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ONCOLOGY

APPLIED EARLY ECONOMIC MODELLING FOR COMBINATION THERAPIES IN ONCOLOGY: NOVEL VALUE-BASED PRICING APPROACH

WORKSHOP

For distribution to ISPOR Asia Participants

SEPTEMBER 05, 2016

CONFIDENTIAL

NEW YORK CITY
SAN FRANCISCO
LONDON
SHANGHAI

OVERVIEW

1700 – 1710	1710 – 1730	1730 – 1745	1745 – 1800
INTRODUCTION	**RATIONALE / CHALLENGES**	**CASE STUDY**	**Q&A**
1. Speaker Introductions 2. Objectives	1. Early Economic Modelling 2. How it works	1. Multiple Myeloma	1. Questions / Answers

Today, the session will be run by two speakers.

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The objective of this session is to explore rationale for, as well as opportunities and challenges associated with early economic modelling in oncology

OVERALL PROJECT GOAL

To **explore rationale for, as well as opportunities and challenges associated with early economic modelling in oncology**

PROJECT OBJECTIVES

- ✓ To understand the **environmental drivers** for early economic modelling
- ✓ To understand the **rationale** for use of early economic modelling
- ✓ To evaluate the **challenges and barriers** associated with early economic modelling
- ✓ To understand the **commercial and clinical implications** of early economic modelling
- ✓ To explore a **real-world example** of how early economic modelling was used to **extract actionable conclusions**

Combination therapies in oncology are already coming to the market, with many more on the horizon.

COMBINATION THERAPY
OVERVIEW OF THERAPIES

AVAILABLE THERAPIES

BASE	ADD-ON	MFG	TA	EMA LAUNCH
Herceptin	Perjeta	Roche	HER2+ BC	**Yes** (Mar 2013)
Rituxan	Zydelig	GILEAD	CLL + NHL	**Yes** (Sep 2014)
Mekinist	Tafinlar	GSK	MELANOMA	**YES*** (Sep 2015)
Revlimid + DEX	Kyprolis	AMGEN	MULTIPLE MYELOMA	**YES*** (Dec 2015)

FUTURE THERAPIES**

BASE	ADD-ON	MFG	TA
Yervoy	Opdivo	Bristol-Myers Squibb	MELANOMA
Revlimid + DEX	Nivolumab	Bristol-Myers	MULTIPLE MYELOMA
Revlimid + DEX	Empliciti	Bristol-Myers Squibb	MULTIPLE MYELOMA

**List is not comprehensive, but representative of launches expected in upcoming months; research completed in April 2016
NHL: Non-Hodgkin's lymphoma **DEX**: dexamethasone

SOURCE: CBPartners Prior Experience

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Early economic models are based on the best available known information, as well as likely scenarios for the unknown variables.

WHAT IS AN EARLY ECONOMIC MODEL?

- It can assess **anticipated cost-effectiveness** in different **subpopulations**, across different **comparators**, and in different **indications**
- **NOT** designed to be **as robust as the cost-effectiveness models**
- Interface is **flexible** and designed to be **exploratory** to help shape an initial understanding of the **likely drivers of cost-effectiveness.**

WHAT IS THE PURPOSE?

When designed for use in oncology, there are two questions answered:

1. Based on **anticipated clinical data**, what **cost-effective price** is supported?
2. In order **to achieve a desired price** for your asset, what **minimum incremental overall survival** (OS) / **progression-free survival** (PFS) relative to the **current standard of care** need to be achieved?"

WHO SHOULD USE IT?

- Should be designed for both **health economists** and **non-health economists**
- Analysis modules
  - **Clinically supported price**
  - **Minimum efficacy** necessary to support desired price
  - **Sensitivity analyses**
  - **Cost-effectiveness accessibility** curves
  - Expected **value of perfect information**

