

Highlights and Selected Abstracts from SNO 2016

By Chris Tse

The 21st Annual Scientific Meeting of the Society for Neuro-oncology (SNO 2016) took place in Scottsdale, Arizona on 18-20 November, 2016. There were over 2,350 attendees (200 more than in 2015) and 1,024 abstracts submitted (a record number, and 100 more than last year). This report highlights some selected abstracts from the conference.

Moving The Chains

In his 2016 SNO presidential address, E. Antonio Chiocca, used the American football analogy “moving the chains” to describe the steady but incremental progress made in the field of neuro-oncology over recent years. With advancements in new therapies, such as tumour treating fields and immunotherapies, and a greater understanding of underlying tumour biology, the stakes are higher to show benefit for a new therapy.

A definite game changer in 2016 was the updated **WHO classification of Central Nervous System (CNS) Tumours**, and this was the subject of several presentations throughout the conference. The most notable of these was delivered by pathologist Dr David Louis, this year’s recipient of the Victor Levin Award. In his keynote lecture Dr Louis explained how the new classification uses molecular parameters in addition to histology to re-define many brain tumour types, including IDH-wildtype and IDH mutant glioblastoma, H3 K27M-mutant diffuse midline glioma, and RELA fusion-positive ependymoma. These, and other important new classifications, will help guide future brain tumour diagnoses, treatment and research decisions.



E. Antonio Chiocca delivers his presidential address at SNO 2016

Successes and Setbacks

LTBK-01: Dr Roger Stupp presented this late breaking abstract reporting on the final analysis from EF-14, the phase 3 pivotal trial of Novocure’s **tumour treating fields** (Optune), in combination with temozolomide (TMZ), for newly diagnosed glioblastoma. This trial enrolled 695 patients who were randomised by a 2:1 ratio to Optune plus TMZ versus TMZ alone. The final data confirmed the previously reported interim results, showing median overall survival (mOS) from randomisation of Optune plus TMZ compared with TMZ alone at 20.8 months v 16.0 months respectively (HR = 0.65, p=0.0006). The median Progression Free Survival (mPFS) was 6.7 months for Optune plus TMZ compared with 4.0 months for TMZ alone.

Longer term analysis of survival at 2, 3 and 4 years showed 42.5%, 23.5%, 17.3% respectively for Optune plus TMZ against 30.0%, 15.9% and 10.4% for TMZ alone. Dr Stupp concluded that “adjuvant therapy with TT Fields significantly prolongs PFS and OS in patients with newly diagnosed GBM and should now be considered part of the standard of care for these patients”.

ATIM-03: One of the undoubted disappointments of 2016 was the ACT IV trial, a double-blinded, phase 3 trial of Celldex’s **rindopepimut** (Rintega) in newly diagnosed, EGFRvIII-positive GBM. This trial was stopped at the second interim analysis (futility boundary crossed, HR=0.99). The final analysis was presented by Dr Michael Weller. ACT IV enrolled 745 patients in more than 200 clinical trial sites across 22 countries. In the population with minimal residual disease (MRD) the mOS from randomisation was 20.1 months for rindopepimut compared with 20.0 months in the

control arm (HR=1.01, p=0.93). In patients with bulky disease, rindopepimut showed a slight advantage with mOS = 14.8 months versus 14.1 months in the control arm (HR=0.79, p=0.066) however this was not supported by the analyses of immune response, which were similar across all patient cohorts. Dr Weller concluded that no survival benefit was seen, despite achieving consistent rindopepimut-induced humoral (antibody) response, because the control arm survival exceeded predicted outcome based on historical matched data.

Immunotherapy Approaches

ATIM-35: Following their success in other cancer types, several checkpoint inhibitors are in clinical trials for brain tumours. Dr David Reardon reported results of the phase 1b KEYNOTE-028 multi-cohort (“basket”) trial of Merck’s checkpoint inhibitor **pembrolizumab** (Keytruda) in patients with recurrent, PD-L1-positive GBM. Pembrolizumab is an anti-PD-1 checkpoint inhibitor which is already approved in several countries for metastatic melanoma, metastatic non small cell lung cancer (NSCLC), and some head and neck cancers. The GBM cohort consisted of 25 bevacizumab-naïve, recurrent GBM patients. Primary endpoints were overall response rate (ORR) by RECIST v1.1 and safety.

