Should Rare Oncology Treatments be Considered True Orphans?

ISPOR EU 2017 – Issue Panel IP9

Tuesday 7th November 8:45 am

Moderator: Annabel Griffiths (Consultant – Rare Diseases Lead, Costello Medical Consulting)
Panellists: Ivana Cattaneo (Public Affairs Director, Novartis Oncology Europe)
Pan Pantziarka (Project Coordinator, Anticancer Fund)
Elangovan Gajraj (Senior Technical Adviser, NICE Scientific Advice)

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Should Rare Oncology Treatments be Considered True Orphans?

Rare disease: prevalence of <5 in 10,000[1]
Ultra-rare disease: prevalence of <1 in 50,000[2]
Rare cancer: incidence of <6 in 100,000 persons per year[3]

Should **Rare** Oncology Treatments be Considered True Orphans?

1. European Union. Regulation No 141/2000. 1999. Available at: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32000R0141. Last accessed 25.10.17.
2. European Union. Regulation No 536/2014.2014. Available at: http://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf. Last accessed 25.10.17.
3. RARECARE. Available at http://www.rarecare.eu/rarecancers/rarecancers.asp. Last accessed 25.10.17.

Rare disease: prevalence of <5 in 10,000[1]
Ultra-rare disease: prevalence of <1 in 50,000[2]
Rare cancer: incidence of <6 in 100,000 persons per year[3]

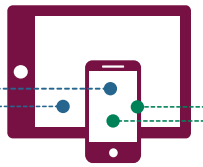
Should **Rare** Oncology Treatments be Considered True **Orphans**?

Life-threatening or chronically debilitating disease[4]
Unlikely sufficient returns from marketing to justify investment[4]
Must be of significant benefit to those affected by the condition[4]

1. European Union. Regulation No 141/2000. 1999. Available at: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32000R0141. Last accessed 25.10.17.
2. European Union. Regulation No 536/2014.2014. Available at: http://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf. Last accessed 25.10.17.
3. RARECARE. Available at http://www.rarecare.eu/rarecancers/rarecancers.asp. Last accessed 25.10.17.
4. European Medicines Agency. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp&mid=WC0b01ac0580b18a41. Last accessed 25.10.17.

[T]he convergence of [the organ and gene models of cancer] means that **almost any cancer medication can be maneuvered into an orphan disease category**.[1]

When drugmakers 'salami-slice' they undermine precision medicine efforts[2]



Unmet Need in Rare Cancers Remains High[3]

CCR Perspectives in Drug Approval

Rare Cancer Trial Design: Lessons from FDA Approvals[4]

1. Bagley N. Thinking straight about orphan drugs, Part 5. Available at https://theincidentaleconomist.com/wordpress/thinking-straight-about-orphan-drugs-part-5/. Last accessed 25.10.17.
2. Marling R. Salami-slicing, precision medicine and the Orphan Drug Act. Available at https://www.christenseninstitute.org/blog/salami-slicing-precision-medicine-orphan-drug-act/. Last accessed 25.10.17.
3. Decision Resources. Unmet need in rare cancers remains high. Available at https://www.prnewswire.com/news-releases/unmet-need-in-rare-cancers-remains-high-236018681.html. Last accessed 25.10.17.
4. Gaddipati H. *et al.* Rare Cancer Trial Design: Lessons from FDA Approvals. Clinical Cancer Research. 2012.

When drugmakers 'salami-slice' they undermine precision medicine efforts[1]

How much do you agree?

Unmet Need in Rare Cancers Remains High[2]

1. Marling R. Salami-slicing, precision medicine and the Orphan Drug Act. Available at https://www.christenseninstitute.org/blog/salami-slicing-precision-medicine-orphan-drug-act/. Last accessed 25.10.17.
2. Decision Resources. Unmet need in rare cancers remains high. Available at https://www.prnewswire.com/news-releases/unmet-need-in-rare-cancers-remains-high-236018681.html. Last accessed 25.10.17.