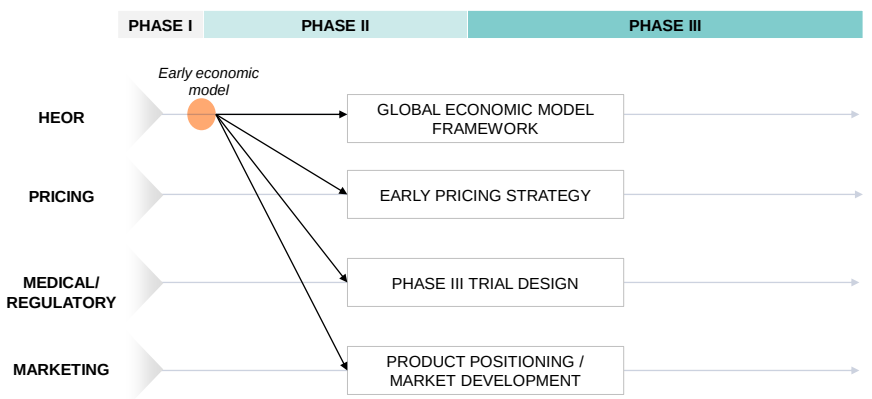
WHAT DATA IS NEEDED TO USE THIS MODEL?

- At a **minimum**:
  - **Comparator data**, including median or mean OS and PFS, **dosing** schedule and **pricing**
  - Key asset data, including **pricing** of marketed **regimen components**, **survival** assumptions
  - **All other inputs** necessary for the model to run properly are stored in a broadly applicable **'base case'** and can be **modified if necessary**
  - E.g., AE rates / costing; utilities and disutilities; and, healthcare resource utilisation rates and costs

SOURCE: CBPartners Prior Experience

Early economic models can be useful in the clinical and commercial development of new health technologies.

EARLY ECONOMIC MODELS
RATIONALE



SOURCE: CBPartners Prior Experience

Early economic models can be used to answer different key questions relative to 'late' economic models.

EARLY ECONOMIC MODELS
QUESTIONS ANSWERED

'LATE' MODEL	EARLY MODEL
What is the **economic value** of this asset?	How does **economic positioning** of the product **affect go / no-go decisions** for development?
What is the **ICER for** this product from **the relevant market perspective?**	What **level of efficacy** (and which endpoints), is required to **demonstrate cost-effectiveness**?
Which **parameters drive costs and cost offsets** for this product?	Which **efficacy parameters** are the **biggest drivers** of cost-effectiveness?
What is the **economic value** of this product at its **anticipated price** in this market?	What **preliminary price can be supported** for the product for the purposes of forecasting?
How do the **PHASE III clinical outcomes** translate into **economic benefits**?	Which **endpoints should be investigated** in Phase III clinical trials?
What is the **relative cost-effectiveness** in **different sub-groups?**	Which **populations / indications** should be targeted?

Early stage models aim to **inform internal decisions related to product development**, while **late stage** models aim to **inform external decision-making on resource allocation**

SOURCE: CBPartners Prior Experience

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As early models inform different types of decisions, they differ in terms of structure, complexity and certainty.

EARLY ECONOMIC MODELS
COMPARISON WITH LATE MODELS

	'LATE' MODEL	EARLY MODEL
FLEXIBILTY	**LESS FLEXIBLE** As late stage models **aim to answer specific questions** their **structure needs to be fixed,** designed to consider costs and health outcomes in **a specified population and indication**	**MORE FLEXIBLE** As early models aim to **answer a wider set of questions** their **structure** needs to be **flexible** to consider different indications and populations
COMPLEXITY	**MORE COMPLEX** Late stage models are **usually more complex** to **more accurately reflect disease progression and risks** and incorporate all available data	**SIMPLER** Early models typically have a **simpler structure**, both because of the **requirement to maintain flexibility** and because **less data is likely to be available**
CERTAINTY	**GREATER ACCURACY** As the late stage models are **more complex** and **populated with more accurate data** the results are more certain and can be used to inform external decisions	**LESS CERTAIN** The results of early economic models are **less certain** as they **aim to be indicative** of relative cost-effectiveness therefore they should not be shared externally

SOURCE: CBPartners Prior Experience

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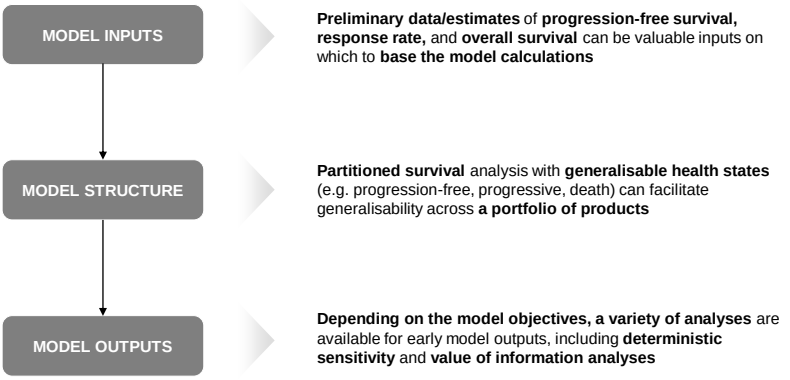
A range of factors can be considered in the development of an early model for a product portfolio.

