



The EAA Chapter France

Convention Proceedings

September 18th, 2026

**The French Perspective:
A Multi-Stakeholder Glance into
the Initial EU HTA Assessments**

AGENDA

09:30 Welcome Message & Introduction (*Étienne Lengliné, Hôpital St Louis, EHA, HAS/ Jörg Ruof, EAA*)

09:45 Plenary Session Part 1 – French Perspective on the Status of the EU HTA Process

- Health Policy Introduction, France (*Yannick Neuder, National Assembly, CHU Grenoble Alpes, virtual*)
- Status Update on EU HTA from the Coordination Group (*Diane Lastennet, HAS, HTACG JCA SG*)
- Overview of National Implications of EU HTA for France (*Lionel Collet, HAS*)

10:45 Coffee Break

11:00 Plenary Session Part 2 – French Stakeholder Perspective on EU HTA

- Considerations from a French Patient Point of View (*Laure Guérault-Accolas, Patients en réseau*)
- Considerations from a French Clinician Point of View (*Jean-Yves Blay, Centre Léon Bérard, ESMO, virtual*)
- Considerations from a French HTD Point of View (*Auriane Cano-Chancel, AstraZeneca, LEEM*)
- Legal Considerations: National Reception of JCA in France (*Francis Megerlin, Université de Strasbourg*)
followed by Plenary Discussion

12:30 Lunch

13:30 Plenary Session Part 3 – Comparing Applied EU HTA Methods and Clinical Considerations with the State of the Art in France (*moderated by Bruno Falissard & Jean-Francois Bergmann, Université Paris Cité*)

- Cross-JCA Methods Overview & Statistical Considerations (*Bruno Falissard, Université Paris-Saclay*)
- JCA Reports Revisited: Patient & Clinical Commentary on JCAs
- Content of EU HTA Assessments: French Patient Insights (*Anne-Pierre Pickaert, HAS*)
- EU HTA in Paediatric Low-grade Glioma: Lessons Learned (*Gilles Vassal, SIOPE, Institute Gustave Roussy*)
- EU HTA in ES-SCLC & Standard of Care in France (*Nicolas Girard, Institute Curie*)
- EU HTA in SMA & Standard of Care in France (*Vincent Laugel, CHRU de Strasbourg*)
- EU HTA in Breast Cancer & Standard of Care in France[§] (*Jean-Yves Pierga, Institute Curie*)
followed by Plenary Discussion

15:25 Summary and Wrap Up

15:30 End of Convention

[§] subject to availability of the respective JCA report

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Editorial

A Multi-Stakeholder Glance into the Initial EU HTA Assessments – the French Perspective



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In December 2021, the Regulation (EU) 2021/2282 on Health Technology Assessment (HTAR) was adopted by the European Parliament, and came into force in January 2025, setting the scene for a joint Health Technology Assessments (HTA) across the European Union (EU). Its overall aim is defined in recital 3 of the EU HTAR: ‘HTA is able to contribute to the promotion of innovation, which offers the best outcomes for patients and society as a whole, and is an important tool for ensuring proper application and use of health technologies’.¹

EU HTA Founding Principle 1: The Science vs Value Dichotomy

A key structural component embedded in the EU HTAR is the clear separation of a centrally coordinated, scientific, and non-judgmental assessment from the subsequent value-centric appraisal decisions that remain within the remit of the individual EU member states and guide national pricing and reimbursement. This principle differs from e.g., the regulatory pathway where both, assessment and decision making on the marketing authorization, are performed centrally.

Thus, understanding and embracing the science vs. value dichotomy is critical for a successful implementation of the EU HTAR. While scientific assessments refer to the technical and scientific evaluation of evidence, appraisal decisions apply value judgments e.g., by transferring and ranking available relative effectiveness evidence into an ordinal categorization system.² Across Europe only a subset of countries has implemented such categorical systems. Best known are the French (ASMR, Amélioration de Service Médical Rendu ranging from ASMR 1, major, to ASMR 5, no clinical improvement) and the German system (categorizing the added benefit from an innovative treatment on a scale from 1, major added benefit, to 6, less benefit).

EU HTA Founding Principle 2: The Equity vs Excellence Dilemma

A second key structural feature of the EU HTAR is the inherent ‘equity/ excellence’ dilemma.³ As stated in recital 25 and article 8.6 of the regulation: ‘The assessment scope for joint clinical assessments should be inclusive and should reflect all Member State’s needs in terms of data and analyses...’. Consequently, multiple PICO (Population/ Intervention/ Comparator/ Outcomes) schemes may result from the details requested by the various EU Member States depending on their respective national treatment standards. The recent joint clinical assessment (JCA) of Tarlatamab in extensive-stage small cell lung cancer was based on 7 partially overlapping PICO schemes covering 4 distinct populations.⁴ While such equity-centric inclusion of PICO schemes is mandated by the regulation, it appears obvious that in an increasingly competitive global environment an alignment of European evidence needs is required to strengthen Europe’s voice in global clinical development programs.

Also, recital 9 suggests that health technologies should be ‘compared with the best available alternative, that takes into account the level of innovation and benefit for patients’; and recital 5 stipulates that HTA should also inform where a health technology becomes obsolete. The bottom line is: While equity is of utmost importance and social relevance, innovation is driven by clinical and scientific excellence rather than equity and, as mentioned in recital 1 of the regulation, EU HTA should foster innovation across the Union.

Considering these two key features of the EU HTAR a necessity for leadership within Europe’s two most relevant markets, France and Germany, is evident. This is in line with the Joint Declaration on Strengthening the Pharmaceutical Industry in Europe that was

recently issued by the two Ministries of Health.⁵ More specifically France and Germany should:

- I. Indicate how to manage the science vs value dichotomy i.e., how to best translate the new scientific EU JCA reports into (e.g., categorical) valuation systems on an EU member state level, and
- II. Address the equity vs excellence dilemma by focusing their national scoping schemes (e.g., the comparative treatment required to conduct the national appraisals) on excellence i.e., the best possible standard of care. Thus, the Health Technology Developer may know which PICO schemes are ‘the first among the equals’ to provide sound (ideally derived from a well – designed randomised controlled trial) evidence against.

The European Access Academy (EAA) was founded in 2021 and aims to facilitate and further support the successful implementation of the EU HTA Regulation (www.euaac.org). With the availability of the initial EU JCA reports the goals of this first meeting of the EAA Chapter France are to i) provide a topline overview of the ‘State of Play’ from a national French point of view; ii) apply a French multi-stakeholder perspective appropriately reflecting

all three pillars of evidence-based medicine (data excellence/ patient perspective/ clinician perspective), iii) revisiting the initial EU JCAs taking into account respective French treatment guidelines and standards of care and consider how the Transparency Commission decisions might evolve in light of the suggested PICO schemes, i.e. for the list of the clinically relevant comparators and/or the definition of the target population for reimbursement in France.

