Dinutuximab: a newly approved immunotherapy for the treatment of neuroblastoma
• Adam’s Dad

• Chair & Research Trustee/Director, Solving Kids’ Cancer Europe

• Consumer Member, UK NCRI Children’s Cancer Clinical Studies Group & Neuroblastoma Group

• Patient Expert NICE, dinutuximab & dinutuximab beta
• Diagnosed high-risk neuroblastoma, July 2009
• 4-years of continuous treatment in UK, Germany, and America
• Died July 2013 at 9-years old
Scope

- GD2 as a target antigen in cancer
- Anti-GD2 monoclonal antibodies
- Dinutuximab and dinutuximab beta
  - Early development
  - Major clinical trials
  - Approval & reimbursement
- Other anti-GD2 antibodies
- Reflections on anti-GD2 antibodies & HTAs
- Anti-GD2 – where next?
Ganglioside GD2

Source: How Unituxin Works (http://www.unituxin.com/about-unituxin/mechanism-of-action/antibody-therapy/)
Ganglioside GD2

- Gangliosides first discovered in 1942
- GD2 is a cell surface molecule
- Highly expressed on a variety of human cancers including neuroblastoma
- Tumour associated antigen
- Anti-GD2 antibodies bind to GD2 and recruit the immune system to attack and kill the cell

Source: How Unituxin Works (http://www.unituxin.com/about-unituxin/mechanism-of-action/antibody-therapy/)
Ganglioside GD2

- GD2 is also found on normal cells
- Expressed in CNS
- Expressed on peripheral nerve fibers
- Major toxicity of anti-GD2 antibodies is neuropathic pain requiring large doses of analgesia
- Anti-GD2 antibodies do not cross blood-brain barrier

Source: How Unituxin Works (http://www.unituxin.com/about-unituxin/mechanism-of-action/antibody-therapy/)
Ganglioside GD2

- Not a ‘perfect’ target
- Ranked 12th most important cancer antigen by National Cancer Institute Pilot Program
Anti-GD2 Monoclonal Antibodies

- **A mouse is vaccinated to start the formation of antibodies**
- **Spleen cells that form antibodies are collected from the mouse in an operation**
- **These are fused with tumour cells called myeloma cells**
- **Antibodies are collected**
- **These are grown in the laboratory and those that produce antibodies are separated**
- **This forms hybridoma cells**

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**Year**
- **1985/1986/1989**
- **1990/2004**
- **2004/2012/2012**

*Year is earliest reference to antibody in a published paper according to search of pubmed*
Anti-GD2 Monoclonal Antibodies

- Passive Immunotherapy
- +Cytokines – IL-2, GM-CSF
- Minimal Residual Disease

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*Year is earliest reference to antibody in a published paper according to search of pubmed
• First phase 1 trials of murine 14.G2a published early 90s

• ch14.18 developed from 14.18 [Journal of Immunology 1990] – more potent than 14.G2a

• Phase 1 trials in ch14.18 mid-90s [Reisfeld, Yu, Gillies, Handgretinger, Sondel]

• POG / CCG ch14.18 with GM-CSF and IL-2 respectively

• CCG/COG Phase 1 A0935A ch14.18 + GM-CSF + IL-2 [1997]

• COG Phase 3 ANBL0032 ch14.18 + GM-CSF + IL-2 [2001]
ch14.18/SP2/0
dinutuximab
ch14.18/SP2/0
dinutuximab

- New Brunswick Biotech ➔ Damon ➔ Repligen ➔ Abbott ➔ ¬

- 1996 : Alice Yu travelled to DNC (Decision Network Committee) at NCI to review imaging studies etc.

