Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

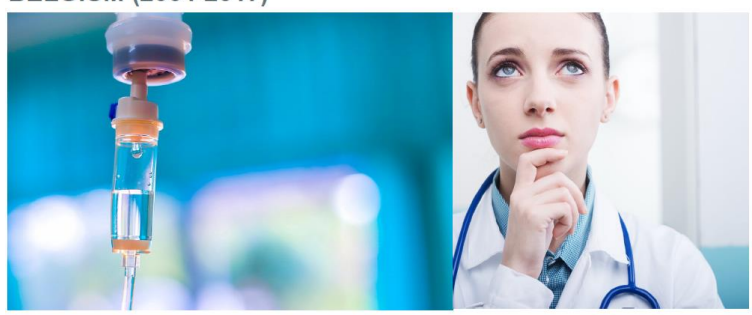
Do innovative medicines against cancer always have a real added value?
What can/should we do better when allowing drugs on the market?

Mattias Neyt (KCE), MSc, PhD
Senior health economist

10 October 2024

- Source: https://kce.fgov.be/en/do-innovative-medicines-against-cancer-always-have-a-real-added-value

BENEFITS AND COSTS OF INNOVATIVE ONCOLOGY DRUGS IN BELGIUM (2004-2017)



DOWNLOADS

Synthesis in English (50 p.) (2.77 MB)

Scientific report in English (352 p.) (11.5 MB)

Supplement in English (1142p.) (12.88 MB)

2021 www.kce.fgov.be

- Mattias Neyt (KCE), Carl Devos (KCE), Nancy Thiry (KCE), Geert Silversmit (BCR), Cindy De Gendt (BCR), Nancy Van Damme (BCR), Diego Castanares-Zapatero (KCE), Nicolas Fairon (KCE), Frank Hulstaert (KCE), Leen Verleye (KCE)

Research questions

- RQ1: What is the evolution in overall survival in a broad **selection of oncology indications** and the budget impact of introducing new cancer drugs in the last 15 years in Belgium?
- RQ2: What is known in the literature about the benefits (e.g. impact on overall survival and QoL) and cost-effectiveness for a broad **selection of new cancer drugs**?

Methods

- Belgian observational data
  - Belgian Cancer Registry (2004-2017) & Intermutualistic Agency (oncology drugs, 5y FU, health care act 2018) & vital status (January 2020)
- International literature
  - Systematic reviews (survival), HTA reports (economic evaluations)

Selection

- 40 different drugs in 12 cancer types
  - + : broad picture
- Focus on stage IV (where applicable)

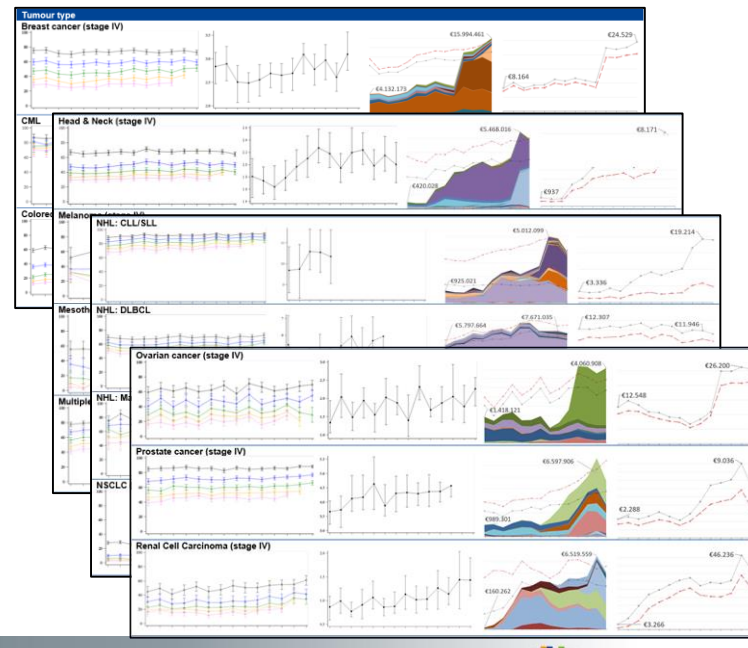
Table 3 – List of selected drugs in 12 cancer types

Female Breast cancers	pertuzumab, trastuzumab emtansine, palbociclib+, abemaciclib+, and ribociclib+
Chronic myeloid leukaemia	imatinib, nilotinib, dasatinib, bosutinib+, and ponatinib+
Colorectal cancer (Colon and rectum*)	bevacizumab, cetuximab, panitumumab, aflibercept, and regorafenib
Head and Neck cancers	cetuximab
Malignant melanoma of skin	ipilimumab, pembrolizumab, nivolumab, dabrafenib, vemurafenib, and trametinib
Mesothelioma	pemetrexed+
Multiple myeloma	lenalidomide, pomalidomide, bortezomib and daratumumab+
Non Hodgkin Lymphoma**	rituximab, ibrutinib and obinutuzumab+
Non-small-cell lung cancer	erlotinib, gefitinib, ~~pemetrexed~~+, afatinib & crizotinib, nivolumab*** and pembrolizumab***
Ovarian cancer	bevacizumab
Prostate cancer	enzalutamide
Renal cancer	sunitinib, pazopanib, everolimus, sorafinib, axitinib, temsirolimus, and nivolumab

