Endpoints and quality of life

PFS, OS, quality of life and medico-economic assessment in oncology

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Troisième Journée de Restitution des Rencontres de Pharmacologie et de Recherche Clinique Pour l'Innovation Thérapeutique et les Technologies de Santé, 23 Mars 2016

Round table n°3
Objectives

- **Understand how the choice of endpoints (OS, PFS and QoL) for oncology drugs affects decisions for market access and reimbursement in France and in Europe and issue recommendations**

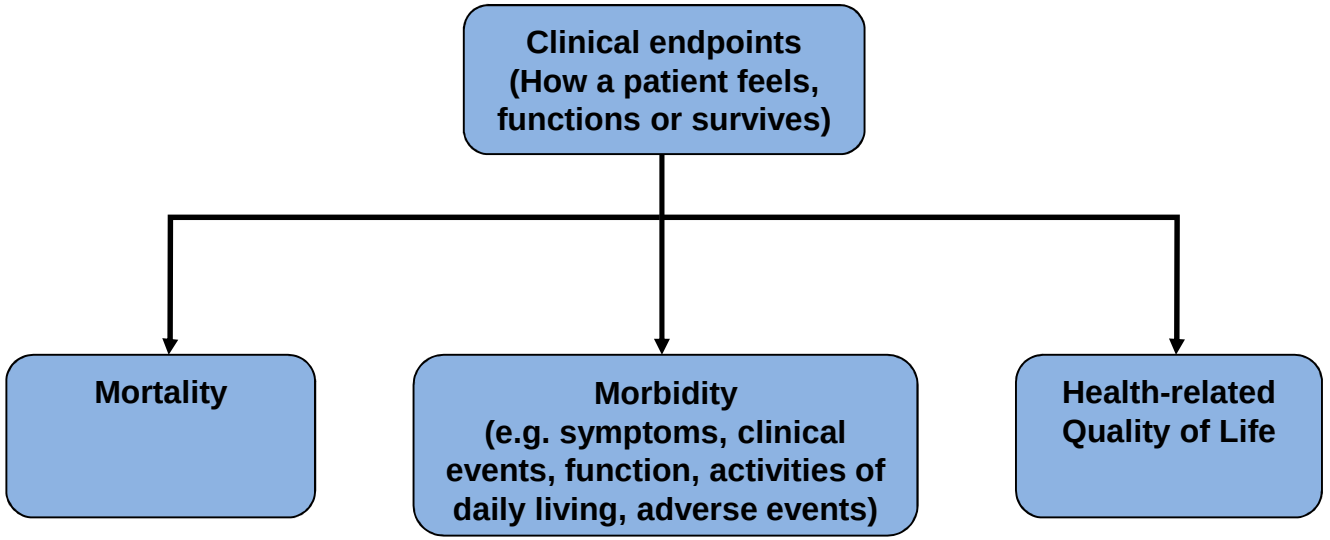
- Analysis:
  1. clinical benefit assessment in Europe and in France
  2. examples of assessment of 4 anticancer drugs by some European HTA agencies
  3. efficiency as criterion to support decision making process in France

Measuring clinical benefit

- Added clinical benefit :
  - HT does more good than harm (has an added benefit) in a target population compared to one or more intervention alternatives (standard of care) for achieving the desired results when provided under the usual circumstances of health care practice
- Added clinical benefit of a new drug is assessed:
  - in **adequate patient population** (population granted MA or more restricted)
  - in comparison to an **adequate comparator** (defined by HTA bodies)
  - **on relevant clinical endpoints:**
    - Primary endpoint (final patient-relevant endpoint or acceptable surrogate)
    - Other endpoints considered relevant for the disease and aim of treatment

Measuring clinical benefit ctd

- Patient relevant endpoints for relative effectiveness assessment (REA) whatever the disease: **morbidity, mortality and quality of life**
- Clinical outcome = how patient feels, functions and survives



http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Model%20for%20Rapid%20REA%20of%20pharmaceuticals_final_20130311_reduced.pdf

Measuring clinical benefit ctd

Measurement of clinical benefit: always comparative

Patient relevant clinical endpoints assessing effectiveness of anticancer drugs: OS, PFS, HRQoL

