Multimodal immunotherapy with IO-Vac® for patients with GBM: a single institution experience

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IOZK | NEW PERSPECTIVES IN CANCER THERAPY

Multimodal immunotherapy with IO-Vac® for patients with GBM:

a single institution experience

Stefaan W. Van Gool, on behalf of the IOZK Team

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Standard of care; Stupp 2005, 2009
Neurosurgery + radiochemotherapy + chemotherapy

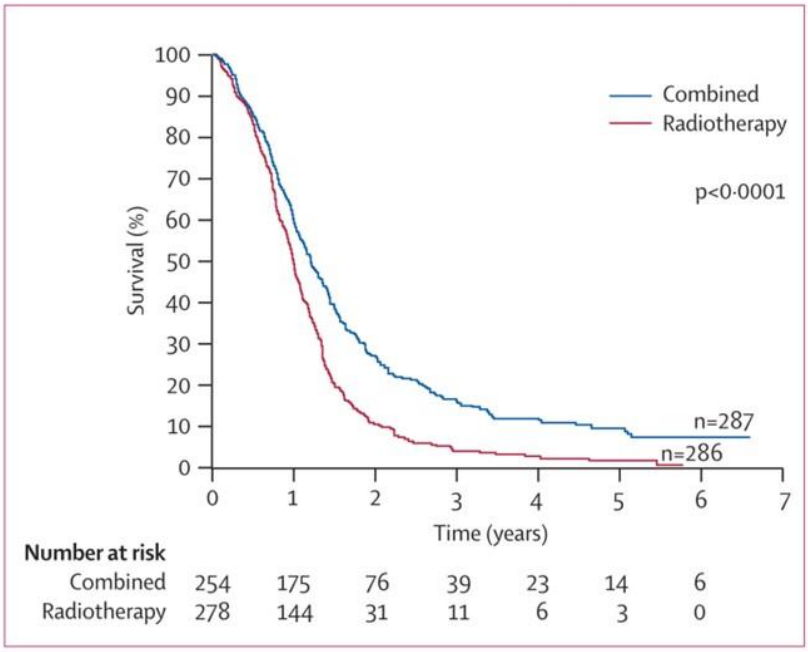

Figure 2: **Kaplan-Meier estimates of overall survival by treatment group**

1

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Standard of care; Stupp 2005, 2009
Neurosurgery + radiochemotherapy + chemotherapy

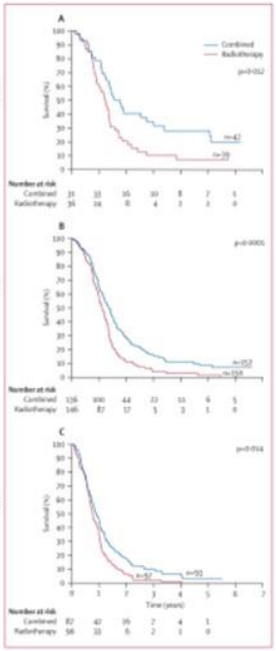
Stratification in randomization
WHO performance; Extent of resection; Treatment center

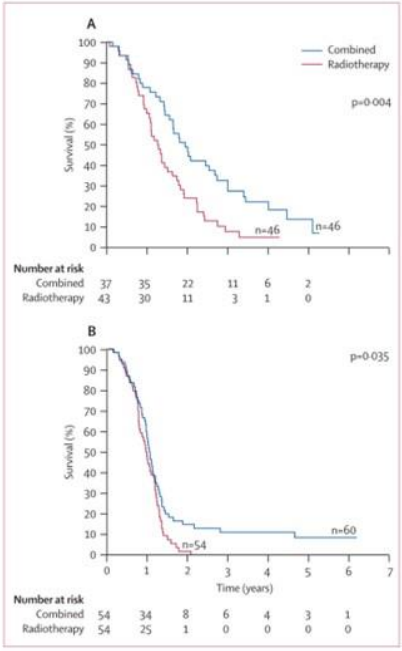
Post-hoc Subgroup analysis
MGMT promoter methylation status

RPA3

RPA4

RPA5





2

Phase I / phase II trials; DC vaccination for GBM

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Efficacy and safety of dendritic cell vaccines for patients with glioblastoma: A meta-analysis of randomized controlled trials

Li Lv[1], Jiangchao Huang[1], Haipeng Xi, Xiangyang Zhou*

Department of Neurosurgery, First Affiliated Hospital, University of South China, Hengyang 421001, Hunan Providence, China

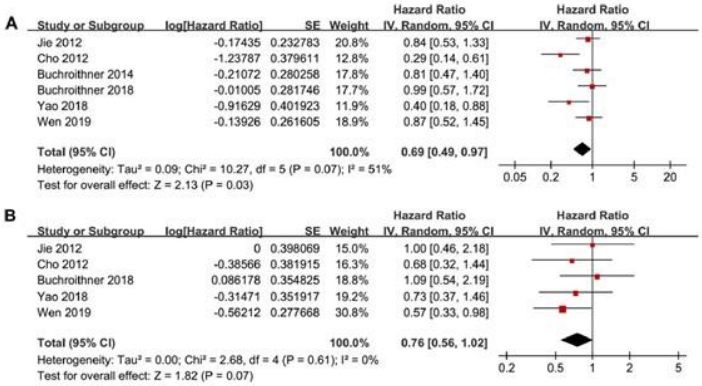

Fig. 2. Forest plots for the meta-analyses comparing the efficacy outcomes between DC-based vaccination and control for glioblastoma; A, overall survival; and B, progression-free survival;