EARLY ECONOMIC MODELS
DISCUSSION



SOURCE: CBPartners Prior Experience

Before early economic modelling begins, structural considerations must be aligned upon.

INTERFACE STRUCTURE / ANALYSIS MODULES

- What are the pros / cons of employing a **partitioned survival vs. a Markov model**?
- Will a typical **3-state model** satisfy the broadest possible set of analogues?
- What should be the **base case market** from a **costing** perspective?
- What are the key interface study **endpoints**?
- Which **analyses should be performed** within the interface, and how should these vary based on the intervention question posed?

INTERVENTION QUESTIONS / SCENARIOS

- What are the **key questions** the **interface should help to answer**?
- How many **scenarios** should the user be able to **investigate at one time**?

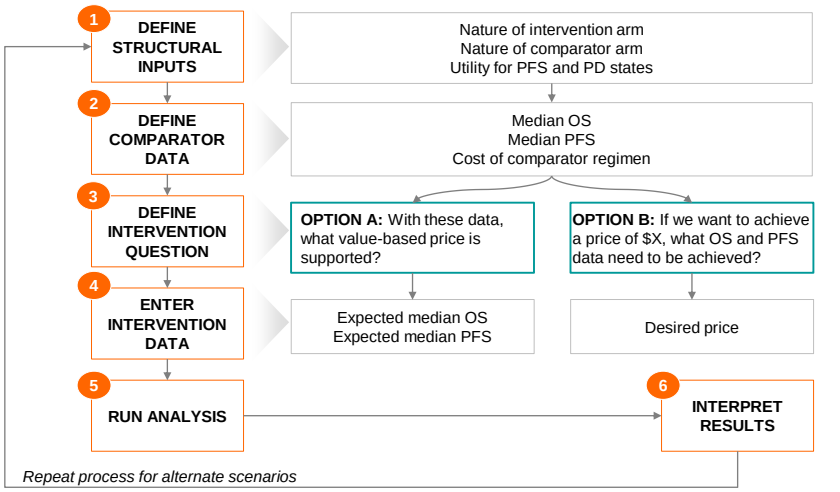
HARD-CODED VS. MODIFIABLE INPUTS

- What **variables should be user-modifiable vs. hard-coded**? How will this vary based on the intervention question being asked?

SOURCE: CBPartners Prior Experience

Once built, the model's utilisation will follow a specific flow in order to elicit the desired information for the asset.

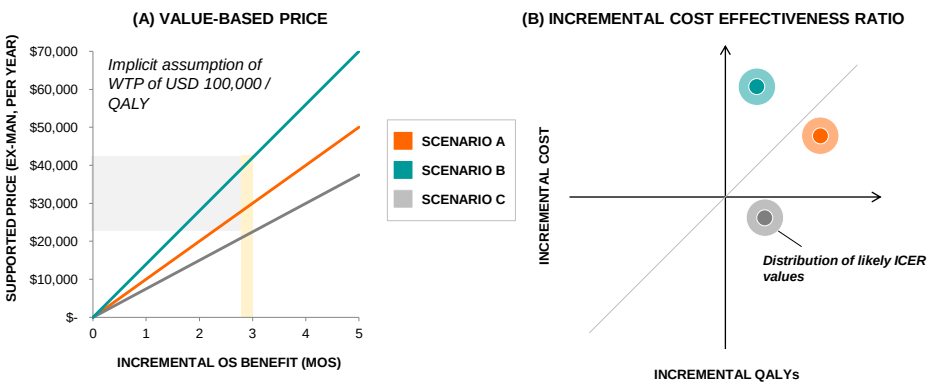
EARLY ECONOMIC MODEL VALUE interface ILLUSTRATIVE
POTENTIAL FLOW



SOURCE: CBPartners Prior Experience

Several visualisations are possible for the early economic model interface outputs.

