Electronic Supplementary Material

Article title: Economic Evaluation of a Tumour-Agnostic Therapy: Dutch Economic Value of Larotrectinib in TRK Fusion-Positive Cancers

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Author list: Renee E. Michels, Carlos H. Arteaga, Michel L. Peters, Ellen Kapiteijn, Carla M. L. Van Herpen, Marieke Krol

Corresponding author: Renee E. Michels (renee_michels@hotmail.com)

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# APPENDIX 1 BASELINE CHARACTERISTICS

Table 1: Baseline characteristics of larotrectinib patients [1]

|                                      | Age <18 (n = 34) | Age >= 18 (n = 68) | Total (102) |
|--------------------------------------|------------------|--------------------|-------------|
| Age, mean (SD)                       | 5.2 (4.9)        | 53 (16.7)          | 37.1 (26.6) |
| Sex, male n (%)                      | 15 (44%)         | 39 (57%)           | 54 (53%)    |
| Race, n (%)                          |                  |                    |             |
| White                                | 21 (62%)         | 52 (76%)           | 73 (72%)    |
| Black                                | 1 (3%)           | 4 (6%)             | 5 (5%)      |
| Asian                                | 1 (3%)           | 3 (4%)             | 4 (4%)      |
| All others                           | 11 (32%)         | 9 (13%)            | 20 (20%)    |
| Body surface area, m2 mean (SD)      | 0.74 (0.4)       | 1.88 (0.31)        | 1.49 (0.6)  |
| Primary tumour type, n (%)           |                  |                    |             |
| Appendix                             | 0                | 1 (1%)             | 1 (1%)      |
| Bone sarcoma                         | 0                | 2 (3%)             | 2 (2%)      |
| Breast                               | 0                | 1 (1%)             | 1 (1%)      |
| Cholangiocarcinoma                   | 0                | 2 (3%)             | 2 (2%)      |
| Colon                                | 0                | 6 (95)             | 6 (6%)      |
| Congenital mesoblastic nephroma      | 1 (3%)           | 0                  | 1 (1%)      |
| GIST                                 | 1 (3%)           | 4 (6%)             | 5 (5%)      |
| IFS                                  | 13 (38%)         | 0                  | 13 (38%)    |
| Lung                                 | 0                | 7 (10%)            | 7 (7%)      |
| Melanoma                             | 1 (3%)           | 6 (9%)             | 7 (7%)      |
| Pancreas                             | 0                | 1 (3%)             | 1 (1%)      |
| Primary CNS                          | 6 (18%)          | 3 (4%)             | 9 (9%)      |
| Salivary gland                       | 0                | 17 (25%)           | 17 (17%)    |
| Soft tissue sarcoma                  | 11 (32%)         | 9 (13%)            | 20 (20%)    |
| Thyroid                              | 1 (3%)           | 9 (13%)            | 10 (10%)    |
| Disease extent at enrolment, n (%)   |                  |                    |             |
| Locally advanced                     | 14 (41%)         | 6 (9%)             | 20 (20%)    |
| Metastatic                           | 15 (44%)         | 62 (91%)           | 77 (75%)    |
| Other                                | 5 (15%)          | 0                  | 5 (5%)      |
| Tumour stage at diagnosis, n (%)     |                  |                    |             |
| I                                    | 7 (21%)          | 4 (6%)             | 11 (10.8)   |
| II                                   | 8 (24%)          | 8 (12%)            | 16 (15.7)   |
| III                                  | 10 (29%)         | 17 (25%)           | 27 (26.5)   |
| IV                                   | 5 (15%)          | 22 (32%)           | 27 (26.5)   |
| Not reported                         | 4 (12%)          | 17 (25%)           | 21 (20.6)   |
| Baseline ECOG, n (%)                 |                  |                    |             |
| 0                                    | 26 (76%)         | 21 (31%)           | 47 (46%)    |
| 1                                    | 5 (15%)          | 39 (57%)           | 44 (43%)    |
| 2                                    | 3 (9%)           | 8 (12%)            | 11 (11%)    |
| Time on treatment, months            |                  |                    |             |
| mean (SD)                            | 11.7 (7.2)       | 13.3 (10.5)        | 12.8 (9.5)  |
| median (Q1, Q3)                      | 9.6 (6.6, 16.3)  | 11.6 (5.2, 19.7)   | 10.0 (5.5, 18.4) |
| Min, max                             | 2.8, 27.6        | 0.0, 40.7          | 0.0, 40.7   |

SD: Standard deviation, GIST: Gastrointestinal Stromal, IFS: Infantile fibrosarcoma, CNS: Central nervous system, CR: Complete response, ECOG: Eastern Cooperative Oncology Group
APPENDIX 2 EFFICACY

The patients who were evaluable for efficacy outcomes are included in the model (Bayer SMPC). The data-cut used for the model inputs was the 30th of July 2018. Table 7 gives an overview of the clinical outcomes in these analysis sets as reported in the SMPC [1]. The main efficacy outcomes of interest in the model were progression free survival (PFS) and overall survival (OS). These are based on the below outputs, and they are reported in more detail below the table.

Table 2: Results from the larotrectinib clinical trial program

| Analysis in solid tumours including primary CNS tumours (n=102) | Overall response rate (ORR)% (n) [95% CI] |
|----------------|--------------------------------------|
| Complete response (CR) | 15% (15) [
| Surgical complete response | 1% (1) |
| Partial response (PR) | 51% (52) |
| Time to first response (median, months) [range] | 1.81 [0.95, 14.55] |
| Duration of response (median, months) [range] | NR [1.6+, 38.7+] |
| % with duration ≥ 6 months | 88% |
| % with duration ≥ 12 months | 75% |

At the point of data-cut, the median duration of follow-up for the PFS in the analysis group excluding CNS tumours was 13.8 months. The median independent review committee assessed PFS was 27.4 months (13.8-NE). However, 63% was censored (no disease progression at time of data-cut). For the OS, the median duration of follow-up was 16.7 months in the analysis group excluding CNS tumours. The median OS was not estimable (NE). At the point of data-cut, 85% of patients was alive.

In the analysis group for the CNS tumours, the median duration follow-up was 5.5 months for PFS. The median investigator assessed PFS was 6.3 months. However, 67% was censored (no disease progression at time of data-cut). For the OS, the median duration of follow-up was 4.6 months in the analysis group for the CNS tumours. The median OS was NE. At the point of data-cut, 100% of patients was alive.

A more conservative choice was made, as this was deemed more appropriate for modelling the clinical efficacy of larotrectinib. The choice for Weibull resulted from assessing clinical feasibility and from visual fit. Weibull features more feasible clinical outputs as assessed during the validation process of the global model. In fact, besides Akaike Information Criteria (AIC), clinical plausibility was considered as well. It was decided to set by default PFS and OS for larotrectinib to Weibull, in order to reflect clinical plausibility and allow change in hazard with aging.

Table 8 shows the chosen parametric curves chosen for the base case setting. The choice was based on statistical, clinical, and visual fit.

Table 3: Modelled parametric curve in base case analysis

| Model input | Parametric curve chosen | Source |
|-------------|-------------------------|--------|
| Larotrectinib PFS | Weibull | Analysis of Bayer larotrectinib clinical trial program [1] |
| Larotrectinib OS | Weibull | Analysis of Bayer larotrectinib clinical trial program [1] |
| NSCLC PFS | Log-Normal | [10] |
| NSCLC OS | Log-Normal | [11] |
Table 4: Fit assessment for larotrectinib PFS

| Distribution       | Shape       | Scale       | AIC      | BIC      |
|--------------------|-------------|-------------|----------|----------|
| Exponential (lambda) | 0.03294294  |             | 328.56   | 330.17   |
| Gompertz (gamma, lambda) | -0.05039619 | 0.04879833  | 326.44   | 329.66   |
| Log-logistic (p, lambda) | 1.0104106   | 0.04386114  | 327.14   | 330.37   |
| Log-normal (sigma, mu) | 1.7347294   | 3.1452093   | 325.13   | 328.35   |
| Weibull (p, lambda)   | 0.85548562  | 0.04854379  | 329.24   | 332.46   |
| Generalised gamma (mu, ln(sigma), kappa) | 2.645       | 0.697139202 | 326.16   | 330.99   |

Besides Akaike Information Criteria (AIC), clinical plausibility was considered as well for larotrectinib. It was decided to set by default PFS and OS for larotrectinib to Weibull, in order to reflect clinical plausibility and allow change in hazard with aging.

Table 5: Fit assessment for larotrectinib OS

| Distribution       | Shape       | Scale       | AIC      | BIC      |
|--------------------|-------------|-------------|----------|----------|
| Exponential (lambda) | 0.00928033  |             | 161.036  | 161.675  |
| Gompertz (gamma, lambda) | -0.04986387 | 0.01449888  | 161.293  | 162.571  |
| Log-logistic (p, lambda) | 0.94056116  | 0.04386114  | 162.372  | 163.65   |
| Log-normal (sigma, mu) | 1.7347294   | 3.1452093   | 161.077  | 162.356  |
| Weibull (p, lambda)   | 0.88472944  | 0.01294034  | 162.756  | 164.034  |
| Generalised gamma (mu, ln(sigma), kappa) | 2.667       | 1.039216079 | 161.089  | 163.006  |

Besides Akaike Information Criteria (AIC), clinical plausibility was considered as well for larotrectinib. It was decided to set by default PFS and OS for larotrectinib to Weibull, in order to reflect clinical plausibility and allow change in hazard with aging.

1 For salivary gland PFS there was only information available for the exponential curve.
2 In several instances, the methods used to model time-to-event outcomes in previous appraisals were more complex than application of a simple fitted distribution. Specifically, for comparators in breast and melanoma tumours, a more complex model such as a piecewise or spline model was determined by the NICE Committee to be the preferred method. This approach was also used for the Netherlands. A more detailed description of this is given in the technical report of the cost-effectiveness model.
3 All curves were chosen based on statistical, clinical, and visual fit. For this specific curve, the best statistical fit resulted in an illogical visual fit. Therefore, the log-logistic was chosen.
4 For the Breast cancer clinical input, the KM curves were complete. It was not necessary to extrapolate these data.
### Table 6: PFS

| Distribution                                   | Shape | Scale  | Delta squared | Shape | Scale  | Least square | AIC  | BIC  |
|-----------------------------------------------|-------|--------|---------------|-------|--------|-------------|------|------|
| Exponential (lambda)                          | 0.0039793 | 28 | 0.82135755 | 0.0026595 | 69 | 0.2579999 | 27 | 0.0013668 | 85 | 27.456 | 3 | 29.2178 | 1 | 0.0065520 | 39 | 122.374 | 1 | 124.548 | 5 | 0.00196 | 1 | 331.81 | 8 |
| Gompertz (gamma, lambda)                      | - | 35.997377 | 29 | 20.871359 | 12.861234 | 45 | 4.8743417 | 55 | 1.4350952 | 68 | 2.9706484 | 25 | -0.0083873 | 78 | 0.0021992 | 78 | 28.9712 | 4 | 52.4936 | 4 | -0.0012921 | 0.0073115 | 86 | 124.010 | 9 | 128.359 | 6 | 0.00050 | 3 | 0.00177 | 3 | 345.27 | 4 | 351.94 | 0 |
| Log-logistic (p, lambda)                      | 2.0358589 | 75 | 2.49523E-05 | 0.1910365 | 52 | 0.9710364 | 17 | 0.0040968 | 25 | 0.1184697 | 77 | 0.8602031 | 56 | 0.0027544 | 96 | 29.2021 | 9 | 52.7245 | 9 | -0.0002382 | 0.0002382 | 112.251 | 9 | 116.600 | 7 | 1.53267 | 1 | 0.00144 | 2 | 336.11 | 7 | 342.77 | 7 |
| Log-normal (sigma, mu)                        | 5.1072326 | 58 | 5.1502773 | 1.910365 | 52 | 0.9710364 | 17 | 0.0040968 | 25 | 0.1184697 | 77 | 0.8602031 | 56 | 0.0027544 | 96 | 29.2021 | 9 | 52.7245 | 9 | -0.0002382 | 0.0002382 | 112.251 | 9 | 116.600 | 7 | 1.53267 | 1 | 0.00144 | 2 | 336.11 | 7 | 342.77 | 7 |
| Weibull (p, lambda)                            | 1.4974234 | 37 | 0.0002912 | 0.0787098 | 64 | 0.7930201 | 44 | 0.0073546 | 87 | 0.1484867 | 83 | 0.8282252 | 67 | 0.0030365 | 66 | 29.2653 | 6 | 52.7877 | 5 | 0.1178601 | 0.1484867 | 112.321 | 9 | 122.733 | 6 | 1.21789 | 8 | 0.00155 | 3 | 341.14 | 7 | 347.81 | 3 |

