Entrectinib: a tumor-agnostic treatment for NTRK gene fusion-positive (NTRK+) cancers

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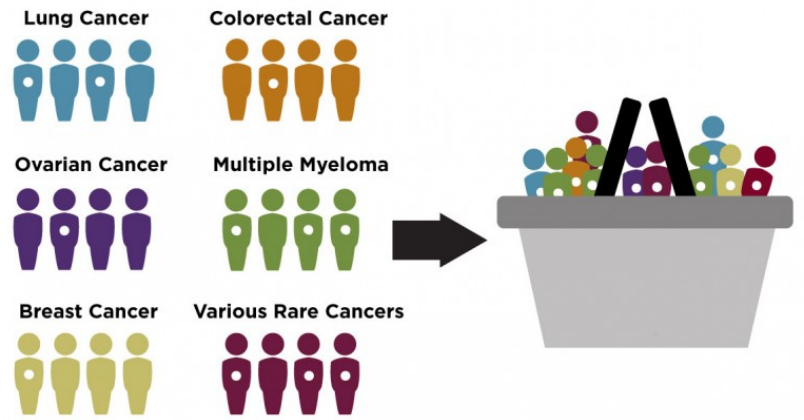
ENTRECTINIB

- **Tumor-agnostic** treatment for adult patients with locally advanced or metastatic solid tumors caused by neurotrophic receptor tyrosine kinase (NTRK) fusions
- An **inhibitor of TRK A/B/C proteins**, designed to cross the blood-brain barrier and remain in the central nervous system
- Shown to have a durable response and **long survival** (median OS 33.8 months)[1]
- NTRK fusions are **rare**: prevalence 0.3-1%
- Identifying the target group requires introduction of a(n additional) **test**:
  IHC:~€400 ; NGS-RNA: ~€1700
- Entrectinib costs **€5,900** per month in NL

1 Bazhenova et al, ESMO 2021; n=121

CHALLENGE

- EMA/FDA approved based on **single arm** trials
- **Basket trials** with **small** number of NTRK+ patients (n=121; 14 different tumor types)[1]
- Little known about **prognostic value** of NTRK+, but preliminary evidence suggests it worsens prognosis
- Comparator (SoC) cannot be modelled with historical data on all patients with the same tumor types, because these data are an **unknown combination of those with but mostly without the NTRK fusion**
- Little known about (downstream consequences of) **test strategy**



1 Bazhenova et al, ESMO 2021; n=121

CHALLENGE TO IMPLEMENT RECOMMENDATIONS

11. Where possible, use effectiveness data from trials with **two (or more) alternative treatment strategies**.

13. When the comparative effectiveness of a treatment for patients with a specific genetic marker is estimated using an **external data source** for the comparator, account for the **prognostic value** of the genetic marker and **differences in its prevalence** across the different data sources.

9. When a treatment requires the use of a test to stratify patients, include the **(downstream) costs and health outcomes of testing** for both individuals who test **positive** and individuals who test **negative** in the model.

