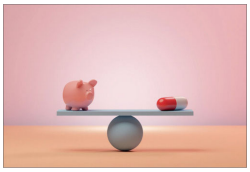
Cancer drug assessment: integrating clinical benefit, innovations and economic impact



Sirkku Jyrkkiö
MD, PhD, Head of Division
Turku University Central Hospital

CHOICES IN HEALTH CARE

1

We are not working on these issues for the first time…Challenges and opportunities remain…

Our review highlights that there is potential to strengthen and improve the current regulatory environment. We identified the following key requirements for a reform package: greater coordination; capacity building; stronger incentives; increased information sharing for implementation of policies; and policies to consider the current challenge for dual financing in Finland.

© World Health Organization 2008, on behalf of the European Observatory on Health Systems and Policies

2

PUBLICITY, MEDIA

TALOUSSANOMAT

Tutkijat: Kela maksaa jätti-korvauksia syöpälääkkeistä, joiden teho ei ole varma

Kela syöpälääkekorvaukset ovat kolminkertaistuneet kymmenessä vuodessa. Se maksaa paljon korvauksia kalliista lääkkeistä, joiden teho on epävarma.

TERVEYSUUTISET

Miksi lääkkeet ovat niin kalliita? Yksi taho nappaa suurimman siivun

Eri lääkkeiden hinnat muodostuvat eri tavoin. Kalliin lääkkeen hinnasta isoin osa on lääkeyhtiön ja -tukun osuus.

IL.FI

TERVEYS IS.FI

Useiden kalliiden syöpälääkkeiden patenttisuoja on päättymässä – kilpailu voi tuoda kymmenien miljoonien eurojen säästöt

Yhden verisyöpälääkkeen myynnin avautuminen kilpailulle säästi yhdeksässä kuukaudessa yli 30 miljoonaa euroa verorahoja, Kela kertoo.

Suomi laahaa perässä uusimpien syöpähoitojen käytössä – syövän immuunihoitojen käyttö Suomessa alle Euroopan keskitason

Mediuutiset

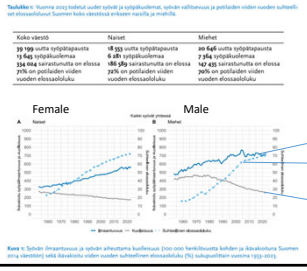
16.10.2024

Potilaat odottavat – uusien syöpälääkkeiden arviointia ja käyttöönottoa on sujuvoitettava

Lääketeollisuus ry

3

The age-standardized five-year relative survival rate is improving – the trend is heading in the right direction



- Incidence
- Age-standardized five-year relative survival rate
- Mortality

Finnish Cancer Registry

4

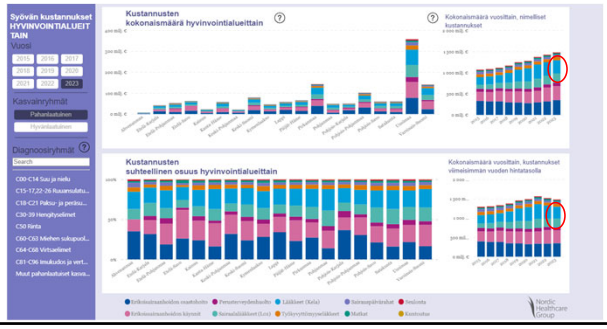
The increase in cancer-related cost has decelerated

The web-based tool facilitates yearly tracking of expenditures related to cancer care

https://syopajarjestot.fi/syovan-hoidon-kustannukset

5

Total cost by well being counties



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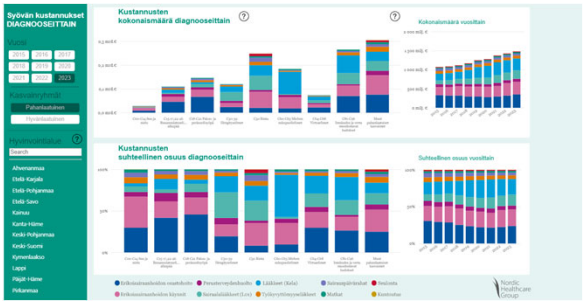
Total cost by diagnosis



