Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix. Supplementary Methods

External Comparator Populations (ECPs)
To obtain ECPs rigorously matched to our DCVax-L study population, and minimize potential bias, 4 sets of pre-specified analyses were independently performed to (i) select closely matched, contemporaneous RCTs from which to obtain the ECPs, (ii) validate the ECP methodology by applying it to the comparator trials, (iii) check for potential biases through sensitivity analyses and (iv) adjust for imbalances in individual patient characteristics.

Matched Comparator Studies for ECPs
The nGBM and rGBM ECPs were determined by an independent expert firm (York Health Economics Consortium), and were comprised of patient data from the control arms of contemporaneous formal RCTs closely matched to the current study based on 14 criteria pre-specified in the SAP (7 for nGBM and 7 for rGBM). For nGBM the criteria included: 1) contemporaneous study time period; 2) reported outcomes (including survival); 3) same standard of care used (radiation and temozolomide); 4) randomized study design; 5) patients aged >18; 6) KM curves available for survival and for subgroups; and 7) publication in English. The criteria for rGBM at first recurrence were similar., with one difference being that lomustine, bevacizumab or best supportive care were allowed as treatment for the control arms. Based on these criteria, 5 RCTs for nGBM and 10 RCTs for rGBM were matched to our study, and were designated as the ECPs in our SAP **(eTable 1)**. These studies also met the "fit for purpose" criteria outlined by Mishra-Kalyani, et al.[1]. The studies that contributed to the ECP provided high quality survival data, with overall lost to follow-up (ltfu) rates of 2% or less (except one study[2] that had an ltfu rate of 6%). Similarly, the DCVax-L study had less than 2% of patients lost to follow-up.

Validation of the ECP Approach
To further validate the accuracy of the approach and rule out false positive results, each RCT comparator study was evaluated using the same [pooled] ECP that served as the control for the DCVax-L study, instead of using the original control arm in that RCT comparator study, in order to determine whether using this ECP would have changed the outcome originally reported (i.e., primary endpoint met or unmet). This analysis showed that the RCTs that originally failed to show statistically significant survival benefit also failed to show significant survival benefit when the treatment arm of the RCT was compared to our pooled ECP instead of to the original RCT controls, and the one RCT that had a positive outcome was also positive under this ECP approach.

Sensitivity Analyses
Although the ECP comparator studies were closely matched with the current study, small non-significant differences could potentially impact outcomes. To address this and further validate the nGBM ECP, we conducted 5 sensitivity analyses, removing each of the 5 comparator studies from the ECP, one at a time. We also conducted a 6th sensitivity analysis, removing 2 of the 5 nGBM comparator trials[3], as it was unclear whether they excluded patients with early progression at the time of enrollment, as was done in our study and in 3 of the 5 comparators[2,4,5].

Adjustment for Individual Patient Characteristics in ECPs
A fourth set of analyses was conducted to adjust for differences in the individual patient characteristics in the DCVax-L cohort vs. the ECPs. Propensity score matching could not be used because the ECP data were not accessible on a patient-by-patient basis, despite efforts to obtain such data. However, the percentages of specific patient characteristics were available for the ECP. Accordingly, we used Matching-Adjusted Indirect Comparison (MAIC) methodology (widely used in health economic analyses) to adjust for even small differences and re-assess survival outcomes[6-8]. This methodology applies a weight to each individual patient in the DCVax-L population in such a way that the sum of the weights for patients in each category for a characteristic achieves a match with the external control population. By way of example, if the external population included 50 males and 50 females and the DCVax-L population included 60 males and 40 females, the males would need to be down-weighted to achieve the required 50:50 balance. Applying a weight of 0.67 to each individual male and a weight of 1 to each individual female would achieve that balance, resulting in a new population with effectively 40 males and 40 females. When there are several characteristics to be matched (simultaneously), the mathematics by which the weights are applied to individual patients becomes more complex.

