

Summary and Briefing

EUROPEAN HEALTHCARE INNOVATION LEADERSHIP NETWORK
BREAST CANCER WORKING GROUP

26 JUNE 2009

Setting the agenda for change

Overview

Initiated by the European Healthcare Innovation Leadership Network, the Breast Cancer 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 members are committed to elucidating a value framework for new breast cancer medicines and developing approaches to overcome barriers to innovation in addressing unmet needs in this therapeutic area through more effective collaboration among all stakeholders. The Working Group held its first meeting in Paris on 19 May 2009. This document summarises that day's discussion and the potential areas for collaboration that emerge from it and sets the agenda for the Working Group's second meeting on 9 July 2009.

Table of contents

Overview	1
Attendance and outcomes	2
Identifying opportunities for improved patient outcomes.....	3
Identifying underserved patient populations.....	4
Developing targeted treatments	5
Focusing on molecular signatures of response	7
Targeting prevention	8
Demonstrating value in breast cancer drug development.....	9
Considering endpoints beyond survival	9
Accounting for new mechanisms of action	9
Placing endpoints in the context of disease stage	10
Assessing impact on quality of life.....	10
Setting the agenda for change: Developing a “21 st century” breast cancer drug development template	11
Address specific patient subpopulations	12
Agree optimal early phase 2 multi-stakeholder interactions	12
Provide guidance on and linkage to post-launch activities.....	13

Summary and Briefing

EUROPEAN HEALTHCARE INNOVATION LEADERSHIP NETWORK
BREAST CANCER WORKING GROUP

Attendance and outcomes

Participants welcomed the meeting as an opportunity “to start a new game with new players, including payers, regulators, and patient groups.” A regulator reflected on the unique level of inclusiveness afforded by the Working Group, noting that “we usually meet, from a regulatory point of view, with academic people without anybody else, sometimes with industry without anybody else, very rarely with patients, and meeting with two of those people, three of those people, four and maybe more is very interesting. We must reflect together if we want things to progress.” At end of the day, a medical expert praised the level of cooperation achieved. He said: “I have been sitting in advisory boards with regulators and payers for years and it was always a confrontation; it was never a co-operation ... Today, even if we had different positions on several aspects, the general feeling was trying to establish points of contact and common shared values. This is a big step forward.”

The meeting comprised a mixture of plenary discussion, focused work in breakout groups as well as individual consideration of questions posed to the group. Tapestry Networks used polling to gauge participant views and obtain group priority rankings of emerging initiatives. Table 1 below contains the membership of the Working Group by stakeholder group, with those unable to attend indicated by a lighter font colour.

Table 1
Meeting attendance by stakeholder group

Medical subject matter experts

Jonas Bergh, Karolinska Institute, Sweden

PierFranco Conte, Universitaria di Modena, Italy

Jindřich Fínek, University Hospital Plzen, Czech Republic

Anthony Howell, The Christie NHS Foundation Trust, UK

David Khayat, Pitié-Salpêtrière Hospital, France

Jan Lubinski, Pomeranian Medical University, Poland

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, Ministry of Health, Czech Republic