Final Endpoint: overall survival improvement

Intermediate Endpoints:

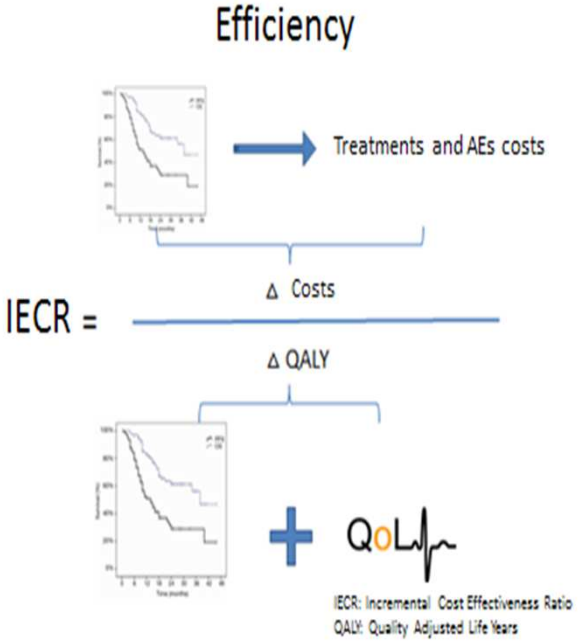
- Duration of the observed effect: improvement in progression-free survival and disease-free survival
- Improvement in key disease symptoms
- Possibility to access curative alternative treatments (e.g. surgery or new chemotherapy)

Safety

Improvement or lack of noticeable alteration of quality of life.

Efficiency

Numerator: impact of PFS and OS on costs
Denominator: overall survival and survival weighted on quality of life



PFS, OS and HRQoL, have an impact on the ICER denominator, but also on the numerator through treatment duration and cost

Clinical benefit need to be expressed identically= QALYs (Quality adjusted life years): the preferred measure

ICER may be:

- main decision criterion for acceptation of financing by the national payer
- a criterion to help decision making, but not the sole criterion

Medico-economic assessment

GERMANY

S Lange

Medico-economic assessment

- Medico-economic evaluation is not used for setting drug price.
- Clinical benefit of a new drug evaluated by the IQWIG and expressed in quantity of added benefit is taken into account for the price setting.
- Economic evaluation can be prepared by the company during the pricing negotiation in case of disagreement with the payers.