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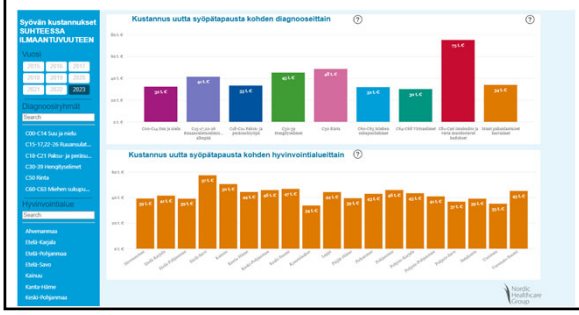
Cost per new cancer case by diagnosis



8

Unique Finnish system

Dual-channel financing of pharmaceutical treatment is a unique Finnish system where the funding of medicines is split into two separate channels based on who administers the medicine and how it is financed

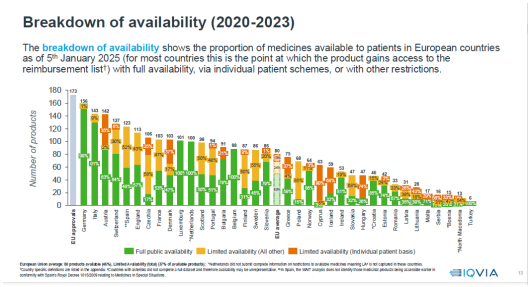
Hospital medicines: Medicines administered in public hospitals are financed through tax revenues allocated to regional welfare areas (well-being services counties). These medicines are usually provided to patients during hospital stays or outpatient clinic visits without any direct cost to the patient.

Outpatient medicines: Medicines prescribed by doctors for use outside hospitals are purchased by patients at pharmacies. Part of the cost is reimbursed by the Social Insurance Institution of Finland (Kela), funded through patients' health insurance contributions and state tax revenues. Patients always pay a co-payment for these medicines.

→ Separate assessment and decision-making pathways

9

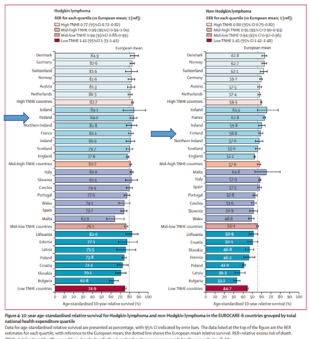
Finland is close to average on the availability of products



10

Cancer treatment outcomes vary between countries

- Health habits
- Accessibility of the healthcare system
- ...also the availability of medications and radiotherapy and surgery etc.



Lancet Oncol 2024; 25: 731–43
Published Online May 1, 2024
https://doi.org/10.1016/S1470-2045(24)00141-4

11

Cost and value of cancer medicines in a single-payer public health system in Ontario, Canada: a cross-sectional study

Joseph C Del Paggio, Rohini Naipaul, Scott Gavura, Rebecca E Mercer, Rachel Kovers, Bishal Gyawali, Brooke E Wilson, Christopher M Booth

Summary

Background The financial impact of cancer medicines on health systems is not well known. We describe temporal trends in expenditure on cancer medicines within the single-payer health system of Ontario, Canada, and the extent of clinical benefit these treatments offer.

Lancet Oncol 2024; 25: 431–38
See Comment page 412
Department of Oncology,

The worries are global...

