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An integrated valuation model for payer and investor

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ABSTRACT

Background: In order to optimize positioning and associated drug price for both payer and investor, it is for a company essential to forecast the potential market access attractiveness for the new drug for different indications at the early onset of the clinical development program. This analysis must include the constraints from the perspective of the payer, but also the biotech companies, who require a minimum drug price to satisfy their investors. This paper aims to provide an Integrated Valuation Model for payer and investor, bridging concepts from health economics and economic valuation reflecting the perspectives of the payer and the investor for a drug in early clinical development phase. The concept is illustrated for a new hypothetical drug (Product X) in advanced breast cancer in 1-line, 2-line, and 3-line position.

Methods: The Integrated Valuation Model includes the outcomes of the budget impact model, pricing matrix model, and cost-effectiveness model reflecting the payer's perspective. These models are interacted and linked with a discounted cash flow model in order to reflect also the economic value from the investor's perspective.

Results: The maximum price in 1-line position is €269.7 for the payer and the minimum price is €14.7 for the investor, which are unit prices per administration corresponding with treatment regimens for the comparative treatments. In 2-line position, the maximum price is €274.1 for the payer and the minimum price for the investor increases to €184.5 for the investor because of the smaller market size in 2-line position, which leads to a smaller pricing corridor to satisfy both payer and investor. Consequently, Product X has market access attractiveness for both payer and investor in 1-line and 2-line position. However, the minimum price €942.7 in 3-line position for the investor is higher than the maximum price €283.3 for the payer, which means there is no market potential.

Conclusion: The practical strategic application of the Integrated Valuation Model is optimization of positioning and price of Product X. Hence, it can be a transparent tool in early-stage development of a compound based on upfront assessment of market access attractiveness for the payer and the investor.

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Introduction

Rational

EMA or FDA registration used to be the most important predictor of the future sales of a new innovative drug, which instantly would increase the economic value of the company, in particular of biotech companies with a limited number of products in the pipeline. However, new hurdles for market access and other restricting drug policy changes have emerged from the beginning of this century, which have become constraints for the actual future sales, both in number of units sold and monetary values, as well as the potential drug price. [1] The critical determinants for reimbursement are now: indication, positioning, comparator, efficacy and safety, cost-effectiveness, and budget impact. In order to maximize the probability of reimbursement at an acceptable drug price at time of launch, it is for a company essential to forecast the potential market size and acceptable price for the new drug at the early onset of the clinical development program.

There are several methods for assessment of the appropriate pricing level of new drugs, but the most commonly used approach is value-based pricing. [2] A fair price of the new technology according to this concept would not exceed the price that would lead to an incremental cost-effectiveness ratio (ICER) equal to the upper threshold. [3] A cost-effectiveness analysis provides this ICER, which is the additional cost for a quality adjusted life year (QALY), e.g., a life year gained in perfect health, [2] For example, in 2016 the Dutch National Health Care Institute ("Zorginstituut Nederland' – Zin) advised the Dutch Ministry of Health a discount of 55% for pertuzumab, which would lower the ICER from

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€150,000 per QALY in advanced breast cancer, to €80,000 per QALY, the upper threshold for oncology in the Netherlands [4,5]. The consequence is that such a high price discount probably leads to a negative net present value for the investor, which means that the rate of return required to persuade the investor for the initial investment, is not sufficient. [1]

Finally, oncology drugs with an acceptable ICER can still have a high impact on the payer's budget, because an acceptable ICER is not equivalent to a measure of affordability, and consequently payers may not be able to afford these drugs due to limited budgets.

We must include these constraints from the perspective of both payers and biotech companies in the proposed early phase forecast: health authorities are not willing to pay a drug price exceeding the ICER in some EU countries, and/or cannot pay the drug price because of limited budgets, but biotech companies require a minimum drug price to satisfy their investors.

This paper aims to describe an Integrated Valuation Model, which integrates the perspective of payer and investor, by bridging concepts from financial economics and health economics for the forecast of potential market size and acceptable price for an oncology drug in early clinical development phase. This Integrated Valuation Model is illustrated for a new hypothetical drug in advanced breast cancer.

