Title

Radiotherapy, Temozolomide and anti-programmed cell death protein 1 treatments modulate the immune microenvironment in experimental high-grade glioma

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Previous presentations

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The Authors declare no conflict of interest

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1 **Abstract**

2 **Background.** The lack of immune synergy with conventional chemoradiation could explain the failure of
3 checkpoint inhibitors in current clinical trials for high-grade gliomas (HGGs).

4 **Objective.** To analyze the impact of radiotherapy (RT), Temozolomide (TMZ) and anti-programmed cell
5 death protein 1 (α PD1) (as single or combined treatments) on the immune microenvironment of
6 experimental HGGs.

7 **Methods.** Mice harboring neurosphere (NS)/CT-2A HGGs received RT (4 Gy, single dose), TMZ (50 mg/kg,
8 four doses) and α PD1 (100 μ g, three doses) as monotherapies or combinations. The influence on
9 survival, tumor volume and tumor-infiltrating immune cells was analyzed.

10 **Results.** RT increased total T cells ($p=0.0159$) and CD8⁺ T cells ($p=0.0078$) compared to TMZ. Lymphocyte
11 subpopulations resulting from TMZ or α PD1 treatment were comparable with those of controls. RT
12 reduced M2 tumor-associated macrophages/microglia (TAMs, $p=0.0019$) and monocytic myeloid
13 derived suppressor cells (mMDSCs, $p=0.0003$) compared to controls. The effect on mMDSC was also
14 seen following TMZ and α PD1 treatment, although less pronounced ($p=0.0439$ and $p=0.0538$,
15 respectively). Combining RT with TMZ reduced CD8⁺ T cells ($p=0.0145$) compared to RT alone. Adding
16 α PD1 partially mitigated this effect as shown by the increased CD8⁺ T cells/Tregs ratio, even if this result
17 failed to reach statistical significance ($p=0.0973$). Changing the combination sequence of RT, TMZ and
18 α PD1 did not alter survival nor the immune effects.

19 **Conclusion.** RT, TMZ and α PD1 modify the immune microenvironment of HGG. The combination of RT
20 with TMZ induces a strong immune suppression which cannot be effectively counteracted by α PD1.

21 Keywords

22 High-grade glioma, Glioblastoma, Combination therapies, Immunotherapy, PD1, Temozolomide,

23 Stereotactic radiotherapy

24

25 Running title

26 Radiotherapy, Temozolomide and α PD1 modulate high-grade glioma immunity

27 **List of abbreviations**

28

29 (α)PD1: (anti) programmed cell death protein 1

30 CBCT: cone beam computed tomography

31 CD: cluster of differentiation

32 CTR: control

33 DMEM/F12: Dulbecco's modified Eagle medium / nutrient mixture F-12

34 EGF: epidermal growth factor

35 FBS: fetal bovine serum

36 FGF: fibroblast growth factor

37 FVD: fixable viability dye

38 FWO: Fonds Wetenschappelijk Onderzoek

39 GBM: glioblastoma

40 HGG: high grade glioma

41 HIF-1 α : hypoxia-inducible factor-1 α

42 IMDM: Iso-cove's modified Dulbeccos's medium

43 IP: intraperitoneal

44 m and gMDSC: granulocytic and monocytic myeloid derived suppressor cell

45 MRI: magnetic resonance imaging

46 nRs: non-responders

47 NS: neurospheres

48 PBS: phosphate-buffered saline

49 PD

50 PDL1: programmed cell death protein 1 ligand

51 RARE: rapid acquisition relaxation enhancement

52 Rs: responders

53 RT: radiotherapy

54 SAARP: small animal radiation research platform

55 T2w: T2-weighted

56 TAM: tumor-associated macrophages/microglia

57 TGF- β : transforming growth factor β

- 58 TMZ: Temozolomide
- 59 Treg: regulatory T cell
- 60 VEGF-A: vascular-endothelial growth factor A

61 Introduction

62

63 Given the poor efficacy of current standard of care treatment, high-grade gliomas (HGGs) still
64 represent an unmet clinical need.^{1,2} Immunotherapy provided positive results in preclinical studies;
65 however, clinical trials have failed to replicate such results in patients.³⁻⁸ Importantly, only few animal
66 studies assessed the combinatory effects of conventional and immune therapies; therefore, empirical
67 combination schedules have been used for patients.⁹ Since conventional and immune therapies can
68 heterogeneously modulate the tumor-immune microenvironment, these treatments could have been
69 administered to HGG patients in non/low-synergistic combinations possibly reducing the efficacy of
70 immunotherapy itself.¹⁰⁻¹⁵ However, the effects of conventional and immune therapies on the immune
71 biology of HGG have not been systematically analyzed yet.^{10,16} In this study, we aimed at filling this
72 knowledge gap by assessing the impact of radiotherapy (RT), Temozolomide (TMZ) and anti-
73 programmed cell death protein 1 treatment (α PD1) on the local immune microenvironment of
74 experimental HGG.

Materials and methods

Figure 1 shows the experimental design. Below a summary of a methods. Extensive description is available as Supplemental digital content 1 and 2.