Bengt Jönsson, Stockholm School of Economics, Sweden

Summary and Briefing

EUROPEAN HEALTHCARE INNOVATION LEADERSHIP NETWORK
BREAST CANCER WORKING GROUP

Medical subject matter experts

Miguel Martin, Hospital Universitario San Carlos, Spain

Laurent Mignot, Institut Curie, France

John Robertson, University of Nottingham, UK

Karol Sikora, CancerPartners UK, UK

Michael Untch, HELIOS Klinikum, Germany

Luca Gianni, Istituto Tumori di Milano

Christian Jackisch, Hospital Offenbach GmbH

Michel Marty, Hôpital Universitaire Saint Louis

Larry Norton, Memorial Sloan-Kettering Cancer Center

Martin Piccart, Institut Jules Bordet

Eric Winer, Dana-Farber Cancer Institute

Industry representatives

Jim Baker, Johnson & Johnson

Alan Barge, AstraZeneca

Paolo Paoletti, GlaxoSmithKline

Payers, regulators, health economists and advisers

Bertil Johnsson, Medical Products Agency, Sweden

Sören Olofsson, Region Skåne, Sweden

Patient representatives

Els borst-Eilers, Dutch Federation of Cancer Patients

Susan Knox, EUROPA DONNA, European Breast Cancer Coalition

Guest

Eric Abadie, Chairman, EMEA CHMP, Europe

Identifying opportunities for improved patient outcomes

Participants called for improved value-based patient outcomes by lamenting the confluence of rising healthcare costs and decreasing incremental benefits provided by new medicines. A regulator complained that “we are marketing more and more drugs with marginal benefits,” leading a medical expert to warn: “It is clear that we cannot go on like this with cancer. No society can afford to pay the costs as they go. The thing that is missing, and what we can help to get, is the value equation.” Another medical expert implored industry “to look at all the tools to increase value, which includes segregating population, looking for biomarkers and, most

importantly, looking for surrogates of response within 24 or 48 hours of administering a high-cost drug.”

Participants foresee the potential for improving health outcomes in breast cancer both through focusing on “*which are the brilliant ideas where you have excellence in science*” as “*the basis [for] more rapid achievements*” as well as through making better use of existing health technologies. As to the latter point, a payer-adviser explained that “*there is a real frustration that it is not a question of having more technology but more a question of really understanding the nuances of how the technologies we already have available can be best used, in what sequence and who will benefit most.*”

It is against this backdrop that the working group considered opportunities for improved patient outcomes, the most prominent among them being the following:

- Identifying underserved patient populations
- Developing targeted treatments
- Focusing on molecular signatures of response
- Targeting prevention

We address each of these below.

Identifying underserved patient populations

The Working Group’s consideration of underserved patient populations presented a duality. On the one hand, participants identified the need as one of providing better treatment to breast cancer patients in need of drug therapy. On the other, participants pointed out a similar need to identify those low-risk patients for whom drug therapy is not needed and many of whom currently receive treatment unnecessarily.

A medical expert asserted that “*you could argue that all patient populations are ill-served.*” However, as participants provided greater specificity, the following subgroups emerged:

- Triple negative patients
- HER-2- and hormone-failing patients
- Patients whose cancer recurs and becomes drug-resistant
- BRCA mutation carriers as an example of genetically-defined subgroups
- High-risk patients who would benefit from preventive therapies
- Low-risk patients who do not benefit from adjuvant drug therapy

As to the first of these groups, an industry participant noted that “*there are populations you can define by those who do not respond to current therapies.*” Continuing, a medical expert explained that “*when the patient relapses, we know ... how to treat them. However, we are not good at dealing with the vast numbers of patients who become resistant and die.*” Another

medical expert argued that defining subgroups based on genetic markers, such as BRCA1 mutation is *“absolutely critical ... to create revolutionary progress.”* He described outstanding results in BRCA1 mutation carriers using an existing drug, lapatinib. A fellow medical expert noted that *“we do not serve the population of women who are at risk whom we need to target with prevention.”*

Finally, as to patients who receive treatment unnecessarily, a medical expert said that *“in breast cancer we do not work out who does not need treatment or does not need chemotherapy.”* Another medical expert went further: *“Every day in my clinic I suspect that I treat three out of four patients with breast cancer unnecessarily because they would never relapse even without treatment.”* This is the result using *“accepted guidelines.”*

Developing targeted treatments

Multiple participants voiced dissatisfaction with what they saw as a ‘one-size-fits-all’ approach to drug development and sounded a call for targeted treatments for well-defined subpopulations. A medical expert lamented that, under the current paradigm, *“we are just putting drugs on the market, most of them of marginal value. We are giving the same drug to everybody ... I think the goal for our development of drugs should be looking for the right drug for the right patient.”* A fellow medical expert added that *“there should be a greater understanding amongst clinicians and pharma of how to make use of targeted drugs and how to increase the sophistication of study designs.”* A regulator sounded the call for aligning the full range of available resources behind the development of targeted treatments, exhorting that: *“We need a better approach. It is very important to get as much biological information as we can, frozen tissues, characterisation of the receptors and so on, and this could be performed pre-authorisation and post-authorisation.”*

