

might stratify the risk better than the current criteria have also been evaluated. Despite the discordance among the results of previous studies, CDKN2A/2B homozygous deletions have been shown prognostic significance in high-grade IDH-mutant astrocytomas and microvascular proliferation stratifies IDH-mutant gliomas lacking a CDKN2A homozygous deletion, suggesting that the integration of molecular information and traditional histological findings is still essential for achieving maximum risk stratification of adult cases of IDH-mutant diffuse gliomas. The grading scheme for adult IDH-mutant as well as wild-type gliomas should therefore be revised in the next WHO update.

## SL3

#### PRIMARY CNS LYMPHOMA: CURRENT CONCEPTS AND THERAPEUTIC PERSPECTIVES

Christian Grommes; Department of Neurology, Memorial Sloan Kettering Cancer Center

The lecture will summarize current standards of disease staging and treatment of Primary Central Nervous System Lymphoma (PCNSL). Concepts underlying the current first-line treatment regimen will be presented and current controversies in the treatment of PCNSL, including choice of induction regimen, choice of consolidation, and the roles of surgery/radiation/intrathecal therapy, will be discussed. In addition, the presentation will summarize novel insights into the pathophysiology of PCNSL, particularly the B-cell receptor signaling pathway (BCR). Results of completed and ongoing clinical trials targeting the BCR will be presented. The treatment standards in the recurrent setting will be summarized and additional novel therapeutic avenues, eg, immune checkpoint inhibition will be discussed. Furthermore, novel combinational clinical trials in recurrent/refractory setting will be discussed. Moreover, the diagnostic and prognostic value of novel, genomic testing and their integration into clinical trial development and clinical decision making will be discussed.

**Key words:** -Primary Central Nervous System Lymphoma, chemotherapy regimen, salvage therapy, B-cell receptor signaling pathway

## S5-KL-1

#### CURRENT TREATMENT FOR DLBCL AND PROPHYLAXIS AND TREATMENT FOR SECONDARY CNS LYMPHOMA.

Koji Izutsu; Department of Hematology, National Cancer Center Hospital

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of lymphoma, comprising 30% of all lymphoma cases. More than 60% of patients can be cured with current standard treatment, R-CHOP. On the other hand, prognosis of patients with relapsed or refractory DLBCL is disappointing with less than 10% being cured with salvage chemotherapy followed by high-dose chemotherapy with autologous stem cell transplantation. Prognosis of patients with central nervous system (CNS) relapse is especially poor because of a limited treatment option. Thus, evaluating risks of CNS relapse at diagnosis and administering prophylaxis including intrathecal methotrexate (MTX) or systemic high-dose MTX concurrently with R-CHOP or as consolidation therapy in high-risk patients are often-used approach. Clinically, higher risk according to the International Prognostic Index and extranodal involvement in organs such as kidney, adrenal gland, breast, testis, or bone marrow are considered to be high-risk for CNS relapse. Recently, CNS-International Prognostic Index has been proposed to integrate aforementioned risk factors. Moreover, patients with intravascular large B-cell lymphoma, CD5+ DLBCL, double hit lymphoma are reported as high-risk for CNS relapse. Further, the MYD88 L265P mutation, a common mutation in primary CNS DLBCL (PCNSL) is also common in DLBCL of testis or breast, which are the sites associated with CNS relapse.

Strategies for CNS prophylaxis have not established yet, and it is still unclear whether intrathecal MTX or high-dose MTX can prevent CNS relapse. Moreover, treatment for secondary CNS relapse have not been established. In particular, for those with both CNS and extra-CNS lesions, effective treatment options are very limited. The role of novel agents such as BTK inhibitors, lenalidomide, and immune check point inhibitors, whose efficacy have been shown for PCNSL, should be investigated further in the management of secondary CNS lymphoma.

**Key words:** Secondary CNS lymphoma, prophylaxis

## S5-KL-1

#### CANCER GENOMIC MEDICINE: FROM BENCH TO CLINIC

Hiroyuki Aburatani; Genomescience Laboratory, Research Center for Advanced Science and Technology, The University of Tokyo

Over the last two decades, genomic technology such as microarray and next generation sequencing (NGS) enabled comprehensive analysis of cancer genome. International cancer genome consortium, established in 2007, completed the analysis of 25,000 cases and has brought discovery of novel cancer driver genes and improved our understanding cancer biology. For

example, discovery of IDH1/2 mutation in various cancers created a new concept, 2-hydroxyglutarate as Oncometabolite. The mutational signature patterns allow us to predict how the individual cancer was developed. Anti-cancer drugs, such as alkylating agents, occasionally modify the bases and introduce mutations through mispairing in replication.

