Modeling Sequential Treatment vs Separate Lines of Treatment in Oncology

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Agenda and Objectives

- Background & Objectives
  - To delineate the role of sequential versus line-specific modelling in oncology, detail the rationale, considerations, and challenges

- Rationale for sequential models vs line specific?
  - What has been done?
  - Why to consider it in oncology?
  - When
  - How
  - For whom
  - Interpreting results

- Examples
  1. Two models in prostate cancer
  2. Treatments in chronic lymphocytic leukaemia
  3. Melanoma
Background

- Models capturing treatment sequences have been used to some extent in most major therapeutic areas
- Treatment sequencing are commonly used and well accepted in:
  - Rheumatoid arthritis: sequential models are standard (Birmingham Rheumatoid Arthritis Model (BRAM model since 2001)
  - Mental health (schizophrenia, bipolar, depression)
  - Diabetes
- In oncology, models with treatment sequencing are less common

Where and why are treatment sequence models used

- Reflect treatment guidelines or clinical practice
  - Capture multiple events happening as a consequence of disease
- Assess where a new treatment belongs in a sequence (e.g. RA)
- Disease-specific rationales:
  - Diabetes —reflect treatment algorithm dictated by disease progression, age, etc.
  - Infectious disease — to track treatment history and development of resistance
  - Historical reasons — e.g. in RA a precedent was set with the BRAM model
- HTAs often require model analyses to consider a lifetime time horizon. In chronic diseases given longer survival, treatment switching is relatively routine.
What about treatment sequences for oncology?

- In late-stage oncology, the need for treatment sequences has historically been low:
  - Relatively short survival
  - Patients had fewer treatment options
  - Treatment options didn’t impact survival (more like palliative care), making it less important to model them explicitly
  - Treatments tend to be licensed by line of treatment, often in later lines initially

- However, capturing treatment sequences will become increasingly relevant:
  - As more treatment options are becoming available
  - As more novel treatments confer significant survival benefits even in late line use
  - As life expectancy increases (with the advent of novel, effective treatment options), many cancers are becoming more similar to chronic diseases and will need to be modelled accordingly.
  - With concerns with price of innovative treatments

Increase in Survival in Oncology Indications Overtime

- Survival trends
  - In UK, cancer survival has more than doubled in last 40 years\(^1\)
  - In US, similar trends are seen\(^2\)

- Some new treatments are changing survival trajectories
  - An analysis of HTA reports found average increased OS of 3.43 months between 2003 and 2013 associated with new cancer drugs
  - 43% increased OS by 3 months or longer

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3. [https://jamanetwork.com/journals/jamaoncology/article-abstract/2594542](https://jamanetwork.com/journals/jamaoncology/article-abstract/2594542)
Increase in Oncology Treatment Options Over Time

- The number and type of treatment options in oncology are increasing, with some novel agents often conferring significant benefits.

![Graph showing increase in oncology treatment options over time](http://www.imshealth.com/en/thought-leadership/quintilesims-institute/reports/global-oncology-trends-2017)

Patient Flow – Diagram of New Patient Experience

- Key features:
  - Patients receive multiple treatments over the course of their disease
  - The experience (sequence and timing of treatments) varies by patient

What is a Sequential Model?

- Sequential: An explicit modelling of multiple treatment lines. Accounts for the efficacy, safety, costs, and quality of life associated with each line/phase. Treatment switches due to clinical reasons, such as loss of efficacy, adverse events, and other

### Sequential vs. By Line

**Sequential**
- Initial treatment
- Off initial treatment
- First subsequent treatment
- Off first subsequent treatment
- Second subsequent treatment
- Off second subsequent treatment

**By Line**
- Initial treatment
- Post-progression/recurrence

A “by line” model collapses the explicit capture of subsequent treatment lines

### How do you choose?

<table>
<thead>
<tr>
<th>Question</th>
<th>Sequential</th>
<th>By Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assess where a new treatment belongs in a sequence?</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>If the selection, efficacy, and/or cost of subsequent treatments are affected by prior treatments</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>• Are you comparing earlier line use vs line later use?</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>• Will your treatment affect downstream treatment lines?</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>• Inclusion of treatment free intervals</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Capturing multiple intermediate events (e.g. progression and delay to chemotherapy)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>If subsequent treatment not expensive, subsequent pathways the same regardless of initial treatment</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Last line of treatment vs BSC and the preceding sequence is unchangeable</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Considerations/Challenges

