Challenges in the Value Assessment, Pricing, and Funding of Targeted Combination Therapies in Oncology

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Moderator: Prof Lou Garrison, University of Washington, Seattle (WA)

Prof. Lou Garrison, PhD
University of Washington, Seattle (WA), USA

Dávid Dankó, PhD
Ideas & Solutions, Budapest, Hungary

Lionel Perrier, PhD
Centre Léon Bérard, Lyon, France

Mickael Lothgren, PhD
Amgen Global Health Economics
Head Economic Modeling COE
Amgen (Europe) GmbH, Rotkreuz, Switzerland
Disclaimer

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The presenter did not receive any honorarium or financial support related to the presentation, including travel, accommodation or conference registration.
What is (Economic) “Value”?  

• From an economic perspective:  
  • Value is what someone is (actually) willing to pay or forgo to obtain something (opportunity cost)

• Implications:  
  • Value varies across individuals, across indications for the same medicine, and dynamically over time

  • Value is difficult to measure in health care because of insurance

An Academic (Health Economics) Perspective on Value Attribution for Combination Treatments

• Combination treatments involve “complementary” goods or inputs.

• In a static sense, the value created is a product of the synergy of the inputs: it may be impossible to identify the marginal contribution.

• The value created for the consumer (i.e., patient) is not specific to one input: hence, the division of rewards among the inputs is essentially arbitrary.
  • E.g., ham and cheese panini (3 inputs + labor)
Some Examples of Combination Treatments

• A oncologist prescribing a medicine as monotherapy

• A personalized medicine diagnostic test and a complementary medicine

• Two innovative medicines taken in combination for treatment

• A biosimilar and a patented medicine used in same regimen

Rewarding Innovation in Medicines—Principles and Implications

• The key principle or philosophy for rewarding innovation via patents for medicines is that innovators receive the “value of their marginal product” (VMP) during their patent life, subject to competition within a drug class.

• Implication: Indication-specific rewards—at a minimum, payment should be tied to an indication as the VMP will vary by indication
  • Challenge: administering this requires (a) real-world data (RWD) on use by indication, and (b) ideally RWD on outcomes and thus the VMP (i.e., cost-effectiveness)
Problem map of challenges related to targeted combination therapies

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This presentation follows a non-country-specific approach. Ultimately, however, most challenges related to targeted combination therapies (TCTs) will also be specific to individual health care systems.
Challenges linked to targeted combination therapies are multi-faceted...

Targeted combination therapy (TCT) involves the combined use of targeted anti-cancer medicines to enable parallel inhibition mechanisms in several molecular pathways, or multiple levels of blockade of the same pathway. Challenges include:

- Not cost-effective
- Value attribution
- Trial designs
- Backbone versus add-on
- Missing hard endpoints
- High prices and high budget impact
- Delayed access

... and from a payer perspective, they often boil down to access restrictions / staggered access:

- High budget impact (and insufficient budgets)
- Inefficient prices (backbone vs add-on)
- Limited evidence and missing hard endpoints

These issues can lead to:

- Restrictions on patient and prescriber eligibility
- Conventional rebates or budget caps
Our recently completed research organized TCT-related challenges into cause & effect relationships

Financial challenges and policy solutions linked to TCTs remain almost fully unexplored in academic literature.*

Based on review of HTA reports and recommendations, no HTA agency or P&R body uses differentiated criteria for assessing and deciding on TCTs.**

For-profit organizations regularly address TCTs, but problem statements are either incomplete or underlying analysis is not publicly accessible.

Problem map to dissect causes and consequences (together with Prof Lou Garrison and Prof Jean-Yves Blay)


** analysis of reports and recommendations for 14 TCTs by HTA agencies and P&R bodies in Australia, Canada, England, France, Germany, Scotland, and Sweden.

*** internet research to identify conference presentations, 'white papers' by consultancy organizations, and online articles.

The resulting problem map is quite daunting...