12

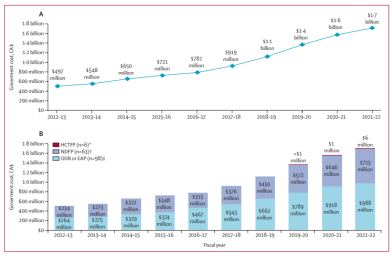


Figure 1: Annual public expenditure on anti-cancer drugs in Ontario, Canada, 2012–22

(A) Total expenditure. Annual expenditures are reported for parenteral cancer drugs (n=59) reimbursed by the NDFP, take-home cancer drugs (n=58) reimbursed by the ODBF, and in-patient cancer drugs (n=6) reimbursed by the HCTFP. For drugs reimbursed by the ODBF, the costs also include associated pharmacy fees. Costs reported do not reflect manufacturer rebates (if applicable). (B) Expenditure by drug class (intravenous vs oral or injectable). For drugs reimbursed by the ODBF, the Government cost also includes associated pharmacy fees. EAP=Exceptional Access Program. HCTFP=High-Cost Therapy Funding Program. NDFP=New Drug Funding Program. ODBF=Ontario Drug Benefit Program. †The HCTFP pays for injectable and oral cancer drugs primarily administered in the inpatient hospital setting, which include those used in paediatric neuroblastoma (dinutuximab) and acute leukaemias (pemtumumab, gilteritinib, midostaurin, and pegaspargase). ‡The NDFP pays for injectable cancer drugs administered in outpatient hospital clinics. §The ODBF pays for cancer drugs, mostly oral, that are taken at home, including drugs approved by the EAP. For drugs reimbursed by ODBF, the government cost also includes associated pharmacy fees.

www.thelancet.com/oncology Vol 25 April 2024

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Proportional expenditure on the top-ten iv medicine relative to proportional disease burden

"Very expensive" dg: myeloma and melanoma

Insufficient evidence

- Insufficient effectiveness
- Less usage

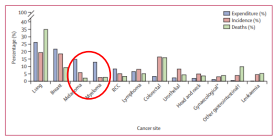

Figure 2: Proportional expenditure on the top-ten intravenous cancer medicines (by expenditure) in the Ontario health system in the 2021–22 fiscal year relative to the proportional disease burden

This analysis reflects only those medicines included in the top-ten list of cancer medicines expenditures in Ontario in 2021–22, which account for 83% of all expenditures on intravenous cancer medicines. *Cervix or ovary. †Oesophagogastric and hepatocellular carcinoma.

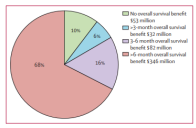

Figure 3: Proportion of expenditure in the Ontario health system on top-ten intravenous cancer medicines (by expenditure) in the 2021–22 fiscal year, stratified by randomised clinical trial evidence for overall survival

Currency is CA$. The top-ten medicines account for 83% of all expenditures on intravenous cancer medicines.

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JAMA Oncology | Original Investigation

Evolution of the Randomized Clinical Trial in the Era of Precision Oncology

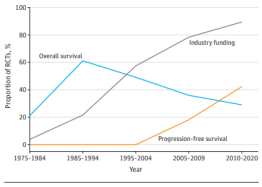
Joseph C. Del Paggio, MD; John S. Berry; Wilma M. Hopman, MA; Elizabeth A. Eisenhauer, MD; Vinay Prasad, MD; Bishal Gyawali, MD, PhD; Christopher M. Booth, MD

CONCLUSIONS AND RELEVANCE This cohort study suggests that contemporary oncology RCTs now largely measure putative surrogate end points and are almost exclusively funded by the pharmaceutical industry. The increasing role of medical writers warrants attention. To demonstrate that new cancer treatments are high value, the oncology community needs to consider the extent to which study end points and target effect size provide meaningful benefit to patients.

- RCT studies are funded by industry
- Usage of putative surrogate endpoints
- Professional writers

JAMA Oncol. 2021;7(5):728-734. doi:10.1001/jamaoncol.2021.0379
Published online March 25, 2021.

