Indirect treatment comparisons of time-to-event outcomes with mis-matched 'time-zero': methodology and application in resectable non-small cell lung cancer

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Declaration of Interests

- This study was supported by Bristol Myers Squibb
- Individual disclosures
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  - Lucherini S, Vo L, Chaudhary MA, Varol N, Lam P: Employees of Bristol-Myers Squibb
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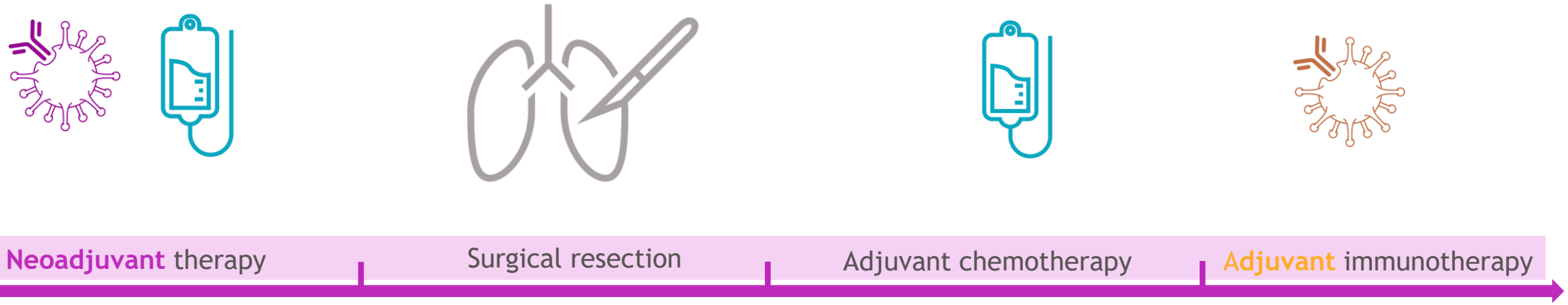
  - Spicer J: **Consulting, advisory role, or honoraria**: AstraZeneca, Merck, Roche, BMS, Novartis, Chemocentryx, Amgen, Protalix Biotherapies, Xenetic Biosciences, Regeneron; **Grant to institution**: AstraZeneca, Merck, Roche, CLS Therapeutics, Protalix Biotherapies; **Clinical trial leadership role**: BMS, Novartis, AstraZeneca, Merck, Roche

Motivation

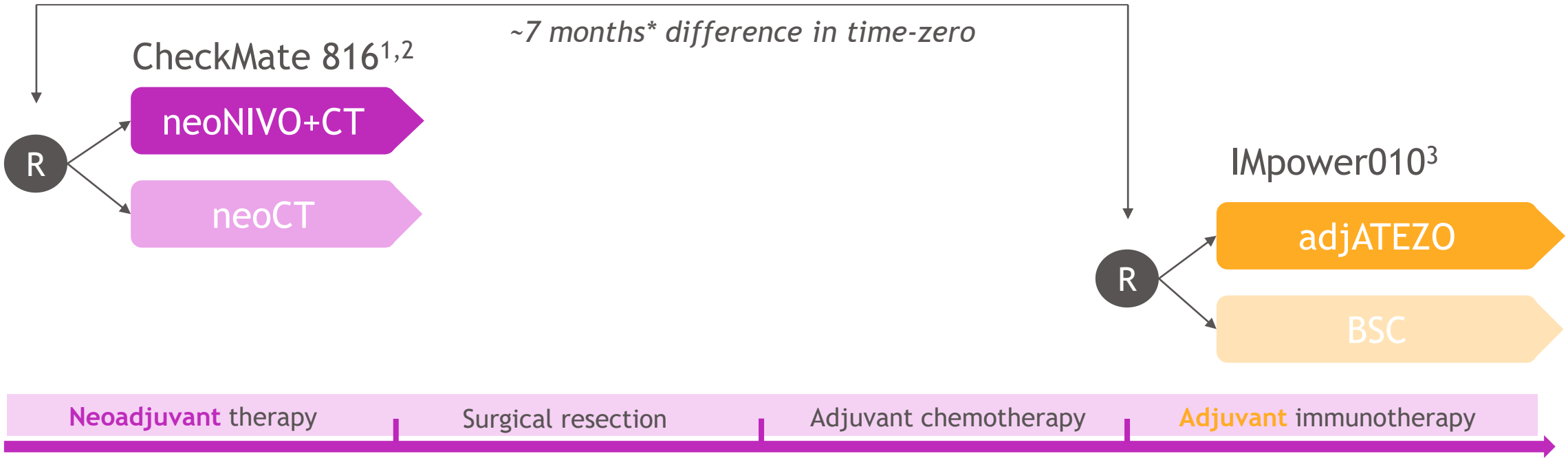
- Recent approvals of immune checkpoint inhibitors for resectable non-small cell lung cancer (rNSCLC) include*:
  - **Neoadjuvant** nivolumab plus chemotherapy (CT) (neoNIVO+CT)
  - **Adjuvant** atezolizumab (adjATEZO), following resection and adjuvant CT (adjCT)



**Additional approvals and data disclosures for immune checkpoint inhibitors have emerged in 2023: adjuvant pembrolizumab was approved in January 2023 by the United States Food and Drug Administration, based on KEYNOTE-091 / PEARLS; in March 2023, the KEYNOTE-671 trial (involving peri-operative pembrolizumab) was reported to have met its primary endpoint (press release); and results from the AEGEAN trial, involving peri-operative durvalumab, were reported in April 2023.*

Motivation

- Head-to-head comparisons between neoNIVO+CT and adjATEZO are unavailable
- Differences in “time-zero” preclude traditional indirect treatment comparisons of event-free survival (EFS)



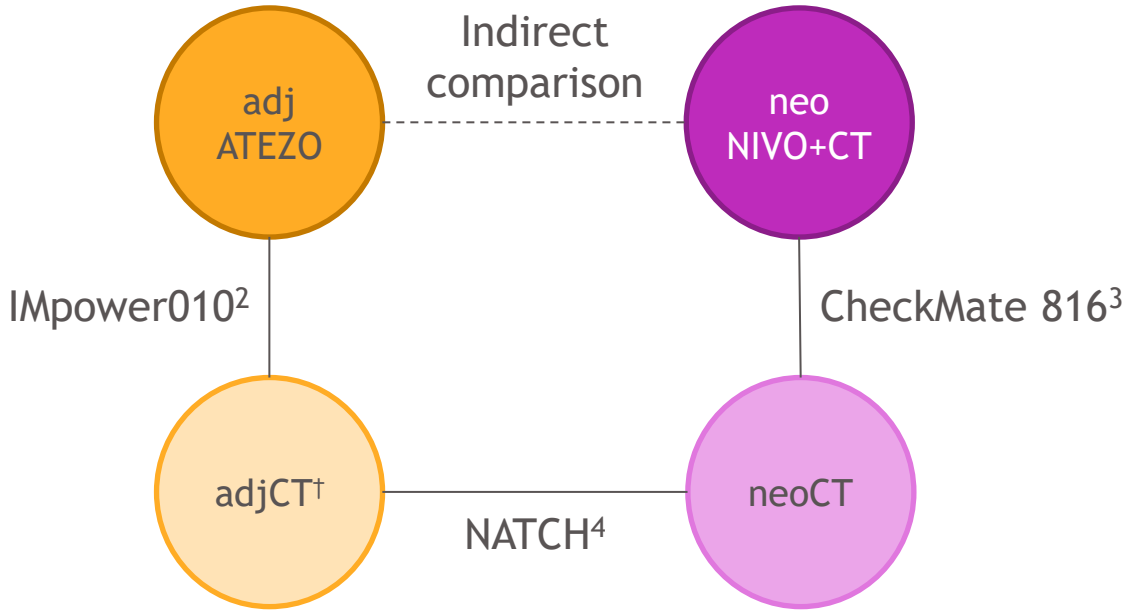
*7-month offset in time-zero was estimated based on literature review and clinical expert consultation as: Time to surgery [4 weeks (1 month)] + Time from surgery to adjCT initiation [9 weeks (2.1 months)] + Duration of adjCT (first to last dose) [14 weeks (3.2 months)] + Last dose of adjCT to initiation of adjATEZO [3 weeks (0.7 months)].

