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Relevance of using international real-world data in regulatory and HTA decision making

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Washington DC

Ashley Jaksa, MPH
Scientific Partnerships Lead
Aetion

Rami Ben-Joseph, PhD
Head, Big Data Real World Evidence
BD-RWE
Jazz Pharmaceuticals

Kelvin Chan, MD, MSc, PhD
Oncologist at Sunnybrook Odette
Cancer Center and Associate Professor
at University of Toronto

Pall Jonsson, PhD
Programme Director
Data and RWE National Institute
for Health and Care Excellence

Our session

MODERATED BY

Ashley Jaksa, MPH
Scientific Partnerships Lead
Aetion

OUR PANELISTS

Rami Ben-Joseph, PhD
Head, Big Data Real World Evidence BD-RWE
Jazz Pharmaceuticals

Kelvin Chan, MD, MSc, PhD
Oncologist
Sunnybrook Odette Cancer Center
Associate Professor
University of Toronto

Pall Jonsson, PhD
Programme Director, Data and RWE
National Institute for Health and Care Excellence

Disclosures

Ashley Jaksa: employee at Aetion, Inc.

Rami Ben-Joseph: employee at Jazz Pharmaceuticals

Kelvin Chan: self-employed, affiliated with the University of Toronto

Pall Jonsson: employee at National Institute for Health and Care Excellence

Overview of global RWD access challenges and stakeholder guidance on use of international data

Ashley Jaksa
Scientific Partnerships Lead,
Aetion

Stakeholders agree that RWD must be fit-for-purpose: reliable and relevant

Table 1. Real-world evidence recommendations and gaps within building blocks (cont.).

Building block	Recommendation	Authors that agree	Gaps in recommendations	Ref.
Data source: fit-for-purpose	Duke-Margolis states that **elements of a fit-for-purpose dataset** include: • data relevancy, including the availability of key data elements (i.e., exposure, outcomes and covariates), ability for patient-level linking, representativeness, sufficient subjects, and longitudinally; and • data reliability, including accuracy, validity, conformance, plausibility, completeness, data provenance, and transparency in data processing	**FDA** generally agrees, but its recommendation omits the following components: sufficient subjects, longitudinally, and validity and plausibility of key data elements. **EMA** generally agrees, but its recommendation omits covariate availability, conformance and plausibility **CADTH/Health Canada** generally agrees, but its recommendation omits conformance and plausibility **Hall *et al.*** generally agrees but lacks discussion on data provenance **IQWiG** generally agrees, but its recommendations don't include the need for sufficient subjects, and, while implied, don't specifically require accuracy of outcomes and exposure IQWiG also omits conformance and plausibility	Recommendations are high-level and lack criteria on how to operationalize and meeting each element and minimum criteria	[12,20,37, 42,44,45]

Source: Jaksa et al. 2021. Organized structure of real-world evidence best practices: moving from fragmented recommendations to comprehensive guidance. JCER.

Data fit-for-purpose (FFP)

For RWD to be FFP, must be both reliable and relevant

Data reliability

Accuracy (*of data attributes*)

- Validity
- Conformance
- Plausibility
- Consistency

Completeness

Provenance

Transparency of data processing

Data relevancy

Availability of key data elements (*of variables*)

