Meeting Summary

EUROPEAN HEALTHCARE INNOVATION LEADERSHIP NETWORK
BREAST CANCER WORKING GROUP

31 DECEMBER 2009

Improving Health Outcomes in Breast Cancer: Advancing the Shared Value Framework

Introduction

The Breast Cancer Working Group convened for its third meeting on 11 November 2009 in Berlin. Initiated by the European Healthcare Innovation Leadership Network, the Working Group brings together world-class thought leaders and decision makers from the ranks of medical experts, regulators, payers and advisers, patient representatives and industry. Working together over the course of 2009, Working Group participants are committed to addressing unmet needs in breast cancer by establishing a Shared Value Framework[1] and developing approaches to overcome barriers to innovation through more effective collaboration among all stakeholders.

The Shared Value Framework is a recommended approach arising from this collaboration to encourage changes in how the value of new medicines can be assessed, demonstrated, captured and rewarded, with the end goal of improving health outcomes. To move towards the tangible outcome of a Shared Value Framework, the Working Group has focused on generating elements of a "21st century" breast cancer drug development template. The goal of its proponents is to provide an improved process for drug development that refocuses on shared definitions of value across healthcare stakeholders and accelerates patient access to innovative medicines. The template consists of three major components:

- A tiered set of value indicators and measures required to demonstrate benefit in addressing unmet needs along the drug development lifecycle
- A process for early consultation with regulators, HTA and payers that includes engagement of patient and clinical perspectives
- Principles and criteria for use of post-launch mechanisms to encourage innovation and value-based pricing

During its third meeting, the Working Group finalised the first two elements of this template. Participants validated a menu of tiered value indicators in breast cancer that integrated outcomes from a set of Scenario exercises generated and taken by the Working Group earlier this year. The Working Group also generated initial design guidance for novel multi-stakeholder consultations, highlighting topic areas as potential agenda items for such consultations, and recommended a roadmap for piloting them in 2010.

The meeting was preceded by multiple rounds of discussion with participants to set the agenda and capture the views of those unable to attend. The session comprised a mixture of plenary

[1] See ViewPoints, "Aligning perspectives on value" at http://www.tapestrynetworks.com/documents/Tapestry_European_Healthcare_Innovation_Leadership_Network_ViewPoints_Sept08.pdf

discussion, focused work in breakout groups, and individual consideration to obtain perspectives on emerging issues. A modified version of the Chatham House Rule was used throughout the day, whereby names of participants and their affiliations are a matter of public record, but comments made during meetings are not attributed to individuals or organisations. This document summarises that day's discussion and provides the recommendations to be presented to the European Healthcare Innovation Leadership Network meeting on 21–22 January 2010. *Table 1*, below, contains the full membership of the Working Group, by stakeholder category, whose views have been reflected in the formulation of the recommendations.

Table 1
Breast Cancer Working Group Participants

Medical subject matter experts

Jonas Bergh, Karolinska Institute, Sweden

PierFranco Conte, Universitaria di Modena, Italy

Jindřich Fínek University Hospital Plzen, Czech Republic

Luca Gianni, Instituto Tumori di Milano, Italy

Anthony Howell, The Christie NHS Foundation Trust, UK

Christian Jackisch, Hospital Offenbach GmbH, Germany

David Khayat, Pitié-Salpêtrière Hospital, France

Jan Lubiński, Pomeranian Medical University, Poland

Miguel Martin, Hospital Universitario San Carlos, Spain

Larry Norton, Memorial Sloan-Kettering, US

John Robertson, University of Nottingham, UK

Karol Sikora, CancerPartners UK, UK

Michael Untch, HELIOS Klinikum, Germany

Payers, regulators, health economists and advisers

Johannes Bruns, Deutsche Krebsgesellschaft, Germany

Karl Claxton, University of York, UK

Pierre Démolis, AFSSAPS, France

Harald Enzmann, BfArM, Germany

Pavel Hroboň, Czech Republic

Bengt Jönsson, Stockholm School of Economics, Sweden

Bertil Jonsson, Medical Products Agency, Sweden

Sören Olofsson, Region Skåne, Sweden

Patient representatives

Els Borst-Eilers, Dutch Federation of Cancer Patients, The Netherlands

Susan Knox, EUROPA DONNA, European Breast Cancer Coalition

Industry representatives

Jim Baker, Johnson & Johnson

Alan Barge, AstraZeneca

Paolo Paoletti, GlaxoSmithKline

Executive summary

The Breast Cancer Working Group validated a consensus framework of value indicators and measures for breast cancer medicines developed over the course of the past year. Participants affirmed the need for enhanced collaboration among stakeholders prior to the regulatory and reimbursement review process, to support sustainable development of innovative medicines. The Working Group took initial steps to provide design guidance for such a collaborative process, and agreed a high-level roadmap for testing and piloting consultations in 2010. As discussed in greater depth later in this document, the following were the meeting's principal outcomes:

- **Common ground in a tiered model of value indicators to assess value in breast cancer medicines.** *(page 5)* The Working Group collectively agreed upon and validated a consensus base of therapeutic and clinical endpoints that are consistent across stakeholder groups and Member States. Participants distinguished the current acceptable hard endpoints needed for registration from those that are emerging or require additional demonstration evidence to support future usage for registration and reimbursement purposes. For economic indicators, participants agreed economic inputs into differing Member State models can be generalised and can be separated from the evaluation of those inputs. Finally, acknowledging the cultural and geographical issues that uniquely impact each Member State's healthcare system, participants believe that economic evaluation models would continue to be specific to Member States or sets of Member States with similar approaches.
- **Scenarios: an early test of value indicators, assessing increments and relative components of value** *(page 10)* The *Health Outcome and Innovation Scenarios* developed by the Working Group provided participants with a novel way of evaluating emerging medicines relative to a given comparator. The Scenarios were designed to determine which medicinal profiles hold the most therapeutic value to patients, as well as to identify which therapies were most likely to receive market authorisation and reimbursement approval. Each tested specific hypotheses selected by the Working Group that highlighted the borderline or "grey areas" in determining the value of breast cancer drugs in development. Participants used the web-based comparative medicinal profiles provided by the Scenarios to define a meaningful increment of value across a range of potential indicators for assessment of a new breast cancer medicine. Synthesis of the outcomes and the ensuing discussions highlighted the following points:
    - Value across stakeholders was seen to be directly linked to demonstration of hard clinical endpoints. In particular, participants agreed that overall survival (OS) and/or progression-free survival (PFS) were the most critical measures of efficacy, with the endpoint being dependent on the context of the disease setting.
    - Safety – including toxicity and tolerability – and/or patient-reported quality of life measures were important but generally secondary to demonstration of efficacy.
    - In general, if a medicine was highly efficacious relative to the standard of care, high cost relative to a comparator was not a barrier to recognising value. However,

introducing risk shares noticeably improved the likelihood of reimbursement for medicines with uncertain or potentially limited value relative to the comparator.