In this context, participants pointed out the value of obtaining tumour tissue samples from as many patients as possible, both as a basis for targeted treatment of the individual patient, and for the purpose of creating a large database for correlative studies to evaluate how tumours with various characteristics react to different treatments. Speaking on behalf of his breakout group, a participant explained: *“To improve efficiency we need biological samples and to work on subsets of patients up front.”* Another participant summarised his breakout group’s conclusion that tissue is necessary *“to enable us to do the gene profile analysis that we need to enable us to target the drugs.”*

Barriers to progress in targeted treatments

While participants evinced a broad consensus as to the need for developing and matching targeted treatments to well-defined subpopulations, they also acknowledged a number of challenges to progress in this arena. These included:

- **Identifying the appropriate segments is far from trivial.** Summarising the deliberations of his breakout group, a participant noted that *“there was general agreement that the biggest challenge was to segment the populations and define ... which populations of patients do or do not benefit from currently available drugs.”* This challenge is due in part to *“significant scientific gaps in understanding,”* as well as to

Summary and Briefing

EUROPEAN HEALTHCARE INNOVATION LEADERSHIP NETWORK
BREAST CANCER WORKING GROUP

difficulties “in most large-scale clinical trials as to accessing tumour tissue and being able to analyse it in a uniform and meaningful way.”

- **The regulatory requirements for licensing targeted treatments are ill-defined.** An industry participant explained that, “as new therapies become more and more targeted, there are a number of challenges for the regulators as to how they will shape approval processes, ways of evaluating efficacy and eventually value.”
- **The added task of finding and validating appropriate markers as the basis for targeting reduces the remaining exclusivity period of the drug.** As a medical expert stated plaintively, “one of the difficulties with targeted therapy is finding a biomarker for the target before the patent runs out.”
- **Identifying for whom a given drug is effective entails also identifying for whom it is not, thereby reducing the drug’s potential market.** Participants were divided in their view of whether industry requires new or different incentives to catalyse targeted drug development. A medical expert asserted that such development “probably is against the interests of the pharma companies.” A regulator stated this view more provocatively: “There is no incentive for pharmaceutical companies to reduce the market for one of their drugs by identifying a subgroup of patients for whom the drug will not be effective.” An industry participant countered that, “today drug companies are very much interested in ensuring that only those patients get our drugs who will get the maximum benefit, and that those who don’t get that benefit stop receiving the drug as soon as possible.”

Approaches for overcoming barriers

Participants identified two approaches for overcoming at least some of these challenges. The first of these would address the incentive problem for industry to focus on the smaller markets that patient subpopulations represent, while the second would provide an accelerated regulatory path and the potential for an extended period of data exclusivity:

- **Risk-sharing ties payment to clinical efficacy.** An industry participant reported an emerging trend toward risk sharing. He said, “what is happening increasingly around the world is the notion of risk-sharing. People will not pay for drugs unless we give them the money back when the drug does not work.” He noted that, under such a regime, “we have an enormous incentive to identify patients who are most likely to benefit from our drugs, because that is the only way to get reimbursed.”
- **Orphan drug status for targeted drugs can pave the way for small-market development.** Participants in a breakout group considered how to incentivise industry to develop drugs that, by definition, have limited markets. Reporting out, a participant explained the group’s approach: “We talked about defining multiple segments of breast cancer as potential orphan indications ... providing longer degrees of data exclusivity or having a different way of approaching data exclusivity to provide the incentive.”