Medico-economic assessment

UK

Medico-economic assessment UK

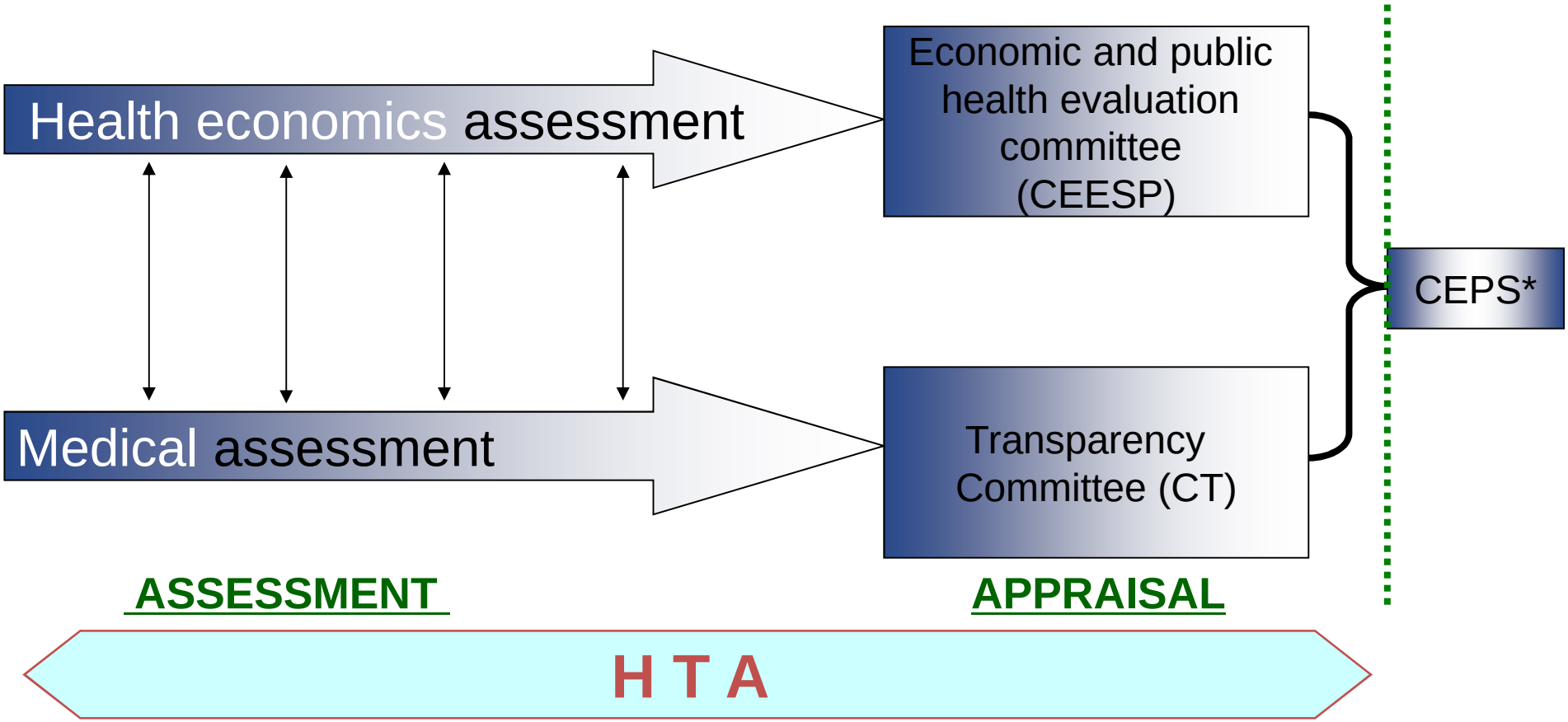
- Based on cost per QALYs.
- Clinical benefit: general principles apply, with a high importance given in oncology to mortality and quality of life.
- Efficiency models submitted by companies are analyzed by experts mandated by the NICE (National Institute of Health and Clinical Excellence) who produce
  - critical analysis of the data used by the companies
  - an alternative model in conformity with the hypotheses indicated by the NICE.

Medico-economic assessment

FRANCE 

Coordinated assessment/appraisal (HAS)

- **Provides the pricing committee (CEPS) an assessment of an added clinical benefit and an economic opinion**



Medico-economic evaluation

- **CT (HAS):** opinion on ASMR (added clinical benefit)
- **CEESP (HAS):**
  - benefits and costs related to the treatments compared based on models that extrapolate results observed in clinical trials (lifetime or other relevant time horizon);
  - all comparators, including drugs with no MA or drugs used outside MA
  - non binding opinion within 90 days for:
    - innovations (i.e. claim by the company of ASMR 1 to 3
    - « significant impact on health insurance expenditures »Expenditures above 20 M Euros / year

- No predefined ICER threshold = efficiency frontier

- **CEPS (independent committee)**: pricing negotiation

  The preferred regulation tool is the price volume agreement, sometimes completed by performance agreements

Rules governing price setting by CEPS

- Primary considerations when setting prices:
  - **added clinical benefit** (ASMR),
  - prices of **comparators**,
  - forecast **sales volumes** (clawback payments in case of overshooting)
- Link between ASMR and price
  - drugs that provide **no added clinical benefit** (ASMR 5) (HAS)
    - price less than the comparator (exception: comparator old drug)
    - **no savings** on treatment costs: **no reimbursement**
  - ASMR 4 (minor added benefit): negotiation
  - drugs with ASMR 1-3 : EU price (price not inferior to the lowest price in 4 European countries)

Evaluation of oncology drugs

Main criterion: differences in **median OS** versus adequate comparator (2,5 – 3 months and more)(CT)

Recent analysis (PRIORITIS):

- **ASMR 5**: irrelevant comparator, weakness in methodology, short follow-up duration, primary criteria not achieved, low quantity of effect **(<2 months** gain in median OS), inclusion criteria too restrictive, bad safety.
- **ASMR 4**: OS gain = **2.7 months** (2 to 3 months); exception in pancreas cancer with a gain of 1.8 months in the absence of treatment alternatives (e.g. Abraxane).
- **ASMR 3**: OS gain = **3 months**, benefits on other criteria: safety, few alternative treatments. ASMR 3 can be granted even in the absence of evidence on OS improvement, with a benefit on PFS, in some specific cases of unfulfilled therapeutic need.
- **ASMR 2**: OS gain = **5.8 months**, significant safety improvements.