- Debate over the definition of the comparator as well as increments of value highlighted the usefulness of multi-stakeholder interactions early in the drug development process to provide clarity on these and other topics relevant to assessing value in a new medicine.

- **Design of pilots to prototype new Phase II multi-party interactions.** *(page 13)* Participants affirmed the need for enhanced collaboration amongst all stakeholders to increase understanding of a Shared Value Framework of medicines. These interactions would refocus efforts on delivery of improved patient outcomes and reduce the risk associated with the development of innovative medicines by providing greater long-term visibility to all stakeholders. Participants recommended piloting such interactions to test the Shared Value Framework with existing compounds currently under development. Participants began addressing several outstanding Phase II pilot design questions, including balancing collaboration and independence between stakeholders, ensuring the suitable representation of stakeholders, developing relevant briefing documents and mechanisms to ensure consistent understanding of issues, and identifying the appropriate level of transparency for the pilots.

- **Path forward and conclusion.** *(page 19)* The meeting concluded with agreement on the need for tangible action to move forward with the pilots in the coming year, with the Working Group focusing on broadening the impact of the Shared Value Framework, providing greater clarification on the individuals/organisations to be involved and governance principles to guide the pilots, and developing a more detailed process design for the pilots early next year. A representative of the Breast Cancer Working Group will report the recommendations of the participants to the European Healthcare Innovation Leadership Network meeting to be held in London on 21–22 January 2010.

Advancing a 21st century drug development template

At the Working Group's previous meeting on 9 July 2009, participants discussed improvements to the current drug development process that can be piloted on specific medicines currently under development and, ultimately, can demonstrate the benefit of creating and applying a Shared Value Framework[2]. In this context, participants highlighted specific early-clinical, Phase II and post-launch opportunities for improved collaboration, as well as systemic changes that would enhance the success of these initiatives. The meeting concluded with a call for the concrete realisation of the goals of the Working Group by developing pilots that demonstrate progress via this *"community of common purpose"* within the broad definitions of the Shared Value Framework. Rather than taking up the opportunities described above in a piecemeal approach, Tapestry Networks has integrated the Working Group recommendations into a "21st

[2] See BCWG II Meeting Summary "The Agenda for Change: Improving Health Outcomes in Breast Cancer" at http://www.tapestrynetworks.com/documents/Tapestry_EHILN_BCWGSummary_Jul09.pdf

century drug development template" for breast cancer that can be deployed along the drug development lifecycle. Tapestry Networks has validated this approach with Working Group participants, and key insights are summarised below.

Common ground in a tiered view of indicators and measures for assessing value in breast cancer medicines

The Working Group has agreed on a shared viewpoint of a tiered model of value indicators to assess new medicines in support of the common goal of improving patient outcomes in breast cancer. This tiered view consists of a consensus base of therapeutic value indicators applicable to a specific disease indication, followed by generalisable economic inputs and Member State-specific societal indicators. Participants agreed that these inputs can be separated from the outputs produced by models of assessment required at the Member State level. This model is illustrated by the exhibit below (Exhibit A).

Using this tiered model as a framework**,** the Working Group has refined the results to serve as a comprehensive consensus framework that contains the characteristics of a medicine that are relevant to assessing its therapeutic value in the treatment of breast cancer. Participants do not suggest that a given drug should demonstrate performance along every value component included in the framework. Rather, the framework is intended as a menu of indicators and measures from which stakeholders can select the relevant value demonstrations so as to satisfy the requirements of a given regulatory or reimbursement dossier, with customisation requirements as needed. For example, one clinician explained how *"the indicators and measures of relevance will depend on the indication and therapeutic setting"* of the specific disease.

Consensus on therapeutic value indicators

Weighing the roles of median overall survival (mOS) and progression-free survival (PFS)

The Group broadly agrees with one regulator participant, who states that *"The most important thing we would like to see is the demonstration of efficacy with overall survival as the gold standard."* However, many participants acknowledge (in the words of one clinician) that *"we cannot expect any benefit in the overall survival for every setting in breast cancer;"* e.g. it is challenging to demonstrate survival *"in the adjuvant setting of breast cancer because the expected survival is already quite long."* In such a setting, as stated by a regulator participant, *"Early progression-free survival is the best marker, while at the latest stages of disease you can obtain measurable survival benefits."* In sum, *"The desired value increments and size of benefit must be balanced across the stages of the disease."* Added an industry participant, *"We need to accept the limitations in the use of overall survival, accept validation of good progression, and focus on best ways to assess progression-free survival."*

In considering other disease progression indicators, participants all agreed that objective response rate (ORR) and the duration of that response, as well as the control of metastasis, can be useful as early indicators of efficacy; however, they are not themselves sufficient clinical endpoints, and, dependent on the disease context, should be linked to firmer clinical endpoints of PFS and mOS. As stated by a clinician participant, such endpoints could be about either local control of tumour growth or impact on survival through the proxy of metastatic rates: *"The only quality assurance outcome measure is overall survival, and then you can divide it into either local control, that is tumour reoccurrence within theoretical local confines of the original disease, while the other issue to look at is the impact on survival, e.g. through the control of distant metastases."*

