immunotherapy: **n = 25**



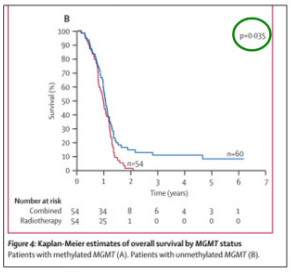


Figure 4: Kaplan-Meier estimates of overall survival by MGMT status
Patients with methylated MGMT (A). Patients with unmethylated MGMT (B).

Results. The median OS of group-1 patients was 11m (2y OS: 0%). Surprisingly the median OS of group-2 patients was 22m with 2y OS of 36% (CI95%: 16-57), which was significantly (Log-rank: p = 0.0001) different from group-1. Addition of immunotherapy to the Standard of Care treatment was very well tolerated without additional severe adverse reactions. The data are compared with the subanalysis of MGMT promoter-unmethylated GBM patients, published by Stupp et al. Lancet Oncol 2019.

mOS months	Median OS	2y OS
S + RT (Stupp, 2009)	*11.8*	*1.8% (0.1-8.6)*
S + RT + **IO-Vac® + ICDm**	**11.25**	**0%**
S + RCT + TMZm (Stupp, 2009)	*12.6*	*14.8% (7-2-25)*
S + RCT + TMZm/**ICD + IO-Vac® + ICDm**	**22.07**	**36% (15.7-56.8)**

Conclusion. The data of our retrospective analysis suggest that addition of IMI after local therapy on its own has no relevant effect on OS in these GBM patients, similar to the addition of maintenance TMZ. However, the combination of both TMZ + IMI during and after TMZm significantly improves OS.