This matching was done on the characteristics of age, sex, race, MGMT methylation status, and KPS score, combined with one of either extent of resection or with residual disease. The MAIC weights required to adjust the DCVax-L cohort to match the characteristics of the external comparators were calculated in the statistical program 'R'. These weights were checked to ensure that the characteristics of the re-weighted DCVax-L population matched those of the ECP, as well as for any outliers (particularly large weights) that could strongly influence the results of the analysis. Results between the unweighted and weighted (or matched) analyses were compared to confirm the results.

eTable 1. Survival Outcomes for the Control Groups of the Trials That Comprise the ECPs

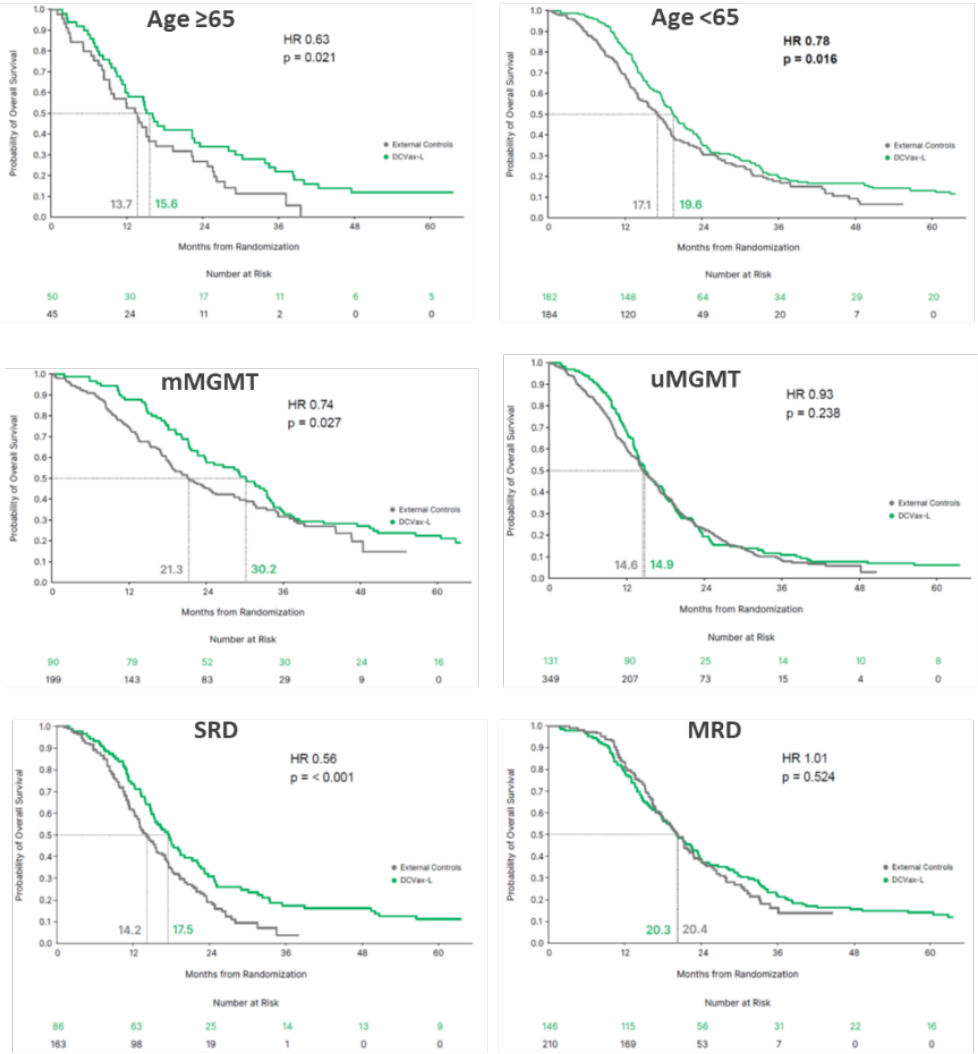
Newly Diagnosed Glioblastoma			
Study	**n**	**Median OS (months)**	**95% CI (months)**
Gilbert et al 2013	411	16.6	14.9 – 18.0
Gilbert et al. 2014	309	16.1	14.8 – 18.7
Weller et al. 2017	374	17.4	16.2 – 18.8
Stupp et al. 2017	229	16.0	14.0 – 18.4
Wen et al. 2019	43	15.0	12.3 – 23.1
Aggregate Newly Diagnosed[1]	**1,366**	**16.5**	**16.0 – 17.5**
Recurrent Glioblastoma at First Relapse			
Study	**n**	**Median OS (months)**	**95% CI (months)**
Wick et al. 2010	92	7.1	6.0 – 8.8
Taal et al. 2014	46	8.0	6.0 – 11.0
Brandes et al. 2016	40	7.5	5.6 – 10.3
Cloughesy et al. 2017	65	12.6	n.a.[2]
Wick et al. 2017	149	8.6	7.6 – 10.4
Brandes et al. 2018	62	5.5	3.9 – 7.2
Galanis et al. 2019	38	7.7	n.a.[2]
Lombardi et al. 2019	60	5.6	4.7 – 7.3
Narita et al. 2019	30	8.0	4.8 – 12.9
Lee et al. 2020	58	11.5	8.4 – 14.2
Aggregate Recurrent GBM[1]	**640**	**7.8**	**7.2 – 8.2**