+/-: the cancer drugs that were added/deleted, based on the suggestions from external experts.
** It was decided to group colon cancer (ICD-10 C18-C19) and rectum cancer (ICD-10 C20) and look at colorectal adenocarcinoma (ICD-10 C18-C20). ** During the expert meeting, it was decided to limit Non-Hodgkin Lymphoma to the following three types: chronic lymphocytic leukaemia & small lymphocytic lymphoma, Diffuse Large B-cell Lymphoma, and Mantle cell lymphoma *** Based on the updated information including incidence year 2017, immunotherapy (nivolumab and pembrolizumab) is also added for this cancer type.*

Summary

- Half: (slight) improvements
- Other half: no clear improvements…
- Almost always (large) increases gross drug exp. & mean treatment costs
- Remark: nuance needed (see discussion)



Summary

- 12 cancer indications:
  - 1. Breast cancer (st. IV)
  - 2. Chronic Myeloid Leukaemia
  - 3. Colorectal cancer (st. IV)
  - 4. Head & neck cancer (st. IV)
  - 5. Melanoma (st. IV)
    - Ex. Nuance (st. NA)
  - 6. Mesothelioma (st. III/IV/X)
  - 7. Multiple myeloma
  - 8. Non-Hodgkin Lymphoma
    - ➢ CLL/SLL, DLBCL, Mantle cell lymphoma
  - 9. Non-small cell lung cancer (st. IV)
    - Ex. nuance
  - 10. Ovarian cancer (st. IV)
  - 11. Prostate cancer (st. IV)
  - 12. Renal cell carcinoma (st. IV)

Summary

- (Cost-)effectiveness: general findings and problems
  - Greatest uncertainty: impact OS
    - ➢ Lack head-to-head, immature data, surrogate endpoints, cross-over
  - Impact QoL – also large uncertainty
    - ➢ Not always measured (disease-specific & generic utility instrument), if measured – considered confidential (!)
  - Choice comparator
  - Confidential prices
    - Price/discount intervention (& comparator & FU treatments…)
    - Decision maker's ICER (transparency & accountability)

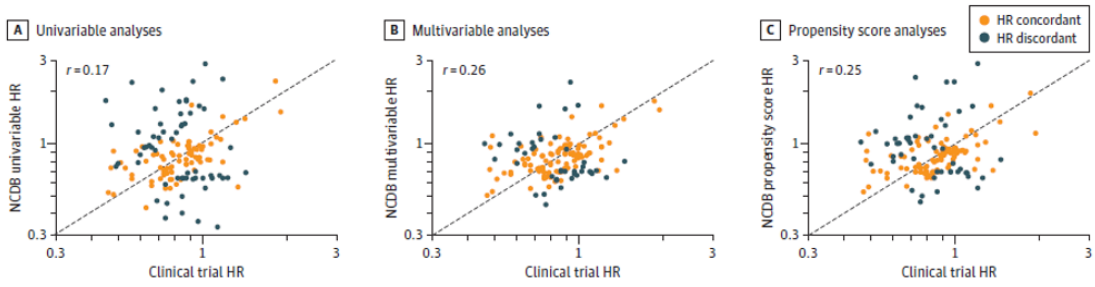
Discussion

Learn from the past to do better in the future

- Real-world observational data
  - Misinformation relative treatment effect
  - Remark: limited benefits in overall survival
- The use of progression-free survival as a surrogate endpoint
  - Evidence: link with OS & QoL
  - QoL as an important endpoint (~EUnetHTA guidelines HRQoL)
- Our recommendations & …

  … link with HTA regulation: big opportunities
  - Pre-market: JSC
  - After JCA

HR from RCTs vs. observational data



Hazard ratios shown for univariable analyses (A), multivariable analyses (B), and propensity score analyses (C). Each point on the scatter plot represents the HR for overall survival from 1 of the 141 randomized clinical trials in this study and the corresponding analysis within the NCDB. Yellow dots represent NCDB analyses in which the NCDB HR falls within the 95% CI of the HR in the clinical trial (concordant), and blue dots represent HRs from the NCDB analyses that fall outside the 95% CI of the HR in the clinical trial (discordant). The gray dashed line shows where clinical trial HRs equal NCDB HRs. The intersection of the axes represents an HR equal to 1.

Source: Kumar et al. (2020)

Banerjee, JAMA Oncol (2020)

Their findings are discouraging. Propensity-matched hazard ratios for overall survival from CER-based analyses fell outside the 95% CIs of their RCT counterparts 36% of the time (with 64% falling within). Furthermore, observational studies led to a different inference regarding therapeutic efficacy 55% of the time (ie, point estimates that were either in a different direction, nonsignificant in CER vs significant in RCT or significant in CER but nonsignificant in RCT).