Brain tumor model. A syngeneic, immunocompetent, orthotopic HGG model, based on CT-2A neurospheres (NS/CT-2A, C57BL/6J background), was used for this study.^{17,18}

Brain tumor infiltrating immune cells. Mononuclear cells were isolated from brain tumors and stained for tumor-associated microglia/macrophages (TAMs), monocytic and granulocytic myeloid-derived suppressor cells (mMDSCs and gMDSCs) and T cells.^{17,19}

Magnetic resonance imaging (MRI). A 7T Biospec small animal MRI system (Bruker BioSpin) was used to verify tumor engraftment and calculate tumor volumes.¹⁷

Radiotherapy. Stereotactic external beam image-guided arc irradiation was performed using a Small Animal Radiation Research Platform (SARRP, Xstrahl Life Sciences). Each irradiated mouse received a single dose of 4 Gy.

Chemotherapy. TMZ capsules (Temodal®, Merk Sharp&Dohme) were dissolved in PBS and each TMZ-treated mouse received four doses of 50 mg/kg by oral gavage on alternate days.

Immunotherapy. The α PD1 blocking antibodies were purified from α PD1 hybridoma (clone RPMI-14) cultures.²⁰ Each α PD1-treated mouse received three doses of 100 μ g α PD1 by intraperitoneal (IP) injection on alternate days.

Results

RT, TMZ and α PD1 monotherapies modulate the tumor-immune microenvironment. Compared to controls, RT and TMZ were capable to prolong survival significantly ($p=0.004$ for both treatments; Figure 2). Conversely, α PD1 only provided a short and non-significant survival advantage ($p=0.2169$). Immunomonitoring data demonstrated the capacity of all the treatments to modify the immune microenvironment of NS/CT-2A tumors, with heterogeneous effects. In the context of the adaptive immune system (Figure 3A), RT decreased total and CD8⁺ T cells compared to controls, but these results failed to reach statistical significance ($p=0.0983$ and $p=0.0835$, respectively). However, when compared with TMZ-treated animals, RT-treated mice had significantly higher total T cells ($p=0.0159$), CD8⁺ T cells ($p=0.0078$). A non-statistically significant increase of CD8⁺ T cells/Tregs ratio ($p=0.0618$) was also observed. Surprisingly, α PD1 did not have a relevant effect on the T cell compartment. Even if to different extents, all the treatments were capable to modify the innate immune system (Figure 3B). RT and TMZ significantly decreased total TAMs ($p=0.0008$ and $p=0.0292$, respectively), while α PD1 induced a reduction of this immune subpopulation which was not supported by statistics ($p=0.0727$). However, only RT was able to significantly reduce the inhibitory M2 fraction of TAMs ($p=0.019$). The modulation of MDSCs was similar: compared to controls, RT and TMZ induced a significant reduction mMDSCs ($p=0.0003$ and $p=0.0439$, respectively) while α PD1 induced a reduction this cell population which failed to reach statistical significance ($p=0.0538$). Notably, the strongest reduction in mMDSCs was seen in RT-treated mice. TMZ also induced a significant increase of gMDSCs compared to controls ($p=0.0021$), TMZ ($p=0.0261$) and α PD1 ($p=0.0098$). Of note, mMDSCs were approximately 40-times more abundant than gMDSC.

Response to monotherapies is related to the immune profile. Brain MRI was performed before and after the treatment (Figure 1A) and mice were then categorized as responders (Rs) when showing a fold-increase of tumor volume lower than controls ($n=8$) or non-responders (nRs) when showing a fold-

increase of tumor volume equal or higher than controls (n=7, Figure 4A). Compared to nRs, Rs mice showed a significantly higher total T cells and CD8⁺ T cells (p=0.0058 and p=0.0497, respectively), and significantly lower Tregs, total TAMs and M2 TAMs (p=0.0007, p=0.0046 and p=0.0041, respectively; Figure 4B). Rs and nRs did not show any significant difference in mMDSCs and gMDSCs (p=0.62 and p=0.7821, respectively).

The combination of RT and TMZ induces an increase of immune suppression which cannot be sufficiently counteracted by α PD1. The administration of TMZ after RT induced a significant survival advantage compared to RT alone (p=0.0142), while the addition of α PD1 only provided a further survival benefit which failed the statistical tests (p=0.0842; Figure 5). Nevertheless, the administration of TMZ after RT did not result in an immune synergy. Compared to mice treated with RT alone, animals receiving RT-TMZ showed a significant reduction of cytotoxic CD8⁺ T cells (p_{adj} =0.0145) and no modification of immunosuppressive Tregs (p_{adj} =0.7519; Figure 6A). The addition of α PD1 to the therapeutic scheme (RT-TMZ- α PD1) induced a moderate increase of CD8⁺ T cells/Tregs ratio, however not supported by statistics (p_{adj} =0.0973, (Figure 6A). CD8⁺ T cells and Tregs remained substantially unchanged. In this experiment, PD1 and CD69 stainings were used to evaluate T cell function. Within the populations of CD4⁺ T cells and Tregs, RT-TMZ- α PD1 significantly reduced the amount of PD1⁺ cells compared with both RT (p_{adj} =0.0136 for CD4⁺ T cells and p_{adj} =0.0034 for Tregs, respectively) and RT-TMZ (p_{adj} =0.0142 for CD4⁺ T cells and p_{adj} =0.0011 for Tregs, respectively; Figure 6B). No significant variations of PD1⁺ lymphocytes within the populations of CD8⁺ T cells and FoxP3⁺CD4⁺ T cells (effector CD4⁺ T cells) were found (Figure 6B). The different treatments did not significantly influence the proportion of cells expressing CD69 in the CD4⁺ T cells, CD8⁺ T cells or Tregs populations (Supplemental digital content 3, Figure S3.1A). In the context of the innate immune system, RT-TMZ- α PD1-treated mice showed reduced total TAMs, M2 TAMs and mMDSCs compared to other treatment groups. However, because of the large inter-individual variability, these results were not supported by statistics (Supplemental digital content 3, Figure S3.1B)