- Exposure
- Outcome
- Covariate
- Patient-level linking *(if applicable)*

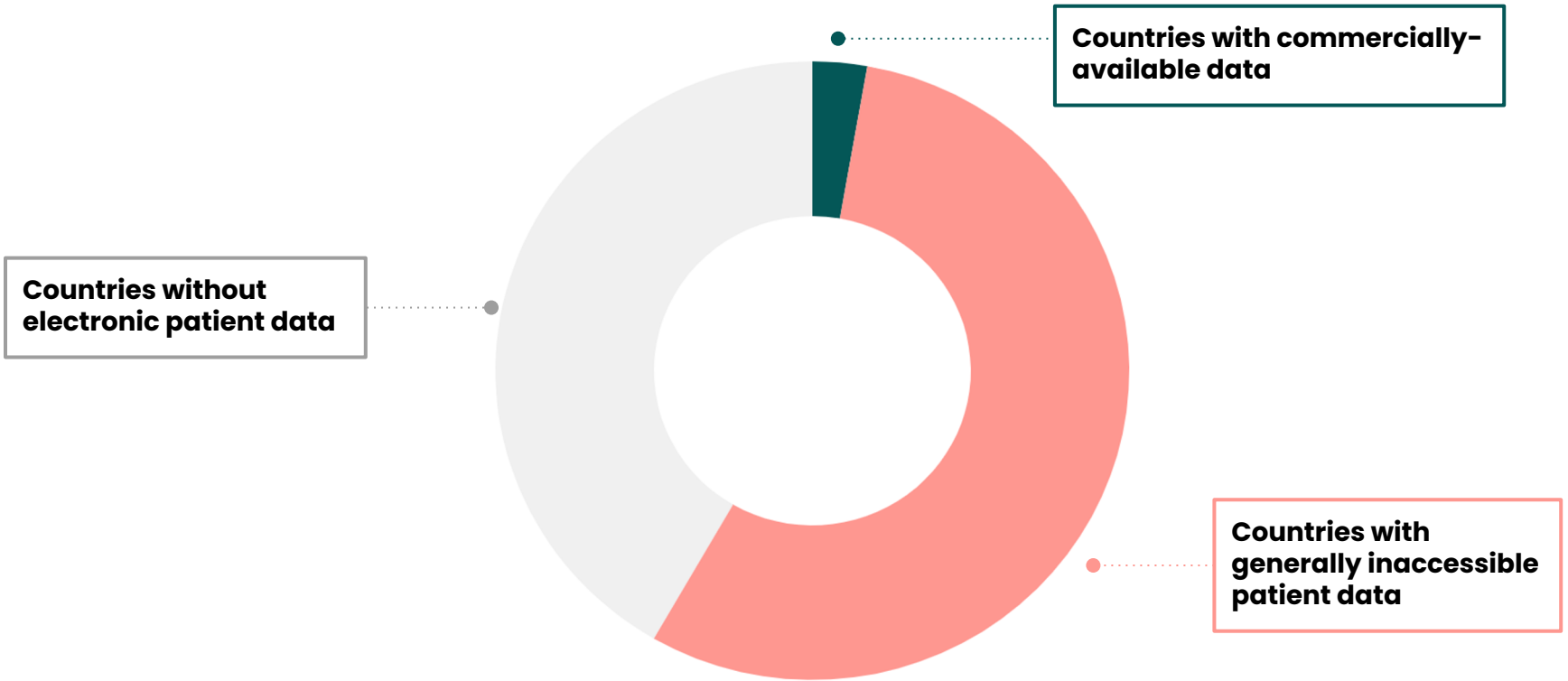
Representativeness

Sufficient subjects

Longitudinality

Sources:
1. Characterizing RWD Quality and Relevancy for Regulatory Purposes white paper. Duke Margolis Center for Health Policy. October 2018.
2. Determining Real-World Data's Fitness for Use and the Role of Reliability white paper. Duke Margolis Center for Health Policy. September 2019.

RWD access is challenging, especially outside the US



Recent guidance on use of international data

Stakeholder	Guidance document	Explicitly mentions international RWD	Recommendation
IQWiG Germany 2020	Routine practice data for the benefit assessment of drugs	Yes	"analyses that use data generated outside of the German healthcare context of interest **must justify** that these **data can be classified as routine practice data in terms of health care in Germany** or that deviations are not relevant for the effect estimate."
FDA US 2021	Assessing EHR and claims for regulatory decision-making	Yes	For non-U.S. data sources, FDA recommends providing an **explanation of how the healthcare system and prescribing and use practices might affect the generalizability** of the study results to the U.S. population
HAS France 2021	Real-world studies for the assessment of medicinal products and medical devices	Yes	"**document the representativeness of centers, investigators, and patients**" and "to support representativeness, compare the characteristics of participating centres with non-participating, and patients included with those not included"
MHRA UK 2021	The use of real-world data in clinical studies to support regulatory decisions	No	MHRA does note that the RWD population must be **"representative"** of the population of interest.
NICE UK 2022	NICE's RWE Framework	Yes	"International data is likely to be of particular value when an intervention has been available in another country before becoming available in the UK or in the context of rare diseases." "**Consideration needs to be given as to how any differences in the treatment pathways or care settings** seen in the analytical sample and the NHS **may impact on the relevance of results**. This is especially important when using international data."