### Table 7: PFS continued

| Distribution                                   | Shape | Scale  | Delta squared | Shape | Scale  | Delta squared | Shape | Scale  | Delta squared | Shape | Scale  | Delta squared | Shape | Scale  | Delta squared | Shape | Scale  | Delta squared | Shape | Scale  |
|-----------------------------------------------|-------|--------|---------------|-------|--------|---------------|-------|--------|---------------|-------|--------|---------------|-------|--------|---------------|-------|--------|---------------|-------|--------|
| Exponential (lambda)                          | 0.003256613 | 37 | 1.174749099 | 0.003455553 | 87 | 0.536667031 | 1 | 0.0013668 | 85 | 27.456 | 3 | 29.2178 | 1 | 0.0065520 | 39 | 122.374 | 1 | 124.548 | 5 | 0.00196 | 1 | 331.81 | 8 |
| Gompertz (gamma, lambda)                      | - | 35.997377 | 29 | 20.871359 | 12.861234 | 45 | 4.8743417 | 55 | 1.4350952 | 68 | 2.9706484 | 25 | -0.0083873 | 78 | 0.0021992 | 78 | 28.9712 | 4 | 52.4936 | 4 | -0.0012921 | 0.0073115 | 86 | 124.010 | 9 | 128.359 | 6 | 0.00050 | 3 | 0.00177 | 3 | 345.27 | 4 | 351.94 | 0 |
| Log-logistic (p, lambda)                      | 2.0358589 | 75 | 2.49523E-05 | 0.1910365 | 52 | 0.9710364 | 17 | 0.0040968 | 25 | 0.1184697 | 77 | 0.8602031 | 56 | 0.0027544 | 96 | 29.2021 | 9 | 52.7245 | 9 | -0.0002382 | 0.0002382 | 112.251 | 9 | 116.600 | 7 | 1.53267 | 1 | 0.00144 | 2 | 336.11 | 7 | 342.77 | 7 |
| Log-normal (sigma, mu)                        | 5.1072326 | 58 | 5.1502773 | 1.910365 | 52 | 0.9710364 | 17 | 0.0040968 | 25 | 0.1184697 | 77 | 0.8602031 | 56 | 0.0027544 | 96 | 29.2021 | 9 | 52.7245 | 9 | -0.0002382 | 0.0002382 | 112.251 | 9 | 116.600 | 7 | 1.53267 | 1 | 0.00144 | 2 | 336.11 | 7 | 342.77 | 7 |
| Weibull (p, lambda)                            | 1.4974234 | 37 | 0.0002912 | 0.0787098 | 64 | 0.7930201 | 44 | 0.0073546 | 87 | 0.1484867 | 83 | 0.8282252 | 67 | 0.0030365 | 66 | 29.2653 | 6 | 52.7877 | 5 | 0.1178601 | 0.1484867 | 112.321 | 9 | 122.733 | 6 | 1.21789 | 8 | 0.00155 | 3 | 341.14 | 7 | 347.81 | 3 |
### Table 8: OS

| Distribution          | Shape | Scale | Delta squared | Shape | Scale | Least square | AIC         | BIC         | Shape | Scale | AIC         | BIC         |
|-----------------------|-------|-------|---------------|-------|-------|--------------|-------------|-------------|-------|-------|-------------|-------------|
| Exponential (lambda)  | 0.001541362 | 0.590601385 | 0.000995022 | 0.068297167 | 0.001938707 | 219.3932 | 222.5806 | 0.002094281 | 118.6016 | 120.776 |
| Gompertz (gamma, lambda) | -3.816010455 | 1.737444012 | 12.44482406 | -4.895373599 | 1.408379772 | 211.3812 | 217.7619 | 0.0033474 | 0.001281487 | 117.4045 | 121.7532 |
| Log-logistic (p, lambda) | 1.8094945475 | 1.72533E-05 | 0.047386984 | 0.001263186 | 0.001263186 | 221.8512 | 223.2328 | 1.861306015 | 0.000102269 | 114.8958 | 119.8443 |
| Log-normal (sigma, mu) | 0.919262486 | 6.058388237 | 0.073968937 | 0.840861680 | 0.002621821 | 1.26073321 | 217.8412 | 221.2161 | 0.474355431 | 0.000102269 | 114.8958 | 119.8443 |
| Weibull (p, lambda)   | 1.368707975 | 0.0016619 | 0.022237353 | 0.840861680 | 0.002621821 | 1.26073321 | 217.8412 | 221.2161 | 0.474355431 | 0.000102269 | 114.8958 | 119.8443 |

* Source for OS of Thyroid – sorafenib: Brose 2014; hard coded within survival curves sheet from the sorafenib model

### Table 9: OS continued

| Distribution          | Shape | Scale | Delta squared | Shape | Scale | Delta squared | AIC         | BIC         | Shape | Scale | AIC         | BIC         |
|-----------------------|-------|-------|---------------|-------|-------|---------------|-------------|-------------|-------|-------|-------------|-------------|
| Exponential (lambda)  | 0.00194453 | 0.795342944 | 0.002294945 | 0.76275582 | 0.002296793 | 42.06719 | 42.83978 | 0.001066351 | 511.0237 | 511.0237 |
| Gompertz (gamma, lambda) | -3.240037546 | 1.551271007 | 7.987408866 | -3.99031642 | 1.942949511 | 13.72495036 | 0.001475 | 0.00152526 | 43.0317 | 44.57688 | 0.000905 | 0.00164268 | 493.1177 |
| Log-logistic (p, lambda) | 2.322811115 | 1.54729E-06 | 0.922176904 | 2.322811115 | 1.54729E-06 | 0.286983993 | 2.679684918 | 1.75847E-07 | 36.7672 | 38.3199 | 1.528808881 | 7.18258E-05 | 474.0728 |
| Log-normal (sigma, mu) | 0.7148069992 | 5.759464039 | 0.127961033 | 0.765383689 | 5.736964997 | 0.303302214 | 0.674922282 | 5.818751 | 37.4062 | 39.9458 | 1.134049324 | 6.312416 | 471.4438 |
| Weibull (p, lambda)   | 1.835592927 | 1.7486E-05 | 0.048195864 | 1.512683319 | 0.00011335 | 0.109255226 | 1.653478747 | 4.12813E-05 | 40.1011 | 41.65529 | 0.994877664 | 0.00103852 | 513.0175 |
Figure 1: PFS curve larotrectinib

![Larotrectinib: PFS](image1)

- Exponential
- Log-logistic
- Log-normal
- Weibull
- KM
- Gompertz
- Generalised gamma

Figure 2: OS curve larotrectinib

![Larotrectinib: OS](image2)

- Exponential
- Log-logistic
- Log-normal
- Weibull
- KM
- Gompertz
- Generalised gamma
- Selected curve
APPENDIX 3 COSTING

Drug acquisition cost

First, unitary drug acquisition costs parameters for the intervention and weighted comparator SoC treatments were included to reflect the Dutch situation. Drug acquisition costs were implemented from medicijnkosten.nl (March 2019), excluding VAT [42], apart from the cost of larotrectinib which was given by the manufacturer (Bayer).

Table 10. Unit cost, drug acquisition

| Product                  | Strength (mg) | Number of tabs | mg/pack | Unit Cost (Excl. 9% VAT) |
|--------------------------|---------------|----------------|---------|--------------------------|
| Larotrectinib 100mg      | 100           | 56             | 5600    | €4,993.33                |
| Larotrectinib 25mg       | 25            | 56             | 1400    | €1,248.33                |
| Sorafenib                | 200           | 1              | 200     | €32.38                   |
| Lomustine                | 40            | 1              | 40      | €35.08                   |
| **Product**              | **Strength (mg)** | **Size (ml)** | **mg/pack** | **Unit Cost (Excl. 9% VAT)** |
| 5-fluorouracil (1000mg pack) | 50            | 20             | 100     | €6.25                    |
| 5-fluorouracil (5000mg pack) | 50            | 100            | 5000    | €31.45                   |
| Carboplatin (50mg pack)  | 10            | 5              | 50      | €15.30                   |
| Carboplatin (150mg pack) | 10            | 15             | 150     | €45.90                   |
| Carboplatin (600mg pack) | 10            | 60             | 600     | €183.63                  |
| Cisplatin (10 mg pack)   | 1             | 10             | 10      | €4.14                    |
| Cisplatin (100mg pack)   | 1             | 100            | 100     | €41.67                   |
| Cisplatin (50 mg pack)   | 1             | 50             | 50      | €20.77                   |
| Dacarbazine (1000mg pack) | 1000          | 1              | 1000    | €87.15                   |
| Etoposide (100mg pack)   | 20            | 5              | 100     | €13.33                   |
| Irinotecan (40mg pack)   | 20            | 2              | 40      | €52.27                   |
| Leucovorin (400mg pack)  | 10            | 40             | 400     | €110.37                  |
| Oxaliplatin (50mg pack)  | 5             | 10             | 50      | €100.40                  |
| Panitumumab (100 mg pack) | 20            | 5              | 100     | €444.13                  |
| Pembrolizumab (100mg pack) | 25            | 4              | 100     | €2,624.37                |
| Vinorelbine (10mg pack)  | 10            | 1              | 10      | €22.39                   |
| Vinorelbine (50mg pack)  | 10            | 5              | 50      | €112.10                  |

**VAT**: Value added tax, mg: milligram, ml: millilitre

Treatment costs

Whereas a unitary drug administration cost for oral treatments (tablets/capsules/solution) was assumed to be 0, the unitary cost of IV treatment delivery was set to €277.40 (€269 inflated to 2019 prices) based on data published by Mihajlovic et al. [43]. A summary of calculated treatment costs is given in Table 16.

Table 11. Treatment cost (NL)

| Tumour location | Description                  | Cost per day of treatment | Drug acquisition | Administration |
|-----------------|------------------------------|---------------------------|------------------|----------------|
| Pan-tumour      | Larotrectinib 100mg          | €178.33                   | €0.00            |
|                 | Larotrectinib 100mg - paediatric | €131.97           | €0.00            |
|                 | Larotrectinib 25mg           | €131.97                   | €0.00            |
|                 | Larotrectinib solution       | €131.97                   | €0.00            |
| NSCLC           | Pembrolizumab                | €249.9                    | €9.9             |
| Salivary        | Cisplatin + vinorelbine      | €13.85                    | €26.4            |
| Tumour location | Description | Cost per day of treatment |
|-----------------|-------------|--------------------------|
|                 |             | Drug acquisition | Administration |
| Melanoma        | Chemotherapy (e.g., Dacarbazine) | €8.3 | €13.2 |
| Colorectal      | FOLFIRI + Panitumumab | €210.7 | €39.6 |
| SCLC            | Carboplatin + Etoposide | €12.1 | €29.7 |
| Breast          | TPC (e.g., Vinorelbine) | €19.20 | €39.63 |
| Children combined | BSC      | €0.00 | €0.00 |
| Primary CNS     | Lomustine  | €5.85 | €0.00 |
| Pancreas        | FOLFIRINOX | €80.75 | €39.63 |
| Thyroid         | Sorafenib  | €129.50 | €0.00 |

NSCLC: Non-small cell lung cancer, SCLC: Small cell lung cancer, CNS: Central nervous system, TPC: Treatment of physician’s choice

Table 12: Health care resource unitary price (NL) – Disease management

| Component                        | Unit cost | Source | Details                                           |
|----------------------------------|-----------|--------|---------------------------------------------------|
| Oncologist visit                 | €135.72   |        | “Kosten omtrent overig zorggebruik” - report previously considered by ZIN |
| GP visit (home/surgery)          | €51.41    |        |                                                  |
| Plastic surgeon visit            | €169.62   | [44]   |                                                  |
| Depression management            | €65.80    |        | Psychologist visit                                |
| Nutritional supportive care visit| €51.41    |        | Assumed equal to cost of GP visit                 |
| Speech therapy visit             | €51.41    |        |                                                  |
| Pain management                  | €279.68   | [45]   | Proxy: “Ondersteunende en verlichtende zorg met 1 of 2 polikliniekbezoeken/consultaties op afstand bij borstkanker” |
| CT scan (one area)               | €240.22   |        | Computerized Tomography Scan of One Area          |
| CT scan (three areas)            | €240.22   | [46]   | Computerized Tomography Scan of Three Areas       |
| MRI scan                         | €277.92   |        | MRI                                               |
| Ultrasound                       | €90.48    |        | Proxy: Echography                                |
| Full blood count                 | €29.88    |        |                                                  |
| Chest X-ray                      | €41.13    |        |                                                  |
| Bone scan                        | €90.48    |        | Bone scintigraphy                                |
| ECG                              | €41.13    |        | Assumed equal to Chest X-ray                     |
| Liver function test              | €1.34     | [44]   | Assumed equal to complete metabolic panel         |
| Total protein                    | €1.34     |        |                                                  |
| Urinalysis                       | €1.34     |        |                                                  |
| Clinical/laboratory test         | €1.34     |        |                                                  |
| Coagulation panel (PT/PT-INR, PTT)| €1.34    |        |                                                  |

CT: Computed tomography, MRI: Magnetic resonance imaging, ECG: Electrocardiogram, PT: prothrombin time, INR: International normalized ratio, PTT: Partial thromboplastin time
End-of-life costs

End-of-life costs for dying patients are included separately into the CEM, irrespective of tumour location and treatment. The cost incurred at death is a weighted sum of DBC codes for end-of-life care (990040003, 990040007, 990040009) based on the number of patients in internal medicine this palliative care quantified for this indication, in the year 2018 inflated to 2019, amounting to €819.12.