- Challenges and considerations for review through examples
  - Model approaches
  - Events Captured and Endpoints
  - Data considerations
  - Audience

What’s Been Done

1: Two models in prostate cancer
2: Treatments in chronic lymphocytic leukaemia
3: Melanoma
Example – No. 1 Treatment in Prostate Cancer

- Treatment sequences for abiraterone acetate and enzalutamide chemotherapy naïve (prechemotherapy) models
- Rationale: New life extending treatments including abiraterone and enzalutamide had become available in later line (post-docetaxel). New indication was pre-chemotherapy. Guidelines and clinical practice are organized by treatment phases and pathways.

<table>
<thead>
<tr>
<th>Decision-question</th>
<th>What are the CEs of Abiraterone or Enzalutamide in chemotherapy naïve patients?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target audience</td>
<td>HTA (NICE)</td>
</tr>
<tr>
<td>What was captured</td>
<td>Newly evolved treatment pathways</td>
</tr>
</tbody>
</table>

Chemotherapy naïve mCRPC

Abiraterone Treatment Sequence Model

- Compared Abiraterone vs. BSC
- Treatment sequences modelled:
  - Included treatment free intervals
  - All treatments can lead to death
- Structure: DES powered by risk equations informed by the Phase III clinical trial

- Accurate reflection of disease and treatment landscape
- Capture key benefit from AA: delaying time to chemotherapy
- Risk equation from developed the trial inform time in a phase. More accurately capture treatment sequences that may affect survival
- + classical DES advantages: simulation of specific patients trajectories, tracking survival by treatment, ...

1) Chemotherapy naïve mCRPC
   - Abiraterone
   - Docetaxel
   - Active treatment excluding abiraterone
   - BSC

2) BSC
   - Docetaxel
   - Active treatment including abiraterone
   - BSC
Use of inverse probability of censoring weighting (IPCW) to adjust for cross-over (some treatments not available in UK)

Post-progression further stratified for subsequent treatments

Requiring simplifications:
- OS modelled separately from lines of treatment
- Treatment sequence has no effect on survival
- % patients w/ docetaxel has no effect on survival
- No capture of important survival modifiers

Enzalutamide Markov Model

- Compared enzalutamide vs. BSC

Overall survival

Endpoints of interest
- Delay to chemotherapy of interest in addition to first PFS phase
- Changing assumption on % receiving treatment doesn’t directly impact OS

Simplifications required given memoryless feature of Markov

Validation approach
- Used estimated OS plotted against trial OS. Compared model generated HR with trial generated HR.
- OS directly from trial

Summary

<table>
<thead>
<tr>
<th></th>
<th>Abiraterone</th>
<th>Enzalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approach</td>
<td>DES</td>
<td>Markov for time on treatment but with OS directly projected</td>
</tr>
<tr>
<td>OS</td>
<td>Sum of mortality over the treatment lines/ phases was used to calculate OS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Changing assumption of % receiving treatment impacts OS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Modelled OS directly; adjusted using statistical methods (IPCW)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Changing assumption on % receiving treatment doesn’t directly impact OS</td>
<td></td>
</tr>
<tr>
<td>Endpoints of interest</td>
<td>Delay to chemotherapy of interest in addition to first PFS phase</td>
<td></td>
</tr>
<tr>
<td>Treatment states</td>
<td>Risk equations used; Time varying functions could be used</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Simplifications required given memoryless feature of Markov</td>
<td></td>
</tr>
<tr>
<td>HFA challenges</td>
<td>Apparent complexity of modeling approach and risk equations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Criticized for separating the treatment stages from OS so these were independent of each other</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time in post-docetaxel state was worse than shown in Phase III post-docetaxel trial</td>
<td></td>
</tr>
<tr>
<td>Validation approach</td>
<td>Used estimated OS plotted against trial OS. Compared model generated HR with trial generated HR.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OS directly from trial</td>
<td></td>
</tr>
</tbody>
</table>
In an ideal world....