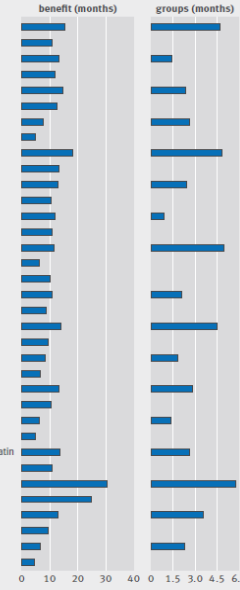
Limited benefits in overall survival

- Davis et al. (2017): evidence EMA approved cancer drugs
  - Significant prolongation of survival in just over a third (24/68, 35%) of all drug indications
    - ➢ The magnitude of the overall survival benefit ranged from 1.0 to 5.8 months (median 2.7 months) (see next slide)
  - For the 44 (65%) remaining drug indications: no conclusive evidence at time of market authorisation that the drugs offered survival benefits

Extra

- Magnitude of benefit

Agent	Cancer site	Indication	Intervention and control groups	Median OS benefit (months)	Difference between groups (months)	Hazard ratio (95% CI)
Abiraterone acetate	Prostate	After chemo mCRPC (+pred)	Group 1: Abiraterone acetate + pred Group 2: PBO + pred	14.8 10.9	3.9	0.74 (0.64 to 0.86)
Aflibercept	Colorectal	2nd line mCRC (+FOLFIRI)	Group 1: Aflibercept followed by FOLFIRI Group 2: PBO followed by FOLFIRI	13.5 12.1	1.4	0.82 (0.71 to 0.94)
Cabazitaxel	Prostate	Hormone refractory mPC (+pred) previously treated with docetaxel	Group 1: Cabazitaxel + pred Group 2: Mitoxantrone + pred	15.1 12.7	2.4	0.70 (0.59 to 0.83)
Decitabine	Haematological	1st line AML in chemo ineligible adults aged ≥65	Group 1: Decitabine and/or supportive care Group 2: Cytarabine and/or supportive care	7.7 5.1	2.6	0.82 (0.68 to 0.99)
Enzalutamide	Prostate	mCRPC previously treated with docetaxel	Group 1:MDV3100 – enzlutamide Group 2: PBO	18.4 13.6	4.8	0.63 (0.53 to 0.75)
Eribulin	Breast	3rd line mBC	Group 1: Eribulin Group 2: Physician's choice	13.1 10.6	2.5	0.81 (0.66 to 0.99)
Erlotinib	Lung	Maintenance therapy in mNSCLC (previously platinum based chemo)	Group 1: Platinum based chemo + erlotinib Group 2: Platinum based chemo + PBO	12.0 11.2	0.8	0.81 (0.70 to 0.95)
Ipilimumab	Haematological	2nd line unresectable or metastatic melanoma	Group 1: Ipilimumab + gp 100 Group 2: gp 100 + PBO Group 3: Ipilimumab + PBO	10.1 6.4 10.0	3.7	0.68 (0.55 to 0.85) 0.66 (0.51 to 0.87)
Ipilimumab	Haematological	1st line unresectable or metastatic melanoma	Group 1: Dacarbazine + ipilimumab Group 2: Dacarbazine + PBO	11.2 9.1	2.1	0.72 (0.59 to 0.87)
Lapatinib	Breast	HER2+ HR- mBC (+trastuzumab) Previous trastuzumab + chemo	Group 1: Lapatinib + trastuzumab Group 2: Lapatinib	10.6 8.4	2.2	0.74 (0.57 to 0.97)
Paclitaxel (nab-paclitaxel)	Pancreas	1st line (+gemcitabine) metastatic pancreatic adenoca	Group 1: Abraxane (paclitaxel) + gemcitabine Group 2: Gemcitabine	8.5 6.7	1.8	0.72 (0.62 to 0.84)
Pemetrexed	Lung	Maintenance for mNSCLC (non-squam) after platinum based doublet chemo (with gemcitabine or taxane)	Group 1: Pemetrexed + BSC Group 2: Placebo + BSC	13.4 10.3	3.1	0.79 (0.65 to 0.95)
Regorafenib	Colorectal	mCRC either after previous therapy with or eligible for 5-FU based chemo or VEGFi or EGFRi therapy	Group 1: Regorafenib + BSC Group 2: PBO + BSC	6.4 5.0	1.4	0.79 (0.66 to 0.93)
Trastuzumab	Stomach	1st line HER2+ mGC or mGOJ adenoca	Group 1: Trastuzumab + (5-FU or capecatebine) and cisplatin Group 2: (5-FU or capecatebine) and cisplatin	13.8 11.1	2.7	0.74 (0.60 to 0.91)
Trastuzumab emtansine	Breast	HER2+ unresectable or mBC after trastuzumab and/or taxane therapy	Group 1: Trastuzumab emtansine Group 2: Lapatinib + capecatebine	9.6 6.4	3.2	0.68 (0.55 to 0.85)
Vemurafenib	Haematological	Unresectable or metastatic melanoma (BRAFV600 mut)	Group 1: Vemurafenib Group 2: Dacarbazine	13.2 9.6	3.6	0.62 (0.49 to 0.77)
Vinflunine	Urinary	Advanced or metastatic TCC or urothelial tract previous platinum regimen	Group 1: Vinflunine + BSC Group 2: BSC	6.9 6.4	0.5	0.78 (0.61 to 0.96)



