The good, the bad, and the uncertain: An analysis of regulated medicines information for cancer patients

Dr Courtney Davis, Health Action International

Presentation to Joint PCWP-HCPWP Meeting

Amsterdam, 19th September 2023

Acknowledgements

Funding

hai EUROPE

UKRI Economic and Social Research Council

Research team

Anita K. Wagner
Harvard Medical School

Maximilian Salcher-Konrad
LSE

Henry Scowcroft
Alzheimer's Research UK

Adrian Pokorny
University of Sydney

Barbara Mintzes
University of Sydney

Huseyin Naci
LSE

Patients' and consumers' information needs

Patients value high-quality written information from trustworthy and reliable sources

Written information about drug *benefits* as well as harms, and important *uncertainties* and *knowledge gaps*[a]

Numerous regulatory consultations between EMA and its network of patient & consumer representatives confirm that:

"benefits and risks must always be communicated together"[b]

[a]Coulter et al., 1999; Coulter et al, 2006; Grime et al., 2007; Raynor et al., 2007; Autorité de Santé, 2008; Hamrosi et al., 2013; van Dijk et al., 2014; European Patients Forum, 2017; Schneider et al. 2021; Treadgold et al., 2022

[b] EMA 'Information on the Benefit-Risk of Medicines: Patients' and Consumers' and Healthcare Professionals' Expectations', 2009

Challenges in cancer care

Many new cancer drugs approved on limited evidence (short, single arm trials; lacking information about the outcomes most important to patients)

Patients must balance toxicity of treatment against sometimes marginal, or unclear benefits[a]

Extensive evidence that patients with cancer may *overestimate* drug benefits and misunderstand the intent of treatment

Amongst 1193 patients with metastatic lung or colorectal cancer, around 70% and 80% mistakenly believed chemotherapy might cure the cancer[b]

[a] Davis et al. *BMJ 2017;359:j4530;* Salcher-Konrad et al., Millbank Quarterly, 2020;98(4):1219-56

[b] Weeks et al., NEJM 2012; 367(17):1616-1625

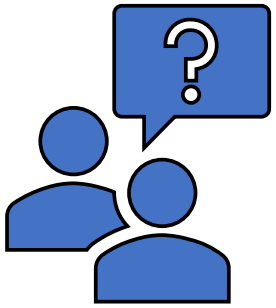
Policy context – opportunities for tackling misperceptions and communicating accurate information on drug benefits

- Regulated product information:
  - Summary of Product Characteristics (SmPC) for healthcare professionals
  - Package Leaflet for patients

- Current EU legislation does not *require,* but *permits* inclusion of benefit information in statutory patient package leaflets (Article 62 of Council Directive 2001/83/EC)

- EPAR summaries for the public (‘Medicines Overviews’)
- Written by EMA medical writers and includes a section on the benefits shown in clinical studies.

Does regulated medicines information in the EU meet patients' information needs?



- Evaluated frequency with which relevant and accurate information about *drug benefits*, and related uncertainties, was communicated to patients, consumers and clinicians
- 29 anticancer drugs for 32 indications receiving first marketing authorisation by EMA 2017-2019
- Compared information across the following key sources (116 documents):

EPAR

Summary of Product Characteristics

Package Leaflet

Public Summary ('Medicines Overview')