Methods

Value scan

The first step for the development of the Integrated Valuation Model is the assessment of the key clinical and economic decision criteria as mentioned in Table 1. Additional criteria may be included depending on the disease area, e.g., social values and equity. The expected clinical product profile (PFS: progression-free survival, OS: overall survival, and safety) of the new product compared with standard of care oncology, especially gain in OS, are the basis for forecasting the clinical assessment by the health authorities, but these clinical data are also input parameters for the cost-effectiveness model and budget impact analysis. The budget impact model is supplemented with incidence data and split in four levels: new drug only (level-2), total drugs (level-2), total medical costs (level-3), and total costs, including indirect costs (level-4). Finally, all clinical, cost-effectiveness, and budget impact data are included in the pricing matrix model. The outcomes of the budget impact model, pricing matrix model, and cost-effectiveness model reflect the payer's perspective.

The pricing matrix model is based on the Analytical Hierarchy Process, which is applied for multicriteria decision-making in healthcare [6,7]. This pricing matrix model is used in the Integrated Valuation Model for the assessment of the pricing potential of a new drug based on linking its target product profile (efficacy and safety) with the key clinical and economic decision criteria for reimbursement. The three models are included in the Valuation Model to reflect the value from the payer's perspective and are interacted and linked with a discounted cash flow model in order to reflect also the economic value from the investor's perspective (Figure 1). For example, the pricing matrix model may generate a possible drug price, which needs downward adjustment, when it leads to an ICER in the cost-effectiveness model, which is higher than the threshold.

The input parameters for the cost-effectiveness model, budget impact model, and pricing matrix model rely on the position of the new product in the treatment pathway (e.g., 1-line or 2-line) and the most likely comparator treatments in terms of clinical and economic outcomes at time of launch.

Finally, the resulting acceptable drug price for the payer also has to satisfy the minimum return of investment for the investor. This acceptable price is directly related to the positioning of the new product, which determines the number of patients and consequently the potential market size for the investor and also the budget impact for national payers. Therefore the cost-effectiveness model, budget impact model, and pricing

Table 1. Key decision criteria.

Criteria	Source	Outcome
Efficacy and safety: target product profile	Early clinical data and assumptions	Incremental gain in PS and OS safety profile (AEs)
Budget impact	Budget impact model	BI: level 1, level 2, level 3 and level-4
Drug price	Pricing matrix model	Optimal price acceptability
Cost-effectiveness	Cost-effectiveness model	Cost per QALY
Financial valuation	Discounted cash flow model	NPV – BE price

AE: adverse events; BE price: break-even price; BI: budget impact; NPV: net present value; PFS: progression free survival; OS: overall survival; QALY: quality adjusted life year.

Figure 1. Interaction between pricing, health economics, budget impact and discounted cash flows.

matrix model, are linked with the discounted cash flow model in order to align the chances of registration and reimbursement, potential market volume, pricing potential of the drug, with the economic value for the investor. Table 2 shows the relationships how these different models are linked.

The goal of an early value scan for a new oncology drug (product X) in advanced breast cancer is:

- To generate various scenarios (e.g., base case, pessimistic and optimistic) for the expected clinical product profile of the new oncology drug. The goal is to predict the incremental clinical benefit of Product X in the possible positions (e.g., 1-line, 2-line, 3-line) versus the expected comparators (standard care) in each position. The focus is primarily on the clinical benefit: progression-free survival (PFS), overall survival (OS), and safety profile (incidence of adverse events). Secondary product characteristics are administration and ease of use: e.g., route of administration, frequency of administration, dosing, need of monitoring, and mechanism of action. Quality of Life (QoL) is also an important clinical outcome and is especially a critical parameter in the cost-effectiveness analysis generating the incremental cost per QALY gained. The finally chosen position for Product X defines the indication (label) for registration and design of forthcoming clinical trials.

Table 2. Relationships between different models in the integrated valuation model.