We are very much looking forward to a successful first meeting of EAA’s Chapter France in Paris and an encouraging and stimulating discussion on the initial EU HTA Assessments from a French perspective. We would like to thank Université Paris Cité for making available its premises for the meeting, all presenters for their respective contributions and, last but not least, the sponsors for making such a meeting possible.

Bruno Falissard, Étienne Lengliné, Jean-François Bergmann & Jörg Ruof
on behalf of the EAA Faculty

1) <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32021R2282>

2) <https://doi.org/10.3390/jmahp12040028>

3) https://irp.cdn-website.com/e52b6f19/files/uploaded/Strasbourg+Ruof_2.0.pdf

4) https://health.ec.europa.eu/publications/joint-clinical-assessment-report-tarlatamab-imdylltra_en

5) https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/J/Joint_Declaration/260518_English_Joint_Declaration_FR-DE_pharma_unterschrieben.pdf

EAA Convention Speaker Abstracts

Health Policy Introduction, France

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Dr. Yannick Neuder is a cardiologist at CHU Grenoble Alpes, where he has headed the Cardiovascular and Thoracic Pole since 2011, specializing in heart failure and heart transplantation. Alongside his medical career, he has held elected office at local, regional and national level: mayor of Saint-Étienne-de-Saint-Geoirs (2002-2019), founding president of Bièvre Isère Communauté (2014-2022), and vice-president of the Auvergne-Rhône-Alpes regional council (2016-2022). Elected deputy for Isère's 7th constituency in 2022 and re-elected in 2024, he serves as General

Rapporteur of the National Assembly's Social Affairs Committee. From December 2024 to September 2025, he served as Minister of Health and Access to Care in the government led by François Bayrou, before returning to clinical practice at CHU Grenoble Alpes. This dual experience as a practicing cardiologist and former Health Minister gives him a distinctive vantage point on the implementation of EU Health Technology Assessment and its impact on the French healthcare system.

Status Update on EU HTA from the Coordination Group

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The implementation of the EU HTA Regulation has introduced a new framework for European cooperation in HTA, establishing Joint Clinical Assessments (JCAs) and Joint Scientific Consultations (JSCs) to support harmonised clinical evaluations across Member States. Since January 2025, mandatory JCAs have applied to centrally authorised oncology medicinal products and advanced therapy medicinal products, marking the operational launch of the Regulation. In parallel, the first JCA for selected medical devices have recently been initiated, extending the implementation of the Regulation beyond medicinal products.

This initial implementation phase has demonstrated the feasibility of coordinated European clinical assessments within the timelines defined by the Regulation. To date, three JCA reports have been published, while shared governance structures, methodologies, and collaborative procedures have enabled Member States to jointly define assessment scopes, conduct clinical assessments, and adopt JCA reports.

Operational experience has also highlighted a number of challenges associated with the implementation of this new framework. Growing assessment volumes, the mobilisation of expertise across Member States, review capacity, stakeholder interactions, and continuous process optimisation remains critical factors for ensuring the efficiency, consistency, and long-term sustainability of the system. In parallel, Joint Scientific Consultations are supporting earlier dialogue on evidence generation and promoting greater alignment between developers and HTA bodies.

As the scope of the Regulation progressively expands, the experience gained during this first year provides valuable insights into the practical implementation of the European HTA framework and helps identify priorities for its continued development with important implications for HTA bodies, regulators, and health technology developers.

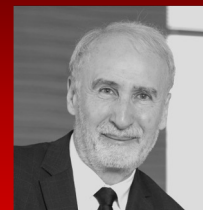
Diane Lastennet was awarded a PhD in Public Health - Cardiovascular epidemiology at Université Paris Cité. Between 2017 and 2021 she worked at Hôpitaux Universitaires Pitié Salpêtrière - Charles Foix, before she joined Haute Autorité de Santé. There, she was initially responsible for public health and assessment of vaccines and since 2024 she is scientific project lead for the evaluation of pharmaceuticals. She represents France in the EU Member State JCA Subgroup and in early 2026 she was appointed co-chair of the HTA CG Subgroup on JCA.

Overview of National Implications of EU HTA for France

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The regulation on Health Technology Assessment (HTAR) introduces two European procedures: Joint Scientific Consultations (JSCs) during research and development and Joint Clinical Assessments (JCAs) during the marketing authorisation phase. These processes precede national appraisal and reimbursement procedures.

For the French National Authority for Health (HAS), HTAR implementation has added European HTA responsibilities for medicines and medical device to its existing national assessment activities. While clinical assessments may now be conducted at European level, reimbursement decisions remain a national competence. Health technology developers must still submit reimbursement applications, and French committees continue to appraise technologies according to national principles.

To prepare for implementation, HAS launched an integrated action plan including staff and expert training, stakeholder outreach, dedicated organisational arrangements for participation in HTA Coordination Group and subgroups activities, reinforcement of methodological and biostatistical expertise, and structured expert input into national PICO development.

Key operational challenges include integrating JCA outputs into national assessment processes and adapting submission templates and reporting formats. Some procedures remain unchanged, while others are evolving, notably early dialogues and assessment pathways relying on clinical data already submitted at European level.

As of 16 July 2026, four JCAs had been endorsed, fourteen were ongoing, and several implementation challenges had emerged, including complex PICOs, consolidation of Member State requirements, dossier quality issues, and evolving regulatory timelines. The first year has nevertheless significantly improved understanding of the European process and demonstrated that coordinated health technology assessments are feasible. HAS has been and continues to be involved as assessor or co-assessor in four JCAs for medicinal products and aims at participating as assessor in the first JCAs for medical devices in the next months.

The publication of the first JCA reports marks a major milestone and the beginning of a new phase focused on practical integration, continuous learning, process refinement, capacity building, collaboration, and long-term sustainability.

Professor Lionel Collet, President of the French National Authority for Health (HAS), Vice-Chairman of the Heads of HTA Agencies Group (HAG)

Lionel Collet is a Doctor of Medicine and Human Biology, a full member of the French National Academy of Medicine and an honorary member of the French Council of State. He has been President of the French National Authority for Health (HAS) and Vice-Chairman of the Heads of HTA Agencies Group (HAG) since 2023. Prior to this, he held a number of key positions in clinical practice, research and higher education as a University Professor and Hospital Practitioner, Head of the Audiology and ENT department at the Lyon University Hospital and director of the Neuroscience and Sensory System Laboratory at the CNRS, before becoming President of the Claude Bernard Lyon I University and the National Consortium of University Presidents. He was Chief of Staff to the Minister for Higher Education and Research, Geneviève Fioraso, and then Special Advisor to Agnès Buzyn, then Minister for Health and Solidarity. He has also chaired a number of French health bodies, including the INVS, the EPRUS, Santé Publique France, the AP-HP College of Ethics and the National Council for Periodic Certification.

Retours experience et perspectives d'une patiente et d'une association

Quand le principe de réalité vient heurter la volonté

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Our non-profit organisation Patients en Réseau has been contributing regularly since 2018 and has organised itself to respond consistently to requests for contributions from the HAS since the early access reform in 2021. The EU HTA reform was announced, and we followed the relevant webinars and information sessions. However, to date we have not yet been able to genuinely take part in the first calls for input. Laure will lay out the obstacles and difficulties encountered, along with prospects for improving this situation, given the major importance of ensuring patients' voices are represented in health technology assessments.