ORR was 4% while 12 patients (48%) had stable disease (SD). Median duration of SD was an encouraging 39.4 weeks (range, 7.1+ to 85.9+ weeks). Although 73% of patients experienced an adverse event (AE) there were no treatment-related deaths or discontinuations and the overall safety profile was described as manageable. Progression free survival (PFS) at 6 and 12 months was 44% and 16% respectively. Overall survival (OS) at 6 and 12 months was 85% and 74%. Median PFS was 3 months (95% CI, 2-9) and median OS was 14 months (95% CI, 10-not reached). Dr Reardon concluded that further investigation of anti-PD-1 therapy in recurrent GBM was warranted and that a large, multi-centre, randomised phase 2 trial is now being planned.

ATIM-04: David Reardon also presented interim results from the phase 2 study of the PD-L1-inhibitor **durvalumab** (MEDI4736) in recurrent GBM. This is a five arm study with one arm for newly diagnosed GBM patients and four arms for recurrent GBM patients. Data from the bevacizumab-naïve recurrent GBM arm (n=30) which received durvalumab monotherapy was reported. Durvalumab was well tolerated with no Grade 4 or 5 treatment-related adverse events (TRAEs). Partial response (PR) was achieved by 4 patients (13.3%) while 14 patients (46.7%) had stable disease (SD) giving an overall Disease Control Rate of 18 patients (60.0%). Progression free survival at 6 months (PFS-6) was 20.0% (CI 90%) and median PFS was 13.9 weeks (CI 95%, 8.1, 24.0).



Kathy Oliver and brain tumour patient advocates Steven Keating and Laureline Gatellier at the IBTA booth

All patients who met PFS-6 were alive for more than one year, indicating promising durability of response. Median overall survival (mOS) was 28.9 weeks, overall survival at 6 months (OS-6) was 59.0% and OS-12 was 44.4%. The acceptable safety profile and encouraging efficacy results lead Dr Reardon to conclude that further investigation of durvalumab in recurrent GBM is warranted.

ATIM-21: “**IMA950** peptide-based vaccine adjuvanted with Poly-ICLC in combination with standard therapy in newly diagnosed HLA-A2 glioblastoma patients” was presented by Dr Denis Migliorini. This open label, single arm, phase 1/2 trial has enrolled 19 patients to date. Patients received standard concomitant radio-chemotherapy with TMZ followed by the IMA950 vaccine and adjuvant TMZ. Primary objectives were safety and immunogenicity. Secondary objectives were PFS, OS, immunological endpoints and correlation with clinical outcome. After the first 6 patients were dosed, the protocol was amended due to lack of peptide-specific immune response. The remaining 13 patients were split into

two arms, one receiving the vaccine subcutaneously and the other intramuscularly. The revised protocol fared better, with two patients showing an objective immune response. Median overall survival across all cohorts was 19 months. Three of the 13 patients under the amended protocol are still undergoing therapy and 5 others have completed study protocol and are being monitored without recurrence. There was no clear difference between the subcutaneous and intramuscular injections. IMA950 was well tolerated with the most common side effect being local inflammatory reaction at the injection site with mild fever. Dr Migliorini suggested that the next step could be combining IMA950 with PD1/PDL1 inhibitors, given the now established role of immune checkpoints in adaptive immune resistance to anti-tumour vaccines.

Novel solutions showing promise

ACTR-07: Dr Martin van den Bent presented results from the phase 1b trial of AbbVie's novel antibody drug conjugate **ABT-414**. ABT-414 consists of an antibody targeting the EGFR receptor conjugated with the potent cytotoxic agent monomethyl auristatin F (MMAF). ABT-414 binds amplified EGFR on the tumour cell surface, enters the cell and releases the cytotoxin. The cytotoxin binds to microtubules, leading to cell death. This trial enrolled patients with newly diagnosed or recurrent GBM. Primary endpoints were safety, pharmacokinetic (PK) profile and optimum dose. Results for an expansion cohort of recurrent GBM patients (n=60), all EGFR amplified, were reported. Ocular toxicity was the most common adverse event (AE) including blurred vision, eye pain, dry eye, photophobia and keratitis. The PFS-6 was 28.3% and OS-6 was 73.3%. Two further trials are being conducted: a global, randomised trial of ABT-414 alone or with TMZ, vs TMZ or lomustine ([Intelligence 2](#)) has completed accrual in EGFR amplified, recurrent GBM; and a global, randomised trial in EGFR amplified, newly diagnosed GBM ([Intelligence 1](#)) evaluating the addition of ABT-414 to standard therapy (RT/TMZ) is currently enrolling.