Source: Davis et al., BMJ, 2017

The use of PFS as a surrogate endpoint

- Is PFS a valid surrogate for OS?
  - SR Ciani (2014): in advanced solid tumors
    - "The strength of the association between the two surrogates and OS was generally low. The level of evidence (observation-level versus treatment-level) available varied considerably by cancer type, by evaluation tools and was not always consistent even within one specific cancer type."
  - SR Prasad (2015): in Oncology
    - "most trial-level validation studies of surrogate end points in oncology find low correlations with survival." and that "the evidence supporting the use of surrogate end points in oncology is limited."
  - Gyawali et al. (2020): Evaluating the evidence behind the surrogate measures included in the FDA's table of surrogate endpoints as supporting approval of cancer drugs (breast cancer)
    - "The results from correlation studies evaluating pCR, DFS, ORR, and PFS suggest that the treatment effects on none of these surrogate measures were strongly correlated with treatment effects on OS."

- Can PFS be considered as a surrogate for QoL?
  - QoL as an endpoint: 190/352 trials (54%), reported in 147/190 trials (77%)
  - Correlation: weak

IJC International Journal of Cancer 29 October 2018

Association between progression-free survival and patients' quality of life in cancer clinical trials

Abstract

Quality of life outcomes provide essential information for patients and physicians in oncology care. However, the validity of progression-free survival (PFS) as a surrogate for quality of life, and the inclusion and reporting of quality of life endpoints in clinical trials, is unclear. We performed a retrospective study of phase III clinical trials of drugs for advanced or metastatic solid tumors published between 2010 and 2015. Correlation coefficient (*r*) and area under the ROC curve (AUC) for association between PFS and positive quality of life were evaluated. Of the 352 Phase 3 trials included, 190 (54%) included a quality of life endpoint, of which 23% did not report pre-specified quality of life outcomes; a total of 125,962 patients were enrolled in studies lacking, or not reporting, quality of life outcomes. Among the 147 trials that reported quality of life outcomes, 99 (67%) reported no effect, 38 (26%) reported a positive effect and 10 (7%) reported a negative effect of treatment on patients' global quality of life. The association between PFS and improvement in global quality of life was weak ($r = 0.34$; AUC = 0.72), as was the association between PFS and improvement in any domain of quality of life. In conclusion, PFS benefit was not strongly correlated with improvements in patients' quality of life, and, despite the palliative intent of treatments in the advanced/metastatic setting, the availability of quality of life data from clinical trials of cancer drugs was poor.

- Arguments used to link PFS to QoL
  - chemotherapy ~toxicities and negative impact QoL
  - anxiety
  - ability to work
  - …

➔ rather arguments to include instruments that are able to measure the impact on these elements…

Remark: use of both disease-specific and generic utility instruments in complement! (EUnetHTA guideline HRQoL)

Extra

- FYI – guidance on outcomes for joint clinical assessments (JCAs)
  - Problem is recognized

The use of surrogate outcomes in the assessment of the relative effectiveness of a health technology can be controversial since the validity of surrogate outcomes has rarely been fully established in a rigorous manner (35–38). Only a few surrogate outcomes have been shown to be true measures of tangible clinical benefit.

  - HTD should provide evidence for the association (~correlation ≥0.85)

3.3.2 Association between surrogate outcomes and patient-centred outcomes

If the HTD is unable to provide data for an outcome of interest that has been specified in the scope, but another outcome (regardless of whether this has been requested in the scope or not) is believed to provide indirect information regarding the outcome of interest (i.e. is considered a surrogate outcome for the outcome of interest), this should be described in the dossier. The HTD should explain for which outcome of interest a surrogate is applied and demonstrate the strength of the association between the surrogate outcome and the outcome of interest and the association of treatment effects on the surrogate and the outcome of interest (see Section 3.3.3 for more details on level of evidence for surrogacy). For example, if the outcomes "mortality" and "HbA1C" are both specified as outcomes in a scope, the HTD is only required to demonstrate the strength of the association between HbA1C and mortality, if the data for mortality is not available or very limited (e.g. due to very limited events), and the HTD considers HbA1C to provide information about the technology's expected effect on mortality.

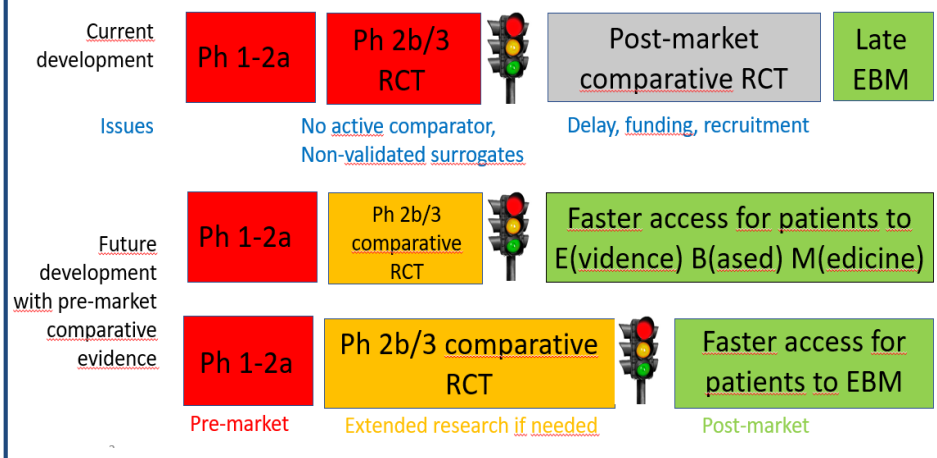
Recommendations (2021)