Notre association Patients en réseau contribue régulièrement depuis 2018 et s'est organisée pour répondre régulièrement aux demandes de contributions de la HAS depuis la réforme de l'accès précoce en 2021. La réforme EU HTA a été annoncée et nous avons suivi webinaires et sessions information. Cependant, à ce jour nous n'avons pas pu réellement participer aux premières sollicitations. Laure explicitera les freins et difficultés et les perspectives pour améliorer cette situation au regard de l'enjeu majeur de porter la voix des patients dans les évaluations.

Laure GUEROULT-ACCOLAS is the founder of the non-profit organisation Patients en réseau, of which she is the Managing Director. A Doctor of Pharmacy, she chose to professionalise her patient expertise following her own experience of cancer, which notably upended her professional career. A postgraduate diploma (DU) in Therapeutic Education, followed by a DU in Cancer Care Pathway Support from the Université des Patients – Sorbonne Université, confirmed this choice.

Through the organisation Patients en réseau, she is strongly committed to actions in health democracy, promoting prevention, screening programmes, clinical research and the transformation of health care pathways, notably through the joint leadership of Article 51 AKO@dom PICTO. She has been contributing to the Haute Autorité de Santé in France since 2018.

To date, the organisation Patients en Réseau offers through its website and mobile application <https://monreseaucancer.org>, a social network with five communities covering breast, lung, gynaecological and colorectal cancers, as well as one dedicated to family carers. Patients en Réseau aims to make everyday life easier in the face of illness: people can break out of isolation, exchange with others, find reliable information, and access practical resources (useful contacts, events, personalised support).

French Stakeholder Perspective on EU HTA Considerations from a French Clinician Point of View

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Health Technology Assessment (HTA) plays a central role in translating therapeutic innovation into patient access. Across Europe, the same clinical evidence may be assessed by multiple national agencies, using sometimes different methodologies.

One evidence base, one European clinical assessment:

Clinical evidence does not change at national borders. Repeating the scientific assessment of the same pivotal trials in every Member State adds limited value while consuming substantial resources for regulators, investigators, healthcare professionals, industrial partners, and HTA bodies. European Joint Clinical Assessment should therefore become the common scientific reference for Member States, avoiding systematic duplication at national level. European HTA should simplify assessment and not create an additional layer of evaluation. National decisions may differ according to healthcare priorities and economic considerations, but the underlying scientific assessment of relative clinical effectiveness should increasingly be shared.

Equality of methodology does not guarantee equity:

Evidence generation is fundamentally constrained by disease prevalence. In rare cancers and rare diseases, large randomized trials, multiple adequately powered comparisons, mature survival endpoints, and extensive subgroup analyses may be impossible. Applying methodological

standards developed for common diseases without accounting for rarity creates a false equal process and an intrinsically inequitable outcome. Patients should not be denied access because the epidemiology of their disease makes conventional evidence requirements unattainable. European HTA should therefore adopt proportionate, disease-adapted methodologies that integrate disease rarity, unmet medical need, effect size, feasibility of evidence generation, and the totality of available evidence. Appropriate use of single-arm studies, external controls, real-world evidence, Bayesian approaches, surrogate endpoints, and conditional access linked to prospective evidence generation should be considered when conventional randomized evidence cannot reasonably be produced.

The ethical obligation to use positive trial results

Patients participating in phase III trials accept uncertainty, potential toxicity, and personal constraints to generate knowledge intended to improve future care. Investigators, healthcare systems, public institutions, and society invest substantial money, time and resources in these studies. When a phase III trial is approved scientifically and ethically by national competent authorities, and meets its prespecified primary endpoint, demonstrates clinically meaningful benefit, and has an acceptable benefit-risk profile, failure to translate this evidence into access requires compelling justification.

In the absence of major concerns regarding safety or validity, denying access to an intervention that improves survival is inconsistent with the principles of respect for participants, scientific integrity, social value, and responsible stewardship of resources.

Authorizing and supporting clinical research while subsequently disregarding its positive results risks undermining the social contract underpinning clinical research. Scientific evidence should not automatically dictate reimbursement. Ethical research does not end with publication; its ultimate purpose is to improve outcomes for all patients.

The Declaration of Helsinki states that provisions should be made for post-trial access to beneficial interventions. This ethical obligation may reasonably extend to future patients beyond those enrolled in the study.

Conclusion:

Europe needs a system based on one shared scientific assessment, avoiding duplication, methodologies adapted to rarity, and a commitment to translating meaningful evidence into equitable patient access.

Jean-Yves Blay is Professor of Medical Oncology at the University of Lyon I, Director General of the Cancer Center Léon Bérard in Lyon, and President of UNICANCER, the Federation of Comprehensive Cancer Centers in France. His work focuses on sarcoma, rare cancers, guiding targeted treatments using genomics, and immuno-oncology. He is heading several research initiatives and networks including the H2020 ERN on Rare Solid Tumors, the Network of Reference Centres for Sarcomas in France (NETSARC+), and the French NCI Integrated Site of Innovative Research on Cancer (LYRICAN.) He is Chairman of the French Sarcoma Group, member of the French National Academy of Medicine, Director of Public Policies of ESMO, and former president of the EORTC. He has co-authored more than 1000 articles and was awarded numerous prizes and awards for his work.

From Procedural Launch to Decision-Making Value Considerations from a French HTD's Point of View

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The application of the EU HTA Regulation in 2025 opened a new phase in European cooperation on the clinical assessment of innovative medicines. For the pharmaceutical industry, this reform is a major opportunity to reduce unnecessary duplication across countries, support a more coherent approach to comparative clinical evidence, and ultimately contribute to faster and more predictable patient access to innovation. As the first Joint Clinical Assessments (JCAs) emerge, the key question is now how this new European layer will be used in practice to support clearer and more consistent national decision-making.

Establishing a common European clinical evidence base is an important step forward, particularly in areas where evidence generation is complex and companies have historically faced multiple overlapping requests from national systems. Early experience shows that resource efficiency will be critical to success. This applies to public authorities, patient organisations, clinical experts, and companies alike. If the process becomes too burdensome during scoping, evidence clarification, and dossier management, there is a risk that effort is absorbed by the procedure itself rather than directed toward the questions most relevant for assessment and reimbursement.

This is especially visible in the PICO elaboration exercise. A well-designed PICO should help identify the questions most likely to make the joint assessment usable across Member States. However, if the

process seeks to accommodate every possible national preference in parallel, it may generate excessive complexity without proportional gain in practical utility. Likewise, if uncertainty is framed too broadly or too systematically, the process may risk amplifying perceived evidence gaps rather than supporting balanced interpretation of available data, especially in settings where evidence generation is inherently difficult, including rare diseases and other areas in which conventional comparative approaches are not always feasible at launch. The priority should therefore be to make the process more focused, transparent, and operationally efficient, with clearer prioritisation of clinically meaningful questions and greater predictability in evidence requirements.