TEST STRATEGY

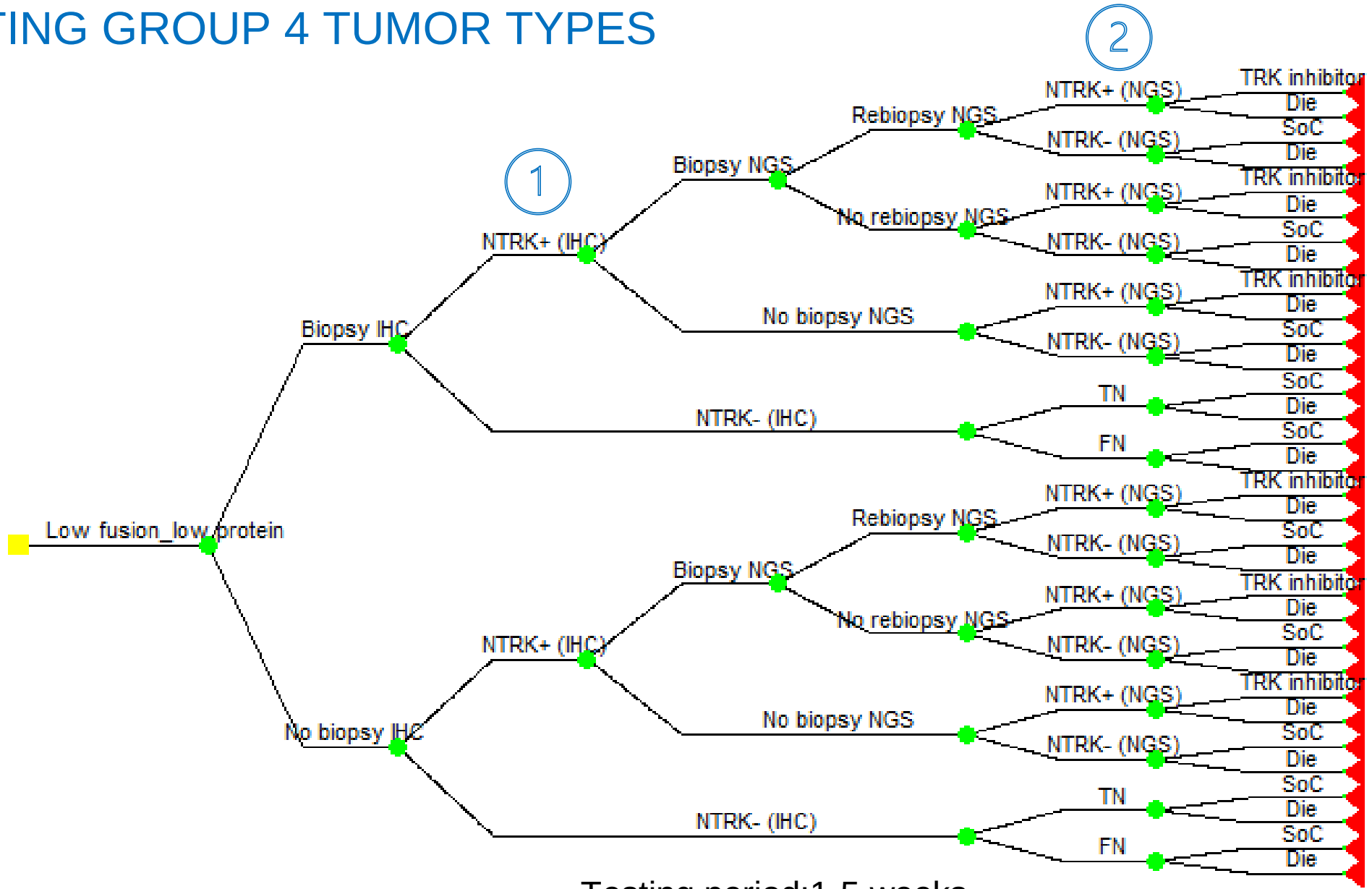
- Two tests: **IHC** (Se 73-100%; Sp 50-100%) and **NGS-RNA** (Se and Sp 100%)

- To model the testing phase, the tumor types were categorised into **4 a-priori groups**
  - Based on 2020 “Consensus report” developed by group of experts, which outlines envisioned NTRK testing policy in Dutch clinical practice

1. Non-small cell lung cancer (NSCLC): no new test
2. Tumor types with high NTRK fusion prevalence: NGS-RNA
3. Tumor types with low NTRK fusion prevalence but wild-type* TRK protein expression: NGS-RNA
4. Tumor types with low NTRK fusion prevalence and no/very little wild-type* TRK protein expression: IHC+NGS-RNA