Abbreviations: adjATEZO = adjuvant atezolizumab; BSC = best supportive care; neoCT = neoadjuvant chemotherapy; neoNIVO+CT = neoadjuvant nivolumab plus chemotherapy; R = randomization.

[1] Forde et al. 2022 DOI: 10.1056/NEJMoa2202170; [2] Forde et al. 2023 European Lung Cancer Congress; [3] Felip et al. 2021 DOI: 10.1016/S0140-6736(21)02098-5

Evidence base

- 3 RCTs formed the evidence base, identified via systematic literature review
  - The endpoint of interest was EFS*, measured using hazard ratios (HR)
- Indirect treatment comparison methodology was adapted from standard approaches[1]



** Captured as disease-free survival (DFS) in NATCH and IMpower010*

† In IMpower 010, the control arm (best supportive care), was provided after receipt of adjCT. With time-zero offset adjustments, this best supportive care arm is considered the same as the adjCT arm in NATCH.

Abbreviations: *adjATEZO = adjuvant atezolizumab; adjCT = adjuvant chemotherapy; EFS = event-free survival; neoCT = neoadjuvant chemotherapy; neoNIVO+CT = neoadjuvant nivolumab plus chemotherapy; RCT = randomized controlled trial.*

[1] Jansen et al. 2011 DOI: 10.1016/j.jval.2011.04.002; [2] Felip et al. 2021 DOI: 10.1016/S0140-6736(21)02098-5; [3] Forde et al. 2023 European Lung Cancer Congress; [4] Felip et al. 2010 DOI: 10.1200/JCO.2009.27.6204

Time-zero adjustment

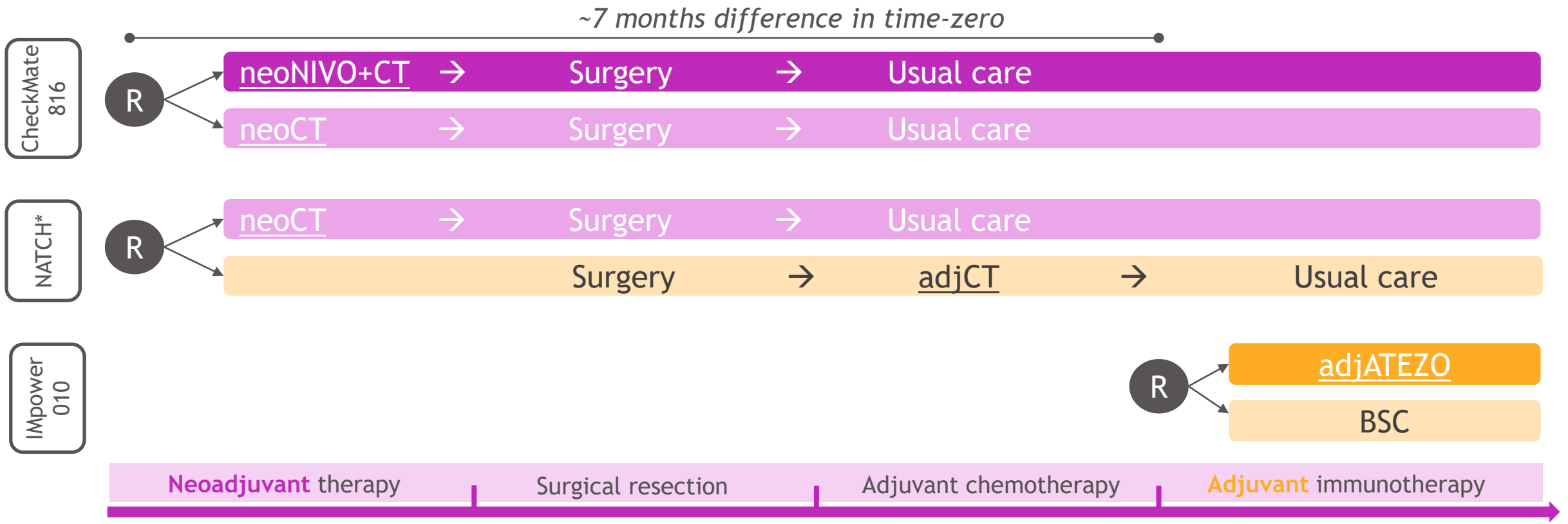
- Our objective was to develop a method that adjusts for differences in time-zero
- First, three concepts will be described regarding the time-zero mismatch:

1. Differences in relative treatment effects over time
2. Selection bias*: survivorship
3. Selection bias*: other emerging eligibility criteria

*In the context of indirect treatment comparisons, selection bias refers to systematic differences in patient characteristics across trials, on factors that influence relative effect estimates.

Differences in relative treatment effects over time

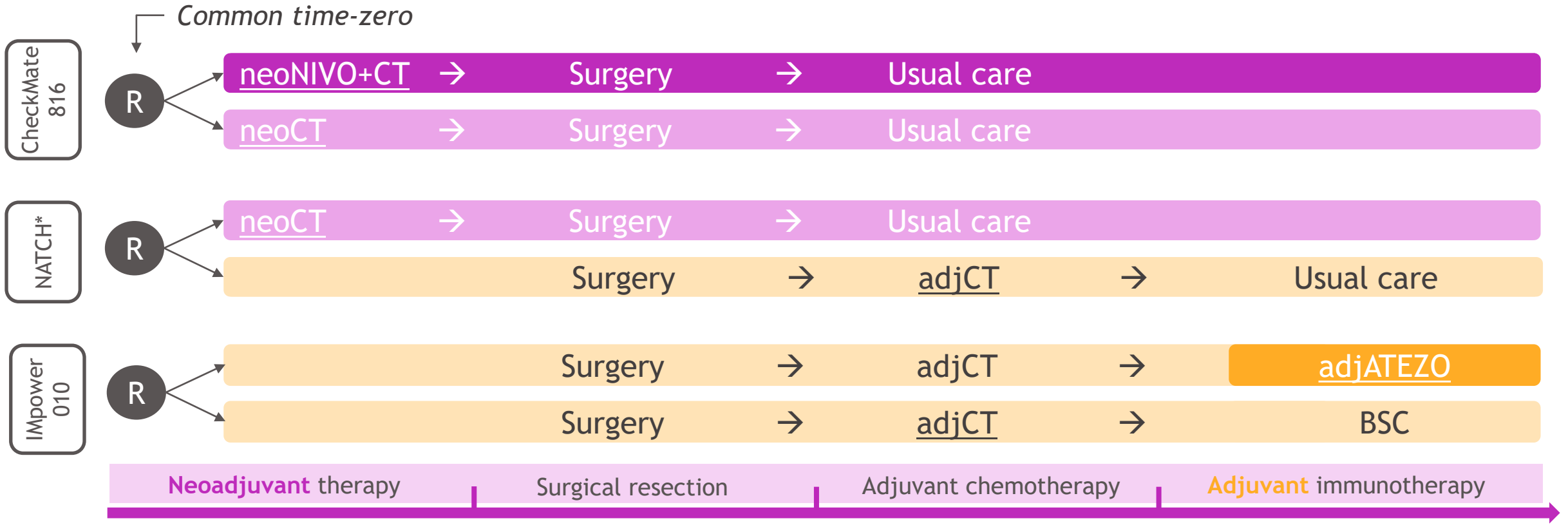
- We established a common time-zero to align with CheckMate 816 and with NATCH



**NATCH was designed to compare neoCT vs. surgery and adjCT vs. surgery but was not powered for comparisons between neoCT and adjCT.*
Note: underlined terms correspond to labels in the evidence networks
***Abbreviations**: adjATEZO = adjuvant atezolizumab; adjCT = adjuvant chemotherapy; BSC = best supportive care; neoCT = neoadjuvant chemotherapy; neoNIVO+CT = neoadjuvant nivolumab plus chemotherapy; R = randomization.*

Differences in relative treatment effects over time

- We established a common time-zero to align with CheckMate 816 and with NATCH
- No systematic differences between IMpower010 trial arms during the first 7 months