Focusing on molecular signatures of response

A sharpening focus on patient subpopulations accentuates the importance of biomarkers and companion diagnostics as tools to select patients most likely to respond to a particular therapy or to measure the effect of treatment. Along this vein, a breakout group focused on tapping the potential of molecular signatures of response as a value-enhancing opportunity, both *“as a predictor of response, and conversely lack of response, to a drug prior to the administration of it.”* This approach explores *“ways to get information about the tumour from blood testing”* and can serve as an alternative to *“pathology samples and tissue samples ... [that we] conventionally think of.”*

The breakout group acknowledged barriers at both the pre-clinical and the clinical stages of drug development to the full realisation of molecular signatures’ potential. Pre-clinical barriers include the time pressure for rapid development, or *“speed incentive,”* which is driven by the perceived need to get drugs to the market as quickly as possible given the limited period of exclusivity granted by patent law. However, opinions were divided within the breakout group as to the impact of targeted development on the speed of development, with one participant opining that *“if you can define the patients that are going to do well or going to get the best response, it potentially makes development faster.”*

Breakout group members also considered the impact on price of highly targeted development. They noted the possibility that *“if the groups are too small the price per patient becomes overwhelming and therefore not worth the investment.”* One solution to this dilemma lies in the possibility that *“if you identify targeted therapies then the targets span across a number of different cancers,”* leading to a patient population of sufficient size to justify the investment in drug development. By implication, a participant suggested that *“this is where drug development needs to change: you’re not going to say I’m going to develop a drug for breast cancer. Rather, you’re going to develop a drug that targets a particular mechanism.”* Here breakout group participants identified the compartmentalisation of drug development into different types of cancer as an organisational barrier to progress.

At the clinical stage, *“there is a lack of linkage with the discovery phase of the drug. There is not much incentive”* to develop markers because, historically, industry’s view of success *“hinge[s] on the speed of getting through the various milestones in a drug’s development.”* Speaking for his breakout group, the medical expert noted a likely disconnect between *“the commercial viewpoint”* and a *“post-marketing R&D strategy looking at segregating populations.”* Adding to this difficulty is that, historically, *“post-marketing commitments are not always fulfilled.”*

The group’s proposed solutions include extension of exclusivity and variable pricing:

- ***Pausing the exclusivity period during pre-clinical investigation of biomarkers.***
The breakout group’s recommendation for the pre-clinical stage was *“to define incentives. We have to put clock stopping in place around IP in the discovery if you start to go down a track [of molecular signature development].”*

- ***Variable pricing to incentivise data generation during clinical application.***
Turning to the post-launch environment, the group reported that *“the most interesting concept was variable pricing.”* Under such a scheme, the developer would be granted conditional approval and would *“start at a low price for a lot of patients.”* As the developer would *“begin to segregate the patients showing more benefit from those showing less [benefit], the actual value of the drug and therefore the price of the drug would start to escalate.”*

Targeting prevention

Another area of breakout group focus in canvassing opportunities for improved patient outcomes was the potential benefit of prevention. Reporting for the group, a medical expert raised the question of whether prevention is an *“orphan”* in the breast cancer landscape. He explained: *“there are in breast cancer some interesting drugs in prevention at the moment, better than Tamoxifen, better than Raloxifene,”* and cited Lasofoxifene as a drug with the potential to *“prevent heart disease, prevent osteoporosis and prevent breast cancer.”* He concluded that, if these effects were validated, *“people would be more interested in prevention.”*

The breakout group identified two barriers to increased progress in prevention as: *“(1) a lack of thought about it; and (2) lack of incentive for going into it.”* As to the former, the medical expert suggested that, *“from a pharma point of view they might need to think of a new business model.”*

He summed up the Group’s recommendations for overcoming these barriers: *“in terms of prevention, we need long-term strategies, long-term investment and perhaps patent extension.”* The first of these approaches calls for *“more interaction between private and public funding and between pharmaceutical companies and national organisations. We realise that much of prevention, such as exercise and weight control, is outside the realm of pharmaceutical interventions.”* The call for extended periods of exclusivity rests on an acknowledgment of the length of time required to demonstrate value in prevention: *“you often have to have an extended patent life to make prevention studies worthwhile for pharma. One way to accomplish this is through the benefits that flow from orphan drug status.”*

As we prepare for our upcoming meeting, you may wish to reflect on the following questions:

- ? Which underserved patient population do you consider as presenting the most addressable opportunity for progress? Why?
- ? What strategies would you recommend to encourage innovation in a world of increasingly targeted treatments?
- ? What issues do you envision in providing access to treatments that increasingly rely on expensive diagnostic tests and combination therapies? How might you address these?
- ? What might be done to encourage more effective approaches to prevention?