EARLY ECONOMIC MODEL VALUE interface ILLUSTRATIVE
EXAMPLE OUTPUTS



POTENTIAL SCENARIO VARIABLES

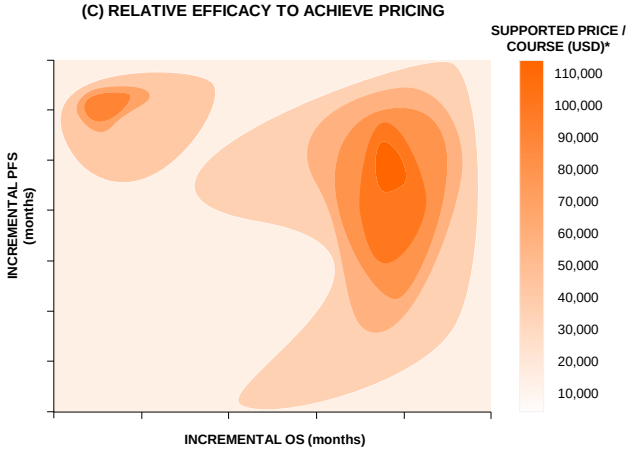
- Choice of comparator
- Expected state utilities
- Intervention adverse event profiles
- Intervention patient subpopulations

SOURCE: CBPartners Prior Experience

Solving for the minimum relative efficacy (with OS and PFS as variables) to achieve our desired price will require two-dimensional visualisation.

EARLY ECONOMIC MODEL VALUE INTERFACE ILLUSTRATIVE
EXAMPLE OUTPUTS

(C) RELATIVE EFFICACY TO ACHIEVE PRICING



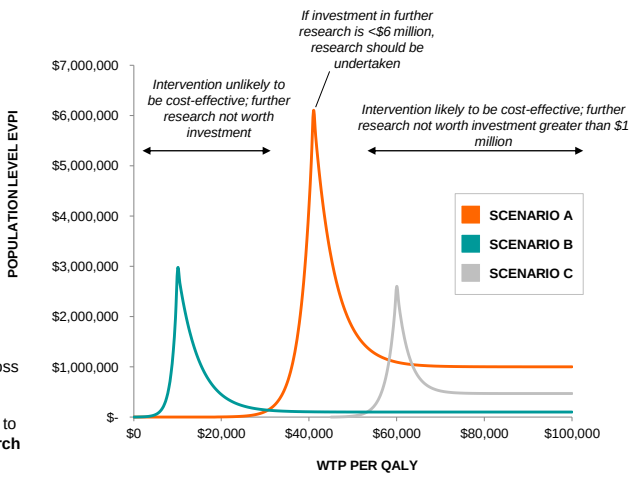
*At given WTP threshold

SOURCE: CBPartners Prior Experience

A value of information analysis can help to inform whether further investment in research is likely to be cost-effective.

EARLY ECONOMIC MODEL VALUE INTERFACE ILLUSTRATIVE
VALUE OF INFORMATION ANALYSIS

1. **PERFORM PSA-BASED NMB ANALYSIS**
2. **PERFORM PATIENT LEVEL EVPI ANALYSIS**
3. **TRANSFORM TO POPULATION LEVEL EVPI**



- A population-based EVPI can help to **prioritise research investment** across **different indications**
- EVPI analysis can also be structured to **isolate the impact of further research on a specific variable** (e.g. QoL, decrease in hospitalisations, etc.)

SOURCE: CBPartners Prior Experience

The following sources are recommended to be queried in order to arrive at the set of data that will be used to develop the model inputs for the proof-of-concept exercise.