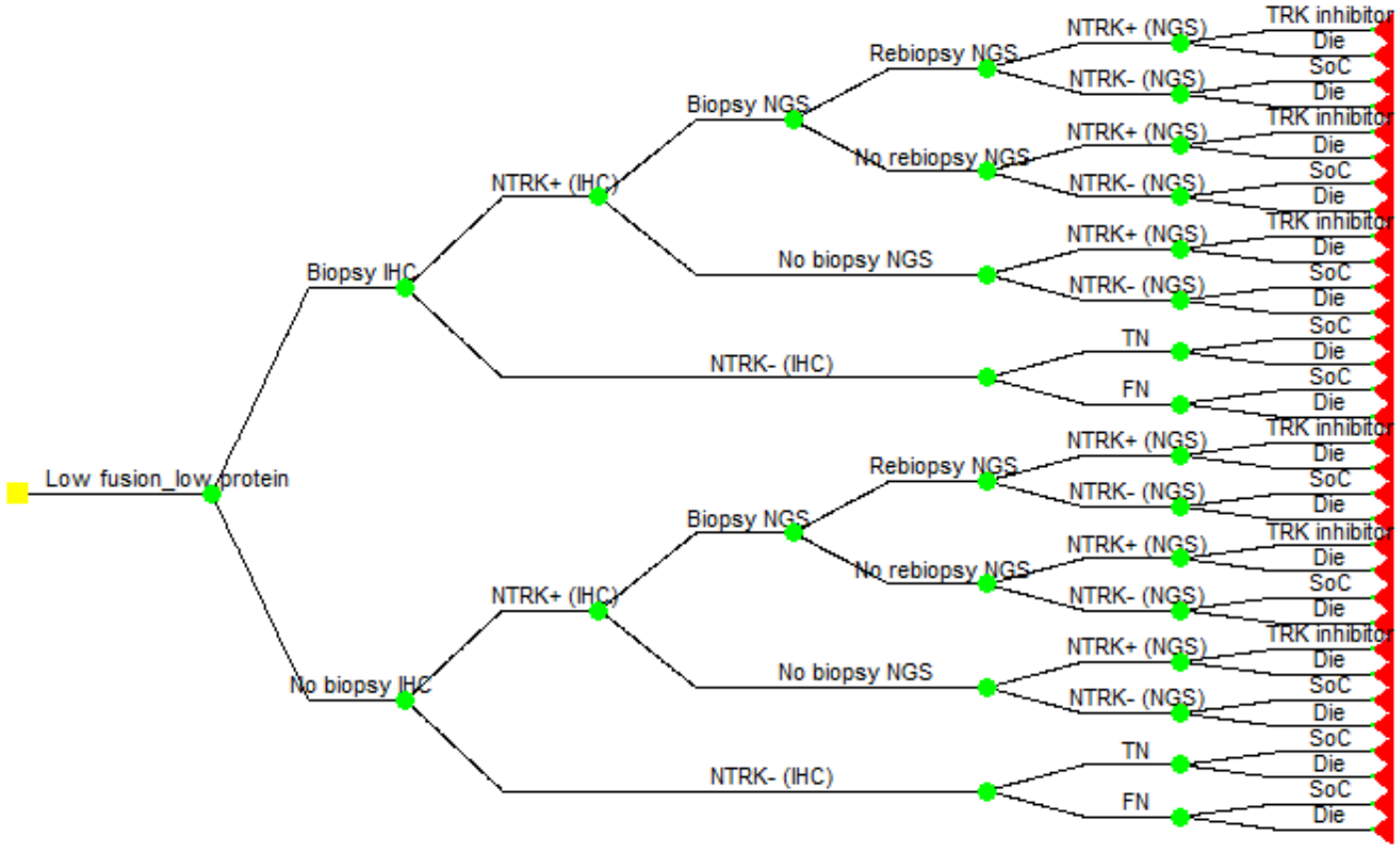
*wild type: naturally occurring in the type of tissue in which the cancer is located