- Biopharmaceutical Resource Branch to produce ch14.18 at NCI-at-Frederick located at Fort Detrick ➔ ANBL0032

- July 2010 : NCI Cooperative Research and Development Agreement with United Therapeutics Corporation (UTC)

- April 2014 : United Therapeutics submitted Biologics Licensing Application (BLA) for Unituxin®

Dr. Alice Yu
COG-ANBL0032

- Opened in 166 institutions across USA, Canada, and Australia
- Planned accrual 386 patients to detect 15% difference in 3yr EFS (50% vs. 65%) over < 5 years
- Dose of 25 mg/m²/d as minimum 10-hour infusion for 4 consecutive days
- Terminated for superior EFS after 226 (58%) patients accrued between 2001 and 2008
- EFS at 2yrs ch14.18 arm (66% ± 5%) vs. standard arm (46% ± 5%) (p=0.01)

ASCT=Autologous Stem Cell Transplantation; EBRT=Radiotherapy; RA=13-cis-retinoic acid/isotretinoin
• Raw dataset for 13 Jan 2009 data analysis was corrupted and not available

• 30 June 2009 data used for ‘confirmatory analysis’ (2yr EFS: 65.6% vs. 48.1%, p=0.033)

• 30 June 2012 data used for ‘supportive analysis’ (3yr EFS: 62.8% vs. 50.9%, p=0.099)

• Observed p-value on 7th interim assessment did not cross alpha boundary (Nominal α=0.0108, p-value=0.0115)

• Study design not statistically powered for overall survival

• 77% of ANBL0931 patients completed treatment. Neuropathic pain (51%), pyrexia (40%), infusion-related reactions (25%), capillary leak syndrome (23%), hypotension (16%), sepsis (16%)
EMA Review | Unituxin®

• Additional data analysis requested – overall survival as at March 2014

• Increase in EFS in 13-cis RA arm between Jan/June 2009 data due to data corrections

• Overall survival analyses unequivocally demonstrate benefit of immunotherapy – statistically and clinically significant

• August 2015 : EMA marketing authorisation granted for the European Union
October 2015: Single Technology Appraisal (STA)

- All supporting evidence apart from ANBL0032 dismissed
- Requested updated EFS data analysis as at March 2014
- Critical of ANBL0032 early stopping + use of single study data with immature follow-up
- No special dispensation within “methods guidance” for very young patient population

Three appraisal meetings (two public) ➔ simple discount patient access scheme ➔ still not cost-effective

July 2016: Decision not to recommend dinutuximab (ICER = £ per QALY too high)

- March 2014 analysis should be basis for decision-making
- Cure threshold of 10 years ➔ approx. 50% of patients considered cured regardless of treatment
- Uncaptured health-related benefits and impact on parents and families not captured by models
- Company highlighted significant cost of administration in economic models over and above drug cost

QALY=Quality Adjusted Life Year; ICER=Incremental Cost Effectiveness Ratio
Solving Kids’ Cancer Appeal

Solving Kids’ Cancer Europe appealed decision unilaterally without support from United Therapeutics
- First time any organisation had launched appeal without pharmaceutical company involvement
- Pro-bono support from Covington & Burling LLP in London

Appeal permitted on two grounds.

1. NICE has exceeded its powers:
   - Breach of Children Act 2004 and UN Convention on the Rights of the Child

2. The recommendation is unreasonable in light of the evidence submitted to NICE:
   - It was unreasonable for the Institute to use a 10-year cure point given the evidence before it

Appeal on 10-year cure point accepted as valid after expert input from Dr. Wendy London, COG statistician
Solving Kids’ Cancer Appeal

- September 2016: Appeal Panel Hearing – quasi-judicial process
  - Written and oral submissions
  - No evidence in committee papers that the Committee had considered the special position of children
  - 11 of 114 patients censored prior to 5 years but 58 from 5-10 years ⇒ wide 95% CI ± 25% at 10 years

- November 2016: Appeal Panel Decision – both appeal points upheld
  - Committee should consider whether there is anything particular to this patient group as children that should be taken into account in the appraisal, if so take it into account, if not say so with reasons
  - Committee directed to review range of cure points and associated ICERs between 5 and 10 years and FAD should contain balanced reasoning for their choice

- February 2017: Appraisal is suspended as UTC withdraw drug supply outside USA

- EMA marketing authorisation withdrawn
Unituxin®

- $500m gross profit since launch in Q3 2015
- Annual contribution to profit is just 4%
- Construction of new cell culture and purification facility started in 2017 – online 2021
- No plans to re-enter market in Europe
- CADTH pan-Canadian Oncology Drug Review (pCODR) submitted 1st October 2018¹ – frontline approved indication only?
- Australia/New Zealand – supply incl. for future COG trials?