Demonstrating value in breast cancer drug development

Participants' opening remarks at the Paris meeting drew immediate attention to the definition of value, saying *“drug development and the evaluation framework is somewhat out of sync regarding the definition of value,”* while a medical expert agreed that *“I would like to have a discussion on value and people's perception of that. People all have their own standards we need alignment.”* These statements reflect the great underlying interest of Network members and Working Group participants in enhancing clarity and alignment regarding the kinds of endpoints that are most relevant for use in clinical trials and post-launch studies. Such clarity is needed to guide industry's R&D and investment decisions. A payer-adviser put it plainly: *“regulators and payers have a responsibility to signal value to the private sector so they can make good decisions.”*

Considering endpoints beyond survival

Reflecting on the “straw man” value framework developed by Tapestry Networks, participants agreed that, at a very high level, *“the two things that matter to everyone is how long you live and how well you live.”* As a payer-adviser put it, *“a complete measure of health outcome ... includes length and quality of life and the impact on resource use.”* Despite this truism, value demonstration in breast cancer has focused almost exclusively on the additional length of life offered by a treatment. While all agree that *“survival is a very important endpoint,”* participants are also frustrated by what many consider to be an excessive emphasis on it and suggest that *“it shouldn't be the only endpoint.”*

In particular, as more is understood about different types of breast cancer and therapeutic interventions begin to turn some forms of breast cancer into a chronic disease, participants asked whether overall survival is still the only appropriate measure of success. One challenge with overall survival as a clinical endpoint is that *“to get a survival endpoint takes too long, or the study is too large.”*

As an alternative, participants are looking to one or more broader measures of disease control. Speaking for a break-out group, a medical expert reported: *“There was a general feeling that disease control was more important necessarily than overall survival. Sometimes overall survival would be relevant, but disease control was a measure of efficacy, and that was perhaps more important.”*

Accounting for new mechanisms of action

Several participants indicated that existing endpoints fail to capture the benefits provided by drugs with new, non-cytotoxic mechanisms of action. A medical expert explained: *“We created the idea of measuring the efficacy criteria about 20-30 years ago when we started treatment with chemotherapy. Now we are using biological drugs whose function is quite different from that of a cytotoxic agent, and we can stabilise the disease for months and years.”* Especially those in industry believe it is important to agree alternative endpoints appropriate for *“these targeted*

therapies that may not cure the cancer – but may turn it into a chronic disease.” They suggested “circulating cancer cells or DNA in the plasma” as two indicators “that could be considered.”

Placing endpoints in the context of disease stage

Participants acknowledged that *“relative value rankings are partly related to stage of disease”* and questioned whether *“we are looking at the wrong indicators of success.”* For example, a regulator pointed out that *“progression-free survival is not a natural discussion in an adjuvant setting.”* More broadly, a medical expert argued that *“it is very difficult to show an improvement in survival with modern drugs because the prognosis of people that we are putting into trials is so good.”* According to one medical expert, for most patients the question *“is not survival anymore; now it is preventing metastasis or recurrence.”* Others agreed, noting: *“In reality, we wish to know the patient with nodal involvement”* and *“Inhibition of metastasis formation is an extremely important endpoint.”*

Assessing impact on quality of life

Participants also voiced concern that measures of treatment effectiveness were divorced from the patient herself. A medical expert explained: *“I would like to focus on the greatest discrepancy in my daily clinical practice. I am treating a patient but measuring the diameter of a tumour in centimetres. I see the challenge for today in creating new guidelines in the system of measuring the efficacy of not only cancer treatment but also cancer care.”* Conceived of broadly, this suggests measures of quality of life – an area whose incorporation into a value framework for breast cancer received lukewarm support at best from participants. However, a number of participants expressed the view that the toxicity and side effects of a drug should be considered at least so as to offset its therapeutic benefits, particularly in late-stage settings.