Product information

Findings

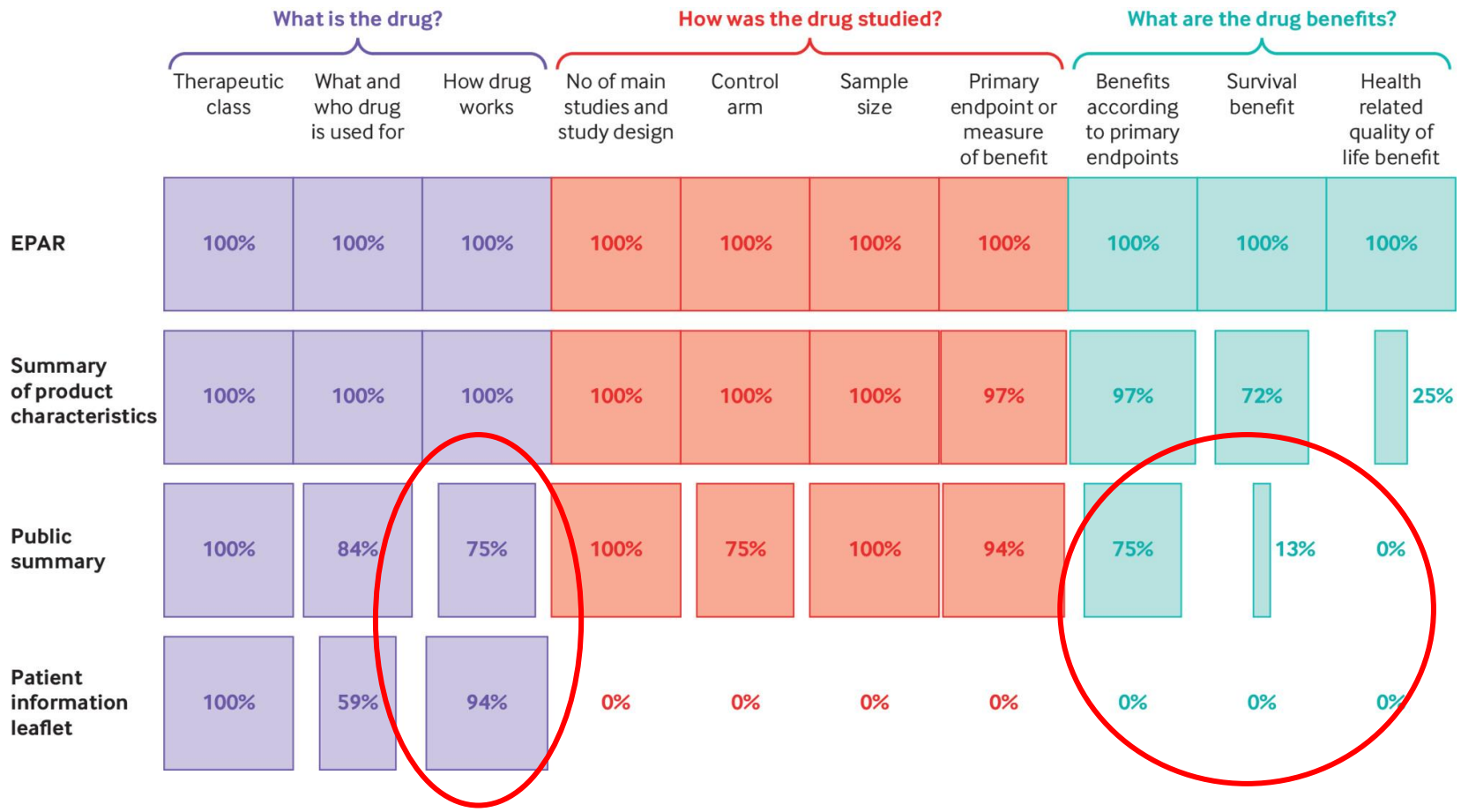
Many drugs approved based on weak study designs, 40% lacked a comparator

EMA assessors frequently raised concerns with respect to deficiencies in the design, conduct, analysis or findings of studies to support market authorization

Vast majority of drugs (72%) approved without evidence that they extend survival or improve the quality of patients' lives

Approvals based on surrogate endpoints such as tumour response and progression-free survival that do not predict improved length or quality of life

Communication of information about a drug, how it was studied, and evidence of benefit.



Courtney Davis et al. BMJ 2023;380:bmj-2022-073711

Problem 1:

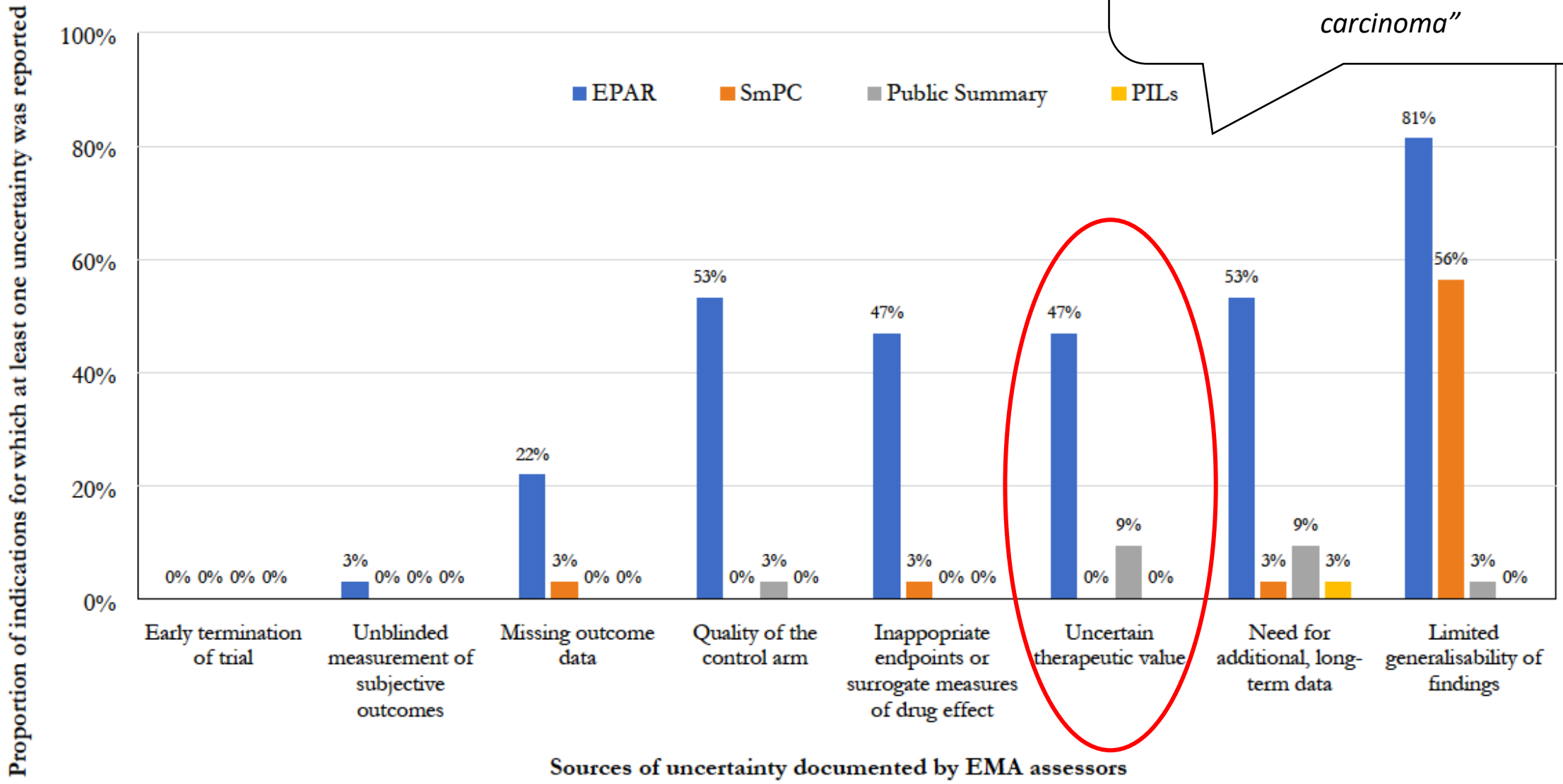
Regulated anticancer drug information prioritises the *least* important types of benefit information for patients

Results of a modified Delphi consensus conference:

- Most important categories of information:
- "What difference did the drug make for patients in clinical studies?" (92% deemed this 'essential')
- "What is *not* known about the drug's benefits" (79% deemed this 'essential')
- *Least* important category of information: "How does the drug work?" (12% deemed this 'essential', 62% deemed this 'not important')

"there are substantial uncertainties regarding the efficacy of atezolizumab for the treatment of adult patients with advanced or metastatic urothelial carcinoma"

Figure 4. Communication of concerns of EMA assessors about study methods and findings



Public summary for atezolizumab for urothelial cancer

Under the section: What benefits of Tecentriq have been shown in studies?