- See synthesis for a full overview… (~extra slides)
- Focus: better balance between 'early' access & generating evidence on the true added value
  … over the life cycle of an 'innovative' drug
  Both at: (2 crucial moments with high leverage)
  - EMA/JCA level: start (RCTs, comparator, endpoints, (in)appropriate cross-over, etc.) + transparent publication of results, use of conditional approval, etc.
  - (inter)national level: application of MEAs, international collaboration

- High potential HTA regulation
  - JSC (~PICOS)
  - JCA
    - Impact scoping (~PICO)
    - ➔ post-market collaboration
      - ➢ Further research
      - ➢ Price negotiations

Towards comparative evidence generation in phase 2b/3

Jointly approved by regulators and HTA/payers
with public (co-)financing of trial infrastructure



HAVE BETTER EVIDENCE AT MARKET LAUNCH! (←→ MEAs)

FYI – Recommendations (2021)

- Part 1/5
- Have better evidence at market launch

To the European Commission, the European Medicines Agency (EMA) & the NIHDI:

1. We recommend not focusing primarily on early access to "innovative" oncology drugs. The primary concern should be to provide timely access to medicines for which clear and reliable added value for the patient has been demonstrated. Below we give concrete recommendations to achieve this goal.

To the European Commission, EMA & companies:

2. We recommend conducting studies already in the pre-marketing phase that are suitable for registration purposes, reimbursement decisions and support for physicians and patients when taking decisions about treatments. Since it is more difficult to provide additional evidence of effectiveness after marketing authorisation was granted, it is crucial to start the necessary studies in a timely manner.
3. In designing these studies, we recommend that there is more focus on including the correct (active) comparator(s), relevant endpoints (including overall survival and quality of life) and adequate follow-up without inappropriate crossover of patients.
   - A close collaboration of HTA agencies/payers with the support of EMA for this approach to start up practice-relevant studies in the pre-marketing phase must be legally anchored in European law (see recommendation 5).
   - Given the often uncertain and limited added value of cancer drugs, randomised studies must be prioritised as the most reliable source for estimating the added value of new interventions. Non-randomised observational data should not simply be regarded as a reliable study design for estimating the treatment effect.
   - These randomised trials should pay due attention to the following:
     - Including a population that reflects the future target population.
     - Incorporating the standard treatment as a comparator. Elements of treatment optimisation (e.g. the duration of the treatment) should also already be evaluated in the pre-marketing phase.

- Pre-market
- PICO
- RCT

- Part 2/5

- Relevant endpoints are quality of life and survival. These should be included in the studies where possible.
- Surrogate endpoints can only be useful where they are sufficiently scientifically validated for the specific condition and mechanism of action of the drug. We recommend following the EUnetHTA guideline whereby data on overall survival as well as quality of life should be systematically collected in the metastatic setting (stage IV).
- Measuring quality of life, using both disease-specific and generic utility tools (as also recommended by EUnetHTA). Quality of life should also be measured throughout the full follow-up of the study (e.g. also after disease progression).
- Strictly avoiding inappropriate crossover of patients in the study.

4. We recommend strict monitoring regarding the timely and complete reporting of all study results. For example, the impact on quality of life must be reported transparently (i.e. results for all treatment arms and all time points when this outcome was measured). The full results of clinical studies should be made public and never be confidential. Like other key endpoints, quality of life and overall survival should be included in the EPAR (European Public Assessment Report).

To the Minister of Public Health and the European Commission, regarding EMA:

5. We recommend that the European Commission adjust the regulatory framework for the EMA, while respecting the difference in competences between the EMA and the national authorities. It should be enshrined that through mandatory early dialogues, the input of the payers and HTA bodies in the member states is taken into account when drafting the protocol of the confirmatory clinical trials. This will help to prevent the studies designed from not providing the information needed to support subsequent reimbursement decisions (see also recommendations 2 and 3).
6. We recommend the European Commission urging the EMA to make more selective use of conditional marketing authorisation if evidence as to the treatment's effect is insufficient. This approval must then be made conditional, with an explicit requirement to collect the required data within a certain period. Conditional approval should be automatically withdrawn if the necessary studies are not initiated/continued/delivered. This should be sufficient incentive to deliver the required data on time. It should be further investigated which criteria can be used for the selective application of the conditional market authorisation and how compliance with the conditions imposed can be monitored.