SNO delegates arrive for a sunrise session at the conference centre at the Fairmont Princess Hotel in Scottsdale, Arizona

ACTR-46: Ever since a genome wide sequencing of glioblastomas revealed somatic mutations in the IDH1 and IDH2 genes, researchers have sought to exploit these mutations as therapeutic targets. Approximately 5% of GBMs and 80% of grade II/III gliomas harbour the R132H IDH1 mutation (or its related IDH2 mutation). Agios's **AG-120** is an oral inhibitor of IDH1 which has been shown to reduce 2-HG (the onco-metabolite produced by IDH1 mutant cells) in IDH1-mutant cancer cells. Dr Ingo Mellinghoff presented data from a phase 1 dose escalation and expansion study of AG-120 which enrolled 66 patients with recurrent or progressive IDH mutated glioma. In the dose escalation arm (n=20), 500mg daily was identified as the recommended dose for the expansion phase.

Treatment was well tolerated with the majority of adverse events classified as grade 1 or 2. In the expansion phase, patients were split into two cohorts: non-enhancing IDH-mutant glioma (n=24) and enhancing glioma (n=22). In cohort 1 (non-enhancing glioma) 9% had minor response, 83% had stable disease and 9% had progressive disease. Volumetric analysis (by imaging) showed a decrease in tumour growth rate compared to pre-treatment rate in 64% of patients. As of 1 Aug 2016, 42% of patients remained on AG-120. Based on this study, Dr Mellinghoff concluded that further evaluation of IDH inhibitors in glioma was warranted. A [phase 1 study](#) of **AG-881**, a pan-IDH inhibitor, has opened for patients with glioma or other solid tumours with mutated IDH1 or IDH2.

Updates for grade II/III gliomas

ACTR-09: Dr Martin van den Bent presented updated survival data from the EORTC's [TAVAREC](#) trial. This was a randomised phase 2 trial of Roche's **bevacizumab** (Avastin) plus **temozolomide** (TMZ) versus TMZ monotherapy in patients with 1p/19q intact grade II and grade III recurrent glioma. The primary endpoint was 12 month overall survival (OS-12) and 155 patients were enrolled, randomised 1:1 to each arm. In the per protocol (PP) population, OS-12 was 61% in the TMZ alone arm versus 56% in the TMZ+Avastin arm. The overall response rate (ORR) was 40% in the TMZ alone arm versus 47% in the TMZ+Avastin arm. Progression free survival at 6 months (PFS-6) was 56% in both arms. Prior to TAVAREC there were no controlled trials investigating the role of bevacizumab in grade II/III recurrent glioma. The results of this study indicate no improvement of OS or PFS with the addition of Avastin to TMZ, leading the investigators to conclude that no further investigation of Avastin in this population is justified.

ACTR-04: Martin van den Bent also reported interim analysis from the EORTC randomised [phase 3 CATNON trial](#) on concurrent and adjuvant **temozolomide** (TMZ) in anaplastic glioma without 1p/19q co-deletion.

This trial enrolled a total of 748 patients with newly diagnosed grade III glioma without 1p/19q co-deletion. All patients received radiotherapy (RT) and were then randomised into four arms: i) RT alone; ii) RT with concurrent daily 75 mg/m² TMZ; iii) RT followed by 12 cycles of 150-200 mg/m² adjuvant TMZ on 5/28 schedule; iv) RT with both concurrent and adjuvant TMZ. At the pre-specified interim analysis, both groups receiving adjuvant TMZ were showing better overall survival (OS) (HR=0.645, p=0.0014) and longer PFS (HR=0.586, p < 0.0001). Patients were also stratified for MGMT status. MGMT was prognostic for OS but at this stage did not predict improved outcome to adjuvant TMZ.



IBTA chair Kathy Oliver speaking at the SNO International Outreach Meeting at SNO 2016

Treatments on the horizon

ATIM-05: Dr Manish Aghi presented updated survival and safety data from three phase 1, ascending dose studies of Tocagen's **Toca 511** and **Toca FC**. Toca 511 is a replicating retroviral vector which delivers a prodrug-activator gene cytosine deaminase (CD) into the tumour cells. Toca FC (extended release 5-fluorocytosine or 5-FC) is then administered orally and is converted by CD in the tumour cells to the cytotoxic 5-fluorouracil (5-FU). In the higher dose cohort (n=24), there was clinical benefit in 41.7% of patients (3 complete responses, 2 partial responses and 5 patients with stable disease). Median OS was 14.4 months and the median duration of response was 20.7 months. All patients with an objective response remain alive 24 to 43 months from study entry. Interestingly, immunological studies showed significant increases in proliferating peripheral blood T cells after treatment with Toca 511 and Toca FC. There is an ongoing [phase 2/3 trial](#) (Toca 5) for patients with glioblastoma or anaplastic astrocytoma at 1st or 2nd recurrence.