Currently we are aware that cancer is a genetic disease, where accumulation of genetic and epigenetic alterations in the genome leads to cellular transformation, and that mutation in each patient is unique. To realize the personalized oncology, clinical sequencing test was developed. This year a couple of NGS-based cancer panel tests have been approved for reimbursement by nation-wide healthcare system in Japan.

In this seminar I will discuss the future improvement in genomic oncology.

**Key words:** cancer genome, genomic oncology, mutation signature

## EL2

#### CHANGES IN JAPANESE ACADEMIC CLINICAL TRIALS AND FRAMEWORKS FOR PLANNING CLINICAL TRIALS

Kenichi Nakamura; JCOG Operations Office/Clinical Research Support Office, National Cancer Center Hospital

After the enforcement of the Japanese Clinical Trials Act, the number of investigator-initiated registration-directed trials (IIRDT, Chiken) is increasing while the number of non-registration academic trials is decreasing. Pharmaceutical companies tend to make an investment in IIRDT because the data derived from IIRDT can be utilized for new drug application for PMDA, which means the goals and return are clear for industries. On the other hand, the reason of the decrease of non-registration academic trials is the burden of cost and procedures specified in the Clinical Trials Act. In order to start academic trials, certain amount of research budget is indispensable due to the cost for certified review board and clinical trial insurance. Also, even minor changes of site information in jRCT should be submitted to certified review board and the hospital directors of all participating sites, which is one of the most serious burden for investigators. Confirmation of COI declaration in participating sites is another burden for investigators/sites. Under these circumstances, the number of non-registration academic trials will be decreasing for the time being.

In the Clinical Trials Act era, investigators must prepare some budget to start clinical trials. In order to obtain public funding, social/scientific value and scientific validity are substantially important. To express the social value sufficiently, the purpose of the trial should focus not on the researcher's interest but on the contribution for patients. In terms of scientific validity, the framework of PICO is useful; PICO means Patient, Intervention, Control and Outcome. Utilization of this framework and the consistency of these four factors are essential to make the trial design sound.

**Key words:** Clinical Trials Act, Chiken, Clinical Trial Design

## ANGIOGENESIS/INVASION (ANGI)

## ANGI-01

#### ALTERATION IN IMMUNE REGULATORY CELLS BEFORE AND AFTER TREATMENT BY STUPP REGIMEN WITH OR WITHOUT BEVACIZUMAB FOR GLIOBLASTOMA

Toshihide Tanaka<sup>1</sup>, Ryota Tamura, Yohei Yamamoto, Yukina Morimoto, Akihiko Teshigawara<sup>1</sup>, Satoru Tochigi<sup>1</sup>, Yuzuru Hasegawa<sup>1</sup>, Jun Takei, Yasuharu Akasaki, Hikaru Sasaki, Yuichi Murayama; <sup>1</sup>Department of Neurosurgery, Jikei University School of Medicine, Kashiwa Hospital, Chiba, Japan

**BACKGROUND:** In our previous study, bevacizumab (Bev), a humanized anti-vascular endothelial growth factor monoclonal antibody, downregulated the expression of programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) immune checkpoint molecules, suppressed the infiltration of immunosuppressing cells such as regulatory T cells (Tregs) and tumor-associated macrophages (TAMs), and induces cytotoxic T lymphocytes (CTL) infiltration. To explore the possibility that inhibition of immunosuppressive cell infiltration and induction of CTL were attributed to not only Bev alone but also radiation (RT) or temozolomide (TMZ), we re-evaluated those alterations in the tumor tissue obtained from patients before and after the treatment using Stupp regimen (RT concomitant with TMZ) without Bev therapy. **MATERIALS & METHODS:** We analyzed 10 tumor tissues from 5 patients with GBMs, which were paired samples of pre- and post-standard chemoradiotherapy (Stupp regimen: RT plus concomitant and adjuvant TMZ). Immunohistochemical analyses were performed on formalin-fixed, paraffin-embedded tissue of 10 tumors. The sections were stained with anti-Ki-67, anti-VEGF-A, anti-VEGFR1, anti-VEGFR2, anti-CD34, anti-HIF1 alpha, anti-CA9, anti-nestin, anti-PD-1, anti-PD-L1, anti-CD4, anti-CD8, anti-Foxp3, and anti-CD163 antibodies. All expressions were assessed by authors with blinded clinical information. **RESULTS:** Immunohistochemical analyses demonstrated that the expres-