Adverse events costs

Costs associated with the management of adverse events were based on information made available by ZIN from recent submissions reviews. Whenever this information was not available, DBC-zorgproducten rates or assumptions were used:

Table 13: Adverse event costs

| Adverse event                  | Total cost | Source | Details                           |
|--------------------------------|------------|--------|-----------------------------------|
| Anaemia                        | €1,800.96  |        |                                   |
| Abnormal liver function        | €332.02    | [47]   | Proxy: Liver toxicity             |
| Alanine/Aspartate aminotransferase increased | €332.02    |        |                                   |
| Colitis                        | €385.56    |        |                                   |
| Diarrhoea                      | €43.18     |        |                                   |
| Fatigue                        | €131.95    | [44]   | Proxy: Malaise/fatigue            |
| Leukopenia                     | €1,348.14  |        | Assumed equal to neutropenia      |
| Nausea                         | €585.56    |        |                                   |
| Rash/skin reaction             | €89.06     |        |                                   |
| Thrombocytopenia               | €92.00     |        |                                   |
| Vomiting                       | €158.47    |        |                                   |
| Anorexia                       | €90.95     |        | Proxy: Decreased appetite         |
| Febrile neutropenia            | €2,964.71  | [48]   |                                   |
| Neutropenia                    | €1,318.95  |        |                                   |
| Stomatitis                     | €113.50    |        |                                   |
| Infection                      | €1,118.70  |        |                                   |
| Pneumonitis                    | €695.61    | [45]   |                                   |
| Pulmonary embolism             | €732.24    |        |                                   |
| Increase alkaline phosphatase level | €332.02    |        | Assumed equal to Alanine aminotransferase increased |
| Increase creatinine level      | €332.02    |        | Assumed equal to Alanine aminotransferase increased |
| Increase in total bilirubin    | €332.02    |        | Assumed equal to Alanine aminotransferase increased |
| Lymphocyte count decreased/lymphopenia | €1,348.14  |        | Assumed equal to neutropenia      |

Non-medical costs

In line with the latest Dutch guidelines for economic evaluations published by the Dutch National Health Care Institute [5], non-medical costs are included in the base case analysis (i.e. friction costing was applied). For this purpose, informal care costs, travel costs and productivity costs, were added to the global CEM in order to implement the societal perspective. Applicable tariffs were obtained from the costing manual chapter of the guideline for economic evaluations and were inflated to 2019 levels.

Informal care costs

An estimated unpaid hourly wage (year: 2014) of €14.00 was inflated to €14.71 (2019 price level) [5]. This tariff is used to estimate the cost that would be incurred in order to replace one hour of unpaid work (“Tijdkosten van mantelzorgers”). The need for informal care depends (a) on the health state (PFS, PD) where the patient is at, and
(b) whether the patient is an adult or a paediatric patient, as shown in the table below. The source for the quantity of hours necessary for an adult was extracted from the advice package published by ZIN for osimertinib (Tagrisso®) in NSCLC [24]. It was assumed that the quantity of hours necessary for a paediatric patient would be twice as many than in the case of adults:

### Table 14: Informal care cost

| Parameter                        | Population | PFS  | PD   | Source       |
|----------------------------------|------------|------|------|--------------|
| Weekly hours of informal care    | Adults     | 8.0  | 12.0 | [24] (pg. 85) |
|                                  | Paediatric | 16   | 24   | Assumption   |
| Weekly cost of informal care     | Adults     | €117.71 | €176.56 | Calculation |
|                                  | Paediatric | €235.41 | €353.12 | Calculation |

*PFS: Progression free survival, PD: Progressed disease*

### Travel costs

Travel costs associated with normal disease management (cost of attending a point of care in order to receive treatment, undergo examinations, etc.), and the corresponding parking allowance cost were considered in the analysis, using the standard costing and distance from the ZIN costing manual [5]. In the PFS health state, the typical number of trips to the healthcare facility was estimated by considering the number of visits. For adults, costs were separated for oral and IV treatment. In the PD health state, one additional trip (accounting for an additional assessment visit) was considered. It was assumed that paediatric patients would incur twice as many visits than their adult counterparts:
Productivity costs

The friction cost approach was used to include productivity costs. A friction period of 12 weeks (85 calendar days) was considered. The cost of productivity loss associated with death and the cost of productivity loss associated with absenteeism until the retirement age was included in the analysis. In its costing manual (2016) [5], ZIN provides the average labour cost per hour (2014) for a paid worker: € 36.52 (i.e. € 34.75 in 2014 euros inflated to 2019 price level). The table below presents the parameters used for the calculation of productivity loss. Note that productivity losses do not apply for cycles after the patient reach the retirement age. The legal retirement age in the Netherlands is 67 years [49] and therefore a productivity loss of € 0 was applied to the patients of 67 years and older. Further, it does not apply to children, thus, in the model, these are applied only once a patient reached 18 years old and further.

Table 15. Parameters used in the calculation of the cost of productivity loss (adults)

| Parameter | Value (2019) | Source / comment |
|-----------|--------------|-----------------|
| Length of friction period | 12 weeks | [5] |
| Costs per hour | € 36.52 | [5] (inflated to 2019 euros) |
| Hours per workday | 8 hours | Assumption |
| Full-time employment | 40.7% | |
| Part-time employment | 37.3% | [50] |
| Paid work percentage (out of 40-hour working week, full-time employment) | 99.25% | |
| Paid work percentage (out of 40-hour working week, part-time employment) | 50.75% | [51] |
| Paid work percentage (out of 40-hour working week, overall) | 72.5% | |
| Proportion of working week foregone by disease - PFS | 60% | |
| Proportion of working week foregone by disease - PD | 100% | [24] (pg. 85) |
| Proportion of working week foregone by disease - Death | 100% | |

PFS: Progression free survival, PD: Progressed disease

Indirect medical costs

The PAID toolkit allows to select the costs associated to all diseases excluding the one related to the intervention assessed. In this case, one individual selection was made for each of the tumour locations considered in the analysis (provided the level of granularity offered the PAID 1.1 toolkit). Costs were inflated to reflect 2019 values. [52]
APPENDIX 4 RESOURCE UTILISATION

Health state resource utilisation (disease management)

Two approaches were used in order to determine the cost associated with disease management in each of the two health states considered (a) Progression-free survival, and (b) Progressed disease.

1. Inputs based on previous ZIN submissions: NSCLC, SLCL, breast

Firstly, for the following tumour locations, it was possible to source envelope values from a review of previous submissions to ZIN or from the literature, reflecting health state costing exercises already considered in the Netherlands for applications in similar indications:

- **NSCLC**: A cost €50.85 per each seven-day-cycle was set to the PFS health state and a cost of €15.77 was set to the PD health state (values inflated to 2019 price level). Due to the lack of inputs for SCLC healthcare resource utilisation, SCLC was costed the same as NSCLC. [53] (pg. 78)
- **Breast**: A cost of €371.64 per each seven-day-cycle was set to the PFS health state and a cost of €529.59 was set to the PD health state. [54]

2. Inputs based on micro-costing: Salivary, melanoma, colorectal, pancreas and thyroid, children, primary CNS

Secondly, a micro-costing approach was used for the following tumour locations: salivary, melanoma, colorectal, pancreas, and thyroid. It was conservatively assumed that the costs for thyroid are also applied for children combined and primary CNS, because of being the least expensive and not rewarding time spent on PFS versus time spent on PD. For salivary gland, Dutch expert opinion was available for health state specific resource use from the ad boards. No Dutch health state specific resource use was available for melanoma, colorectal, pancreas and thyroid. For these tumour localizations, the health state resource utilisation from the global (UK) CEM was used, reflecting clinical practice in the UK. The tables below feature the healthcare resource use costs.

**Table 16: Rates adverse events larotrectinib arm [1]**

| Adverse event       | Rate  |
|---------------------|-------|
| Anaemia             | 7.30% |
| Neutropenia         | 7.30% |

**Table 17: Rates adverse events NSCLC [10] [11]**

| Adverse event            | Rate  |
|--------------------------|-------|
| Diarrhoea                | 3.90% |
| Rash/skin reaction       | 6.50% |

**Table 18: Rates adverse events Salivary gland [12]**

| Adverse event | Rate  |
|---------------|-------|
| Nausea        | 0.06% |
### Table 19: Rates adverse events melanoma [13]

| Adverse event | Rate  |
|---------------|-------|
| Diarrhoea     | 10.00%|

### Table 20: Rates adverse events colorectal [14]

| Adverse event          | Rate  |
|------------------------|-------|
| Rash/skin reaction     | 37.00%|
| Neutropenia            | 20.00%|
| Diarrhoea              | 14.00%|
| Stomatitis             | 8.00% |
| Leukopenia             | 7.00% |
| Pulmonary embolism     | 5.00% |

### Table 21: Rates adverse events SCLC [15]

| Adverse event | Rate  |
|---------------|-------|
| Rash/skin reaction | 37.00%|
| Neutropenia   | 20.00%|
| Diarrhoea     | 14.00%|
| Stomatitis    | 8.00% |
| Leukopenia    | 7.00% |

### Table 22: Rates adverse events breast [16]

| Adverse event | Rate  |
|---------------|-------|
| Neutropenia   | 21.00%|
| Leukopenia    | 6.00% |
| Anaemia       | 4.00% |
| Fatigue       | 10.00%|

### Table 23: rates adverse events children (combined) [17]
| Adverse event                        | Rate   |
|-------------------------------------|--------|
| Diarrhoea                           | 13,00% |
| Anaemia                             | 28,00% |
| Febrile neutropenia                 | 13,00% |
| Neutropenia                         | 34,00% |

Table 24: Rates adverse events primary CNS [18]

| Adverse event                              | Rate   |
|--------------------------------------------|--------|
| Fatigue                                    | 9,40%  |
| Lymphocyte count decreased/lymphopenia     | 7,80%  |
| Pulmonary embolism                         | 0,00%  |
| Thrombocytopenia                           | 22,00% |
| Neutropenia                                | 3,10%  |
| Leukopenia                                 | 4,70%  |

Table 25: Rates adverse events pancreas [19]

| Adverse event                        | Rate   |
|-------------------------------------|--------|
| Neutropenia                         | 21,00% |
| Febrile neutropenia                 | 0,00%  |
| Thrombocytopenia                    | 3,60%  |
| Anaemia                             | 6,00%  |
| Fatigue                             | 17,80% |
| Vomiting                            | 8,30%  |
| Diarrhoea                           | 0,00%  |
| Alanine/Aspartate aminotransferase increased | 20,80% |
| Pulmonary embolism                  | 4,10%  |