Figure 2. Temporal Trends in Primary End Point and Industry Funding of Randomized Clinical Trials (RCTs) of Breast, Colorectal, and Non–Small Cell Lung Cancer Published in Major Journals Over 5 Decades, 1975-2020



15

Comments and Controversies

Check for updates

Progression-Free Survival Should Not Be Used as a Primary End Point for Registration of Anticancer Drugs

Christopher M. Booth, MD; Elizabeth A. Eisenhauer, MD; Bishal Gyawali, MD, PhD; and Ian F. Tannock, MD, PhD

DOI: https://doi.org/10.1200/JCO.23.01423

TABLE 1. Reasons Why PFS Is an Inappropriate Primary End Point in Most Trials Evaluating Anticancer Drugs

Improvement in PFS is seldom a surrogate for, nor reliably predictive of, improvement in OS
Improvement in PFS is not a surrogate for, nor predictive of, improvement in QoL
PFS does not recognize that the balance between benefit and harm depends not only on changes in tumor size but also on toxicity
PFS measurement and comparisons are subject to error and bias because of
Timing of assessment
Measurement error in assessing tumor progression
Informative censoring because of uneven dropout between groups in an RCT
Improvement in PFS is widely misunderstood by patients and the public to imply improvement in survival

Abbreviations: OS, overall survival; PFS, progression-free survival; QoL, quality of life; RCT, randomized controlled trial.

Accepted August 8, 2023
Published September 21, 2023

J Clin Oncol 41:4968-4972
© 2023 by American Society of Clinical Oncology

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Conclusions

While surrogate endpoints help trials to complete early, they can also be potentially misleading. Although surrogate measures have a role in offering early access to therapies via accelerated approval, putative surrogate endpoints should be properly validated before accepting them as endpoints for traditional approvals. A more efficient approach to drug development would be to conduct RCTs powered for OS that definitively answers the effect of the drug on clinical endpoints rather than to conduct multiple trials with surrogate endpoints and resulting uncertainty regarding the effect of the drug on survival. Alternatively, as proposed in the new FDA guidance, a one-trial approach of conducting an RCT that is powered for OS from the outset but the same RCT sufficing for early accelerated approval based on responses/PFS and mature regular approval based on OS offers a reasonable balance between speed and efficacy. OS should also be the defacto endpoint specially in later line settings or where the median OS is less than a year. PFS should be better renamed as PFI given the public and patient confusion regarding the phrase. QOL outcomes should be directly tested in trials and not inferred based on surrogates.

Frequently asked questions on surrogate endpoints in oncology-opportunities, pitfalls, and the way forward

Abhand Mittal, Myung Sun Kim, Sherno Dunn, Kristin Wright, and Bishal Gyawali

We need randomized studies in which the power calculation is based on overall survival as the primary endpoint

eClinicalMedicine
2024;70: 102824
Published Online XXX
https://doi.org/10.1016/j.eclinm.2024.102824

17

Check for updates

Overall Survival, Progression-Free Survival, and Tumor Response Benefit Supporting Initial US Food and Drug Administration Approval and Indication Extension of New Cancer Drugs, 2003-2021

Daniel Tobias Michaeli, MD[1,2], and Thomas Michaeli, MD[1,2,3]

J Clin Oncol 40:4095-4106. © 2022 by American Society of Clinical Oncology

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA REGISTRATION

- 124 cancer medicine approved by FDA
- 71 % based on phase III RCT, median N=331
- OS benefit median 2,8 m
- PFS benefit median 3,3 m

18

An increasing number of clinicians question the benefits of some newer cancer medicines

World Health Organization

Pages 11-13

- **Concerns over insufficient evidence of benefits on clinical outcomes**
  - Inadequate evidence base
    - Only one-third of cancer medicines approved by US Food and Drug Administration (2008–2012) and European Medicines Agency (2009–2013) had established evidence of prolonged survival at the time of approval
  - Modest survival gains
    - Among cancer medicines approved on the basis of extended survival, overall survival was extended for a median 2.7 months (range: 1.0 month to 5.8 months)
- **Concerns about safety profile**
  - Greater risk of 'toxic death' (OR=1.4) and treatment discontinuation (OR=1.33) for newer targeted drugs than control

