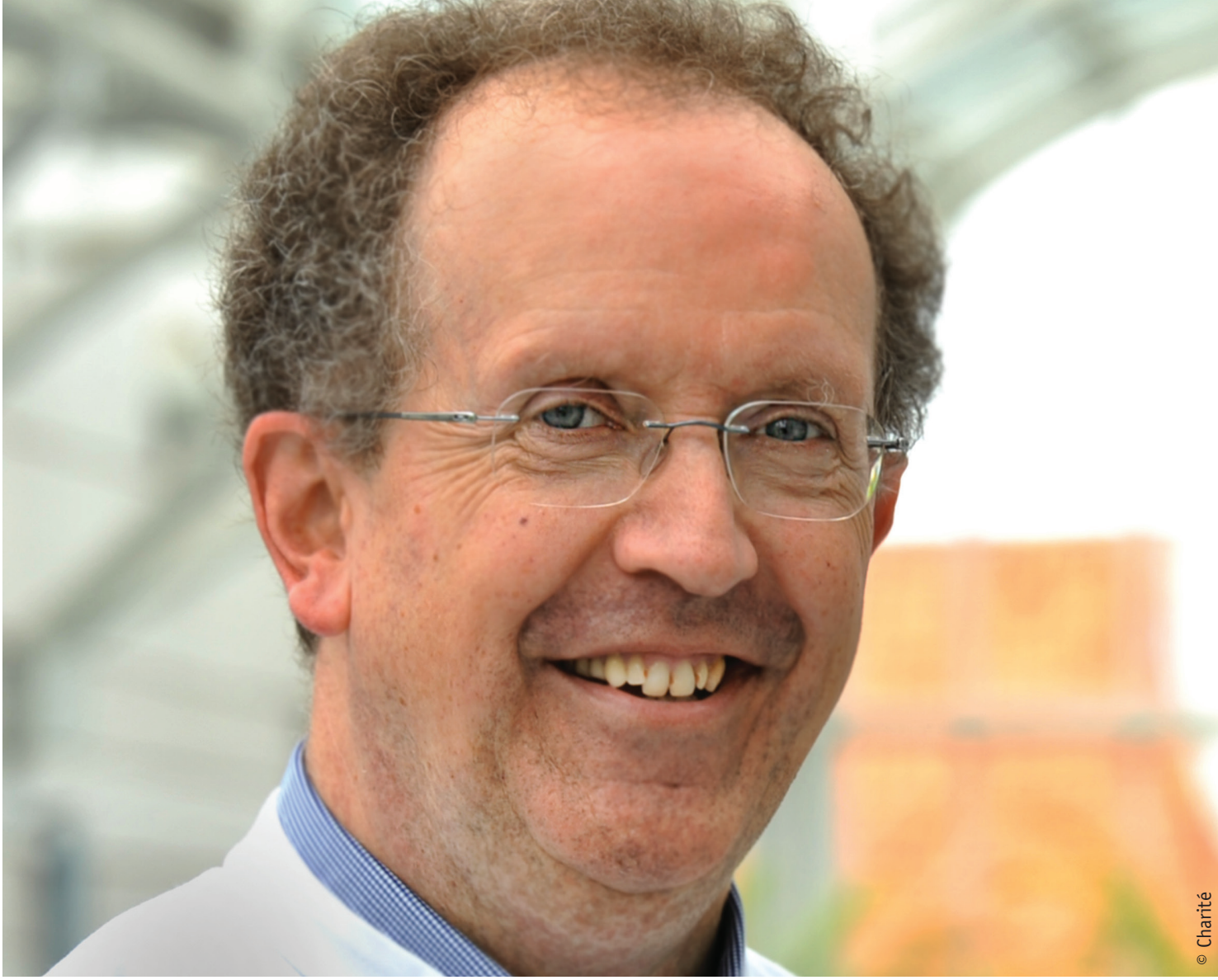


'We need to link measure lues more closely to PRO'