Sequences should be undertaken if they are believed to:

- Provide a more accurate estimation of the decision problem ICER

- An added benefit is that it requires the modeller to make explicit assumptions that are otherwise implicit and potentially not discussed

The optimal sequence(s) could be ascertained when new interventions enter the market

Previous sequences within NICE

NICE / HTA funders are familiar with sequences: it make sense if expensive drugs can be reserved only for those patients that require them

TA164 (Gout) The use of cheaper allopurinol prior to the more expensive febuxostat was recommended

TA375 (RA) The evaluation of biologics before or after conventional DMARDs was explicitly evaluated using sequences

TA433 (PsA) The failure of the company to evaluate all sequences was a key point of the Appeal
Evidence that sequenced models could provided different recommendations?

- Case study of idelalisib (idela) and venetoclax for CLL

- Venetoclax is positioned after idela, [idela was appraised before venetoclax]

- Markedly different estimations of survival post-progression for those who received idela in the appraisals of idela and venetoclax

- Plausible that a sequenced model would provide different results to the two single appraisals at current PAS / MAA for those without a 17p deletion or TP53 mutation.

MAA: managed access agreement. PAS: patient access scheme

Idela guidance (TA359 – published Oct 2015)

- Positive recommendation for adults with CLL who have a 17p deletion or a TP53 mutation, provided the agreed PAS was applied

- A key factor was the estimation of post-progression survival (PPS) following idela treatment which was
  - Approaching 2 years for those with 17p deletion or TP53 mutation
  - In the region of 4 years for those without 17p deletion or TP53 mutation
NICE review of Venetoclax

- NICE reviewed Venetoclax (TA10077 – published Oct 2017)
- Positive recommendation for adults with CLL provided the conditions in the managed access agreement are followed

In the appraisal the ERG used the PPS data from the Idela 116 study, with a resultant OS of approximately 4 years for those on BSC with no 17p deletion / TP53 mutation

In ACD 2 the Committee stated that venetoclax would not meet the End of Life criteria in this patient group, based on OS

This sparked a flurry of responses from clinicians that the four years’ OS does not match clinical experience post idela (or ibrutinib). The committee accepted this
Hindsight review of idela / venetoclax (no 17p deletion / TP53 mutation group)

- If clinicians are correct re PPS for idela
  - Post survival benefit accepted for idela too great. If the clinician perceived PPS was used the ICER for idela increased
  - It is plausible that the conclusion would have changed using the clinician estimated PPS been used

- If clinicians are incorrect
  - Venetoclax may not met the End of Life criteria
  - It is plausible that the conclusion would change

- So, whichever way we look at it, it is plausible that one of the two positive recommendations are wrong. This is a direct result of having two models with different parameters rather than a sequenced model

.........But we don’t live in an ideal world

We have limited time, a limited pool of people experienced in HTA, and potential continual disruption to recommendations would cause confusion

Re-appraising previous drugs each time a new intervention becomes available is not on the radar of funders. It is clear that NICE STAs can only provide recommendations on the intervention in question

Models require more computational time if near-optimal sequences are to be identified (Jon Tosh PhD thesis explored simulated annealing within RA)

However, there is a clear case that comparing the positioning of a drug in alternative lines of therapy should be undertaken in a sequenced approach.
Is there a preferred approach for sequenced models?

- The answer is dependent on the amount of data required to be processed within the model.

- Individual patient models (IPM) (see NICE TSD 15) are likely to be more appropriate when:
  - Patient characteristics, or patient history affect the likelihood of future events.
  - When timing of events matter (i.e. not using exponential distributions) - incorporating this within cohort models would need many tunnel states or additional health states.

- In the RA MTA (TA375), 4 models were IPM and 2 cohort models. The Assessment Group model was also an IPM.

Is there a preferred approach for IPMs?

- Where IPM are deemed appropriate there is a choice between discrete event simulation (DES) and Markovian approaches.