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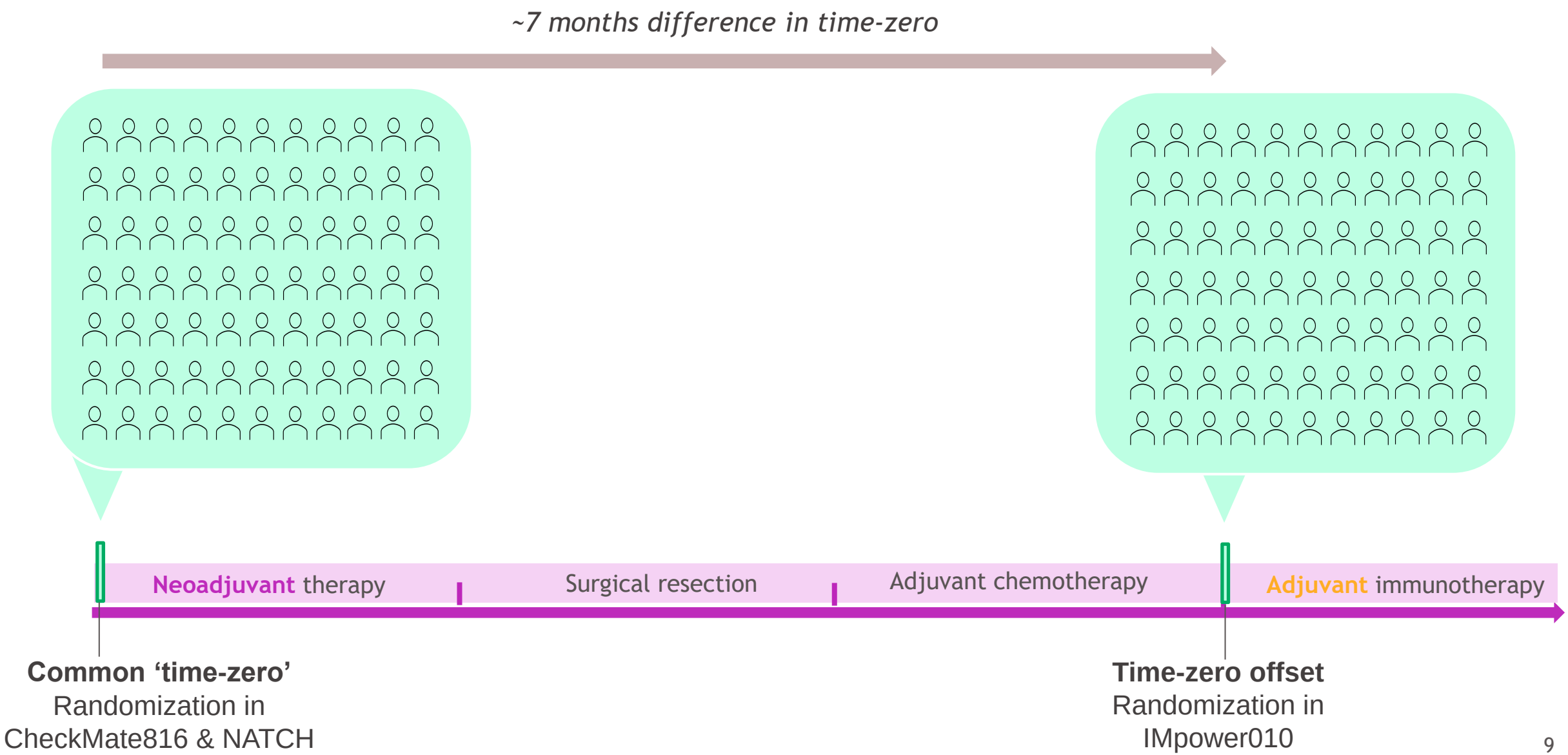
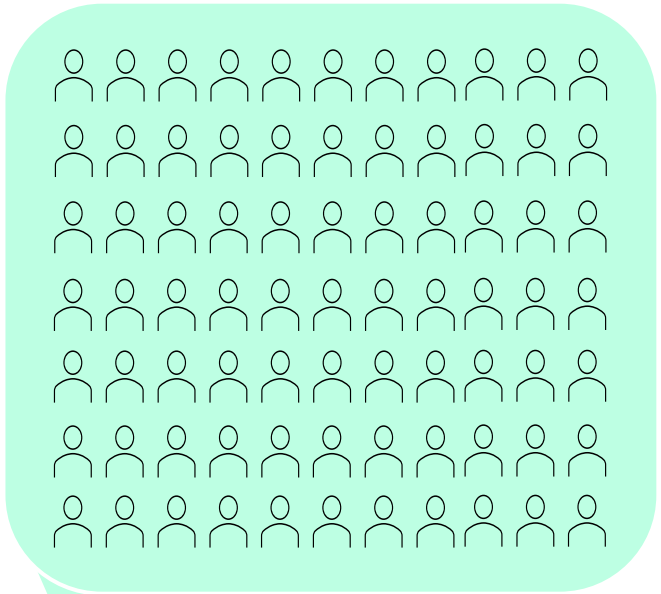
Selection bias due to survivorship and other eligibility criteria that emerge during time-zero offset



Selection bias due to survivorship and other eligibility criteria that emerge during time-zero offset

~7 months difference in time-zero



Over time patients may:

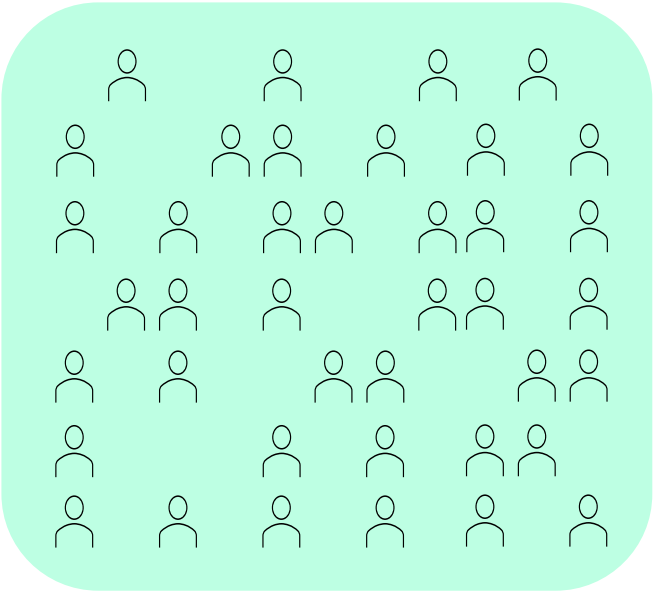
- × Die
- × Experience progression or recurrence

Event-free survival events

Or, may not:

- × Receive surgery
- × Achieve a complete resection (R0)
- × Receive adjCT
- × Receive adjATEZO

Other events



Neoadjuvant therapy | Surgical resection | Adjuvant chemotherapy | **Adjuvant** immunotherapy

Common 'time-zero'
Randomization in CheckMate816 & NATCH

Time-zero offset
Randomization in IMpower010

Implications of time-zero adjustment

- Next, indirect treatment comparison adaptations will be introduced, to address the issues arising from time-zero offsets:

1. Differences in relative treatment effects over time
2. Selection bias*: survivorship
3. Selection bias*: other emerging eligibility criteria