ATIM-19 and **ATIM-25:** There were two presentations about Immunocellular Therapeutics' dendritic cell (DC) vaccine **ICT-107** at the meeting. ICT-107 is a DC vaccine which is pulsed with six tumour antigens commonly expressed in GBM, currently being tested in a pivotal [phase 3 trial](#) in newly diagnosed GBM patients. In the first presentation, Dr Steven Swanson showed that treatment with ICT-107 resulted in the development of a measurable anti-tumour T cell response in some patients, which was associated with improved survival. In the second presentation, Dr Surasak Phuphanich reported on long term survivors from a prior phase 1 study of ICT-107 in newly diagnosed GBM. In this small trial (n=16), median PFS was 16.9 months and median OS was 38.4 months. However 6 of the 16 patients (38%) survived > 8 years and 3 patients are still disease free, with the longest survivor over 10.2 years. Five of the six long term survivors expressed all six tumour antigens, while all six survivors expressed 4 cancer stem cell antigens.

DDIS-11: In the Anticancer Drug Discovery and Development Conference, held in the two days prior to the SNO Annual Meeting, Del Mar Pharmaceuticals' CEO Jeffrey Bacha presented a report on **VAL-083** (dianhydrogalactitol), a small sugar derivative which readily crosses the blood-brain-barrier and is preferentially taken up by cancer cells. VAL-083 is a bifunctional alkylating agent which forms a cross link at the N⁷ position of guanine, causing DNA double-strand breaks and cell-cycle arrest in the S/G₂-phase. This mechanism of action is distinct from other alkylating agents, such as temozolomide and CCNU. In vitro studies have shown VAL-083's cytotoxic activity to be independent of both MGMT and p53 status, suggesting a potential therapy for unmethylated-MGMT GBM patients, and that it potentiates radiation in GBM cancer stem cells. There is also potential synergy with topoisomerase inhibitors such as irinotecan and etoposide, which require cells to be in the S-phase of the cell cycle for activity. Three clinical trials of VAL-083 are planned: a phase 3 randomised study in recurrent GBM patients who have failed bevacizumab, and two phase 2 studies in patients with unmethylated-MGMT, one for [recurrent GBM](#) and one for newly diagnosed GBM.

EXTH-18: Also at the Anticancer Drug Discovery and Development conference was an in vitro study on **ibudilast** (AV411) and temozolomide (TMZ) presented by Dr Kerrie McDonald. Ibudilast is approved in Japan for chronic asthma, bronchitis and multiple sclerosis (MS). In the USA it has recently received orphan drug designation as a potential treatment for amyotrophic lateral sclerosis (ALS). Ibudilast is an anti-inflammatory agent which blocks macrophage inhibitory factor (MIF) which, along with CD74, is highly expressed in recurrent GBM tumours. A preclinical study of ibudilast combined with TMZ in patient-derived cell lines showed inhibition of cell growth and reduced MIF protein. Interestingly, these results were achieved independent of MGMT methylation status. An in vivo study testing six different dose and combinations in patient-derived xenograft models is ongoing. Data from this study was unavailable as the mice were surviving longer than expected. Dr McDonald hopes to initiate human clinical trials in the near future.

The IBTA at SNO 2016

The IBTA was once again delighted to exhibit at the 21st Society for Neuro-Oncology Annual Scientific Meeting (SNO 2016). This year's meeting continued the trend of year on year growth, with record numbers of attendees and abstracts submitted. Two particular highlights for the IBTA were the presentation on patient advocacy and neurosurgery in sub-Saharan Africa given by our chair, Kathy Oliver, at the SNO International Outreach Meeting, and the SNO 2016 Public Service Award presented to Dr Mary Lovely who, amongst her other leading roles in the world of neuro-oncology, is an IBTA special advisor. In her acceptance speech, Dr Lovely described her international work with the IBTA as one of the highlights of her career. Last but not least, the IBTA would like to thank the SNO administration team, lead by Chas Haynes and Linda Greer, for their wonderful skills and dedication to ensuring the meeting ran smoothly. See you all in San Francisco in 2017!



IBTA special advisor, Dr Mary Lovely, delivers her acceptance speech for the SNO 2016 Public Service Award

Chris Tse (23 November 2016)

For and on behalf of the International Brain Tumour Alliance (IBTA)

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