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Poll: When drugmakers 'salami-slice' they undermine precision medicine efforts

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Poll: Unmet need in rare cancers remains high

The Panel

Ivana Cattaneo
Public Affairs Director, Novartis Oncology Europe

Pan Pantziarka
Project Coordinator, Anticancer Fund

Elangovan Gajraj
Senior Technical Adviser, NICE Scientific Advice

Questions Posed to the Panel

1. Should rare cancers and other rare diseases be considered distinct?
2. Are companies justified in receiving orphan benefits for cancer drugs with several indications?
3. Should a separate rare cancer reimbursement process be introduced – if so, how?

- Each panellist will speak for ~10 minutes
- There will then be a brief opportunity for the other panellists to respond
- After all panellists have presented there will be a ~15 minute discussion session

- Questions and comments from the audience will be taken during the discussion session

Public Affairs
Oncology Region Europe

SHOULD RARE ONCOLOGY TREATMENTS BE CONSIDERED TRUE ORPHANS?

November 7th, 2017

NOVARTIS

Should rare cancers and other rare diseases be considered distinct?

EURORDIS
Rare Diseases Europe

Mapping out the similarities and differences between rare cancers and rare diseases 2015-2016

DATE	21 November 2016
AUTHORS	Jan Geissler, Chronic Myeloid Leukemia Advocates Network Kathy Oliver, International Brain Tumour Alliance (IBTA) Ariane Weinman, EURORDIS
ADVISORS	**Members of the EURORDIS Policy Action Group – Rare Cancers:** Catherine Vergely - children with cancers' Association ISIS, France; Dawn Greene – Cope in a million - Pheochromocytoma Survivor, UK; Drakoulis Yannoukakos, Greek National Alliance for Rare Diseases (PERPA); Eric Low - Myeloma UK **Steering Committee of Rare Cancers Europe:** Prof Paolo Casali – European Society of Medical Oncology (ESMO); Markus Wartenberg – Sarcoma Patients EuroNet (SPAEN); Susanna Lulo, Novartis
CONTRIBUTORS	**Members of EURORDIS** patient organisations for rare cancers (including paediatric cancers) or rare diseases which may give rise to cancers

Very similar

Somehow related

Very different

NOVARTIS

Are companies justified in receiving orphan benefits for cancer drugs with several indications?

NOVARTIS

Scientific advances brought our understanding of molecular causes of cancer to the next level

Treatment of cancer is becoming increasingly personalized by targeting genetic mutations that give rise to the disease.

NOVARTIS

Should a separate rare cancer reimbursement process be introduced – if so how?

Should Rare Oncology Treatments be Considered True Orphans?

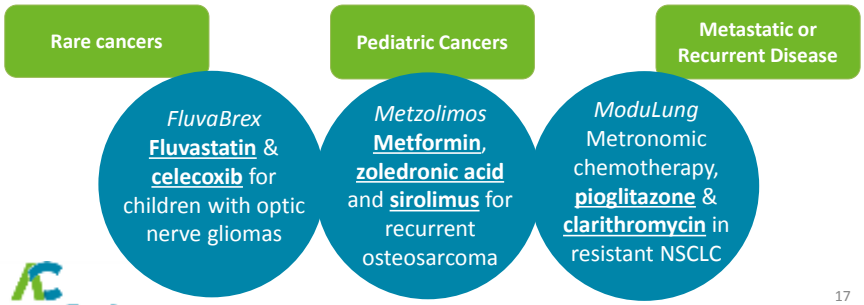
Pan Pantziarka, PhD

The Anticancer Fund

Conflict of Interest:
Nothing to declare.

Introducing the Anticancer Fund

- Founded in 2009 by Belgian entrepreneur Luc Verelst as Reliable Cancer Therapies, later the Anticancer Fund
- A not-for-profit, private foundation
- Supports the development of promising therapies with *little or no commercial value (e.g. drug repurposing)*
- Focus on areas of high unmet needs