Participants distinguished between two categories of indicators: those that are current *"acceptable hard endpoints in practice today, such as mOS and PFS,"* and those that are still emerging and may be useful from a technical perspective. Included in the table below are the prospective therapeutic indicators (*e.g.,* circulating tumour cells) marked in italics that the Group concludes (in the words of a clinician participant) *"are helpful from a scientific point of view and for decisions on whether to develop a new drug, but at present lack sufficient body of evidence to support their use as primary clinical endpoints and are not helpful in the registration process or clinical decisions."* However, as science progresses, these markers may eventually warrant future attention. As affirmed by an industry participant, *"The jury is still out for circulating cancer cells, but when we started work years ago, we were still thinking about the role of PFS, and now we see validation of that work. The field may move on."*

Safety and side effects

Participants have agreed that safety and side effects, while important, are generally secondary to efficacy in considering value of a new medicine. One clinician summarised that *"side effects are a much less objective endpoint, and* [are] *often difficult to quantify and hence the data is valued less."* However, as pointed out by a regulator, *"It is possible to accept an application with a*

relatively permissive non-inferiority demonstration, due to the fact that the new product was better tolerated as compared to an old product, for example in non-small cell cancer."

Patient–reported quality of life

Participants acknowledge the importance of patient-reported quality of life (QoL). However, due to the lack of widely-accepted measures, participants believe that QoL is secondary to the relative impact of a medicine on efficacy, safety and side effects. As a regulator states, *"We all feel that supporting quality of life improvement is important, especially in the domain of cancer. But most cancer treatments result in a very poor quality of life. For this reason, we tend to focus more on level of toxicity – not because it is less important but just because we do not have the right tools for measuring quality of life."* As another clinician points out, *"So many of the questions on quality of life in the tools currently used are totally unrelated to the treatment of cancer,"* while a patient advocate added, *"You'd expect QoL to be related to improvements in toxicity and tolerability in treatment, so in essence there is overlap in the measures."*

Innovation

The group recognises the innovation conundrum: while conceptually, medicinal innovation is widely recognised as a critical goal across stakeholders, it is quite difficult to precisely define or measure. Many participants feel that innovation needs to be linked to gains in therapeutic endpoints, rather than solely being a technical demonstration, for example, merely demonstrating a new mechanism of action without proven clinical gains. A regulator stated, *"While innovation is very important, it is not a goal per se. Innovation must be supported by basic clinical outcomes."* A payer echoed this position and summarised that *"innovation alone is useless without gains in efficacy."* However, another regulator did acknowledge that his peers do sometimes *"accept a slightly decreased level of evidence because we want a new class of drugs to be developed further, or because we expect further information on efficacy to emerge post-launch. We hope that these drugs will transform the treatment even if, at the time of submission, the evidence is not that great."* Mindful that this *"is not a formalised regulatory approach,"* a regulator cautiously claimed that this is *"still the reality."*

Reproduced below is the base of therapeutic value indicators developed by the Working Group.

Therapeutic value components		
Value component	**Measure**	**Timing of demonstration**
Current endpoints for assessing value for registration/reimbursement purposes (relevant usage determined by context of the disease stage)		
Survival	▪ Median overall survival (mOS) segmented by disease stage	▪ Pre-launch for metastatic; post-launch potentially in adjuvant setting
Tumour stabilisation	▪ Progression-free survival (PFS) or disease-free survival (DFS), dependent on disease stage context	▪ Pre-launch, with potential link to OS dependent on disease context

Therapeutic value components (*continued*)		
Value component	**Measure**	**Timing of demonstration**
Reduction of tumour size	▪ Objective response rate (ORR) ▪ Duration of response	▪ Pre-launch, with link to mOS
Prevention of reoccurrence	▪ Rate of local reoccurrence of tumour	
Inhibition of metastasis	▪ Rate of metastasis (as proxy for impact on survival)	
Emerging or scientific endpoints useful for decisions on drug development		
Delayed disease progression	▪ *Circulating tumour cells*	▪ *Pre-launch, need link to OS (these indicators are considered very early in development, and have yet to accumulate the body of evidence required to be convincing as clinical endpoints)*
Delayed disease progression	▪ *DNA in plasma*	
Drug safety, side effects, quality of life (QoL)		
Increased tolerability	▪ % discontinuing treatment relative to the comparator	▪ Pre-launch; post-launch re-examination if possible
Reduced toxicity	▪ Total Grade 3 & 4 side effects (% serious adverse events) ▪ % occurrence of adverse events impacting treatment decisions	▪ Pre-launch; post-launch re-examination if possible
Patient-reported QoL	▪ *% reporting meaningful clinical difference in QoL (measure and collection design to be agreed on – current lack of consensus)*	▪ *Pre-launch; post-launch re-examination if possible*
QoL	▪ *Q-TWiST: Quality-Adjusted Time Without Symptoms of Disease or Toxicity of Treatment*	▪ *Pre-launch; post-launch re-examination if possible*
Innovation		
Level of innovation	▪ Linked to efficacy or impact on safety/side effects/QoL ▪ Advancement of field of treatment	▪ Pre-launch

Note: *Italics indicates indicators whose consensus on usage for registration and reimbursement purposes is still open.*

Economic value indicators: consensus on economic inputs is achievable

On the next level of indicators required for new medicines – demonstration of economic value – participants agreed that consensus on economic inputs into the different Member State models is achievable and can be separated from the evaluation of those inputs. As a payer summarises, *"I do believe we could list the items that are needed by different evaluation models to assess the economical advantages of a drug or of a treatment. On that, everybody can agree."* As noted by a payer-adviser, these inputs are valuable in that *"the question of value needs to include how much we are going to pay for it, and in doing that, we need to account for the consequences of paying more, which in a budget-constrained healthcare system means someone else may forgo some health elsewhere."*

One point noted by a payer–adviser participant on economic assessments is the *"distinction between utilisation of resources from prices. Together, they make up cost but when you think about cross-jurisdictions, you might see some commonality in terms of utilisations, e.g. style of medical practice, but very different prices. So it may be useful to think of cost in terms of these two dimensions of inputs."*

Reproduced below are illustrations of economic value components discussed by Working Group participants:

Economic value components		
Value component	**Measure**	**Timing of demonstration**
Illustrative cross-model economic inputs	▪ Treatment price (or price ranges dependent on treatment scenarios) ▪ Utilisation rate ▪ Total acquisition cost ▪ Patient life–years gained ▪ QoL or societal impact aspect on life–years gained	▪ Pre-launch; post-launch re-examination if possible (e.g. for cost)

Member State-specific value indicators and evaluation models of medicinal value: customisation required by country

Participants agreed that economic values rest on the foundation of societal values, and cost evaluations might be (in a payer–adviser's words) *"taken to include future related healthcare costs that are related to the condition you are treating, or even more broadly, to all future related and unrelated costs even beyond the healthcare system, dependent on how you evaluate costs."* Given this, there may be additional value indicators that remain Member State-specific (the "third tier" in the value framework seen in Exhibit A). Moreover, all agreed that they collectively remain in the early stages of determining how to combine the economic inputs into useful, aligned evaluation models across Member States. Participants therefore remained sceptical

that true harmonisation on economic evaluation can be achieved across Member States with different cultural and societal preferences as well as budgetary realities. As one participant noted, *"We are left with differences, and some of these differences are cultural. When we would do a formal economic evaluation of drugs, you have some parts where tradition and societal preferences make patients more dependent on the social system, and here the input of costs and economic measures is completely different. On a European scale, the assessment of the benefits and risks in terms of costs for the society will be very different if we compare Italy to UK or if we compare Portugal to Estonia."*

Many participants believe they lack the background to judge economic values and models. While accepting that this is an economist and payer-led decision, participants believed that an increased understanding of economic assessments would be helpful: *"We are faced with treatments that have the same costs but that have big differences in clinical effect. How is this evaluated?"* asks a clinician. Agreeing, a payer stated that *"all improvements in therapeutic endpoints are valuable ... It is a matter of what we have to pay for it ... We understand that development of science in this difficult field goes in small steps; the problem is that price increases are going in huge steps."* This point about educating all parties on the economic endpoints is one that participants in discussing recommendations (see later section on ***Design of pilots to prototype new Phase II multi-party interactions***).

Illustrative systemic economic indicators dependent on health system		
Value component	**Measure**	**Timing of demonstration**
Healthcare system cost	▪ Total net cost to healthcare system per year	▪ Pre-launch model; post-launch re-examination
Pharmaceutical cost	▪ Total net cost to pharmaceutical (drug) spending per year	▪ Pre-launch model; post-launch re-examination
Patient-borne cost	▪ Total net cost borne by patients per year	▪ Pre-launch model; post-launch re-examination

Health Outcome and Innovation Scenarios: An initial test of breast cancer value indicators, assessing increments and relative components of value

The Working Group participants agreed that one effective way to test the value indicators was through the use of anonymised drug profiles. This Scenario-driven method allowed the Group to understand increments of value and the relative nature of value indicators, as well as the core parameters of new interactions needed to support these indicators. This approach is effectively a precursor to Phase II pilots that are emerging as the backbone of the Network's 2010 activities. As reflected by a clinician participant, *"The Scenarios in some sense reflect the real world of how decisions are made, with different perspectives and backgrounds having to weigh in on critical decisions, from patients to purchasers based on given limited data."*

Methodology of the Scenarios

Using a web-based Scenario approach, the Working Group participants have evaluated new medicine profiles relative to a given comparator to determine the medicinal profiles most likely to receive market authorisation and reimbursement approval. The Group had previously identified the HER-2-failing sub-population as a patient class with clear unmet needs, and this was the focus of the Scenarios[3]. Each Scenario profile tested a different set of value indicators from the menu identified by the Breast Cancer Working Group described earlier. Key considerations when evaluating a drug include determining the right combination of value indicators to test, identifying the specific increments of value needed for approval, and highlighting an innovative or "transformational" medicine versus a "me too" medicine delivering only small incremental improvements. As one payer interviewed mentioned, *"many new cancer drugs are not fulfilling the promise made by their commercialisation departments."* Working Group participants selected scenarios to test specific hypotheses that they believed lay in the "grey areas" of breast cancer drug development. All participants were provided a briefing document that described the landscape and context of the therapy area and the available comparative treatments. Specific hypotheses tested in the Scenarios are listed in Appendix A, and an illustration of one of the multiple Scenario profiles that explored the value of specific endpoints and value increments, is shown in detail in Appendix B.

One participant summarised the value of this exercise as an opportunity to *"agree on the inputs and a methodology for evaluating drugs, which by itself would be incredible progress."* Participants did acknowledge the limitations of the Scenarios*: "How can decisions be made when understanding of ORR may be incomplete?"* declared a clinician. A payer–representative believed having more context would make for a richer decision process, a point the Group reflected as part of the pilot design guidance discussed later in this document. Nonetheless, a number of participants felt that it did reflect aspects of reality in the decision processes made in assessing medicines. A payer participant framed the Scenarios as testing *"what should be taken into consideration to assess value,"* while an industry member framed the Scenarios as a first step towards an *"evolution to a harmonised regulatory–payer environment with a common set of value indicators."*

The challenge of defining Standard of Care

Defining Standard of Care (SOC) or clinical comparator was a key element to the Scenarios (see further discussion below), as the benefit from a therapy is invariably defined by an improvement over the SOC. A regulator participant commented that *"the major question of the Scenarios is Standard of Care – how do you evaluate Standard of Care in an area that is evolving like breast cancer where clinical guidelines are unclear and where different treatment centres can use different approaches to care even if they are in the same region?"* A payer acknowledged the technical challenges faced by industry: *"When starting the development of a new breast cancer medicine, most agree on the Standard of Care. But with so much going on in the cancer field,*

[3] The specific sub-population was identified as HER-2+. Prior treatments in patients with advanced breast cancer potentially consist of regimens that include anthracycline, taxane and trastuzumab. The new medicine is essentially defined as a second-line therapy for these trastuzumab-refractory patients (i.e. patients that had disease progression under a previous trastuzumab regimen).

by the time you finish clinical trials 5–10 years later, the perception of what Standard of Care is has moved on and your results might look much less compelling."