Table 26: Rates adverse events thyroid [20]

| Adverse event                        | Rate   |
|-------------------------------------|--------|
| Rash/skin reaction                  | 25,10% |
| Diarrhoea                           | 5,80%  |
Table 27: Healthcare resource utilisation for larotrectinib and per tumour location

| Healthcare use     | Progression-free start up (one-off) | Progression-free per cycle | Progressed disease - start up (one-off) | Progressed disease - per cycle | Death - start up (one-off) |
|--------------------|------------------------------------|----------------------------|----------------------------------------|-------------------------------|---------------------------|
| Larotrectinib      | €117.76                            | €33.30                     | €207.94                                | €40.15                        | €401.37                   |
| Salivary           | €375.94                            | €49.88                     | €375.94                                | €52.39                        | €819.12                   |
| Colorectal         | €0.00                              | €37.14                     | €1,103.42                              | €54.62                        | €819.12                   |
| Breast             | €0.00                              | €371.64                    | €0.00                                  | €529.59                       | €819.12                   |
| Pancreas           | €439.48                            | €100.86                    | €0.00                                  | €78.34                        | €819.12                   |
| NSCLC              | €0.00                              | €50.85                     | €0.00                                  | €105.77                       | €819.12                   |
| Melanoma           | €706.57                            | €118.76                    | €954.17                                | €118.76                       | €819.12                   |
| SCLC               | €0.00                              | €50.85                     | €0.00                                  | €105.77                       | €819.12                   |
| Thyroid            | €0.00                              | €62.50                     | €0.00                                  | €62.50                        | €819.12                   |
| Children combined  | €0.00                              | €62.50                     | €0.00                                  | €62.50                        | €819.12                   |
| Component                               | Seven-day-cycle | Start up |
|-----------------------------------------|-----------------|----------|
|                                        | Salivary | Melanoma | Colorectal | Pancreas | Thyroid | Salivary | Melanoma | Colorectal | Pancreas | Thyroid |
| Oncologist visit                       | 0.058    | 0.377    | 0.250      | 0.077    | 1.00    | 1.0     |
| Outpatient visit, GP/nurse visit       | 0.018    | 0.063    | 0.5        | 1.00     | 0.08    |
| Radiation oncologist visit             | 0.014    |          |            |          |         |         |
| Oncology inpatient visit               | 0.015    |          |            | 0.077    | 1.00    |
| Plastic surgeon visit                  | 0.007    |          | 0.03       |          |         |
| Full blood count                       | 0.300    | 0.750    | 0.077      | 1.20     | 1.00    |
| Complete metabolic panel               | 0.285    |          |            | 1.20     |         |
| Coagulation panel                      |          | 0.077    |            |          |         |
| Lactate dehydrogenase                  | 0.285    | 0.750    | 0.538      | 1.0      |
| Liver function test                    |          |          |            | 0.231    |
| Thyroid function test                  |          |          |            | 0.077    |
| Urine test                             |          |          | 0.077      |         |
| Protein test                           |          |          | 0.077      |         |
| CT scan                                | 0.076    | 0.184    | 0.083      | 0.077    | 1.00    | 2.46    |
| MRI scan                               | 0.015    |          | 0.077      | 0.06     | 0.10    |
| Bone scan                              | 0.001    |          | 0.077      | 0.19     |
| ECG                                    | 0.008    |          | 0.06       |         |
| Chest x-ray                           | 0.076    |          | 0.20       |         |
| Depression management                  | 0.019    |          |            |         |
| Nutritional support                    | 0.019    |          |            |         |
| Pain and symptom management            | 0.076    |          |            |         |
| Speech therapy                         | 0.004    |          |            |         |
### Table 29: Health care resource utilisation rates used in the model – Disease management in PD

| Component                          | Seven-day-cycle | Start up |
|------------------------------------|-----------------|----------|
|                                    | Salivary        | Melanoma | Colorectal | Pancreas | Thyroid | Salivary | Melanoma | Colorectal | Pancreas | Thyroid |
| Anti-tumour treatment              |                 |          |            |          |         |          |          |            |          |         |
| Palliative care visit              |                 | 0.077    | 1.00       | 1.80     |          |          |          |            |          |         |
| Oncologist visit                   | 0.076+          |          | 0.750      | 1.62     | 0.077   |          |          |            |          |         |
| Radiation oncologist visit         | 0.377           |          | 1.00       | 1.80     | 0.077   |          |          |            |          |         |
| Outpatient visit, GP/nurse visit   | 0.014           | 1.063    | 0.5        | 0.06     |          |          |          |            |          |         |
| Oncology inpatient visit           | 0.018           |          | 1.00       | 1.80     | 0.077   |          |          |            |          |         |
| Plastic surgeon visit              | 0.015           |          | 0.5        | 0.06     |          |          |          |            |          |         |
| Full blood count                   | 0.007           | 0.750    | 0.077      | 1.62     |          |          |          |            |          |         |
| Complete metabolic panel           | 0.300           |          | 1.62       |          |          |          |          |            |          |         |
| Coagulation test                   |                 | 0.077    | 1.00       | 1.80     | 0.077   |          |          |            |          |         |
| Urine test                         |                 | 0.077    |            |          |          |          |          |            |          |         |
| Lactate dehydrogenase              |                 | 0.285    | 1.00       | 1.80     | 0.077   |          |          |            |          |         |
| Liver function test                |                 | 0.750    | 0.077      | 1.62     |          |          |          |            |          |         |
| Thyroid function test              |                 | 0.231    | 0.077      |          |          |          |          |            |          |         |
| Protein test                       |                 | 0.077    |            |          |          |          |          |            |          |         |
| CT scan                            | 0.076+          | 0.285    | 0.083      | 0.077    | 1.00    | 2.01     |          |            |          |         |
| MRI scan                           | 0.184           |          | 0.077      |          | 0.077   |          |          |            |          | 0.15    |

GP: General practitioner, CT: Computed tomography, MRI: Magnetic resonance imaging, ECG: Electrocardiogram. *All frequencies were sourced from NICE technology appraisal documents [55] [56] [57] [58], unless specified otherwise. †Values validated by a Dutch expert in the treatment of advanced salivary gland carcinoma.
| Component                        | Seven-day-cycle | Start up |
|----------------------------------|-----------------|----------|
|                                  | Salivary        | Melanoma | Colorectal | Pancreas | Thyroid | Salivary | Melanoma | Colorectal | Pancreas | Thyroid |
| Bone scan                        | 0.015           | 0.077    | 0.01       |
| ECG                              | 0.001           |          | 0.04       |
| Chest x-ray                      | 0.008           |          | 0.07       |
| Depression management            | 0.019           |          |            |
| Nutritional support              | 0.019           |          |            |
| Pain and symptom management      | 0.076           |          |            |
| Speech therapy                   | 0.004           |          |            |
| Additional management medication  | 0.002           |          |            |
| Thyroxine                        |                 | 0.251    |            |
| Calcium and Vitamin D            |                 |          | 7.000      |

GP: General practitioner, CT: Computed tomography, MRI: Magnetic resonance imaging, ECG: Electrocardiogram. * All frequencies were sourced from NICE technology appraisal documents [55] [56] [57] [58], unless specified otherwise. † Values validated by the Dutch clinical experts (Salivary). ≈ Unspecified treatment incorporated as lump cost in first cycle, (Begeleiding bij de behandeling met chemotherapie bij uitzaaiingen bij een kwaadaardig gezwel DBC-zorgproduct 020117020 [45].
APPENDIX 5 SENSITIVITY ANALYSES

Scenario analyses

Healthcare perspective

In the base case model, the societal perspective is applied as is requested in the Dutch guidelines for economic evaluations [5]. The healthcare perspective is applied in the scenario analysis. This means that the non-medical costs (informal care costs, productivity costs and travel costs) are excluded from the analysis.

Indirect medical costs

A scenario is run in which future unrelated medical costs are included. Future unrelated medical costs refer to costs in life-years gained caused by all diseases other than (i.e., unrelated to) the disease for whom the intervention is being assessed. The PAID tool van Van Baal et al. [52] was used to estimate unrelated medical cost in a standardized manner. Future unrelated medical costs incurred by the patient alive at each cycle of the model were obtained from the latest published version of the toolkit (PAID 1.1) which estimates costs based on data on costs of illness and mortality rates from 2013. Costs are estimated by age and gender.

Excluding productivity costs

In the base case model, productivity costs are included. However, it is possible that the friction period of 12 weeks has already passed before larotrectinib was initiated (i.e. during earlier treatment lines). Therefore, a scenario analysis is run in which productivity costs are excluded.

Dutch epidemiology for SoC tumour location weighting

In the base case model, the weighting according to the tumour localizations from the larotrectinib clinical trial program is used to inform the relative weight in the weighted SoC arm. However, these were not in accordance with the weighting found in Dutch clinical practice. These are however used in the base case analysis as these reflect the weighting that informs the clinical efficacy and safety of larotrectinib.

In order to investigate the impact on the model results, a scenario analysis is run in which the weighting of the tumour localizations in the weighted SoC arm is based on epidemiological data on the presence of the various tumour localizations in the Dutch setting (Table 35). Please note that the weighting of tumour localizations for the larotrectinib arm remains unchanged based on the weighting in the larotrectinib clinical trial program. These calculation for the number of TRK+ patients according to Dutch epidemiology weighting does not take into account whether patients are eligible for systemic treatment, i.e., 100% of patients are considered eligible for systemic treatment. Additionally, it does not take into account the percentage of patients who are tested for NTRK gene fusions. Therefore, the number reflects the maximum number of eligible patients.

Table 30: Weighting of patients per tumour location

| Tumour Location | No. of TRK+ patients (Dutch epidemiology weighting) | Weighting of tumour locations (according to Dutch epidemiology weighting) |
|-----------------|----------------------------------------------------|-------------------------------------------------------------------------|
| NSCLC           | 23                                                 | 21%                                                                     |
| Salivary        | 4                                                  | 4%                                                                      |
| Melanoma        | 15                                                 | 14%                                                                     |
| Colorectal      | 25                                                 | 23%                                                                     |
| SCLC            | 6                                                  | 5%                                                                      |
| Breast          | 9                                                  | 8%                                                                      |
| Children combined | 3                                                   | 3%                                                                      |
| Primary CNS     | 15                                                 | 14%                                                                     |
Selecting 2nd or 3rd best OS/PFS parametric option for all interventions

In this scenario, the impact on the model results is investigated of selecting the 2nd or 3rd best fitting option for all parametric survival curves, based on statistical fit. Two scenarios are run in which for all curves either the 2nd or 3rd best fitting options are selected based on the AIC (Table 36). This approach was chosen based on statistical fit. Including more parametric options would yield an unmanageable level of scenarios whilst providing a marginal level of additional information regarding the sensitivity of the analyses.

Table 31: 2nd and 3rd best OS/PFS parametric option for all interventions

| Model input     | Base case parametric curve | 2nd best parametric curve | 3rd best parametric curve |
|-----------------|-----------------------------|---------------------------|---------------------------|
| Larotrectinib PFS | Weibull                     | Log-normal                | Generalised gamma         |
| Larotrectinib OS | Weibull                     | Exponential               | Log-normal                |
| NSCLC PFS       | Log-Normal                  | Gompertz                  | Log-logistic              |
| NSCLC OS        | Log-Normal                  | Log-logistic              | Exponential               |
| Salivary gland PFS | Exponential                | N/A                       | N/A                       |
| Salivary gland OS | Log-logistic                | N/A                       | N/A                       |
| Melanoma PFS    | Piecewise                  | N/A                       | N/A                       |
| Melanoma OS     | Log-logistic                | N/A                       | N/A                       |
| Colorectal PFS  | Weibull                     | Gompertz                  | Log-logistic              |
| Colorectal OS   | Weibull                     | Log-logistic              | Log-normal                |
| SCLC PFS        | Log-logistic                | Weibull                   | Gompertz                  |
| SCLC OS         | Weibull                     | Gompertz                  | Log-logistic              |
| Breast PFS      | KM                          | N/A                       | N/A                       |
| Breast OS       | Piecewise                  | N/A                       | N/A                       |
| Children PFS    | Gompertz                   | Log-normal                | Log-logistic              |
| Children OS     | Log-normal                  | Log-logistic              | Gompertz                  |
| Primary CNS PFS | Log-normal                  | Log-logistic              | Exponential               |
| Primary CNS OS  | Log-normal                  | Log-logistic              | Weibull                   |
| Thyroid PFS     | Exponential                 | Log-normal                | Log-logistic              |
| Thyroid OS      | Exponential                 | N/A                       | N/A                       |
| Pancreas PFS    | Weibull                     | Gompertz                  | Exponential               |
| Pancreas OS     | Weibull                     | Gompertz                  | Exponential               |

* For salivary gland PFS there was only information available for the exponential curve, therefore no 2nd or 3rd best is tested.
‡ As the piecewise is selected based on previous appraisals, no 2nd or 3rd best is tested.
Δ As the KM curves were completely available, it was not necessarry to extrapolate these data, therefore no 2nd or 3rd best is tested.

Testing all alternative OS/PFS parametric survival curves for larotrectinib

In this scenario, the impact on the model results is investigated of selecting the different available options in the model the parametric survival curves of larotrectinib (Table 9 and Table 10). All 36 combinations of larotrectinib OS (6 options) and PFS (6 options) are considered, in combination with the base case parametric curves for SoC (Table 8). This approach was chosen as it keeps the number of scenarios to a manageable level while still varying the parametric curves for OS and PFS of larotrectinib across all available options, which can be considered most
informative. The included scenarios are displayed in Table 37. Please note that there are a total of 35 scenario’s as the combination of using the Weibull curve for OS and PFS is considered in the base case analysis.