Source: ¹https://www.cadth.ca/unituxin-neuroblastoma-details
**ch14.18/SP2/0**

**dinutuximab**

- **1980**: Phase 1 trial of ch14.18
- **1988**: Phase 1 trial of 14.G2a
- **1989**: IND for mAb ch14.18 (first for chimeric antibody). Approved in 1991
- **1991**: Phase 1 trial of ch14.18
- **1992**: Pilot study of ch14.18 + GM-CSF
- **1994**: Phase 2 trial of ch14.18 + GM-CSF (POG-9347)
- **1997**: Phase 1 trial of ch14.18 + GM-CSF (CCG-0935)
- **04/1997**: NB97 Frontline Trial of GPOH [Germany]
- **09/2004**: Published JCO ch14.18/SP2/0 dinutuximab
- **12/2002**: ch14.18 stopped
- **26/10/2001**: Phase 3 trial of ch14.18 + GM-CSF + IL-2 (COG-ANBL0032)
- **31/07/2015**: ANBL0032 Closed. (1449 patients enrolled)
- **12/2002**: PK study of ch14.18 (NCI) vs. ch14.18 (UTC) (DIV-NB-201)
- **2000**: COG is formed
- **2009**: FDA trial of ch14.18 CSF + IL-2 ANBL0931
- **2009**: FDA approved by FDA 10/03/2015 EMA 14/08/2015
- **2010**: Unituxin® approved by FDA 10/03/2015 EMA 14/08/2015
- **09/2004**: Published JCO Consolidation Treatment With Chimeric Anti-GD2 Antibody-A14.18 in Children Older Than 1 Year With Metastatic Neuroblastoma
- **03/2000**: Phase 1 trial of GM-CSF + IL-2 (CCG-0935)
- **12/2002**: ch14.18 stopped
- **26/10/2001**: Phase 3 trial of ch14.18 + GM-CSF + IL-2 (COG-ANBL0032)
- **31/07/2015**: ANBL0032 Closed. (1449 patients enrolled)
Consolidation Treatment With Chimeric Anti-GD2-Antibody ch14.18 in Children Older Than 1 Year With Metastatic Neuroblastoma
Thorsten Simon, Barbara Hero, Andreas Fuldum, Rupert Handgretinger, Martin Schrappe, Dietrich Niedhammer, and Frank Berthold

ABSTRACT

Purpose
Antibody treatment is considered tolerable and potentially effective in the therapy of neuroblastoma. We have analyzed stage 4 neuroblastoma patients older than 1 year who underwent consolidation treatment with the chimeric monoclonal anti-GD2-antibody ch14.18.

Patients and Methods
Stage 4 patients older than 1 year who completed initial treatment without event were eligible. ch14.18 was scheduled in a dose of 20 mg/m²/d during 5 days in six cycles every 2 months. Patients who did not receive ch14.18 served as controls.

Results
Of 334 assessable patients, 166 received ch14.18, 99 received a 12-month low-dose maintenance chemotherapy (MT) instead, and 69 had no additional treatment. During 69 of 14.18 cycles, fever (58% of cycles), abnormal C reactive protein without infection (35%), cough (24%), rash (22%), and pain (16%) were the main side effects. Univariate analysis found similar event-free survival (EFS) for the three groups (3-year EFS, 46.6% ± 4.1%, 44.4% ± 4.9%, 37.1% ± 5.9% for patients treated with antibody ch14.18, MT, and no additional therapy, respectively; log-rank test, P = 0.314). For overall survival (OS), ch14.18 treatment (3-year OS, 66.5% ± 3.9%) was superior to MT (3-year OS, 56.6% ± 5.6%) or no additional therapy (3-year OS, 46.8% ± 6.2%; log-rank test, P = 0.018). Separate univariate analysis of patients with autologous stem-cell transplantation revealed no difference between patients with ch14.18 treatment and no additional consolidation. Multivariate analysis failed to demonstrate an advantage of antibody treatment for EFS and OS.