SEARCH STRATEGY
SUGGESTED SOURCES

LITERATURE

Epidemiological and clinical data; clinical practice guidelines

DATA ON FILE

- *Latest data from on-going studies*

CONGRESS ABSTRACTS

American Society of Clinical Oncology

European Society for Medical Oncology

International Society for Pharmacoeconomics and Outcomes Research

REGULATORY / ACCESS LANDSCAPE

Updated market landscape for asset and its competitors; utility data (NICE / SMC submissions)

SOURCE: CBPartners Prior Experience

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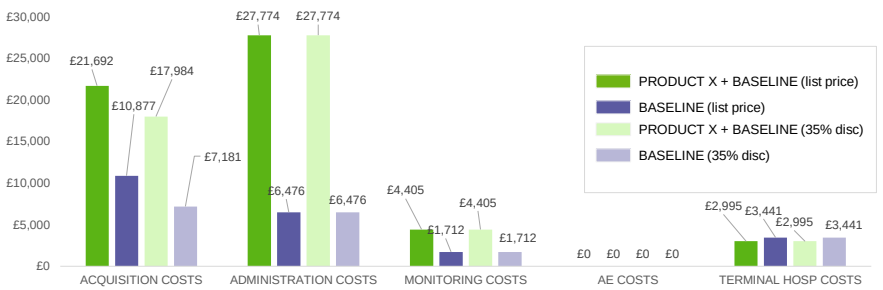
The following case study is a real-world example of a product being considered for approval in MM indications.

SOURCE: CBPartners / SANOFI Prior Experience

In this analysis, ≥2L MM indications PRODUCT X achieves a cost-effective price at a WTP of GBP 20,000 / QALY.

TOTAL COSTS RESULTS
PRODUCT X + BASELINE, BASELINE

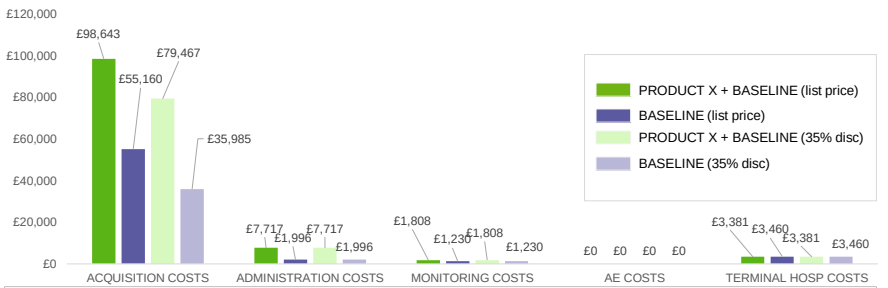


KEY POINTS
- For PRODUCT X, **a threshold of £20,000 / QALY** can generate a sustainable price for the product's acquisition costs due to **the baseline therapy** not being taken into progression and administered for a median of seven cycles
- When BASELINE is discounted, the acquisition costs decrease and the price of PRODUCT X increases slightly
- **Acquisition and administration costs of the intervention** are the main driver behind the relative difference in costs, while **terminal care costs** are **generally similar** across both arms

SOURCE: CBPartners / SANOFI Prior Experience

In this analysis, ≥2L MM indications PRODUCT X cannot achieve a cost-effective price at a WTP of GBP 20,000 due to the high costs of the baseline therapy.

TOTAL COSTS RESULTS
PRODUCT X + BASELINE, BASELINE



KEY POINTS

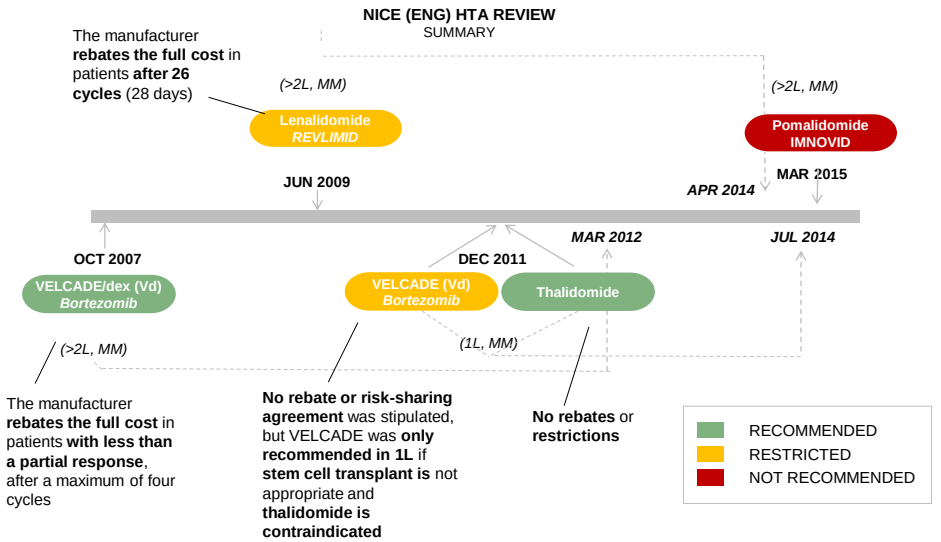
- For PRODUCT X, only a **very high WTP** can generate a positive value for PRODUCT X's acquisition cost, as the **increased costs from BASELINE** due to **increased PFS** vastly increase PRODUCT X-independent acquisition costs
- **Acquisition costs of the non-PRODUCT X components** of the comparator therapy are the main driver behind the relative difference in costs, while **monitoring and terminal care costs** are **generally similar** across both arms