From a French perspective, the success of the EU framework will depend on its interaction with existing HAS processes. The European JCA should serve as a credible common clinical foundation, while national bodies remain responsible for those dimensions that are appropriately national, including appraisal in light of French clinical practice and the reimbursement framework. But this articulation must be organised as complementarity rather than duplication. The value of the JCA would be weakened if national processes were systematically to recreate distinct clinical assessment expectations at appraisal stage, thereby limiting the practical convergence the Regulation is intended to achieve. More broadly, transparency – and still more

success – should be measured not only by the volume of information produced, but by the extent to which that information remains usable and actionable for decision-makers.

The most important question now is whether the first JCAs will effectively contribute to more transparent, more predictable, and more convergent reimbursement pathways across Europe. The reform will have delivered on its ambition when European assessments help reduce avoidable reassessment, clarify and

streamline evidence requirements, and support more consistent use of clinical evidence in national decisions. If, by contrast, the practical effect were to increase downstream uncertainty or create disproportionate entry barriers for some innovations, the intended benefits for patients and health systems would be called into question. For patients, this should mean a system that is easier to understand, less duplicative, and better able to support timely access to innovative treatments.

Auriane Cano-Chancel is Country President of AstraZeneca France. She has recently been appointed Vice-President of LEEM and Chair of the LEEM HTA Commission. Auriane has been with AstraZeneca for over a decade and brings extensive global, regional, and in-market experience. Before assuming her current role, she served as Head of Oncology & Haematology France, where she led the medical, commercial, diagnostics, and innovation activities supporting the next wave of oncology innovation. She previously held international responsibilities in Cambridge as Global Commercial Lead in Immuno-Oncology, and earlier held roles in France across Oncology and the cardiovascular and renal area. Prior to joining AstraZeneca, she was Strategic Director at Ipsen and an Associate at L.E.K. Consulting. Auriane Cano-Chancel is a graduate of École Polytechnique and holds an MPhil in Bioscience Enterprise from the University of Cambridge.

Legal Considerations: National Reception of JCA in France

Réception de l'évaluation clinique commune : aspects de droit français

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Le règlement européen sur l'évaluation des technologies de santé vise à défragmenter l'évaluation clinique comparative de certains produits de santé autorisés dans l'Union, pour faciliter la tâche de leurs développeurs, alléger la charge des autorités nationales et faciliter l'accès des patients. À cette fin, il prévoit une évaluation clinique commune (ECC), dont les États membres doivent tenir « dûment compte » dans leurs processus décisionnels. Si l'évaluation clinique commune devrait homogénéiser la perception initiale de la valeur clinique des nouveaux produits, elle

ne préjuge pas des étapes nationales ultérieures, dont la fluidité est un enjeu pour toutes les parties prenantes. Alors que le principe de « due consideration » s'applique dans divers contextes nationaux, sa nature et portée rendent peu probable une jurisprudence européenne. Nous esquissons ici l'intégration de l'ECC en droit français, et le défi accru que représente, partout, la gestion de l'incertitude concernant la valeur des produits, et potentiellement les mécanismes de sa réassurance contractuelle.

Juriste en droit international et comparé, Francis Megerlin est notamment professeur (Health Laws & Systemics) à l'université de Strasbourg, et Senior Fellow au Berkeley Center for Health Technology de l'université de Californie à Berkeley. Ses recherches et missions internationales portent notamment sur la regulatory science, l'évaluation des technologies de santé, les contrats d'accès au marché, la tarification et les méthodes de paiement des technologies avancées. Ses activités incluent l'aide à la décision publique et l'assistance à des réformes nationales.

Cross-JCA Methods Overview & Statistical Considerations

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The implementation of European Joint Clinical Assessments (JCA) marks an evolution in Health Technology Assessment (HTA) across the European Union. By promoting a shared framework for the evaluation of new health technologies, the JCA process aims to improve methodological harmonization, reduce duplication of assessments between Member States, and facilitate more consistent access to innovative therapies.

This presentation will provide an overview of the methodological principles underlying cross-JCA evaluations, with a particular focus on statistical considerations. Special attention will be given to the central role of comparative effectiveness assessment, subgroup analyses, indirect treatment comparisons, and the interpretation of clinically meaningful effects. The

presentation will also discuss methodological challenges related to missing data, multiplicity, external validity, real-world evidence, and the increasing complexity of innovative trial designs such as adaptive, basket, or platform trials.

Beyond technical aspects, we will examine the broader epistemological tension between methodological rigor, regulatory expectations, transparency requirements, and the practical constraints of decision-making in HTA. While classical statistical inference remains the cornerstone of JCA evaluations, emerging approaches involving Bayesian methods, causal inference techniques, and artificial intelligence-assisted analyses may progressively influence future assessment strategies.

Professor Bruno Falissard is a French mathematician, psychiatrist, and scientist. He is Professor of Biostatistics at the Paris-Saclay Medical University, Director of CESP (INSERM Research Centre for Epidemiology and Population Health), and former President of the International Association for Child and Adolescent Psychiatry and Allied Professions. His research interests include pharmaceutical evaluation, evaluation of unconventional treatments, epistemology and research methodology in medicine, psychiatry, psychoanalysis and neuroscience.

Content of EU HTA Assessments – French Patient Insights

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This presentation will provide an overarching patient perspective on Joint Clinical Assessment (JCA) reports published by September 2026. The discussion will focus on key strengths, gaps, and areas for improvement in these assessments.

The session aims to explore what current JCA reports could mean for patient advocacy, including how advocates can leverage them in their work, what

opportunities exist to push for greater patient involvement and transparency, and what could be potential red flags, such as limitations in patient input or information accessibility.

By sharing these insights, the presentation seeks to empower patient advocates to engage more effectively with JCA processes and outcomes and call for adjustments.

Ms. Anne-Pierre Pickaert is a French patient advocate and a member of the Transparency Commission at HAS. She has volunteered with hemato-oncology patient organisations and has served as a board member of the Francophone Society of Bone Marrow Transplant and Cellular Therapies (SFGM-TC). Alongside her volunteering, Anne-Pierre works as a health communication and access to medicines advisor, supporting patient communities both within and beyond her original disease area. Anne-Pierre holds a Master of Science in Economic Evaluation for Health Technology Assessment from the University of York (United Kingdom).

EU HTA in Paediatric Low-grade Glioma: Lessons Learned

Gilles Vassal

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The first ever EU Joint Clinical Assessment (JCA) report under the EU HTA regulation concerned a targeted therapy for a rare paediatric brain cancer, namely tovorafenib for the treatment of patients ≥ 6 months of age with a paediatric low grade glioma (pLGG) showing a BRAF fusion or rearrangements or a BRAF V600E mutation and progressing after one or more lines of systemic therapies (EU indication).