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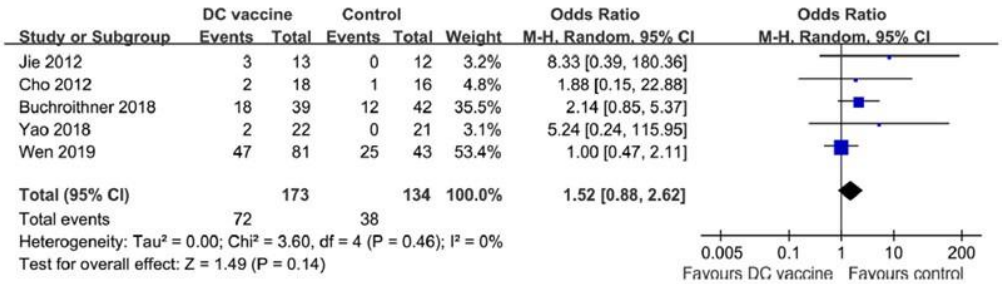


Fig. 3. Forest plots for the meta-analyses comparing the overall incidence of adverse events in patients with glioblastoma allocated to DC-based vaccination and control groups;

Oxford centre for evidence

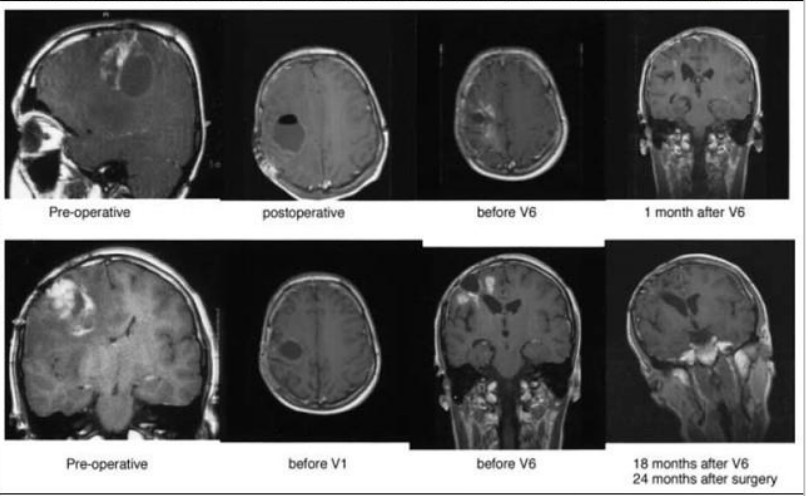
Level	Therapy/prevention, aetiology/harm	Prognosis
1a	SR (with homogeneity*) of RCTs	SR (with of incepti ies; CDR different
1b	Individual RCT (with narrow Confidence Interval‡)	Individua hort stud follow-up ted in a si
1c	All or none§	All or nor
2a	SR (with homogeneity*) of cohort studies	SR (with of either cohort stu ted contro RCTs
2b	Individual cohort study (including low quality RCT; e.g., < 80% follow-up)	Retrospec study or treated co als in an R of CDR† split-samp
2c	"Outcomes" Research; Ecological studies	"Outcome
3a	SR (with homoge- neity*) of case-control studies	
3b	Individual Case-Control Study	

J Neurosurg (Pediatrics 5) 100:492–497, 2004

Transient local response and persistent tumor control in a child with recurrent malignant glioma: treatment with combination therapy including dendritic cell therapy

Case report

Steven De Vleeschouwer, M.D., Frank Van Calenbergh, M.D., Philippe Demaerel, M.D., Ph.D., Patrick Flamen, M.D., Ph.D., Stefan Rutkowski, M.D., Eckhart Kaempgen, M.D., Ph.D., Johannes E. Wolff, M.D., Ph.D., Christian Plets, M.D., Ph.D., Raf Sciot, M.D., Ph.D., and Stefaan W. Van Gool, M.D., Ph.D.



analyses incorporating clinically sensible variations.

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frontiers in Oncology

REVIEW
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Brain tumor immunotherapy: what have we learned so far?

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HGG-2006

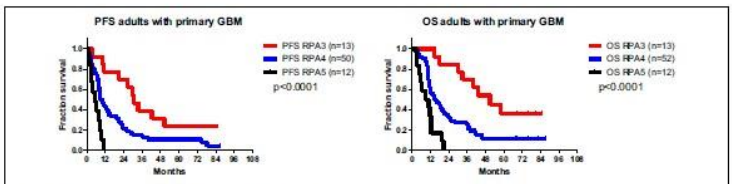

FIGURE 4 | PFS and OS of adults with primary diagnosis of GBM.