From	Data	To
Clinical target profile	Efficacy, safety, ease of use*	BI model
	Efficacy, safety, ease of use	CE model
	Efficacy, safety, ease of use	Pricing matrix model
	Efficacy, safety, ease of use	DCF model
From	**Data**	**To**
BI model	Population size	DCF model
BI model	Budget impact	Pricing matrix model
CE model	ICER	Pricing matrix model

BI model: budget impact model; DCF model: discounted cash flow model; CE model: cost-effectiveness model.
* Include administration

The minimal level of clinical benefit for Product X may be based on the NICE criteria, stating that a new treatment should extend life by more than 3 months, when life expectancy for people with the condition is less than 24 months. [8,9] The minimal level of clinical benefit may also be based on the ASCO Value in Cancer Care Framework or the ESMO Magnitude. [10,11]

- To optimize the design of scheduled clinical trials from a clinical and market access point of view. For example, the expected optimal positioning of Product X in future treatment practice may determine the study population in the clinical studies, as well as minimal number of patients for relevant subpopulations for an appropriate statistical analysis for possibly restricted use. An indication for subpopulation is an option, when the clinical benefit in total population is not sufficient, or the ICER and budget impact in total population are economically not acceptable.

Integrated valuation model

Model properties

The Integrated Valuation Model, which is applied in this example to advanced breast cancer is constrained to HER2-positive patients and the model includes the following subpopulations: 1-line, 2-line, and 3-line treatment. Table 3 shows the comparator treatment for each position and the route of administration is reported for comparative treatments in 1-line, 2-line, and 3-line position. The assumption is that Product X has similar route of administration as comparative treatment in each position in order to avoid any bias due to route of administration.

The analysis is based on a 3-way comparison of Product X versus the most recent reimbursed innovative drug and its comparative treatment (the previous standard treatment) in the previous health technology assessment report for this previous innovative drug. The advantage of the 3-way comparison is that it includes consistency: for example, if A is similar to B and B is superior to C, than A should also be superior to C. The previous

Table 3. Possible positions of product X in treatment pathway in the integrated valuation model.

Position	Comparator	
	Previous innovative drug	Previous standard treatment
1-line	pertuzumab+trastuzumab +docetaxel	trastuzumab+taxaan (docetaxel of paclitaxel)
2-line	lapatinib+capecitabine	capecitabine
3-line	eribulin	treatment of physician's choice' (TPC)

TPC: capecitabine, vinorelbine, gemcitabine, taxanes, anthracyclines and other chemotherapy.

standard treatment in 3-line is based on chemotherapy and excludes the minimal fraction (< 5%) of patients on hormonal therapy [12].

The Integrated Valuation Model is based on national country-specific data for the models reflecting the perspective of the payer, whereas the investor's discounted cash flow model is based on international data. The Integrated Valuation Model consists of parameters with an actual value and statistical distribution, like progression-free survival and overall survival of the current treatments. In addition, the model also contains many parameters, which are based on forecasts instead of actual data. Examples are incremental gain in PS and OS of Product X, annual growth of population size, market uptakes curves for Product X, and substitution effects by Product X. Forecasts are not actual values with a statistical distribution, which complicate the use of standard sensitivity analyses. A scenario analysis is based on alternative input values of the parameters or other model assumptions, e.g., positioning as 1-line, 2-line, or 3-line treatment. [13] Hence, scenario analyses are more appropriate to capture uncertainty in the Integrated Valuation Model, because the most critical parameters in the model are forecasts instead of actual values.

Country-specific models and data – the payer perspective

The focus of the current analysis is on the payer in Western EU markets. We preferred to use data from one country, e.g., Dutch published dossiers in order to have a consistent data set. The clinical data on PFS, OS and AEs are from international clinical trials, the epidemiology data on annual incidence were extrapolated to Western markets, and the Dutch ICERs were assumed to reflect also the incremental cost-effectiveness from an international perspective. Sensitivity and scenario analyses were performed to show the spread in outcomes, e.g., for countries using the ICER (UK, Netherlands) and countries not using the ICER (Germany, Italy) where clinical benefit and budget impact are main relevant economic criteria. In this example national country-specific data for expensive oncology drugs in advanced breast cancer are based on published information by Dutch Zin for (Table 4), which are used as approximation for other Western markets. [12,14,15]

The epidemiology and costing data were updated to 2021 (year of valuation of Product X), which were in the Integrated Valuation Model further extrapolated to 2029 (registration), 2030 (reimbursement) and subsequent years (sales of Product X). The budget impart model was based on the 1-line annual incidence data from the Health Technology Assessment (HTA) report for pertuzumab, and the epidemiology data on HER2 status, early vs. metastatic status, progression and treatment patterns (chemotherapy vs. no chemotherapy) were used to calculate the annual incidence of patients for the 2-line and 3-line position. The budget impact model considers population and patient budget impact at four levels: level 1-Product X only; level 2-total drugs; level 3-total medical costs, including administration costs. A scenario analysis based on society perspective also includes direct non-medical and indirect costs due to lost productivity (level 4). The budget impact analysis does not include discounting. [16]

Table 4. Clinical data.

