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

Disease area	Total TAs	Number of TAs with treatment sequencing	Percentage with treatment sequencing
Oncology	93	13	14
Autoimmune	33	7	21
Cardiovascular	26	6	23
Neurology/mental health	13	4	31
Infectious disease	12	2	17
Diabetes	8	2	25
Other	63	6	10

TAs technology appraisals

Source: Zheng, Pan, Sorensen. PharmacoEconomic (2017) 35:15-24

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.

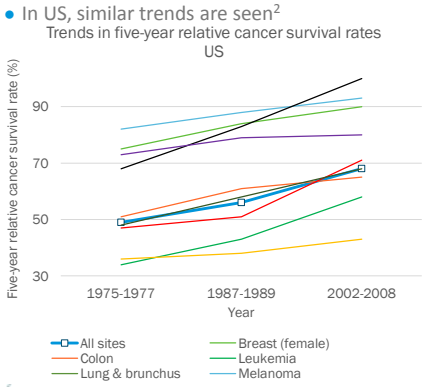
Zheng, Pan, Sorensen. PharmacoEconomic (2017) 35:15-24

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[3]

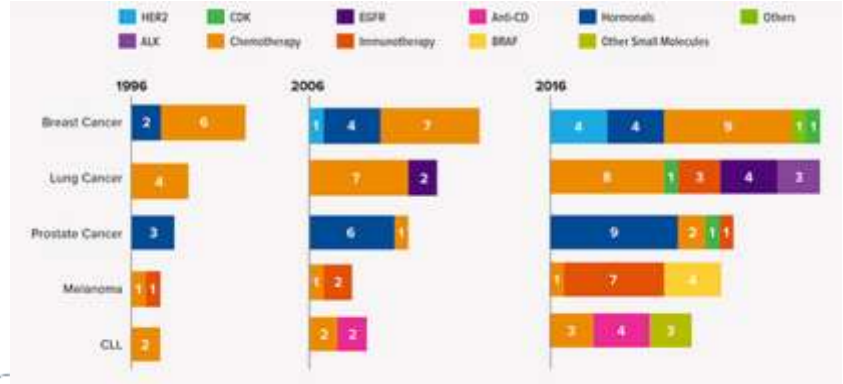
1. Sources: UK Cancer Researtch. http://www.cancerresearchuk.org/health-professional/cancer-statistics/survival. Accessed October 2017

2. SEER Cancer Statistics Review 1975-2009 (SEER 9 registries). National Cancer Institute, 2012

3. hhtps://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.

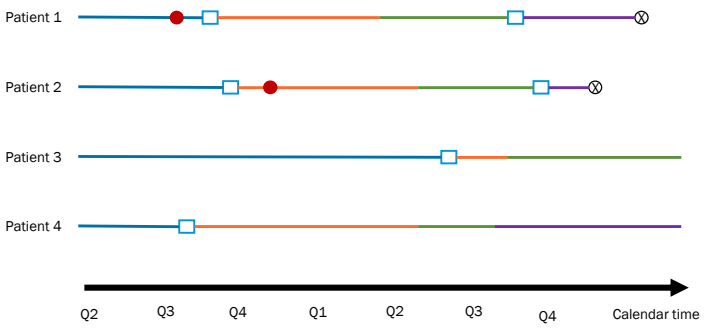


Source: Drugs@FDA, Feb 2017; QuintilesIMS, ARK R&D Intelligence, Feb 2017; QuintilesIMS Institute, Mar 2017

Figure found at: http://www.imshealth.com/en/thought-leadership/quintilesims-institute/reports/global_oncology_trends_2017