One line of thinking among participants is that quality of life and minimising side effects are important, but are secondary to improving overall survival and are difficult to measure. One payer-adviser participant commented that such data should be *“supportive, but only in context of objective disease-related endpoint improvement.”* Moreover, the challenge with these types of measures, according to a medical expert, is that they are *“extremely difficult to obtain and to separate from a placebo effect.”* A regulator echoed this view, arguing *“the tools we have today ... are usually not specific to a given drug and when these drugs have specific and large side effects it’s very difficult to form an opinion.”*

The importance of side effects and short-term treatment toxicity also varies by disease stage. Patients may have a high degree of tolerance for transient discomfort where treatment can impact the likelihood of overall survival. A medical expert noted that patients display a significant tolerance for treatment-induced toxicity in the adjuvant setting: *“Where we are trying to eliminate micro-metastatic disease to improve survival, if you ask the patient ... what she will put up with to have a 2% improvement in survival or a 5% improvement in survival, it is quite a lot. She will take a lot of symptoms in the short term during the time of adjuvant treatment to improve survival subsequently.”* Indeed, according to a medical expert, in the adjuvant setting

symptoms can be indicators of response to certain treatments. He explained that *“in the adjuvant situation with adjuvant endocrine therapy, if you had symptoms you did better.”*

However, in the context of late stage disease, several participants considered side effects-related quality of life to be of primary importance. Speaking for his breakout group, a regulator explained: *“If we obtain, for a given treatment, a two-month difference in progression-free survival and if the treatment is well tolerated, it could be considered as a benefit. The problems begin as soon as the treatment is not very well tolerated. Could we consider the benefit/risk assessment to be a positive one if the patients gain two months of progression free survival as an advantage with a new treatment at the expense of almost unbearable side effects?”* His implied answer was “no.”

In preparation for our upcoming meeting, you may wish to reflect on the following questions:

- ❓ In light of what you view as the most addressable subpopulation, what do you believe are the most significant issues related to demonstrating value of a treatment? What endpoints do you recommend be used to demonstrate value? How would you assess the effectiveness of a treatment over time in the real world?
- ❓ What is the role of quality of life assessments when demonstrating the value of a new medicine for your recommended subpopulation?

Setting the agenda for change:

Developing a “21st century” breast cancer drug development template

While many participants have applauded the unique opportunity presented by the Working Group for a 360-degree dialogue across all relevant stakeholders, you also understand that the promise of the Group will be realised only if its deliberations lead to concrete, tangible results that mark progress in delivering improved outcomes for breast cancer patients. In furtherance of this goal, Tapestry Networks has synthesised the results of the 19 May meeting into a set of emerging Working Group goals. We have done so with the understanding that any focused approach will of necessity exclude some worthwhile initiatives.

The cornerstone of this proposal is what might be termed a “21st century” template for breast cancer drug development. The underlying assumption behind this approach is the desire to bring the expertise of the Group to bear on an improved process for drug development that can be piloted on specific technologies and, eventually, generalised to other therapeutic areas. Its three key components are the following:

- Address specific patient subpopulations
- Agree optimal early phase 2 multi-stakeholder interactions
- Provide guidance on and linkage to post-launch activities

We address each of these below, augmented by relevant insight gained to date through the Working Group process. While the creation of this drug development template is an important

contribution, its ultimate value will be realised when it is applied to specific phase II assets in the pipelines of industry participants.

Address specific patient subpopulations

This element of the drug development template may contain the following aspects:

- Generate consensus list of “high-value” subpopulations to address
- Consider stage-appropriate / subpopulation-appropriate surrogates acceptable to regulators & payers

Participants have made clear – and industry is aware – that future innovation in the treatment of breast cancer is closely tied to targeted therapies. According to an industry leader, the expectation within pharma is that reimbursement increasingly will be tied to a drug’s effectiveness in a given patient, which creates a strong incentive toward segmentation of patient populations.