Outcomes			Data	Previous innovative drug	Previous standard treatment
1-line	efficacy	PFS	actual	18.7	12.4
		OS	actual	56.5	40.8
		sAE	actual	15.0%	25.1%
2-line	efficacy	PFS	actual	8.4	4.4
		OS	actual	17.6	15.2
		sAE	actual	107.2%	107.9%
3-line	efficacy	PFS	actual	3.7	2.2
		OS	actual	13.1	10.6
		sAE	actual	209.0%	103.0%
Administration				**Previous standard care**	**Previous innovative drug**
1-line	route		actual	IV	IV
	frequency		actual	cycle 21/ 28 days	cycle 21/ 28 days
2-line	route		actual	oral (lapatinib) and IV	IV
	frequency		actual	oral: daily IV:cycle 21/ 28 days	cycle 21/ 28 days
3-line	route		actual	IV	IV
	frequency		actual	cycle 21/ 28 days	cycle 21/ 28 days

IV: intravenous; PFS: progression free survival; OS: overall survival; sAE: serious adverse events;

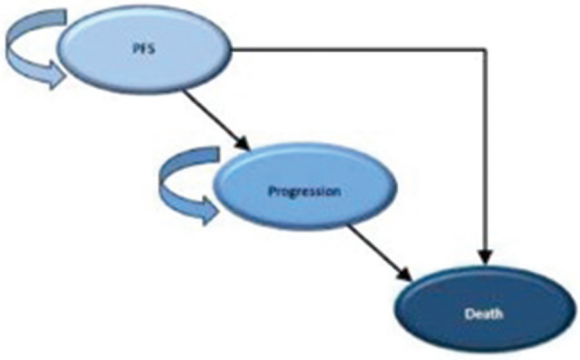

Figure 2. Structure of the cost-effectiveness models.

The cost-effectiveness models for 1-line, 2-line, and 3-line position are based on the usual Markov model structure in oncology with 3 mutually exclusive health states: 'progression free survival' ('PFS'), 'progression' and 'death' (Figure 2). [17] The 'progression' state after failure to 1-line treatment becomes the initial 'PFS' state for 2-line treatment, and subsequent progression leads to initial 'PFS' state for 3-line treatment. The model includes for the 'PFS' state the costs and disutilities of adverse events (AEs). The discount rate for costs and QALYs is respectively 4% and 1.5% according to Dutch pharmacoeconomic research guidelines. [18]

The assessment of the pricing potential of Product X in the pricing matrix model is based on decision makers' preferences for clinical outcomes (efficacy, safety, ease of use), cost-effectiveness and budgetary impact. [7] When the initial price of Product X equals the price of standard treatment, the decision-maker will choose Product X, if it has a higher efficacy or better safety profile than standard therapy. Subsequently the price of Product X is raised until the preference will switch to another comparative treatment (previous innovative drug or standard treatment), which is the upper price limit for Product X. [19]

The base case analysis is based on a discrete approach with rejection of reimbursement, if the ICER of Product X exceeds the threshold of €80,000 per QALY. A scenario analysis is based on a more continuous impact of the ICER: the higher the ICER, the lower the probability of reimbursement, which can be balanced in the overall priority vector by e.g., a favourable effectiveness. Another scenario analysis excludes the ICER from the criteria, which is relevant for considering countries, like Germany or Italy, where ICER is not included in the reimbursement assessment, and mainly clinical benefit and budget impact are relevant economic criteria.

