A selected review of abstracts from the 19th annual meeting of the Society for Neuro-Oncology

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SUMMARY The Society for Neuro-Oncology is the largest neuro-oncology meeting in the USA that meets annually and provides a multiday venue presenting new brain cancer clinical trials and basic research data primarily pertaining to gliomas. The Society for Neuro-Oncology 2014 meeting comprising one education day, 3 days of presentation, over 200 oral presentations and 600 abstracts provides a comprehensive overview of neuro-oncology that includes metastatic diseases of the CNS as well as primary brain tumors. This summary attempts to highlight select abstracts presented at this year's meeting in a short review that provides a synopsis of a large and multifaceted meeting.

Metastatic disease to the CNS

• Parenchymal brain metastases

A study by Brastianos *et al.* [1] evaluated 101 matched primary tumors, brain metastases (BMs) and normal brain tissue interrogated by whole-genome sequencing. The analysis was designed to estimate the clonal architecture of the primary tumor and BMs thereby permitting construction of a phylogenetic tree from each patient. The results suggest that every BM arises from a single clone and both the primary tumor and the BMs share a common ancestor. Additionally, subclonal mutations within the BMs were seen and resulted in a different mutational signature when compared with the primary tumor. Novel mutational drivers were found in the BMs suggesting that clinically actionable mutations in the primary tumor are not necessarily reflective of the mutational composition of the BMs and that tissue analysis of the BMs may determine possible unique druggable targets.

Berghoff *et al.* [2] in a study of 170 BMs neurosurgical specimens performed a semiquantitative immunohistochemistry analysis of tumor-infiltrating lymphocytes (TILs). The majority of BMs (>90%) showed variable density of TILs and survival was positively correlated with the density of TILs, particularly CD3⁺ TILs. Additionally, membranous PDL1 expression was seen in 21% of BMs however was unassociated with outcome.

• Leptomeningeal metastases

LeRhun *et al.* [3] presented a case series of 112 patients with solid tumor related leptomeningeal metastases (LMs) all treated with intra-cerebrospinal fluid (CSF) liposomal cytarabine by way of a ventricular access device. A total of 12 complications (8% of all patients) related to the use of a ventricular device were seen including infection in seven, hemorrhage in two, leukoencephalopathy in two and device malposition in one. Two patients died as a consequence of a device-related complication. The retrospective study concluded that the use of a ventricular device for administration

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of intra-CSF chemotherapy is safe and with a comparatively low rate of device-related complications. Raizer *et al.* [4] presented preliminary Phase I data regarding the pharmacokinetics of intra-CSF trastuzumab in patients with LMs and based upon the results, a Phase II trial has commenced in patients with HER2/neu positive tumors and LMs.

Primary brain tumors

• Primary CNS lymphomas

Weller *et al.* [5] presented the final results of the German PCNSL trial comparing in patients with a complete response to high-dose methotrexate either whole brain radiation (WBRT) or observation only. Regardless if the analysis was performed in the intent to treat population ($n = 410$) or patients treated as specified per protocol ($n = 340$), there was no difference in progression-free survival (PFS) or overall survival (OS) in patients treated with WBRT compared with observation only. The study concludes that the potential-added neurotoxicity of WBRT need be balanced with marginal gains in survival.

• Gliomas

Low-grade gliomas

Buckner *et al.* [6] presented the results of the randomized Phase III Radiation Treatment Oncology Group trial (RTOG 9802) trial in high-risk low-grade gliomas (LGGs) comparing up-front RT (radiation therapy) only to RT + PCV (procarbazine, cyclonoxyl-chorethyl-nitrosourea [CCNU], vincristine) chemotherapy. In total, 251 patients (107 [43%] oligodendroglioma, 79 [31%] oligoastrocytoma, 65 astrocytoma [26%]) were accrued to trial and high risk was defined as either aged >40 years or less than complete resection of the LGGs. Median, 5-year and 10-year survival all favored RT + PCV (7.8 vs 13.3 years; 63 vs 72%; 40 vs 60%). Similarly and based on 10-year survival, RT + PCV resulted in better outcomes in all LGG histology (oligodendroglioma 57 vs 79%; oligoastrocytoma 25 vs 51%; astrocytoma 27 vs 43%). The median number of PCV cycles administered was 4 and 75% of patients completed the prescribed six cycles. There was $<5\%$ grade III toxicity observed with PCV and based on mini-mental status exams, 92% of patients had no deterioration during therapy. The study was however performed without molecular analysis of the LGGs (i.e., 1p19q codeletion, *IDH1* or *ATRX* mutation) and the definition

