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

Issue Panel #17, ISPOR Europe 2018

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

ISPOR
Improving healthcare decisions

Moderator and panelists

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

Prof Lou Garrison

INTRODUCTION

Disclaimer

My research on this topic is partially supported by unrestricted funding from Amgen (Europe) GmbH and Roche. The views and ideas expressed in this presentation are those of the presenter.

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

5

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)

Dávid Dankó

Problem map of challenges related to targeted combination therapies

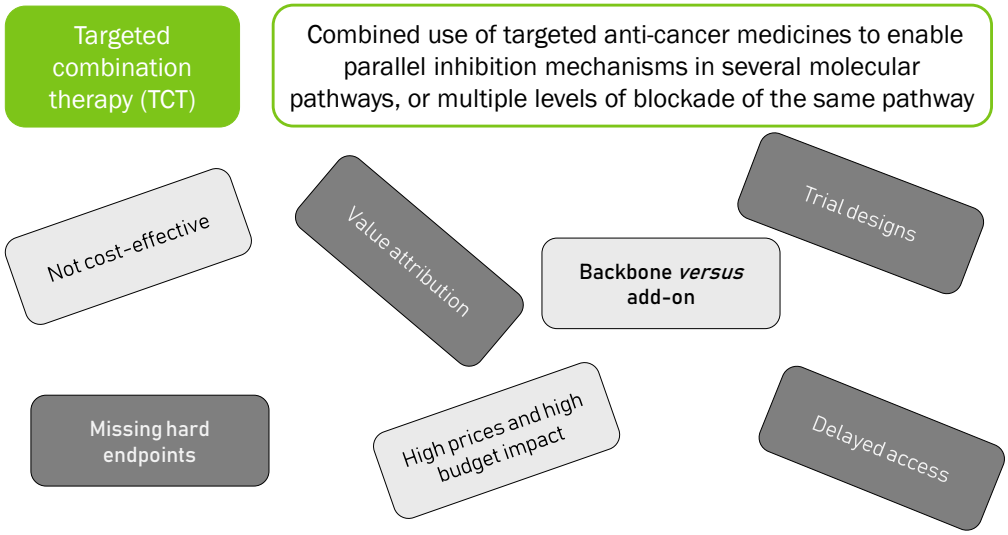
Disclaimer

The research underlying this presentation was supported in 2017 by an unrestricted grant from Amgen (Europe) GmbH. The views and ideas expressed in this presentation are those of the presenter.

The presenter did not receive any honorarium or financial support related to the presentation, including travel, accommodation or conference registration.

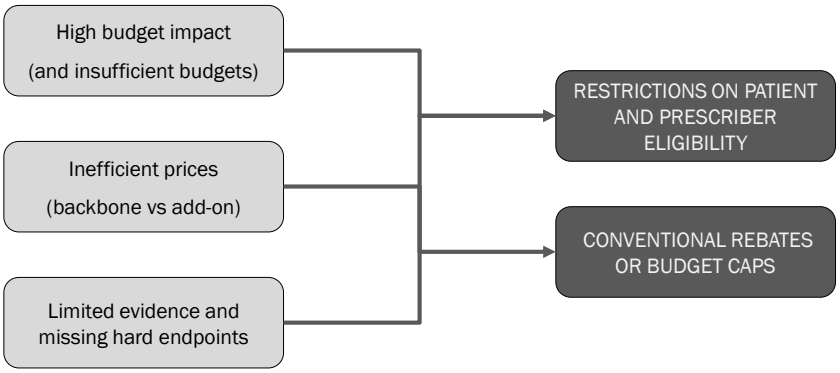
This presentation follows a non-country-specific approach. Ultimately, however, most challenges related to targete combination therapies (TCTs) will also be specific to individual health care systems.