Financial valuation – the investor component

The concept of the financial valuation for innovative drugs is summarised here, and more details are provided in a preceding publication. [1] The present value equation provides the discounted cash flows, which are used to compute the time value of money and compounding returns.

$$NPV = CF_1/((1+r)^1 + CF_2/((1+r)^2 + \text{---} + CF_n/((1+r)^n \quad (1)$$

Where

NPV = net present value

CF = (free) cash flows

n = the number of years before the future cash flow occurs

r = cost of capital

Cash flows from operations correspond with the future sales from Product X and the costs for R&D, production, and marketing. The R&D costs of unsuccessful clinical programs should be assigned to Product X. The cost of capital is the minimum rate of return necessary to convince the investor to make an investment, which is based on the cost of capital in the market for pharmaceutical (9%) and biotechnology companies (12%). [20,21] A more recent paper by Wouters confirms that these costs of capital figures are still appropriate for current investment decisions. [22] The cost of capital for biotechnology is considered higher because of small firm premium and other factors, which increase risk for the investor. The expectations at the time of investment, year 2021 in this analysis, determine the cost of capital in the financial valuation. [21] The discounted cash flow model computes the minimum break-even (BE) price for Product X, where the net present value (NPV) is zero. The actual drug price for Product X, should be at least higher than the BE price in order to yield a positive NPV and attract investors. The time horizon for the cash flows is 20 years from year 1, following patent registration until the end of the patent period. The assumption is that Product X is registered at year 8 and obtains reimbursement within one year leaving 11 years for actual sales before expiration of the patent.

Table 5 provides the international input data for the Integrated Valuation Model for the discounted cash flow model. The budget impact sections of the Dutch health technology assessment reports provide information on potential numbers of patients for The Netherlands, which are extrapolated to global market size. [12,14,15] The base case analysis is based on the Western markets, which are the real

viable market for pharmaceuticals (947 million). A scenario analysis is based on a larger global market by including non-Western countries (1,745 million).

We include also scenario analyses based the entry of Product X: 1) a 1-line registration after 5 years following initial 2-line registration, and 2) a 2-line registration after 5 years following initial 3-line registration.

The probabilities related to reimbursement (Table 5) consist of the probability of reimbursement in indication according to label (95%), and adjustment for actual eligible patients (95%). These forecasts are based on our expert opinion with reimbursement applications.

Diffusion curves or uptake reflect the annual proportion of patients switching from current treatments to Product X (Table 5). The maximum uptake of the previous innovative drug is 70% based on the consulted HTA reports. [12,14,15]

Results

Base case analysis

The key input data for the Integrated Valuation Model are the potential number of patients in 1-line, 2-line, and 3-line position, which are respectively 655, 293 and 117 patients in The Netherlands. The IV administration for Product X is based on intervals of 3 weeks, whereas the oral administration is based on daily oral dose. Therefore the price for Product X as IV is adjusted to oral dose to compare analyses for 1-line position with 2-line and 3-line position.

Table 6 shows the results of the base case analysis, which is based on the discrete approach, e.g., rejection of Product X, if ICER exceeds the threshold of €80,000 per QALY. The maximum price in 1-line position is €269.7 for the payer and the minimum price, e.g., BE price, is €14.7 for the investor, which are unit prices per administration corresponding with treatment regimens for the comparative treatments. Hence any price between €14.7 and €269.7 would be acceptable and attractive for both the payer and the investor.

In 2-line position, the maximum price is €274.1 for the payer and the minimum price for the investor increases to €184.5 for the investor because of the smaller market size in 2-line position, which leads to a smaller pricing corridor to satisfy both payer and investor. Consequently, Product X has market access attractiveness for both payer and investor in 1-line and 2-line position. However, the minimum price €942.7 in 3-line position for the investor is higher than the maximum price €283.3 for the payer, which means there is no market potential: the €283 is not acceptable for the investor and the €942.7 is not acceptable for the payer. The market for 3-line position is limited because of the low number of potential patients. However, the total cost for

Table 5. Data for discounted cash flow model.