Table 32. Alternative OS/PFS parametric survival curves for larotrectinib

| Larotrectinib OS* | Larotrectinib PFS* |
|------------------|-------------------|
| Weibull          | Exponential       |
| Weibull          | Gompertz          |
| Weibull          | Log-logistic      |
| Weibull          | Log-normal        |
| Weibull          | Generalized Gamma |
| Exponential      | Weibull           |
| Exponential      | Exponential       |
| Exponential      | Gompertz          |
| Exponential      | Log-logistic      |
| Exponential      | Log-normal        |
| Exponential      | Generalized Gamma |
| Gompertz         | Weibull           |
| Gompertz         | Exponential       |
| Gompertz         | Gompertz          |
| Gompertz         | Log-logistic      |
| Gompertz         | Log-normal        |
| Gompertz         | Generalized Gamma |
| Log-logistic     | Weibull           |
| Log-logistic     | Exponential       |
| Log-logistic     | Gompertz          |
| Log-logistic     | Log-logistic      |
| Log-logistic     | Log-normal        |
| Log-logistic     | Generalized Gamma |
| Log-normal       | Weibull           |
| Log-normal       | Exponential       |
| Log-normal       | Gompertz          |
| Log-normal       | Log-logistic      |
| Log-normal       | Log-normal        |
| Log-normal       | Generalized Gamma |
| Generalized Gamma| Weibull           |
| Generalized Gamma| Exponential       |
| Generalized Gamma| Gompertz          |
| Generalized Gamma| Log-logistic      |
| Generalized Gamma| Log-normal        |
| Generalized Gamma| Generalized Gamma |

* these parametric curves are combined with the base case parametric curve for SoC (Table 8).

Scenario analysis

The results of the scenario analyses are displayed in Table 38. For none of the scenario analyses, the ICER exceeds the applicable WTP threshold of € 80,000/QALY.
Table 33: Results of scenario analyses

| Scenario                                                                 | Incremental Lys | Incremental QALYs | Incremental costs | ICER (€/QALY) | Deviation from base case ICER |
|--------------------------------------------------------------------------|-----------------|-------------------|-------------------|---------------|-----------------------------|
| Base case                                                                | 7.48            | 5.61              | € 232,260         | € 41,424      | N/A                         |
| Healthcare perspective                                                  | 7.48            | 5.61              | € 160,135         | € 28,560      | -31.1%                      |
| Including the indirect medical costs                                    | 7.48            | 5.61              | € 246,617         | € 43,985      | +6.2%                       |
| Excluding productivity costs                                            | 7.48            | 5.61              | € 229,418         | € 40,917      | -1.2%                       |
| Dutch epidemiology for SoC tumour location weighting                     | 7.37            | 5.57              | € 187,927         | € 33,758      | -18.5%                      |
| Selecting 2nd best OS/PFS parametric option for all interventions        | 5.31            | 4.18              | € 276,117         | € 66,008      | +59.3%                      |
| Excluding productivity costs                                            | 11.64           | 9.17              | € 481,364         | € 52,477      | +26.7%                      |
| Larotrectinib OS: Weibull; Larotrectinib PFS: Exponential; SoC OS/PFS as in base case | 7.48 | 5.56 | € 209,244 | € 37,625 | -9.2% |
| Scenario                                                                 | Incremental LYs | Incremental QALYs | Incremental costs | ICER (€/QALY) | Deviation from base case ICER  |
|-------------------------------------------------------------------------|-----------------|-------------------|-------------------|---------------|-----------------------------|
| Larotrectinib OS: Gompertz; Larotrectinib PFS: Log-normal; SoC OS/PFS as in base case | 23.44           | 17.49             | € 465,662         | € 26,623      | -35.7%                      |
| Larotrectinib OS: Gompertz; Larotrectinib PFS: Generalized Gamma; SoC OS/PFS as in base case | 23.44           | 17.81             | € 577,773         | € 32,444      | -21.7%                      |
| Larotrectinib OS: Log-logistic; Larotrectinib PFS: Weibull; SoC OS/PFS as in base case | 11.41           | 8.47              | € 265,653         | € 31,349      | -24.3%                      |
| Larotrectinib OS: Log-logistic; Larotrectinib PFS: Exponential; SoC OS/PFS as in base case | 11.41           | 8.43              | € 242,636         | € 28,788      | -30.5%                      |
| Larotrectinib OS: Log-logistic; Larotrectinib PFS: Gompertz; SoC OS/PFS as in base case | 11.41           | 9.22              | € 542,645         | € 58,873      | +42.1%                      |
| Larotrectinib OS: Log-logistic; Larotrectinib PFS: Log-logistic; SoC OS/PFS as in base case | 11.41           | 8.68              | € 347,619         | € 40,026      | -3.4%                       |
| Larotrectinib OS: Log-logistic; Larotrectinib PFS: Log-normal; SoC OS/PFS as in base case | 11.41           | 8.71              | € 359,783         | € 41,320      | -0.3%                       |
| Larotrectinib OS: Log-logistic; Larotrectinib PFS: Generalized Gamma; SoC OS/PFS as in base case | 11.41           | 9.01              | € 468,924         | € 52,061      | +25.7%                      |
| Larotrectinib OS: Log-normal; Larotrectinib PFS: Weibull; SoC OS/PFS as in base case | 13.87           | 10.26             | € 287,976         | € 28,055      | -32.3%                      |
| Larotrectinib OS: Log-normal; Larotrectinib PFS: Exponential; SoC OS/PFS as in base case | 13.87           | 10.22             | € 264,960         | € 25,928      | -37.4%                      |
| Larotrectinib OS: Log-normal; Larotrectinib PFS: Gompertz; SoC OS/PFS as in base case | 13.87           | 11.16             | € 611,535         | € 54,785      | +32.3%                      |
| Larotrectinib OS: Log-normal; Larotrectinib PFS: Log-logistic; SoC OS/PFS as in base case | 13.87           | 10.48             | € 370,081         | € 35,325      | -14.7%                      |
| Larotrectinib OS: Log-normal; Larotrectinib PFS: Log-normal; SoC OS/PFS as in base case | 13.87           | 10.50             | € 382,211         | € 36,406      | -12.1%                      |
| Larotrectinib OS: Log-normal; Larotrectinib PFS: Generalized Gamma; SoC OS/PFS as in base case | 13.87           | 10.81             | € 492,595         | € 45,586      | +10.0%                      |
| Larotrectinib OS: Generalized Gamma; Larotrectinib PFS: Weibull; SoC OS/PFS as in base case | 22.00           | 16.20             | € 360,973         | € 22,278      | -46.2%                      |
| Larotrectinib OS: Generalized Gamma; Larotrectinib PFS: Exponential; SoC OS/PFS as in base case | 22.00           | 16.16             | € 337,957         | € 20,916      | -49.5%                      |
| Larotrectinib OS: Generalized Gamma; Larotrectinib PFS: Gompertz; SoC OS/PFS as in base case | 22.00           | 17.27             | € 724,429         | € 41,944      | +1.3%                       |
| Larotrectinib OS: Generalized Gamma; Larotrectinib PFS: Log-logistic; SoC OS/PFS as in base case | 22.00           | 16.42             | € 443,305         | € 27,004      | -34.8%                      |
| Larotrectinib OS: Generalized Gamma; Larotrectinib PFS: Exponential; SoC OS/PFS as in base case | 22.00           | 16.44             | € 455,381         | € 27,702      | -33.1%                      |
Table 34: Parameter limits used in sensitivity analyses

| Parameter | Base case | Min | Max | Distribution |
|-----------|-----------|-----|-----|--------------|
| OS exponential shape/scale (lambda) - Larotrectinib adults | 0.009280 | 0.01 | 0.01 | Normal |
| OS gompertz shape (gamma) Larotrectinib adults | -0.049864 | -0.04 | -0.06 | Normal |
| OS gompertz scale (lambda) - Larotrectinib adults | 0.014499 | 0.01 | 0.02 | Normal |
| OS log-logistic shape (p) - Larotrectinib adults | 0.940561 | 0.75 | 1.13 | Normal |
| OS log-logistic scale (lambda) - Larotrectinib adults | 0.012267 | 0.01 | 0.01 | Normal |
| OS log-normal shape (sigma) - Larotrectinib adults | 2.073876 | 1.66 | 2.49 | Normal |
| OS log-normal scale (mu) - Larotrectinib adults | 4.963970 | 3.97 | 5.96 | Normal |
| OS weibull shape (p) - Larotrectinib adults | 0.884729 | 0.71 | 1.06 | Normal |
| OS weibull scale (lambda) - Larotrectinib adults | 0.012940 | 0.01 | 0.02 | Normal |
| OS gen gamma mu - Larotrectinib adults | 2.667000 | 2.13 | 3.20 | Normal |
| OS gen gamma ln(sigma) - Larotrectinib adults | 1.039216 | 0.83 | 1.25 | Normal |
| OS gen gamma kappa - Larotrectinib adults | -3.819000 | -3.06 | -4.58 | Normal |
| PFS exponential shape/scale (lambda) - Larotrectinib adults | 0.03 | 0.03 | 0.04 | Normal |
| PFS gompertz shape (gamma) Larotrectinib adults | -0.05 | -0.04 | -0.06 | Normal |
| PFS gompertz scale (lambda) - Larotrectinib adults | 0.05 | 0.04 | 0.06 | Normal |
| PFS log-logistic shape (p) - Larotrectinib adults | 1.01 | 0.81 | 1.21 | Normal |
| PFS log-logistic scale (lambda) - Larotrectinib adults | 0.04 | 0.04 | 0.05 | Normal |
| PFS log-normal shape (sigma) - Larotrectinib adults | 1.73 | 1.39 | 2.08 | Normal |
| PFS log-normal scale (mu) - Larotrectinib adults | 3.15 | 2.52 | 3.77 | Normal |
| PFS weibull shape (p) - Larotrectinib adults | 0.86 | 0.68 | 1.03 | Normal |
| PFS weibull scale (lambda) - Larotrectinib adults | 0.05 | 0.04 | 0.06 | Normal |
| PFS gen gamma mu - Larotrectinib adults | 2.645000 | 2.12 | 3.17 | Normal |
| PFS gen gamma ln(sigma) - Larotrectinib adults | 0.697139 | 0.56 | 0.84 | Normal |
| PFS gen gamma kappa - Larotrectinib adults | -0.850000 | -0.68 | -1.02 | Normal |
| TTD exponential shape/scale (lambda) - Larotrectinib adults | 0.03 | 0.03 | 0.04 | Normal |
| TTD gompertz shape (gamma) Larotrectinib adults | -0.06 | -0.04 | -0.07 | Normal |
| TTD gompertz scale (lambda) - Larotrectinib adults | 0.05 | 0.04 | 0.06 | Normal |
| TTD log-logistic shape (p) - Larotrectinib adults | 1.00 | 0.80 | 1.20 | Normal |
| TTD log-logistic scale (lambda) - Larotrectinib adults | 0.05 | 0.04 | 0.06 | Normal |
| TTD log-normal shape (sigma) - Larotrectinib adults | 1.72 | 1.38 | 2.07 | Normal |
| TTD log-normal scale (mu) - Larotrectinib adults | 3.10 | 2.48 | 3.72 | Normal |
| TTD weibull shape (p) - Larotrectinib adults | 0.83 | 0.66 | 1.00 | Normal |
| TTD weibull scale (lambda) - Larotrectinib adults | 0.05 | 0.04 | 0.06 | Normal |
| TTD gen gamma mu - Larotrectinib adults | 2.222000 | 1.78 | 2.67 | Normal |
| TTD gen gamma ln(sigma) - Larotrectinib adults | 0.657002 | 0.53 | 0.79 | Normal |
| TTD gen gamma kappa - Larotrectinib adults | -1.337000 | -1.07 | -1.60 | Normal |
| Complete response utility - Larotrectinib adults | 0.82 | 0.66 | 0.98 | Beta |

Log-normal; SoC OS/PFS as in base case
Larotrectinib OS: Generalized Gamma; Larotrectinib PFS: Generalized Gamma; SoC OS/PFS as in base case