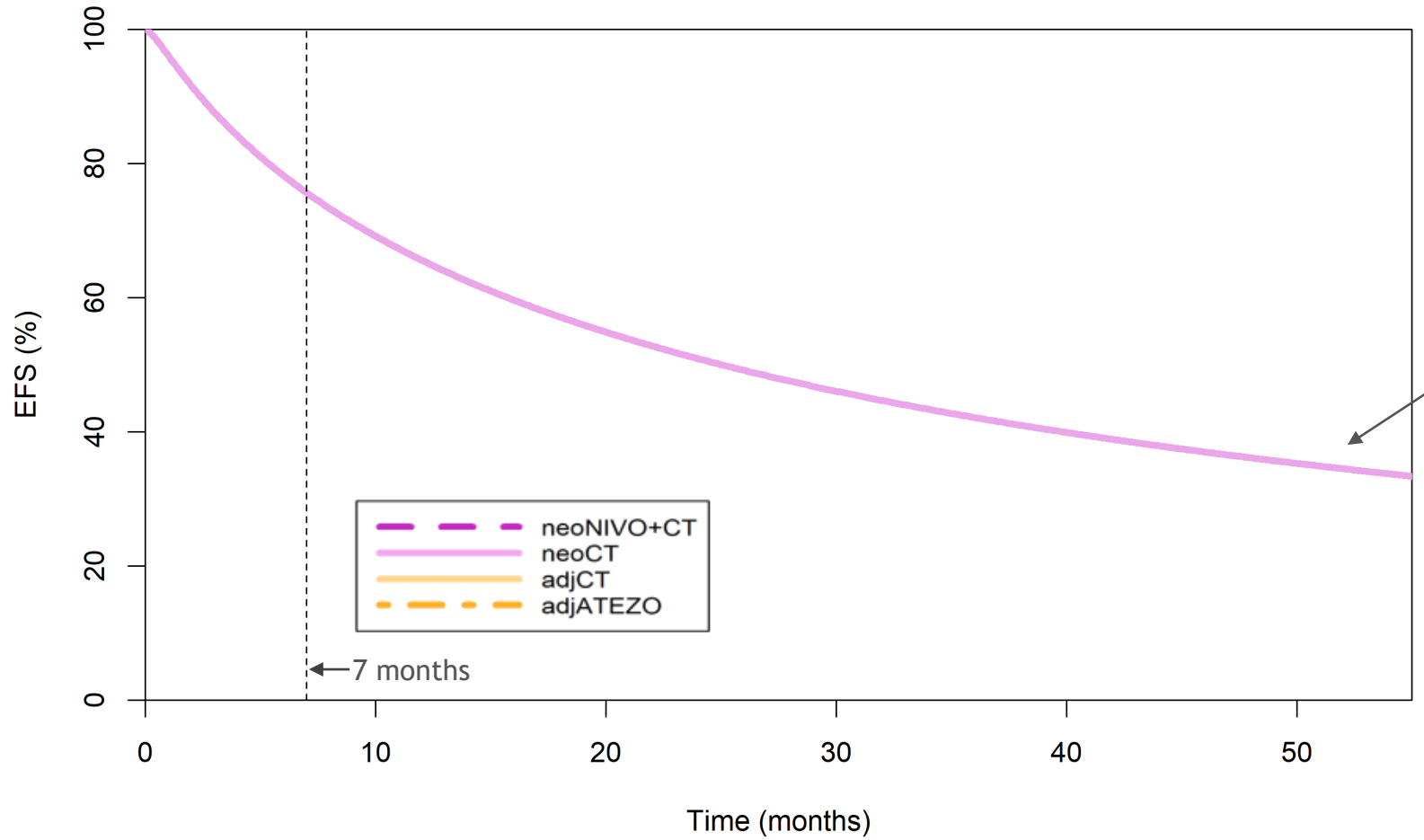
Time-varying hazard ratios

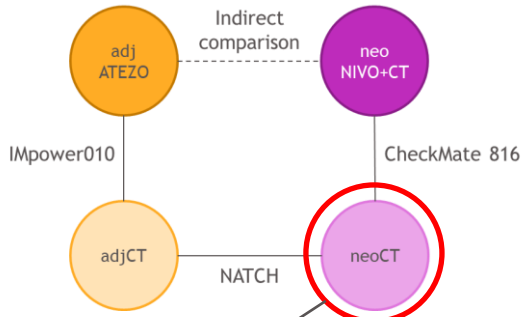
Mixture modeling

In the context of indirect treatment comparisons, selection bias refers to systematic differences in patient characteristics across trials, on factors that influence relative effect estimates.

Methodological approach for addressing time-zero offset

Generate EFS curve for a reference treatment, from the common time-zero

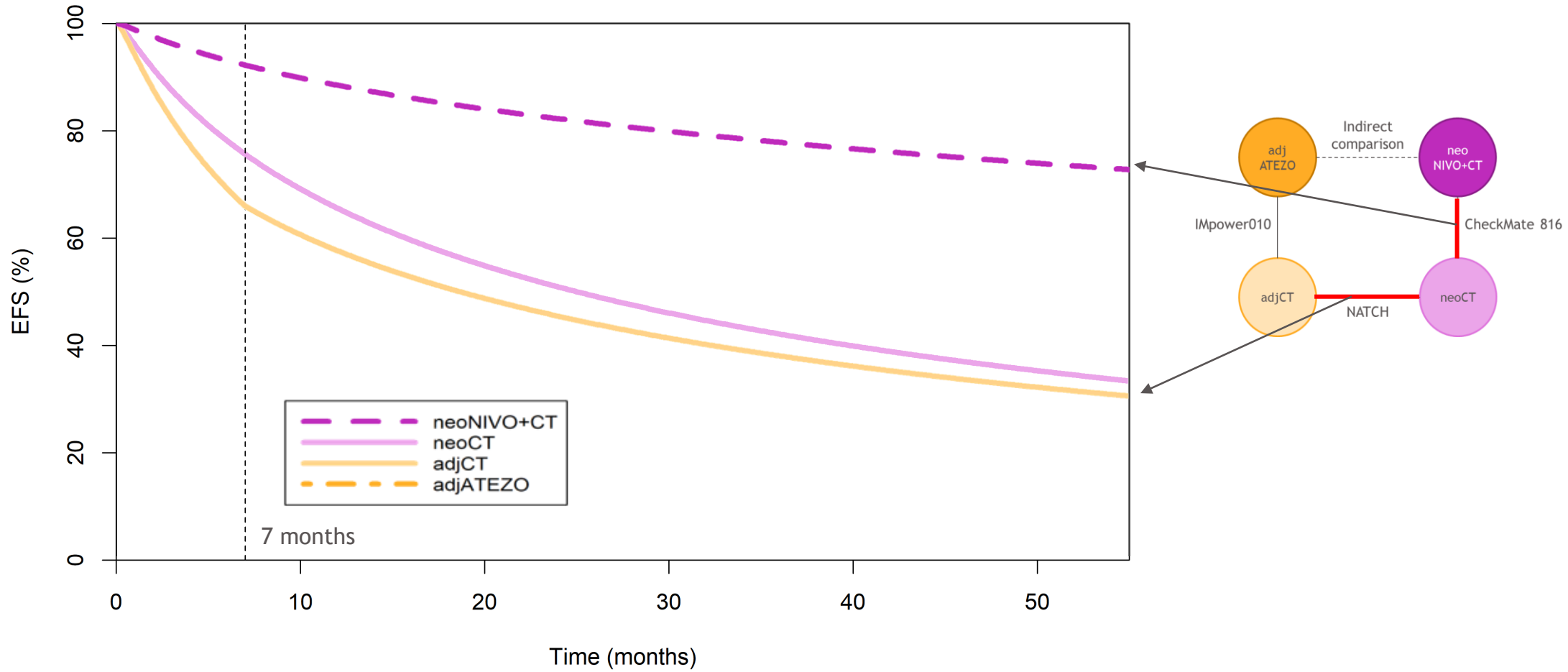




Abbreviations: *adjATEZO = adjuvant atezolizumab; adjCT = adjuvant chemotherapy; EFS = event-free survival; neoCT = neoadjuvant chemotherapy; neoNIVO+CT = neoadjuvant nivolumab plus chemotherapy*