Challenges linked to targeted combination therapies are multi-faceted…



11

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



12

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

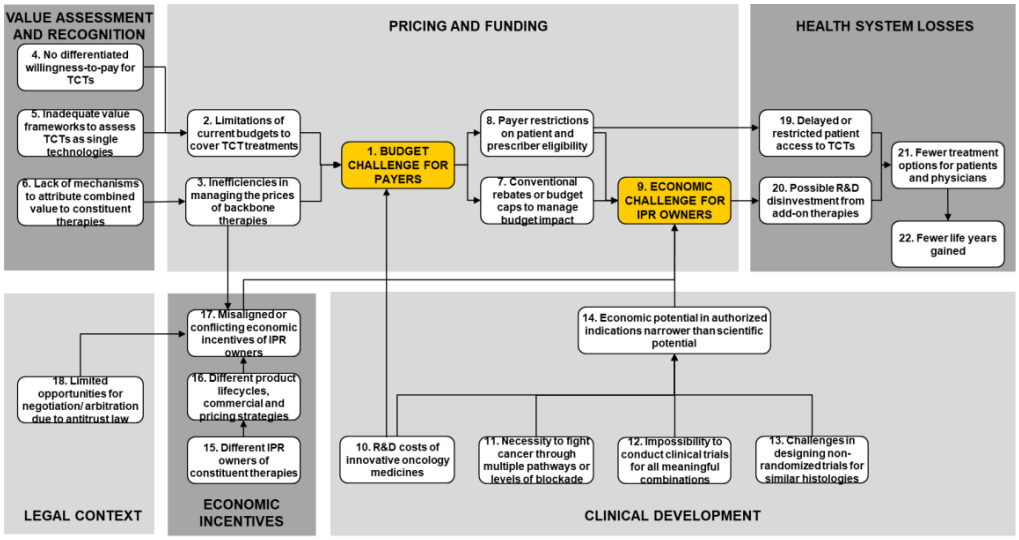
Problem map to dissect causes and consequences (together with Prof Lou Garrison and Prof Jean-Yves Blay)

Manuscript under review in

* Recent publication - Persson U, Norlin JM. Multi-indication and Combination Pricing and Reimbursement of Pharmaceuticals: Opportunities for Improved Health Care through Faster Uptake of New Innovations. Appl Health Econ Health Policy 2018; 16: 157–165., ** 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

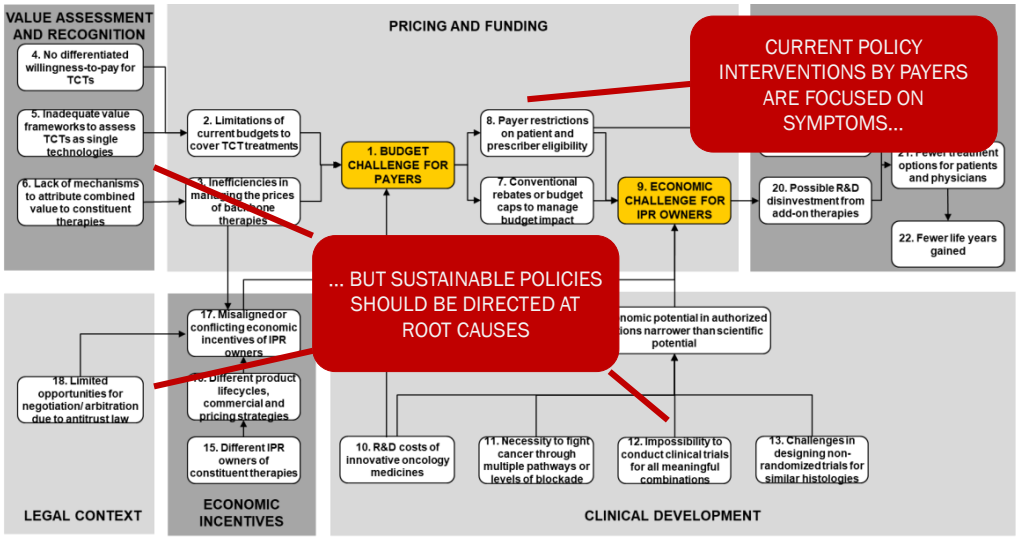
13

The resulting problem map is quite daunting…



14

… but it confirms the unsustainability of current policy approaches which are mostly focused on symptoms