Patient Flow – Diagram of New Patient Experience

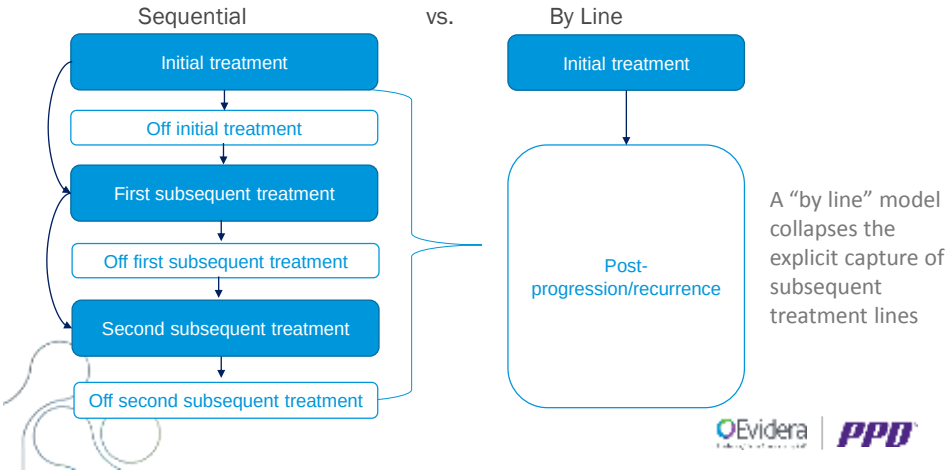
- Key features:
  - Patients receive multiple treatments over the course of their disease
  - The experience (sequence and timing of treatments) varies by patient



First-line treatment
Treatment-free interval
Second-line treatment
Third-line treatment
Patient progresses
Patient stops a treatment
Patient dies

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



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

How do you choose?

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

Considerations/Challenges

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

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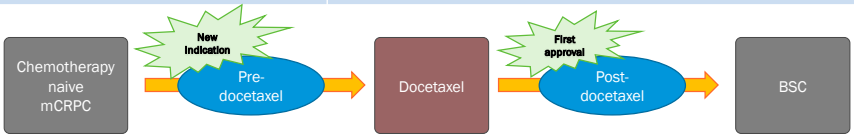
What's Been Done

1: Two models in prostate cancer
2: Treatments in chronic lymphocytic leukaemia
3: Melanoma

Example – No. 1 Treatment in Prostate Cancer

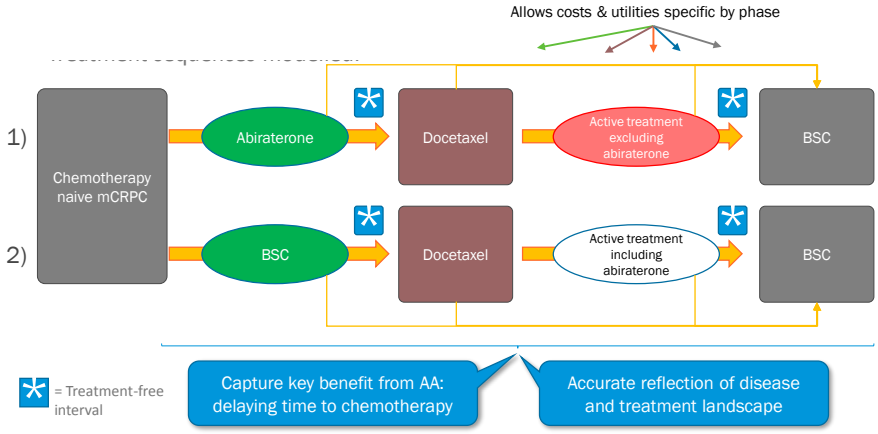
- Treatment sequences for abiraterone acetate and enzalutamide chemotherapy naïve (prechemotherapy) models
- Rationale: New life extending treatments including abiraterone and enzalutamide had become available in later line (post-docetaxel). New indication was pre-chemotherapy. Guidelines and clinical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

Decision-question	What are the CEs of Abiraterone or Enzalutamide in chemotherapy naïve patients?
Target audience	HTA (NICE)
What was captured:	Newly evolved treatment pathways



Modeling approach used	1. Abiraterone approach: DES 2. Enzalutamide approach: Markov for time on treatment but with OS directly projected