LGG represent one third of paediatric CNS malignancies. The group is composed of different histologies and locations (cerebellum, hemisphere, optic pathway, brainstem, spine) and considered as a chronic disease with prolonged disease trajectories, recurrent progression and repeated therapeutic interventions. Half of patients require one line or more of systemic treatments. Only recently, activation of the MAPkinase pathway has been recognized as a major oncogenic driver of pLGG. The most frequent alterations are BRAF fusion or rearrangements (40% of tumors), followed by BRAF V600E mutations and NF1 loss or mutation as well as many other rare alterations.

Tovorafenib is a type II BRAF inhibitor, targeting all BRAF alterations while dabrafenib (approved for the treatment of pLGG) targets only BRAF V600E mutation. The EU marketing approval was delivered on the benefit/risk assessment of a single arm trial reporting a 67% ORR with a median duration of response of 16.6 months in 77 patients with rr pLGG. A randomized phase III trial of tovorafenib versus chemotherapy is ongoing in newly diagnosed patients.

The JCA defined 8 PICO5s in three populations: population 1 of the full claimed indication,

population 2 of patients >1 year with BRAF V600E mutation (ie the indication of dabrafenib - in PICO 5), population 3 of patients with BRAF fusion, rearrangement or V600 (non E) mutation. Only one of the 8 PICO5s, namely PICO5, had data to study comparative evidence!. Indeed, chemotherapy (mainly off label use of vincristine/carboplatin and vinblastine) has been used for years to treat pLGG patients without information on any biomarker alteration. This explains the lack of data in the now biomarker defined populations of the PICO5s.

The 8 PICO5s correspond to a theoretical definition of what would be ideal regarding assessment of biomarker driven comparative evidence for a pan BRAF inhibitor (which is different for the one already approved for a subset of pLGG). The JCA report suggests then that comparative data for all 8 PICO5s are required to conduct a proper assessment on the comparative evidence regarding Tovorafenib in pLGG. This is not taking into account the situation of therapies for rare or ultra-rare diseases where comprehensive comparative data are not available as they are for adult common diseases. This also raises the question on how this JCA report will be used by the national HTA bodies when making their decision. As well as the ultimate question of accessibility of all children with pLGG in Europe to this EU centrally approved targeted therapy.

This first JCA report calls for an improved assessment of health technologies in rare and ultra-rare diseases, including ATMPs, taking into account the specificities of these diseases and patients' needs.

Gilles Vassal is a paediatrician and pharmacologist, former Professor of Oncology at Paris Saclay University and Gustave Roussy. Founder and former president of the Innovative Therapies for Children and adolescents with Cancer (ITCC), he is currently the Industry strategy lead of this pan European network developing new medicinal products in early phase paediatric cancer trials. Former President of SIOPE, he is currently Board Member, in charge of the Oncopolicy agenda and representing the Society in the EU HTA stakeholder network.

EU HTA in ES-SCLC & Standard of Care in France

SCLC, from orphan disease to hot topic

Nicolas Girard

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Small cell lung cancer (SCLC) is a highly aggressive neuroendocrine carcinoma that accounts for approximately 10–15% of all lung cancer diagnoses worldwide. It is strongly associated with tobacco exposure, with more than 95% of patients having a history of smoking. SCLC is characterized by rapid proliferation, a high metastatic potential, and frequent relapse after initial treatment, resulting in a poor prognosis. In France, SCLC represents nearly 6,000 new cases annually, and approximately two-thirds of patients present with extensive-stage disease (ES-SCLC) at diagnosis. Despite therapeutic advances, the five-year overall survival remains below 10%, highlighting the urgent need for more effective treatment strategies.

For more than three decades, the standard first-line treatment for ES-SCLC consisted of platinum-based chemotherapy, using either cisplatin or carboplatin in combination with etoposide. Although objective response rates range from 60% to 70%, most patients experience disease progression within a few months due to the rapid development of chemoresistance. Consequently, long-term survival has remained disappointingly limited.

The integration of immune checkpoint inhibitors into first-line therapy has significantly changed the therapeutic landscape of ES-SCLC, even if the magnitude of benefit has been regarded as limited by HTAs. The phase III IMpower133 trial demonstrated that the addition of atezolizumab, an anti-programmed death-ligand 1 (PD-L1) monoclonal antibody, to carboplatin and etoposide significantly improved both overall survival (OS) and

progression-free survival (PFS) compared with chemotherapy alone. Similarly, the phase III CASPIAN trial established durvalumab combined with platinum-etoposide as another first-line standard of care, providing a durable survival benefit with an acceptable safety profile.

These landmark studies established chemoimmunotherapy as the new standard treatment for patients with ES-SCLC. The phase III ASTRUM-005 trial evaluated the PD-1 inhibitor serplulimab in combination with carboplatin and etoposide, demonstrating a significant improvement in both OS and PFS compared with chemotherapy alone; this trial was mostly conducted in Asian patients, but surprisingly for the thoracic oncology community, serplulimab was approved and reimbursed in France with a similar assessment than atezolizumab and durvalumab, making a case for subsequent studies. Maintenance strategies have also emerged as promising therapeutic options. The phase III IMforte study investigated maintenance lurbinectedin combined with atezolizumab following induction chemoimmunotherapy and reported clinically meaningful improvements in survival outcomes compared with atezolizumab maintenance alone; the strategy of data readout for this trial may have led to a perception of limited benefit, together with the publication of a press release of the LAGOON trial with lurbinectedin second-line.

In parallel, transforming progress in survival is made with the DeLLphi-304 and DeLLphi-305 phase III trials are evaluating tarlatamab, a first-in-class bispecific T-cell

engager targeting delta-like ligand 3 (DLL3), a protein highly expressed on SCLC cells. These studies are investigating tarlatamab either as monotherapy in second-line or as maintenance after first-line chemoimmunotherapy. Preliminary results suggest major durable antitumor activity and manageable toxicity, positioning DLL3-directed therapies as one of the most promising advances in SCLC treatment. Early access program is now open, one year after the publication of the DeLLphi-304 trial.

New agents assessed through ongoing clinical trials are antibody drug conjugate, and bispecific antibodies. Combination in the first line is the key question for future strategies, with many methodological questions for HTAs to assess the contribution of components while ensuring rapid assessment of the value of these regimens from phase I/II to phase III trials.

Professor Nicolas Girard is Head of the Thorax Institute Curie-Montsouris, Head of Medical Oncology at Institut Curie, Paris, and Professor of Thoracic Oncology and Respiratory Medicine at the UVSQ, Paris Saclay University, France.

Professor Girard is a leading pneumologist specialising in clinical and translational research projects focused on improving the treatment of thoracic cancers such as lung cancer. His expertise ranges from the development of perioperative strategies in resectable tumours, to the management of locally-advanced disease in EGFR-mutant NSCLC, small-cell lung cancer, and lung cancer screening. He is an expert in the management of thymic tumors, authors of the ESMO clinical practice guidelines for these tumors; he authored multiples clinical and preclinical studies on thymomas.

Professor Girard's current research interests include the development of precision medicine and immunotherapy monitoring in lung cancer and other rare thoracic tumours. Furthermore, Professor Girard has co-authored over 400 scientific articles in peer-reviewed journals, specialising within the landscape of thoracic oncology.