Interview: Prof. Dr Bernhard Wörmann, Medical Director of the German Society for Haematology and Medical Oncology (DGHO)

The different benefit assessments of pembrolizumab ('Keytruda') by IQWiG and the ESMO, which Institute Director Dr Thomas Kaiser addressed in the 'Monitor Health Services Research' cover interview in issue 02/25, raises fundamental questions about the methodology and prioritisation of treatment parameters. The focus is on the weighting of relapse prevention versus toxicity - a field of tension between oncological efficacy and patient-centred safety assessment. MVF spoke about this duality with Prof. Bernhard Wörmann, MD, Medical Director of the German Society for Haematology and Medical Oncology (DGHO).

>> Professor Wörmann, as Medical Director of the German Society for Haematology and Medical Oncology (DGHO), you are significantly involved in the evaluation and further development of oncological and haematological care. The early benefit assessment of oncological and haematological drugs has shown that the relationship between benefits and risks, in particular the handling and commenting of toxicities, plays a central role. To what extent do you consider the current procedures for considering dose adjustments or treatment discontinuations due to toxicities in the dossiers of the pharmaceutical companies and in the IQWiG assessments to be sufficient and adequate?

In principle, the cure or at least the alleviation of symptoms is the first priority for the patient. Accordingly, a conceptual distinction must be made between drugs that directly combat diseases and drugs that prevent diseases or relapses. When weighing up the benefits against possible harm, the benefit assessment approaches clinical reality. With every drug therapy, especially in oncology, this weighing up is a matter of individualised patient care. In practice, we have the advantage of being able to react individually to side effects that have occurred and been experienced, e.g. by adjusting the dose. In the benefit assessment, the collective of patients from the authorisation studies is seen as a whole, which of course cannot do justice to heterogeneity. The consideration of diversity has become even more challenging in recent years in the authorisation studies, now that we are increasingly paying attention to ethnic - and also genetic - diversity. This also applies, for example, to the metabolisation of drugs.

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With regard to the consideration of toxicities: Are there specific aspects where you see a need for improvement from the DGHO's professional perspective, both in the presentation by the companies and in the assessment by IQWiG? This could, for example, concern the standardisation of the reporting pathways for adverse events or the weighting of different severity levels of toxicities.

The standardised scales used in studies to record adverse events allow a grading within the respective symptom. This is a strength because it enables standardisation and thus comparability. The major weakness of this approach is that it does not differentiate between 'measured' and 'experienced' adverse events. Specifically, thrombocytopenia with values between 25,000 and 50,000 is classified as severity grade 3, but is usually asymptomatic and almost always transient. In contrast, grade 2 sensory or motor polyneuropathy, for example, can lead to a musician's inability to work. The basic rule 'we don't treat laboratory values, we treat people' also applies to side effects. Here, measured values must be more closely linked to elements of the patient-reported outcome, or PRO for short.

'For patients and practitioners, it is evident that the response to treatment is a positive message that influences the overall attitude to life and also life planning. '

To what extent do patient-reported outcomes (PROs) play a role in recording and commenting on toxicities in the benefit assessment of oncologicals and haematologicals? Do you see any untapped potential here to incorporate the patient perspective on the tolerability of therapies more strongly into the assessment? For example, the FDA recommends the development of Patient Reported Outcome Measures (PROMs) with the involvement of patients.

Patient participation is essential. In the G-BA, the patient community has institutionalised representation with highly committed employees who interact closely with self-help. In recent years, we have observed with great concern that almost all IQWiG reports in haematology and oncology have been prepared without patient participation. A correction is urgently needed here: patients must be integrated and also be reflected in the content of the final documents. It will be exciting to see whether this integration now also succeeds at the EU HTA level. Many patient representatives have applied for the stakeholder network, have fulfilled the regulatory requirements and have been accepted. This is also associated with high expectations. This integration process has already been successful in German guidelines.

