Neuroblastoma Children’s Cancer Alliance UK

New Drugs on the Horizon for Neuroblastoma

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on behalf of
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London, 30th November 2013
New Drugs on the Horizon for Neuroblastoma

- Why new drugs are needed and drug development
- New drugs on the horizon
- Drugs we want to develop
- BEACON neuroblastoma study
- Future
New Drugs on the Horizon for Neuroblastoma

Why are new drugs needed?

- To introduce new drugs into frontline therapy which together with immunotherapy and new forms of radiotherapy will improve the rate of cure for children with high risk neuroblastoma
- To improve treatment for relapsed neuroblastoma
- To offer more options to parents and children
After a drought of new drugs being available we are about to have a monsoon
Drug Development

<table>
<thead>
<tr>
<th>New Drug Progress</th>
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<td>Pre-clinical → Phase I → Phase II → Phase III (frontline)</td>
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**Attrition Rate of Drugs**
- 95% Attrition from Concept to Phase I
- 95% Attrition from Phase I to Phase III

**Activity/Response**
- Phase I: All drugs - 10%
- Phase I: Molecular targeted drugs - 4%
- **Phase I: Molecular targeted drugs + selected patients - >50%**
Why Has the Introduction of New Drugs into the Clinic Been Slow?

- Low number of drugs available for investigation in children

- **Clinical trials not optimally designed** – they **do not** always:
  - Select the best drug
  - Ask a clear scientific question
  - Select patients who might benefit from a new drug
  - Understand what is happening in the tumour
  - Compare with a standard treatment

- Clinical trials take a long time to develop
Molecula\textit{rly Targeted Therapeutics}

Based on the understanding of what drives the cancer cell

- Drugs that target the specific molecules required for the growth of cancer tissue - not present in normal tissue
- Ideally “reduced” toxicity
- Adult Targets as examples:
  - Lung Cancer – EGFR, EML4-ALK
  - Melanoma – BRAF V600E
  - Breast + Ovarian – BRCA1/2
  - Breast Cancer - HER2
- Used in conjunction with predictive biomarkers: \textit{What is the best drug for an individual patient?}

\textbf{Glivec} \\
- in chronic myeloid leukaemia – 2001
The Changing Focus of Adult Anticancer Drug Development
The Changing Focus of Neuroblastoma Treatment

Develop better drugs faster

Past

Drugs

Which patients respond best?

Current and future

Determine molecular profile of the patient’s tumour

Determine which drugs are most appropriate
Accelerating Drug Development

We want to follow the successes of adult drug development (Glivec)

The way forward:

“a paradigm shift towards more biological, hypothesis-driven clinical trials”

- Selection of agents
- Biology and testing in the best pre-clinical models - investigate genetically engineered murine models
- Incorporation of biomarkers and selection of patients
- Novel trial design and rapid integration Phase I - Frontline
- Paediatric Drug Development Networks
- Interaction between all key-stake-holders: academia/clinicians, pharma, regulators and parents
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Neuroblastoma Drug Development

- ENCCA/ITCC New Drug Development Strategy [NDDS] - consensus on prioritisation of **current** new targets and drugs: ALK, Aurora kinase, BIRC5, CHK1, MDM2, mTORC1/2, (CDK)... regular review with evolving science and new drugs

- Prioritise Phase I studies: short/rapid dose escalation (limited number of patients), explore early signals of activity at recommended Phase II dose in expansion cohorts (more patients)

- Evaluate in Multi-Arm Multi-Stage Study - BEACON

- Molecular characterisation of neuroblastoma tumours to deliver personalised - precision medicine
Neuroblastoma Drug Development

• **Phase I portfolio** – LEE001, Abraxane, Regorafenib, Volasertib Ponatinib, Afatinib ....identify drugs for next BEACON study

• **BEACON - Neuroblastoma** - for all relapsed neuroblastoma

• Molecular characterisation

• **Anaplastic Lymphoma Kinase (ALK)** - first molecular predictive biomarker in neuroblastoma
  - LDK378 [novel selective ALK inhibitor]
  - Others novel selective ALK inhibitor being evaluated

• Combination studies
  - Crizotinib with temsirolimus [ALK/MET and mTOR inhibitor]
Early Phase Studies 2013 Neuroblastoma