One prominent benefit from Phase II pilots is that all parties can align on the methodology or principles that will be used to define the SOC to use as a comparator. Should SOC be defined by whatever is common in clinical practice, or potentially as a blended comparator of SOCs? A few health systems go so far as to heavily codify recommended SOC (for example, the "Chemotherapy Planning Oncology Resource Tool" developed by the Pharmaceutical Oncology Initiative Partnership to address variations between UK providers in the uptake of cancer drugs approved by NICE)[4].

While there are many different approaches, visibility into the methodology for selecting SOC can remove some of the ambiguity from the drug development process. As one industry participant again reinforced, it is *"critical that we get the Standard of Care to be debated as much as the profile of the new medicine, because SOC drives payment and pricing decisions as much as the profile of a new drug."*

Assessing increments and relative components of value through the Scenarios

The value of a new breast cancer medicine was directly linked to demonstration of hard clinical endpoints. In particular, demonstration of efficacy was considered the most critical measure across all stakeholders. While considerations of safety – including toxicity and tolerability – and/or patient-reported QoL measures were important, when weighed against efficacy, these latter indicators were secondary and hence were considered insufficient for licensing and reimbursement as stand-alone indicators.

The Scenarios confirmed that OS and/or PFS were the most critical measures for efficacy, with the endpoint being dependent on the context of the disease setting, (e.g. it is more realistic to demonstrate OS in advanced-stage breast cancer.) Reflecting on the Scenario outcomes, a number of participants considered an ideal incremental gain for OS and proportionally for PFS to be 3 months' gain in the metastatic setting, particularly given the movement towards targeted therapies. In a clinician's words, *"Clearly if you can identify a limited group of patients, there's a high probability of benefit to be expected, and you would expect this gain."* In actuality, participants acknowledged that 1–2-month gains can be significant, dependent on risk: benefit gains, and could be considered measurable value. Participants recognised, in the words of a payer–advisor, that *"we have been spoiled by trastuzumab gains, with expectations that significant advances would reflect what has been achieved by that medication."* Moreover, participants agreed that focusing solely on the absolute value of the median can mislead as expressed by a payer–advisor participant, *"The shape of the survival curve and methods to extrapolate and tailor that survival curve in a reasonable way needs to be taken into consideration."*

In general, if a medicine was highly efficacious relative to the SOC, high cost relative to a comparator was not a barrier to recognising value. As stated by a payer, *"From an economic*

[4] http://www.abpi.org.uk/%2Fpublications%2Fpdfs%2FPORTBrochure.pdf

point of view, we make a clear distinction between the improvement in the outcome, which may be the survival and quality adjusted survival. On the other side, we have the costs, and it is important to keep these two separate. But in the end, what we want to have is a longer and better life for patients – and this is what we recognise. Measuring progress and valuing progress are distinct issues."

For medicines with uncertain or potentially limited value relative to a comparator, likelihood to reimburse declined noticeably with higher relative costs of those medicines as *"the payer is facing a decision today about how to best make use of money within limited healthcare budgets."* However, introducing risk shares within the Scenarios dramatically improved the likelihood of reimbursement for these more uncertain but potentially promising medicines, highlighting the advantages of providing flexibility in pricing as related to value demonstration. As voiced by a payer–adviser, *"It is absolutely critical that if we are serious about value-based pricing, that prices go up as well as down, and the flexibility needs to be a mechanism built into the system."* Additionally, in thinking about incentives to support appropriate value demonstrations and the timing required to do quality development (in the words of an industry participant, *"without being always in the rush of taking decisions because the clock is ticking,")* participants reiterated that rethinking data exclusivity may be a useful tool to promote appropriate development.

Finally, stakeholders affirmed the consensus view that innovation should be linked to efficacy and that providing *"merely a technical demonstration showcasing a new mechanism of action was insufficient for approval."*

Additional questions emerging from the Scenarios

In developing and taking the Scenarios, participants identified a list of issues, in addition to the SOC, that require robust and transparent discussions to support assessment of a new medicine. These include the following:

- How should a sub-population be defined for a trial?
- What are the evidence requirements for accompanying diagnostics or tests for sub-populations responsive to treatment, and what are the acceptable boundaries for false positives/negatives in a diagnostic and/or test that identifies a sub-population?
- What are the efficacy, toxicity and tolerability endpoints and associated increments of value?
- How are QoL measures and collection design best defined? How relevant are QoL measures, given the indications of efficacy and toxicity/tolerability that are already present?
- What are the regional valuation models to be used for assessment, and how can we generalise economic inputs across those models?
- What value indicators should be measured post-launch?

Participants noted the difficulty of addressing many of these questions through a static set of value indicators. However, participants believed this further supported the need for collaborative consultations in Phase II.

Recommendation to launch pilots to prototype Phase II interactions

Participants affirmed the need to develop Phase II pilots to support the direction first proposed by the Working Group at the second meeting in London[5]. All involved share the view that the current model for bringing new medicines to market is unsustainable and that change will be required from all stakeholders. There is strong support for redefining how value in medicines can be more effectively demonstrated, assessed, captured and rewarded. As part of this work, participants across stakeholder groups and geographies believe there is an important opportunity to better align evidence requirements and clinical trial design to support both licensing and reimbursement, and to move towards concrete realisation would be an affirmation of the ideas developed by the Working Group. As one participant stated, *"I would very much support pilots with company assets to spread the ideas and tools developed by this Group."* While acknowledging the potential value from the fictitious drugs captured in the Scenarios, several participants also stated that *"the time is now"* to begin launching pilots with real assets and to *"move beyond"* theoretical conversations towards how to implement a 21st century drug development template. The overall mood of participants was well described by one who stated that, after several years of vigorous debate, *"it's now time to have a go at this and find out if we can accomplish something transformational."*

The opportunities presented by pilots could (in the words of a patient advocate) significantly *"refocus drug development and processes to improve patient outcomes,"* while reducing risk for all stakeholders and allowing more optimal resourcing with greater visibility. Visibility could inform of future drug expenditures for payers and of internal resources needed to meet oversight needs for regulators, and provide an early view on a drug's promise, as well as facilitating better "go/no go" decisions within industry. Appendix C contains a summary of the opportunity and the potential impact of introducing new Phase II interactions.