Where exactly can PROs help here?

In the early benefit assessment as part of the German AMNOG procedure, PROs could help to close a gap in the content: Progression-free survival (PFS) is not assessed as a valid endpoint by the G-BA, IQWiG has no methodology for this. This is problematic because many studies are focussed on this endpoint. Specifically, around one third of the oncological approval studies have the PFT as the primary endpoint. It is regularly accepted as relevant by all ethics committees of the participating study centres in Germany.

What would argue against this?

The substantive argument against PHRs are concerns that parameters for recording progression in most studies are only based on imaging and/or laboratory analyses, and these are not relevant to patients. For patients and practitioners, it is evident that the response to treatment is a positive message that influences the overall attitude towards life and also life planning. A bridge between the positions is a link between the PHR and PRO parameters such as symptom relief, stabilisation and/or improvement in quality of life and/or reduction of therapy-associated toxicity. We call this 'PHR plus'.

Where do these different perspectives come from?

The early benefit assessment at the G-BA is the basis for pricing in Germany. In the procedures and also in the hearings, a block formation emerged relatively quickly after the start in 2011/2012. On the one hand, there is the pharmaceutical company, which presents the data as positively as possible, for example by presenting the results of a new, but not pre-specified data section or similar. On the other

hand, there is the HTA report, which looks for weaknesses, ignores PFS and, for example, proposes a methodologically correct but substantively unsubstantiated interaction as the basis for further subgroup formation.

How can this Gordian knot be cut?

With more evidence and reference to the current state of knowledge. Instead of another methods paper, we established a collaboration with Prof Nathan Cherny from the Department of Medical Oncology, Shaare Zedek Medical Center, Jerusalem (Israel) for oncologicals back in 2017. Professor Cherny played a leading role in the development and validation of an instrument for the clinical benefit assessment of new drugs. This was the basis of the Magnitude of Clinical Benefit Scale of the European Society for Medical Oncology (ESMO MCBS), first published in 2015 (1). It has since been further developed (2) and most recently supplemented by a separate evaluation tool for haematological neoplasms (3). The evaluation differentiates between curative and non-curative intent. Decisive parameters for curative intent therapy are (4):

- Increase in the overall survival rate after 3 years
- Improvement in disease-free survival
- Reduction in toxicity or improvement in quality of life
- Cost reduction with the same therapy results.

Decisive parameters for therapy with non-curative intention are (5)

- Prolongation of the median overall survival time, differentiated according to the survival time in the control arm, i.e. based on unmet medical need
- Prolongation of progression-free survival, differentiated according to the PFS in the control arm
- Improvement in other endpoints, e.g. symptoms or transfusion requirements
- Improvement in quality of life, based on CONSORT-PRO, SPIRIT-PRO and SISAQOL
- Reduction of therapy-associated toxicity.

Differences between the high relevance of toxicity in the ESMO MCBS compared to other instruments have also been published (6).

In clinical practice, treatment decisions in oncology and haematology are always made on an individual basis. To what extent do the standardised procedures of early benefit assessment succeed in adequately reflecting the clinical relevance of toxicity differences between therapies and generating relevant information for healthcare practice?



Prof. Dr. med. Bernhard Wörmann

studied human medicine in Münster and Montpellier. He then completed his specialist training first in pathology (Münster) and radiology (Dortmund), then also in internal medicine (Munich, Münster), supplemented by a post-doctoral fellowship in immunology (Minneapolis, MN, USA). In addition to his scientific work and habilitation in Münster, he continued his further training in haematology and oncology (Münster, Göttingen). Professor Wörmann was Chief Physician for Internal Medicine with a focus on haematology and oncology at Braunschweig Municipal Hospital. He has been Medical Director of the German Society for Haematology and Medical Oncology (DGHO) since 2010 and has been a doctor at the Outpatient Health Centre at the Virchow Campus, Clinic for Haematology, Oncology and Tumour Immunology since 2011.