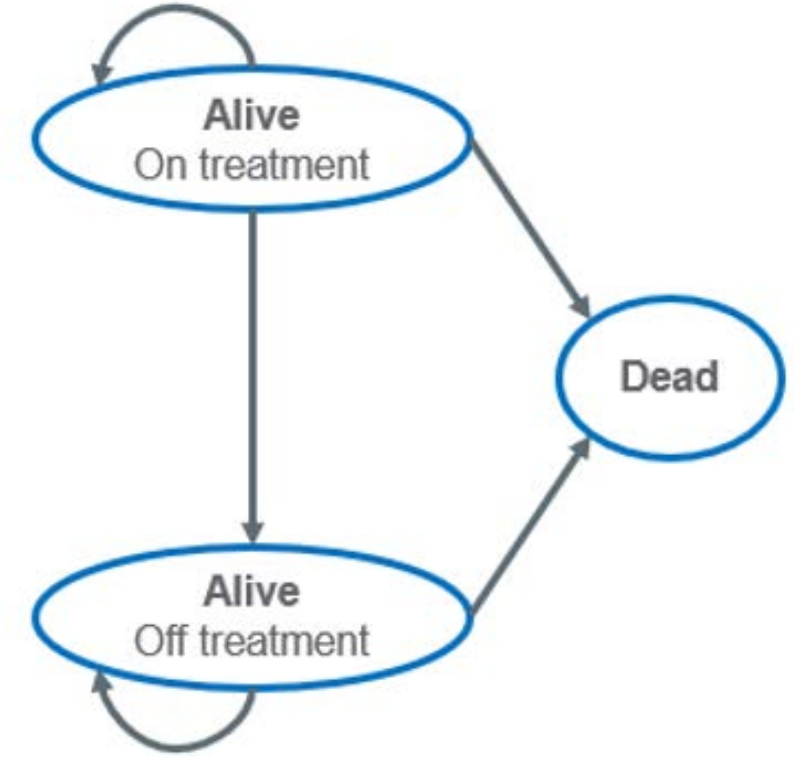
TESTING GROUP 4 TUMOR TYPES



Testing period:1-5 weeks

DECISION TREE + MICRO SIMULATION MODEL IN R





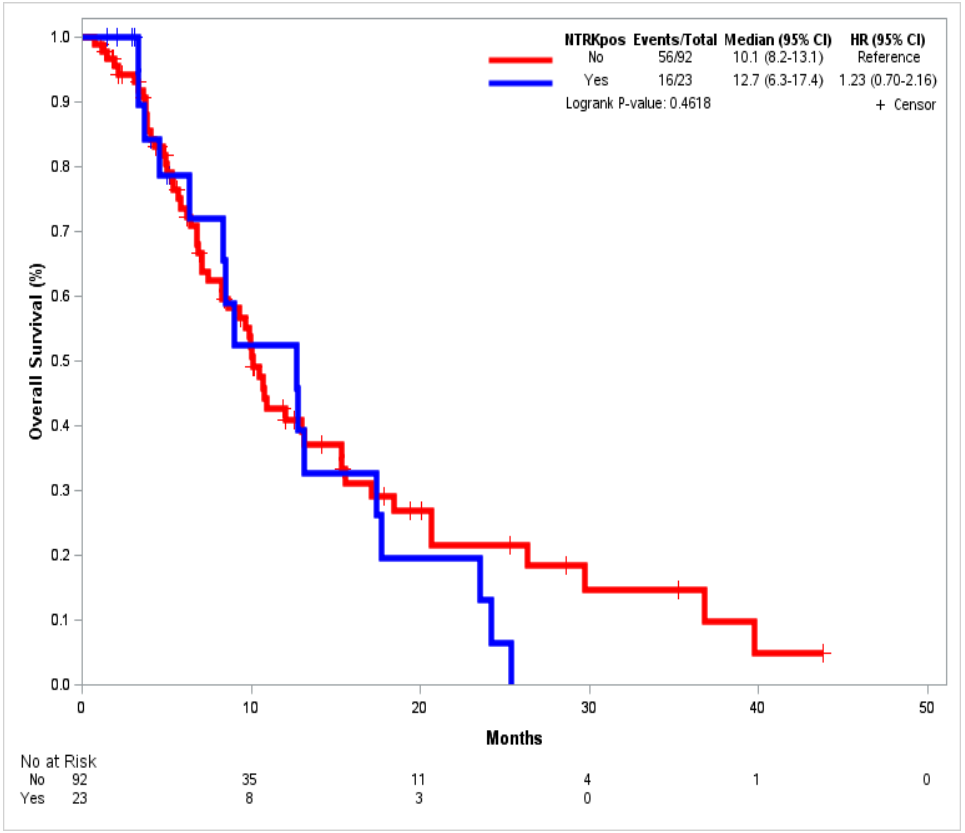
Decision to receive additional treatment

Start treatment

Death

EXTERNAL DATA FROM HARTWIG MEDICAL FOUNDATION

- CPCT-02 study, in which whole-genome sequencing was performed for metastatic cancer patients (n=3,547 with known tumor location)
- 23 NTRK+ patients were matched with 92 NTRK- patients
- In an unadjusted analysis, the HR for NTRK+ patients was 1.23 [95% CI: 0.70, 2.16]
- After adjusting for age, gender and previous line of treatment, the multivariable Cox regression found an **HR of 1.32** [95% CI: 0.75, 2.33], confirming the results of the unadjusted analysis.
- Same approach for time to treatment discontinuation (**HR: 1.45** [95% CI: 1.90-2.34]