In triple combination schedules, changing the sequence of administration of RT, TMZ and α PD1 did not significantly modify survival (Supplemental digital content 3, Figure S3.2). In line with this result, immune monitoring analysis did not show significant differences in the adaptive or in the innate immune compartment (Supplemental digital content 3, Figure S3.3A and B, respectively). In view of the detrimental immune impact of TMZ in combination treatment, we performed a supplementary experiment in which we combined RT with α PD1 without TMZ. However, the survival RT- α PD1 treated mice was significantly shorter than mice treated with RT-TMZ- α PD1 ($p=0.0126$) and not significantly different from that of mice treated with RT alone ($p=0.7275$; Figure S3.4). A larger difference in survival was present between mice treated with RT- α PD1 and RT-TMZ and it was in the favor of the latter therapeutic scheme; however, this result was not supported by statistics ($p=0.0654$). Considering the absence of a survival advantage, we did not analyzed the immune modifications following RT- α PD1.

Discussion

To date, checkpoint inhibitors substantially failed to replicate in HGG patients the results obtained in preclinical research or in other types of malignancies.^{3,21–23} In this regards, the negative results of the Checkmate-143 and Checkmate-498 randomized trials are particularly relevant.^{8,24} Checkpoint inhibitors are usually administered to HGG patients in combination with standard radio-chemotherapy; however, the efficacy of such combination and the presence of a true immunological synergism have rarely been assessed prior to clinical application. In the available literature, we found that the efficacy of α PD1/L1 combined with TMZ, RT, or both was tested only in five, two a no preclinical studies, respectively (Table 1 and Supplemental digital content 4).^{25–31} Interestingly, all these studies were conducted with the GL261 model (or its analog, the GL26 model) and only in two of them also another model was used. Such a lack of knowledge concerning the combinatory effects of chemo-radiation and checkpoint inhibitors is particularly relevant since RT and TMZ can have a variable impact on the immune biology of HGG. RT is generally considered as being capable to promote antitumor immunity via generation of immunogenic cell death. However, depending on the therapeutic and experimental setting, RT can also be immune suppressive.^{16,32–36} Systemically-administered TMZ is well known for inducing lymphopenia and it is therefore generally considered immune suppressive.¹⁰ However, TMZ has also been linked to an increased mutational load and antigen-specific T cells, potentially improving antitumor immunity.^{37–39}

To the best of our knowledge, this study represents the first systematic analysis of the effects of RT, TMZ and α PD1, as single agents and in combination, on the local immune microenvironment of HGGs. As monotherapy, RT was the most effective in stimulating the immune reaction against HGG. RT, TMZ and α PD1 had a positive impact on the innate immune system by decreasing total TAMs and mMDSCs. However, RT induced the most pronounced drop of total TAMs and mMDSCs, and it was the only treatment capable to significantly decrease inhibitory M2 TAMs. RT also exerted a positive effect on adaptive immunity, by increasing total T cells, CD8⁺ T cells and CD8⁺ T cells/Tregs ratio. Interestingly,

these differences were statistically significant when comparing RT versus TMZ and not RT versus controls. Surprisingly, in the monotherapy setting α PD1 was not able to significantly modulate the adaptive immune system while it showed some sort of positive impact on the innate immunity by reducing total TAMs and mMDSCs (even if also these results failed to reach statistical significance).

The comparison of the immune phenotype of Rs and nRs mice demonstrated that mice responding to treatment share a significantly more activated immune phenotype. Interestingly, Rs mice were found in all the treatment groups (obviously with different proportions), indicating that an improved antitumor immunity could represent an important factor for any treatment (not only immunotherapy) to be successful.