1. Budget challenge for Payers
   - 1.1. Budget constraints for payer decisions
   - 1.2. Limited capacity to prioritize different indications
   - 1.3. Limited willingness to pay for TCTs

2. Pricing and Funding
   - 2.1. Current budget limitations for TCTs
   - 2.2. Missed opportunities
   - 2.3. Difficulties in managing the prices of new technologies

3. Legal Context
   - 3.1. Limited opportunities for negotiation or arbitration
   - 3.2. Different product lifecycles, commercial and pricing strategies
   - 3.3. Different P&R owners of constituent therapies

4. Economic incentives
   - 4.1. Differentiated incentives for P&T agents
   - 4.2. Different R&D costs of innovative oncology medicines
   - 4.3. Different costs of multiple pathways or levels of stockpiling

5. Clinical Development
   - 5.1. Necessity for new cancer treatments
   - 5.2. Necessity for R&D investment
   - 5.3. Necessity for clinical trials for new oncology medications

6. Economic challenge for P&R Owners
   - 6.1. Limited capacity to manage budget impact
   - 6.2. Limited willingness to pay for TCTs
   - 6.3. Limited opportunities for negotiation or arbitration

7. Health System Losses
   - 7.1. Delayed or restricted patient access to TCTs
   - 7.2. Possible R&D disinvestment from new oncology medications
   - 7.3. Funding shortfalls

8. Payer restrictions on patient and prescriber eligibility
   - 8.1. Limited capacity to manage budget impact
   - 8.2. Limited willingness to pay for TCTs

9. Difficulties in managing the prices of new technologies
   - 9.1. Limited capacity to manage budget impact
   - 9.2. Limited willingness to pay for TCTs

10. Economic incentives for P&R Owners
    - 10.1. Limited opportunities for negotiation or arbitration
    - 10.2. Differentiated incentives for P&T agents
    - 10.3. Different R&D costs of innovative oncology medicines

11. Clinical Development
    - 11.1. Necessity for new cancer treatments
    - 11.2. Necessity for R&D investment
    - 11.3. Necessity for clinical trials for new oncology medications

12. Health System Losses
    - 12.1. Delayed or restricted patient access to TCTs
    - 12.2. Possible R&D disinvestment from new oncology medications
    - 12.3. Funding shortfalls
... but it confirms the unsustainability of current policy approaches which are mostly focused on symptoms

CURRENT POLICY INTERVENTIONS BY PAYERS ARE FOCUSED ON SYMPTOMS...

... BUT SUSTAINABLE POLICIES SHOULD BE DIRECTED AT ROOT CAUSES

Our analysis also gives some directions to improve the quality of policy dialogue about targeted combination therapies

**SHORT TERM**

**Assessment of TCTs as single technologies**: revised methodologies needed

Wider economic analyses, derived value components, added benefit analysis

**Value attribution**: new techniques must be built into the general HTA process in a way which suits local health system requirements

Negotiation-based approaches, safe harbour clauses, price revisions

**Design of registration trials**: trial setups that allow different histologies in one trial seem most useful (e.g. basket and umbrella trials)

**MID-TERM**

**Willingness-to-pay thresholds**: as we come to know more about TCTs, WTPs may be adjusted to changes in underlying science and societal requirements
Dealing with combination therapies within hospitals: the example of the Léon Bérard Cancer Center

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**Key characteristics of the Léon Bérard Cancer Center**

- Private non-profit organization dedicated to cancer treatment
- Affiliated to the National Federation of Centers for the Fight Against Cancer (20 centers across France, and the FNCLCC–Groupe UNICANCER)
- Certified by the Haute Autorité de Santé (HAS)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Details</th>
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<tr>
<td>30,000 patients (in 2017)</td>
<td>&gt;20% of followed patients enrolled in a clinical trial over 200 protocols open to inclusions in the center</td>
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<td>11 operating rooms</td>
<td>4 rooms for interventional radiology</td>
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<td>1,500 employees</td>
<td>(170 doctors, 550 auxiliary nurses &amp; nurses, 500 researchers)</td>
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<td>6 linear accelerators Tomo &amp; Cyberknife®, 2 Pet Scan, 3 gamma camera, 2 MRI, 3 CT-Scan, 1 Intrabeam...</td>
<td>310 beds &amp; outpatient beds</td>
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<tr>
<td>220 beds within Home hospitalization service</td>
<td>15,000 m² dedicated for research</td>
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**A cancer center involved in several international networks**