1) Based on reconstructed individual patient data (IPD); 2) not available from referenced publication

eTable 2. Other Baseline Characteristics

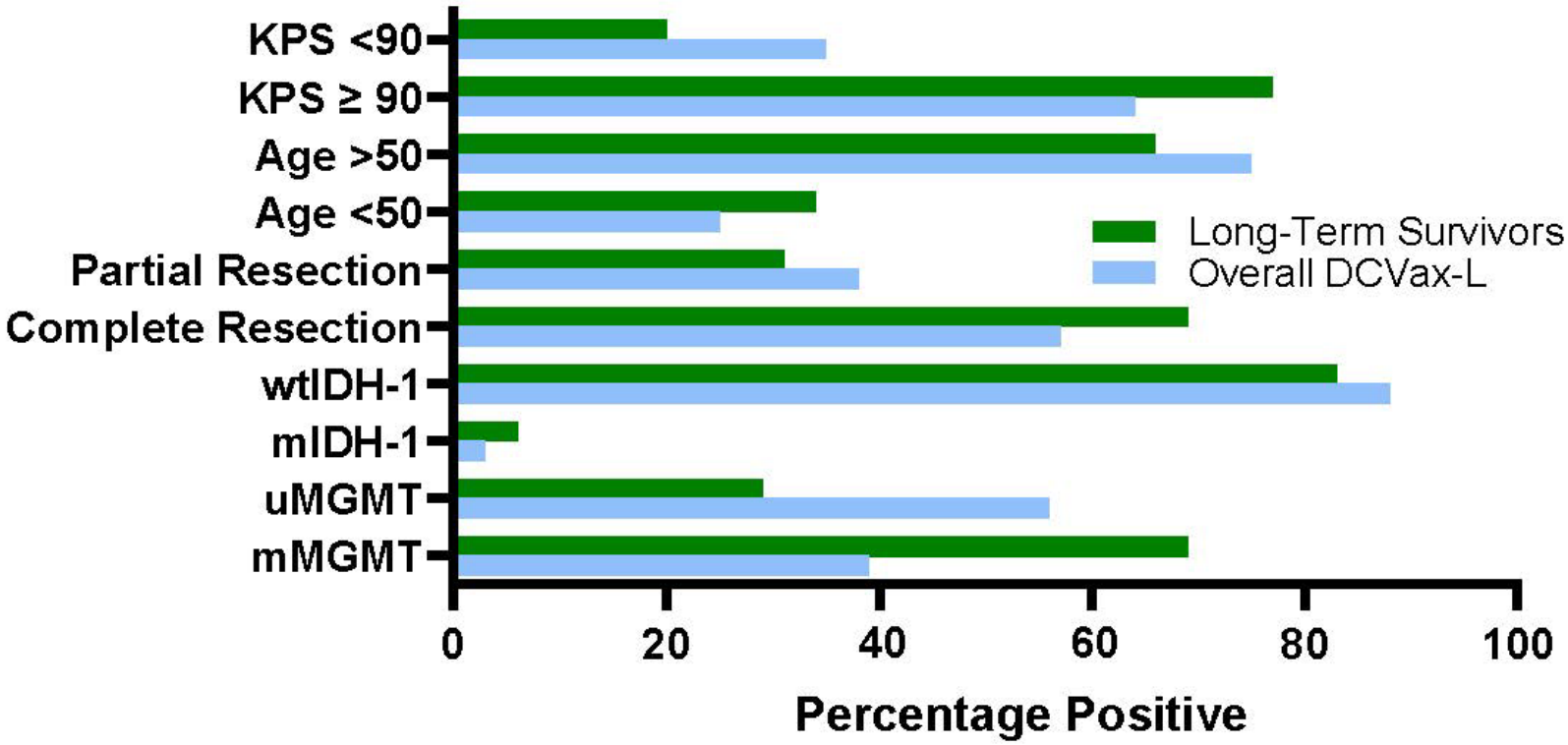
	Patients, No.	Median age, y	Patients, %													
			Age group, y		KPS			Race			IDH-1			Resection		
			<50	≥50	<90	≥90	Missing	White	Non-White	Other/missing	Mut	WT	Missing	Comp	Part	Other/Missing
Gilbert 2013	411		27	73	34	66	0	78	3	19				56	41	3
Gilbert 2014	309		21	79	39	62	0	95	4	1				59	39	3
Stupp 2017	229				32	65	3	88	12	0	3	49	48	54	34	13
Weller 2017	374							90	10	0						
Wen 2019	43		28	72	40	61	0							74	26	0
All nGBM ECP	1366		25	75	35	64	1	87	7	6	3	49	48	57	38	5
nGBM DCVax	232		25	75	30	69	1	89	7	4	3	88	9	63	37	0
Cloughesy 2017	65	55	26	74				99	0	2	9	91	0			
Wick 2010	92		30	70												
Brandes 2016	40							73	3	25	3	73	25			
Wick 2017	149	60	20	80												
Narita 2019	30	59														
Brandes 2019	62	59														
Taal 2014	46	56									7	93	0			
Lombardi 2019	60	59									0	100	0			
Lee 2020	58	58	29	71				91	3	5	0	100	0			
Galanis 2019	38	57														
All rGBM ECP	640		25	75				90	2	8	4	93	4			
rGBM DCVax	64	56	27	73				84	0	16	3	84	12			