Conclusion
Consolidation treatment of stage 4 neuroblastoma with ch14.18 was associated with considerable but manageable side effects. Compared with oral maintenance chemotherapy and no consolidation treatment, ch14.18 had no clear impact on the outcome of patients.
In conclusion, this retrospective analysis demonstrated a considerable but manageable toxicity of MAB ch14.18 treatment. Univariate analysis found an advantage of ch14.18 treatment for overall survival but not for EFS in stage 4 neuroblastoma. Multivariate analysis did not confirm such a benefit. Because of these results, the MAB ch14.18 treatment is not continued in the current German neuroblastoma trial.

- ch14.18 produced by BioInvent in Sweden
- 20 mg/m²/d over 8-12 hour for 5 days
- 6 cycles – every 2 months for one year
- Non-randomised study design
- Published September 2004
ch14.18/CHO
dinutuximab beta

- Design of GPOH study + observed improvement in 3-yr OS ➞ rationale for randomisation in SIOPEN HR-NBL-1 trial

- R2 randomisation (13-cis RA ± ch14.18)

- 2004: Antibody recloned into Chinese hamster ovary cells

- 2005: Phase 1 ch14.18/CHO in 15 R/R patients

- 2007: R2 activated 11/2006 – 33 patients randomised

- 2009: R2 amended to 13-cis RA + ch14.18/CHO ± s/c IL-2 ➞ unacceptable to randomise to no antibody
HR-NBL-1/SIOPEN (R2)

- HR-NBL-1/SIOPEN trial opened in 128 SIOPEN member institutions across 18 countries
- Randomised 406 patients between 22/10/2009 and 12/08/2013
- Dose of 20 mg/m²/d as minimum 8-hour infusion for 5 consecutive days
- EFS at 3yrs – 56% (49-63) for dinutuximab beta vs. 60% (53-66) for dinutuximab beta + s/c IL-2 (p=0.76)
- 87% of patients on dinutuximab beta alone received all treatment vs. 62% for dinutuximab beta + s/c IL-2

ASCT=Autologous Stem Cell Transplantation; EBRT=Radiotherapy; RA=13-cis-retinoic acid/isotretinoin
ch14.18/CHO
dinutuximab beta

- June 2011: Apeiron Biologics acquired rights to ch14.18/CHO
- Dec 2011: LTI (Long-term infusion) study – dose schedule of 10mg/m²/d + s/c IL-2 given over 10 days ➞ favourable toxicity profile of antibody plus IL-2 and ~30% response rate
- HR-NBL-1 R2 results suggested patients who received all doses of ch14.18/CHO + IL-2 might do better
- April 2014: R4 randomisation of ch14.18/CHO (cont. inf.) ± half-dose s/c IL-2 ➞ LTI study amended to same randomised question in relapsed, refractory and non-R4 eligible patients
- May 2015: Apeiron submitted dinutuximab beta (APN311/ISQETTE) to EMA for marketing authorisation
- October 2016: EUSA Pharma, UK purchase exclusive global commercialisation rights to dinutuximab beta
- May 2017: EMA marketing authorisation granted under exceptional circumstances (with IL-2 for R/R pts)

CHMP=Committee for Medicinal Products for Human Use
• November 2017: Single Technology Appraisal (STA)
  - Slide on Solving Kids’ Cancer appeal in dinutuximab appraisal
  - Clear appreciation of potential sensitivities around this kind of appraisal
  - No director comparator evidence – use of R1 (BuMel vs. CEM ASCT) not fit for purpose
  - R/R not considered further – evidence ‘unfit for purpose’ + patients in studies had no prior anti-GD2

• April 2018: Second (public) appraisal committee meeting
  - MAIC comparison with isotretinoin arm of COG-ANBL0032 as required by Committee

• May 2018: Decision not to recommend dinutuximab beta

• June 2018: Third (public) appraisal committee meeting

• July 2018: Dinutuximab beta recommended on commercial-in-confidence discount scheme
  - ICER more than £40,000 – above upper threshold normally accepted by NICE for STAs

• 10-day continuous infusion of dinutuximab beta is now standard of care without any (R4) results

MAIC=Matching Adjusted Indirect Comparison; STC=Simulated Treatment Comparison
• Highlights the issue and danger of relying on pure data analysis and model-fitting

• Company submission supports a lower ICER at later time points for cure threshold ➔ winner!