In broader discussions with key stakeholders and opinion leaders beyond this Working Group, all believe Phase II interactions are not happening as frequently as they could or involving as many of the needed participants as should be at the table. The few Phase II interactions that do take place tend to be, as one senior regulator explained, *"bilateral conversations between industry and a regulator"* and *"very rarely involve payers, regardless of Member State."* An industry participant seconded this position, stating that *"Phase II interactions in Europe between industry and payers are absolutely not happening."*

All agreed that key questions to be addressed by the pilot are:

- What is the emerging value of this drug to all stakeholders?

[5] See Breast Cancer Working Group 9 July 2009 Meeting Summary at http://www.tapestrynetworks.com/documents/Tapestry_EHILN_BCWGSummary_Jul09.pdf

- How should this value be demonstrated?
- What are the implications for Phase III trial design and post-launch activities?

In the words of an industry participant, *"At present, companies have no means of external input into our 'go/no go' decision. What we need to know is, does the drug hit a relevant target with an unmet need, and what is the standard of care for that indication? Would payers be willing to reimburse it given an adequate value demonstration? What conditions are required in post-launch?"*

Defining key pilot parameters

Participants started to address several outstanding pilot design questions and recommended process steps to further pursue topics raised during the Working Group discussions. Summarised below is the initial design guidance proposed by the participants.

Governance principles for the pilots

Several pilot governance principles were considered, including:

- **Balance the benefits of cross-stakeholder collaboration with the retention of role independence.** The tension between stakeholder independence and collaboration is of particular importance, since a lack of collaboration would function as a *"gating factor for the success of new forms of interaction."* Noted by another regulator participant, *"In the framing of the pilots, in order to give scientific or regulatory advice, special authorisation from my agency would be required. I cannot just speak as an individual."* Given these requirements, participants recommended obtaining official sanction from organisations to allow decision-makers the authority to participate in the pilots; but, also have those organisations promote participation in a manner that allows flexibility and openness to pursue innovative processes and thinking. This could be achieved by setting clear expectations and governance principles, and appropriately preparing pilot participants similar to the Working Group briefing processes. Related to this point is the need to engage the appropriate individuals and organisations, in a payer's words, "*to seek out people who are able to think outside of their organisation, who are interested in thinking beyond their own role."* All recognised the challenges involved, and declared by a payer–adviser, *"Individuals make so much difference. The success of this pilot lies on which individuals are involved...."* Emphasised a regulator participant, *"You need to try to do two things at the same time… you need those people from the organisations who, on the one hand, are in the position really to contribute to decisions within the organisations and, on the other hand, they must not be the defenders of the status quo. That is the challenge. Try to find those, get them involved."*
- **Acknowledge that this process will require behaviour changes on the part of all stakeholders.** In the words of a payer–adviser, *"We would all need to understand that all stakeholders would need to give up some control in exchange for achieving greater outcomes ... Industry would need to bring all data to the table, and reasoning behind*

pricing. Regulators would need to listen to patients and payers; payers would need to provide clear criteria earlier in the process … This may not be comfortable, but this should be the expectation." As an industry participant summed up, *"All participants – the key stakeholders – need to understand that they can win and they can lose … that the outcome could be negative, for example, for a drug."*

- **Ensure process transparency while protecting confidentiality of content.** All agreed that the objectives, structure, participants and process details of the pilots should be fully transparent. Participants agreed the need to protect outcomes related to a specific compound in order to protect the confidentiality of compounds in early development. As stated by a patient advocate, *"Transparency is the best approach … We certainly need complete transparency around the process itself, if not the content."* A regulatory participant stressed, *"It is common practice in the regulatory environment to have some confidential recommendations. But we will need absolute transparency on who is talking to whom and on what topics. We can cut out details that are trade secrets, but we need to be careful not to look like an undefined group in a 'hush-hush' meeting making secret decisions."* A clinician concurred that *"if you start exposing trade secrets, you will take away innovation, particularly since a lot of new compounds are fairly close to each other, and by releasing information, you'd be at a competitive disadvantage."*
- **Share lessons and general clinical guidelines derived from the pilots.** *Participants agreed that there is an opportunity to provide generalisable guidelines on non-competitive clinical questions after the pilots. For example, providing specific requirements for a diagnostic for a given treatment population, such as acceptable rate of false positives to be kept in mind; or trial population definitions for a given disease stage in breast cancer; or basic elements such as process* commonalities in the nature of the pilots *that each new pilot, as it starts, can learn from. As stated by an industry participant, "It would be invaluable to share those lessons."*
- **Agree non-binding outcomes.** Due to the innovative nature of the pilots, participants recommended that advice provided in the consultations should be non-binding and should not displace existing channels for regulatory and reimbursement approval.

In summary on governance principles, participants highlighted the need to identify and agree an overall governance framework in which the pilots are conducted. Most, if not all, of the design elements discussed herein will require codification and agreement among pilot participants as a set of ground rules. The participation of both public officials and leaders of private industry, as well as the high value of the assets under discussion, will make it necessary to pay particular attention to the governance framework in which the pilots are conducted. As a payer cautioned, *"There is a concern that public officials be impartial toward the participating and non-participating companies. Public officials will want to avoid any misunderstanding regarding their participation."*

Structure and process guidance for the pilots

We summarise the Working Group's recommendations regarding pilot structure and process guidance below.