HGG-2010
RCT

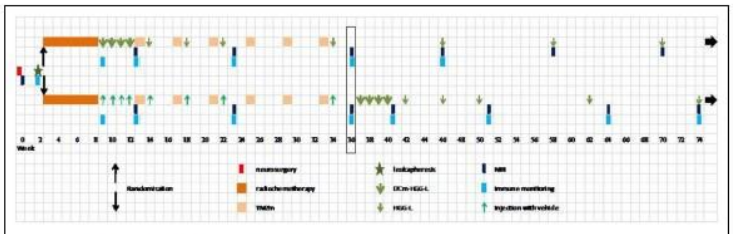

FIGURE 5 | Outline of the phase IIb randomized clinical trial HGG-2010.

Table 1. Risk factors for stratification in randomization or for in/exclusion criteria.

1. Recursive Partitioning Analysis (RPA) clinical classification
   - Grading
   - Extent of resection
   - Age
   - Karnofsky performance index
   - Mental status
   - Dose of radiotherapy
2. Molecular biology of tumor
   - Tumor mutational burden
   - Epigenetic sub-typing
   - Molecular machinery of tumor cell clones
   - Metabolic features of tumor
3. Load of glioma cancer stem cells in connection to periventricular zones of the brain
4. Tumor–host immune reaction
   - Tumor antigen expression
   - Check point expression
   - Inflammatory response, M1/M2 balance, Tumor-associated macrophages, myeloid-derived suppressor cells, microglia reactivity
   - T-cell infiltration
   - Vascularization and oxidative stress
5. Systemic immune compartment
   - Cell numbers under standard of care treatment
   - Th1/Th2 balance
   - Presence of Treg
   - Presence of MDSC
   - Level of natural killer cell reactivity
6. Systemic treatments outside standard of care
   - Steroids
   - Anti-angiogenic drugs
   - Complementary medicines

Van Gool, Cancers 2021

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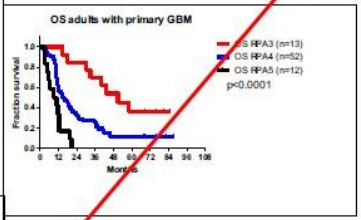
REVIEW
published: 17 June 2015
doi: 10.3389/fonc.2015.00098

mmunotherapy: what ned so far?

y, KU Leuven, Leuven, Belgium

Stratifications
Ethical issues
GLP/GTP/GMP/GCP
Costs



Ardon, 2010
Ardon, 2012

HGG-2010
RCT

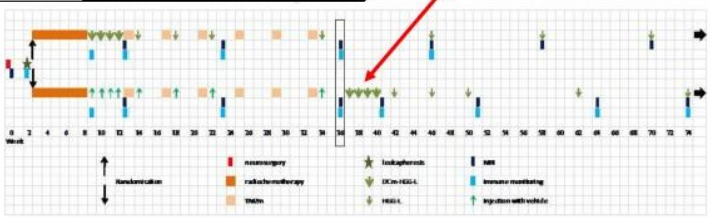


FIGURE 5 | Outline of the phase IIb randomized clinical trial HGG-2010.