In [a] study involving 931 patients with urothelial cancer, ***those given Tecentriq lived slightly longer (8.6 months) than patients given chemotherapy (8 months) although the difference could be due to chance.*** Response was seen even in patients whose cancer cells did not produce much PD-L1."

Does not communicate that the drug failed to demonstrate a gain in overall survival despite the study being powered to detect such a gain

Problem 2:

Patient leaflets & public summaries contain potentially confusing and misleading information

Potentially misleading information on drug mechanism of action in PILs:

Drug X: "attacks the tumour cells", "triggers the death of cancer calls" "[causes] modified T cells [to] find the cancer cells and destroy them"

Potentially misleading descriptions of surrogate endpoints (eg. overall response rate and progression-free survival)

*OR: "overall, using the most stringent, up-to-date criteria, the disease **responded to treatment** in about 28% of patients…"*

*PFS: "Patients taking Fotivda **lived for longer without their disease worsening**…"*

Problematic descriptions of surrogate endpoints

- A study by FDA found common descriptions of ORR & PFS (eg. ‘time patient lives with the disease but it does not get worse’) were misunderstood by patients and the public who thought these endpoints definitions were all variations of living longer.[a]

- RCT involving nearly 900 US adults, showed that without an explicit disclosure (‘We do not know whether drug x helps patients live longer’) people were more likely to report that an ORR or PFS benefit meant that people would live longer.[b]

[a] [b]Sullivan et al. The Oncologist 2020; 25:1060-1066; [b] Sullivan et al., The Oncologist 2023; 5;28(7):e542-e553.

Implications

- Information produced or disseminated by drug regulators could help to address common misperceptions

- BUT critical information needed for informed decision-making and consent to treatment is frequently missing from regulated information sources for new cancer drugs

- At worst, information that *is* communicated may compound patient misunderstanding

Way Forward?

- Patient leaftets
  - EMA's QRD initiative – revised QRD template
  - EU Legislative review? Improvements to patient information leaflets
- EMA communications
  - Opportunities to improve EMA's public summaries/medicines overviews

- Drugs Facts Boxes – adopt evidence-based principles of effective communication about drug benefits, harms and uncertainties
- Shown in large randomized trials in nationally representative population to improve patient knowledge, comprehension and decision-making processes.

Lunesta Study Findings

788 healthy adults with insomnia for at least 1 month – sleeping less than 6.5 hours per night and/or taking more than 30 minutes to fall asleep – were given LUNESTA or a sugar pill nightly for 6 months. Here's what happened:

What difference did LUNESTA make?	People given a sugar pill	People given LUNESTA (3 mg each night)
Did Lunesta help?		
LUNESTA users fell asleep faster (15 minutes faster due to drug)	**45 minutes to fall asleep**	**30 minutes to fall asleep**
LUNESTA users slept longer (37 minutes longer due to drug)	**5 hours 45 minutes**	**6 hours 22 minutes**
Did Lunesta have side effects?		
Life threatening side effects:		
No difference between LUNESTA and a sugar pill	**None observed**	**None observed**
Symptom side effects:		
More had unpleasant taste in their mouth (additional 20% due to drug)	**6%**	**26%**
More had dizziness (additional 7% due to drug)	**3%**	**10%**
More had drowsiness (additional 6% due to drug)	**3%**	**9%**
More had dry mouth (additional 5% due to drug)	**2%**	**7%**
More had nausea (additional 5% due to drug)	**6%**	**11%**

Source: https://dartmed.dartmouth.edu/spring08/html/disc_drugs_we.php

Statins for CHD

Statins

NICE recommends **atorvastatin 80mg** in those with a previous MI to reduce the risk of further cardiovascular events.

Benefits | **Harms**

Medical history: Previous MI or Acute Coronary Syndrome

Reduce risk of: Fatal or non-fatal MI

key

ARR 5.8%
Absolute Risk Reduction

NNT 17
Number Needed to Treat

RRR 40%
Relative Risk Reduction

EXPLAIN STATS

If 100 people with a previous MI take a statin for 5 years, 5.8 will avoid a fatal or non-fatal MI compared to those who do not take a statin

https://gpevidence.org/conditions/coronary-heart-disease/