What is new in brain tumour clinical trials and how to get your patients into them

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Overview

• Standard of care

• What is new?

• Current research strategies and studies
Standard of care

- Multi-disciplinary management

- Optimal surgery + radio-chemotherapy
  - GBM: RT + concurrent and adjuvant Temozolomide (Stupp 2005)
  - Elderly GBM patients: short course RT + Temozolomide (Perry, 2017)
  - Gd III astrocytoma: RT + adjuvant Temozolomide (CATNON 2016)
  - Oligodendroglioma GdII and III: RT + adjuvant PCV chemotherapy (EORTC 26951)
Neuro pathology

Gliomatosis cerebri

Oligo-astrocytoma

Tissue pathology/morphology

+ Molecular pathology
• Prognostic biomarkers:
  • 1p19q co-del, IDH mutation, TERT mutation:

Eckel-Passow et al. NEJM. 372;26. 2015.
Neuro pathology

- Prognostic biomarkers:
  - 1p19q co-del, IDH mutation, TERT mutation:
  - Trumps grade for prognosis

- Integrated diagnosis now standard
- Basis for clinical management decisions
- Necessary in all clinical studies

Eckel-Passow et al. NEJM. 372;26. 2015.
New agent studies

Targeted agents

• Long list of recent –ve studies in VEGF, EGFR targeting
• Abbvie agent: EGFR targeting antibody-drug conjugate (ABT-414)

Immunotherapies

• Pharma studies using immune checkpoint inhibitors (Checkmate)
• Oncolytic virus studies (REO-Glio)

Radiation sensitisers

• Many new agents becoming available
• PARP inhibitors (PARADIGM-I and II)

Others

• Sativex (GW Pharma)
Immunotherapy studies
Immunotherapy studies

Principles:
- Harness innate immune system to target tumour
- Challenging in immune privileged sites in CNS
- Evidence that tumour micro-environment is immunosuppressive (as is therapy)
- Local Radiotherapy may promote immune activation

Approaches:
- De-repress local immunity (immune checkpoint inhibitors)
- Promote local immunity (deliver immune adjuvants eg viruses)
- Promote systemic immunity (eg with tumour vaccine, activated T-cells)
Immunotherapy studies

Recently reported studies:

- Checkmate 143: Nivolumab vs Bevacizumab in recurrent GBM. -ve
- DCVax: completed, data awaited
- Keynote-028: Ph 1b Pembrolizumab in PD-L1 positive recurrent GBM
  PFS 6 = 45%

On-going studies:

- Checkmate 498 and 548 – Nivolumab with standard (chemo)-radiotherapy
- 92 registered on ClinicalTrials.gov
In set up:

- Ph I/II in newly diagnosed adult GBM patients
- Oncolytic virus (REOvirus) added to standard of care
- Toxicity and immune end points

Status: Funding agreed, likely start Q2 2017
New diagnosed Glioblastoma patients suitable for standard chemoradiotherapy after surgery / Biopsy

Consent

Screening investigations to confirm eligibility

Registration

Treatment period

**Dose levels:**
- Level -1: GMCSF 50mcg/day D1-3, reovirus TCID$_{50}$5x10$^9$ D4-5
- Level 1: GMCSF (50mcg/day D1-3, reovirus TCID$_{50}$1x10$^{10}$ D4-5
- Level 2: GMCSF 50mcg/day D1-3, reovirus TCID$_{50}$3x10$^{10}$ D4-5

**CTRT period:**
RT 60Gy + TMZ for 6 weeks
GMCSF/Reovirus week 1 and 4

**Brain MRI week 4 after CTRT**

**ADJUVANT CT period:**
Adjuvant TMZ + GMCSF/Reovirus monthly

Follow-up

**ON-TREATMENT MONITORING & FOLLOW UP**

- Clinical review at weekly during chemoradiotherapy period with immunologic readouts at weeks 1 and 4
- Monthly review during adjuvant TMZ+GMC/reovirus with immunologic readouts at months 1,3 and 6.
- 3 months MRI scan until disease progression or end of trial.

**PRIMARY END-POINT**

- Dose escalation cohort: Toxicity and identification of MTD and RD
- Dose expansion cohort: Late toxicity

**Dose escalation cohort:** Up to 12 pt. treated according to dose levels.
**Dose expansion cohort:** Up to 12 pt treated at recommended dose
Study proposal

REO-RELAPSE

• Ph IIa single arm study of re-irradiation + REOLYSIN-GMCSF

• Summary:

![Diagram showing study protocol]

- Recurrent GBM post Stupp regime
- Hypofractionated RT 35Gy/10F + REO-GMCSF
- 3 weekly To progression
Targeting EGFR
Targeting EGFR

Principles:
• EGFR (cell surface growth factor) drives growth and survival in glioma
• EGFR frequently mutated and/or over-expressed in glioma
• Inhibiting EGFR signalling should inhibit glioma growth