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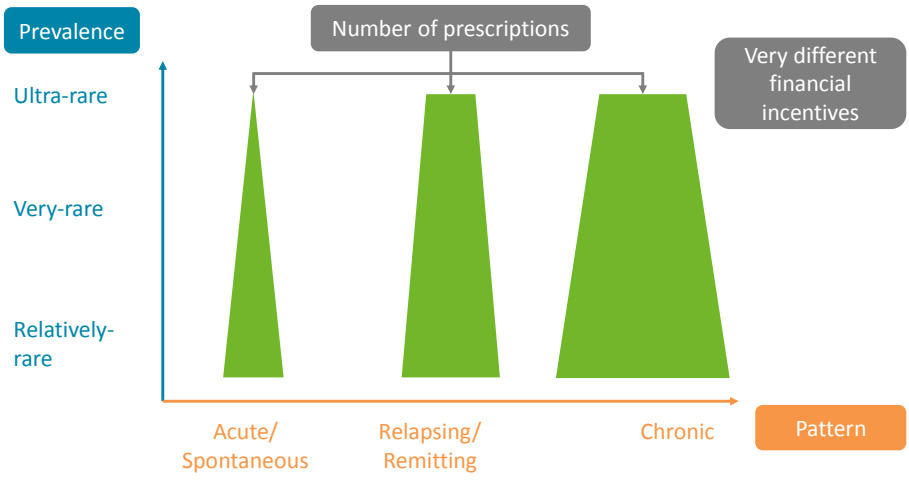
17

ODD – A Blunt Instrument?



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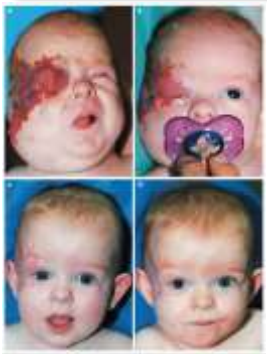
18

The hemangioma story…

Incidental observation in a child treated with propranolol shows rapid and sustained effects on infantile hemangioma – results repeated in 10 other children.



Léauté-Labrèze et al. 2008. *The New England Journal of Medicine* 358:2649–51.

Results confirmed in numerous patients and trials

Léauté-Labrèze et al. 2015. A randomized, controlled trial of oral propranolol in infantile hemangioma. *The New England journal of medicine* 372:735–46.

Drug reformulated for infants

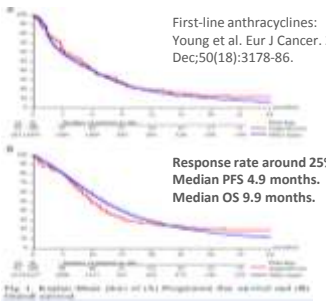
Hemangeol – FDA Approved March 2014

Hemangiol – EMA Approved Feb 2014

Successfully repurposed

Anticancer Fund

Rare cancer – Angiosarcoma



First-line anthracyclines: Young et al. Eur J Cancer. 2014 Dec;50(18):3178-86.

Response rate around 25%. Median PFS 4.9 months. Median OS 9.9 months.

- Angiosarcoma is a rare vascular soft-tissue sarcoma with an incidence of 1 – 2 per million per year (SEER or NCIN data).
- They make up 2%-3% of all soft tissue sarcomas.
- Standard first line treatments are taxane or anthracycline-based chemotherapy, with surgery and radiotherapy options.

Wide range of evidence sources for anticancer effects of propranolol – lab work, animal models, retrospective human data, case reports, some trials…

ReDO – propranolol as an anticancer agent. Pantziarka et al. Ecancermedicalscience. 2016 Oct 12;10:680.

Angiosarcoma/propranolol – multiple published case reports, on-going clinical trial. Anticancer Fund granted ODD

Chow W et al . 2015. Growth Attenuation of Cutaneous Angiosarcoma With Propranolol-Mediated β-Blockade. *JAMA dermatology*:1–4.

Propranolol – financial incentives?

- Millions of prescriptions for long-term use of propranolol in primary indications (e.g. hypertension)
- For angiosarcoma? A few hundred prescriptions per year for short-term use. Not even a rounding error…
- No clinically justifiable reason to reformulate
- Clinicians will use the generic version if a high-priced formulation becomes available
- ***Orphan drug designation does not work in such cases***
- Other mechanisms required – non-commercial label-extension?

Anticancer Fund

Should rare oncology treatments be considered true orphans?