Incremental LYs | Incremental QALYs | Incremental costs | ICER (€/QALY) | Deviation from base case ICER
---|---|---|---|---
22.00 | 16.76 | € 567,297 | € 33,858 | -18.3%
| Parameter                                                                 | Base case | Min    | Max    | Distribution |
|--------------------------------------------------------------------------|-----------|--------|--------|--------------|
| Progressed disease utility - Larotrectinib adults                        | 0.73      | 0.58   | 0.88   | Beta         |
| Progression free health state start cost - Larotrectinib adults          | 126.00    | 100.80 | 151.20 | Gamma        |
| Progression free health state cost - Larotrectinib adults                | 87.57     | 70.05  | 105.08 | Gamma        |
| Progressed disease state start cost - Larotrectinib adults               | 394.56    | 315.65 | 473.47 | Gamma        |
| Progressed disease state cost - Larotrectinib adults                     | 118.21    | 94.57  | 141.86 | Gamma        |
| Death health state start cost - Larotrectinib adults                     | 819.12    | 655.29 | 982.94 | Gamma        |
| P. loss cost Adults PFS NSCLC                                            | 6239.66   | 4991.72| 7487.59| Gamma        |
| P. loss cost Adults PFS Salivary                                         | 6239.66   | 4991.72| 7487.59| Gamma        |
| P. loss cost Adults PFS Melanoma                                         | 6104.56   | 4883.64| 7325.47| Gamma        |
| P. loss cost Adults PFS Colorectal                                       | 6239.66   | 4991.72| 7487.59| Gamma        |
| P. loss cost Adults PFS SCLC                                             | 6239.66   | 4991.72| 7487.59| Gamma        |
| OS exponential shape/scale (lambda) - NSCLC                              | 0.0009995 | 0.00   | 0.00   | Normal       |
| OS gompertz shape (gamma)NSCLC                                           | -4.895374 | -3.92  | -5.87  | Normal       |
| OS gompertz scale (lambda) - NSCLC                                       | 1.408380  | 1.13   | 1.69   | Normal       |
| OS log-logistic shape (p) - NSCLC                                        | 1.001362  | 0.80   | 1.20   | Normal       |
| OS log-logistic scale (lambda) - NSCLC                                   | 0.001263  | 0.00   | 0.00   | Normal       |
| OS log-normal shape (sigma) - NSCLC                                      | 1.705524  | 1.36   | 2.05   | Normal       |
| OS log-normal scale (mu) - NSCLC                                        | 6.692893  | 5.35   | 8.03   | Normal       |
| OS weibull shape (p) - NSCLC                                             | 0.840862  | 0.67   | 1.01   | Normal       |
| OS weibull scale (lambda) - NSCLC                                        | 0.002622  | 0.00   | 0.00   | Normal       |
| PFS exponential shape/scale (lambda) - NSCLC                            | 0.00      | 0.00   | 0.00   | Normal       |
| PFS gompertz shape (gamma)NSCLC                                          | -4.87     | -3.90  | -5.85  | Normal       |
| PFS gompertz scale (lambda) - NSCLC                                      | 1.44      | 1.15   | 1.72   | Normal       |
| PFS log-logistic shape (p) - NSCLC                                       | 0.97      | 0.78   | 1.17   | Normal       |
| PFS log-logistic scale (lambda) - NSCLC                                 | 0.00      | 0.00   | 0.00   | Normal       |
| PFS log-normal shape (sigma) - NSCLC                                     | 1.72      | 1.38   | 2.06   | Normal       |
| PFS log-normal scale (mu) - NSCLC                                       | 5.67      | 4.54   | 6.81   | Normal       |
| PFS weibull shape (p) - NSCLC                                            | 0.79      | 0.63   | 0.95   | Normal       |
| PFS weibull scale (lambda) - NSCLC                                       | 0.01      | 0.01   | 0.01   | Normal       |
| Adverse event disutility (weighted average) - NSCLC                      | 0.00      | 0.00   | 0.00   | Normal       |
| Treatment specific disutility - NSCLC                                    | 0.00      | 0.00   | 0.00   | Normal       |
| Complete response utility - NSCLC                                        | 0.82      | 0.66   | 0.98   | Beta         |
| Progressed disease utility - NSCLC                                       | 0.73      | 0.58   | 0.88   | Beta         |
| Adverse event cost (weighted average) - NSCLC                           | 7.47      | 5.98   | 8.97   | Gamma        |
| Progression free health state start cost - NSCLC                        | 0.00      | 0.00   | 0.00   | Gamma        |
| Progression free health state cost - NSCLC                              | 50.85     | 40.68  | 61.02  | Gamma        |
| Progressed disease state start cost - NSCLC                             | 0.00      | 0.00   | 0.00   | Gamma        |
| Progressed disease state cost - NSCLC                                    | 105.77    | 84.61  | 126.92 | Gamma        |
| Death health state cost - NSCLC                                         | 819.12    | 655.29 | 982.94 | Gamma        |
| OS exponential shape/scale (lambda) - Salivary                           | 0.002227  | 0.00   | 0.00   | Normal       |
| OS gompertz shape (gamma)Salivary                                       | 0.001475  | 0.00   | 0.00   | Normal       |
| OS gompertz scale (lambda) - Salivary                                   | 0.001525  | 0.00   | 0.00   | Normal       |
| OS log-logistic shape (p) - Salivary                                    | 2.679805  | 2.14   | 3.22   | Normal       |
| OS log-logistic scale (lambda) - Salivary                               | 0.000000  | 0.00   | 0.00   | Normal       |
| OS log-normal shape (sigma) - Salivary                                  | 0.674942  | 0.54   | 0.81   | Normal       |
| OS log-normal scale (mu) - Salivary                                     | 5.818751  | 4.66   | 6.98   | Normal       |
| OS weibull shape (p) - Salivary                                         | 1.653479  | 1.32   | 1.98   | Normal       |
| Parameter                                                        | Base case | Min     | Max     | Distribution |
|-----------------------------------------------------------------|-----------|---------|---------|--------------|
| OS weibull scale (lambda) - Salivary                             | 0.000041  | 0.00    | 0.00    | Normal       |
| PFS exponential shape/scale (lambda) - Salivary                  | 0.00      | 0.00    | 0.00    | Normal       |
| PFS gompertz shape (gamma) - Salivary                            | 0.00      | 0.00    | 0.00    | Normal       |
| PFS gompertz scale (lambda) - Salivary                           | 0.00      | 0.00    | 0.00    | Normal       |
| PFS log-logistic shape (p) - Salivary                            | 0.00      | 0.00    | 0.00    | Normal       |
| PFS log-logistic scale (lambda) - Salivary                       | 0.00      | 0.00    | 0.00    | Normal       |
| PFS log-normal shape (sigma) - Salivary                          | 0.00      | 0.00    | 0.00    | Normal       |
| PFS log-normal scale (mu) - Salivary                             | 0.00      | 0.00    | 0.00    | Normal       |
| PFS weibull shape (p) - Salivary                                 | 0.00      | 0.00    | 0.00    | Normal       |
| PFS weibull scale (lambda) - Salivary                            | 0.00      | 0.00    | 0.00    | Normal       |
| Adverse event disutility (weighted average) - Salivary           | 0.00      | 0.00    | 0.00    | Normal       |
| Treatment specific disutility - Salivary                         | 0.00      | 0.00    | 0.00    | Normal       |
| Complete response utility - Salivary                             | 0.82      | 0.66    | 0.98    | Beta         |
| Progressed disease utility - Salivary                            | 0.73      | 0.58    | 0.88    | Beta         |
| Adverse event cost (weighted average) - Salivary                 | 2.04      | 1.63    | 2.44    | Gamma        |
| Progression free health state start cost - Salivary              | 375.94    | 300.75  | 451.13  | Gamma        |
| Progression free health state cost - Salivary                   | 49.88     | 39.91   | 59.86   | Gamma        |
| Progressed disease health state start cost - Salivary            | 375.94    | 300.75  | 451.13  | Gamma        |
| Progressed disease health state cost - Salivary                  | 52.39     | 41.91   | 62.87   | Gamma        |
| Death health state start cost - Salivary                         | 819.12    | 655.29  | 982.94  | Gamma        |
| P.loss cost Adults PFS breast                                    | 4747.99   | 3798.39 | 5697.58 | Gamma        |
| P.loss cost Adults PFS Primary CNS                               | 6091.09   | 4872.87 | 7309.31 | Gamma        |
| P.loss cost Adults PFS Pancreas                                  | 6239.66   | 4991.72 | 7487.59 | Gamma        |
| P.loss cost Adults PFS Thyroid                                   | 6239.66   | 4991.72 | 7487.59 | Gamma        |
| P.loss cost Adults PD NSCLC                                      | 4159.77   | 3327.82 | 4991.72 | Gamma        |
| OS exponential shape/scale (lambda) - Melanoma                   | 0.001939  | 0.00    | 0.00    | Normal       |
| OS gompertz shape (gamma) - Melanoma                            | 0.000059  | 0.00    | 0.00    | Normal       |
| OS gompertz scale (lambda) - Melanoma                            | 0.001916  | 0.00    | 0.00    | Normal       |
| OS log-logistic shape (p) - Melanoma                             | 1.440212  | 1.15    | 1.73    | Normal       |
| OS log-logistic scale (lambda) - Melanoma                        | 0.000250  | 0.00    | 0.00    | Normal       |
| OS log-normal shape (sigma) - Melanoma                           | 1.267033  | 1.01    | 1.52    | Normal       |
| OS log-normal scale (mu) - Melanoma                              | 5.781835  | 4.63    | 6.94    | Normal       |
| OS weibull shape (p) - Melanoma                                  | 1.140926  | 0.91    | 1.37    | Normal       |
| OS weibull scale (lambda) - Melanoma                             | 0.000868  | 0.00    | 0.00    | Normal       |
| PFS exponential shape/scale (lambda) - Melanoma                  | 0.00      | 0.00    | 0.00    | Normal       |
| PFS gompertz shape (gamma) - Melanoma                            | -0.01     | -0.01   | -0.01   | Normal       |
| PFS gompertz scale (lambda) - Melanoma                           | 0.00      | 0.00    | 0.00    | Normal       |
| PFS log-logistic shape (p) - Melanoma                            | 0.87      | 0.70    | 1.04    | Normal       |
| PFS log-logistic scale (lambda) - Melanoma                       | 0.00      | 0.00    | 0.00    | Normal       |
| PFS log-normal shape (sigma) - Melanoma                          | 2.41      | 1.93    | 2.90    | Normal       |
| PFS log-normal scale (mu) - Melanoma                             | 7.26      | 5.81    | 8.71    | Normal       |
| PFS weibull shape (p) - Melanoma                                 | 0.83      | 0.66    | 0.99    | Normal       |
| PFS weibull scale (lambda) - Melanoma                            | 0.00      | 0.00    | 0.00    | Normal       |
| Adverse event disutility (weighted average) - Melanoma           | 0.00      | 0.00    | -0.01   | Normal       |
| Treatment specific disutility - Melanoma                         | 0.00      | 0.00    | 0.00    | Normal       |
| Complete response utility - Melanoma                             | 0.82      | 0.66    | 0.98    | Beta         |
| Progressed disease utility - Melanoma                            | 0.73      | 0.58    | 0.88    | Beta         |
| Adverse event cost (weighted average) - Melanoma                 | 4.32      | 3.45    | 5.18    | Gamma        |
| Progression free health state start cost - Melanoma              | 706.57    | 565.26  | 847.89  | Gamma        |
| Progression free health state cost - Melanoma                   | 118.76    | 95.01   | 142.51  | Gamma        |
| Parameter                                                                 | Base case | Min     | Max     | Distribution |
|--------------------------------------------------------------------------|-----------|---------|---------|--------------|
| Progressed disease health state start cost - Melanoma                    | 954.17    | 763.33  | 1145.00 | Gamma        |
| Progressed disease health state cost - Melanoma                          | 118.76    | 95.01   | 142.51  | Gamma        |
| Death health state start cost - Melanoma                                  | 819.12    | 655.29  | 982.94  | Gamma        |
| P.loss cost Adults PD Salivary                                            | 4159.77   | 3327.82 | 4991.72 | Gamma        |
| P.loss cost Adults PD Melanoma                                            | 4159.77   | 3327.82 | 4991.72 | Gamma        |
| P.loss cost Adults PD Pancreas                                            | 4159.77   | 3327.82 | 4991.72 | Gamma        |
| P.loss cost Adults PD SCLC                                                | 4159.77   | 3327.82 | 4991.72 | Gamma        |
| P.loss cost Adults PD breast                                              | 4159.77   | 3327.82 | 4991.72 | Gamma        |
| OS exponential shape/scale (lambda) - Colorectal                          | 0.001541  | 0.00    | 0.00    | Normal       |