• Implausible and not supported by clinical experience not appropriate/relevant ➔ dismissed!
NICE Highly Specialized Technologies (HST)

- Department of Health and Social Care (DHSC) provides list of evaluation topics
- Higher upper ICER threshold (~£100,000) and total annual cost to NHS must be < £20m

“...The HST guidance recognises the particular circumstances of these very rare conditions – the vulnerability of very small patient groups with limited treatment options, the nature and extent of the evidence, and the challenge for manufacturers in making a reasonable return on their investment because of the very small populations treated.

In evaluating these drugs, NICE takes into account a greater range of criteria about the benefits and costs of highly specialised technologies than is the case with its appraisals of mainstream drugs and treatments. We do this because applying our standard approach to treatments for very small groups of patients would result in us always recommending against their use. This would be unfair.”

Sir Andrew Dillon, NICE Chief Executive, 2015
NICE asks EUSA pharma to drop price of neuroblastoma drug

May 4, 2018

NICE has said EUSA Pharma’s Qarziba for the rare childhood cancer high-risk neuroblastoma should not get regular funding from the NHS – but could be given interim funding on the Cancer Drugs Fund following a price cut.

The cost-effectiveness body said in first draft guidance that evidence suggests Qarziba (dinutuximab beta) could increase overall survival compared with standard treatment, but there is “substantial uncertainty” about its long-term benefits.

A NICE appraisal committee would like to recommend Qarziba for funding on the Cancer Drugs Fund (CDF) through a managed access scheme – but EUSA Pharma will have to drop its price first.

CDF funding would allow Qarziba to be funded for around two years while further data is gathered to support regular funding on the NHS.


Taking lenient stance, NICE backs neuroblastoma drug

July 12, 2018

NICE has recommended EUSA Pharma’s neuroblastoma treatment Qarziba (dinutuximab beta) in final draft guidance after taking a lenient stance because of the rare nature of the disease, and after the manufacturer agreed to cut its price.

In its guidance NICE said that the cost-effectiveness estimate of more than £40,000 per Quality Adjusted Life Year gained was higher than what it usually considers to be a good use of NHS resources.

But in the guidance NICE said it was taking into account “uncaptured health related benefits, the rarity and severity of the disease, and the potential lifetime benefit” for children with neuroblastoma.

European regulators gave a licence to Qarziba under “exceptional circumstances” because the manufacturer was unable to provide the usual level of efficacy and safety data because of the rarity of the condition.

**England & Wales & NI**: Approved for patients with no prior anti-GD2 incl. refractory (PR + ASCT)

**Scotland**: Approved by SMC for frontline high-risk, relapsed and refractory patients

**Ireland**: Submissions to NCPE and NCCP – negotiations ongoing since late 2018

**Germany**: “NUB” status – as per routine procedures reimbursement negotiated separately by hospitals

ียว available mainly in university hospitals. Normally “NUB” evolves to “ZE” iew available in all hospitals

**France**: HTA (HAS) / Pricing (CEPS) separate bodies. HAS clinical assessment ASMR IV (minor) for frontline high-risk and ASMR V (none) for relapse/refractory iew generally ASMR I to III reimbursed

ียว Health ministry reimbursement of EUR 4m to Dec 2019 for frontline (only product with such funding)

**Spain**: National scientific/technical review iew Ministry of Health/17 regional health systems/company negotiate price iew interim each hospital/regional health system decisions on patient-by-patient basis iew could still become available in some regions/hospitals and not others (40+ paediatric centres in Spain)

