HTA Challenges for Cell and Gene (C&G) Therapies

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Disclaimer

• Speaking and consultancy fees: Amgen, Daicchi Sankyo, Janssen, Novartis, Pfizer, Takeda.
Background

• Unique opportunities for improving patient management but also important challenges

• First indications in small populations but significant pipeline activity
  – 30-60 products by 2030; $12.5-$100bn haematological cancer treatment costs*

• Separate HTA process for C&G therapies not yet developed
  – High levels of clinical uncertainty
  – Affordability and budget impact concerns

• Risk sharing and ‘managed entry’ agreements (MEA) key to initial approvals

• Concerns remain over affordability and different market dynamics

What is HTA?

Health Technology Assessment (HTA)

- Assesses the added value of a new health technology compared to the current standard of care
- Therapeutic effect, side-effects, impact on quality of life and costs
- Systematic and multidisciplinary process

Purpose

- Provide policy-makers with evidence based information, so they can formulate health policies that are safe, effective, patient-focused and cost-effective

International examples

- England (NICE), France (HAS), Germany (G-BA)
- Australia (PBAC), Canada (CADTH), Thailand (HITAP)
### Key HTA challenges for C&G therapies

#### Evidential
- Surrogate endpoints
- Curative potential
- Small trials
- Historical data comparisons
- Generalizability of evidence from specialist centers

#### Price and affordability
- One-time administration
- Large upfront price
- Infrastructure costs
- “Real challenge is not HTA but budget impact” (Towse, 2014)

#### Uncertainty
- Uncertain duration of benefit
- Strength of surrogate relationships
- Type of managed entry agreement
  - I. Outcome based
  - II. Financial based
Are existing HTA processes fit for purpose for CAR-T?
Conclusions from UK (NICE) and USA (ICER)

• **NICE**
  – Existing methodology and decision framework is applicable
  – Decision uncertainty a major factor
  – Practical, workable payment methodologies important in managing uncertainties and facilitating early patient access

• **ICER**
  – Core elements of ICER’s assessments are suitable
  – Adaptations may help address distinctive issues:
    • Relationship of evidence to value
    • Transparent and consistency in approach to elements of additional value (QALY weights/modifiers)
    • Broader societal discussion on how to share economic surplus (different market dynamics)
### General Learnings from UK HTA Appraisals of CAR-T

<table>
<thead>
<tr>
<th>Category</th>
<th>Relevant Points</th>
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<tbody>
<tr>
<td>Target Population and Proposed Positioning</td>
<td>• Marketing authorization broader than trial populations</td>
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<td></td>
<td>• Concerns over relevant comparator/standard of care</td>
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<td>Violation of ITT Principle</td>
<td>• Manufacturing failures</td>
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<td>• Death prior to infusion</td>
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<td>Extrapolation Approaches Central</td>
<td>• Cure? Longer term excess mortality? Possible late relapse?</td>
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<td></td>
<td>• Implications for HRQoL and cost assumptions</td>
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<tr>
<td>Resource and Cost Uncertainties</td>
<td>• Bridging vs lymphodepleting chemotherapy</td>
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<td></td>
<td>• Administration and monitoring requirements (inpatient vs ambulatory)</td>
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<td>• Management of AEs (CRS and B-cell aplasia; ICU; readmission)</td>
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<tr>
<td>Implementation Issues</td>
<td>• New service specification and phased implementation</td>
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<td>• Training requirements</td>
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Extrapolating survival

Data source: Tisagenlecleucel (Kymriah®) overall survival, as reported by Schuster et al. (2018). DOI: 10.1056/NEJMoa1804980
Extrapolating survival
Extrapolating survival
NICE Reference Case (UK)

• Use of the Quality-Adjusted Life Year (QALY) central
• Health service perspective for costs
• Range of motivating factors
  – The nature of NICE’s decisions
  – Consistency between appraisals
  – Consistency within appraisals
• Reference case ≠ standardisation
1. Cost-per-QALY analyses have strengths and limitations

2. Frameworks that focus on coverage/reimbursement should consider cost per QALY, as a starting point

3. Consider elements not normally included in CEAs (e.g., severity of illness, equity, risk protection) but more research needed.

4. Test and consider using structured deliberative processes
Additional elements of value for C&G therapies?
Augmented cost-effectiveness analysis

Multi-criteria decision analysis
Structured deliberative processes

• No existing method of aggregation is perfect
  – Pragmatic approaches needed
  – Severity weights already reality
  – Equity adjusted approaches developing
• Advantages of structured deliberation
  – Transparency and accountability
  – Consistency
• Cost per QALY widely used starting point (US and Europe)
  – ‘Aid to’ rather than ‘substitute for’ informed decision making
### Proposed checklist for C&G therapies

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<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Clinical effectiveness</td>
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<td>Validation given?</td>
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<td>Surrogate endpoint used</td>
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<td>Prevalence ______</td>
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<td>Rare disease</td>
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<td>Serious condition</td>
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<td>Single-arm trial</td>
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<td>Matched historical cohort used?</td>
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<td>Pediatric population</td>
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<td>Age range ______</td>
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<td>Reporting of adverse consequences and risks</td>
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<td>Size of clinical trial</td>
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<td>Length of clinical trial</td>
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<td>Extrapolation to long-term outcomes</td>
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<td><strong>Elements of value</strong></td>
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<td><strong>Quantification</strong></td>
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<td>Severe disease</td>
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<td>Value to caregivers</td>
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<td>Insurance value</td>
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<td>Scientific spillovers</td>
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<td>Lack of alternatives</td>
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<td>Substantial improvement in life expectancy</td>
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<td><strong>Other considerations</strong></td>
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<td>Discounting</td>
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<td>Different discount rates explored</td>
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<td>Uncertainty</td>
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<td>Alternative payment models explored</td>
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Managing uncertainty and risk sharing

- One-off treatment cost increases financial risk
  - Irrecoverable costs vs repeat treatment
- Financial arrangements/risk sharing can eliminate additional risks
  - Outcomes-related payment and amortization particularly relevant
- Schemes should entail genuine and appropriate sharing of risk at the point of approval
- Need greater awareness and consistency in the application of methods to address financial risks
Budget impact and affordability

- Broader challenges to conventional HTA methods
  - Affordability and ‘fair-price’ concerns
  - Prevalent population and first-mover advantage
  - Limited potential for brand-to-brand competition; Lack of generic entry
- Development of HTA approaches which explicitly consider sharing of surplus distribution
  - QALY cap (no allowance for cost-offsets)
  - Mock patent cliff (allowance for cost-offsets for specific period)
  - Shared savings (% of cost offsets)
Conclusions

• CAR-T is a ground-breaking therapy
  – Conventional value/HTA frameworks have been successfully applied to CAR-T but many challenges from study designs
  – Further research needed on distinctive features not captured in QALY
  – Important role for structured deliberative process

• Managed entry and flexible pricing important for initial approvals
  – Need for constructive dialogue between stakeholders - progressive reflection of value as knowledge increases
  – Scope to better communicate benefits of access vs risks/uncertainties under different scenarios