of high risk was novel. Nonetheless, the study suggests that all patients with high-risk LGGs as defined by RTOG 9802 be treated with RT + PCV, a practice changing treatment paradigm that recapitulates results of RTOG 9402 and EORTC 25691 in WHO grade III anaplastic oligodendroglial tumors. Whether temozolomide (TMZ) can be substituted for PCV is unclear as is whether PCV chemotherapy can be administered as first-line therapy with deferred RT. Both issues are being addressed in new clinical trials.

Glioblastoma

Radiology

Huang *et al.* [7] using the BRAIN clinical trial data attempted to validate the RANO criteria when compared with the Macdonald brain tumor response criteria. The RANO criteria incorporate T2W/FLAIR MRI changes to determine response unlike the Macdonald criteria. Both median PFS (4.6 months RANO vs 6.4 months Macdonald) and objective response rates (33% RANO vs 39% Macdonald) differed in a significant manner from response determined by Macdonald criteria.

Ellingson *et al.* [8] used contrast enhanced subtraction MRI maps in 80 glioblastoma (GBM) patients and when compared with standard post-contrast T1W MRI markedly improved the ability to assess and measure residual tumor post-operatively as well as when patients are treated with bevacizumab (BEV).

Angiogenesis

Park *et al.* [9] investigated periostin, osteoblast specific factor-2, and suggests that it has a role in glioma invasion, resistance to anti-angiogenesis therapy and mesenchymal differentiation, in other words, epithelial mesenchymal transition. Pham *et al.* [10] presented data demonstrating that antiangiogenic inhibitors upregulate CXCR4 and thereby enhance glioma invasion in a transforming growth factor-beta signaling dependent pathway as a possible mechanism of resistance to VEGF inhibitor. Scholtz *et al.* [11] demonstrated *in vitro* that targeting the TIE2/angiopoietin signaling pathway overcomes in part evasion to VEGF inhibition. Tabouret *et al.* [12] presented data showing that a switch in recurrent GBM from the hypoxia inducible factor/VEGF signaling pathway to the stroma-derived factor/CXCR4 pathway may in part account for evasion to angiogenic inhibitors.

Up-front trials

In an expedited late breaking abstract and oral presentation, Stupp [13] presented an analysis of the Novocure (NH, USA) up-front study, EF-14, comparing standard of care (SOC; RT + concomitant and adjuvant TMZ) with or without the Novocure device. The presentation was based on a preliminary evaluation of the initial 315 patients accrued to study (study enrollment to date is 692 patients of the expected 700 specified by protocol). Median PFS was 7.1 months in the Novocure arm and 4 months in the SOC arm (hazard ratio [HR]: 0.76); and similarly, median OS was 19.6 (Novocure) versus 16.6 months (SOC only; HR 0.76). Two-year survivorship was 43% in the Novocure arm and 29% in the SOC arm. These early results led to the study conclusion that Novocure is practice changing and should now in conjunction with RT + TMZ represent the new SOC for the treatment of newly diagnosed GBM. Additionally, based upon this analysis the sponsor and the disease and safety management board decided to cross over all patients on the EF-14 trial not currently receiving the device thereby prematurely terminating the study despite the protocol enrollment target of 700 patients for which the trial was statistically powered. Additionally and unexplained is the PFS in the SOC arm that was 2–3 months less than seen in other contemporary up-front GBM trials.

Two studies were presented regarding the AVAglio trial in which up-front BEV was used with SOC and compared with SOC only. Phillips *et al.* [14] presented data suggesting that GBM defined as proneural by molecular subtyping may represent a subgroup in which BEV used in the up-front setting is beneficial both with regard to PFS and OS. Wick *et al.* [15] presented a retrospective substudy in which patients enrolled in AVAglio who did receive therapy post-BEV progression, in other words, no crossover to BEV, in the SOC only arm showed inferior median OS compared with up-front BEV + SOC (8 vs 11.6 months).