- Surrogates
- All results
- Early dialogues
- Conditional market authorization

- Part 3/5

To the NIHDI:

7. When reviewing each submitted dossier, we recommend checking that all study results are present (for all studies initiated and for all endpoints incl. quality of life) when reviewing each file.
8. We recommend only accepting the use of surrogate endpoints where they are sufficiently scientifically validated.
9. We recommend using the system of managed entry agreements (MEAs) more selectively and ensuring the necessary data are actually collected. We recommend striving more for an evidence generation system that also helps to resolve the clinical uncertainties. The moment of the reimbursement decision can be used as leverage to achieve this. To make this run efficiently, we recommend the following:
   a. We emphasize that the uncertainties should initially be addressed at European level (see recommendations regarding EMA). Where there is still a major residual uncertainty, it can be determined at a national level which type of study is necessary to answer the outstanding research questions. International cooperation is recommended for this (e.g. in the context of the BeNeLuxA initiative).
   b. We recommend paying attention to the correct study design for collecting further information in order to answer the original research questions. When using observational data from registers, they must be critically examined whether the available data will be able to provide an answer to the open research question. While registry-based RCTs can be a reliable source for identifying treatment effect, this is questionable with non-randomised registry information. We refer again to other requirements for further research (see recommendations regarding EMA).
   c. This question about the correct study design must be asked when concluding the agreement and must be part of this agreement. Failure to start/continue/complete the study on time should automatically lead to termination of the agreement in order to provide the necessary incentives to carry out this study on time.
   d. In order to make randomised research possible in practice, a restriction on the reimbursement to study patients can be considered in a first phase. An intervention by the payer to execute this study can be considered exceptionally (and put into perspective with the expenditure if the intervention were to be reimbursed without any

- Registries vs registry-based RCTs
- Conditional reimbursement

- Part 4/5

other condition). This does not alter the fact that the companies must make every effort to start the necessary studies before marketing authorisation is granted.

10. Given the lack of transparency and unsustainability of the current confidential price system, we recommend working with other countries to move towards a system with more transparent and acceptable public prices, which would eliminate/reduce the need for confidential agreements with artificially high public prices. An exception to the confidential prices could be that a lower price is agreed in anticipation of more reliable and relevant study results.
11. We recommend making all the assessment files of all reimbursement applications public (including those from before 2019). No results of clinical studies should be treated as confidential.

To the BCR & NIHDI:

12. We recommend requesting permission to have permanent access to reimbursement data for a longer period (>5 years), possibly until the patient's death.
13. We recommend making it possible to collect more refined data on, among others, sub-populations based on biomarkers (e.g. HER2 overexpression in breast cancer). This can be done by automatically forwarding the test results from the lab systems or by optimising the use of innovative techniques such as Natural Language Processing. It may also be useful to collect biomarker data in view of a relevant historical control group in the rare cases where a randomised trial is really not possible, especially in very small sub-populations.
14. We also recommend systematically collecting data on progression and relapse.

To all parties involved in clinical research, including the Medical Ethics Committees:

15. We recommend that due consideration be given in every clinical trial to the measurement and timely and complete reporting of quality of life (see also EUnetHTA guidelines in recommendation 3).

- Etc…

- Part 5/5

To physicians, nurses, patients, patient representatives and independent research institutions:

16. **We recommend supporting the demand for more reliable and relevant information about the added value of cancer drugs and demanding data that are important for clinical decisions (such as longevity and quality of life).**
17. **All parties must be aware that rapid access to innovative medicines only makes sense if there is clear added value for the patient. Rapid access without (generating) sufficient evidence of the drug's added value is detrimental to all parties.**
18. **The industry, physicians and patients must be aware that reimbursement of a contracted product is temporary and may be discontinued, especially if there are uncertainties about clinical efficacy.**

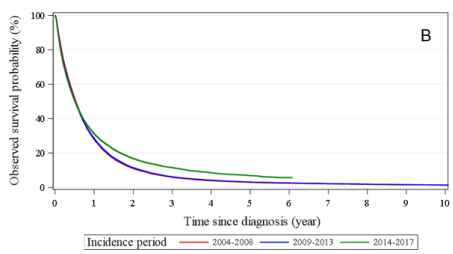
To all actors in society, including patient representatives, healthcare providers, industry, policy makers, the general public, etc.:

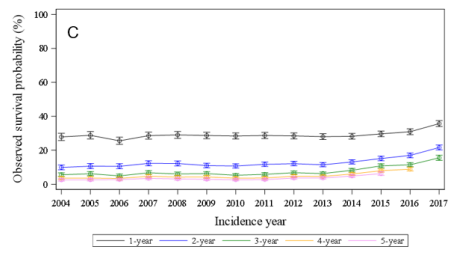
19. **A public debate is desirable on various aspects of the reimbursement of medicines, such as identifying the added value of innovative medicines, (rapid) access, affordability, etc.**