- International consortia (WIN (GCIG, ICGC, SIOPe...)
- French Federation of Cancer Centers (FNCLCC/Unicancer)
- International rare cancer networks (Sarcoma Ovarian, Mesothelioma, Pediatrics, Thyroid...)
- European Commission (FP6, FP7, H2020)
- Major national grants (LYRIC, AURAGEN...)
- EORTC
- European Commission (FP6, FP7, H2020)
The analysis of the first 2676 patients of the ProfiLER Study

- Prospective molecular profiling trial exploring cancer cell genomic alterations to guide targeted treatment
- Histologically (or cytologically) confirmed diagnosis of advanced malignant tumor of any histological type
- Any age
- Availability of archival (or freshly collected FFPE tumor sample) for DNA extraction
- Targeted sequencing of 69 cancer-related genes

Enrolled
N = 2,676

Tumor genomic profiles
N = 1,944

At least one actionable alterations N = 1,004 (52%)

At least one Molecular Targeted Agents (MTA) recommended
N = 676 (35%)

Patients treated with recommended MTA N = 143 (7%)

No recommendation N = 328 (33%)
MTA not available, n = 135
MTA previously administered, n = 30
Early death, n = 65
Others, n = 98

TCTs in clinical practice in the Léon Bérard Cancer Center

- 7-10% of advanced cancer patients screened in profile really received targeted therapy (50% expressed some targets)

- Combinations just started: MDM2/CDK4, tremelimumab/durvalumab as experimental treatment arms in basket, aromatase inhibitors with CDK4i in routine in breast cancer

- Which pathology? Those with approved licenses or double hits

- Which drugs? Experimental targeted agents (e.g. MDM2 inhibitors, + CDK4i) or immunotherapies

Highlights from the clinician

Costly genomic screening is now routinely needed to guide treatments with novel agents (in combinations AND single).

Currently, most treatments are immunotherapies or experimental targeted agents (Immunotherapy combinations are still more empirical).

Needs to integrate translational research in more routine settings (whole cancer research continuum).

Assessment of results in real-life is needed for the physician, payer and patients.

Highlights for the economist

Increasing use is associated with a growing target population (new indications, new lines of treatment, more screening).

Payers perceive TCTs as being risky due to asymmetric information, and the risk associated with irreversible decisions.

Difficulty to identify appropriate comparators.


Real-world evidence is gaining importance from an economic perspective, too (e.g. patient-reported outcomes).

Uncertainty is still high (e.g. overall survival results).

LEGAL CONTEXT

15. Different IPR owners of constituent therapies.

ECONOMIC INCENTIVES

14. R&D costs of innovative oncology medicines.

11. Necessity to fight cancer through multiple pathways or levels of blockade.

12. Infeasibility to conduct clinical trials for all meaningful combinations.

13. Designing randomized similar trials.

CLINICAL DEVELOPMENT

10. Delayed or restricted patient access to TCTs.

Paying treatment options for patients and physicians.

21. Fewer treatment years gained.

INFRASTRUCTURES

19. Delayed or restricted patient access to TCTs.

20. Possible R&D disinvestment from add-on therapies.

18. Potential R&D disinvestment from add-on therapies.

17. Potential R&D disinvestment from add-on therapies.


15. Potential R&D disinvestment from add-on therapies.


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2. Potential R&D disinvestment from add-on therapies.

1. Potential R&D disinvestment from add-on therapies.
Mickael Lothgren

Economic Evaluation of Combination Therapies: Methods and Implications – An Industry Perspective

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Industry has a clear interest in finding solutions

- Current situation affects manufacturers of both backbone and add-on therapies

- Also relevant for other stakeholders including patients, health care providers, and society

- Health economics and HTA challenges affect clinical development decisions
  - HTA authority decisions affect future investments
  - Industry makes development decisions today that will dictate possible product launches in 5-10 years
  - How do the current and emerging challenges of combination therapy HTA affect innovation?