In combination experiments, mice treated with RT-TMZ (mimicking the current standard of care⁴⁰) survived longer than those treated with RT alone. However, such combination was immunologically detrimental since it induced significantly lower CD8⁺ T cells and a similar amount of immune suppressive cells (Tregs, mMDSCs and M2 TAMs) compared to RT alone. The survival advantage provided by TMZ was therefore probably due to direct cytotoxicity and not to an immune synergy. This tumor- and treatment-induced immune suppression does not represent an ideal substrate for immunotherapy, and indeed the addition of α PD1 to the treatment schedule (RT-TMZ- α PD1) was only capable to weakly counteract such immunosuppressive burden. Despite promoting a moderate improvement of adaptive immunity, α PD1 did not substantially improve the T cell activation status since it could not significantly reduce the amount of exhausted PD1⁺ lymphocytes. Interestingly, mice treated with RT-TMZ- α PD1 demonstrated a significant reduction of PD1⁺ Tregs. Given the limited and contrasting available evidence, the interpretation of this finding cannot be univocal. PD1 signaling has been demonstrate to sustain Tregs proliferation and function, therefor α PD1 treatment could appear as an appropriate strategy to reduce Tregs-mediated immune suppression.⁴¹ However, PD1⁺ Tregs have been shown to have a weaker immune suppressive function compared to their PD1⁻ counterpart.⁴² In this view, the elimination of PD1⁺ Tregs would only provide a limited benefit. The results of our study seems to be more in line with this second hypothesis: despite the reduction of PD1⁺ Tregs, mice

receiving radiochemotherapy and checkpoint blockade did not show a significant reduction of the amount of total Tregs compared with mice receiving only radiochemotherapy. Moreover, the amount and functional status of cytotoxic CD8⁺ T cells were also comparable in the two groups. The resulting impact on survival was limited: despite the presence of one long-term survivor, the survival of mice treated with RT-TMZ- α PD1 did not statistically differ from that of animals receiving RT-TMZ. In view of the detrimental immune effect of TMZ, we also investigated the survival effects the combination of RT and α PD1 without TMZ. However, such treatment did not provided a survival advantage. This therapeutic option has already been tested in patients in the Checkmate 498 trial (NCT 02617589): also in this study, α PD1 failed to increase survival compared to the control arm.⁴³

The flow-cytometry time points were chosen based on the need of having all mice still alive and not at end stage. Therefore, time for analysis was set on day 20 for monotherapy experiments and on day 28 for combinatory experiments. It is commonly considered that the developing an adaptive immune response requires at least two weeks. However, new evidence indicates that (at least in mice) the modifications of adaptive immunity could be already detected two days after the end of checkpoint immunotherapy, supporting our choice of the time points for immune analysis.⁴⁴

Our positive results in mice treated with RT are in line with previous studies mostly showing that ionizing radiation can evoke a powerful immune response.^{11,16,45–47} Conversely, contradicting results are available concerning the immune modulatory capacity of TMZ.^{10,48} A recent study (published after the conclusion of our experiments) showed that the standard TMZ dosage (also used in our study) abolished the α PD1 effect in experimental GBM while a lower dosage did not.²⁵ Our results confirm that TMZ at standard dosage negatively affects the HGG immune microenvironment when combined with RT. In the present study, α PD1 was capable to only marginally change such immune landscape. Even if in contrast with other preclinical studies (performed with other tumor models)^{25,49,50}, our findings are in line with the negative results of the (already mentioned) most recent clinical trials.^{8,24} This confirms the translational impact of our approach. It is interesting to note that (in monotherapy experiments) α PD1 did not have relevant effects on the T cell compartment whereas it showed statistically significant

effects on innate immunity. This is in line with evidence proving the broad expression of PD1 on immune cells and its involvement in MDSCs regulation.^{51–53} To the best of our knowledge, our study represents the first demonstration of the possibility to modulate MDSCs via checkpoint blockade in HGG. Nevertheless, we believe that the current knowledge of immune checkpoint biology is still insufficient and that further studies are necessary.

This study has some limitations. First, we used one single tumor model (NS/CT-2A). However, this model shows an increased immune suppression (higher Tregs) compared to its monolayer-based counterpart; therefore, it is particularly suitable for immunotherapy studies.¹⁷ Second, immune cells were analyzed only with flow-cytometry, which does not provide information concerning the spatial distribution of immune cells. Nevertheless, flow-cytometry has the strong advantage of combining multiple markers thereby providing a very detailed characterization of immune landscape. Third, steroid treatment was not included in this study. Since corticosteroids are often used in HGG patients, their immunomodulatory properties should be taken into account.⁵⁴ Fourth, we characterized the suppression of adaptive immunity by measuring variations of Tregs and CD8⁺ T lymphocytes. Assessing other markers such as Lag-3, Tim-3 and Ctla-4 would have been provided more insights on lymphocytes exhaustion; however, we believe that our results already provide a sufficient indication of the immune status of the tumor microenvironment.

Conclusions

This study demonstrates that RT, TMZ and α PD1 are capable to induce treatment-specific “immune signatures” in HGG and that a positive immune reaction against the tumor is a fundamental prerequisite for the treatments to be successful. In line with the most recent clinical trials, in our setting the addition of α PD1 to the standard radio-chemotherapeutic regimen did not provide a significant survival benefit. This was due to lack of sufficient immune synergy between conventional and immune treatments, and highlights the need to re-design our combinatorial therapeutic strategies for HGG.

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Figure captions

Figure 1. Experimental outline. The study was aimed at evaluating the survival and the immune modulation induced by stereotactic MRI-guided arc RT (4 Gy, single dose), oral TMZ (50 mg/kg, four doses) or intraperitoneal α PD1 (100 μ g, three doses) as single agents or in combination on NS/CT-2A tumor-bearing mice. Control mice were left untreated. **A**; monotherapy experiment aimed at comparing RT, TMZ and α PD1 as single agents. **B**; combination experiment aimed at comparing RT, RT followed by TMZ (RT-TMZ) and RT-TMZ followed by α PD1 (RT-TMZ- α PD1). **C**; combination experiment aimed at comparing different triple combination schedule including RT, TMZ and α PD1.