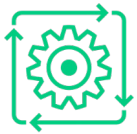
There is consensus on the need for “representativeness”

However, how to operationally define “representativeness” is lacking

KEY THEMES

RWD must be representative (patients, treatment pathways, health care system, prescribing practices)

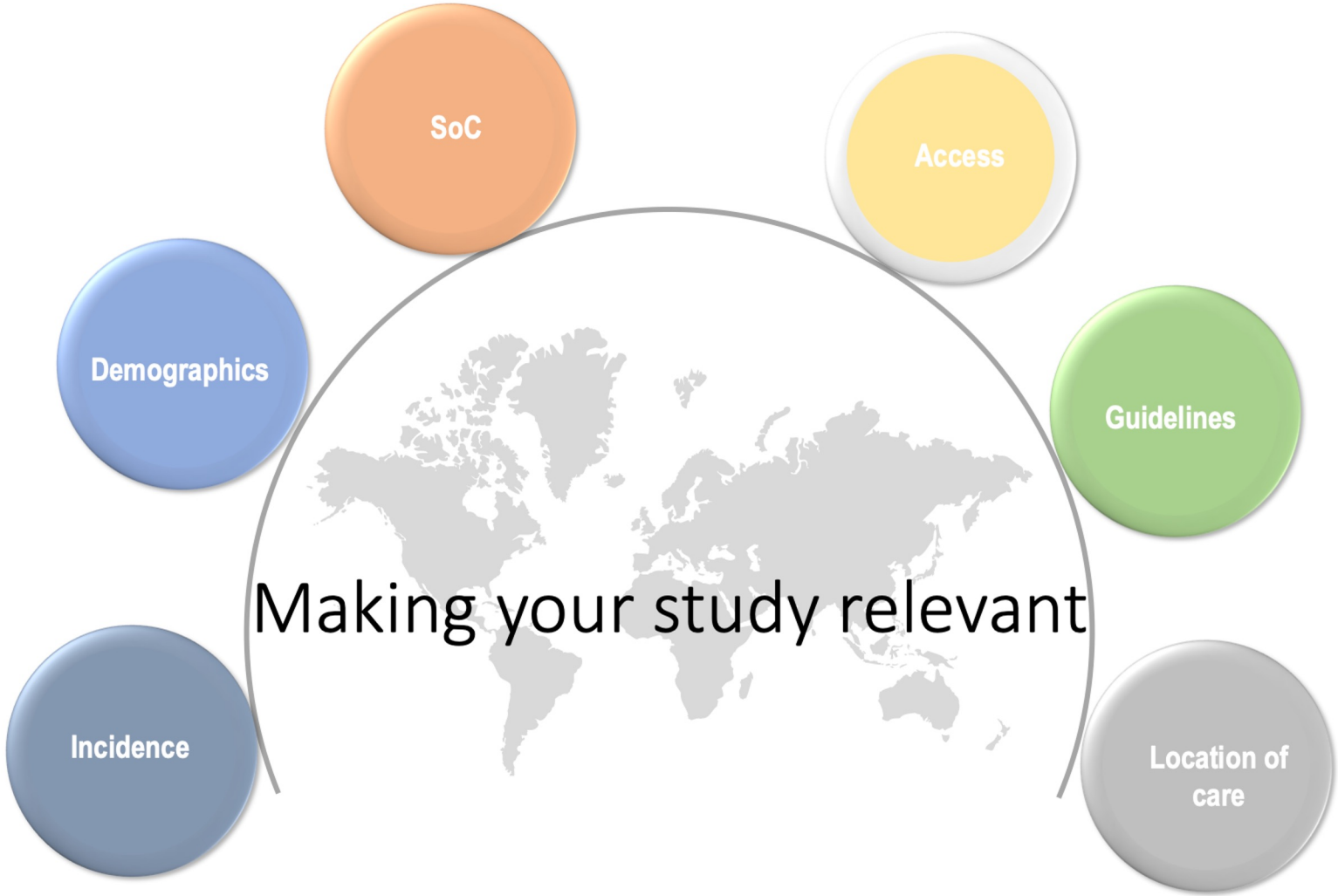
Justify use of international RWD



Evaluate how country differences can impact results

UNANSWERED QUESTIONS

- Vague in how to determine representativeness. What does good look like?
- Does type of study matter (e.g., comparative effectiveness vs. natural history of disease)?
- Can types of RWD sources differ in representativeness? (e.g., claims vs. registry)


SoC
Access
Demographics
Guidelines
Making your study relevant
Incidence
Location of care

Using International Real-World Data in HTA Decision Making

Páll Jónsson

Programme Director
Data and Real World Evidence

NICE National Institute for Health and Care Excellence

NICE's guiding principles for evidence

3.2 Guiding principles for evidence

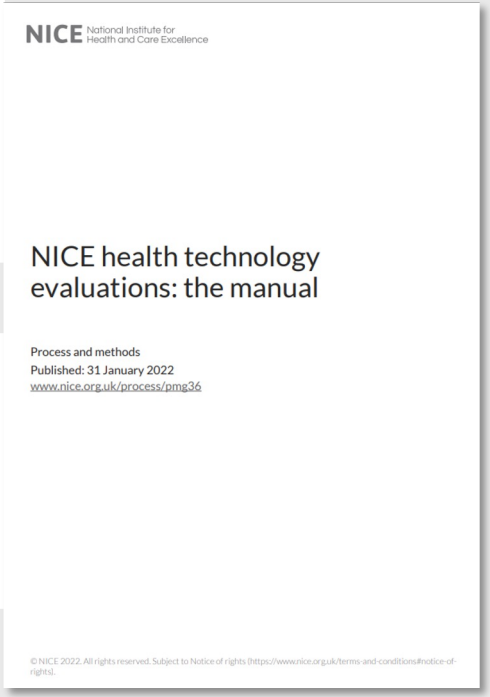
3.2.1 The evidence considered by the committee should be:

- Relevant to the evaluation in terms of patient groups, comparators, perspective, outcomes and resource use as defined in the scope. It should include transparent reporting of data, study design, analysis, and results.

3.3 Types of evidence

3.3.1 NICE considers all types of evidence in its evaluations. This includes evidence from published and unpublished data, data from non-UK sources, databases of ongoing clinical trials, end-to-end studies, conference proceedings, and data from registries, real-world evidence and other observational sources.

NICE



* NICE health technology evaluations: the manual. www.nice.org.uk/process/pmg36

HTAs ask a range of questions: data needs reflect this

Data needs (example research questions)	• Characterising care pathways and treatment patterns • Characterising natural history and event rates • Capture patient outcomes and experiences • Design, populate and validate economic models • Identify and characterise health inequalities • Determine impact of interventions on service delivery and decisions about care	Establish effectiveness and comparative effectiveness of interventions
What does NICE say?*	"Real-world data, if representative of the target population and of sufficient quality, is the most appropriate source of evidence for most of these use cases"	"Randomised controlled trials are the preferred source of evidence on the effectiveness of interventions"