PFS/OS

- PFS :
  - endpoint with an intrinsic value in relation with quality of life and other clinical benefits (symptoms reduction) & resource use
  - an intermediate clinical endpoint: correlation with overall survival needs to be proven when the latter is not available
    - particularly important in cancers with long survivals
    - However:
      - intermediate endpoints tend to overestimate the medical benefit,
      - **should be validated for each tumor, each stage and each type of treatment,** which makes them difficult to use.
- OS preferred

Case studies (FR, UK, DE)

Trastuzumab-emtansine (breast cancer)

- FR and DE: major added benefit based on 6m improvement in OS
- UK: no reimbursement (high cost)

Vismodegib (basocellular carcinoma

- Finally reimbursed (FR, DE, UK?) based on PFS, low quality data but no alternative
- No reimbursment in several EU countries (no OS data, open study)

Lenalidomide (myeloma)

- Assessment ongoing
- Reimbursed in UK based on PFS and of £25,300 per QALY.

Dabrafenib (metastatic melanoma with a BRAF V600 mutation)

- No added benefit (FR, DE), finally reimbursed based on small improvement in PFS (no data on OS)
- UK: inadequate comparator; finally approved in the frame of a price agreement with the company («patient access scheme »)

Negative decision does not necessarily imply absence of access to the market

LESSONS LEARNED
Case studies and other oncology drugs (FR, UK, DE)

- **OS data requested to support added benefit**
  - PFS not considered adequate
  - Lower added benefit if only PFS data
  - Data on other patient-relevant endpoints and HRQoL (EQ 5D) recommended
- **OS is not the only relevant endpoint**
  - speed of action, response rate, duration of response, duration of treatment, side effects profile, effectiveness in relevant subpopulations
  - REA should anticipate clinical practice guidelines:
    - data to support potential place of the product in the treatment strategy within the same line of treatment needed:
      - slowly progressing vs fast progressing patients, comparison of different treatment strategies, sequential regimens?
- **Interim analysis not recommended**
  - especially on PFS
  - also on OS whenever possible (mature OS data requested)
- **Comparison with relevant comparators (defined by HTA bodies)**
  - Choice of comparator depends on pre-treatment (if any) and tumour mutation(s)
  - No added benefit if inadequate comparator (exceptions)

Round Table n°3
Recommendations

1. Studies conducted to collect data on clinical benefit and costs need to be comparative, and demonstrate in addition to survival, other clinical benefits relevant for patients (symptoms, morbidity, quality of life).

2. It is recommended not to ask for comparisons with products that are not marketed or are used outside their MA.

3. To inform the users on economic evaluations and on the uncertainty related to comparisons between products, it is recommended to create a scale that allows to score levels of evidence : direct vs indirect comparisons with and without validation ; phase 2 *vs* phase 3 data ; data on French resource use *vs* customization of an international model.

4. Quality of life and utilities:

    1. Generic questionnaires that allow QALYs calculations (EQ5D) should be systematically included in addition to disease-specific questionnaires.

5. PFS and OS data are mandatory for building models. Extrapolation on cost and survival after the first progression is complex:

    1. Products used vary according to prescribers;
    2. There can be an impact of the treatment arm on the response to the next treatments.

Round Table n°3
Recommendations (ctd)

6.It is recommended to collect information on the post-progression outcomes particularly with the next lines of treatment (nature of the product, duration, treatment-free interval, access to a curative treatment, survival) and to anticipate the collection of post-progression data in the protocol in order to describe the complete treatment strategy.

7. Time horizon: In order to better describe uncertainties related to extrapolation beyond the end of the study, produce an evolution model of the product ICER assessed according to of the time horizon with hypotheses adjusted to life expectancy for the given tumors (at 3 years, 5 years, 10 years for example) in addition to entire lifetime.

THANK YOU

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