Approaches:
• Small molecule drugs or antibodies targeting EGFR (as in breast cancer)
• Small molecule drugs targeting EGFR signalling inside cell (eg mTOR)
• Use surface EGFR as target to deliver other agents
Recently reported studies:

- ACT-IV: Rindopepimut for EGFRVIIImut GBM with standard chemo-rad. –ve
- EORTC 26082: Ph II study of Temsirolimus vs TMZ with radiotherapy in GBM without MGMT promotor methylation. -ve

On-going studies:

- Intellance 1: ABT-414 with chemo-radiotherapy in EGFR over-expressing GBM
ABT-414

EGFR residues ~287-302
Biomarker selection for ABT-414

Multiple patient selection assays are being developed

- EGFR amplified
  - EGFR FISH

- EGFRVIII
  - RT-PCR

- EGFR overexpressed
  - RT-PCR
RTOG 3508/M13-813
Intellance 1

**Radiation Therapy**
~60 Gy administered in ~30 fractions over 42 days (per local prescribing information or local institutional guidelines)

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**TMZ**
Daily for 42 days (up to 49 days) per local prescribing information

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**ABT-414/placebo**
Week 1
W1

**ABT-414/placebo**
Week 3
W3

**ABT-414/placebo**
Week 5
W5

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**Weekly Study Visits**

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**4 Week Recovery**

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**Cycles 1 – 6:** TMZ + ABT-414/pbo,
Cycles 7 – 12: ABT-414/pbo

- TMZ: D1 – D5 of each cycle
- ABT-414/pbo: D1 and D15 of each cycle

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**q8 weeks until progression**

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**Post-Progression Survival Assessment**
q3 months

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**= Tumor Assessment:** 72h post surgery, ≤7d before Chemoradiation (baseline), C1D1, D1 of every odd-numbered cycle (3, 5, 7, etc.), each Follow-Up Visit, and Final Study Drug Visit (if not done in last 3 weeks)

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**ABT-414/pbo cycles may be continued at investigator’s discretion as long as disease progression has not occurred**
Targeting DNA repair
Principles:

- Cells rely on DNA repair after cytotoxic damage (Radiotherapy, chemotherapy)
- Glioma cells more dependent on specific repair pathways compared to normal brain
- Inhibiting repair should enhance the effects of radiotherapy and chemotherapy

Approaches:

- Small molecule inhibitors of specific repair proteins
Adding PARPi Olaparib to standard of care as radiation sensitiser

PARADIGM:
Olaparib and short course RT
Elderly/poor performance patients

PARADIGM II:
Olaparib + standard of care
GBM patients stratified by MGMT

*In both parallels, there will be a dose expansion phase – a total of 10 patients (including the 3-6 patients in the MTD cohort) will be recruited into each expansion phase.
Other new agents
Cannabinoids

Principles:
• Glioma cells express cannabinoid receptors
• Activating cannabinoid signalling may promote glioma cell death (autophagy)
• Cannabinoids may enhance effects of other treatments (TMZ)

Approaches:
• Cannabinoid combinations (optimise tumour toxicity, reduce CNS side effects)
• Apply agents used in other settings
• Use as adjuvant to standard treatments
The Sativex Study

‘A two part study to assess the tolerability, safety and pharmacodynamics of Sativex in combination with dose-intense Temozolomide in patients with recurrent glioblastoma’
Sativex (GW Pharma)

Cannabinoid mix

- 1:1 THC + CBD
- From *Cannabis sativa*
- (≠ cannabis)
- Oromucosal spray
- Individual dose titration
- Widely used in MS, cancer pain, nausea, epilepsy
Open label PhI, run in to randomised, placebo controlled Ph Ib
Eligibility

• Recurrent GBM (not secondary GBM)
• 1st recurrence, suitable for second-line TMZ
• KPS > 60%

Exclusion

• Cannabis use, substance abuse inc alcohol
• Schizophrenia
• Cardiac history
• <4 weeks since chemo or 12 weeks since RT
Study overview

Ph I end points
- PK of TMZ and metabolites
- Adverse events

Ph Ib end points
- PFS 6
- Median survival
- 1y survival
- Biomarker (serum midkine levels)
Ph I cohort I (n=3) completed May 2014
SRT met June 18th
• Toxicities mild (<Gd III)
• Mainly GI and neuro-psych

Ph I cohort II open June 2014 (n=3)

Recruitment to Ph Ib started Sept 2014
Last patient entered June 2015

Preliminary data reported in GW press release March 2017
Abstract submitted to ASCO meeting July 2017
How to access clinical studies?

Local oncology team

National data bases

http://csg.ncri.org.uk/portfolio/portfolio-maps/

http://www.nhs.uk/Conditions/brain-tumours/Pages/Clinical-trial.aspx

International data bases

https://clinicaltrials.gov/

Funding organisations

http://www.cancerresearchuk.org/our-research/our-research-by-cancer-type/our-research-on-brain-tumours

https://www.thebraintumourcharity.org/understanding-brain-tumours/clinical-trials/clinical-trials-database/

Support groups

http://brainstrust.org.uk/brain-tumour-hub/