Figure 2. Survival of mice treated with of RT, TMZ and α PD1 monotherapies. Survival analysis shows that both RT and TMZ induced a significant survival benefit (more relevant for RT), while the survival of α PD1-treated mice was comparable with that of the controls.

Figure 3. Immune characterization of mice treated with RT, TMZ and α PD1 monotherapies. **A**; impact of the treatments on the adaptive immune system of the tumor microenvironment. When compared to controls, RT induced a trend towards an increase of total T cells and CD8⁺ T cells. When compared with TMZ, RT significantly increased CD8⁺ T cells and CD8⁺ T cells/Tregs ratio. α PD1 did not induce significant modification of the T cells. **B**; impact of the treatments on the innate immune system of the tumor microenvironment. Total TAMs were significantly reduced after RT and TMZ treatment (to a greater extent by RT), whereas α PD1 only induced a trend towards such a decrease. However, only RT was capable to significantly reduce the proportion of the immune suppressive M2 TAMs. Similar results were found in the context of MDSCs. The monocytic subtype was significantly reduced by RT and TMZ (to a

greater extent by RT), while α PD1 induced a strong trend towards a reduction of this type of cells. The granulocytic subtype was significantly higher in TMZ-treated mice compared to the other conditions.

Figure 4. Immune characterization of mice responding and not responding to RT, TMZ and α PD1 monotherapies. **A;** modification in tumor volume (fold variation, measured with T2w-MRI) between the start and the end of the treatments (d11 and d19 post tumor cells inoculation, respectively). Treated mice were considered non-responders when the fold increase in tumor volume was equal or higher than that of the controls. Conversely, treated mice were considered responders when the fold increase in tumor volume was lower than that of the controls. Even if in different proportion, any treatment was capable to induce both responders and non-responders. **B;** characterization of the tumor-immune microenvironment of responder and non-responder mice. Responders showed an increased immune activation against the tumor and a reduced immune suppression, with significantly higher total T cells and CD8⁺ T cells and significantly lower Tregs, total TAMs and M2 TAMs compared to non-responders.

Figure 5. Survival of mice treated with RT alone or combined with TMZ and α PD1. The combination of RT with TMZ promoted a significant survival benefit compared with RT alone. The further addition of α PD1 at the end of the therapeutic scheme induced a trend towards a further prolongation of survival.

Figure 6. Immune characterization of mice treated with RT alone or combined with TMZ and α PD1. **A;** impact of the treatments on total T cell, CD8⁺ T cells and Tregs in the tumor microenvironment. The administration of TMZ following RT induced a significant reduction of CD8⁺ T cells. Such a negative impact on the immune status of the mice was not altered after the administration of α PD1. The analysis of the CD8⁺ T cells/Tregs ratio showed a non-significant reduction after RT-TMZ compared to RT alone and a trend towards an increase after RT-TMZ- α PD1 compared to RT-TMZ. No significant modifications of Tregs were found between groups. **B;** impact of the treatments on the PD1⁺ fractions of CD4⁺ T cells, Tregs, CD4⁺FoxP3⁺ T cells and CD8⁺ T cells. RT-TMZ- α PD1 significantly reduced the fraction of PD1⁺ cells

448 within the CD4⁺ T cell and Treg populations in comparison with both RT and RT-TMZ. No significant
449 impact was found in CD4⁺FoxP3⁻ T cells and CD8⁺ T cells.

450 **Supplemental digital content**

451

452 **Supplemental digital content 1**

453 Title: supplemental materials and methods

454 File type: PDF.

455

456 **Supplemental digital content 2**

457 Title: workflow for stereotactic radiotherapy

458 File type: PDF

459

460 **Supplemental digital content 3**

461 Title: supplemental figures

462 File type: PDF

463 **Legends**

464 *Figure S3.1. A; impact of the treatments on the CD69+ fractions of CD4+ T cells, Tregs, CD4+FoxP3- T*
465 *cells and CD8+ T cells within the tumor microenvironment. No significant modifications were found. B;*
466 *Impact of the treatments on the innate immune system of the tumor microenvironment. RT-TMZ- α PD1*
467 *treated mice seemed to have reduced total TAMs, M2 TAMs and mMDSCs. However, because of the*
468 *large inter-individual variability, these findings were not supported by statistics.*

469 *Figure S3.2. Survival of mice treated with triple combinations of RT, TMZ and α PD1. No significant*
470 *differences in mice survival were found between the combination schedules of RT, TMZ and α PD1.*

471 *Figure S3.3. Immune characterization of mice treated with triple combinations of RT, TMZ and α PD1.*
472 *The different therapeutic combinations of RT, TMZ and α PD1 did not induced significant differences in*
473 *the adaptive (A) or innate (B) immune system of the microenvironment of NS/CT-2A tumors.*

474 *Figure S3.4. Survival of mice treated RT- α PD1 in comparison with RT, RT-TMZ and RT-TMZ- α PD1. The*
475 *survival of mice treated with RT- α PD1 was significantly shorter than mice treated with RT-TMZ- α PD1*
476 *(p=0.0126) and not significantly different from that of mice treated with RT alone (p=0.7275). A larger*

477 difference in survival was present between mice treated with RT- α PD1 and RT-TMZ, in the favor of the
478 latter therapeutic scheme; however, this result was not supported by statistics ($p=0.0654$).