Antonopoulos, 2019
Dejaegher, 2021

ANTICANCER RESEARCH *39*: 2043-2051 (2019)
doi:10.21873/anticanres.13315

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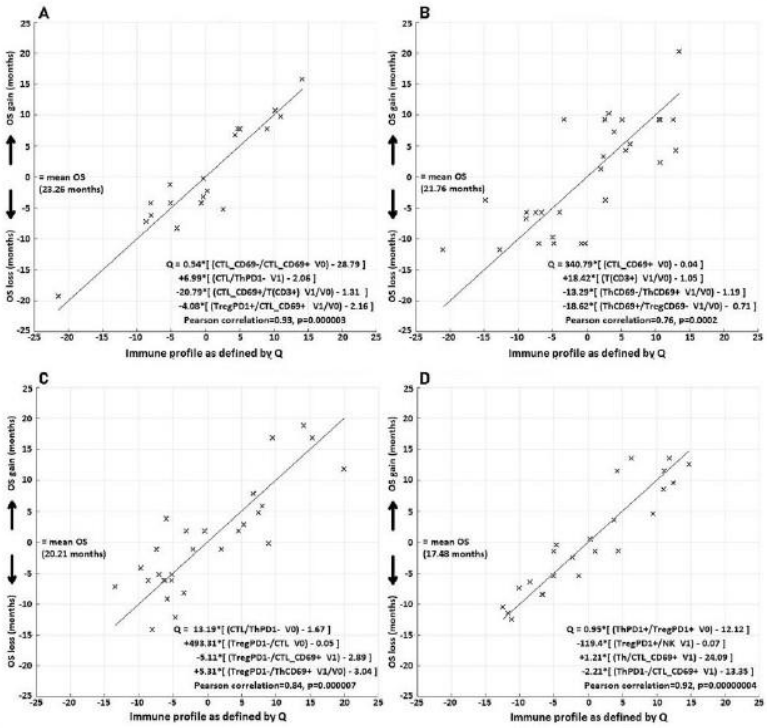
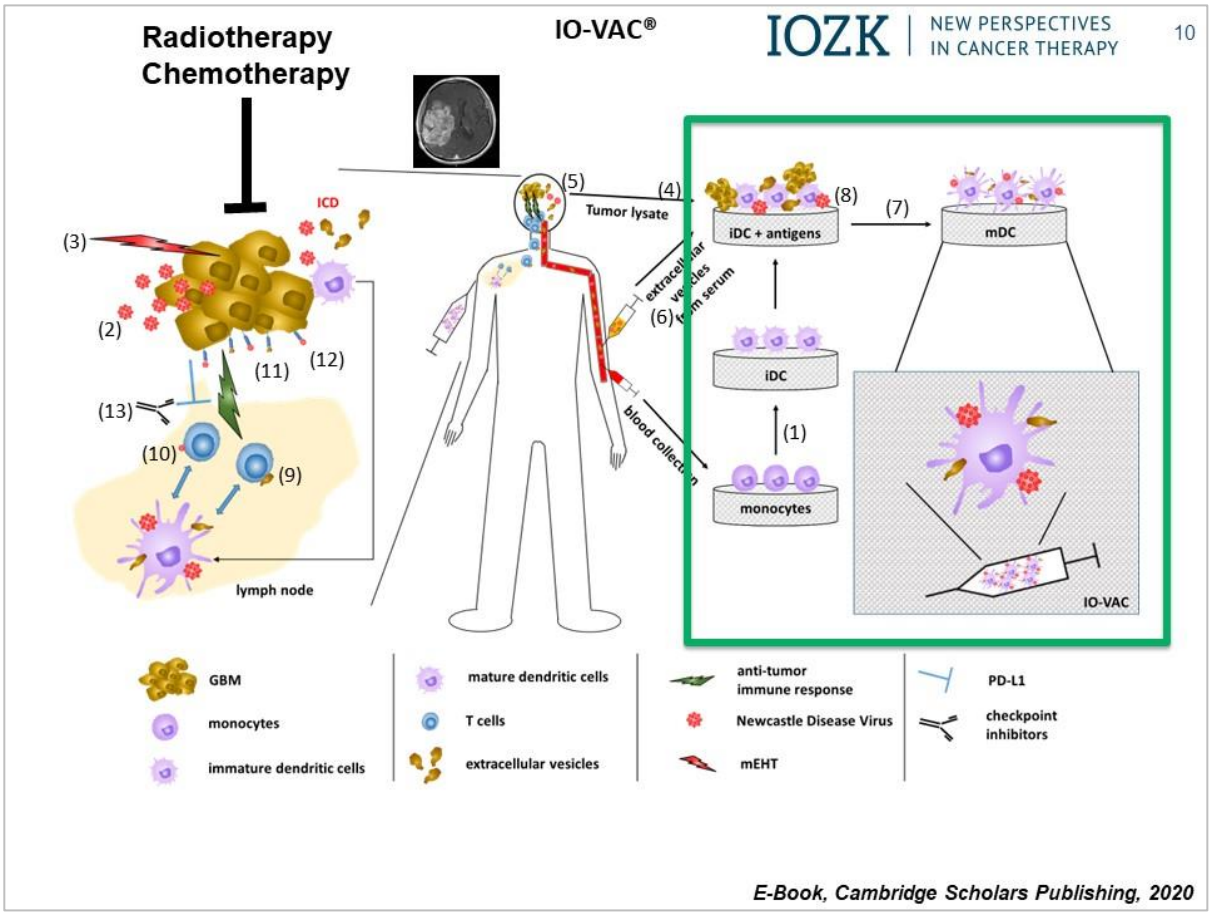


Figure 2. *Canonical correlation analysis of immune profiles versus overall survival (OS). The immune profile is composed of the different FACS-derived quantities (features). Diagrams for four subgroups are shown. A: Vaccination during temozolomide maintenance chemotherapy (TMZm), no residual tumor volume after resection; B: vaccination after TMZm, no residual tumor volume after resection; C: vaccination during TMZm, non-zero residual tumor volume after resection; D: vaccination after TMZm, non-zero residual tumor volume after resection. Each diagram depicts the strong correlation between Q (x-axis), where Q is the sum of quantities of the form: coefficient × [feature − mean of feature in the specific subgroup], and OS (y-axis) expressed as the quantity OS being the individual OS in months minus the mean OS, i.e. mean OS for the specific subgroup.*

Table I. *Overall survival (OS) data of the total study population and subgroups residual tumor volume (RTV).*

Patient group	No. of patients	Median OS (months)	2-Year OS rate (%)	95%CI
Total group	101	19	33.66	24.66-42.88
Early vaccination, RTV=0	19	22	40.2	18.4-61.2
Late vaccination, RTV=0	29	23	44.8	26.5-61.5
Early vaccination, RTV>0	28	19	25	11-41.7
Late vaccination, RTV>0	25	16	28	12.4-46