However, participants also have noted the difficulty of gaining regulatory approval for drugs that show substantial effects in only a subset of the population on which they are tested. An industry leader recounted the difficulty of convincing a regulatory agency to consider such subgroup effects to be dispositive of a drug’s effectiveness. He related: *“The FDA have said to us ‘That was a very interesting hypothesis generating experiment, now go and repeat it properly,’ which then adds another three years and \$200 million onto the cost of the experiment, which, if you are only targeting 10% of patients with breast cancer, makes it financially non-tenable.”*

Participants should consider how to adapt study designs to subgroup-focused drug development, as well as the potential need for up-front biomarkers to identify the subpopulation most likely to benefit. Such questions are likely to be appropriate and necessary subjects of early interactions between drug developers and other stakeholders.

Agree optimal early phase 2 multi-stakeholder interactions

This element of the drug development template may contain the following aspects:

- Provide early approval and reimbursement guidance
 - Clarify which value components influence regulatory / reimbursement decisions
 - Clarify data and evidence hurdles for approval and reimbursement
- Align regulatory and payer therapeutic value criteria within and across geographies

As to providing earlier approval and reimbursement guidance, a payer-adviser identified a *“consensus [within the Group] about the importance of trying to get clearer, predictable and, from industry’s perspective, more reliable signals they can rely on in making investment decisions much deeper down into the drug development process.”* A fellow payer-adviser highlighted *“the key responsibility on payers and reimbursement authorities to send the clearest predictable signals about what will be paid for,”* while pointing out the concomitant *“responsibility of the*

private sector to make sure those signals get down to the parts of the companies where those decisions are actually being made.”

In what would surely be an ambitious initiative, participants across stakeholder groups have lauded the benefits of a potential harmonisation of requirements between regulatory and reimbursement authorities, as well as among the myriad HTA and reimbursement bodies in Member States. A payer-adviser expressed the views of many in stating that *“collaboration between regulators and payers is something which has to come.”* Progress in this field could come through agreed *“principles on which we could better unite the requirements for registration and for reimbursement,”* as well as consensus on *“how to make these requirements closer and more responsive to existing clinical needs.”* A medical expert called for *“better interaction between the agencies to have common goals, common definitions, what is agreeable and what is approvable.”*

While enthusiastic about the benefits of such harmonisation, participants also are realistic about the difficulties it would entail given that *“our systems in Europe and the modelling that supports decisions across States are quite different.”* The emerging consensus from post-meeting discussions is that the appropriate focus for harmonisation is the dataset that regulatory and reimbursement authorities require across Member States, leaving the utilisation of those data and resulting reimbursement decisions at the national level.

Participants should consider what role the Working Group can play in this process. One option for promoting harmonisation is to agree a consensus value framework for a subpopulation of breast cancer along with the endpoints and measures required to show performance along that framework. The “straw man value framework” that Tapestry Network has syndicated with Working Group members is a move in this direction.

Provide guidance on and linkage to post-launch activities

The post-launch environment received a fair amount of attention at the 19 May meeting as well as in pre-meeting discussions. A government participant summarised the Group’s sentiment in commenting that *“there is a lot of promise in post-launch collection of the data and post-launch analysis, because it could address lots of [issues] being discussed today.”* Participants view post-launch data generation as a tool for accomplishing a number of objectives, including:

- ***Providing earlier patient access to new drugs.*** In what he termed *“a perfect example of a new cooperation between industry, academia and local authorities,”* a medical expert suggests that conditional reimbursement, coupled with post-launch data generation, can grant market access even in the presence of *“open questions.”* Doing so would require that industry *“helps us [the regulator and payer] explore these new questions for a short but accepted duration.”*
- ***Segmenting patient populations.*** Coupled with some form of value-based reimbursement, post-launch data collection can provide an incentive for industry to develop pre-treatment mechanisms for segmenting patient populations. In what may be an over-simplification, a medical expert explained the motivation simply as to *“identify*

Summary and Briefing

EUROPEAN HEALTHCARE INNOVATION LEADERSHIP NETWORK
BREAST CANCER WORKING GROUP

those patients who will have no benefit so [the drug companies] do not have to give out the drug for free for two months.” He concluded that such an approach “should be a real incentive to find that [bio]marker.”