HMF data-cut November 2021

TIME TO DEATH AND TIME TO TREATMENT DISCONTINUATION

SoC

- We fitted parametric distributions to data of NTRK- patients in the Hartwig Medical Foundation database
  - Only for tumor types that were also included in clinical trials entrectinib
  - Separate parametric distributions were fitted for each tumor type, on NTRK- patients that received SoC (excluding experimental treatments)
  - We obtained monthly transition probabilities to death and treatment discontinuation from these distributions
- The estimated HR was applied to NTRK- patients to obtain the transition probabilities for NTRK+ patients

Entrectinib

- We used the exponential distribution for OS in the HE-model submitted to the reimbursement authorities by Roche (n=54 NTRK+ from 12 different tumor types: Doebele et al., Lancet Oncol 2020; 21: 271–82)

COST-EFFECTIVENESS RESULTS: SOCIETAL PERSPECTIVE*

Base case: testing + entrectinib vs no testing

Strategy	Costs (in €)	QALYs	ICER
Testing, Entrectinib for NTRK+ patients, SoC for NTRK- patients	87,631	0.9590	
No NTRK testing, SoC for all patients	86,943	0.9545	
Incremental	687	0.0045	**152,917**

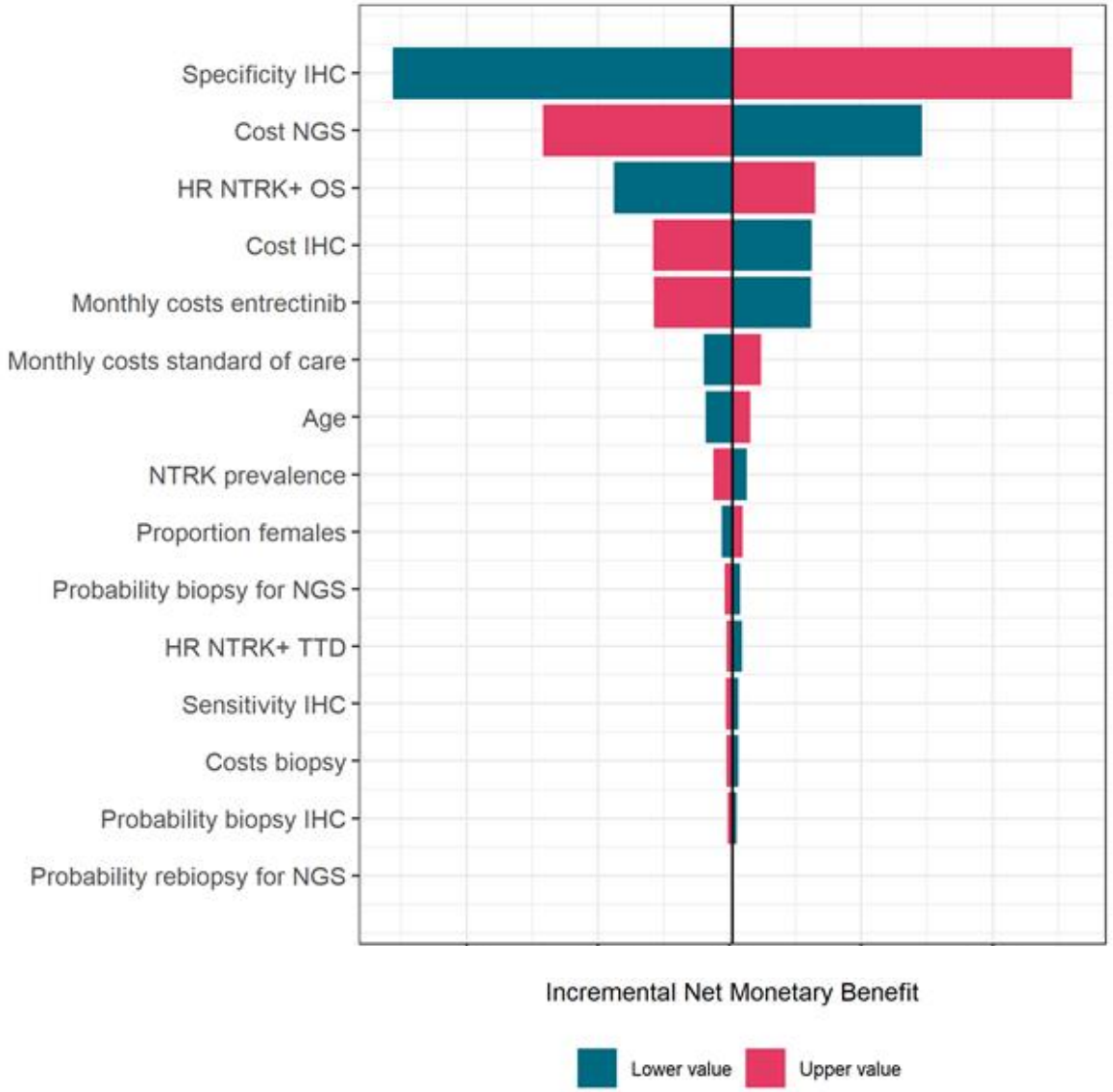
Only 0.32% of all patients tested get entrectinib