Radiotherapy
Chemotherapy
IO-VAC®
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iDC + antigens
mDC
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monocytes
lymph node
IO-VAC
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monocytes
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checkpoint inhibitors
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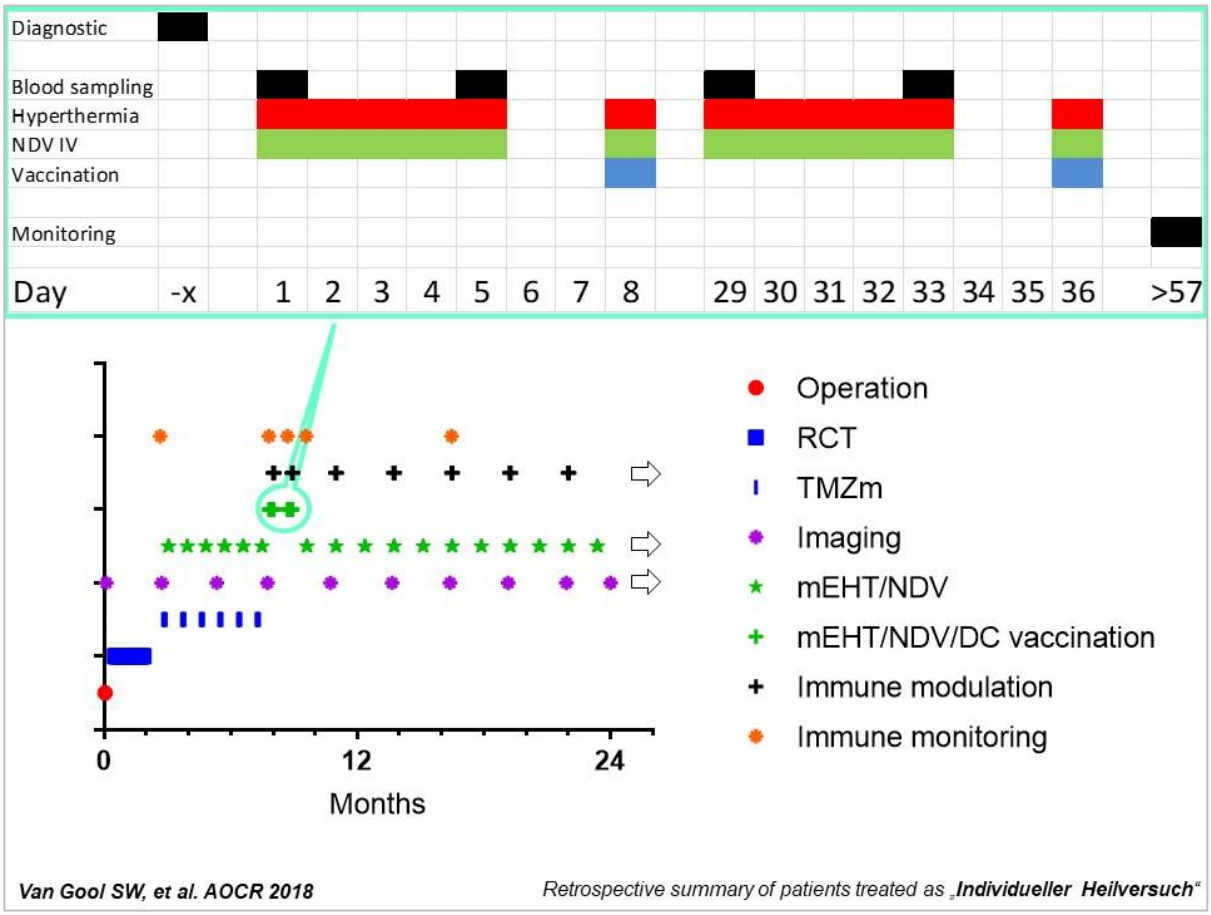
Diagnostic
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Hyperthermia
NDV IV
Vaccination
Monitoring
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0
12
24
Months
Operation
RCT
TMZm
Imaging
mEHT/NDV
mEHT/NDV/DC vaccination
Immune modulation
Immune monitoring
Van Gool SW, et al. AOCR 2018
Retrospective summary of patients treated as „Individueller Heilversuch“

IOZK | NEW PERSPECTIVES IN CANCER THERAPY

Patient selection

Van Gool, Cancers 2021

- Database fixed at 08/06/2021
- 5576 records in Database
- 742 records treated 27/05/2015/2015 till 08/06/2021
- 308 neuro-oncology records treated 27/05/2015/2015 till 08/06/2021
- 194 GBM treated 27/05/2015/2015 till 08/06/2021
- 97 GBM treated in first event 27/05/2015/2015 till 08/06/2021
- Further exclusion
  - <18 years; >75 years
  - LGG in history, IDH1 mutation
  - H3K27M mutation (DMG)
  - GBM as second malignancy post-radiotherapy

- 74 adults with primary GBM in first line treatment
- 66 GBM records IT start 1&2
- **32 GBM records IT start 1&2 MGMT promoter documented unmethylated**
- 1 patient LFU

