come. Patients with PS ≥ 2 at diagnosis carried longer diagnostic delay (31
vs 56 days, p=0.015). Age (HR: 1.02 (1.0–1.049), p=0.045) and diagnosis in
more than 46 days from clinical onset (HR: 2.4 (1.38–4.22), p=0.002)
were identified as risk factors for having poorer PS. CONCLUSION: Stereot.
administration was associated with a diagnostic delay. Younger patients, PS <
2, and, surprisingly, male gender were independent prognostic factors of
better survival in treated patients, OS, even for treated patients was clearly
inferior to that reported in clinical trials.

OS09 IMMUNOLOGY

OS09.1 RADIOSENSTIVITY GENE SIGNATURE AND PD-L1 STATUS
PREICT CLINICAL OUTCOME OF PATIENTS WITH LOWER
GRADE GLIOMA IN THE CANCER GENOME ATLAS (TCGA)
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BACKGROUND AND PURPOSE: A radiosensitivity gene signature that
included 31 genes was identified using microarray data from NCI-60 cancer
cells; however, this signature has not been validated in independent data-
sets for lower grade glioma patients. We investigated the link between
radiosensitivity gene signature and programmed cell death ligand 1 (PD-1) status and
clinical outcome in order to identify a group of patients that would receive
clinical benefit from radiotherapy (RT) combined with anti-PD-1/PD-L1 therapy.
METHODS: We validated the identified gene signature radiosensitivity and analyzed
the PD-L1 status and lower grade glioma in The Cancer Genome Atlas (TCGA) dataset using
bioinformatic tools. To validate the gene signature, 316 samples were divided into two
clusters using a consensus clustering algorithm based on expression profile
of the 31 genes. Two clusters were classified as their radiosensitive (RS) or radioresistant (RR). Patients were also
stratified as PD-L1-high or PD-L1-low based on the median value of CD274
mRNA expression level as surrogates of PD-1. The relationship between the RS/RR groups and PD-L1 status was also assessed and visualized with
heat maps. The prognostic value was evaluated by Kaplan-Meier analysis and
Cox proportional hazard models. RESULTS: Patients assigned to the RS
had better 5-year overall survival (OS) rate than patients in the RR
by univariate analysis (63% vs. 52%, p=0.019) only when patients
were treated with primary RT. The RR group was independently associated with
the PD-L1-high group, and PD-L1 mRNA expression was signific-
tantly higher in the RR group (p<0.001) compared to that of the RS group.
Among patients treated with elective primary or postoperative adjuvant RT,
the RS group had better 5-year OS rate compared to the RR group in the
PD-L1-high group (78% vs. 50%, p=0.031), and this difference was also
significant by multivariate analysis (Hazard ratio=0.38, p=0.031). ESTI-
MATE: The performance of the represented RS/RR gene signature, which
prominently correlated with PD-L1 mRNA expression level (p<0.001), and thus,
we speculated that the PD-L1-high group had more immunogenic tumors,
which could be more sensitive to radiation-induced immunologic cell death.
CONCLUSION: The upregulated radiosensitivity gene signature was also associated with
the PD-L1-high group. The results suggest that the combination of
radiotherapy with immunotherapy would be a promising therapeutic
strategy, and may improve the clinical outcome.