*Societal perspective: incl. health care costs (related and unrelated), informal care costs, excl. productivity costs

Scenario analysis without the test phase

Strategy	Costs (in €)	QALYs	ICER
Entrectinib for NTRK+	135,631	2.210	
SoC for NTRK+	80,566	0.717	
Incremental	55,064	1.493	**36,877**

ONE-WAY SA TESTING + ENTRECTINIB VS NO TESTING



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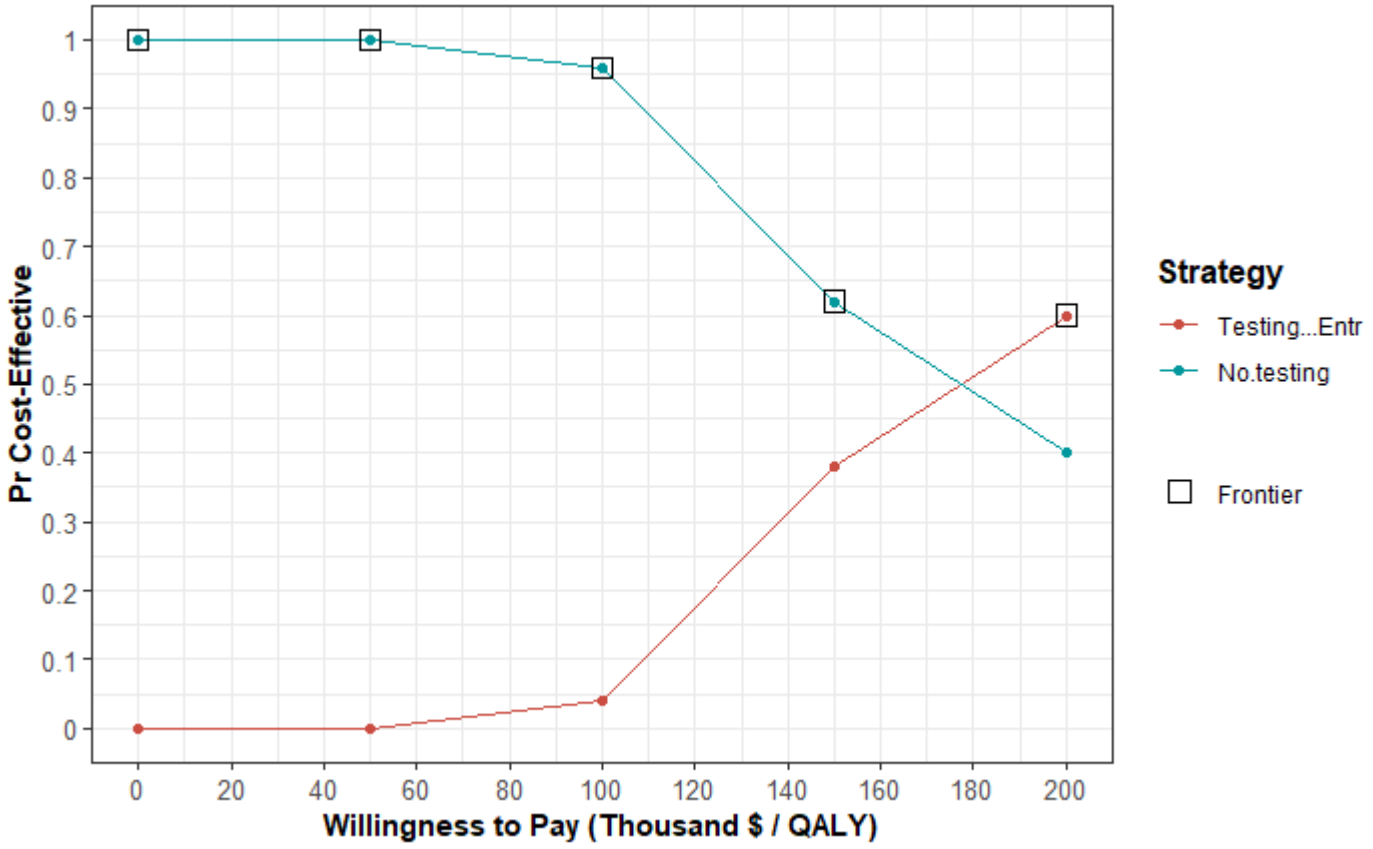

