antimitotic effects of TTFields discerned the positive combinatorial potential of TTFields with other agents targeting the division process. Subsequent to elucidation of anti-mitotic effects, other downstream effects of TTFields include induction of endoplasmic reticulum stress, up-regulation of autophagy and cell death, thus driving immunogenic cell death. Indeed, in several preclinical models, combining TTFields with immunotherapeutics demonstrated enhanced efficacy. Recently, additional novel effects of TTFields were characterized, including inhibition of DNA damage repair responses and induction of transient and reversible permeabilization of the blood brain barrier (BBB). These new findings offer potentially innovative means to optimize treatment outcomes by combining TTFields with radiation therapy and DNA damaging agents, as well as improved delivery of impermeant agents across the BBB. These scientific findings were instrumental in advancing the clinical pipeline of TTFields, which includes conduct of ongoing trials combining TTFields with a variety of modalities, in approved indications and in other solid malignant tumor types. The aim of this talk is to describe TTFields' preclinical research activities and tools, and to specify how these study outcomes have defined and advanced the clinical pipeline.

SS-4

HIGH DOSE CHEMOTHERAPY WITH AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR CNS LYMPHOMA

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High-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (HDT-ASCT) is listed as a consolidation therapy option for primary central nervous system (CNS) lymphoma in the guidelines of western countries. The advantages of HDT-ASCT for primary CNS lymphoma as consolidation are believed to be high rates of long-term remission and lower neurotoxicity, even though its eligibility is limited to younger fit patients. In the Japanese guideline, HDT-ASCT for primary CNS lymphoma is however not recommended in daily practice, mainly because thiotepa was unavailable since 2011. The Japanese registry data for hematopoietic transplantation have shown that primary CNS lymphoma patients were treated with various HDT regimens and thiotepa-containing HDT was associated with better progression free survival (P=.019), lower relapse (P=.042) and a trend toward a survival benefit (Kondo E et al, Biol Blood Marrow Transplant 2019). A pharmacokinetic study of thiotepa(DSP-1958) in HDT-ASCT for lymphoma was conducted in 2017, and thiotepa was approved for HDT-ASCT in lymphoma this March, meaning that optimal HDT regimen for CNS lymphoma is now available in Japan. The treatment strategy of CNS lymphoma needs further development to improve survival and reduce toxicity.

SS-5

CURRENT MANAGEMENT OF PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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Primary CNS Lymphomas (PCNSLs) is a highly aggressive malignant tumor with poor prognosis and increasing incidence in elderly patients. High-dose methotrexate (HD-MTX) followed by whole-brain radiation therapy (WBRT) improves survival in PCNSLs. Several HD-MTX–based regimens, in combination with alkylating agents and rituximab, have been developed that can achieve high and durable complete response rates in patients with newly diagnosed PCNSL. In Japan, the R-MPV regimen using rituximab, HD-MTX, procarbazine, and vincristine has been recognized as the standard treatment for initial induction for newly diagnosed PCNSL. The optimal consolidative therapy for patients with disease responsive to induction chemotherapy is not yet defined. WBRT at standard dose (30–45 Gy) has a risk of neurotoxicity. To minimize the effects of delayed neurotoxicity, high-dose chemotherapy supported by autologous stem cell transplantation, reduced dose WBRT (23.4Gy), non-myeloablative chemotherapy, and maintenance chemotherapy have been addressed in large randomized trials. Gene expression profiling has provided insights into the pathogenesis of PCNSL. Recent insight into the pathophysiology of PCNSL has led to the investigation of targeted agents in the treatment of recurrent disease. In March 2020, Tirabrutinib (TIR), a second-generation oral Bruton's tyrosine kinase inhibitor, was approved for relapsed or refractory PCNSL based on the results of the phase I/II study in Japan. Seventeen of 44 patients treated with TIR at 480 mg fasted QD, an approved dose, had overall response rate of 52.9%, median progression-free survival of 5.8 months, and time to response as short as 0.92 months. The most common adverse event at any grade was rash (32%). The skin-related disorders were manageable with

appropriate skin treatments. However, greater attention and management is needed the case of more rare adverse events such as severe skin-related disorders and pneumocystis pneumonia. This lecture aims to present the recent development in treatment for PCNSL.