- **Ph I/II study CI ch14.18/cho antibody and IL2 (CR CTU)**
- **Ph I/II Lutetium dotatate NBL (CR CTU)**
- **Ph I LEE011 CDK inhibitor (Novartis)**
  - Ph I LDK378 ALK inhibitor (Novartis)
- **Ph I Abraxane (Celgene)**
- **Ph I/II Regorafenib (Bayer)**
- **Ph I/II Abraxane (Celgene)**
- **Ph I Volasertib I (BI)**
- **Ph I/II Crizotinib + temsirolimus - ALK/mTOR (CR CTU)**
- **Ph I/II Trametinib MEK inhibitor (GSK)**
- **Ph I/II trial GD2-CAR transduced T-cells (UCLH)**

- **Earlier stages of planning**
- PI3K Inhibitors
- TORC1/2 Inhibitors
- HSP90 Inhibitors
- PARP Inhibitors
- Fusion Protein IL2 + GD2
- ALK Vaccines
- ALK CAR
- Alk Antibodies
New Drug Trials in Development

- Over 20 new drug trials in development
- MEK inhibitors, PD-1 inhibitors, C-MET inhibitors, AKT inhibitors, TORC 1&2 inhibitors, PI3K inhibitors, HSP90 inhibitors, MDM2 inhibitors, RET inhibitors
- **Combination** studies – study new drugs: individually and then combined
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Neuroblastoma Targets
Focus on the identified molecular abnormalities that initiate and maintain neuroblastoma

Molecular Abnormalities

- MYCN
- Anaplastic lymphoma kinase (ALK)
- p53
- MAPK/RAS/RAF
- ATRX

Treatment Themes

➢ Targeting MYCN
  - Direct
  - Oncoprotein stability
  - Through synthetic lethal interactions by drugging genes that modulate critical functions of MYCN – CHK1

➢ Anaplastic lymphoma kinase (ALK)
  - Angiogenesis
  - MDM2-p53 antagonists
Targeting MYCN Protein Stability

ALK - From the Bench to Bedside and Back Again

Identification of ALK as a major familial neuroblastoma predisposition gene

Kaplan-Meier and long rank analysis of ALK-mutated and ALK-amplified tumours - F1174 mutated versus wild-type cases

- Mutations of ALK gene in 10% neuroblastomas - F1174 & R1275
- Amplification of ALK gene in 4% neuroblastomas

Strategies to target ALK
1. Direct inhibitors – crizotinib, LDK378
2. Combination approach – ALK + mTOR; ALK + HSP90 inhibitors
3. Novel compounds

• F1174 mutation - 58.8% have MYCN amplification

![Graph showing Kaplan-Meier analysis](image-url)
Targeting ALK - Combination Approach

![Graph showing volume change from Day 0.](image)

![Images showing survival over days of treatment.](image)

Teeara Berry, Louis Chesler, Rani George, Cancer Cell 2012
Incorporation of Biomarkers

Predictive - What is the best drug for an individual patient?

Pharmacodynamic - Is the drug working in the way we expected ie ‘hitting the target’?
Predictive Biomarkers - Patient Selection and Pharmacodynamic Biomarkers

Repeat tumour biopsies in children are problematic

Sources of Tumour Cells for Biomarker Studies:

- Bone marrow
- Circulating Tumour Cells
Pharmacodynamic Biomarkers

Ganglioneuroblastoma (7 years old)

Is the drug targeting tumour blood vessels?

DCE MRI – functional imaging biomarker of drug activity

Implemented in the Beacon - Neuroblastoma Trial
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BEACON-Neuroblastoma

A randomized phase IIb trial of Bevacizumab added to Temozolomide ± Irinotecan for children with refractory/relapsed neuroblastoma

Andy Pearson, Lucas Moreno, Dee Wherton, Giuseppe Barone, Keith Wheatley, Veronica Moroz, Elena Brogden, Nicola Graham, Sue Burchill, Andrew Peet, Pam Kearns
BEACON-Neuroblastoma

Phase II, two hypotheses, randomised, open label, 4-arm factorial trial to be run in SIOPEN/ITCC centres

**Biomarker rich** - DCE MRI, Circulating TH, PHOX2B, DCX mRNA, angiogenesis-related biomarkers, tumour profiling, drug pharmacokinetics (PK)

- Relapsed/Refractory Neuroblastoma fulfils eligibility criteria
- Randomisation

| BEVACIZUMA B |
| Temozolomide |
| Temozolomide + Bevacizumab |
| Temozolomide + Irinotecan |
| Temozolomide + Irinotecan + Bevacizumab |
Impact of BEACON