Economic evaluation of monotherapies

New therapy B will substitute A if priced at (or below) WTP threshold.*

Total WTP cost of B is sum of:
1. Total cost of A, \( C_{A_{\text{mono,WTP}}} = \lambda O_A \), and
2. Incremental WTP cost of B vs A based on incremental outcomes of B vs A: \( \Delta C_{B,A_{\text{WTP}}} = \lambda O_{B,A} \)

\[ \Rightarrow \text{Total WTP cost } C_{B_{\text{WTP}}} = \lambda O_A + \lambda O_{B,A} = \lambda (O_A + O_{B,A}) = \lambda O_B \]

*WTP = Willingness to pay; \( \lambda = \text{WTP threshold per unit outcomes; A is launched and priced} \) before B.
Economic evaluation of combinations – What is different?

For combination B&A, B is not replacing A, but is used alongside A. The following applies:

- The value of the combination regimen is given by the total WTP cost of the combination outcomes: $C_{B&A,WTP} = \lambda O_{B&A}$
- The WTP cost of the add-on therapy B is given by the difference of the combination WTP cost and backbone cost on in combination use: $C_{B,WTP} = C_{B&A,WTP} - C_{A_wB&A}$
- The cost of backbone therapy in combination use $C_{A_wB&A} \geq C_{A_mono,WTP}$. Hence the WTP cost of the add-on is $C_{B,WTP} \leq C_{B&A,WTP} - C_{A_mono,WTP} = \lambda O_{B&A} - \lambda O_A = \lambda O_{B&A_A}$

The implied value (cost) of add-on B is less than or equal to the WTP of the incremental combination outcomes.

*WTP = Willingness to pay; $\lambda$ = WTP threshold per unit outcomes.

Example: combination add-on, treatment for life

If...

- Lifelong treatment
- Backbone priced at WTP threshold (based on LY outcomes), and price unchanged

$\Rightarrow$ Combination B&A will only be cost-effective if add-on is priced at zero
Example: Oncology Combinations, Health states and QALYs

Typical oncology 3-health states:
- PF; PD; Dead
- Utility $U_{PD} < U_{PF}$

Initial therapy A:
- $OS_A = PFS_A + PD_A$

Therapy B add-on. Combo B&A outcomes: $\Delta OS = \Delta PFS + \Delta PD$

Incremental QALY:
- $\Delta QALY = \Delta QALY_{PF} + \Delta QALY_{PD}$

Incremental WTP: $\lambda * \Delta QALY$

Example: oncology Add-on, treatment to progression

The following implications for add-on combinations (w treat to progression and backbone price unchanged) can be shown:

1. Combo ratio $PFS/OS = \text{backbone}$ ➔ combination will only be cost-effective at zero price of add-on
2. Combo ratio $PFS/OS \uparrow$ vs backbone ➔ combination will not be cost-effective even at zero price of add-on
3. Combo ratio $PFS/OS \downarrow$ vs backbone ➔ room for (marginal) add-on price

One problem with many manifestations, “not cost effective at zero price” only one of them.
The way forward?

Multifactorial problem. Solution needs multiple components, including:

- HTA and economic evaluation of treatment regimens
- Willingness to pay for health outcomes and innovation
- Develop methodology for outcomes-based value attribution to individual combination components
- Value and indication-based pricing
  - Repricing of combination backbone therapy
  - Pricing by indication or weighted average across indication-specific prices

Summary by Prof Lou Garrison

Discussion
Key Take-Aways

• Complementary treatments complicate value assessment.

• Current HTA processes are not fit-for-purpose for TCTs: response is access restrictions.

• A substantial share of patients have mutational target: use of targeted therapy is increasing.

• There is a growing need for real-world data.

• Indication-specific pricing and methods for value attribution for TCTs are needed.

Discussion