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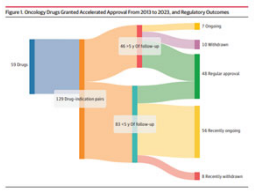
Research

JAMA | Original Investigation

Clinical Benefit and Regulatory Outcomes of Cancer Drugs Receiving Accelerated Approval

Ian T. T. Liu, MD, JD, MPH, MS; Aaron S. Kesselheim, MD, JD, MPH; Edward R. Scheffer Cliff, MBBS, MPH

Figure 1. Oncology Drugs Granted Accelerated Approval From 2013 to 2023, and Regulatory Outcomes



Oncology drugs granted accelerated approval and regulatory outcome, based on follow-up time.

- FU > 5 y
- Several withdrawals
- Multiple drugs had ongoing conformatory trials
- Regular approval: only 2/3 showed improvements in OS or QOL
- FDA had increasingly used surrogate measures

Conclusions

Most cancer drugs granted accelerated approval did not demonstrate benefit in overall survival or quality of life within 5 years of accelerated approval. Patients should be clearly informed about the cancer drugs that use the accelerated approval pathway and do not end up showing benefits in patient-centered clinical outcomes.

JAMA. 2024;331(17):1471-1479. doi:10.1001/jama.2024.2396
Published online April 7, 2024.

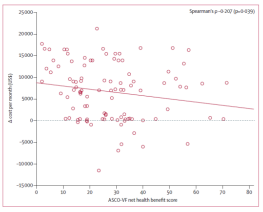
20

Delivery of meaningful cancer care: a retrospective cohort study assessing cost and benefit with the ASCO and ESMO frameworks

THE LANCET Oncology

Joseph C Del Paggio, Richard Sullivan, Deborah Schrag, Wilma M Hopman, Biju Azariah, C S Pramesh, Ian F Tannock, Christopher M Booth

- No association between magnitude of benefit and drug price



Del Paggio et al Lancet Oncol 2017

21

The cancer premium – explaining differences in prices for cancer vs non-cancer drugs with efficacy and epidemiological endpoints in the US, Germany, and Switzerland: a cross sectional study

Miquel Serra-Burriel,[1,2,*] Gellért Pereszlay,[1] Yannic Laufer,[1] Aaron P. Mitchell,[3] and Kerstin N. Vokinger[1,4,*]

[1]Institute of Law, University of Zurich, Switzerland
[2]Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland
[3]Memorial Sloan Kettering Cancer Center, New York, USA

Summary

Background High treatment prices of new cancer drugs are a global public health challenge to patients and healthcare systems. Policymakers in the US and Europe are debating reforms to drug pricing. The objective of this study was to assess whether drug efficacy or epidemiological characteristics (prevalence, incidence, mortality) explain the gap in treatment prices between cancer and non-cancer drugs in the US, Germany, and Switzerland.

eClinicalMedicine 2023;61: 102087
Published Online 12 July 2023
https://doi.org/10.1016/j.eclinm.2023.102087

Discussion

Launch treatment drug prices have increased significantly over the past decade in the US, Germany, and Switzerland. We found significant associations between the efficacy of drugs and treatment prices, epidemiological characteristics of the diseases and treatment prices. However, these features cannot explain the three-fold difference in treatment prices between cancer and non-cancer drugs. This gap –here referred to as the "cancer premium"– was observed both in the US where drug prices can be set freely, and in European countries with price negotiation power.