SOURCE: CBPartners / SANOFI Prior Experience

ENG

In a classic cost-effectiveness market like the UK, only one positive decision made by NICE had no known rebates or restrictions.

NICE (ENG) HTA REVIEW
SUMMARY



SOURCE: CBPartners / SANOFI Prior Experience

ENG

The main reason for the negative decision for POM in >2L was that the ICER was above GBP 50K after the manufacturer was requested to revise their assumptions.

NICE (ENG) HTA REVIEW
POM, >2L, PUBLISHED IN 2015

POM + LD dex was compared to 3 comparators in >2L

POM + LD dex

ASSUMPTIONS
- OS 0.977 years
- Median PFS 0.307

EFFICACY
- 2.225 Mean LYs gained

BORTEZOMIB + LD DEX

THALIDOMIDE + HD DEX + CYCLOPHOSPHAMIDE

BENDAMUSTINE + THALIDOMIDE + LD DEX

ASSUMPTIONS
- OS 0.422 years
- Median PFS 0.249

EFFICACY
- 1.166 Mean LYs

Uncertainty around the clinical evidence and inappropriate assumptions for the utility values and cost assumptions were the main criticisms of the manufacturer's model

MAIN CRITICISMS FROM NICE

- The **SLR** submitted **missed key studies**
- Some of the **comparators** (high dose dex) were **inappropriate**
- The **discounted price bortezomib** was **not applied** (they assumed list price)
- Uncertainty around the **disutility** with **IV drug use** was not considered and **favoured POM**
- There was **no justification** for **only including disutility** for adverse events **in 2%** of patients
- The **disutility** values applied **for adverse events underestimated** the **effect of adverse events**
- The Kaplan-Meier plots for OS in the manufacturers submission **over estimated survival** for POM and **under-estimated survival** for **comparators**

SOURCE: CBPartners / SANOFI Prior Experience

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ENG

There are a number of lessons that should be considered in respect to the clinical evidence and assumptions applied to any NICE HTA submissions.

IMPLICATIONS FOR SUBMISSIONS
ENG; CLINICAL INPUTS

	DO	DO NOT
CLINICAL EVIDENCE	**Ensure** the model is based on **most robust clinical evidence available**	Base clinical evidence **on non-comparable trials / irrelevant studies**
SELECTING INPUTS	Be consistent; **justify selection** of **inputs** for OS / PFS / ORR	'**Cherry pick**' inputs that **favour intervention w/o** robust **justification**
COMPARATORS	**Select comparators** based on **market authorisation / current practice**	Include **comparators** where there is **no market authorisation / not used**
COMPARATORS COST ASSUMPTIONS	Consider the **price** expected to be **applied in practice**	Apply the **list price** if a **discounted price** is expected to apply **in practice**
COMPARATOR EVIDENCE	Ensure **efficacy data** is obtained from **comparable clinical trials**	Obtain **efficacy data** for comparators with **non-comparable assumptions**

SOURCE: CBPartners / SANOFI Prior Experience

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ENG

There are also lessons regarding the model structure and assumptions that should be considered when developing evidence for a product under development.