15

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*
MID-TERM	**Design of registration trials**: trial setups that allow different histologies in one trial seem most useful (e.g. basket and umbrella trials)
	Willingness-to-pay thresholds: as we come to know more about TCTs, WTPs may be adjusted to changes in underlying science and societal requirements

16

Lionel Perrier

Dealing with combination therapies within hospitals: the example of the Léon Bérard Cancer Center

The presenter did not receive any grant, honorarium or financial support related to this presentation, including travel, accommodation or conference registration.

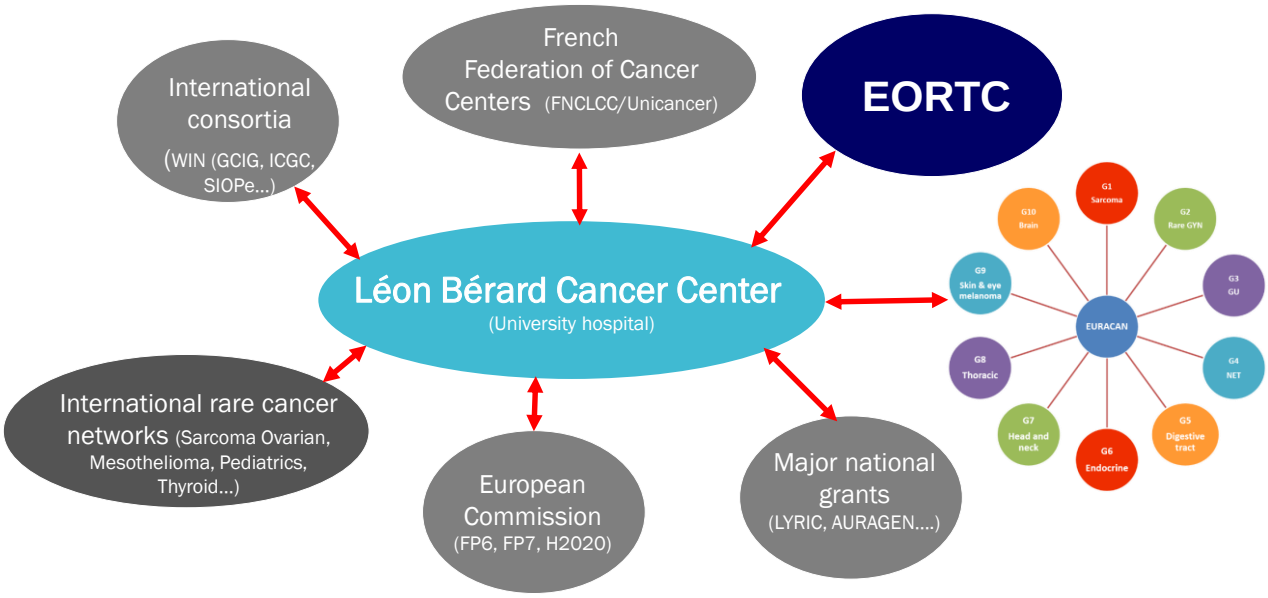
The views and ideas expressed in this presentation are those of the presenter.