12

*Retrospective summary of patients treated as „**Individueller Heilversuch**"*

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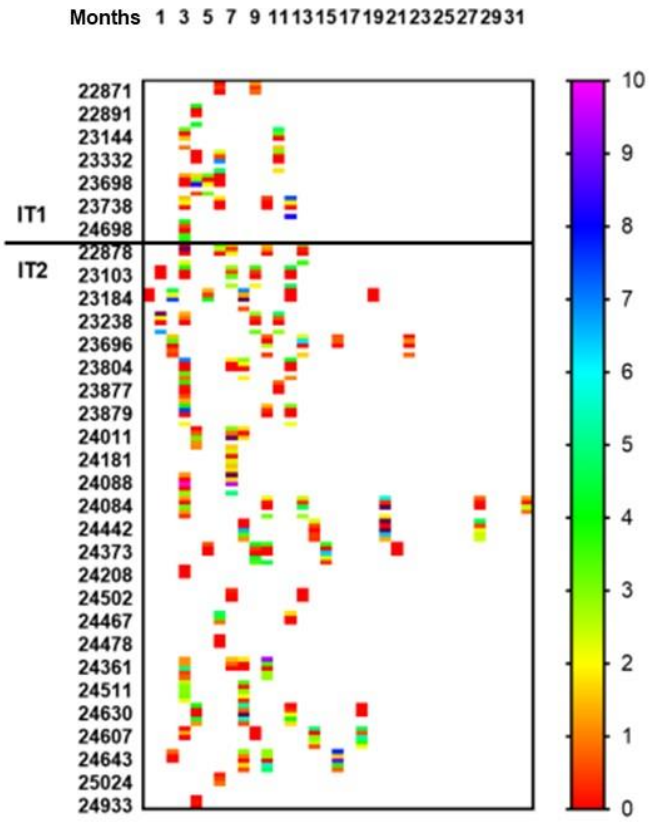

ERBB2
C-kit
Telomerase
MGMT
PDL1

*Retrospective summary of patients treated as „**Individueller Heilversuch**"*

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Are fixed treatment protocols appropriate for the treatment of highly dynamic cancers in permanently changing biological contexts ?

Stratifications
Ethical issues
GLP/GTP/GMP/GCP
Costs
Tumor + host dynamics

→

Repetitive liquid biopsy

Maintenance ICD therapies: actual antigens
Repeat active specific immunotherapies
Actualized modulatory immunotherapies

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

	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			
	L	**N**	**H**	**L**	**N**	**H**
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

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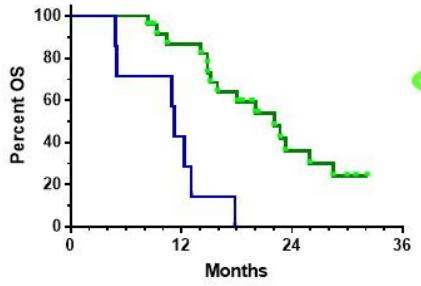
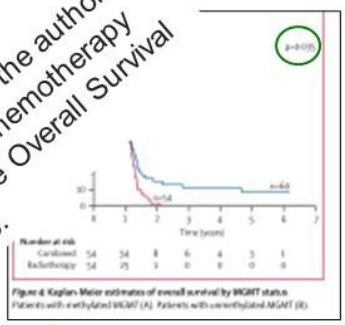
IOZK | NEW PERSPECTIVES IN CANCER THERAPY

IT1: Local therapy -> immunotherapy: **n = 7**

IT2: Surgery -> radiochemotherapy -> TMZm+ICD -> immun[illegible] **= 25**





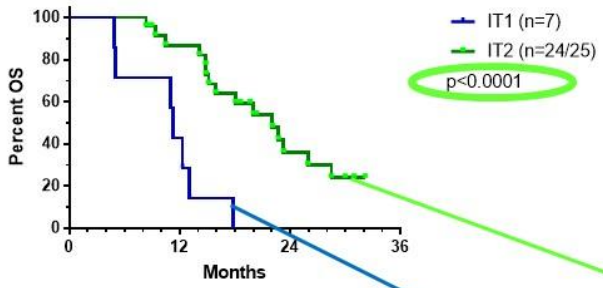
Genes & Immunity Review 26.10.2021
This is a **really interesting clinical study** from Van Gool et al. where the authors investigated the synergyism between the widely utilized anti-GBM chemotherapy like TMZ and individualized multimodal immunotherapy to improve Overall Survival of IDH1 wild-type MGMT promoter-unmethylated GBM patients.

mOS months	[illegible] OS	2y OS
S + RT (Stupp, 2009)	*[illegible].8*	*1.8% (0.1-8.6)*
S ± RT + **IO-Vac®** [illegible]	**11.25**	**0%**
S + RCT + TM[illegible]	*12.6*	*14.8% (7-2-25)*
S + RC[illegible] **+ ICDm**	**22.07**	**36% (15.7-56.8)**

SYNE[illegible]Z and individualized multimodal immunotherapy to improve [illegible] wild type MGMT promoter-unmethylated GBM patients