Panel Discussion. ISPOR 2017, Glasgow

Eli Gajraj, Senior Technical Adviser, NICE Scientific Advice

NICE and 'rare' diseases

Highly Specialised Technologies

- Target patient group is so small that treatment will usually be concentrated in very few centres in the NHS
- Target patient group is distinct for clinical reasons
- Condition is chronic and severely disabling
- Potential for life long use
- Expected to be used exclusively in the context of a highly specialised service
- Likely to have a very high acquisition cost
- Need for national commissioning of the technology is significant.

What is 'rare'?

HST evaluations to date

HST	Disease	Incidence	Patients in England
1	Atypical haemolytic uraemic syndrome	0.4/1,000,000	140
2	Mucopolysaccharidosis Type IV a	1/220,000	74-77
3	Duchenne's muscular dystrophy with nonsense mutation		8-13
4	Fabry's disease		142
5	Type 1 Gaucher's disease	1/50-100,000	50-100
6	Paediatric-onset hypophosphatasia	1/300,000	1-7

EMA – orphan designation – prevalence <5/10,000

In England = < 26,505 patients

NICE National Institute for Health and Care Excellence

Perspective: HST

Given the very small numbers of patients a simple utilitarian approach, in which the greatest gain for the greatest number is valued highly, is unlikely to produce guidance which would recognise the particular circumstances

- vulnerability of very small patient groups
- limited treatment options
- nature and extent of the evidence
- challenge for manufacturers in making a reasonable return on their research and development investment

So to answer the questions…

- Should rare cancers and other rare diseases be considered distinct?
  - No, NICE does not differentiate…..
  - ….though HST conditions are more likely to be rare disease that are not cancers
  - Gap between HST and non-orphan conditions requires alternate policy options
- Are companies justified in receiving orphan benefits for cancer drugs with several indications?
  - No, HST does not deal with subgroups of populations
  - Avoid ‘leakage’ to populations that were not within evaluation remit
  - ‘Return on investment’ depends on size of all eligible populations

NICE National Institute for Health and Care Excellence

What's different about rare diseases?

Potential for a cure	• High upfront cost and uncertain long-term effects
Frequently developed by SMEs/academics	• Lack of funding • Multi-stakeholder expertise • Expensive manufacturing • Complicated logistics
Limited evidence	• RCTs – impossible? • Limited generalisability and external validity • Small sample sizes • Surrogate rather than final outcomes • Short trials – maintenance of effect? • Unknown future adverse effects

HST– different cost-effectiveness decision thresholds

- Decision Threshold £100k/QALY (20-30k/QALY for pharmaceuticals)
- Above £100k/QALY, judgements take account of the **magnitude of benefit** and the additional **QALY weight** that would be needed to support recommendation

Incremental QALYs	Maximum Weight	Effective Threshold
≤ 10	1	£100,000/QALY
11-29	1-3 (sliding scale)	
≥ 30	3	£300,000/QALY

Managed Access Agreements

- **Risk-sharing agreements comprising of:**
  - Commercial Arrangement with NHS England - financial risk management
  - Commitment to collect additional data to address significant uncertainty
  - Time limited and agreement for what happens next
  - Agreed with stakeholders (company, NHS England, patient groups and NICE)

Cancer Drug Fund

- Plausible potential for the drug to satisfy the criteria for routine commissioning, but there is significant remaining clinical uncertainty which needs more investigation, through data collection in the NHS or clinical studies
- Managed Access Agreement consists of two key components:
  - Data Collection Arrangement – this sets out the outcomes that need to be collected in order to resolve the key areas of clinical uncertainty.
  - CDF Commercial Agreement – this determines the cost of the drug during the managed access period.

And to answer the last question.....

- Should a separate rare cancer reimbursement process be introduced - if so how?
  - No, the policy options already exist
  - Issues for evaluation of rare diseases less relevant for 'true' orphan conditions
  - Higher thresholds for rare diseases
  - Managing uncertainty through price agreements and further data collection

Thank you

NICE National Institute for Health and Care Excellence

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Discussion Session

The Panel

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Social Q&A

Summary and Close

Summary

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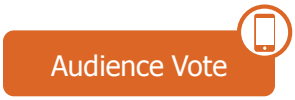

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Acknowledgements

Thank you for your attention

annabel.griffiths@costellomedical.com