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)

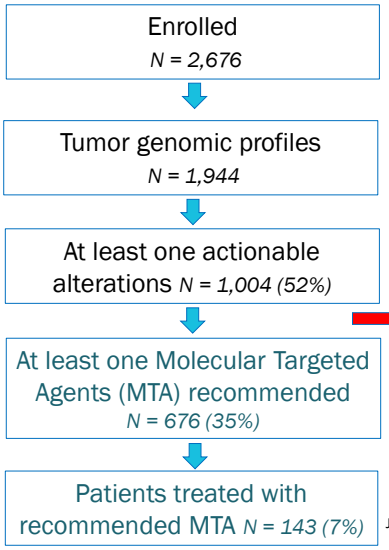
30,000 patients (in 2017) *>20% of followed patients enrolled in a clinical trial* over 200 protocols open to inclusions in the center	11 operating rooms 4 rooms for interventional radiology	1,500 employees *(170 doctors, 550 auxiliary nurses & nurses, 500 researchers)*
6 linear accelerators *Tomo & Cyberknife®*, 2 Pet Scan, 3 gamma camera, 2 MRI, 3 CT-Scan, 1 Intrabeam…	310 beds & outpatient beds 220 beds within Home hospitalization service	15,000 m^2 dedicated for research

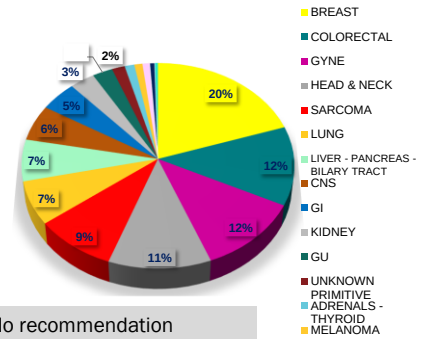
A cancer center involved in several international networks



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





O. Trédan, V. Corset, Q. Wang, R. Varnier, C. Pacaud, A. Torroja, N. Luppi, M. Ezzalfani,M. Myard, X. Jiang, V. Attignon, D. Pissaloux, C. Baudet, PA. Cassier, J. Fayette, M. Carbonnaux, A. Bonneville-Levard, A. Viari, D. Pérol and J-Y. Blay

https://www.targetedonc.com/conference/asco-2017/profiler-study-demonstrates-importance-of-genomic-testing-for-precision-medicine

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

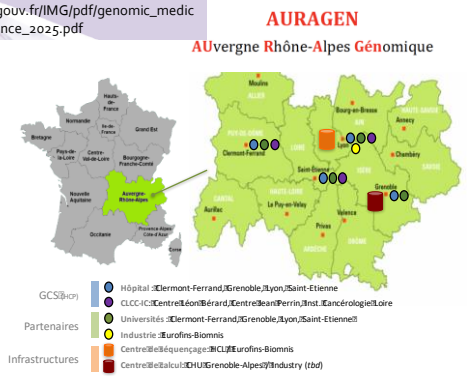
Highlights from the clinician

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

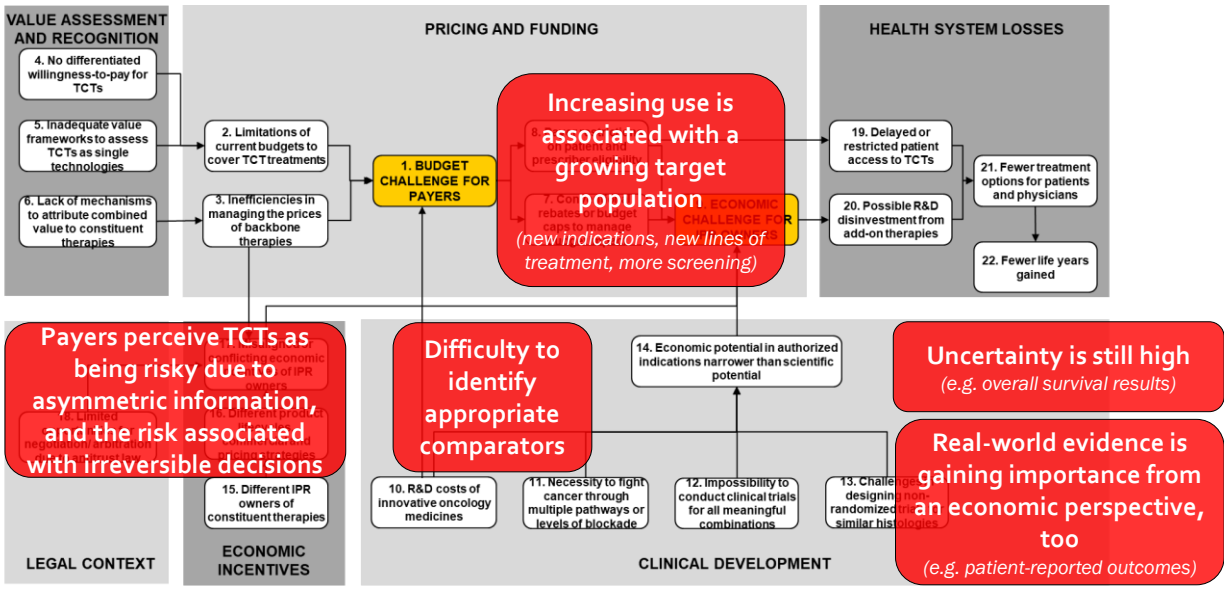
Currently, most treatments are immunotherapies or experimental targeted agents *(Immunotherapy combinations are still more empirical)*