9. Non-small cell lung cancer (st.IV)

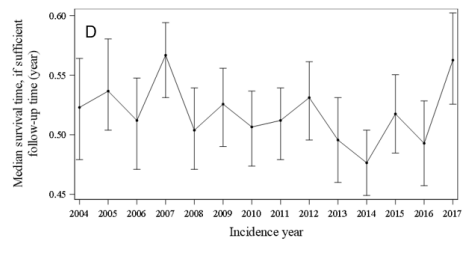
A

Characteristic	Incidence period 2004-2008	2009-2013	2014-2017
Overall	8,819	12,039	11,342
Gender			
Male	6,577 (74.6)	8,404 (69.8)	7,581 (66.8)
Female	2,242 (25.4)	3,635 (30.2)	3,761 (33.2)
Age at diagnosis (year)			
<50 years	632 (7.2)	687 (5.7)	510 (4.5)
50-59 years	1,803 (20.4)	2,456 (20.4)	1,998 (17.6)
60-69 years	2,655 (30.1)	3,748 (31.1)	3,881 (34.2)
70-79 years	2,801 (31.8)	3,581 (29.7)	3,320 (29.3)
80+ years	928 (10.5)	1,567 (13.0)	1,633 (14.4)
WHO - Performance Status			
0 – Asymptomatic	778 (8.8)	1,196 (9.9)	969 (8.5)
1 – Symptomatic but completely ambulatory	4,680 (53.1)	7,129 (59.2)	6,913 (61.0)
2 – Symptomatic, <50% in bed during the day	1,539 (17.5)	1,793 (14.9)	1,873 (16.5)
3 – Symptomatic, >50% in bed, but not bedbound	598 (6.8)	687 (5.7)	679 (6.0)
4 – Bedbound	167 (1.9)	188 (1.6)	154 (1.4)
Not reported	1,057 (12.0)	1,046 (8.7)	754 (6.6)



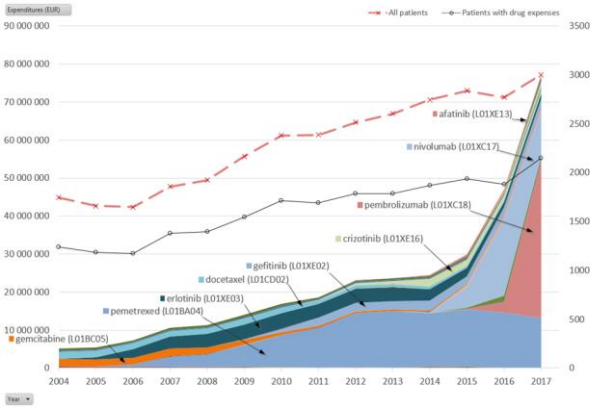


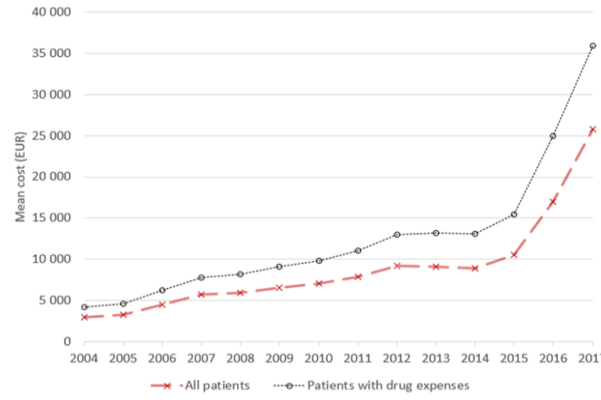
Year: 3-y OS [95%CI]
2004: 5.6 [4.6, 6.7]
2005: 6.2 [5.1, 7.4]
2006: 4.9 [3.9, 6.0]
2007: 6.8 [5.7, 8.0]
2008: 6.1 [5.0, 7.2]
2009: 6.3 [5.3, 7.3]
2010: 5.3 [4.4, 6.2]
2011: 5.8 [4.9, 6.8]
2012: 6.8 [5.8, 7.8]
2013: 6.3 [5.4, 7.3]
2014: 8.2 [7.2, 9.3]
2015: 10.8 [9.7, 12.0]
2016: 11.4 [10.3, 12.7]
2017: 15.5 [14.1, 17.1]



Year: Med. ST [95%CI]
2004: 0.5 [0.5, 0.6]
2005: 0.5 [0.5, 0.6]
2006: 0.5 [0.5, 0.5]
2007: 0.6 [0.5, 0.6]
2008: 0.5 [0.5, 0.5]
2009: 0.5 [0.5, 0.6]
2010: 0.5 [0.5, 0.5]
2011: 0.5 [0.5, 0.5]
2012: 0.5 [0.5, 0.6]
2013: 0.5 [0.5, 0.5]
2014: 0.5 [0.4, 0.5]
2015: 0.5 [0.5, 0.6]
2016: 0.5 [0.5, 0.5]
2017: 0.6 [0.5, 0.6]

9. Non-small cell lung cancer



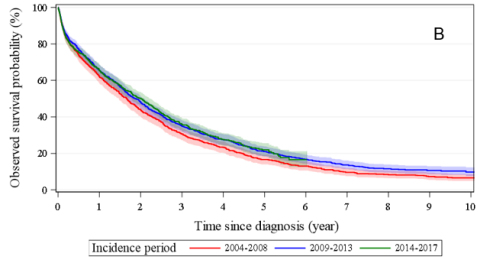


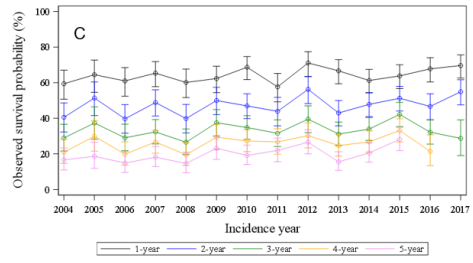
expenses for the first two years after incidence per incidence year (stage IV)

mean cost per patient for the first two years after incidence per incidence year (stage IV)