KNL-1

PATHOLOGIC DIAGNOSIS OF BRAIN TUMORS IN THE MOLECULAR ERA

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The WHO Classification of CNS Tumors, first published in 1979, was revised four times during the recent four decades. The revision was based on the refinement of tumor entities and introduction of new entities, which were facilitated by the development of new investigative techniques, such as immunohistochemistry and molecular cytogenetics. More sophisticated approaches including NGS and methylation analysis will introduce more molecularly defined entities in the next WHO Classification. The molecular analyses are a very powerful tool for brain tumor research. They have disclosed molecular mechanisms of several tumors and discovered unrecognized tumor entities till then. More precise biologic behavior could be estimated by molecular profiles. Furthermore, the development of novel molecular-targeted therapies will be expected. In the clinical practice, brain tumors should be diagnosed stepwise. First, clinical and image information is mandatory. Histopathologic and immunohistochemical findings should be evaluated within the clinical context. For molecularly defined tumors, genetic analyses are necessary. Following the stepwise procedures, the risk of falling in pit-falls may be decreased. In the molecular era, the integrated diagnosis, combined histopathologic and molecular information, of brain tumors is necessary. Recently, the Japanese Society of Pathology (JSP) has started the project which foster next-generation pathologists interested in rare cancers including brain tumors. In addition, some molecular information could be gained through the consultation system run by JSP and the National Cancer Center Japan. To adapt the next, more detailed molecular classification, it may be necessary that the cancer genome panel test become available within the national health insurance system.

MS-1

SURGICAL STRATEGY FOR BRAIN TUMOR BASED ON MOLECULAR AND FUNCTIONAL CONNECTOMICS PROFILES

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It is reported that the development of new perioperative motor deficits was associated with decreased overall survival despite similar extent of resection and adjuvant therapy. The maximum safe resection without any neurological deficits is required to improve overall survival in patients with brain tumor. Surgery is performed with various modalities, such as neuro-monitoring, photodynamic diagnosis, neuro-navigation, awake craniotomy, intraoperative MRI, and so on. Above all, awake craniotomy technique is now the standard procedure to achieve the maximum safe resection in patients with brain tumor. It is well known that before any treatment, gliomas generate globally (and not only focally) altered functional connectomics profiles, with various patterns of neural reorganization allowing different levels of cognitive compensation. Therefore, perioperative cortical mapping and elucidation of functional network, neuroplasticity and reorganization are important for brain tumor surgery. On the other hand, recent studies have proposed several gene signatures as biomarkers for different grades of gliomas from various perspectives. Then, we aimed to identify these biomarkers in pre-operative and/or intra-operative periods, using liquid biopsy, immunostaining and various PCR methods including rapid genotyping assay. In this presentation, we would like to demonstrate our surgical strategy based on molecular and functional connectomics profiles.

MS-2

MINIMALLY INVASIVE GLIOMA SURGERY WITH NAVIGATION SYSTEM AND TUBULAR RETRACTOR

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Navigation systems are reliable and safe for neurological surgery. Navigation is an attractive and innovative therapeutic option. Recently, endo and exoscopic surgeries have been gradually increasing in neurosurgery. We are currently trialing to use 4K and 8K systems to improve the accuracy and safety of our surgical procedures. Surgeries for deep-seated tumors are challenging because of the difficulty in creating a corridor and observing the interface between lesions and the normal area. In total, 315 patients underwent surgery at Okayama University between 2017 and 2019. Among them, we experienced 92 glioma surgeries using navigation systems. Preopera-