	Data	Europe	Large	Selected
Population size	actual	947,065,643	1,744,565,804	1,890,353,578
Probability success trials		base case	scenario	
phase I–II	forecast*	70%	75%	
phase II–III	forecast*	39%	42%	
phase III–IV	forecast*	69%	74%	
Costs marketing			**percentage of sales**	
marketing	forecast*		incl. manufacturing	40%
	forecast*		excl. manufacturing	30%
manufacturing	forecast*		per patient per year	20,000
Costs (€)		base case		
preclinical	forecast*	204,600,000		
phase I	forecast*	78,930,000		
phase II	forecast*	133,930,000		
phase III	forecast*	178,140,000		
phase IV	forecast*	64,150,000		
Probability reimbursement				
reimbursement	forecast**	95%		
eligible	forecast**	95%		
Uptake		70%		
Cost of capital			base case	scenario
			biotech	pharma
cost of capital	actual	CAPM	12%	9%
		build-up method		flexible
			base case	scenario
discount	actual	Budget impact	0%	5%
		Sales	0%	5%

CAPM: capital asset pricing model.
* Forecasts are based on published data on R&D costs and probability of success trials. [20,23]
** Forecasts are based on our expert opinion published in other papers. 1

Table 6. Base case results of the integrated valuation model based on defined improvement of clinical benefit for product X.

Input for clinical benefit	Data	change versus new innovative drug		
PFS (months)	forecast	30% % change – increase		
OS (months)	forecast	20% % change -increase		
sAEs (%)	forecast	10% % change – decrease		
BE price (€)		1-line	2-line	3-line
Investor		€14.7	€184.5	€942.7
Payer	ICER discrete threshold*	€269.7	€274.1	€283.3
	ICER continuous impact**	€339.1	€627.3	€386.8
	ICER excluded***	€373.7	€746.9	€511.3
Reimbursement				
- ICER discrete		yes	yes	no
- ICER continuous impact		yes	yes	no
- ICER excluded		yes	yes	no

BE price: break-even price; ICER: incremental cost-effectiveness ratio; PFS: progression free survival OS: overall survival; sAE: serious adverse events.
* No reimbursement if the ICER > threshold.
** The higher the ICER, the lower the probability of reimbursement.
*** ICER is excluded from the criteria.

the development of an oncology drug in 3-line position is similar to the R&D costs for 1-line position. [20,23] Consequently, the price for an oncology drug in 3-line position is higher than for 1-line position, because the same costs for development can only be recouped on fewer patients.

The ICER increases substantially from 1-line to 2-line to 3-line position, as the drug price in 3-line position captures a larger proportion of fixed R&D costs than in 1-line and 2-line. Another reason is that the possible gain in OS, and consequently also QALYs, is much lower in 3-line position than 1-line and 2-line. Table 4 shows OS is 56.5 months in 1-line and only 13.1 months for 3-line for previous innovative drugs.

A scenario analysis, which is based on more continuous impact of the ICER, e.g., the higher the ICER, the lower the probability of reimbursement, shows that the maximum price increases for the payer in all positions, but there remains a negative gap in the 3-line position (€942.7 versus €386.8). The 2-line position shows highest pricing potential, because in the 1-line and 3-line position, respectively the BIA and ICER are most limiting constraints for the pricing potential.

A second scenario analysis, excluding the ICER from the criteria, shows an additional increase of the maximum prices for the payer in all three positions, especially in the 3-line position. However the BE price (€511.3) for the payer in 3-line position remains below the BE price (€942.7) for the investor. This scenario is relevant for considering countries, like Germany or Italy, where ICER is not included in the reimbursement decision.

Scenario analysis

The results of scenario analyses are presented in Table 7. The benchmark for the scenario analyses are the results in the base case analysis. The change in PFS (months), OS (months), incidence of AEs (%) in the base case analysis are improved in the scenario analyses from 30% to 40% (PFS), 20% to 30% (OS), and 10% to 5% (AEs). A pessimistic scenario has been added based on similar opposite changes. The scenario analysis is based on the comparison of BE price for the investor and the BE price for the payer based on the discrete approach (base case analysis). These scenarios show that improvement in efficacy (PFS and OS) have much more impact on the outcomes than reduction of AEs. The optimistic scenario does not substantially changes the conclusion from the base case analysis that Product X has market potential in 1-line and 2-line position. Contrary, none of the scenario analyses show a higher BE price for the payer than the BE price for the investor in 3-line position.

Scenario analyses for 2-line and 3-line position, which include extension of label to respectively 1-line and 2-line position 5 years after market launch, substantially reduce the BE price for the investor resulting from a higher potential market size. For example the BE prices reduce by 14.7% and 37.3% for respectively 2-line and 3-line position. The BE price for the investor in 3-line position decreases from €942.7 to €501.1, which remains higher than the €283.3 BE price for the payer, but it comes close to the payer's BE price of €511.3, when we exclude the ICER from the decision-making process.