Based on temozolomide as the gold standard

Objectives of Trial

• Identify a backbone regimen for relapsed neuroblastoma

• Identify role of Bevacizumab

Longer Term

• Create international trial network-infrastructure to roll on to “BEACON2" leading to an international drop the loser/octopus design to test all promising phase I drugs

• Test predictive biomarkers and molecular characterisation in the context of a large international trial in neuroblastoma

• Proof of concept and establishment of network for Functional Imaging — Impact of BEACON
International Sponsor
University of Birmingham
CRCTU
CI Andy Pearson

8 National Coordinating Centres
National coordinating investigator identified in each country

32 Sites
Principal investigator in each site

• Open July 2013
• Complete 2015

Ruth Ladenstein - Austria
Hervé Rubie - France
Aurora Castellano - Italy
Victoria Castel - Spain
Jochen Rößler - Germany
Huib Caron - Netherlands
Karsten Nysom - Denmark
Cormac Owens - Dublin

UK, 9 centres: London, Surrey, Birmingham, Manchester, Liverpool, Leeds, Bristol, Glasgow, Newcastle
NL, 2 centres: Rotterdam, Amsterdam
DK, 1 centre: Copenhagen
D, 7 centres: Berlin, Stuttgart, Münster, Frankfurt, Hannover, Freiburg, Köln
BE, 1 centre: Gent
FR, 11 centres: Paris, Villejuif, Marseille, Toulouse, Bordeaux, Lille, Nancy, Lyon, Bordeaux, Nancy
IT, 8 centres: Bologna, Roma, Genova, Milano, Monza, Padova, Verona, Roma Bambino Gesù
CS, 3 centres: Valencia, Barcelona, Madrid

Open July 2013
Complete 2015
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Future
International Links

- SIOPEN
- New links with Germany – GPOH
- Discussions ongoing with Kate Matthay – NANT
- Discussions ongoing with Julie Park – COG
- Ongoing work within ITCC & ENCCA
International Phase II Strategy
“Drop the Loser” - Octopus

versus
Backbone + Direct inhibitor e.g. crizotinib

versus
Backbone + Novel compounds

Individualise therapy for high risk according to tumour genetics
(Backbone from randomized Phase IIb)

versus
Backbone + Combination approach

versus
Backbone + MEK inhibitor

ALK
Integration Phase I - Frontline

ITCC - SIOPEN New Drug Development Strategy

Novel agents should make rapid progress

Phase I ➔ Phase II  Relapse/Non-responder
Frontline studies

Frontline studies stratified by predictive biomarkers - molecular characteristics
Why has Introducing New Drugs into the Clinic Been Slow?

• Low number of drugs available for investigation in children: improved links with pharma and regulators; BDA forum

• Clinical trials:
  - Select the best drug: based on biology and pre-clinical evaluation
  - Ask a clear scientific question
  - Select patients who are most likely to benefit from a new drug: predictive biomarkers
  - Understand what is happening in the tumour: pharmacodynamic biomarkers (laboratory; imaging)
  - Compare with a standard treatment: randomised trials
A large number of drugs are becoming available for neuroblastoma. We must rationally select the best ones for children. Clinical trials are the way forward & much progress is being made. BEACON-Neuroblastoma is a major step forward. Ultimate Goal - Better drugs to cure children with neuroblastoma.
Acknowledgements

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University of Birmingham CRCTU
Cancer Research UK Drug Development Office
Aberrations in Anaplastic Lymphoma Kinase (ALK) Gene

Neuroblastoma – Mutation (8-15% somatic) & Amplification (4%)

Characterisation of ALK Mutations
Neuroblastoma, n=1596 tumours

- Full-length ALK
- Extracellular (Codons 1-1115)
- Kinase Domain (Codons 1116-1392)
- Intracellular (Codons 1393-2056)

F1174 (n=39)  
- T1151M
- M1166R
- I1170N
- I1170S
- I1171N
- I1183T*

F1245 (n=15)  
- L1196MA
- A1200V
- I1250T*
- I1250T#
- R1231Q
- D1270G
- R1275L
- R1275Q#

R1275 (n=54)  
- L1196MA
- A1200V
- I1250T*
- I1250T#
- R1231Q
- D1270G
- R1275L
- R1275Q#

F1174 Residue Mutations:
- Most potent activation of kinase activity
- Co-associates with MYCN amplification - worse prognosis

*=also noted in germline