Methodological approach for addressing time-zero offset

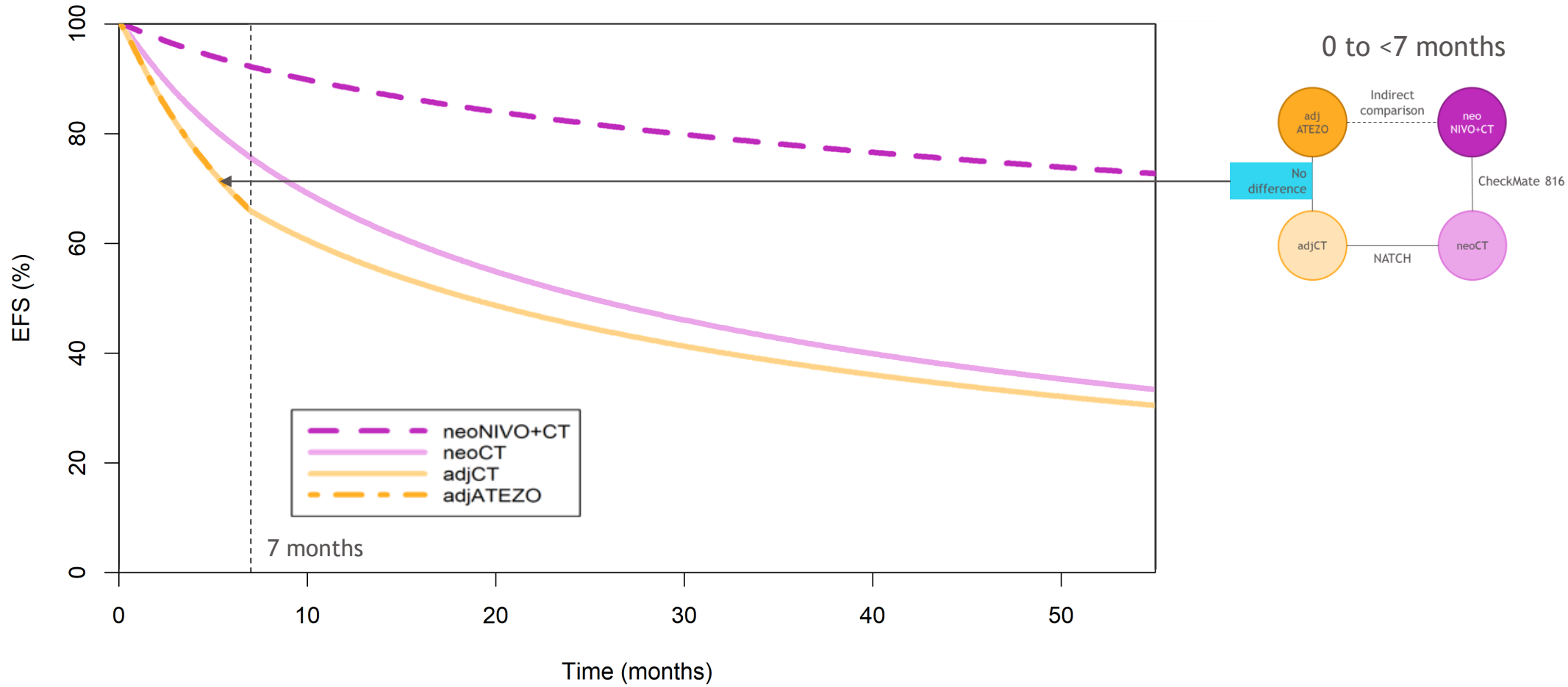
For comparisons <u>without</u> a time-zero offset, apply hazard ratios to generate EFS survival curves



Abbreviations: *adjATEZO = adjuvant atezolizumab; adjCT = adjuvant chemotherapy; EFS = event-free survival; neoCT = neoadjuvant chemotherapy; neoNIVO+CT = neoadjuvant nivolumab plus chemotherapy*

Methodological approach for addressing time-zero offset

For comparisons <u>with</u> a time-zero offset, use piecewise constant hazard ratios*

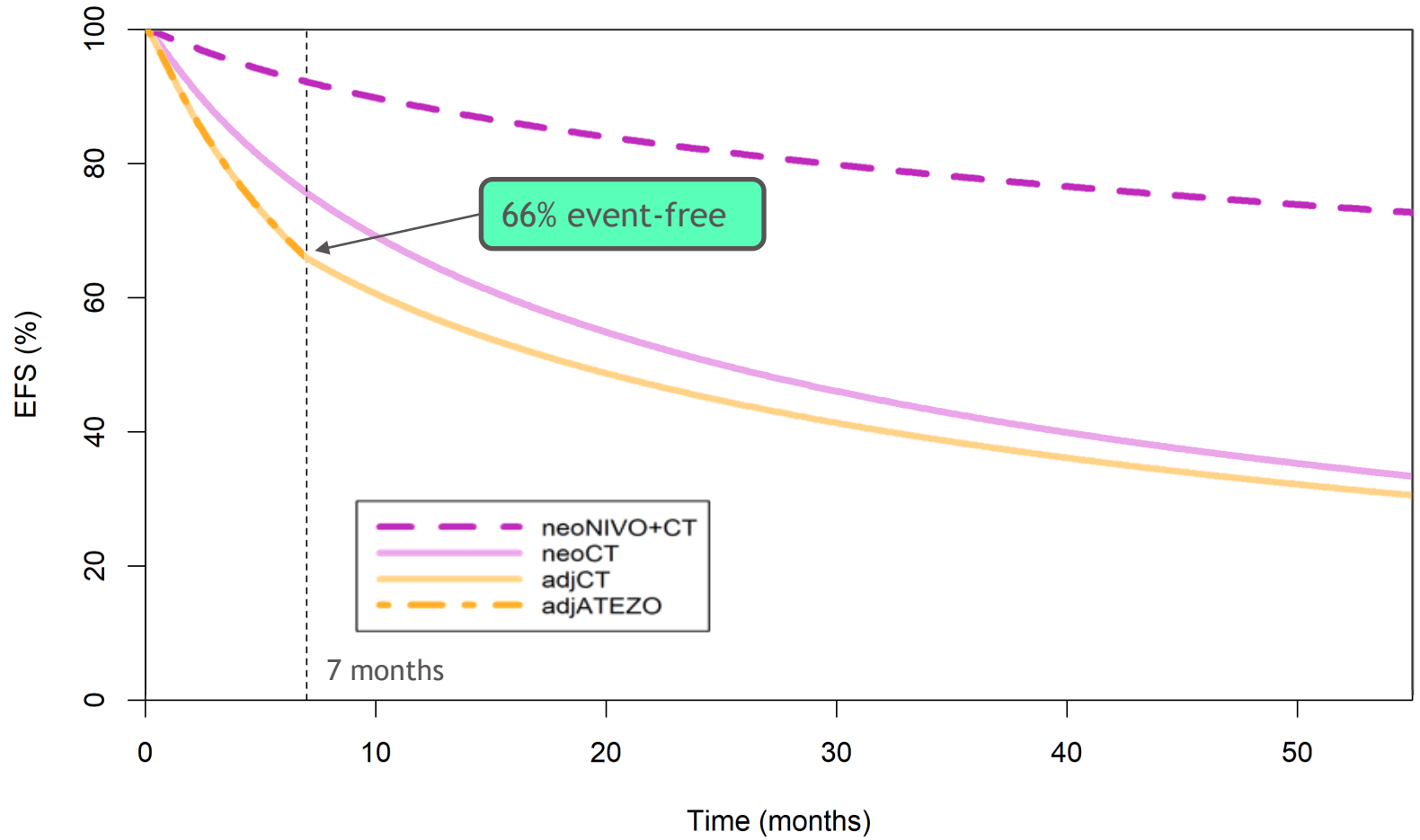


Piecewise constant hazard ratios can also be used for comparisons without a time-zero offset, if appropriate.

Abbreviations: *adjATEZO = adjuvant atezolizumab; adjCT = adjuvant chemotherapy; EFS = event-free survival; neoCT = neoadjuvant chemotherapy; neoNIVO+CT = neoadjuvant nivolumab plus chemotherapy*