Decision making

Internal validity  External validity

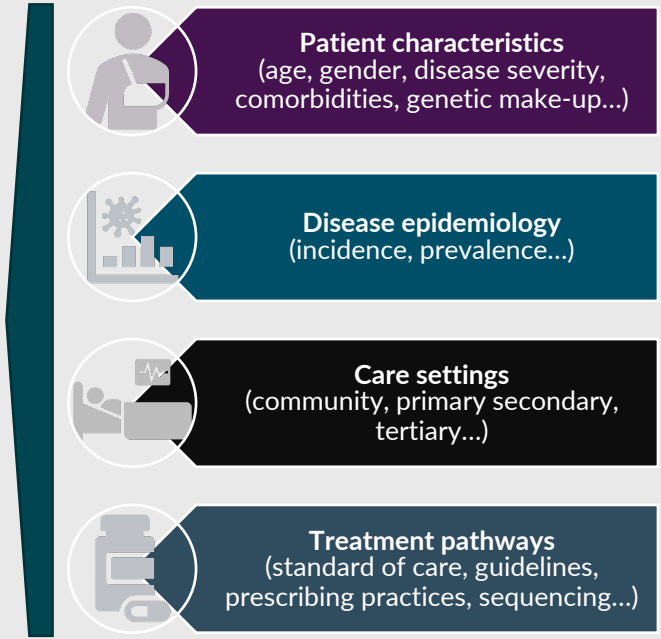
NICE

* NICE's RWE Framework (draft) https://www.nice.org.uk/about/what-we-do/real-world-evidence-framework-feedback

Generalisability to local patient population is important to HTAs and payers…

"External validity is assessed according to the generalisability of the trial evidence, that is, whether the results apply to wider patient groups and to routine clinical practice."*

What is important is very dependent on context, but may include:



NICE

* NICE health technology evaluations: the manual. www.nice.org.uk/process/pmg36

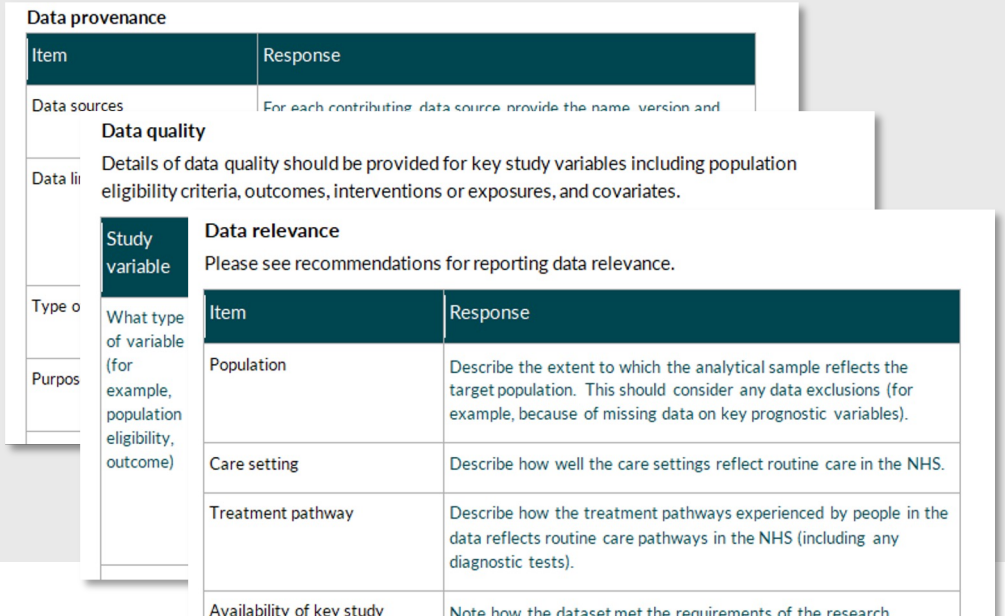
…but data quality and provenance is also important

Transparent reporting: essential to ensure trust in the data source and understand its fitness-for-purpose to address the research question

Data provenance: Reporting on data sources should cover the characteristics of the data, data collection, coverage and governance

NICE's Data Suitability Assessment Tool*

Describes the information needed to assess **data provenance** and its **quality** and **relevance** for addressing specific research questions



Data provenance

Item	Response
Data sources	For each contributing data source provide the name, version and
Data li	
Type o	
Purpos	

Data quality

Details of data quality should be provided for key study variables including population eligibility criteria, outcomes, interventions or exposures, and covariates.

Study variable	Item	Response
What type of variable (for example, population eligibility, outcome)	Population	Describe the extent to which the analytical sample reflects the target population. This should consider any data exclusions (for example, because of missing data on key prognostic variables).
	Care setting	Describe how well the care settings reflect routine care in the NHS.
	Treatment pathway	Describe how the treatment pathways experienced by people in the data reflects routine care pathways in the NHS (including any diagnostic tests).
	Availability of key study	Note how the dataset met the requirements of the research

Data relevance

Please see recommendations for reporting data relevance.