eFigure 1. Survival in Prespecified Subgroups in nGBM



eFigure 1. KM plots for comparisons of patients in pre-specified subgroups between newly diagnosed GBM subjects treated with DCVax-L, and external control subjects. Hazard Ratios (HR) and significance levels (p values) were calculated following the alpha spending rules specified in the SAP.

eFigure 2. Prognostic Characteristics



eReferences

1. Mishra-Kalyani PS, Amiri Kordestani L, Rivera DR, et al. External Control Arms in Oncology: Current Use and Future Directions. *Ann Oncol*. Jan 10 2022;doi:10.1016/j.annonc.2021.12.015
2. Stupp R, Taillibert S, Kanner A, et al. Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma: A Randomized Clinical Trial. *JAMA*. Dec 19 2017;318(23):2306-2316. doi:10.1001/jama.2017.18718
3. Gilbert MR, Wang M, Aldape KD, et al. Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. *J Clin Oncol*. Nov 10 2013;31(32):4085-91. doi:10.1200/JCO.2013.49.6968
4. Weller M, Butowski N, Tran DD, et al. Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial. *Lancet Oncol*. Aug 22 2017;doi:10.1016/S1470-2045(17)30517-X
5. Wen PY, Reardon DA, Armstrong TS, et al. A Randomized Double-Blind Placebo-Controlled Phase II Trial of Dendritic Cell Vaccine ICT-107 in Newly Diagnosed Patients with Glioblastoma. *Clin Cancer Res*. Oct 1 2019;25(19):5799-5807. doi:10.1158/1078-0432.CCR-19-0261
6. Signorovitch J, Swallow E, Kantor E, et al. Everolimus and sunitinib for advanced pancreatic neuroendocrine tumors: a matching-adjusted indirect comparison. *Exp Hematol Oncol*. Dec 6 2013;2(1):32. doi:10.1186/2162-3619-2-32
7. Signorovitch JE, Sikirica V, Erder MH, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. *Value Health*. Sep-Oct 2012;15(6):940-7. doi:10.1016/j.jval.2012.05.004
8. Cartron G, Fox CP, Liu FF, et al. Matching-adjusted indirect treatment comparison of chimeric antigen receptor T-cell therapies for third-line or later treatment of relapsed or refractory large B-cell lymphoma: lisocabtagene maraleucel versus tisagenlecleucel. *Exp Hematol Oncol*. Mar 25 2022;11(1):17. doi:10.1186/s40164-022-00268-z