Discussion

This paper introduces the Integrated Valuation Model, which was illustrated for new Product X in advanced breast cancer. The practical strategic application of this "value for access to market model" is to forecast the potential market access attractiveness for the new drug for different indications at the early onset of the clinical development program. The indications relate

to positioning in 1-line, 2-line or 3-line in this Integrated Valuation Model, but it can be further refined to subpopulations within each position. The results show that the acceptable price for Product X is substantially constrained when the ICER is considered the most critical criterion for market access (e.g., England, The Netherlands), whereas the pricing potential increases when ICER has no or a lower weight in the overall decision making process (e.g., Germany and Italy).

The core model also generates information, which can guide the design of the clinical trial program including: follow-up, definition of study population, most relevant comparator treatment(s), sample size, and clinical and economic endpoints. A scenario analysis shows that increase of efficiency in trial program pays off in more than 8% lower BE price for the investor (Table 7).

The 'time to market' is also a critical factor, which can be shortened by diagnostic testing. An example is Herceptin® (trastuzumab), which is indicated for adjuvant and metastatic breast cancer. When a diagnostic test was used to pre-select HER2 positive patients, the required number of patients for the clinical study decreased from 2,200 to only 470 patents[20]. The timelines for the clinical trial program could be shortened and the associated costs decreased by $35 million. Zelboraf® along with its companion diagnostic the Cobas 4800 BRAF V600E mutation test, which is indicated for metastatic or unresectable melanoma, entered the market within circa 4.5 years after regulatory approval based on an expedited process. A scenario analysis based on estimates from these two examples on earlier 'time to market' showed reduction of BE price for investor varying from 42.0% (3-line position) to 57.2% (2-line position).

This is the first paper to our knowledge that is integrating the payer's perspective and the investor's perspective. The payer's perspective is based on health economic theory, whereas the investor's perspective is based on economic valuation. Hence the potential conceptual differences between economic valuation and health economics may complicate this integration. [24]

The minimum price for the investor's perspective is based on the forecast of the global sales, whereas the maximum price for the payer is based on national market access hurdles in policies. Hence the minimum price for the investor's perspective is an international price, and the maximum price for the payer is a national price. The market access hurdles are country-specific, but a national approach would have no value, because a pharma company is not developing a market access strategy for only one country. Therefore, we used a more aggregated level of the Western EU markets and the maximum price from the payer perspective mainly reflects the European willingness to pay. US prices are usually substantially higher than the prices in Europe, leading to slightly lower overall lower minimum price for Europe.

The assumption in this analysis is that Product X is registered at year 8, which is generally accepted average time to registration, which may be different for biotech start-up compared with 'big pharma' companies, because biotech companies may have limited funding for a clinical program and may have less development time. On the other hand, R&D projects are often acquired by larger pharma companies along the R&D clinical program. A practical reason is that registration and market access requirements do not allow any constraints in clinical development due to funding constraints and therefore only early acquisition by big pharma company is often critical step for successful future registration of the product.

Another difference is that biotech companies often develop drugs for rare diseases, which allows them to benefit from specific accelerated approval policies for orphan drugs by EMA and FDA in order to shorten time to market and reduce development costs, e.g., by a avoiding Phase III trials. This type of innovation is often based on a different mechanism of action, which may also lead to different R&D costs and manufacturing costs. The Integrated Valuation Model allows fine-tuning these parameters to specific orphan indications.

Finally we address study limitations, which require further research. The current model captures standard submodels from finance (DFC model) and health economics (Markov model, budget impact model), but we consider more sophisticated methodologies for future research. Another limitation of the current Integrated Valuation Model is that is based on a deterministic approach. Modern finance theory differentiates between two different kinds of investor risk: diversifiable risk and undiversifiable risk. The undiversifiable, or systematic risk is the risk the investor cannot eliminate through diversification of his or her portfolio of investments, for example macro-economic risks like global recession, which cannot be spread. The technical risks of project failure, probabilities of registration and reimbursement, forecasts of cost and sales are considered statistical risks, which are diversifiable and therefore they do not affect the required rate of return for an investment. Hence if investor is only investing in one project with expected average ICER of €75,000, there is probability of 10% that ICER is €10,000 higher (€85,000) or lower (€65,000), this spread can be diversified, like spread in costs, and

Table 7. Scenario analyses on break-even price (€) for product X.