" Drug pricing reforms should target the cancer premium to improve access of patients to cancer drugs as well as to achieve equity across the different therapeutic areas and sustainability in the health care systems"

22

Applied Health Economics and Health Policy (2022) 20:67–77
https://doi.org/10.1007/s40258-021-00670-4

ORIGINAL RESEARCH ARTICLE

Comparison of Prices and Affordability of Cancer Medicines in 16 Countries in Europe and Latin America

Daniela Moye-Holz[1] · S. Vogler[1]

Accepted: 15 June 2021 / Published online: 6 July 2021
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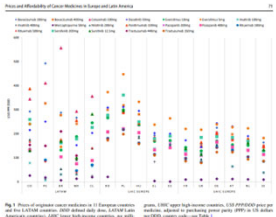

"Premium" cancer medicines are extremely expensive in the lower income countries

23

Original Investigation | Pharmacy and Clinical Pharmacology

Cancer Drug Price and Novelty in Mechanism of Action

Miloš D. Miljković, MD[1]; Jordan Tula, BA[2]; Timothée Olivier, MD[3]; et al

> Author Affiliations | Article Information

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Cite | Permissions | Metrics | Comments

JAMA Netw Open
Published Online: December 11, 2023
2023;6(12):e2347006.
doi:10.1001/jamanetworkopen.2023.47006

Key Points

Question Is the median annual cost of cancer drugs associated with the novelty of cancer drugs approved in the US over a 6-year period?

Findings In this cross-sectional study, between January 1, 2015, and December 31, 2020, there were 224 cancer drug approvals across 119 individual drugs. The median annual cost was $196 000, and there was no significant difference in cost between first-in-class, next-in-class, and subsequent approvals of an already approved drug.

Meaning The results of this study suggest that drug pricing cannot be explained by innovations alone; further study is warranted.

Advertisement

Median annual cost 196 000 USD

24

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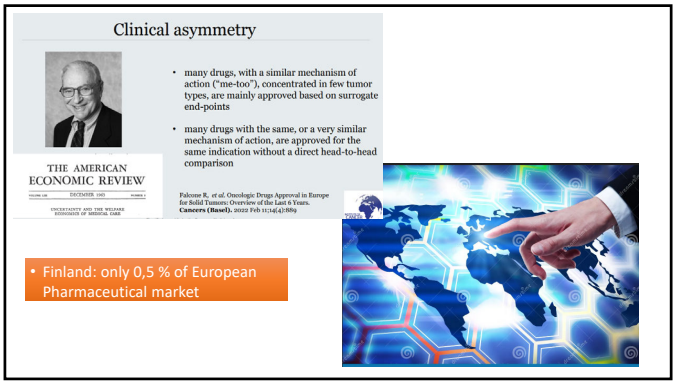

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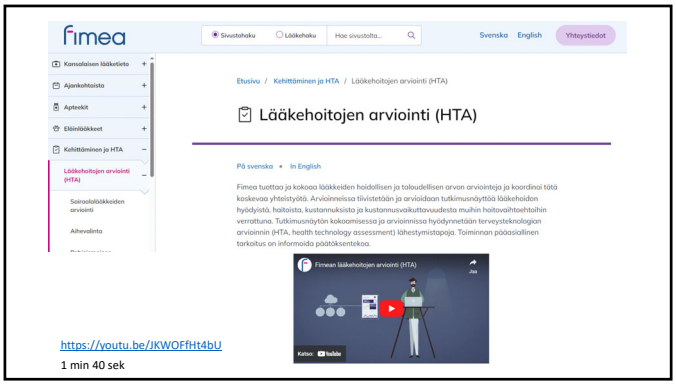
Aim of Health Technology Assessment

- What additional benefit does the product provide compared to current treatment methods – what would be the role of the new product/combination in the treatment portfolio?
- Cost-effectiveness – can we afford this?