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



Mickael Lothgren

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

Disclaimer

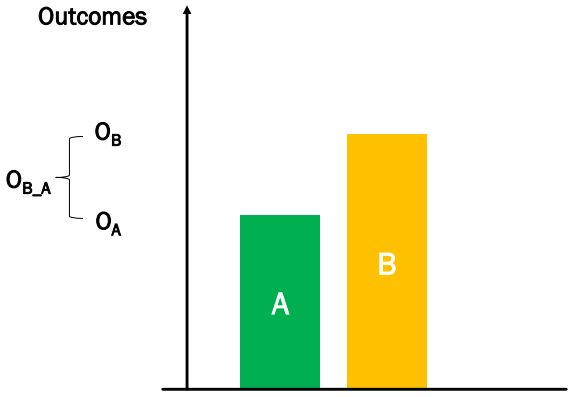
The presenter did not receive any grant, honorarium or financial support related to this presentation, including travel, accommodation or conference registration.

The views and ideas expressed in this presentation are those of the presenter.

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.*

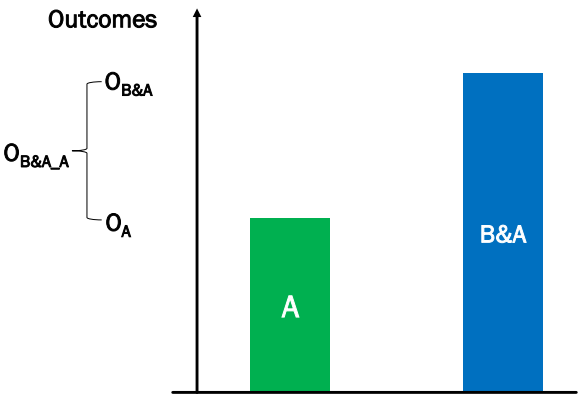
Total WTP cost of B is sum of:

1. Total cost of A, $C_{A\_mono\_WTP} = \lambda O_A$, and
2. Incremental WTP cost of B vs A based on incremental outcomes of B vs A: $\Delta C_{B\_A\_WTP} = \lambda O_{B\_A}$

➔ Total WTP cost $C_{B\_WTP} = \lambda O_A + \lambda O_{B\_A} = \lambda(O_A + O_{B\_A}) = \lambda O_B$

*WTP = Willingness to pay; λ = WTP threshold per unit outcomes; A is launched and priced) before B.

Economic evaluation of combinations – What is different?