*NICE's RWE Framework (draft) https://www.nice.org.uk/about/what-we-do/real-world-evidence-framework-feedback

NICE

Examples of European initiatives to improve access, data quality and transparency of analysis

EHDEN
EUROPEAN HEALTH DATA & EVIDENCE NETWORK

Becoming the
trusted open science community
built with standardised health data
via a European federated network

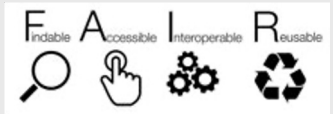
Federated network of health data, standardised to OMOP common data model

Emphasis on standardised analytics, transparency and reproducibility

DARWIN EU

Federated data network, delivering RWE from across Europe and diseases, population and performance of medicines

NICE



Case example: Overseas RWE in NICE guidance

No defined treatment pathway specific to METex14 skipping NSCLC because there are no treatments available in the UK.

Study locations Europe (51%), North America (26%) and Asia (23%). No UK centres

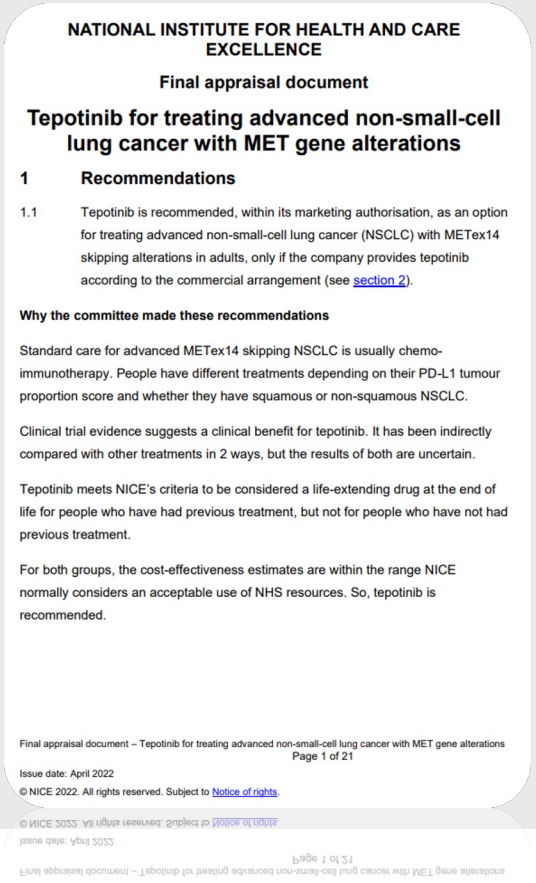
The main evidence for tepotinib came from VISION, a single-arm, open-label, phase 2 trial including people with advanced (locally advanced or metastatic) NSCLC with METex14 skipping alterations or MET amplification.

An indirect comparison was needed, and the company used a real-world cohort from patient-level data specifically for NSCLC with this genetic biomarker.

"The committee agreed that the results of the indirect treatment comparisons were inconsistent and counter to expectations, with chemotherapy sometimes appearing to be more effective than immunotherapy. This could be partially explained by a lack of generalisability to the UK population, because of the mix of comparator treatments and because people in VISION and from the matched comparator cohort were fitter than would be seen in UK clinical practice."

However:

"The committee concluded that the results of the company's original indirect treatment comparisons were highly uncertain but should be taken into account in its decision making."



NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Tepotinib for treating advanced non-small-cell lung cancer with MET gene alterations

1 Recommendations

1.1 Tepotinib is recommended, within its marketing authorisation, as an option for treating advanced non-small-cell lung cancer (NSCLC) with METex14 skipping alterations in adults, only if the company provides tepotinib according to the commercial arrangement (see section 2).

Why the committee made these recommendations

Standard care for advanced METex14 skipping NSCLC is usually chemo-immunotherapy. People have different treatments depending on their PD-L1 tumour proportion score and whether they have squamous or non-squamous NSCLC.

Clinical trial evidence suggests a clinical benefit for tepotinib. It has been indirectly compared with other treatments in 2 ways, but the results of both are uncertain.