Methodological approach for addressing time-zero offset

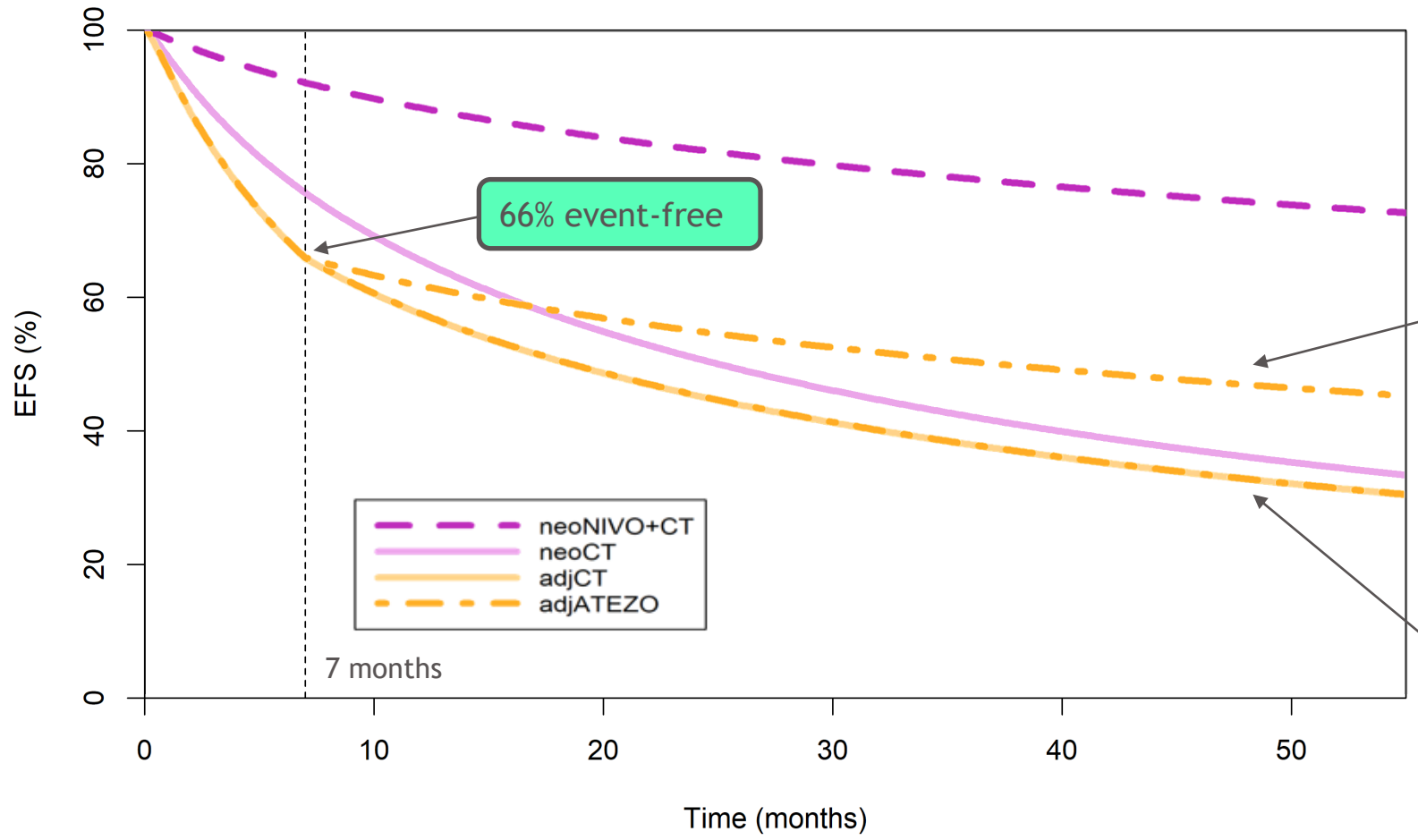
Note that hazard ratios after 7 months are only applied to those who are alive and event-free

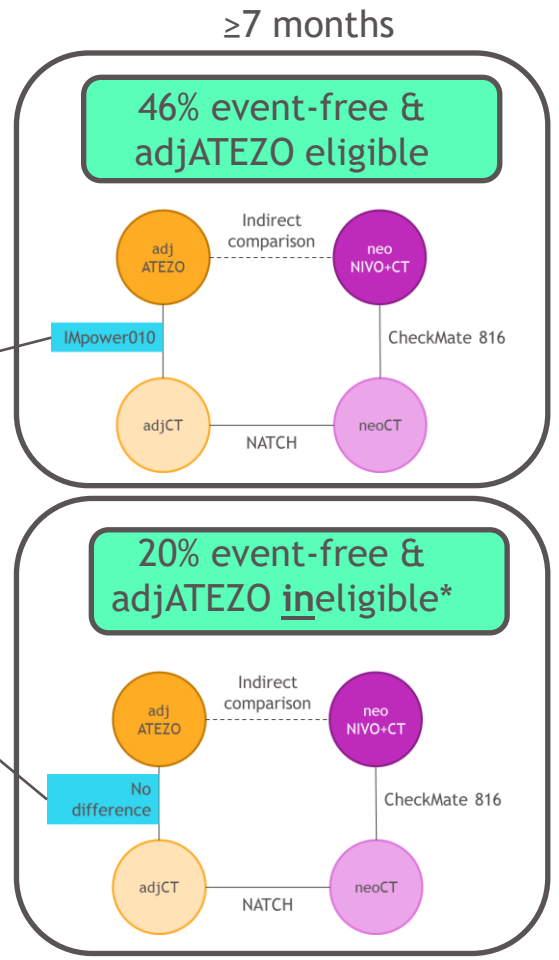


Abbreviations: *adjATEZO = adjuvant atezolizumab; adjCT = adjuvant chemotherapy; EFS = event-free survival; neoCT = neoadjuvant chemotherapy; neoNIVO+CT = neoadjuvant nivolumab plus chemotherapy*

Methodological approach for addressing time-zero offset

After 7 months, model 2 separate populations: adjATEZO eligible + adjATEZO ineligible