EU HTA in SMA & Standard of Care in France

Vincent Laugel

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Spinal muscular atrophy (SMA) is a devastating genetic disorder affecting approximately 1 in 10,000 newborns and historically leading to early death from respiratory failure in most cases. Over the past decade, the therapeutic landscape has been profoundly transformed by the development of several disease-modifying therapies, raising crucial questions about treatment selection, sequencing and access. Systematic newborn screening for SMA, which has been implemented in France since September 2025, represents a major additional step towards earlier diagnosis and treatment, while prompting the medical community to once again reassess therapeutic algorithms and guidelines. Given the rapidly evolving standard of care, the limited availability of direct comparative evidence and the high cost of these therapies, SMA provides a particularly relevant case study in the context of the emerging EU Health Technology

Assessment (HTA) framework and Joint Clinical Assessments (JCA), as exemplified by the very recent JCA for an intrathecal gene therapy.

This session will review the current standard of care for SMA in France, based on evolving national and international consensus, including newborn screening, treatment strategies and multidisciplinary follow-up. It will explore how the EU HTA framework may contribute to more equitable, evidence-based and timely access to innovative therapies in SMA. Particular attention will be paid to the potential challenges and limitations of the PICO approach in SMA, where defining relevant target populations, comparators and clinically meaningful endpoints is particularly complex in a highly dynamic scientific environment and has proven largely influenced by cultural differences in national clinical practices and healthcare systems.

Vincent Laugel is Professor of Paediatric Neurology, Head of the Paediatric Medical and Surgical Department at Strasbourg University Hospital, and Co-Director of the Medical Genetics Laboratory at the Strasbourg Centre for Biomedical Research. His clinical and research activities focus primarily on the development and clinical application of innovative therapies for paediatric neuromuscular diseases. He played a leading role in establishing nationwide newborn screening for spinal muscular atrophy (SMA), which has been implemented in France since 1 September last year. He also coordinates CLEIO, a new national network of academic clinical investigation centres dedicated to advanced therapy medicinal products (ATMPs).

Statements on Published JCA Reports

Tovorafenib/ Ojemda®



European Access Academy®

Tovorafenib: A Glance on One Slide

Indication:

- Monotherapy for the treatment of patients 6 months of age and older with paediatric low-grade glioma (LGG) harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, who have progressed after one or more prior systemic therapies

Guidelines:

- EJC 2024*:
 - Only first line recommendations
 - Mentioning Tovorafenib US approval and EU OD and Firefly 2 planning in 1st line
 - Mentioning targeted treatments for BRAF
- SIOPE 2022**:
 - Only first line recommendations
 - Mentioning targeted treatments for BRAF

Clinical Data:

Firefly 1^{*}:

- P: BRAF altered rr pLGG; fusion: n=101 (74%), rearrangement or fusion: n=14 (10%); V600E mutation: n=22 (16%)
- I: Type II RAF Inhibitor
- C: n/a
- O: efficacy results based on arm 1 (IRC):
 - RANO-HGG: ORR 67%; DOR 16.6m; TTR 3.0m;
 - RAPNO: ORR 51%; DOR 13.8m; TTR 5.3m;
- S: Phase 2; arm 1 (n = 77); arm 2 extension after arm 1 closure (n = 60); data cut-off @ 15 months

EPAR Conclusions:

- Unmet medical need as no authorised treatments in indication
- Positive Benefit Risk Ratio
- Orphan Designation
- Conditional Marketing Authorization: Firefly II RCT data in 1st line expected to provide required additional information

Scoping & HTD Dossier:

- Scoping: 3 Populations/ 8 PICO; 2 addressed by HTD @ 2yr cut-off
- PICO 5: BRAF V600E; pts > 1yr; comparator dabrafenib & trametinib; PAIC: ORR (Odds Ratio 8.23 [1.11; 61.27]); p = 0.040; RANO-LGG; IRC; sensitivity analyses not significant
- PICO 7: BRAF fusion, rearrangement or V600 (non-E) mutation; comparator trametinib; ORR (Odds Ratio 16.01 [6.03; 42.49]); p<0.001; RANO HGG; IRC
- Claiming ORR statistical superiority and commenting on high unmet need

JCA-report; focus PICO 5; in addition, significantly more severe AEs (CTCAE >=3)

PICO 5 unanchored MAIC vs Bouffet⁵; dichotomous outcomes

- 6m PFS (RANO LGG; IRC): RR 1.09 [0.92; 1.30]
- 12m PFS (RANO LGG; IRC): RR 0.92 [0.61; 1.38]
- CR+PR (RANO HGG; INV): OR 0.56 [0.08; 3.84]; p = 0.551
- CR+PR (RANO HGG; IRC): OR 7.26 [0.98; 53.68]; p = 0.052

Cave: Population in Bouffet includes pts with HGG rather than LGG and without prior systemic treatment

PICO 5 unanchored MAIC vs Bouffet⁵; time to event

- 13.67m vs 36.9m; HR 4.8 [2.14; 11.14]; p = 0.011; RMST difference: -6.64 [-13.16; -0.12]; p = 0.046

PICO 7 not considered due to insufficient evidence

* <https://www.ejc.com/section/show?doi=10.1016/j.ejca.2024.02.002>; ** <https://siope.eu/media/documents/esp-low-grade-glioma-lgg.pdf>; <https://doi.org/10.1038/s41591-023-02668-y>; <https://www.nejm.org/doi/full/10.1056/NEJMoa2303815>; AE: Adverse Event; BRAF: V-Raf Murine sarcoma Viral Oncogene Homolog 1 encoding rapidly accelerated fibrosarcoma protein; cR: complete response; cR+PR: common criteria for Adverse events; DOR: duration of Response; EJC: European Journal of Cancer; HGG: High Grade Glioma, HR: Hazard Ratio; HTD: Health Technology Developer; INV: investigator assessed; IRC: independent review committee; (p)LGG: (paediatric) Low Grade Glioma, m: months; MAIC: Matching-adjusted indirect comparison; OD: Orphan Designation; ORR: Objective Response Rate; PAIC: Predictive-adjusted indirect comparison; PFS: progression-free survival; PICO: Population/ Intervention/ Comparator/ Outcomes; PR: partial response; pts: patients; RAF: rapidly accelerated fibrosarcoma kinases; RANO: Response Assessment in Neuro-Oncology; RAPNO: Response Assessment in Neuro-Oncology; RCT: Randomised Controlled Trial, rr: relapsed or refractory; RMST: Restricted Mean Survival Time, RR: Relative Risk, SIOPE: European Society for Paediatric Oncology, TTR: Time to Response, yr: year



European Access Academy®

Tovorafenib: Topline Comments

- Medical Condition with a high unmet medical need
- Limited evidence base in BRAF-altered relapsed/refractory (R/R) pLGG
- No specifically licensed comparator treatments available, therefore patients are currently treated with individualised treatment
- Firefly 1, best available evidence for Tovorafenib is based on a single-arm trial
- Firefly 2, an RCT versus current standard of care chemotherapy in first line LGG patients is currently ongoing
- Due to the limited evidence-base determination of relative effectiveness harbours a particularly high risk of bias in both directions:
 - Type 1 error: falsely assuming an additional benefit
 - Type 2 error: falsely not offering a potentially beneficial medicine to those severely affected children and adolescents
- Only one parent carer and one clinical expert were included – without any records on how or even if input was considered, i.e. limited expert involvement, which is one of the most critical factors for a successful implementation of the regulation

Lurbinectedin/ Zepzelca®



Lurbinectedin[§]: A Glance on One Slide

Indication:

- In combination with atezolizumab for the maintenance treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide.