tively, we performed computed tomography imaging and contrast-enhanced magnetic resonance imaging (MRI) for the neuronavigation system. We experienced Curve(TM) Image Guided Surgery (BrainLab, Munich, Germany). The surgical trajectory was planned with functional MRI and diffusion tensor imaging to protect the eloquent area and critical vasculature of the brain. We used a clear plastic tubular retractor system, the ViewSite Brain Access System, for surgery of deep seated gliomas. We gently inserted and placed the ViewSite using the neuronavigation. The tumor was observed and resected through the ViewSite tubular retractor under a microscope and endoscope. If the tumor was large, we switched the ViewSite tubular retractor to brain spatulas to identify the boundary between the normal brain and lesion. We are currently using the combination of the tubular retractor and brain spatulas using navigation system. Here, we present and analyze our preoperative simulation, surgical procedure, and outcomes.

ES-1

CLINICAL RESULTS OF TUMOR TREATING FIELDS IN PATIENTS WITH GLIOBLASTOMA IN JAPAN, COMPARED WITH GLOBAL SURVEILLANCE

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INTRODUCTION: The tumor treatment field induces apoptosis of tumor cells by providing a low intensity, intermediate frequency, alternating current electric field via a transducer array. TTFields is based on Phase 3 EF-11 and EF-14 trials for glioblastoma in the US FDA and Japan PMDA. Therefore, I will report the statistics of TTFields use in Japan along with recent papers. METHODS: 410 patients were treated with TTFields in Japan (December 2017-), of which 17 were at Tokyo Women's Medical University. We also referred to papers about global post-marketing surveillance and recent studies. RESULTS: Of the 410 patients, 409 (99.8%) were diagnosed with ndGBM(male: female: 33.2%). As of June 2020, 222 patients (54.1%) were on treatment and 188 (45.9%) were discontinued. In 17 cases at TWMU, the average age was 46.3 years. The average treatment period was 218 days, with 6 patients (35%) continuing treatment, 6 patients (35%) discontinuing due to patient wishes, and 5 patients (30%) discontinuing treatment due to recurrence. Side effects were contact dermatitis under the array in 9 patients (57%) and mild malaise in 7 patients (43%). We experienced long-term progression-free cases with TTF use of 25 months (survival 30 months after surgery) with a glioma partially resected and 21 months (survival 27 months after surgery) with a biopsied glioma. In the biopsy case, bevacizumab was used in combination during the treatment. CONCLUSION: In global surveillance, use for rGBM accounts for 39%, but Japan is limited to use for ndGBM due to insurance coverage. In terms of side effects, it showed a good safety profile comparable to previous trials. Long-term progression-free cases have been observed, and it is necessary to examine the characteristics of patients who respond to treatment and the effect of concomitant use with bevacizumab by prospective studies

ES-2

PHASE 3 TRIDENT TRIAL: RADIATION AND TEMOZOLOMIDE WITH OR WITHOUT TUMOR TREATING FIELDS IN NEWLY DIAGNOSED GLIOBLASTOMA

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BACKGROUND: Tumor treating fields (TTFields) is a non-invasive, regional antimitotic treatment approved as a standard-of-care for glioblastoma. In the EF-14 Phase 3 trial, TTFields (200 kHz) plus temozolomide (TMZ) significantly increased survival of patients with newly diagnosed GBM(ndGBM) without increasing systemic toxicity. TTFields-related AEs were mainly skin AEs. In preclinical models, TTFields increase the therapeutic effects of radiation therapy (RT). A pilot study showed that TTFields concomitant with RT and TMZ is well tolerated. The benefit of concomitant TTFields with RT and TMZ will be tested in the TRIDENT trial. METHODS: TRIDENT is an international phase III randomized trial comparing standard RT/TMZ vs the triple combination of RT/TMZ with concomitant TTFields. RT is delivered through the TTFields arrays. Patients in both arms will receive maintenance TTFields/TMZ. TTFields (200 kHz) will be delivered over18 hours/day using Optune. Patients will continue TTFields treatment until second recurrence. Patients with pathologically confirmed ndGBM, over 18 years old, KPS over 70, either sex, post-surgery or biopsy, and amenable for RT/TMZ therapy will be stratified by extent of resection and MGMT promoter methylation status. The primary endpoint is overall survival (OS). Secondary end points: progression free survival (PFS; RANO),