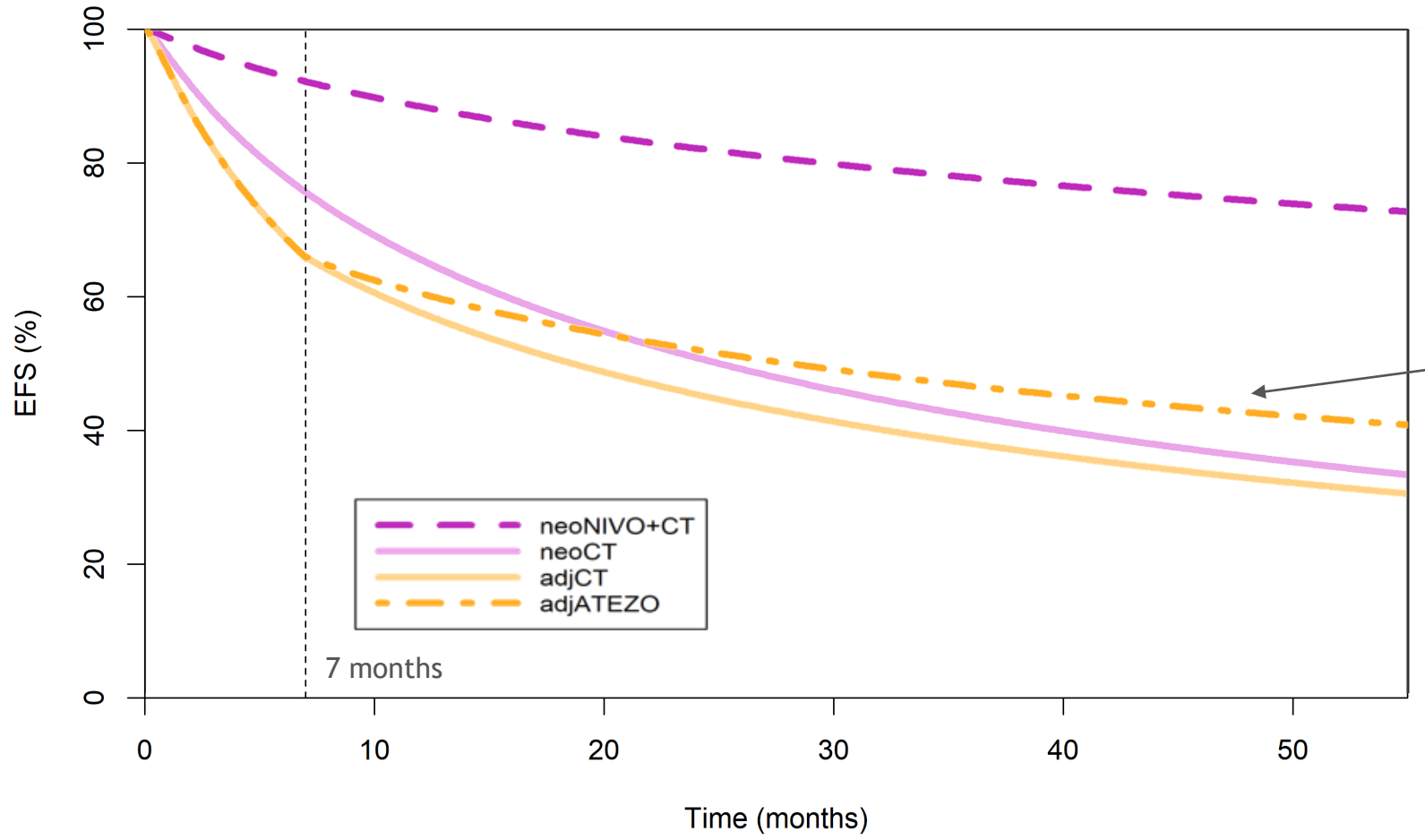


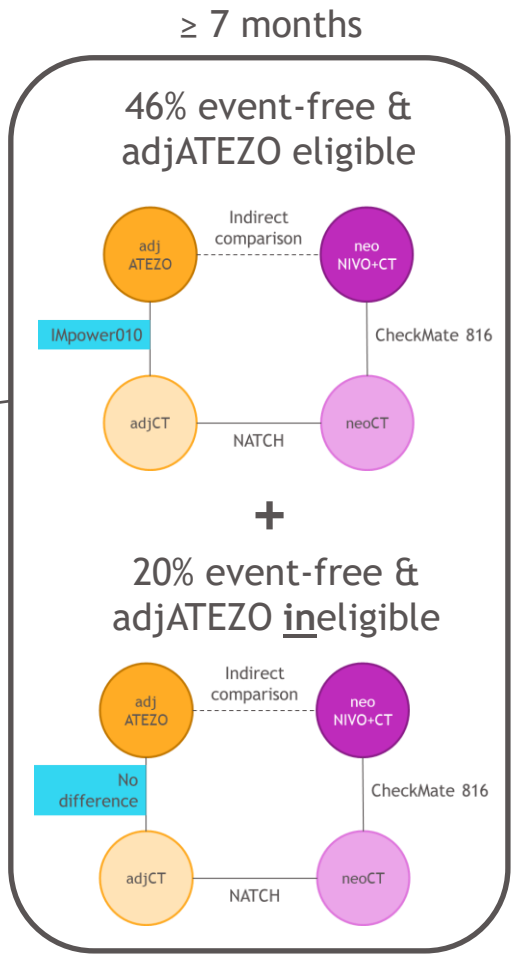
**The 20% estimate was obtained via systematic literature review and clinical expert consultation; inputs ranging from 0% to 40% were tested in sensitivity analyses.*

Abbreviations: *adjATEZO = adjuvant atezolizumab; adjCT = adjuvant chemotherapy; EFS = event-free survival; neoCT = neoadjuvant chemotherapy; neoNIVO+CT = neoadjuvant nivolumab plus chemotherapy*

Methodological approach for addressing time-zero offset

Use mixture modeling to combine these 2 populations

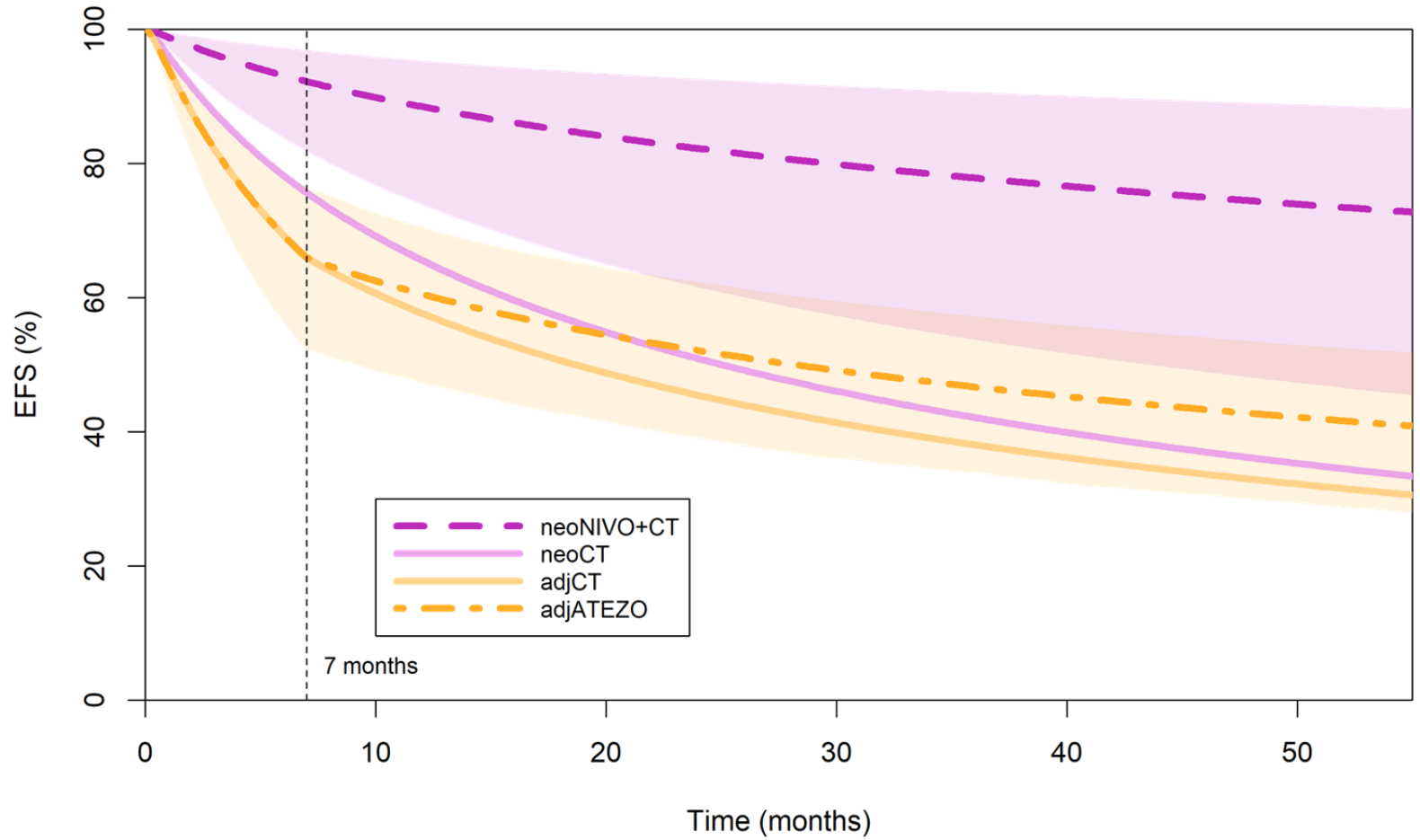




Abbreviations: *adjATEZO = adjuvant atezolizumab; adjCT = adjuvant chemotherapy; EFS = event-free survival; neoCT = neoadjuvant chemotherapy; neoNIVO+CT = neoadjuvant nivolumab plus chemotherapy*

Methodological approach for addressing time-zero offset

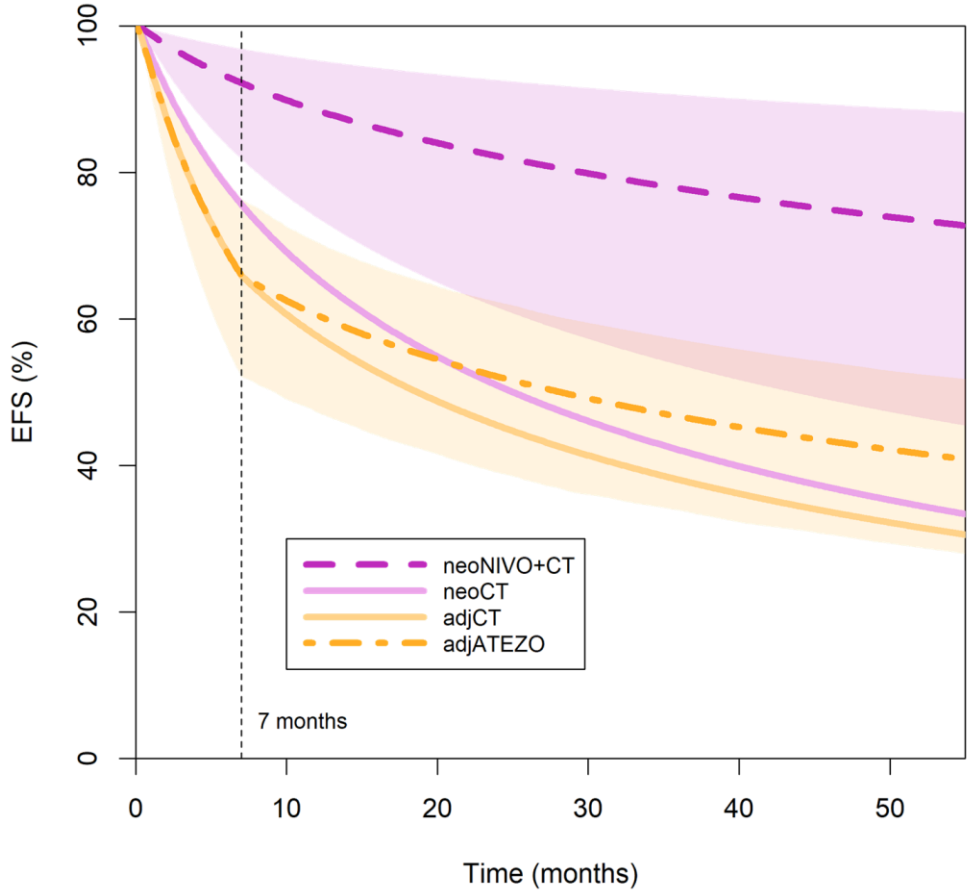
Generate hazard ratio estimates between comparators of interest
Estimate uncertainty using bootstrapping