OS09.2 ENHANCING IMMUNITY WHILE NEUTRALIZING T CELL-
INDUCED IMMUNOSUPPRESSION THROUGH COMBINATORIAL
IMMUNOTHERAPY OF GBLOSTOMA
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Glioblastoma (GBM) is a common malignant brain tumor with a median
overall survival of 14.6 months. Using Hi-Seq. Illumina data from the
cancer genome atlas, we recently discovered the presence of immunosup-
presssive indoleamine 2,3 dioxygenase 1 (IDO1) mRNA in ≥95% of patient-
resected glioblastomas. This was in contrast to the presence of IDO1 in only
49% and 69% of patient-resected grade II (n=225) and grade III glioma
(n=208), respectively. Multivariate statistical analysis demonstrate that, a
high IDO1 mRNA level is a prognostic for GBM patient survival (n=148;
P=0.0076). Coincidently, the presence of mIDH1/2 is associated with a
decline in IDO1 mRNA, regardless of glioma grade (P<0.01). However,
while increased methylation of IDO1-specific CpG motifs correlate with
decreased IDO1 levels in grade II and III glioma (P<0.0005), there is no corre-
lation in GBM. Also puzzling, the canonical IDO1-inducing cytokine, interfer-
ongamma (IFNg), fails to correlate with IDO1 expression in GBM. In
contrast, high expression for markers of tumor-infiltrating T cells, CD3e and
CD8a, strongly correlate both with high IDO1 levels and decreased GBM
patient survival (P<0.0001). To further explore the interaction of T cells,
IDO1 and GBM, humanized mice reconstituted with a human immune sys-
tem (ie. NSG-SGM3-BLT) and intracranially-engrafted human GBM were
kept with control IgG, or anti-human T cell depleting mAb. Our
study showed that the first time that turning on human T cells resident in
human GBM mRNA expression in human glioblastoma (n=3–8/group; P<0.01)
through an IFNg-independent mechanism. To understand the therapeutic
implications of these findings, C37BL6 mice with well-established (14 day para-
implantation) small syngeneic GL261 were treated with control IgG, 10Gy whole
brain radiation (WBR), PD-1 mAb and/or a phosphodiesterase (PDE) inhibitor,
potent, blood brain barrier-penetrating IDO1 inhibitor; BGB-717777. While
neither monotherapy nor dual therapeutic combinations affected sur-
vice, the triple treatment of WBR, with PD-1 and IDO1 blockade, led to a
delay in overall survival and durable survival >40% (group 1 vs. group 3
P<0.0001) that was abrogated by T cell-depleting mAb (n=8–10/
group; P<0.01). These data suggest that, future approaches aimed at elicit-
ing immune-mediated GBM destruction should consider the simultaneous addi-
tion of IDO1 and PD-1 pathway inhibitors to achieve durable survival
in patients with incurable brain cancer.

OS09.3 SYNERGISTIC ACTIVITY OF NKG2D-BASED CHIMERIC
ANTIGEN RECEPTOR (CAR) T CELLS AND RADIOTHERAPY
AGAINST GLIOMA
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INTRODUCTION: Glioblastoma is the most common primary brain
tumor in adults and virtually always lethal despite a multimodal treatment
regimen including surgery, chemotherapy and radiotherapy. Therefore, novel
treatment modalities are needed. Adoptive immunotherapy with genetically
engineered T cells that express a chimeric antigen receptor (CAR) to recognize
and eliminate tumors in a MHC-independent manner is an emerging strategy
that has led to remarkable responses in hematologic malignancies. CARs that
target the natural-killer group 2 member D (NKG2D) system elegantly use
the promiscuous binding properties of the NKG2D receptor that binds to several
tumor-associated ligands. NKG2D-based T cell CARs have never been inves-
tigated in brain glioma. The goal of this study was to evaluate the effect
of chNKG2D T cell therapy on glioma growth in a NSG mouse model.
MATERIAL AND METHODS: CAR T cells were generated by retrovirual transduction of spleenocytes to express
a NKG2D-based CAR (chNKG2D) or wildtype NKG2D (wtNKG2D). For
in vivo studies, murine glioma cells (GL-261, SMA-560, SMA-540, SMA-
407) were co-cultured with chNKG2D or wtNKG2D T cells and we assessed
the cytolytic activity and cytokine production. For in vitro studies, we used
GL-261 cells syngeneic to C57BL/6 mice and monitored tumor growth
in vitro with fluorescence molecular tomography (FMT), flow cytometry and immunohistochemistry. To study the combination of radiotherapy with CAR T cells, mice received a single
subcutaneous dose of local radiation with chNKG2D or wtNKG2D T cell
lines, chNKG2D T cells had a significantly higher specific cytolytic activity
compared to wtNKG2D T cells. Furthermore, chNKG2D T cells produced
more IFNg. In vivo, intravenously injected chNKG2D T cells migrated to
the orthotopic tumor site, were tolerated without toxic effects directly into
the survival and cured a fraction of tumor-bearing mice. This anti-tumor effect
was even more pronounced in case of intratumoral CAR T cell administra-
tion. Survivors were long-term protected against tumor re-challenge. Mecha-
nistically, this was not the result of a classical immune memory response, but
rather due to local persistence of chNKG2D T cells. Radiotherapy augmented
the effect of chNKG2D T cell therapy already after a single application of
a subtherapeutic dose. It promoted migration of CAR T cells to the tumors
and the effector function of CAR T cells. CONCLUSION: We
provide the first systematic preclinical assessment of CAR T cell-based
immunotherapy using a human GBM patient xenograft model.

OS09.4 IDENTIFICATION OF A NOVEL H3.3.K27M MUTATION-
DERIVED NEOANTIGEN EPIPOTE AND CLONING OF H3.3.K27M-
SPECIFIC T-CELL RECEPTOR FOR CAR T CELL THERAPY IN GLIOMA
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Brain cancers are the leading cause of cancer related mortality and morbidity
in children and young adults. Children with diffuse intrinsic brain-