This is a major challenge that we have not yet mastered adequately. We can illustrate this most clearly using the general condition, recorded using the ECOG status. Many studies are limited to patients with ECOG status 0/1, but many older patients in particular have a poorer general condition, i.e. ECOG status 2/3, with a higher risk of adverse events. We can only generate the data required for this through targeted studies in this patient population and/or through registries.

One option also discussed within the specialist societies is the independent assessment of treatment discontinuations as a measure of unacceptable toxicity, but we also recognise the limitations. On the part of patients, the decision/approval to discontinue treatment is based on very different grounds. One parameter is the objective toxicity measured on a scale. More relevant is the perceived toxicity, see the differentiation between measured and experienced side effects discussed above. Even more decisive, however, is the overall situation of the patient, as documented in the case of immune checkpoint inhibitors (CPI). The discontinuation rate for the same CPI is consistently higher in the adjuvant situation at 20 to 30% than in the non-curative situation at 10 to 20%. This is due to the subjective perception and acceptance of side effects depending on the perspective. Patients are more willing to continue a therapy with side effects if their lifespan depends directly on it. However, if they receive the therapy 'only' to reduce the likelihood of recurrence and are possibly already cured in the long term, the perception of side effects is different.

The willingness to discontinue treatment also depends on whether alternatives are available. Here, the situation in Germany is fundamentally different from that in countries where only a few of the newly authorised oncology drugs have been launched on the respective market. A further argument against the assessment of treatment discontinuations outside the specific treatment context is the increasing use of new drugs in combination therapies. Several factors contribute to toxicity here. Depending on the combination partner, the discontinuation rate for the same CPI can vary by a factor of 3.

Your conclusion?

The benefit assessment of new drugs only makes sense in the context of comprehensive, specialist expertise in the respective indication. Today, this expertise is mapped in networks. The learning AMNOG procedure has recognised this and adapted the legal regulations (7). Supporting the G-BA's decision-making process is a time and logistical challenge for the professional associations. We are currently involved in transferring this successful model to the EU level.

Prof Wörmann, thank you very much for your expertise and your willingness to discuss these issues. <<

The interview was conducted by MVF publisher Prof Reinhold Roski and MVF editor-in-chief Peter Stegmaier

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SBK in favour of the primary care system

>> A passage in the current coalition agreement provides for the introduction of a primary doctor system: SHI-insured persons should first go to their GP practice in the event of illness, where an initial assessment will take place, and then be referred to specialist practices if necessary. In addition, opportunities should be created to carry out the initial assessment digitally or via telemedicine. Dr Gertrud Demmler, Director of the Siemens company health insurance fund SBK, believes that this proposal falls short of the mark. The resource of GPs is also a scarce commodity. Instead of establishing just one group of doctors as a gateway to care, Demmler believes that the focus should be on a primary care system. Demmler: 'GP and specialist practices, non-medical staff and digital tools work together in this system. They have the important task of organising care and initially clarifying whether personal doctor-patient contact is even necessary. '

Nevertheless, in her opinion, the coalition paper provides a sensible approach: the possibility of an initial digital assessment is to be created. 'That's good. But it still doesn't go far enough,' explains the SBK board member. In her view, there needs to be an obligation to do so. In order to be able to implement this, patients need the choice between different channels - from apps to (video) telephony. In the further course of treatment, analogue and digital methods would also have to be sensibly interlinked.

It is also necessary to give medical staff more competences, which is not in the coalition paper, but is nevertheless urgently needed. Demmler: 'We need to involve medical professionals much more in the care process. For example, an initial assessment does not always have to be carried out by authorised personnel. A recent survey by the GKV-Spitzenverband (National Association of Statutory Health Insurance Funds) showed that the insured are very much in favour of this.

Demmler's third point is in favour of strengthening health literacy: This would make it easier for all insured persons - regardless of the initial assessment - to decide when a visit to the doctor is necessary and when it is not. <<