IMPLICATIONS FOR SUBMISSIONS
ENG; MODEL STRUCTURE AND ASSUMPTIONS

	DO	DO NOT
MODEL STRUCTURE	Apply a **transparent structure, e.g., Markov**	Have an **unnecessarily complex structure** perceived as a **'black box'**
MAINTENANCE THERAPY & DOSING	Ensure the **assumptions** applied are **consistent and justified**	Apply **dosing / maintenance therapy assumptions** that favour **intervention**
UTILITIES	Source **utility / dis-utility values appropriate** to the **indication**	**Omit dis-utilities for adverse events** or apply dis-utility assumptions for **IVs**
STOPPING RULES	Consider **alternative stopping-rules**	Apply **efficacy assumptions** to **non-responders w/o explicitly stating this**
SCENARIO ANALYSIS	Consider **appropriate** and justified **sub-groups**	

SOURCE: CBPartners / SANOFI Prior Experience

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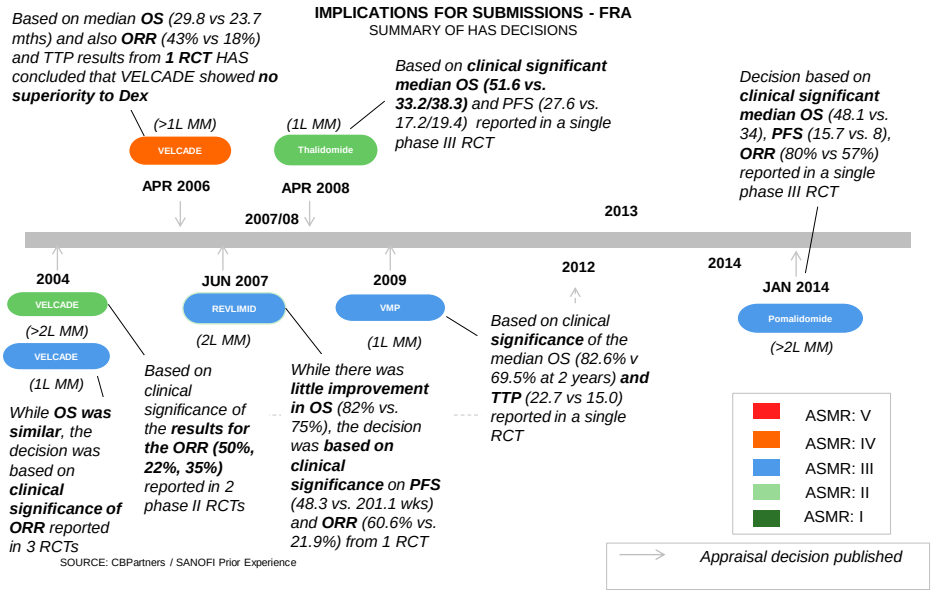
FRA

An ASMR <III has been historically attainable with clinical significant ORR or PFS, even if OS is similar or not available yet and if only reported in a single RCT.

IMPLICATIONS FOR SUBMISSIONS - FRA
SUMMARY OF HAS DECISIONS



SOURCE: CBPartners / SANOFI Prior Experience

FRA

The outcomes of previous HAS decisions should also be considered when preparing to launch a new oncology product.

IMPLICATIONS FOR SUBMISSIONS - FRA
CURRENT ENVIRONMENT

CURRENT ENVIRONMENT

	DO	DO NOT
CLINICAL EVIDENCE	Demonstrate a **clinically significant or substantial OS, PFS** and ORR	**Assume minor improvements** in key clinical endpoints (OS, PFS, ORR) will secure access
	Submit phase II or phase II trials, and **multiple** studies if available	

SOURCE: CBPartners / SANOFI Prior Experience

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FRA

As an economic submission is expected to be required for future launches; hence, the implications of this should also be considered.

IMPLICATIONS FOR SUBMISSIONS
FRA; CLINICAL, ECONOMIC CONSIDERATIONS

FUTURE ENVIRONMENT

	DO	DO NOT
CLINICAL EVIDENCE	Applying the same criteria for clinical evidence submitted to HAS, as detailed in the previous slide	
	Develop economic evidence, applying HAS PE guidelines	**Assume** demonstrating **clinical benefit alone** sufficient to **gain access**
ECONOMIC EVIDENCE	**Ensure all modelling inputs are adequately justified**	**Assume** that **ICER > €75k / QALY** will be **accepted**
	Aim to demonstrate cost-effectiveness as ~ **€75k / QALY**	

*To date, CEESP do **not appear to apply a formal WTP** threshold :*

- *HAS has accepted interventions with ICERs **as high as €300,000/QALY**, but most of the interventions recommended have been around **€75,000 / QALY ,** thus there is a **growing consensus that decisions will be accepted** around this WTP threshold, **with some** decisions **accepted** at a **higher threshold***
- *Compared to NICE, CEESP decisions are **expected to be more flexible** in respect to **ICERs** and more **focused on robust methodology**, **clinical effect**, **burden of illness** and **budget impact***
- ***While price is not fixed based on the economic submission,** price set in the economic dossier is expected to be **an important starting point** for eventual **pricing negotiation with CEPS***

SOURCE: CBPartners / SANOFI Prior Experience

ENG FRA

The HAS guidelines on economic evaluation are broadly aligned with the NICE for economic submissions.