- In the RA MTA (TA375), of the 5 IPMs, 4 used DES and 1 was a Markov model.
Is there a preferred approach for IPMs?

- Perceived advantages of DES include.
  - Use of labels attached to patient reduce the need for combinations of health states
  - No time cycles are required to be defined
  - Ease of debugging*
  - Ease of model adaption*
  - Model speed*

* Dependent on the package used

Is there a preferred approach for IPMs?

- Perceived limitations of DES include
  - Complexity
  - Data Hungry

- I would counter that neither of these limitations are true.
  - The need to specify distributions (which is seen as additional data) formally defines modelling assumptions rather than these being hidden, or implicit, in Markovian approaches.
Most Recent non-HTA Examples

What’s been done outside of HTAs?
Research Questions in Published Sequential Studies

- Optimal Sequence
  - Place of immunotherapies in the treatment of BRAF wild type advanced melanoma
  - Order of HER2+ therapies for mBC
  - Order of targeted therapies in CML
- Capturing clinical practice explicitly
  - Cost-effectiveness of 2nd line therapies in CML...
- Real world cost-effectiveness
  - Impact of 1st line therapy on the cost-effectiveness of 2nd line therapy in mCRC
  - Targeted therapies in mRCC
  - Of multiple myeloma therapies
What’s been done outside of HTAs?

Characteristics

- Modelling Approach
- Maximum Number of Active Lines
- Primary Clinical Data Source

Presentation of Results

**Table 3: Cost-effectiveness results base-case analysis.**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Costs ($)</th>
<th>Life years</th>
<th>QALYs</th>
<th>ICERs ($)</th>
<th>ICURs ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo</td>
<td>94,492</td>
<td>4.86</td>
<td>3.47</td>
<td>Weakly dominated</td>
<td>171,700</td>
</tr>
<tr>
<td>Boscitinib → chemo/SCT</td>
<td>676,243</td>
<td>9.06</td>
<td>6.86</td>
<td>Weakly dominated</td>
<td>171,700</td>
</tr>
<tr>
<td>Imatinib → chemo/SCT</td>
<td>748,272</td>
<td>9.61</td>
<td>7.29</td>
<td>157,900</td>
<td>171,700</td>
</tr>
<tr>
<td>Nilotinib → chemo/SCT</td>
<td>884,222</td>
<td>10.08</td>
<td>7.65</td>
<td>Weakly dominated</td>
<td>171,700</td>
</tr>
<tr>
<td>Dasatinib → chemo/SCT</td>
<td>912,367</td>
<td>10.02</td>
<td>7.81</td>
<td>Dominated</td>
<td>Dominated</td>
</tr>
<tr>
<td>Boscitinib → nilotinib → chemo/SCT</td>
<td>913,682</td>
<td>9.96</td>
<td>7.82</td>
<td>Dominated</td>
<td>Dominated</td>
</tr>
<tr>
<td>Boscitinib → ponatinib → chemo/SCT</td>
<td>947,136</td>
<td>9.92</td>
<td>7.80</td>
<td>Dominated</td>
<td>Dominated</td>
</tr>
<tr>
<td>Imatinib → nilotinib → chemo/SCT</td>
<td>965,597</td>
<td>10.44</td>
<td>8.14</td>
<td>260,800</td>
<td>253,500</td>
</tr>
<tr>
<td>Imatinib → ponatinib → chemo/SCT</td>
<td>995,868</td>
<td>10.40</td>
<td>8.12</td>
<td>Dominated</td>
<td>Dominated</td>
</tr>
<tr>
<td>Imatinib → boscitinib → chemo/SCT</td>
<td>1,020,857</td>
<td>10.57</td>
<td>8.22</td>
<td>Weakly dominated</td>
<td>Weakly dominated</td>
</tr>
<tr>
<td>Boscitinib → dasatinib → chemo/SCT</td>
<td>1,062,120</td>
<td>10.45</td>
<td>8.14</td>
<td>Dominated</td>
<td>Dominated</td>
</tr>
<tr>
<td>Dasatinib → boscitinib → chemo/SCT</td>
<td>1,099,065</td>
<td>10.88</td>
<td>8.43</td>
<td>Weakly dominated</td>
<td>Weakly dominated</td>
</tr>
<tr>
<td>Boscitinib → ponatinib → chemo/SCT</td>
<td>1,108,291</td>
<td>10.80</td>
<td>8.39</td>
<td>Dominated</td>
<td>Dominated</td>
</tr>
<tr>
<td>Nilotinib → dasatinib → chemo/SCT</td>
<td>1,111,549</td>
<td>10.79</td>
<td>8.38</td>
<td>Dominated</td>
<td>Dominated</td>
</tr>
<tr>
<td>Dasatinib → nilotinib → chemo/SCT</td>
<td>1,130,750</td>
<td>10.95</td>
<td>8.48</td>
<td>Weakly dominated</td>
<td>Weakly dominated</td>
</tr>
<tr>
<td>Nilotinib → boscitinib → chemo/SCT</td>
<td>1,139,912</td>
<td>10.75</td>
<td>8.35</td>
<td>Dominated</td>
<td>Dominated</td>
</tr>
<tr>
<td>Dasatinib → ponatinib → chemo/SCT</td>
<td>1,162,092</td>
<td>10.90</td>
<td>8.43</td>
<td>Dominated</td>
<td>Dominated</td>
</tr>
<tr>
<td>Nilotinib → dasatinib → chemo/SCT</td>
<td>1,200,921</td>
<td>11.23</td>
<td>8.67</td>
<td>299,800</td>
<td>443,800</td>
</tr>
</tbody>
</table>