**Biologics Licence Application (BLA)** to the FDA in the U.S. expected – not a biosimilar?
hu3F8 | naxitamab

- 3F8 is a mouse developed by Dr. Nai-Kong Cheung in the 1980s and used extensively at MSKCC
- HAMA response – neutralising anti-mouse antibodies produced by immune system to 'foreign' 3F8
- Used as high-risk neuroblastoma maintenance therapy in combination with GM-CSF
- hu3F8 developed to overcome HAMA and modify Fc portion for enhanced effector function – Phase 1 study in 2011
- Licensed to Y-mAbs Therapeutics in 2015
- Outpatient treatment – 35 minute infusion of hu3F8 on day 1, 3, 5 with s/c GM-CSF day -4 to 0 and day 1 to 5
- 2019: International study of hu3F8 + GM-CSF in R/R with plans to submit a BLA in the U.S.
hu14.18-IL2 | APN301

- Developed and owned by Apeiron Biologics
- Fusion protein of humanized antibody (hu14.18) and IL-2
- “Immunocytokine”
- Tested in Phase I/II clinical trials through Children’s Oncology Group
- Responses in patients with residual disease but none in patients with bulky tumours measurable by MRI/CT
- Current clinical trial of hu14.18-IL2 in combination with haploidentical NK cells by Paul Sondel’s group at University of Wisconsin–Madison (UW)

hu14.18K322A

- Developed at St Jude Children’s Research Hospital
- Produced in rat myeloma cell lines which reduces fucosylation ➔ potentially enhancing ADCC
- 98% human to reduce allergic reactions
- Single “point-mutation” (small structural change) to reduce compliment activation (CDC) ➔ reduce pain ➔ increase dose?
- Used in several Phase I/II studies at St Jude
- Ongoing Phase pilot II study combining hu14.18K322A with induction chemotherapy for frontline patients
The Proposal For an EU HTA Regulation

Strengthening EU cooperation beyond 2020

In 2016, the European Commission started work on strengthening EU cooperation on Health Technology Assessment in response to calls from EU countries, the European Parliament, and interested parties to ensure its sustainability beyond 2020. In its 2017 Work Programme, the European Commission announced that this would extend to improving the functioning of the single market for health technologies.

Legislative proposal

A legislative proposal was adopted by the European Commission on 31 January 2018. It is the result of an extensive reflection process following the results of the impact assessment outlined below. It has been sent to the European Parliament and the Council with the aim of adoption by 2019. The proposal and related information can be found here:

- Legislative proposal (click on the linguistic icon to see the linguistic versions)
- Press release
- Q&A
- Factsheet
The Proposal For an EU HTA Regulation

- Reasons for proposal
  - National processes = multiple data and evidence requests = higher costs and effects on innovation
  - Duplication of work – repeated clinical assessments with potentially different outcomes/conclusions
  - Unsustainability of Union-level HTA cooperation – project-based with short-term funding

- Objectives
  - Improve availability of innovative health technologies for EU patients
  - Ensure efficient use of resources and strengthen quality of HTA across the EU
  - Improve business predictability
  - Promote convergence in HTA tools, procedures and methodologies
  - Reduce duplication of efforts for HTA bodies and industry
  - Ensure the use of joint outputs in Member States
  - Ensure the long-term sustainability of EU HTA cooperation

- Medicinal products undergoing the central marketing authorisation procedure, new active substances and existing products for which the marketing authorisation is extended to a new therapeutic indication
The Proposal For an EU HTA Regulation
06 February 2019

NICE collaborates with the Canadian Agency for Drugs and Technology in Health to offer parallel scientific advice

NICE and the Canadian Agency for Drugs and Technology in Health (CADTH) have launched a new collaboration to offer parallel scientific advice to the life sciences industry.