Product X	Base case		Scenario	
	improvement vs. previous innovative drug		optimistic	pessimistic
PFS (months)	30%		40%	20%
OS (months)	20%		30%	10%
sAEs (%)	10%		5%	15%
Scenario analyses		**1-line**	2-**line**	3-**line**
Base case analysis				
- Investor		14.7	184.5	942.7
- payer	ICER discrete threshold	269.7	274.1	283.3
reimbursement		yes	yes	no
Optimistic scenario				
- Investor		−3.8%	−5.5%	−6.9%
- payer	ICER discrete threshold	17.2%	10.8%	7.7%
- reimbursement	reimbursement	yes	yes	no
Pessimistic scenario				
- Investor		4.4%	6.4%	8.1%
- payer	ICER discrete threshold	−20.2%	−12.7%	−9.0%
- reimbursement		yes	yes	no
Efficacy scenario				
- Investor		0.0%	0.0%	0.0%
- payer	ICER discrete threshold	−12.8%	−27.3%	−18.3%
- reimbursement		yes	yes	no
AE scenario				
- Investor		0.0%	0.0%	0.0%
- payer	ICER discrete threshold	−2.0%	−0.1%	−0.9%
- reimbursement		yes	yes	no
CEA perspective – society				
- Investor		0.0%	0.0%	0.0%
- payer	ICER discrete threshold	8.9%	2.8%	3.0%
- reimbursement		yes	yes	no
Large market				
- Investor		−45.6%	−45.7%	−45.7%
- payer	ICER discrete threshold	0.0%	0.0%	0.0%
- reimbursement		yes	yes	no
Growth pop				
- Investor		22.5%	22.7%	23.0%
- payer	ICER discrete threshold	0.0%	0.0%	0.0%
- reimbursement		yes	yes	no
Extension indication > 5 years				
- Investor		N.A.	−14.7%	−37.3%
- payer	ICER discrete threshold	N.A.	0.0%	0.0%
- reimbursement		yes	yes	no
CAPM – 9%				
- Investor		−32.5%	−30.9%	−29.7%
- payer	ICER discrete threshold	0.0%	0.0%	0.0%
- reimbursement		yes	yes	no
Probabilities failure and costs 10% lower				
- Investor		−8.1%	−8.3%	−8.9%
- payer	ICER discrete threshold	0.0%	0.0%	0.0%
- reimbursement		yes	yes	no
Time to market	5 years + 5% lower cost			
- Investor		−53.1%	−57.2%	−42.0%
- payer	ICER discrete threshold	0.0%	0.0%	0.0%
- reimbursement		yes	yes	no

sAE: serious adverse events; OS: overall survival; PFS: progression free survival; ICER incremental cost-effectiveness ratio; CEA: cost-effectiveness analysis.
* Base case input in brackets.

other above-mentioned parameters. Hence for continuous inclusion of ICER, there is no additional risk. However, the base case analysis is based on discrete approach with rejection of reimbursement, if the ICER of Product X exceeds the threshold of €80,000 per QALY, which is one-sided risk. In this case the higher ICER of €85,000 would lead to rejection of reimbursement, whereas ICER of €65,000 would not lead to different decision, as with ICER of average €75,000. Hence the higher the spread in the distribution of ICERs, the more risk for investor, who may add premium in cost of capital. As ICER is only of other criteria and not used in all countries, an estimate would 1% to 2%. On other hand, if ICER is €85,000 this would probably not lead to real rejection in the end, but a small price discount would be sufficient to lower ICER from €85,000 to €80,000. The investor may transfer this additional uncertainty to premium cost to capital, which is rather subjective. Therefore we recommend further research to explore the appropriate approach how to handle uncertainty the Integrated Valuation Model. A Monte Carlo simulation

may allow the incorporation of standard deviations in the input parameters of cash flows can yield a probability distribution of the NPV. [25]

Conclusion

The practical strategic application of the Integrated Valuation Model is optimization of positioning and price of Product X. Hence, it can be a transparent tool in early stage development of a compound based on upfront assessment of the market access attractiveness for the payer and the investor.

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Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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