Chemo: chemotherapy; ICERs: incremental cost-effectiveness ratios; ICURs: incremental cost-utility ratios; QALY: quality-adjusted life years; SCT: stem-cell transplantation.

Rochau et al. 2015. CML.
Presentation of Results

Challenges for Evaluating Sequential Papers

- Dilution of results of specific lines... everything evens out
  - Cost-effectiveness may be difficult to show
- Where are benefits coming from?
  - More detail is needed
- Potentially very large number of sequences to evaluate
  - Need clinical opinion about realistic sequences
  - Can consider lumping ones that are likely
- Validation
Example – No. 3: Comparing sequences for a disease

- Rationale: Optimal place of immunotherapies for patients with BRAF wild-type advanced melanoma

<table>
<thead>
<tr>
<th>Decision-question</th>
<th>What is the most cost-effective sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target audience</td>
<td>US payers, policy-makers and patients</td>
</tr>
<tr>
<td>What was captured</td>
<td>Sequences with various immune checkpoint inhibitors in the treatment of B-RAF wild type melanoma – compared to each other and a chemo-starting sequence</td>
</tr>
<tr>
<td>Modeling approach</td>
<td>Markov cohort model</td>
</tr>
<tr>
<td>Primary Data Source</td>
<td>Clinical data from line-specific published RCTs</td>
</tr>
</tbody>
</table>

Sequential model in melanoma (1)

- Six sequences evaluated, with a maximum of three lines of therapy

<table>
<thead>
<tr>
<th>Sequences</th>
<th>First line</th>
<th>Second line</th>
<th>Third line</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Nivolumab</td>
<td>Ipilimumab</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Nivo + Ipi</td>
<td>Carboplatin + paclitaxel</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Pembrolizumab q2</td>
<td>Ipilimumab</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Pembrolizumab q3</td>
<td>Ipilimumab</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Ipilimumab</td>
<td>Nivolumab</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Dacarbazine</td>
<td>Ipilimumab</td>
<td>Nivolumab</td>
</tr>
</tbody>
</table>

- Data from publications
  - Digitized PFS and OS curves
  - Response rates
- Methods to estimate clinical efficacy for sequence:
  - PFS 1st line + PFS 2nd line + OS from 2nd line – with Weibull distributions for all of these
Sequential model in melanoma (2)

Fig A1. Markov model depicting the treatment arms seen in CheckMate-066, CheckMate-067, CheckMate-037, KEYNOTE-006, and NCT01099453. a) First-line progression-free survival; b) first-line overall survival; c) progression-free survival after first progression; d) overall survival after first progression; e) overall survival after second progression; f) progression-free survival after second progression; g) overall progression-free survival after third progression; h) overall survival after third progression; i) and drug discontinuation rate. AE, adverse event.