TESTING HECOPERMED RECOMMENDATIONS

Recommendations in guidance	NTRK
Addressed	11
Not applicable	5
Not included	7
Total	23

Guidance items	Recommendations	Application to the MODY case study
Perspective and Discounting	1. For economic evaluations of PM, use the standard perspective as recommended by national HTA guidelines in the base case.	applied
	2. For economic evaluations of PM, use the standard discount rates as recommended by national HTA guidelines in the base case.	applied
Test-Treatment Pathways	3. Identify all relevant test-treatment pathways and justify why the pathways included in the model were selected.	applied
	4. When treatment requires the use of a test to stratify patients, include in the model the (downstream) costs and health outcomes of testing for both individuals who test (false-)positive and individuals who test (false)negative.	applied
	5. Ensure that the data used to estimate the diagnostic accuracy of a testing technology are appropriate to the patient population in the model.	applied
	6. When different cut-off values are in use to determine test results, clearly define the cut-off value assumed in the base case. Investigate the effect of alternative cut-off values on cost-effectiveness results using a sensitivity analysis.	not applicable
	7. When multiple tests are modelled in sequence, consider the interdependence between test results.	applied
	8. If there is a notable risk of increased morbidity or mortality as a result of waiting periods, incorporate in the model the costs and health outcomes due to the waiting periods.	applied
	9. Confirm that the assumed testing costs are accurate in the setting of interest and consider possible variations in costs across laboratories.	applied
	10. If relatives of index patients become eligible for genetic testing when the index patients test positive for a specific genetic marker, include the costs and health outcomes of testing relatives in the economic evaluation of the index patients.	not applicable
Effectiveness Data	11. Where possible, use effectiveness data from trials with two (or more) alternative treatment strategies.	not applicable
	12. When surrogate outcomes are used to estimate final outcomes, specify which data sources were used to estimate the relationship between surrogate and final outcomes and justify any assumptions made about the relationship	not applicable
	13. When the effectiveness of the comparator is estimated using external data, account for a possible time trend in the effectiveness.	not included
	14. When the effectiveness of the comparator for patients with a specific genetic marker is estimated using external data, account for the prognostic value of the genetic marker and differences in its prevalence across the different data sources.	applied
	15. Specify which data sources were used to estimate the association between the genetic marker(s) of interest and clinical outcomes and justify any assumptions made about the association.	applied
Extrapolating Survival	16. When extrapolating survival data beyond the study period, use expert opinion alongside statistical fit to choose the survival model.	not included
	17. When extrapolating survival data beyond the study period, account for any excess mortality and morbidity among long-term survivors.	not included
Additional Elements of Value	18. Only include elements of value recommended by national HTA guidelines in the base case. If additional elements of value are included in a sensitivity analysis, ensure possible elements of negative value are equally considered and included for both the intervention and the comparator.	applied
Incorporating Compliance	19. Include parameters reflecting patient and clinician compliance in economic evaluations for decision-makers who require cost-effectiveness results under realistic circumstances.	not included
	20. When including patient and clinician compliance in economic evaluations, confirm that the assumed compliance is accurate in the setting of interest and consider possible variation in compliance across societal groups.	not applicable
Uncertainty Analysis	21. When expert judgement is used to estimate values for the input parameters in the model, synthesise the elicited values into a probability distribution to be included in a sensitivity analysis.	not included
	22. Identify uncertainties in structural assumptions and decisions and investigate their impact on cost-effectiveness results through a sensitivity analysis. Parameterise structural aspects where possible.	not included
Managed Entry Agreements	23. If a managed entry agreement is being considered for intervention, including its conditions in the model evaluating the intervention.	not included

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Health Economics for Personalised Medicine

THANK YOU!

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POLLING QUESTION

Will our approach of accounting for the prognostic value of being NTRK positive in the 'artificial' comparator arm be acceptable for HTA bodies?