- **Timing for stakeholder consultations.** Participants recommended that timing for these engagements should balance the need for sufficient data to provide a meaningful picture of a medicine's potential with the need for sufficiently early visibility to inform both the "go/no-go" decision and the planning of the development programme. Given the trend towards more targeted oncology programmes, an industry participant noted that *"the timing of these early consultations may be more likely at the end of Phase 1 [after proof of concept] versus end of Phase II."* Agreed a clinician, *"The terminology of Phase II or Phase III settings may be outdated in oncology [Perhaps] the consults could conceivably be about whether a larger scale Phase III* [trial] *would even need to be done if the value has already been clearly demonstrated."*

- **Briefing process and objectives.** The Working Group considered structure and requirements for providing pilot participants with consistent and useful background information prior to the consultation. The briefing mechanisms within the pilot would need to, in a payer's words, *"go beyond just selecting these individuals, but more importantly engaging them in the process to give them a sense of some of the vision we have and some of the issues that have been raised outside of our own personal areas of expertise, very much similar to what we have accomplished in this forum."* Such a process would need to be broader than current engagements. Suggested a payer–adviser, *"The proposal is to do work on both sides, from the industry side and from the payer and regulator side, and before the main meetings to define a few key areas, which decisions are needed to be made, and concentrate on those areas. In particular, some effort would be needed to have payers prepared for such a discussion and to be explicit on their priorities or their criteria."* In sum, participants proposed to *"clearly separate these pilots from the usual consultations between industry and the regulators, and have a verbally defined set of key issues or key interaction points, which should not be too long and have a very tightly managed process to stick to these related points and not to get drawn into scientific or administration details."* One suggestion is to have a two step engagement; the first meeting to agree on the key questions from all stakeholders, and the second to focus on specific discussions on those topics. Details on the preparations and briefings required, the actual process of creating the briefing document and agenda, and the chairing of these meetings will be developed further in light of these comments.

- **Briefing document content.** Participants recommended that, if possible, the pilot briefing documents , in the words of a payer–adviser participant, should share *"more rather than less – to conduct a full appraisal for the context the new medicine would be placed* [in]*, including looking at all the comparators, the evidence available, the evidence to link surrogates to outcomes, to look at the evidence available about quality of life and to look at some of the resource use implications across the different jurisdictions to explore different Scenarios and impacts on pricing ranges."* Given the compounds'

positions in early development and the uncertainty that accompanies that position, briefing pack content details would be further elaborated and validated as needed by the pilot participants prior to the start of the pilot once greater clarity is provided by industry on what data is available.

- **Building a mechanism for assessing diagnostics in conjunction with the drug.** As stated by a clinician participant, *"The pilots must be innovative to the end, which means you must introduce the concept of diagnostics into the design of the trial,* [regarding] *which level of reliability, which level of applicability, and which level of evidence you must have in order to consider the diagnostic* [to be a] *validated tool."* Participants recommended the inclusion of regulatory and HTA agency decision makers with diagnostic-relevant expertise to provide viewpoints needed to address diagnostics parallel with the medicine.
- **Determining how to engage a broader spectrum of payers and address price discussions.** Participants acknowledge the difficulty in engaging payers in pre-registration consultations. From the perspective of an industry leader, *"There is clearly an incentive for me and other members of the industry to do this. I'm not a hundred percent sure what the incentive is for very busy payers to do it, particularly when it is not binding."* To involve payers, discussions would need to include some broad indication of price: in a payer's words, *"Unless you discuss price, it's like Hamlet without the prince of Denmark."* In order to find the best approach to engaging payers beyond those already involved in the Working Group and the Network, we asked participants to consider how payers would benefit from their participation. According to a payer, *"This is very important because these are evaluations at the frontiers of science and knowledge ... If they know what will be coming in the near future; it is very helpful for planning their resource needs."*
- **Appropriate representation of the patient or citizen perspective.** While acknowledging the importance of the patient perspective, many participants believe that patients are generally overly focused on one disease area that directly impacts them, making them emotionally-biased. As such, the voice of advocacy groups may need to be balanced by those of the citizen representative, to reflect society's broader viewpoint. Participants reflected on the situation in France, in which both patient and citizen perspectives were represented at regulatory forums *"in order to engage both groups on the same topic* [and] *educate both on the positions and motivations of the other group, allowing them to eventually reach a consensus."* Additionally, examples were shared from the UK system, in which patient representation at regulatory forums was balanced by sociologists, economists and other citizen viewpoints. Further exploration on these topics, including broader discussions with relevant patient and citizen organisations, was acknowledged by all to be a necessary step in the design of the pilots.
- **Providing a forum for education**. Related to the point on patient perspectives above, both patient advocates and clinicians identified the need to provide an educational forum

to support increased understanding on the evidence requirements and decision processes in assessing value in medicines. This educational aspect of the pilot would need to take into account the range of technical capabilities of the different stakeholder groups. In the words of a patient advocate, *"Advocates are not scientists, so it's difficult for us to evaluate this material quickly. We don't have the resources or the time, and are limited on the people who are highly knowledgeable on the scientific data. I think for patients and advocates to be involved, we have to be sure we have a way to access and be educated on the relevant information, and I think that* [this] *part is essential in terms of how the pilot moves forward."*

- **Testing different pilot designs.** Suggested by a clinician participant, and supported as a valid idea by the larger group, was to *"ensure the pilots were varied enough, with the best structure, rather than just testing and committing to one pilot structure and process."* Testing different elements in each pilot would allow a broader view of what particular elements worked best.
- **Ensuring assets for the pilots.** Given the continued call from participants to move towards more concrete outcomes, identification of actual compounds to pilot new open interactions emerged as a high priority in the meeting discussions. Industry participants unanimously voiced support and agreed to offer potential assets that could be utilised for the pilots. They were also *"excited to see the outcomes and be able to extend the concept more broadly. Dependent on what we have in the pipeline, we are very interested in moving forward with this!"* All acknowledge there is much to be gained in putting forward an actual asset for discussion.

Appendix D outlines an emerging pilot process with initial governance and process details based on discussions within the group.

Measuring success

A payer-adviser summarised the group's view on a successful outcome as *"a process – the interaction of the group; a way of creating common understanding of the important issues."* An industry participant agreed: *"It does not make sense to value the outcome. Rather, what should be evaluated is the process improvement that leads to more aligned and innovative clinical development … achieving specific guidance in an integrated comprehensive way where the different stakeholders agree on what should be best for cancer patients and society."* Concurred a regulator, success would be *"achieving a general picture of rules and criteria that could lead to successful development early in the process."* In a clinician's words, *"Clear decisions on whether the process is worth pursuing"* should be an ultimate outcome.