| OS gompertz shape (gamma)Colorectal                                      | -3.816010 | -3.05   | -4.58   | Normal       |
| OS gompertz scale (lambda) - Colorectal                                   | 1.737444  | 1.39    | 2.08    | Normal       |
| OS log-logistic shape (p) - Colorectal                                    | 1.809495  | 1.45    | 2.17    | Normal       |
| OS log-logistic scale (lambda) - Colorectal                               | 0.000017  | 0.00    | 0.00    | Normal       |
| OS log-normal shape (sigma) - Colorectal                                  | 0.919262  | 0.74    | 1.10    | Normal       |
| OS log-normal scale (mu) - Colorectal                                    | 6.058388  | 4.85    | 7.27    | Normal       |
| OS weibull shape (p) - Colorectal                                         | 1.368708  | 1.09    | 1.64    | Normal       |
| OS weibull scale (lambda) - Colorectal                                   | 0.000166  | 0.00    | 0.00    | Normal       |
| PFS exponential shape/scale (lambda) - Colorectal                         | 20.82     | 16.65   | 24.98   | Normal       |
| PFS gompertz shape (gamma)Colorectal                                     | 2.06      | 1.65    | 2.47    | Normal       |
| PFS gompertz scale (lambda) - Colorectal                                  | -35.98    | -28.78  | -43.17  | Normal       |
| PFS log-logistic shape (p) - Colorectal                                   | 0.00      | 0.00    | 0.00    | Normal       |
| PFS log-logistic scale (lambda) - Colorectal                              | 0.81      | 0.65    | 0.97    | Normal       |
| PFS log-normal scale (mu) - Colorectal                                    | 5.15      | 4.12    | 6.18    | Normal       |
| PFS weibull shape (p) - Colorectal                                        | 1.50      | 1.20    | 1.80    | Normal       |
| PFS weibull scale (lambda) - Colorectal                                   | 0.00      | 0.00    | 0.00    | Normal       |
| Adverse event disutility (weighted average) - Colorectal                  | -0.05     | -0.04   | -0.06   | Normal       |
| Treatment specific disutility - Colorectal                                | 0.00      | 0.00    | 0.00    | Normal       |
| Complete response utility - Colorectal                                    | 0.82      | 0.66    | 0.98    | Beta         |
| Progressed disease utility - Colorectal                                   | 0.73      | 0.58    | 0.88    | Beta         |
| Adverse event cost (weighted average) - Colorectal                        | 442.85    | 354.28  | 531.42  | Gamma        |
| Progression free health state start cost - Colorectal                     | 0.00      | 0.00    | 0.00    | Gamma        |
| Progression free health state cost - Colorectal                           | 37.14     | 29.71   | 44.57   | Gamma        |
| Progressed disease health state start cost - Colorectal                   | 1103.42   | 882.74  | 1324.11 | Gamma        |
| Progressed disease health state cost - Colorectal                         | 54.62     | 43.70   | 65.55   | Gamma        |
| Death health state start cost - Colorectal                                 | 819.12    | 655.29  | 982.94  | Gamma        |
| P.loss cost Adults PD Primary CNS                                         | 4159.77   | 3327.82 | 4991.72 | Gamma        |
| P.loss cost Adults PFS Pancreas                                           | 4159.77   | 3327.82 | 4991.72 | Gamma        |
| P.loss cost Adults PD Thyroid                                             | 4159.77   | 3327.82 | 4991.72 | Gamma        |
| P.loss cost Adults Death NSCLC                                             | 0.00      | 0.00    | 0.00    | Gamma        |
| P.loss cost Adults Death Salivary                                         | 0.00      | 0.00    | 0.00    | Gamma        |
| P.loss cost Adults Death Melanoma                                         | 0.00      | 0.00    | 0.00    | Gamma        |
| P.loss cost Adults Death Colorectal                                       | 0.00      | 0.00    | 0.00    | Gamma        |
| P.loss cost Adults Death SCLC                                              | 0.00      | 0.00    | 0.00    | Gamma        |
| P.loss cost Adults Death Breast                                           | 0.00      | 0.00    | 0.00    | Gamma        |
| P.loss cost Adults Death Primary CNS                                      | 0.00      | 0.00    | 0.00    | Gamma        |
| P.loss cost Adults Death Thyroid                                          | 0.00      | 0.00    | 0.00    | Gamma        |
| Inf. Care cost Adults PFS                                                 | 117.71    | 94.16   | 141.25  | Gamma        |
| Inf. Care cost Adults PD                                                  | 176.56    | 141.25  | 211.87  | Gamma        |
| Parameter                                         | Base case | Min    | Max     | Distribution |
|--------------------------------------------------|-----------|--------|---------|--------------|
| Inf. Care cost Adults Death                       | 0.00      | 0.00   | 0.00    | Gamma        |
| Transportation cost Adults PFS                   | 2.90      | 2.32   | 3.48    | Gamma        |
| Parking allowance cost Adults PFS                | 3.27      | 2.62   | 3.93    | Gamma        |
| Transportation cost Adults PD                    | 3.47      | 2.78   | 4.17    | Gamma        |
| Parking allowance cost Adults PD                 | 3.92      | 3.13   | 4.70    | Gamma        |
| Transportation cost Adults Death                 | 0.00      | 0.00   | 0.00    | Gamma        |
| Parking allowance cost Adults Death              | 0.00      | 0.00   | 0.00    | Gamma        |
| Inf. Care cost Paeds PFS                         | 235.41    | 188.33 | 282.49  | Gamma        |
| Inf. Care cost Paeds PD                          | 353.12    | 282.49 | 423.74  | Gamma        |
| Inf. Care cost Paeds Death                       | 0.00      | 0.00   | 0.00    | Gamma        |
| Transportation cost Paeds Death                  | 0.00      | 0.00   | 0.00    | Gamma        |
| OS exponential shape/scale (lambda) - SCLC       | 0.001945  | 0.00   | 0.00    | Normal       |
| OS gompertz shape (gamma)SCLC                    | -4.240038 | -3.39  | -5.09   | Normal       |
| OS gompertz scale (lambda) - SCLC                | 1.551270  | 1.24   | 1.86    | Normal       |
| OS log-logistic shape (p) - SCLC                 | 2.322811  | 1.86   | 2.79    | Normal       |
| OS log-logistic scale (lambda) - SCLC            | 0.000002  | 0.00   | 0.00    | Normal       |
| OS log-normal shape (sigma) - SCLC               | 0.714607  | 0.57   | 0.86    | Normal       |
| OS log-normal scale (mu) - SCLC                  | 5.759565  | 4.61   | 6.91    | Normal       |
| OS weibull shape (p) - SCLC                      | 1.835309  | 1.47   | 2.20    | Normal       |
| OS weibull scale (lambda) - SCLC                 | 0.000017  | 0.00   | 0.00    | Normal       |
| PFS exponential shape/scale (lambda) - SCLC      | 0.00      | 0.00   | 0.00    | Normal       |
| PFS gompertz shape (gamma)SCLC                   | -4.36     | -3.49  | -5.23   | Normal       |
| PFS gompertz scale (lambda) - SCLC               | 1.58      | 1.26   | 1.90    | Normal       |
| PFS log-logistic shape (p) - SCLC                | 2.64      | 2.11   | 3.16    | Normal       |
| PFS log-logistic scale (lambda) - SCLC           | 0.00      | 0.00   | 0.00    | Normal       |
| PFS log-normal shape (sigma) - SCLC              | 0.65      | 0.51   | 0.76    | Normal       |
| PFS log-normal scale (mu) - SCLC                 | 5.21      | 4.17   | 6.25    | Normal       |
| PFS weibull shape (p) - SCLC                     | 2.09      | 1.67   | 2.51    | Normal       |
| PFS weibull scale (lambda) - SCLC                | 0.00      | 0.00   | 0.00    | Normal       |
| Adverse event disutility (weighted average) - SCLC| -0.01     | -0.01  | -0.01   | Normal       |
| Treatment specific disutility - SCLC             | 0.00      | 0.00   | 0.00    | Normal       |
| Complete response utility - SCLC                 | 0.82      | 0.66   | 0.98    | Beta         |
| Progressed disease utility - SCLC                | 0.73      | 0.58   | 0.88    | Beta         |
| Adverse event cost (weighted average) - SCLC     | 471.04    | 376.83 | 565.25  | Gamma        |
| Progression free health state start cost - SCLC | 0.00      | 0.00   | 0.00    | Gamma        |
| Progression free health state cost - SCLC        | 50.85     | 40.68  | 61.02   | Gamma        |
| Progressed disease health state start cost - SCLC| 0.00      | 0.00   | 0.00    | Gamma        |
| Progressed disease health state cost - SCLC      | 105.77    | 84.61  | 126.92  | Gamma        |
| Death health state cost - SCLC                   | 819.12    | 655.29 | 982.94  | Gamma        |
| OS exponential shape/scale (lambda) - Breast     | 0.021066  | 0.02   | 0.03    | Normal       |
| OS gompertz shape (gamma)Breast                  | 0.000000  | 0.00   | 0.00    | Normal       |
| OS gompertz scale (lambda) - Breast              | 0.000000  | 0.00   | 0.00    | Normal       |
| OS log-logistic shape (p) - Breast               | 0.000000  | 0.00   | 0.00    | Normal       |
| OS log-logistic scale (lambda) - Breast          | 0.000000  | 0.00   | 0.00    | Normal       |
| OS log-normal shape (sigma) - Breast             | 0.000000  | 0.00   | 0.00    | Normal       |
| OS log-normal scale (mu) - Breast                | 0.000000  | 0.00   | 0.00    | Normal       |
| OS weibull shape (p) - Breast                    | 0.000000  | 0.00   | 0.00    | Normal       |
| OS weibull scale (lambda) - Breast               | 0.000000  | 0.00   | 0.00    | Normal       |
| PFS exponential shape/scale (lambda) - Breast    | 0.00      | 0.00   | 0.00    | Normal       |
| PFS gompertz shape (gamma)Breast                 | 0.00      | 0.00   | 0.00    | Normal       |
| Parameter                                                                 | Base case | Min   | Max   | Distribution |
|---------------------------------------------------------------------------|-----------|-------|-------|--------------|
| PFS gompertz scale (lambda) - Breast                                      | 0.00      | 0.00  | 0.00  | Normal       |
| PFS log-logistic shape (p) - Breast                                       | 0.00      | 0.00  | 0.00  | Normal       |
| PFS log-logistic scale (lambda) - Breast                                  | 0.00      | 0.00  | 0.00  | Normal       |
| PFS log-normal shape (lambda) - Breast                                    | 0.00      | 0.00  | 0.00  | Normal       |
| PFS log-normal scale (mu) - Breast                                        | 0.00      | 0.00  | 0.00  | Normal       |
| PFS weibull shape (p) - Breast                                            | 0.00      | 0.00  | 0.00  | Normal       |
| PFS weibull scale (lambda) - Breast                                       | 0.00      | 0.00  | 0.00  | Normal       |
| Adverse event disutility (weighted average) - Breast                      | -0.02     | -0.02 | -0.02 | Normal       |
| Treatment specific disutility - Breast                                    | 0.00      | 0.00  | 0.00  | Normal       |
| Complete response utility - Breast                                        | 0.82      | 0.66  | 0.98  | Beta         |
| Progressed disease utility - Breast                                       | 0.73      | 0.58  | 0.88  | Beta         |
| Adverse event cost (weighted average) - Breast                            | 276.98    | 221.58| 332.38| Gamma        |
| Progression free health state start cost - Breast                         | 0.00      | 0.00  | 0.00  | Gamma        |
| Progression free health state cost - Breast                               | 371.64    | 297.31| 445.96| Gamma        |
| Progressed disease health state start cost - Breast                       | 0.00      | 0.00  | 0.00  | Gamma        |
| Progressed disease health state cost - Breast                             | 529.59    | 423.67| 635.50| Gamma        |
| Death health state start cost - Breast                                    | 819.12    | 655.29| 982.94| Gamma        |
| OS exponential shape/scale (lambda) - Children combined                   | 0.0001066 | 0.00  | 0.00  | Normal       |
| OS gompertz shape (gamma)Children combined                               | -0.000905 | 0.00  | 0.00  | Normal       |
| OS gompertz scale (lambda) - Children combined                            | 0.001643  | 0.00  | 0.00  | Normal       |
| OS log-logistic shape (p) - Children combined                             | 1.528808  | 1.22  | 1.83  | Normal       |
| OS log-logistic scale (lambda) - Children combined                        | 0.000072  | 0.00  | 0.00  | Normal       |
| OS log-normal shape (sigma) - Children combined                           | 1.134049  | 0.91  | 1.36  | Normal       |
| OS log-normal scale (mu) - Children combined                              | 6.312416  | 5.05  | 7.57  | Normal       |
| OS weibull shape (p) - Children combined                                  | 0.994878  | 0.80  | 1.19  | Normal       |
| OS weibull scale (lambda) - Children combined                             | 0.001104  | 0.00  | 0.00  | Normal       |
| PFS exponential shape/scale (lambda) - Children combined                  | 0.00      | 0.00  | 0.00  | Normal       |