1- and 2-year survival rates, overall radiological response (ORR; RANO), progression-free survival (PFS2, PFS6, PFS12); severity and frequency of AEs (CTCAE V5.0); pathological changes in resected GBM tumors post treatment; quality of life (EORTC QLQ-C30); and correlation of OS to TTFields compliance. The hypothesis is that concomitant TTFields/RT/TMZ will significantly improve OS versus RT/TMZ. Sample size (N=950; 475/arm) will detect a HR lower than 0.8 with 5% type I error. Survival will be measured from the time of randomization until date of death. At the time of analysis, patients lost to follow-up or still on protocol follow-up will be censored at the last date known to be alive.

ANGIOGENESIS/INVASION (ANGI)

ANGI-03

FUNCTIONAL ROLES OF CD166/ACTIVATED LEUKOCYTE CELL ADHESION MOLECULE (CD166/ALCAM) FOR GLIOBLASTOMA INVASION

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CD166/activated leukocyte cell adhesion molecule (CD166/ALCAM) is a transmembrane receptor, widely expressed in various tissues, and is involved in several functions such as cell adhesion, neurogenesis and angiogenesis. We have previously reported that CD166/ALCAM is expressed on glioblastoma progenitor cells and is involved in glioblastoma invasion. However, we only have analyzed the functional roles of ALCAM using glioblastoma cell lines, not using patient derived xenografts. In this study, we investigated the functional roles of CD166/ALCAM using patient derived xenografts. We established CD166/ALCAM knocked-down glioblastoma patient derived cell lines by shRNA. For in vitro analysis, we seeded control and CD166/ALCAM knocked-down glioblastoma cells on culture dishes and performed time lapse analysis to investigate cell motility. For in vivo analysis, we orthotopically injected control and CD166/ALCAM knocked-down glioblastoma cells into the immunodeficient mice. When the mice got sick due to the tumor, we dissected the mice and analyzed the difference in invasion by immunohistochemical analysis. We found that CD166/ALCAM knocked-down glioblastoma cells significantly decreased cell motility by time lapse analysis. In addition, CD166/ALCAM knocked-down glioblastoma cells suppressed cell invasion and leptomeningeal metastasis by immunohistochemical analysis from patient derived xenografts. Our results suggest that CD166/ALCAM is involved in glioblastoma invasion, thus future studies are necessary to investigate whether CD166/ALCAM could be a therapeutic target for glioblastoma.

CELL BIOLOGY/METABOLISM/STEM CELLS (CBMS)

CBMS-01

MECHANISM OF BRAIN TUMOR MALIGNANCY CAUSED BY AGING AND SOCIAL ISOLATION

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The rise in population aging worldwide is causing an unparalleled increase in death from many cancers, including glioblastoma (GBM). In advanced countries, the number of elderly people living alone is increasing due to the rapid aging of the population and the socialization of nuclear families. Here, we explored the impact of aging and social isolation on GBM tumorigenesis. In normal brain tissue, aging promoted pathways related to cytokines and inflammation, which were further promoted by social isolation. In tumor tissues, the expression of neuron/synapse-related genes was significantly reduced in aged mice, and their expression was further reduced by social isolation. In addition, the survival period of aged mice was significantly shorter than that of young mice, and the survival period was further shortened by social isolation, which was characteristic of males. This phenomenon was the same in humans, and the survival period in the young group was significantly longer than that in the elderly group, and in the elderly group, the survival period was shortened in the male elderly group living alone. Our data indicate that social isolation contributes to the highly aggressive GBM by the shift to neuro-inflammation in the elderly brain.