479

480 **Supplemental digital content 4**

481 Title: published preclinical studies combining α PD1 with conventional therapies in high-grade gliomas

482 File type: PDF

Table 1. Published preclinical studies combining α PD1 with conventional therapies in high-grade gliomas. The effect of α PD1 combined with TMZ or RT was analyzed in five and two studies, respectively. We found no studying evaluating the efficacy of RT, TMZ and α PD1. Abbreviations: RT, radiotherapy, TMZ, Temozolomide; α PD1, anti-programmed cell death protein 1.

Study	Type of combination	Mouse model	Main finding
Karachi A et al, 2019 ²⁸	α PD-1/L1 + TMZ	GL261 and KR158	Depending on TMZ dosage, the positive effects of α PD1 treatment could either be promoted or abrogated.
Park J et al, 2019 ²⁹	α PD-1/L1 + TMZ	GL261	Combination of α PD1 and TMZ eradicated the tumor in all mice.
Guan X et al, 2018 ²⁷	α PD-1/L1 + TMZ	GL26 and SB28	TMZ showed synergy when combined with α PD1 and HOE642 (inhibitor of the Na/H exchanger isoform 1 (NHE1)). Data concerning the combination of only TMZ and α PD1 are not available.
Dai B et al, 2018 ³⁰	α PD-1/L1 + TMZ	GL261	Combination of TMZ with α PD1 prolonged survival compared with TMZ or α PD1 alone.
Mathios D et al, 2016 ³¹	α PD-1/L1 + TMZ	GL261	Combination of α PD1 with systemic TMZ does not prolong survival compared with TMZ alone. Conversely, α PD1 and local TMZ show synergism.
Kim JE et al, 2017 ³²	α PD-1/L1 + RT	GL261	Combination of RT with α PD1 prolonged survival compared with RT or α PD1 alone.
Zeng J et al, 2013 ³³	α PD-1/L1 + RT	GL261	Combination of RT with α PD1 prolonged survival compared with RT or α PD1 alone.

A

B

C

A

B

A

B

A

B

Supplemental digital content 1

Supplemental materials and methods

Data availability

The datasets produced, used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Brain tumor model

An orthotopic, immunocompetent HGG model recently developed by our group was used for this study.¹ This model is based on CT-2A neurospheres (NS/CT-2A) and it is specifically designed to address the tumor-induced immune suppression. Mycoplasma-free CT-2A cells were provided by Prof. Thomas Seyfried (Boston College, Boston, MA) and were incubated at 37°C in humidified air with 5% CO₂.² CT-2A NS were generated via serum-free culture in Dulbecco's Modified Eagle Medium / Nutrient Mixture F-12 (DMEM/F-12, Sigma-Aldrich) supplemented with epidermal growth factor (EGF, Thermofisher), fibroblast growth factor (FGF, Thermofisher) and B27 supplement (Thermofisher). After enzymatical dissociation (Stempro Accutase, Thermofisher), 5x10³ NS-derived CT-2A cells suspended in 4 µl of DMEM/F-12 medium were stereotactically inoculated in the right striatum of 12-14 weeks old, C57BL/6J mice (Envigo) under general anesthesia (Ketamine/Xylazine, Bayer). Stereotactic coordinates were: 2.5 mm lateral from the midline, 0.5 mm anterior to the bregma and 2.5 mm below the dura mater. After the inoculation of tumor cells, mice were followed up for weight loss and development of clinical symptoms. Endpoints for mice euthanasia were the presence of grade III-IV neurological symptoms or the loss of ≥ 20% of initial body weight. The neurological score was adapted from a previous publication.³

Of note, this model shows an increased immune suppression (higher Tregs) within the tumor microenvironment compared to its monolayer-based counterpart; therefore, it is particularly suitable for brain immunotherapy studies.¹

Brain tumor infiltrating immune cells

Mice were deeply anesthetized with an intraperitoneal (IP) injection of Pentobarbital (Lundbeck) and a transcardial perfusion with phosphate-buffered saline (PBS) was performed. The brains were harvested, mechanically disrupted using a scalpel and enzymatically digested with 1 mg/ml Collagenase I (Thermofisher), 2 mg/ml Dispase I (Thermofisher) and 100 µg/ml DNase I (Sigma Aldrich). After passing through a 70 µm cell strainer (Falcon), brain mononuclear cells were then isolated by means of a 25% Percoll gradient. Immediately after isolation, mononuclear cells were stained for tumor-associated microglia/macrophages (TAMs), monocytic and granulocytic myeloid-derived suppressor cells (mMDSCs)