*Retrospective summary of patients treated as „**Individueller Heilversuch**"*

IOZK | NEW PERSPECTIVES IN CANCER THERAPY



EQ-5D-5L (3125 situations)
* *MO*: Mobility: 1-5
* *SC*: Self-Care: 1-5
* *UA*: Usual Activities: 1-5
* *PD*: Pain/Discomfort: 1-5
* *AD*: Anxiety/Depression: 1-5

VAS: 0-100
KPI: 0-100

Euro	Intake	ICD (**)	DC	Other (*)	Other% (***)	Total	Months	Cost/month
				IT2 (n=17 deceased patients)				
Median	3500,00	5850,00	17600,00	36093,00	55,81	69100,00	13,06	**4725,00**
Min	3000,00	780,00	0,00	11161,00	37,83	17480,00	3,00	2150,00
Max	3500,00	14040,00	42600,00	79872,00	76,64	122876,00	24,00	17314,00
				IT1 (n=7)				
Median	3000,00	2145,00	17600,00	14242,00	39,98	36213,00	5,86	**7124,00**
Min	3000,00	780,00	15400,00	6015,00	23,06	26085,00	1	4024,00
Max	3500,00	5265,00	30100,00	32371,00	53,74	70736,00	10	28626,00

SYNERGY between TMZ and individualized multimodal immunotherapy to improve OS of IDH1 wild type MGMT promoter-unmethylated GBM patients

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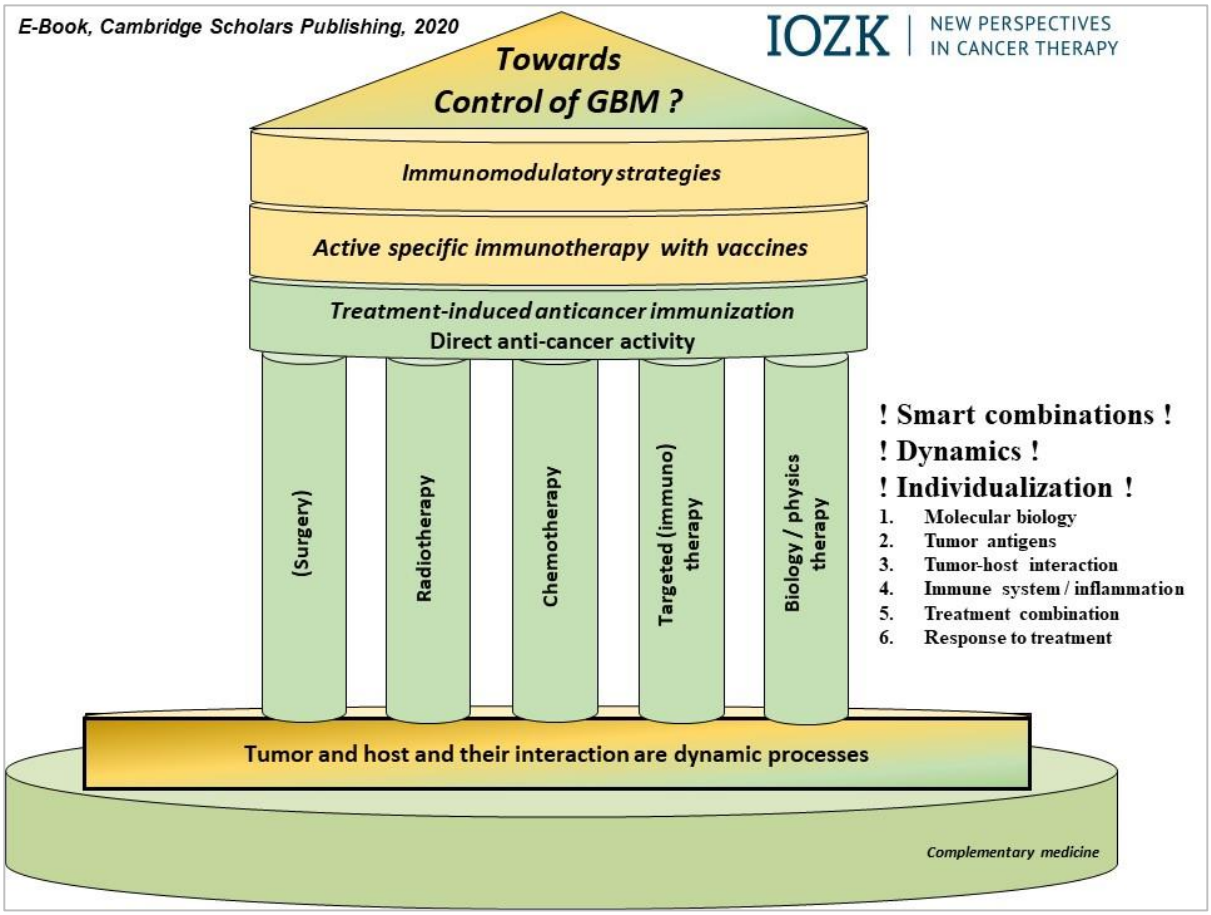