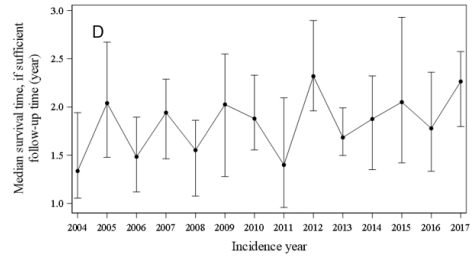
10. Ovarian cancer

A Characteristic	Incidence period 2004-2008	2009-2013	2014-2017
Overall	705	856	779
Gender			
Female	705 (100.0)	856 (100.0)	779 (100.0)
Debulking	149 (21.1)	431 (50.4)	354 (45.4)
Age at diagnosis (year)			
<50 years	56 (7.9)	69 (8.1)	49 (6.3)
50-59 years	114 (16.2)	135 (15.8)	106 (13.6)
60-69 years	183 (26.0)	222 (25.9)	205 (26.3)
70-79 years	212 (30.1)	260 (30.4)	239 (30.7)
80+ years	140 (19.9)	170 (19.9)	180 (23.1)
WHO - Performance Status			
0 – Asymptomatic	73 (10.4)	115 (13.4)	102 (13.1)
1 – Symptomatic but completely ambulatory	320 (45.4)	481 (56.2)	470 (60.3)
2 – Symptomatic, <50% in bed during the day	123 (17.4)	121 (14.1)	100 (12.8)
3 – Symptomatic, >50% in bed, but not bedbound	62 (8.8)	42 (4.9)	39 (5.0)
4 – Bedbound	14 (2.0)	12 (1.4)	8 (1.0)
Not reported	113 (16.0)	85 (9.9)	60 (7.7)



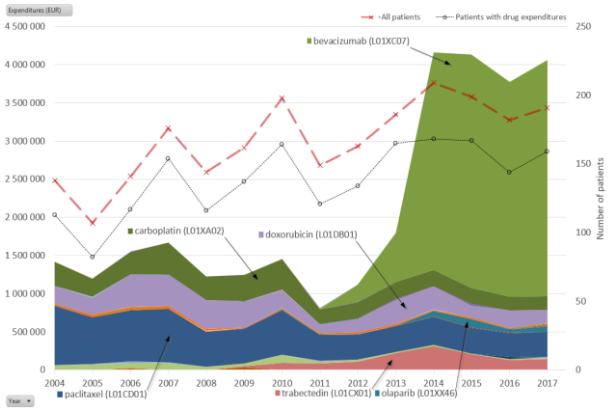


Year: 3-y OS [95%CI]
2004: 29.0 [21.7, 36.7]
2005: 37.4 [28.3, 46.4]
2006: 29.1 [21.8, 36.7]
2007: 32.4 [25.6, 39.3]
2008: 26.6 [19.6, 34.0]
2009: 37.5 [30.1, 45.0]
2010: 34.8 [28.3, 41.5]
2011: 31.6 [24.2, 39.2]
2012: 39.6 [32.0, 47.0]
2013: 31.2 [24.7, 37.9]
2014: 34.0 [27.6, 40.4]
2015: 42.2 [35.3, 49.0]
2016: 32.2 [25.5, 39.1]
2017: 28.8 [19.1, 39.2]

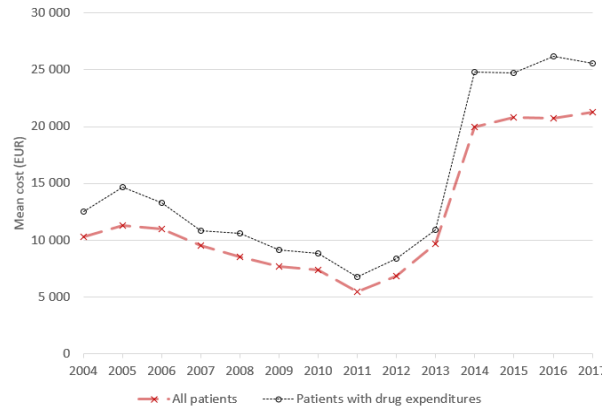


Year: Med. ST [95%CI]
2004: 1.3 [1.1, 1.9]
2005: 2.0 [1.5, 2.7]
2006: 1.5 [1.1, 1.9]
2007: 1.9 [1.5, 2.3]
2008: 1.6 [1.1, 1.9]
2009: 2.0 [1.3, 2.5]
2010: 1.9 [1.6, 2.3]
2011: 1.4 [1.0, 2.1]
2012: 2.3 [2.0, 2.9]
2013: 1.7 [1.5, 2.0]
2014: 1.9 [1.3, 2.3]
2015: 2.1 [1.4, 2.9]
2016: 1.8 [1.3, 2.4]
2017: 2.3 [1.8, 2.6]

10. Ovarian cancer



expenses for the first two years after incidence per incidence year (stage IV)



mean cost per patient for the first two years after incidence per incidence year (stage IV)

Email: mattias.neyt@kce.fgov.be
Report: https://kce.fgov.be/en/do-innovative-medicines-against-cancer-always-have-a-real-added-value

KCE
Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

Belgian Cancer Registry

eunethta European Observatory on Health Systems and Policies INAHTA