and gMDSCs) and T cells as previously described.^{1,4} Dead cells were excluded based on Fixable Viability Dye (FVD) eFluor780 (Thermofisher) positivity. CD4⁺ and CD8⁺ T cells were identified within the total T cells (CD45⁺CD3⁺) population. CD4⁺ T cells also positive for FoxP3 were considered regulatory T cells (Tregs). CD69 and PD1 stainings were used in a subset of experiments in order to evaluate the activation status of T cells. Total TAMs were identified as CD45^{high}CD11b⁺Ly6G⁺F4/80⁺. TAMs also positive for CD206 were considered immune-suppressive alternatively-activated (M2) TAMs. Granulocytic and monocytic MDSCs (gMDSCs and mMDSCs) were identified as CD11b⁺Ly6G⁺Ly6C^{intermediate} and CD11b⁺Ly6G⁺Ly6C^{high} cells, respectively. Samples were acquired using a BD FACSCanto™ II (BD Bioscience) and results were analyzed with the software FlowJo v.10 (FlowJo LLC). Flow cytometry gating strategies and antibodies for T cells, TAMs and MDSCs can be found here below.

T cells gating strategy

T cells antibodies

Target	Fluorophore	Clone	Company
FVD	eFluor 780	-	Thermofisher
CD45	APC	104	eBioscience
CD3	APC eFluor780	145-2C11	eBioscience
CD4	PerCP Cy5.5	RM4-5	eBioscience
CD8	BV421	53-6.7	BD Biosciences
PD1	PE	J43	BD Biosciences

CD69	PE/Cy7	H1.2F3	Biolegend
FoxP3	AF488	R16715	BD Biosciences

Tumor associated macrophages/microglia gating strategy

Tumor associated macrophages/microglia antibodies

Target	Fluorophore	Clone	Company
FVD	eFluor 780	-	Thermofisher
CD11b	PerCp Cy5.5	M1/70	eBioscience
CD45	APC	104	eBioscience
Ly6G	Fitc	1A8	BD Biosciences
F4/80	BV421	T45-2342	BD Biosciences
CD206	PE	C068C2	Biolegend

Myeloid-derived suppressor cells gating strategy

Myeloid-derived suppressor cells antibodies

Target	Fluorophore	Clone	Company
FVD	eFluor 780	-	Thermofisher
CD11b	PerCp Cy5.5	M1/70	eBioscience
Ly6G	Fitc	1A8	BD Biosciences
Ly6C	APC eFluor780	HK1.4	Invitrogen

Magnetic resonance imaging (MRI)

MRI was performed using a 7T Biospec small animal MR system (Biospec 70/30, Bruker BioSpin) and a Paravision 6.0 software (Bruker BioSpin), as previously described.¹ Mice were anesthetized with isoflurane (Baxter) at 1.5-2% and rapid acquisition relaxation enhancement (RARE) T2-weighted (T2w) images were acquired with the following parameters: RARE factor 8, repetition time / echo time 2843.5/35 ms, field of view 25×25 mm, matrix 256×256 pixels, slice thickness 0.5 mm with no slice gap. For each mouse, 25 coronal-oriented slices were acquired covering the whole brain. To measure the tumor volume, the tumor area was manually delineated on each slice using the software ImageJ (<http://rsb.info.nih.gov/ij>) and the total volume was calculated by multiplying the tumor area of each slice by the slice's thickness and summation.

Radiotherapy

Stereotactic external beam MRI-guided arc RT was performed using a Small Animal Radiation Research Platform (SARRP, Xstrahl Life Sciences). Each irradiated mouse received a dosage of 4 Gy delivered in one single administration. Previously acquired T2w-MRI images were transferred to the SAARP workstation and merged with a cone beam computed tomography (CBCT) acquired directly on the SAARP. The irradiation's isocenter was placed visually in the center of the tumor. The treatment plan consisted in one 356° arc with a choice of a square collimator of 5x5 mm such that the entire tumor volume received the prescribed radiation dosage in one single dose. Isodose lines confirmed that any visible tumor received the full radiation dose whereas most of the surrounding healthy brain was spared. During the whole irradiation procedure, mice were kept anesthetized with isoflurane (Baxter) at 1.5-2%. RT workflow is described in Supplemental digital content 2.

Chemotherapy

Temozolomide capsules of 20 mg (Temodal®, Merk Sharp & Dohme) were dissolved in PBS at a concentration of 10 mg/ml. To increase solubility, 10 mg/ml of L-histidine (Sigma Aldrich) was added and the suspension was placed in a sonication bath for 30 minutes. Temozolomide was administered by oral gavage. Each TMZ-treated mouse received four doses of 50 mg/kg on alternate days.

Checkpoint blockade

For the production of the murine α PD1 blocking antibodies, the α PD1 hybridoma (clone RPMI-14) was cultured in Iso-cove's Modified Dulbecco's Medium (IMDM, Lonza) containing 1% (ultralow IgG) fetal bovine serum (FBS) and 50 ug/ml gentamycin. The antibodies were purified from clarified supernatant using thiophilic agarose based affinity chromatography and formulated in PBS sterile filtered over a 0.2 μ m filter.