HEALTH ECONOMIC SUBMISSIONS
SIMILARITIES [1]

	COMMON TO BOTH HAS & NICE GUIDELINES
DATA SOURCING	• Both require similar **methods** for **data identification, production** and **validation,** preferring **systematic literature review**
CLINICAL EVIDENCE	• Both require **similar sources of clinical evidence** (favouring head-to-head RCTs and meta-analysis)
UTILITY DATA	• Cost **utility analysis** is the **preferred type** of analysis in both
SUBGROUP ANALYSIS	• In both, **subpopulations** should be **considered**
TIME HORIZON	• **Time horizon** should be **long-enough to capture** all differences in **costs** and **outcomes**
SENSITIVITY ANALYSIS	• Both require a **sensitivity analysis**, with **probabilistic sensitivity analysis (PSA) being the preferred** for both HAS and NICE

The **guidelines** for developing health economic evaluations are broadly **similar in both countries in terms** of the **preferred** type of analysis, **data inputs** and the **approach to sensitivity** and **sub-group analyses**

SOURCE: CBPartners / SANOFI Prior Experience
1) Massetti, Marc, et al. "A comparison of HAS & NICE guidelines for the economic evaluation of health technologies in the context of their respective national health care systems and cultural environments." *Journal of Market Access & Health Policy* 3 (2015)

ENG

However, there are also some methodological differences in the HAS and NICE guidelines that should be considered when adapting models to FRA.

HEALTH ECONOMIC SUBMISSIONS
DIFFERENCES [1]

	DIFFERENCES BETWEEN NICE & HAS GUIDELINES	
	NICE	HAS
ANALYSIS	Only recommends **cost-utility** analysis	Accepts that **sometimes cost per LY** is more **appropriate than cost / QALY**
POPULATION	The **population** considered should match the market authorisation	All **populations** for whom **health** is **directly or indirectly** affected by the intervention
COMPARATORS	Comparators should have **market authorisation**	The intervention should be **compared** to **all relevant comparator** interventions, **irrespective of market authorisation**
UTILITY	Utility should be derived using **EQ-5D** data sourced from a **UK population**	**Prefers EQ-5D** data to be sourced from a French population but **recognises French EQ-5D data is not always available**
COSTS	**Costs** should be considered from a **NHS and Personal Social Services (PSS) perspective only**	In additional to costs from a **NHS and PSS perspective**, HAS considers **patient travel and time costs**, **costs borne** by other **stakeholders and carer's costs**
DISCOUNTING	Future **costs and outcomes** should be discounted at **3.5%**	Future **costs** and **outcomes** should be **discounted at 4%**

SOURCE: CBPartners / SANOFI Prior Experience
1) Massetti, Marc, et al. "A comparison of HAS & NICE guidelines for the economic evaluation of health technologies in the context of their respective national health care systems and cultural environments." *Journal of Market Access & Health Policy* 3 (2015)

In summary, early economic models serve a useful purpose to inform clinical development, commercial, and payer needs.

EARLY ECONOMIC MODELS
SUMMARY

RECAP OF BENEFITS OF THIS EARLY ECONOMIC INTERFACE

- The Interface is **designed to consider a wide range of scenarios** that can be applied to new drugs, alternative comparators, in different populations and for different indications / lines of therapy
- It is **intended to be used by the different organisational functions** involved in different aspects of the product development process (HEOR, R&D, Pricing and Marketing)
- It can be **used to inform decisions** when **planning research** and acts as a platform to **develop subsequent economic models**
- CSP & VBO analyses can both be used to inform **go/no go decisions** and develop the **economic positions** and **pricing and targeting strategies**
- The results from both the CSP and VBO analyses can be further explored by analysing survival and **costs**, or conducting **sensitivity or EVPI analysis**

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APPENDIX