- **Providing a mechanism for informed expansion of licensed indications.** A payer-adviser laid out the case for post-launch studies in positioning cancer drugs and expanding indications based on real-world clinical experience:

From a payer’s perspective ... the most important issue is how we position new drugs in the market so that we can all feel assured that the patients have a chance to try this new drug without making mistakes. We need to invest in stakeholder collaboration in post-launch trials where we jointly monitor the use of these drugs and draw conclusions on expanding the use of the drugs in an orderly manner.

Participants believe that at least some of these applications of post-launch data generation require incentives or direct funding mechanisms beyond those currently in place. A payer-adviser summed up the available palette: “We are going to either have to think of using public money to invest in providing that evidence or giving the private sector some incentives to do that, whether that is by assigning property rights towards the public good ... or by linking access to the amount of evidence they provide.” We briefly address each of these approaches below:

- **Public-private partnerships for funding.** Several participants expressed the view that there is a role for public funding of post-launch studies, particularly where adequate incentives are not in place for industry to do so. A payer-adviser opined that “the public sector should be making the investment in good evaluative research, where there are not those incentives [for industry].” A fellow payer-adviser added, “There are very interesting ideas for drug studies, but there is no investment. We need to get investment. We have to take it from the government, from the industry and put it together.” A patient advocate added that, because “the public or the government has a responsibility in helping to bring these new drugs to the patient,” the latter stages of drug development should “move on to public/private financing.”
- **Expanded property rights in data.** A payer-adviser suggested assigning “property rights to evidence,” by which industry would “get royalty payments for generating the evidence that makes better use of existing technologies.” One benefit of such an approach to data exclusivity would be to “reward” industry “for making the five years and hundreds of millions of dollars of investment” needed to bring a breast cancer drug into the adjuvant (rather than end-stage) setting, where it “might make a much greater incremental improvement in outcome.”
- **Conditional reimbursement.** Reimbursement can be conditioned on an aggregate assessment of the drug’s effectiveness (evaluated based on analysis of data collected post-launch) or on an assessment of an individual patient’s response to the drug. Successful implementation of a conditional reimbursement regime will require addressing a number

Summary and Briefing

EUROPEAN HEALTHCARE INNOVATION LEADERSHIP NETWORK
BREAST CANCER WORKING GROUP

of design features. For example, a participant hypothesised: “Say you’ve got a drug and you give it and it’s got a 10% response rate. You then get a diagnostic and you get it up to 50% in a sub-group of patients. Are you allowed to charge more in that sub-group of patients?” We also note that an underlying assumption for most participants is that drug prices can move both up or down as a result of post-launch data, while this does not appear to be the case in the above examples.

In preparation for our work on constructing the drug development template, please consider the following questions:

- ❓ What additional components, if any, would need to be included in the drug development template to maximise its utility to all stakeholders?
- ❓ Which components of the 21st century drug development template would you be most interested in helping create?

Tapestry Networks has reached out to participants over the past weeks to validate and refine this agenda and chart a path forward. These discussions have reaffirmed the direction outlined above. Accordingly, we propose the following high-level agenda for the 9 July meeting in London:

- Present and discuss key challenges in improving health outcomes for breast cancer patients by stakeholder group
- Articulate and agree components of development plan template
- Develop work streams to help drive progress in preparation for our final meeting this year on 11 November
- Identify possible candidate assets for pilots on which to apply the template

In preparation, we invite you to consider the questions embedded in this document, as well as the extent to which the Working Group has an ability to drive progress in each of the areas outlined above. We also invite you to consider to which of these initiatives you would consider committing your efforts. Your continued insight and participation will enable us to work together to make progress on this important set of opportunities to better serve breast cancer patients.