Guidelines:

- ESMO 2021*: (ES-SCLC i.e. stage IV or stage III SCLC not eligible for treatment of curative intent)
 - ✓ PS 0-1; No CI for IO: Carboplatin/ Etoposide/ Atezolizumab and maintenance Atezolizumab; Platinum/ Etoposide/ Durvalumab and maintenance Durvalumab
 - ✓ PS 0-1; CI for IO: Carboplatin/ Etoposide; Carboplatin/ Topotecan; Cisplatin/ Irinotecan
 - ✓ PS ≥ 2 due to SCLC: Carboplatin/ Etoposide; Carboplatin/ Gemcitabine
 - ✓ PS ≥ 2 due to comorbidities: Best Supportive Care

Clinical Data:

RCT IMforte^{††}:

- P: ≥ 18 years; treatment-naïve ES-SCLC; no progression following induction with Carboplatin/ Etoposide/ Atezolizumab
- I: Alkylating agent inhibiting various components of SCLC pathology; i.v. maintenance treatment with Lurbinectedin/ Atezolizumab every 3 wk
- C: i.v. maintenance treatment with Atezolizumab every 3 wk
- O: IRF-assessed PFS and OS (13.2 vs 10.6 months; HR 0.73 [0.57; 0.95])
- S: Randomised (randomisation occurred after completing induction treatment; eligible patients did not have progression), Open Label; Phase 3; n = 242: Lurbinectedin/ Atezolizumab; n = 241: Atezolizumab

EPAR Balance of Benefits and Risks[†]:

- Condition characterized by poor prognosis
- Orphan Designation
- Limited but clinically relevant OS gain: 2.8 months median OS gain (13.24 vs 10.64 months; HR 0.73 [95% CI: 0.57, 0.95], p = 0.0174)
- Positive Benefit Risk Ratio; safety profile more burdensome, but benefits outweigh risk

Scoping & HTD Dossier:

- Scoping: 1 Population; 1 PICO; Population similar to indication; Comparator: Atezolizumab monotherapy
- Requested subgroup analysis: PCI yes/ no; brain metastases yes/ no
- Provided data to support the PICO: RCT IMforte (data cut: July 29th, 2024)**
- OS outcomes 13.24 vs 10.65 m OS (HR 0.73 [0.57; 0.95]) supported by 3 supplementary analyses investigating how OS results might have been impacted if NPT was not available
- IRF – assessed PFS outcomes 5.36 vs 2.14 m PFS (HR 0.54 [0.44; 0.67]) supported by supplementary and sensitivity analysis with different censoring regimens
- INV – assessed PFS outcomes 5.36 vs 2.73 m PFS (HR 0.55 [0.45; 0.68]) supported by supplementary and sensitivity analysis with different censoring regimens

JCA: Case number JCA-MP-2024-16

- Leveraging second data cut (Feb 12th, 2025) for the assessment
- Criticizing that formal hypothesis testing is not conducted at last prespecified data cut off
- Commenting on mismatch of indication and IMforte study population (IMforte excluding ECOG ≥ 2 and patients with CNS metastases at baseline)
- OS outcomes 13.90 vs 11.14 m OS (HR 0.81 [0.65; 1.01])
- INV – assessed PFS outcomes 5.55 vs 2.73 m PFS (HR 0.56 [0.46; 0.69])
- Disadvantages for EORTC QLQ C30 & LC13 scales on physical & role functioning; nausea and vomiting
- Disadvantages for severe AE (CTCAE > 3), serious AU, and treatment interruptions due to AE

§ Zepzelca®: Marketing Authorization Holder: PharmaMar; * [https://www.esmoopen.org/article/S0959-2688\(21\)00113-3/fulltext](https://www.esmoopen.org/article/S0959-2688(21)00113-3/fulltext); ** [https://www.thelancet.com/journal/2024/article/S0140-6736\(25\)01011-1/abstract](https://www.thelancet.com/journal/2024/article/S0140-6736(25)01011-1/abstract); + https://www.ema.europa.eu/en/documents/assessment-report/zepzelca-soma-public-assessment-report_en.pdf; AE: Adverse Event; CI: Contraindication; EPAR: European Product Assessment Report; ES-SCLC: Extensive Stage Small Cell Lung Cancer; HR: Hazard Ratio; HTD: Health Technology Developer; INV: Investigator; IO: Immunotherapy; IRF: Independent review facility; i.v.: intravenous; NPT: Non-protocol anti-cancer therapy; OD: Orphan Designation; OS: Overall survival; PCI: prophylactic cranial irradiation; PFS: Progression-free survival; PS: Performance Status; SCLC: Small Cell Lung Cancer; wk: week



Lurbinectedin: Topline Comments

- According to the HTD the Value Proposition of Lurbinectedin in ES-SCLC is based on a significant and clinically meaningful median OS gain of 2.6 months (13.2 vs 10.6 months) and an IRF-assessed PFS gain of 3.2 months (5.36 vs 2.14 months).
- While the EPAR, the Lancet publication, and the HTD dossier are primarily based on the data cut-off July 29th, 2024, the JCA is leveraging the data cut-off Feb 12th, 2025. Results across the two data cuts are rather consistent. However, in the later data cut the OS gain is not significant, increasing the risk of a type 2 error (type 1, resp.) in the later (earlier, resp.) data cut
 - Data Cut July 29th, 2024: OS: HR 0.73 [0.57; 0.95]; p = 0.0174**
 - Data Cut Feb 12th, 2025: OS: HR 0.81 [0.65; 1.01]; p = 0.0605**
- Despite the exploratory nature of the later data cut, the assessors comment that formal hypothesis testing is not conducted on the later data cut. 'Hypothesis testing columns' (NP, not prespecified; NO, nominal p-value; etc) are introduced.
- Only one carer and one clinical expert were included – without any records on how or even if input was considered, i.e. there is limited expert involvement, which is one of the most critical factors for a successful implementation of the regulation and mandated by the three pillars of evidence-based medicine.