| PFS gompertz shape (gamma)Children combined                               | 0.00      | 0.00  | 0.00  | Normal       |
| PFS gompertz scale (lambda) - Children combined                           | 0.00      | 0.00  | 0.00  | Normal       |
| PFS log-logistic shape (p) - Children combined                            | 1.12      | 0.89  | 1.34  | Normal       |
| PFS log-logistic scale (lambda) - Children combined                       | 0.00      | 0.00  | 0.00  | Normal       |
| PFS log-normal shape (sigma) - Children combined                          | 1.56      | 1.25  | 1.87  | Normal       |
| PFS log-normal scale (mu) - Children combined                             | 5.52      | 4.42  | 6.62  | Normal       |
| PFS weibull shape (p) - Children combined                                 | 0.76      | 0.61  | 0.91  | Normal       |
| PFS weibull scale (lambda) - Children combined                            | 0.01      | 0.01  | 0.01  | Normal       |
| Adverse event disutility (weighted average) - Children combined           | -0.02     | -0.01 | -0.02 | Normal       |
| Treatment specific disutility - Children combined                          | 0.00      | 0.00  | 0.00  | Normal       |
| Complete response utility - Children combined                              | 0.82      | 0.66  | 0.98  | Beta         |
| Progressed disease utility - Children combined                             | 0.73      | 0.58  | 0.88  | Beta         |
| Adverse event cost (weighted average) - Children combined                 | 1343.74   | 1074.99| 1612.48| Gamma       |
| Progression free health state start cost - Children combined              | 0.00      | 0.00  | 0.00  | Gamma        |
| Progression free health state cost - Children combined                    | 62.50     | 50.00 | 75.00 | Gamma        |
| Progressed disease health state cost - Children combined                  | 0.00      | 0.00  | 0.00  | Gamma        |
| Progressed disease health state cost - Children combined                  | 62.50     | 50.00 | 75.00 | Gamma        |
| Death health state start cost - Children combined                          | 819.12    | 655.29| 982.94| Gamma        |
| OS exponential shape/scale (lambda) - CNS                                 | 0.0002094 | 0.00  | 0.00  | Normal       |
| OS gompertz shape (gamma)CNS                                              | 0.0003347 | 0.00  | 0.00  | Normal       |
| OS gompertz scale (lambda) - CNS                                          | 0.001281  | 0.00  | 0.00  | Normal       |
| OS log-logistic shape (p) - CNS                                           | 1.861306  | 1.49  | 2.23  | Normal       |
| OS log-logistic scale (lambda) - CNS                                      | 0.000025  | 0.00  | 0.00  | Normal       |
| Parameter                                                                 | Base case  | Min  | Max  | Distribution |
|-------------------------------------------------------------------------|-----------|------|------|--------------|
| OS log-normal shape (sigma) - CNS                                        | 0.967411  | 0.77 | 1.16 | Normal       |
| OS log-normal scale (mu) - CNS                                          | 5.706316  | 4.57 | 6.85 | Normal       |
| OS weibull shape (p) - CNS                                              | 1.547355  | 1.24 | 1.86 | Normal       |
| OS weibull scale (lambda) - CNS                                         | 0.000102  | 0.00 | 0.00 | Normal       |
| PFS exponential shape/scale (lambda) - CNS                              | 0.01      | 0.01 | 0.01 | Normal       |
| PFS gompertz shape (gamma) - CNS                                        | 0.00      | 0.00 | 0.00 | Normal       |
| PFS gompertz scale (lambda) - CNS                                       | 0.01      | 0.01 | 0.01 | Normal       |
| PFS log-logistic shape (p) - CNS                                        | 1.87      | 1.50 | 2.24 | Normal       |
| PFS log-logistic scale (lambda) - CNS                                    | 0.00      | 0.00 | 0.00 | Normal       |
| PFS log-normal shape (sigma) - CNS                                      | 0.91      | 0.73 | 1.09 | Normal       |
| PFS log-normal scale (mu) - CNS                                         | 4.53      | 3.63 | 5.44 | Normal       |
| PFS weibull shape (p) - CNS                                             | 1.18      | 0.94 | 1.41 | Normal       |
| PFS weibull scale (lambda) - CNS                                        | 0.00      | 0.00 | 0.00 | Normal       |
| Adverse event disutility (weighted average) - CNS                       | -0.04     | -0.03| -0.05| Normal       |
| Treatment specific disutility - CNS                                     | 0.00      | 0.00 | 0.00 | Normal       |
| Complete response utility - CNS                                         | 0.82      | 0.66 | 0.98 | Beta         |
| Progressed disease utility - CNS                                        | 0.73      | 0.58 | 0.88 | Beta         |
| Adverse event cost (weighted average) - CNS                             | 137.80    | 110.24| 165.36| Gamma       |
| Progression free health state start cost - CNS                          | 0.00      | 0.00 | 0.00 | Gamma       |
| Progression free health state cost - CNS                                | 62.50     | 50.00| 75.00| Gamma       |
| Progressed disease health state start cost - CNS                       | 0.00      | 0.00 | 0.00 | Gamma       |
| Progressed disease health state start cost - CNS                       | 62.50     | 50.00| 75.00| Gamma       |
| Death health state start cost - CNS                                     | 819.12    | 655.29| 982.94| Gamma       |
| OS exponential shape/scale (lambda) - Pancreas                          | 0.002294  | 0.00 | 0.00 | Normal       |
| OS gompertz shape (gamma) - Pancreas                                    | 3.090316  | -2.47| -3.71| Normal       |
| OS gompertz scale (lambda) - Pancreas                                   | 1.942395  | 1.55 | 2.33 | Normal       |
| OS log-logistic shape (p) - Pancreas                                    | 2.322811  | 1.86 | 2.79 | Normal       |
| OS log-logistic scale (lambda) - Pancreas                               | 0.000002  | 0.00 | 0.00 | Normal       |
| OS log-normal shape (sigma) - Pancreas                                  | 0.767584  | 0.61 | 0.92 | Normal       |
| OS log-normal scale (mu) - Pancreas                                     | 5.737695  | 4.59 | 6.89 | Normal       |
| OS weibull shape (p) - Pancreans                                       | 1.512683  | 1.21 | 1.82 | Normal       |
| OS weibull scale (lambda) - Pancreas                                    | 0.000111  | 0.00 | 0.00 | Normal       |
| PFS exponential shape/scale (lambda) - Pancreas                         | 0.00      | 0.00 | 0.01 | Normal       |
| PFS gompertz shape (gamma) - Pancreans                                 | -4.29     | -3.43| -5.15| Normal       |
| PFS gompertz scale (lambda) - Pancreans                                | 3.24      | 2.59 | 3.89 | Normal       |
| PFS log-logistic shape (p) - Pancreans                                 | 2.49      | 1.99 | 2.99 | Normal       |
| PFS log-logistic scale (lambda) - Pancreans                            | 0.00      | 0.00 | 0.00 | Normal       |
| PFS log-normal shape (sigma) - Pancreans                               | 0.89      | 0.71 | 1.07 | Normal       |
| PFS log-normal scale (mu) - Pancreans                                  | 5.09      | 4.07 | 6.11 | Normal       |
| PFS weibull shape (p) - Pancreans                                     | 1.32      | 1.06 | 1.59 | Normal       |
| PFS weibull scale (lambda) - Pancreans                                 | 0.00      | 0.00 | 0.00 | Normal       |
| Adverse event disutility (weighted average) - Pancreas                 | -0.05     | -0.04| -0.06| Normal       |
| Treatment specific disutility - Pancreans                              | 0.00      | 0.00 | 0.00 | Normal       |
| Complete response utility - Pancreans                                  | 0.82      | 0.66 | 0.98 | Beta         |
| Progressed disease utility - Pancreans                                  | 0.73      | 0.58 | 0.88 | Beta         |
| Adverse event cost (weighted average) - Pancreas                      | 524.07    | 419.26| 629.89| Gamma       |
| Progression free health state start cost - Pancreas                   | 439.48    | 351.58| 527.37| Gamma       |
| Progression free health state cost - Pancreas                          | 100.86    | 80.68| 121.03| Gamma       |
| Progressed disease health state start cost - Pancreas                  | 0.00      | 0.00 | 0.00 | Gamma       |
| Progressed disease health state cost - Pancreas                        | 78.34     | 62.68| 94.01| Gamma       |
| Parameter                                                                 | Base case | Min    | Max    | Distribution |
|---------------------------------------------------------------------------|-----------|--------|--------|--------------|
| Death health state start cost - Pancreas                                  | 819.12    | 655.29 | 982.94 | Gamma        |
| OS exponential shape/scale (lambda) - Thyroid                            | 0.000000  | 0.00   | 0.00   | Normal       |
| OS gompertz shape (gamma) - Thyroid                                      | 0.000000  | 0.00   | 0.00   | Normal       |
| OS gompertz scale (lambda) - Thyroid                                     | 0.000000  | 0.00   | 0.00   | Normal       |
| OS log-logistic shape (p) - Thyroid                                      | 0.000000  | 0.00   | 0.00   | Normal       |
| OS log-logistic scale (lambda) - Thyroid                                 | 0.000000  | 0.00   | 0.00   | Normal       |
| OS log-normal shape (sigma) - Thyroid                                    | 0.000000  | 0.00   | 0.00   | Normal       |
| OS log-normal scale (mu) - Thyroid                                       | 0.000000  | 0.00   | 0.00   | Normal       |
| OS weibull shape (p) - Thyroid                                           | 0.000000  | 0.00   | 0.00   | Normal       |
| OS weibull scale (lambda) - Thyroid                                      | 0.000000  | 0.00   | 0.00   | Normal       |
| PFS exponential shape/scale (lambda) - Thyroid                           | 0.00      | 0.00   | 0.00   | Normal       |
| PFS gompertz shape (gamma) - Thyroid                                     | 0.00      | 0.00   | 0.00   | Normal       |
| PFS gompertz scale (lambda) - Thyroid                                    | 0.00      | 0.00   | 0.00   | Normal       |
| PFS log-logistic shape (p) - Thyroid                                     | 1.53      | 1.23   | 1.84   | Normal       |
| PFS log-logistic scale (lambda) - Thyroid                                | 0.00      | 0.00   | 0.00   | Normal       |
| PFS log-normal shape (sigma) - Thyroid                                   | 1.12      | 0.90   | 1.34   | Normal       |
| PFS log-normal scale (mu) - Thyroid                                      | 5.78      | 4.62   | 6.94   | Normal       |
| PFS weibull shape (p) - Thyroid                                          | 1.22      | 0.97   | 1.46   | Normal       |
| PFS weibull scale (lambda) - Thyroid                                     | 0.00      | 0.00   | 0.00   | Normal       |
| Adverse event disutility (weighted average) - Thyroid                    | -0.02     | -0.01  | -0.02  | Normal       |
| Treatment specific disutility - Thyroid                                   | 0.00      | 0.00   | 0.00   | Normal       |
| Complete response utility - Thyroid                                       | 0.82      | 0.66   | 0.98   | Beta         |
| Progressed disease utility - Thyroid                                      | 0.73      | 0.58   | 0.88   | Beta         |
| Adverse event cost (weighted average) - Thyroid                          | 32.51     | 26.01  | 39.01  | Gamma        |
| Progression free health state cost - Thyroid                             | 0.00      | 0.00   | 0.00   | Gamma        |
| Progression free health state cost - Thyroid                             | 62.50     | 50.00  | 75.00  | Gamma        |
| Progressed disease health state cost - Thyroid                           | 0.00      | 0.00   | 0.00   | Gamma        |
| Progressed disease health state cost - Thyroid                           | 62.50     | 50.00  | 75.00  | Gamma        |
| Death health state start cost - Thyroid                                  | 819.12    | 655.29 | 982.94 | Gamma        |

**EVPI analysis**

The Population Expected Value of Perfect Information (PEVPI) analysis reflects the financial risk expected given the uncertainty around estimates included in the analysis. EVPI calculates the expected costs of uncertainty entailing making the inappropriate decision. EVPI considers the number of times the decision must be made over the lifetime of the technology. Thus, the PEVPI depends on the number of patients that will be treated with larotrectinib, accounting for the incidence of the decision. The number of patients eligible for larotrectinib treatment in the Netherlands was estimated at 34.8 based on epidemiological data and an estimate that 25% of TRK fusion-positive cancer patients are tested for *NTRK* gene fusions, based on clinical expert opinion. The PEVPI for varying lifetime estimates of the technology is given in Figure 7.
Figure 3: Results of the VOI analysis