Statistical analysis

Statistical analysis was performed with Prism v.8.0 (Graphpad Software). For survival, a log-rank (Mantel-Cox) test was used and data were expressed as median survival. For flow cytometry and MRI, normally-distributed data were expressed as mean and standard deviation and unpaired t test with Welch's correction (for comparison between two groups) or parametric ANOVA (for comparison between three or more groups) was used for comparison. Not normally-distributed data were expressed as median and interquartile range and Mann-Whitney (for comparison between two groups) or non-parametric Kruskal-Wallis test (for comparison between three or more groups) was used for comparison. A 2-tailed p-value <0.05 was considered significant.

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Supplemental digital content 2

Workflow for stereotactic radiotherapy

1. The mouse (#) is put under gas anesthesia (Isoflurante 1.5-2%) and installed in the Xstrahl SAARP

2. The CBCT is acquired.

3. Previously-acquired brain T2w MRI images are transferred to the SARRP (*, tumor mass).

4. The brain T2w MRI is manually aligned and merged with the CBCT.

5. The density map is semi-automatically generated based on the CBCT.

6. The irradiation isocenter is manually put in the center of the tumor and dose isolines (resulting from a 5x5 mm square collimator) are calculated. All the visible tumor receives the prescribed irradiation dose and most of the surrounding healthy brain is spared. After checking the correctness of the treatment plan, the irradiation is executed.

Supplemental digital content 3

Supplemental figures

Figure S3.1. A; impact of the treatments on the CD69+ fractions of CD4+ T cells, Tregs,

CD4+FoxP3- T cells and CD8+ T cells within the tumor microenvironment. No significant modifications were found. B; Impact of the treatments on the innate immune system of the tumor microenvironment. RT-TMZ- α PD1 treated mice seemed to have reduced total TAMs, M2 TAMs and mMDSCs. However, because of the large inter-individual variability, these findings were not supported by statistics.

Figure S3.2. Survival of mice treated with triple combinations of RT, TMZ and α PD1. No significant differences in mice survival were found between the combination schedules of RT, TMZ and α PD1.

Figure S3.3. Immune characterization of mice treated with triple combinations of RT, TMZ and α PD1. The different therapeutic combinations of RT, TMZ and α PD1 did not induced significant differences in the adaptive (A) or innate (B) immune system of the microenvironment of NS/CT-2A tumors.

Figure S3.4. Survival of mice treated RT-αPD1 in comparison with RT, RT-TMZ and RT-TMZ-αPD1. The survival of mice treated with RT-αPD1 was significantly shorter than mice treated with RT-TMZ-αPD1 ($p=0.0126$) and not significantly different from that of mice treated with RT alone ($p=0.7275$). A larger difference in survival was present between mice treated with RT-αPD1 and RT-TMZ, in the favor of the latter therapeutic scheme; however, this result was not supported by statistics ($p=0.0654$).

Supplemental digital content 4

Published preclinical studies combining α PD1 with conventional therapies in high-grade gliomas

Medline

("glioblastoma" OR "glioblastomas" OR "glioma" OR "gliomas" OR "high grade glioma" OR "high grade gliomas" OR "high-grade glioma" OR "high-grade gliomas")

AND

("checkpoint inhibitors" OR "checkpoint blockade" OR "antiPD1" OR "antiPD-1" OR "PD1" OR "PD-1" OR "antiPDL1" OR "antiPD-L1" OR "PD-L1")

Results (summary)

Preclinical, α PD-1/L1: 32

Preclinical, α PD-1/L1 + TMZ: 5

Preclinical, α PD-1/L1 + RT: 2

Preclinical, α PD-1/L1 + RT +TMZ: 0

Results (list of publications)

1: Liu JR, Yu CW, Hung PY, Hsin LW, Chern JW. High-selective HDAC6 inhibitor promotes HDAC6 degradation following autophagy modulation and enhanced antitumor immunity in glioblastoma. Biochem Pharmacol. 2019 Mar 15;163:458-471. doi: 10.1016/j.bcp.2019.03.023. [Epub ahead of print] PubMed PMID: 30885763.

2: Rajani KR, Carlstrom LP, Parney IF, Johnson AJ, Warrington AE, Burns TC. Harnessing Radiation Biology to Augment Immunotherapy for Glioblastoma. Front Oncol. 2019 Feb 22;8:656. doi: 10.3389/fonc.2018.00656. eCollection 2018. Review. PubMed PMID: 30854331; PubMed Central PMCID: PMC6395389.

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Nat Med. 2019 Mar;25(3):359-361. doi: 10.1038/s41591-019-0385-7.

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PubMed PMID: 30790064.

9: Ivanov VN, Wu J, Wang TJC, Hei TK. Inhibition of ATM kinase upregulates levels of cell death induced by cannabidiol and γ -irradiation in human glioblastoma cells.

Oncotarget. 2019 Jan 25;10(8):825-846. doi: 10.18632/oncotarget.26582. eCollection 2019 Jan 25.
PubMed PMID: 30783513; PubMed Central PMCID: PMC6368233.

10: Wang X, Guo G, Guan H, Yu Y, Lu J, Yu J. Challenges and potential of PD-1/PD-L1 checkpoint blockade immunotherapy for glioblastoma.

J Exp Clin Cancer Res. 2019 Feb 18;38(1):87. doi: 10.1186/s13046-019-1085-3. Review.
PubMed PMID: 30777100; PubMed Central PMCID: PMC6380009.

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