Path forward

The meeting concluded with agreement on the need for tangible action to move forward the pilots for the coming year. Following the recommendation of both this Breast Cancer Working Group and the parallel Type 2 Diabetes Working Group, and with the support of the European Healthcare Innovation Leadership Network at its January 2010 meeting, Tapestry Networks will

move to a concrete realisation of the Shared Value Frameworks by launching pilots involving existing industry pipeline assets in 2010. These pilots will provide an opportunity to apply the value indicators and measures developed by the Working Groups to assess value as well as pilot a new process for earlier consultation among all stakeholders.

Participants agreed to focus on the following major activities:

1) To broaden the impact of the Shared Value Framework through publication in journals and participation in conferences
2) To encourage support for the pilots, clarify the individuals/organisations who should be involved in them and secure these individuals' participation
3) Finally, all unanimously proposed to reconvene this Working Group in late 2010 to review and reflect on pilot experiences

In addition, the creation of governance frameworks and more detailed design of the pilot process will continue early next year with the involvement of specific pilot participants and their organisations. A working group participant will represent the Breast Cancer Working Group and report on recommendations to the European Healthcare Innovation Leadership Network meeting on 21–22 January 2010.

Conclusion

There is a growing acceptance across Member States and stakeholder groups that by overcoming barriers to collaboration and aligning on value across stakeholders, real progress can be made to address the rising cost of medicines and the declining rate of innovation. While the pilots will not, as one participant said, *"solve the problem of drug development by themselves,"* they are a reflection of the pressing urgency to actively engage the problems this Group and the overarching Network was founded to address. As one leading payer exclaimed, *"If you would have asked me 3 years ago if we could have arranged trilateral meetings between regulators, payers and industry, I would have said 'no way'. But now the time is ripe and all are eager to meet."* Thomas Lönngren, executive director of the European Medicines Agency, emphasised the need for new approaches at the recent TOPRA[6] conference in Stockholm stating *"There will be much necessary discussion to see how we could improve the decision making,* [at least] *from the scientific point of view, because we cannot continue to do what we have done in the same way for the past 20 years."*

The initiative to create Shared Value Frameworks for drug development, assessment and reimbursement thus far has engaged over 100 European healthcare leaders across eight Member States. Those involved share the view that the current model for bringing new medicines to market is unsustainable and that change will be required from all stakeholders. There is strong support for redefining how value in medicines can be more effectively demonstrated, assessed, captured and rewarded. As part of this work, stakeholders believe there is an important opportunity to better align evidence requirements and clinical trial design to support both

[6] The Organisation for Professionals in Regulatory Affairs. Sixth Annual TOPRA symposium held 7 October 2009 in Stockholm.

licensing and reimbursement with the ultimate goal of supporting innovation and improving patient outcomes. The Network and its Working Groups are an important step on that journey.

In closing, the words of the participants who have taken this journey reflect a sense of optimism that collaboration and shared perspectives can achieve the goals to be demonstrated by the pilots: *"It is a common theme among us* [participants] *that we are optimistic ... It is astonishing that there is a shared sense of values and we can each appreciate different perspectives. I am looking forward to seeing the real pilots. That is really exciting and I would love to see what comes out of that!"* declared a payer–adviser. As a regulator stated in reference to the Berlin wall celebrations of reconciliation ongoing outside the meeting hall, *"I would be so optimistic that it is possible to tear walls down. It may not be next year, but I think if such processes as we have seen here will continue; I think it is possible to tear walls down in the future!"*

Appendix A: Selected hypotheses tested in the *Health Outcome and Innovation Scenarios*

- Surrogate value indicators (interim clinical endpoints) are sufficient for regulatory and reimbursement approval if there is promise to conduct post-launch studies to establish a link to a firm endpoint (e.g. OS)
- Some surrogate value indicators (interim clinical endpoints) are of greater value because of having demonstrated higher correlation with survival or other proven endpoints (e.g. PFS) compared with other unproven surrogates[7]
- Payers are willing to pay relatively more per patient when a specific patient selection tool (e.g. companion diagnostic or defined genetic profile) is developed that identifies the appropriate sub-population to target
- Cost effectiveness of a treatment does contribute to licensing and reimbursement decisions, even in systems that do not explicitly have cost-effectiveness as an evaluation criteria
- Reduction of treatment burden and increase in patient tolerability are sufficient to secure approval for new medicines with overall efficacy and safety profiles that are similar to the given comparator
- Patient-reported QoL indicators alone are not sufficient for introduction of a new medicine, but can still contribute to a stronger regulatory and/or reimbursement profile

[7] For example, one early surrogate example might be "C-reactive protein and colorectal cancer," D. Mazhar and S. Ngan, from the Department of Oncology, Medical Day Unit, Chelsea and Westminster Hospital, London, UK

Appendix B: Illustration of a Scenario testing specific endpoints and values

Context provided to participants:

You are involved in a discussion reviewing the results of an interim Phase III trial. Results are comparing a new medicine to the existing SOC (assume capecitabine) from a targeted RCT with a selected patient population, with primary endpoint reported of median overall survival

Sub-population was identified by a specific selection tool (e.g. a companion diagnostic, genetic marker, etc.) which, with a high degree of confidence, identifies patients who will respond to the new medicine (assume incidence of false negatives is ~15% similar to that documented for trastuzumab). However, the potential patient population is sufficiently large that the new medicine will not qualify for "orphan drug status", (estimated 40,000 patients would benefit). Due to identification of the targeted population, the integrated therapy is quite expensive relative to the SOC. Assume all other baseline factors are similar between the comparator and the treatment groups.

Patient population participating in the trial is defined as follows: diagnosed as HER-2+, advanced breast cancer patients with liver and lung metastases; previous treatment consists of chemotherapy with a taxane plus trastuzumab; after 6 months of treatment, tumour progression (increase in size and development of new metastases) is documented.

How do you evaluate the value of the new medicine? How likely is it that you would recommend granting licensing approval? Reimbursement approval? What assumptions (if any) that you made to come to your decision on value when viewing the scenario?

Appendix C: Summary of the opportunity and potential impact of introducing new Phase II interactions

Appendix D: Outline of emerging pilot process and initial implementation details