Sequential model in melanoma – Results over Lifetime Horizon (3)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Cost, Arm Total</th>
<th>Cost, Therapy</th>
<th>QALY, Arm Total</th>
<th>QALY, Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy (decabased)</td>
<td>$146,775</td>
<td>$2,199</td>
<td>$956,338</td>
<td>$477,909</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>$84,255</td>
<td>$204,425</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>$152,400</td>
<td>$144,500</td>
<td>$60,060</td>
<td></td>
</tr>
<tr>
<td>Nivolumab plus Ipilimumab</td>
<td>$175,630</td>
<td>$264,301</td>
<td>$73,066</td>
<td></td>
</tr>
<tr>
<td>Nivolumab (second-line)</td>
<td>$127,020</td>
<td>$92,343</td>
<td>$71,526</td>
<td></td>
</tr>
<tr>
<td>Nivolumab (second-line)</td>
<td>$164,871</td>
<td>$90,243</td>
<td>$71,526</td>
<td></td>
</tr>
<tr>
<td>Nivolumab (third-line)</td>
<td>$172,219</td>
<td>$100,156</td>
<td>$72,313</td>
<td></td>
</tr>
<tr>
<td>Nivolumab (third-line)</td>
<td>$172,219</td>
<td>$100,156</td>
<td>$72,313</td>
<td></td>
</tr>
<tr>
<td>Nivolumab plus Ipilimumab (second-line)</td>
<td>$206,435</td>
<td>$80,734</td>
<td>$5,701</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy (second-line)</td>
<td>$172,219</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

~3 QALYs in most conservative ERG estimate for pem NICE assessment
~3 QALYs in ERG estimate for nivo

Due to use of PFS 1st line + PFS 2nd line + OS 2nd line? Use of Weibull distributions? Application of large disutilities for Grade 1&2 AEs as well?
Was everything captured?

**Figure 4. KM curves from the simulation model for time to subsequent treatment initiation**

![Graph showing KM curves for time to subsequent treatment initiation]


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**Patient Flow – Diagram of Patient Experience**

- Treatment-free interval....

![Diagram of patient flow showing each patient's treatment history and outcomes]

Source: Evidera | PPD
Data requirements: What is needed for a sequential model?

- Individual patient data
- Data source with long follow-up, large samples
  - Piecing separate studies together - difficult
- However, the absence of these ideal sources is not necessarily an argument not to do models sequentially:
  - Line specific models imply many assumptions
- Indirect comparisons difficult are tricky in any case

Conclusions

- Improving “circumstances” for sequential models in oncology
  - LE is increasing
  - Growing number of treatments – therefore ideal sequence is beneficial to know
  - Trial programs for new treatments tend to focus first on later-line use (often extending survival) and move into earlier line use
  - Sequential trials
- Sequential models likely required if one wants an accurate ICER, however
  - Re-evaluation of optimal sequences as new treatments emerge is challenging for HTA decision-makers and may lead to logistical problems for clinicians
- Sequential models can be very helpful in optimal positioning of treatments
- Methodology is known and is in use
Appendix

PFS from Keynote 006
Time on 1st line therapy

**Figure 3. KM curves from the simulation model for time to first-line treatment discontinuation**

Based on the simulation, the proportion of patients still treatment free at 1 year after treatment discontinuation was 42%, 23%, and 20% for NIVO+IPI, NIVO, and IPI, respectively, with the curves flattening thereafter (Figure 4).

**Treatment-free interval – based on multivariate equations**

<table>
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<tr>
<th>Variable</th>
<th>Time to first-line treatment discontinuation</th>
<th>Time to second-line treatment initiation</th>
<th>Time to death; treatment free</th>
<th>OS (%) at first-line treatment discontinuation</th>
<th>LRR level at first-line treatment discontinuation</th>
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