IOZK | NEW PERSPECTIVES IN CANCER THERAPY

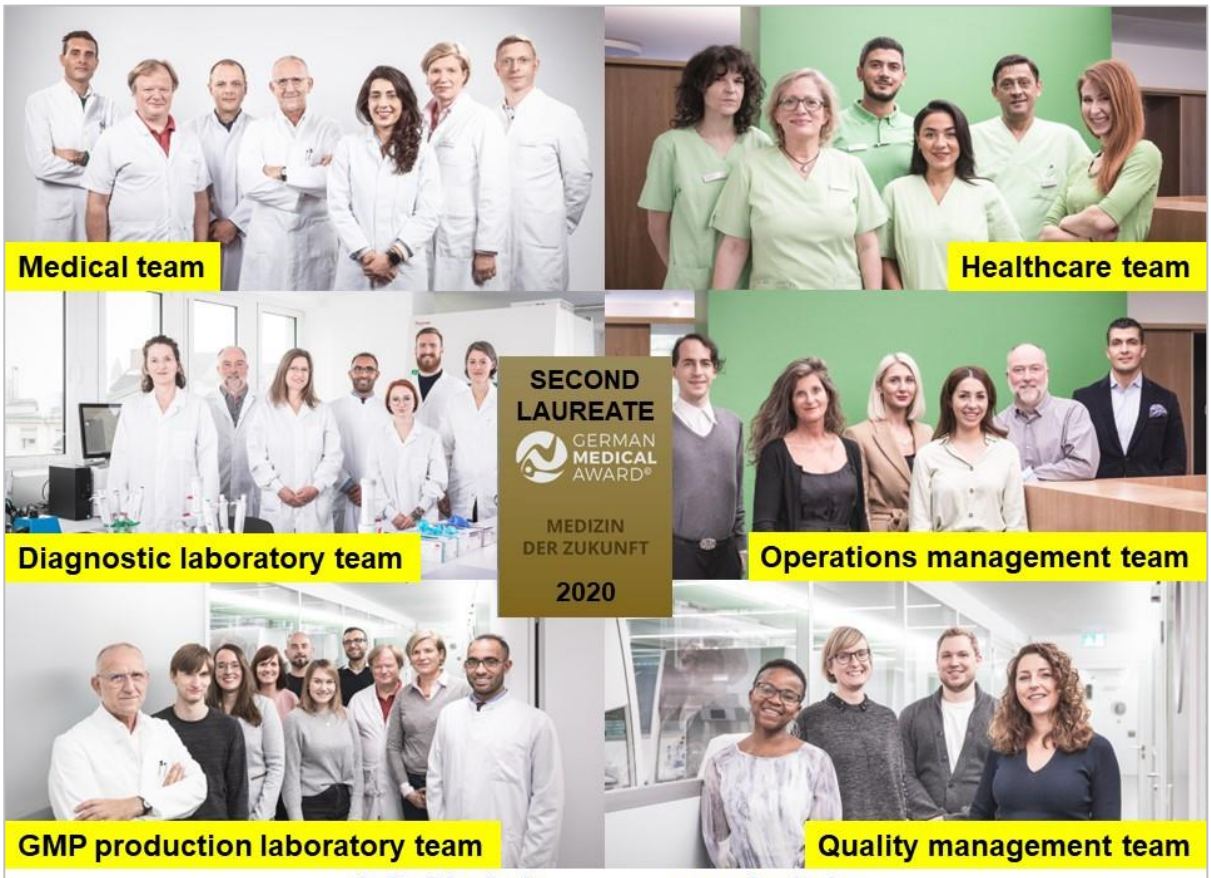
Conclusion

- **Individualized multimodal immunotherapy** can/should be integrated within the **Standard of Care first line treatment for patients with GBM**
- **Old-fashioned RCTs** with fixed treatment protocols are not useful to study complex treatments in **highly dynamic biological processes**
- Focus on **prolongation of life with good quality of life**: EQ-5D-5L
- **Current optimal scenario**
  1. **Surgery**
  2. **Radiochemotherapy**, ± **ICD therapy**
  3. Immune diagnostics
  4. **Maintenance chemotherapy** + **ICD therapy**
  5. 2x Active specific immunotherapy **IO-Vac®** ± Modulatory immunotherapy
  6. Monitoring + ICDm1 therapy ± Modulatory immunotherapy
  7. **Maintenance ICD therapy ± Modulatory immunotherapy** / Monitoring
- **In „Individueller Heilversuch“**

IOZK | NEW PERSPECTIVES IN CANCER THERAPY

Collaboration is opportunity

- **Current optimal scenario**
  1. **Surgery**
  2. **Radiochemotherapy**, ± **ICD therapy**
  3. Immune diagnostics
  4. **Maintenance chemotherapy** + **ICD therapy**
  5. 2x Active specific immunotherapy **IO-Vac®** ± Modulatory immunotherapy
  6. Monitoring + ICDm1 therapy ± Modulatory immunotherapy
  7. **Maintenance ICD therapy** ± **Modulatory immunotherapy** / Monitoring
- **In „Individueller Heilversuch“**
- **Collaboration**
  - **Sharing data under „IOZK patient“**
  - **Ownership of own data and anonymized data from the group**
  - **Co-authorship in common publications**



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