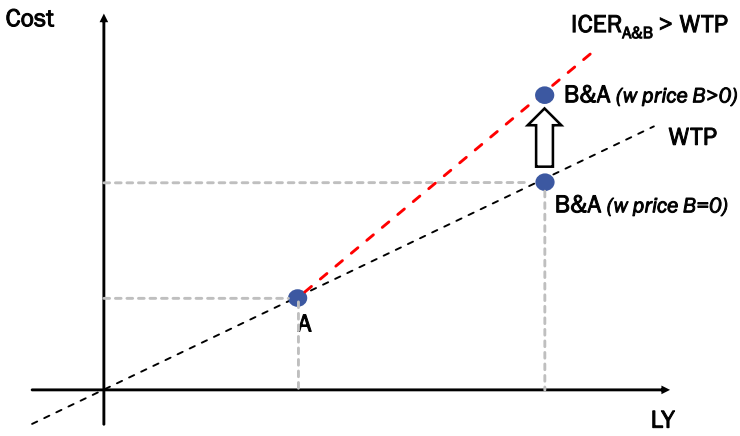
*WTP = Willingness to pay; λ = WTP threshold per unit outcomes.

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.

Example: combination add-on, treatment for life

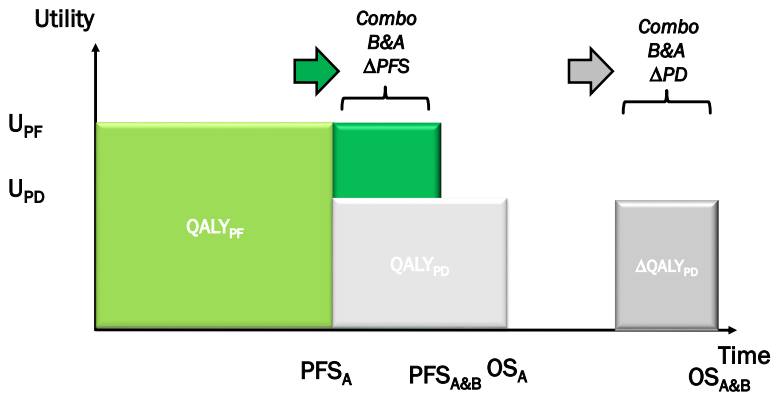


If...

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

➔ Combination B&A will only be cost-effective if add-on is priced at zero

Example: Oncology Combinations, Health states and QALYs



PF – Progression Free; PD – Progressive Disease

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: $\Delta OS = \Delta PFS + \Delta PD$

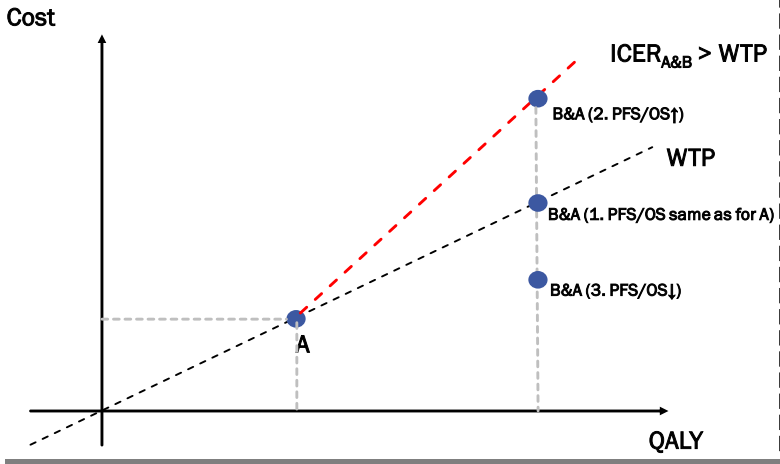
Incremental QALY:

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

Incremental WTP: $\lambda * \Delta QALY$

31

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 = backbone ➔ combination will only be cost-effective at zero price of add-on
2. Combo ratio PFS/OS↑ vs backbone ➔ combination will not be cost-effective even at zero price of add-on
3. Combo ratio PFS/OS↓ vs backbone ➔ room for (marginal) add-on price

One problem with many manifestations, "not cost effective at zero price" only one of them.

32

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