Tarlatamab/ Imdylltra®



Tarlatamab[§]: A Glance on One Slide

Indication:

- Monotherapy for the treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC), who require systemic therapy following disease progression on or after first-line treatment with platinum-based chemotherapy

Guidelines:

- ESMO 2021*: (recurrent SCLC i.e. second-line therapy and beyond)
 - Platinum-resistant relapse (< 3 months TFI)
 - refractory and/or PS >2: BSC; Lurbinectedin
 - PS 0-2: Topotecan; Cyclophosphamide – Doxorubicin - Vincristine; Lurbinectedin
 - Platinum-sensitive relapse (≥ 3 months TFI): rechallenge with Platin - Etoposide; Topotecan; Cyclophosphamide – Doxorubicin - Vincristine

Clinical Data:

RCT DeLLphi-304**:

- P: patients with small-cell lung cancer whose disease had progressed during or after platinum-based chemotherapy
- I: bispecific delta-like ligand 3–directed T-cell engager immunotherapy
- C: chemotherapy (topotecan, lurbinectedin, or amrubicin)
- O: OS (HR=0.60; 95% CI: 0.47, 0.77; p-value <0.001); INV-assessed PFS; PROs
- S: Phase 3; Open Label; n = 254: Tarlatamab; n = 255: Chemotherapy

EPAR Balance of Benefits and Risks*:

- Patient Population with limited treatment options and short life-expectancy
- Orphan Designation
- Preplanned interim analysis sufficiently mature to consider clinically relevant OS Benefit (HR=0.599; 95% CI: 0.468, 0.768; p-value <0.001).
- Positive Benefit Risk Ratio irrespective of DDL3 expression
- Risks (incl CRS and ICANS) are clinically significant but overall manageable

Scoping & HTD Dossier:

- Scoping: 4 Populations (a-d); 7 PICO schemes
 - Platinum-resistant relapse (< 3 months TFI)
 - C: Topotecan; Evidence direct; OS: HR 0.49 [0.34; 0.70]
 - C: CAV; Evidence indirect (MAIC); OS: HR 0.48 [0.32; 0.70]
 - Platinum-sensitive relapse (≥ 3 months TFI):
 - C: rechallenge platinum-based chemotherapy; Evidence indirect (NMA); OS: HR 0.56 [0.37; 0.86]
 - C: Topotecan; Evidence direct; OS: HR 0.59 [0.40; 0.87]
 - C: CAV; Evidence indirect (NMA); OS: HR 0.61 [0.38; 0.99]
 - Not suitable for retreatment with platinum-based chemotherapy; RFI ≤ 6 months
 - Topotecan or CAV; evidence direct; OS: HR 0.56 [0.42; 0.75]
 - Suitable for retreatment with platinum-based chemotherapy; RFI > 6 months
 - Cisplatin-etoposide or carboplatin-etoposide; evidence descriptive; OS: HR na
- Based on totality of evidence, HTD is claiming superior OS benefit, improved PROs and superior safety profile vs. the respective comparators

JCA: Case number JCA-MP-2024-17

- Data for all 7 PICO schemes that were provided by the HTD were included in the JCA report
- PICOs 1,4,6 were answered by DeLLphi-304 trial; PICOs 2,3,5,7 were informed by external evidence (3 RCTs); for DeLLphi-304 data cut-off Jan 29th, 2025, was leveraged
 - Platinum-resistant relapse (< 3 months TFI)
 - OS: 11.1 vs 5.8m; HR 0.491 [0.332; 0.727]; p < 0.001
 - OS: [adjusted base case]: HR 0.48 [0.32; 0.70]; p < 0.001
 - Platinum-sensitive relapse (≥ 3 months TFI):
 - OS vs topotecan: HR 0.63 [0.41; 0.95]; vs carboplatin – etoposide: HR 0.61 [0.39; 0.95]
 - OS: HR 0.628 [0.415; 0.951]
 - OS vs topotecan: HR 0.63 [0.41; 0.95]; vs CAV: HR 0.65 [0.40; 1.08]
 - Not suitable for retreatment with platinum-based chemotherapy; RFI ≤ 6 months
 - OS: HR 0.578 [0.426; 0.786]
 - Suitable for retreatment with platinum-based chemotherapy; RFI > 6 months
 - No results reported for OS

§ Imdylltra®: Marketing Authorization Holder: Amgen; * [https://www.esmoopen.org/article/S0959-6526\(21\)01113-3/fulltext](https://www.esmoopen.org/article/S0959-6526(21)01113-3/fulltext); ** DOI: 10.1056/NEJMoa2502099; + https://www.ema.europa.eu/en/documents/assessment-report/zenzelen-epar-public-assessment-report_en.pdf; BSC: Best Supportive Care; C: Comparator; CAV: Cyclophosphamide, doxorubicin, and vincristine; CFI: Chemotherapy-free interval; CI: Contraindication; CRS: Cytokine Release Syndrome; DDL3: Delta-like ligand; EPAR: European Product Assessment Report; ES-SCLC: Extensive Stage Small Cell Lung Cancer; HR: Hazard Ratio; HTD: Health Technology Developer; INV: Investigator; ICAN: Immune effector cell-associated neurotoxicity syndrome; IRF: Independent review facility; i.v.: intravenous; MAIC: Matching-adjusted indirect comparison; na: not applicable; NMA: Network Meta-analysis; NPT: Non-protocol anti-cancer therapy; OD: Orphan Designation; OS: Overall survival; PCI: prophylactic cranial irradiation; PFS: Progression-free survival; PRO: Patient Reported Outcomes; PS: Performance Status; RFI: recurrence-free interval; SCLC: Small Cell Lung Cancer; TFI: treatment failure interval



Tarlatamab: Topline Comments

- HTD is claiming superiority vs comparator on various dimensions: OS, PROs, and safety
- EMA is suggesting positive benefit / risk ratio; Risk Management Plan to include education on CRS and ICANS
- Scoping comments:
 - Real world relevance of 7 PICO in such last line treatment situation should be revisited
 - It is challenging to single out individual comparators from a multi-comparator trial (n = 185 (73%): topotecan, n=47 (18%); lurbinectedin, 23 (9%); amrubicin) into different PICOs (and request hypothesis testing - see respective column e.g., table 6 of summary report)
 - Populations A & B follow ESMO Guideline; rationale for populations C & D (reason for 6 months cut-off) is unclear. Overlap across the various populations is challenging
- The comprehensive data set including direct and indirect comparisons submitted by the HTD is included in the JCA; ITCs were largely reported.
- JCA with consistent and strong advantage across various PICO schemes and outcome domains:
 - Positive OS outcomes in 5 out of 7 PICOs
 - Positive morbidity outcomes in 2 out of 7 PICOs
 - Positive PRO outcomes in 3 out of 7 PICOs
 - Positive Safety outcomes in 3 out of 7 PICOs
- As a side note: it is of interest that ESMO guidelines already recommend Lurbinectedin 2nd line without a respective authorisation in this indication but don't comment on the current approval in 1st line ES SCLC
- The assessors comment on a lack of information on subsequent therapies resulting in uncertainty; considering the very limited life-expectancy and the lack of therapies in this advanced conditions, the clinical relevance of this recommendation is questionable
- Only two carers and two clinical experts were included – without any records on how or even if input was considered, i.e. there is limited expert involvement, which is one of the most critical factors for a successful implementation of the regulation and mandated by the three pillars of evidence-based medicine.

Contributors

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