Scientific advice helps companies develop the evidence that can demonstrate the value of a new treatment. It does so by using expert opinion from a range of contributors including clinicians, health economists and patient representatives to provide detailed feedback on companies’ plans to generate clinical and economic evidence.
Reflections | anti-GD2 antibodies

- Hindsight is always a wonderful thing
- Life is often messy and complicated … situations evolve … navigating isn’t easy
- Competition between researchers and institutions … drives innovation … and duplication
- 5 anti-GD2 antibodies in ongoing clinical research studies in the same rare paediatric cancer
- Lack of approval and reimbursement may have stalled or even ended development?
- Licensed drugs may be a barrier to further innovation ➔ revenue streams to protect?
- What now for other anti-GD2 antibodies, anti-idiotype antibodies, O-acetyl-GD2?
Reflections | HTAs

- USA simpler market/model → FDA vs. Europe → EMA → national HTAs → national price negotiations?

- Lack of HTA experience (and thus flexibility) in assessing drugs for rare orphan diseases in children?

- No premium placed on children – adding 2 years of life to a 2-year old or a 72-year old is equivalent?

- No allowances for nature and scale of task in developing and testing drugs to treat children with cancer
  - Patient population small and limited → need for cooperative group trials across many institutions
  - Phase 3 trials take a long time, confirmatory trials are infeasible (unethical?)
  - Lack of options/approved drugs not relevant and no joined-up assessment of impact on innovation

- Children + Cancer + mobilised parent/advocate community → powerful movement and force for change

- Political pressure, media storm, public sympathy and support → not normal conditions for HTAs

- Parents and advocates act for children directly … but for manufacturers indirectly
Reflections | HTAs

• Late involvement of pharma, sub-licensing adds complexity, disjointedness and lack of ‘ownership’

• Companies seeking approvals across multiple similar but distinct HTAs “learning on the job”

• Drugs are marketed at very high prices (£150,000+ per child) ⇒ always likely to be a challenge

• Paediatric-only indications / rare diseases patient population is small and limited ⇒ poor revenue growth
  □ Growth depends on additional markets or finding and pursuing adult indication

• Absolute cost to healthcare systems relative to total spend is very small
  □ Estimated total NHS spending on medicines in England in 2016/17 was £17.4bn¹
  □ Acquisition cost of Qarziba® for all eligible high-risk patients < £5m?

• Academic trial designs, execution, and data management should be with principle of filing intent

Source: ¹The Kings Fund – The rising cost of medicines to the NHS: what’s the story?
Parents just want the best for their children

Neuroblastoma Facebook Support Group

Is there a study comparing all three types of antibody treatments?

Nick Bird: No. And nor is there ever likely to be.

Nick Bird: All owned by different commercial companies so only disincentive to make it happen. And any indirect comparison is not going to provide any compelling evidence.

Nick Bird: It makes sense from a business point of view... but when it's your kid it stinks.

Nick Bird: For sure. Ironic situation that there are never enough drugs developed for children with cancer and yet somehow in this case there are at least 4 "me too" drugs being used in the clinic and also variations thereof (i.e. hu14.18-IL2) as well.
Anti-GD2 | The Next Chapter

- [2017] Irinotecan-temozolomide with temsirolimus or dinutuximab in children with R/R neuroblastoma (COG ANBL1221) – 5CR, 4 PR (9/17 pts) in dinutuximab arm

- [2018] Plus expansion cohort – total 11 CR, 10 PR (40% RR, 21/53 pts, 9/21 prior anti-GD2)

- [2017] hu14.18K22A + NK cells in R/R – 4 CR, 1 VGPR, 3 PR (8/13 pts. 9/13 with prior anti-GD2 therapy)

- [2017] hu14.18K22A + GM-CSF + IL-2 concomitantly with Cyclo/Topo in newly diagnosed pts. 32/42 pts (≥ PR) vs. 12/30 in COG pilot study of Cyclo/Topo alone

- [NCT03794349] Irinotecan Hydrochloride, Temozolomide, and Dinutuximab With or Without Eflornithine in Treating Patients With R/R Neuroblastoma (not yet open)

- [NCT03786783] Dinutuximab, Sargramostim, and Combination Chemotherapy in Treating Patients With Newly Diagnosed High-Risk Neuroblastoma (Phase II pilot study - recruiting)

- BEACON Amendment (BEACON Immuno) – Chemotherapy ± dinutuximab beta in R/R Neuroblastoma (funded)