Salvage trials

van den Bent *et al.* [16] reported the final results of the randomized Phase II trial of the Dutch BELOB trial in first recurrent GBM (n = 130) comparing BEV to CCNU to the combination of BEV + CCNU. Based upon a prespecified end point of 9-month OS, the combination was superior to either agent alone (43% in the CCNU arm, 38% in the BEV only arm and

59% in the combination arm). Based upon these preliminary results, the EORTC initiated and is completing a randomized Phase III trial (EORTC 26101) to definitely define the role of BEV + CCNU, a possible new and practice changing chemosynergy regimen for recurrent GBM.

Brandes *et al.* [17] presented the results of the Italian randomized Phase II study AVAreg (n = 91) comparing in recurrent GBM patients BEV versus fotemustine, a nitrosourea chemotherapy. Similar to that of the above-mentioned BELOB trial, there was equivalent 6-month OS outcomes, the primary study end point (62% BEV vs 73% fotemustine).

There were two presentations regarding the TOCA 511 system [18,19] wherein recurrent high-grade gliomas were treated with an intratumoral injection of a retroviral replicating vector (and gene transfer of cytidine deaminase) followed by oral 5-fluorocytosine (TOCA FC) that is converted intratumorally by cytidine deaminase into cytotoxic 5-fluorouracil. Both studies suggest this may a feasible treatment approach in select patients.

Reardon *et al.* [20] reported partial results of the REACT trial, in particular the randomized Phase II study component comparing BEV with or without the EGFRviii peptide vaccine, rindopepimut. Seven hundred patients were screened overall among whom 234 (30%) were positive for expression of the EGFRviii protein and therefore the trial. Seventy-two patients were enrolled in the randomized study. Objective response was 24% in the BEV + vaccine arm and 17% in the BEV + placebo vaccine arm. Similarly PFS-6 was 27% and 11% and median OS was 12 months and 8.8 months. These results suggest rindopepimut may augment response and duration of response in recurrent BEV naïve GBM that expresses the mutant EGFRviii protein to which the peptide vaccine is targeted.

Several other early-phase studies were presented that used a novel vaccine for recurrent GBM including the pilot study of a dendritic cell vaccine directed against cytomegalovirus epitopes (in combination with an anti-CD-25 antibody directed against Treg cells) [21], a survivin peptide mimic vaccine [22] and the randomized Phase II trial of the heptavalent (the glioma specific antigens MAGE-1, HER-2, AIM-2, TRP-2, gp100 and IL13R α 2) dendritic cell vaccine, INT-107, presented by Wen *et al.* [23]. In this later study, 124 patients were randomized

2:1 to active versus inactive vaccine. Median OS favored the INT-107 group by 1.7 months as did PFS (2.2 month improvement). Two very early-phase trials were presented using oncolytic viruses administered intratumorally, in one using a polio/rhinovirus recombinant [24] and the other a novel adenovirus, Delta 24-DRG [25].

Wick *et al.* [26] presented data from the German Glioma Network registry of 1004 patients in first relapse of GBM and indicated 37.3% had no further therapy after initial upfront treatment. Median OS in patients receiving salvage therapy (62.7%) was 14.2 months as contrasted with patients not receiving salvage therapy of 8.7 months. Older patients, patients with incomplete resections and lower performance status constituted the majority of patients not receiving salvage therapy.

Conclusion

SNO 2014 had as highlights several trials that may be practice changing. These include RTOG 9802 wherein high-risk LGGs as defined by the study should now receive RT + PCV instead of RT only. Newly diagnosed GBM based on preliminary (and currently unpublished data) results

from the Novocure EF-14 trial suggests that the device in conjunction with SOC improves both PFS and OS relative to SOC only. If substantiated, this trial likely will be practice changing. The Dutch BELOB trial (and the soon to be presented EORTC corroborative study) may change the manner in which BEV is administered in patients with recurrent GBM by suggesting that the combination of CCNU + BEV is superior to BEV only. Lastly, the results from REACT suggest in patients with tumors expressing the EGFRviii mutant that treatment with BEV + rindopepimut may be superior to BEV only, a possible new indication for immunotherapy in recurrent GBM.

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