Abbreviations: *adjATEZO = adjuvant atezolizumab; adjCT = adjuvant chemotherapy; EFS = event-free survival; neoCT = neoadjuvant chemotherapy; neoNIVO+CT = neoadjuvant nivolumab plus chemotherapy*

neoNIVO+CT vs. adjATEZO:
*Target population: Stage II-IIIA rNSCLC with PD-L1 ≥ 50% and EGFR/ALK -ve**

- With time-zero adjustments, the overall EFS HR for neoNIVO+CT vs. adjATEZO was **HR = 0.34 (95% CI: 0.13, 0.87)**†,‡
- The HR varied over time, with
  - HR, 0 to 7 months = **0.19 (0.06, 0.53)**†
  - HR, 7 to 48 months = **0.49 (0.17, 1.36)**†
- A standard indirect treatment comparison estimate *without time-zero adjustments*¶, was **HR = 0.53 (95% CI: 0.19, 1.49)**†



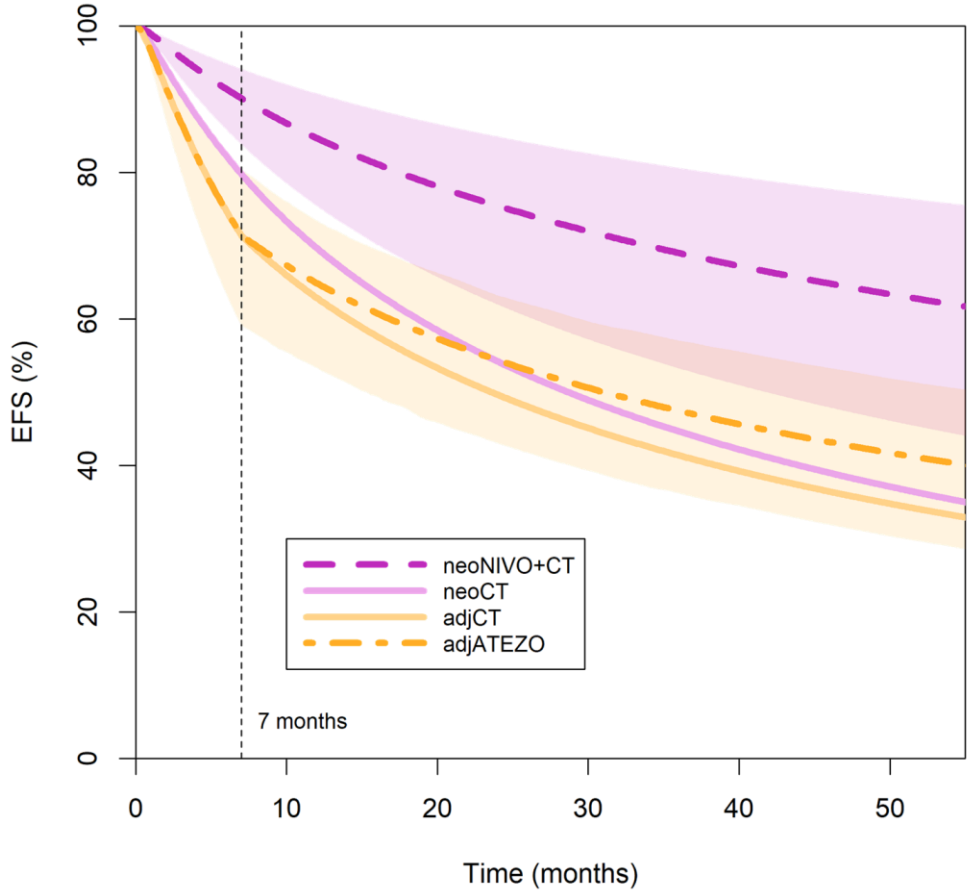
** Aligns with the authorized use of adjATEZO in Europe.*
† HR < 1 favours neoNIVO+CT.
‡ This estimate is based on more mature data from CheckMate 816 compared with the estimate reported in the published abstract (HR = 0.29 [0.11, 0.75])
¶ I.e., a standard indirect treatment comparison based on the network displayed in Slide 5, without implementing any further adjustments

Abbreviations: *adjATEZO = adjuvant atezolizumab; adjCT = adjuvant chemotherapy; CI = confidence interval; EFS = event-free survival; EGFR/ALK -ve = epidermal growth factor receptor [EGFR] mutation and anaplastic lymphoma kinase [ALK] translocation negative; HR = hazard ratio; neoCT = neoadjuvant chemotherapy; neoNIVO+CT = neoadjuvant nivolumab plus chemotherapy; rNSCLC = resectable non-small cell lung cancer*

neoNIVO+CT vs. adjATEZO

*Target population: Stage II-IIIA rNSCLC with PD-L1 ≥ 1%**

- With time-zero adjustments, the overall EFS HR for neoNIVO+CT vs. adjATEZO was **HR = 0.50 (95% CI: 0.27, 0.89)**†,‡
- The HR varied over time, with
  - HR, 0 to 7 months = **0.31 (0.14, 0.60)**†
  - HR, 7 to 48 months = **0.65 (0.33, 1.26)**†
- A standard indirect treatment comparison estimate *without time-zero adjustments*¶, was **HR = 0.62 (95% CI: 0.33, 1.17)**†



** Aligns with the United States Food and Drug Administration approval for adjATEZO.*
† HR < 1 favours neoNIVO+CT.
‡ This estimate is based on more mature data from CheckMate 816 compared with the estimate reported in the published abstract (HR = 0.45 [0.23, 0.81])
¶ I.e., a standard indirect treatment comparison based on the network displayed in Slide 5, without implementing any further adjustments

Abbreviations: *adjATEZO = adjuvant atezolizumab; adjCT = adjuvant chemotherapy; CI = confidence interval; EFS = event-free survival; HR = hazard ratio; neoCT = neoadjuvant chemotherapy; neoNIVO+CT = neoadjuvant nivolumab plus chemotherapy; rNSCLC = resectable non-small cell lung cancer*

Sensitivity analyses

- Key assumptions were tested in sensitivity analyses, e.g.:
  - Duration of time-zero offset
  - Proportion ineligible for adjATEZO
  - Evidence informing neoCT vs. adjCT
  - Similarity assumptions

- Results were robust to these assumptions

Abbreviations: *adjATEZO = adjuvant atezolizumab; adjCT = adjuvant chemotherapy; neoCT = neoadjuvant chemotherapy*

Conclusions

- This research provides a framework for indirect treatment comparisons in the presence of **differences in time-zero**.
- The time-zero-adjusted indirect treatment comparisons addressed:
  - Differences in relative **treatment effects over time**, and
  - Two types of **selection bias**.
- Statistical implementation involved:
  - A **time-varying** hazard ratio framework, and
  - A **mixture modeling** approach.
- The validity of the findings relies on:
  - **Assumptions** for conventional indirect treatment comparisons, plus
  - **Additional assumptions** required for the time-zero offset adjustments.

Further considerations

- Additional analyses in rNSCLC
  - Application to new & potential upcoming approvals of other immune checkpoint inhibitors*
  - Expansion to other target populations, e.g., by PD-L1
  - Application to other endpoints, e.g., overall survival
- General considerations, for application in other settings:
  - Estimating the duration of time-zero offset
  - Establishing expected treatment outcomes & relative effects before/after offset
  - Estimating the proportion of eligible/ineligible patients
- Further considerations
  - Larger networks
  - Incorporating population adjustments, e.g., matching-adjusted indirect comparisons (MAIC)

**E.g., pembrolizumab (KEYNOTE-091, KEYNOTE-671), durvalumab (AEGEAN), nivolumab (CheckMate 77T)*

Abbreviations: *PD-L1 = programmed death ligand 1; rNSCLC = resectable non-small cell lung cancer*

Thank you!