Tepotinib meets NICE's criteria to be considered a life-extending drug at the end of life for people who have had previous treatment, but not for people who have not had previous treatment.

For both groups, the cost-effectiveness estimates are within the range NICE normally considers an acceptable use of NHS resources. So, tepotinib is recommended.

Issue date: April 2022

Other examples: International data informing NICE guidance

TA691

Avelumab for untreated metastatic Merkel cell carcinoma

HST12

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2

TA589

Blinatumomab for treating acute lymphoblastic leukaemia in remission with minimal residual disease activity

TA491

Ibrutinib for treating Waldenstrom's macroglobulinaemia

NICE

Concluding remarks

HTA's will likely see more international RWD in the future

Limited number of guidance using international data available to date – but useful learnings should be captured

Guidance is needed on what constitutes minimum relevance/quality. Is there an opportunity to develop a 'risk-based' framework? One that sets out minimum requirements according to the role of the evidence in decision making.

However, it is difficult to define a universal minimum standard that applies across jurisdictions.

Or do we need transparency requirements rather than minimum standards?

Standardisation of data collection and analysis can help

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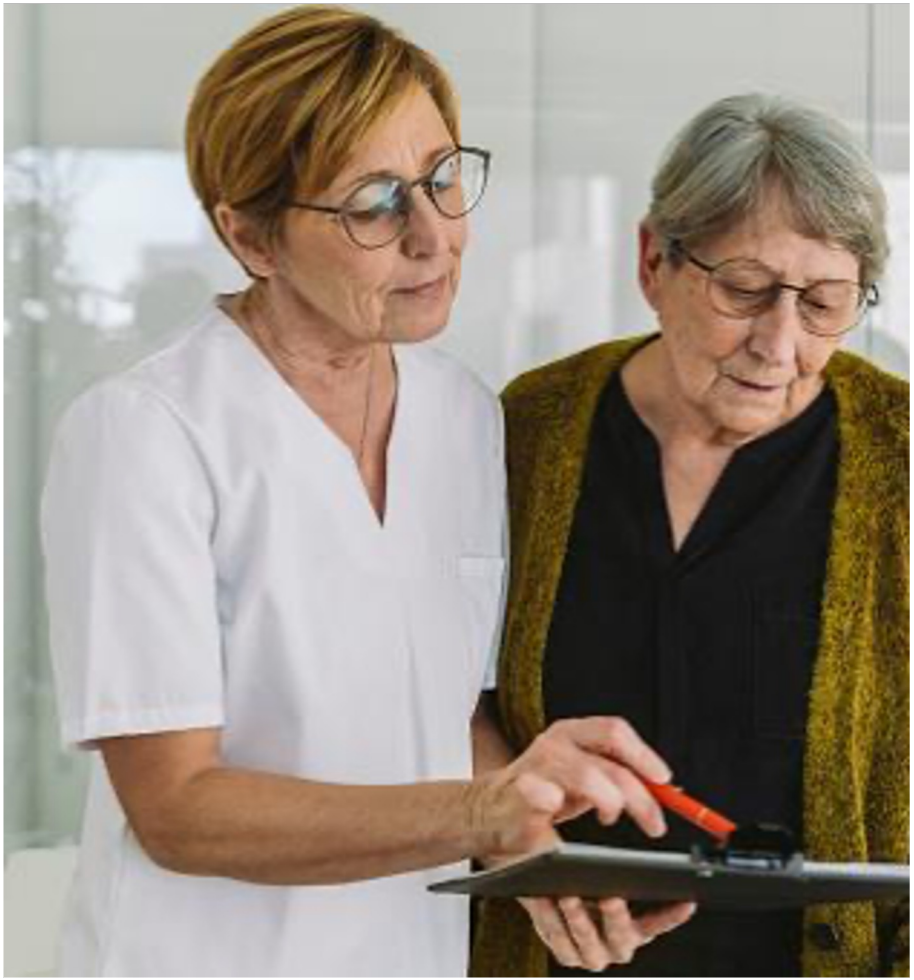

Q&A

Thank you for joining.

Questions? Contact Ashley Jaksa.
ashley.jaksa@aetion.com

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