27



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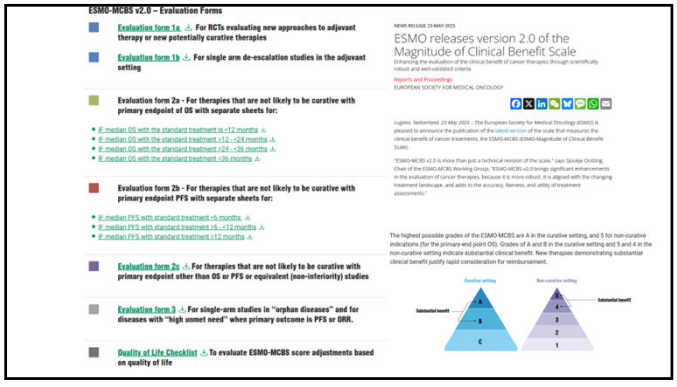

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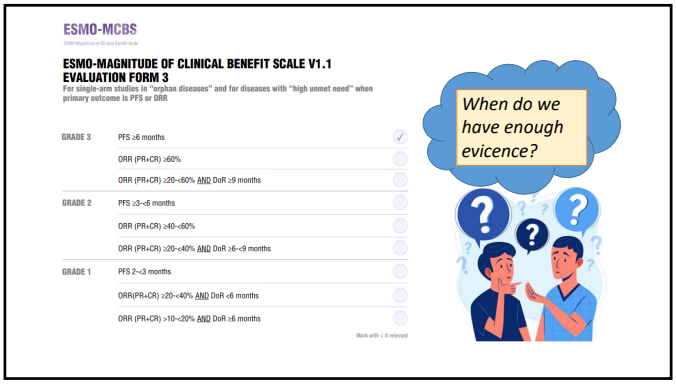


30

If median OS with the standard treatment is ≥12 - <24 months

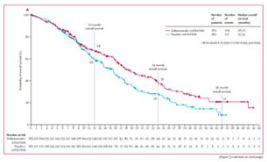
GRADE 4	HR ≤0.70 AND gain ≥5 months	☐
	Increase in 3-year survival alone ≥10% (if >20% of patients on experimental arm have reached 3-year OS)	☐
GRADE 3	HR ≤0.70 AND gain ≥3 - <5 months	☐
GRADE 2	HR ≤0.70 AND gain ≥1.5 - <3 months	☐
	HR >0.70 - 0.75 AND gain ≥1.5 months	☐
GRADE 1	HR >0.75 OR gain <1.5 months	☐

Mark with √ if relevant

31

Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial

Kohei Shitara, Florian Lordick, Yung-Jue Bang, Peter Enzinger, David Ilson, Manish A Shah, Eric Van Cutsem, Rui-Hua Xu, Giuseppe Aprile, Jianming Xu, Joseph Chao, Roberto Pazo-Cid, Yoon-Koo Kang, Jianning Yang, Dharmvid Moran, Pronob Bhattacharyya, Ahsan Arozullah, Jung Wook Park, Mok Oh, Jaffer A Ajani



Lancet 2023; 401: 1655–68
Published Online
April 14, 2023
https://doi.org/10.1016/S0140-6736(23)00620-7

Median OS benefit 2,69 m

- CT + zolbetuximab group 18,23 m
- CT + placebo group 15,54 m

Zolb + mFOLFOX6 ICER 185 000 USD/QALY
Zolb + CAPOX ICER 388 000 USD/QALY

What would be your assessment?

What would you like to pay if your relative has cancer – or yourself?

32

Competition for attention and resources

- Innovations
- Industry interests
- Patient expectations
- Political trends
- ”Public opinion”
- Should we do ”everything possible” for one patient, or accept a reasonable service portfolio based on cost-effectiveness?

33

Take home message

- New cancer medicines are needed
- Current treatments still have significant adverse effects, even though they are so-called targeted therapies
- The benefit gained from medications is limited
- The prices of new medicines are unreasonable
- How much should society contribute to the cost arising from drug developement?
- How can we ensure that sufficient RWD is collected?
- In Finland: Dual financing is a problem (not only a challenge) and more power is needed for negotiations on prices

- **High-quality medical research is the base for cost effective high quality cancer care**

34