Abiraterone Treatment Sequence Model



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, …

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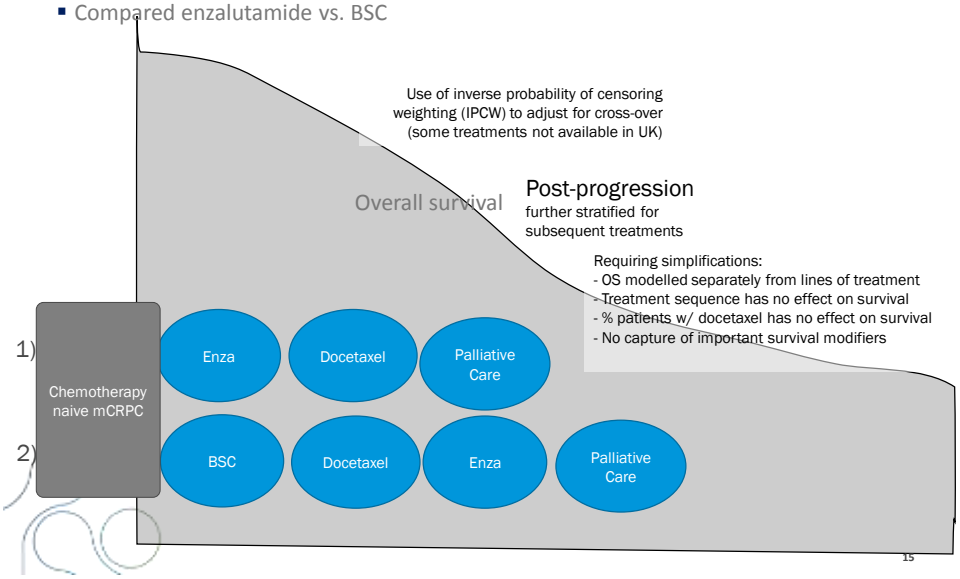
Enzalutamide Markov Model

- Compared enzalutamide vs. BSC



Summary

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

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

NICE review of Venetoclax

- 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.

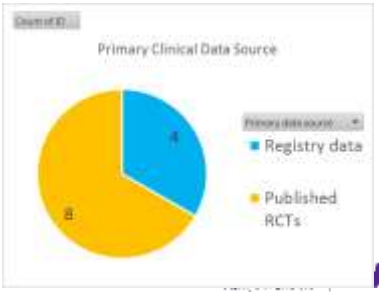
Most Recent non-HTA Examples

Evidera | PPD

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

- Targeted lit search (2015-2017): 12 sequential cancer cost-effectiveness 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



Presentation of Results

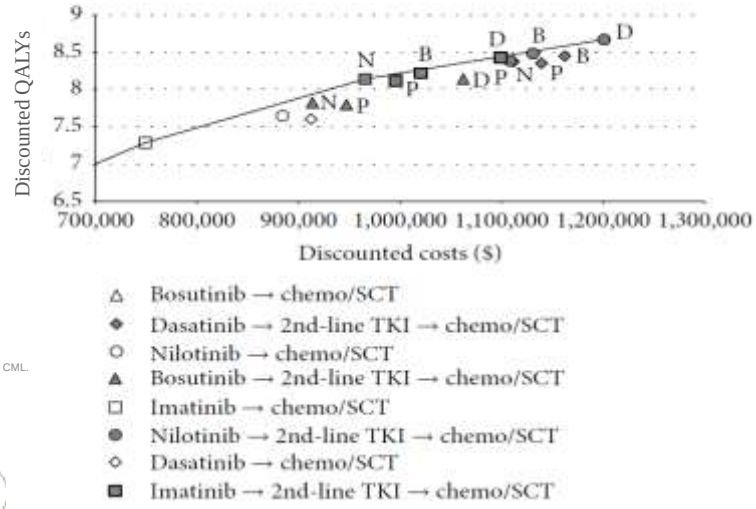
TABLE 3: Cost-effectiveness results base-case analysis.

	Costs ($)	Life years	QALYs	ICERs ($/LY)	ICURs ($/QALYs)
Chemo	94,492	4.86	3.47	—	—
Bosutinib → chemo/SCT	676,243	9.06	6.86	Weakly dominated	Weakly dominated
Imatinib → chemo/SCT	749,272	9.61	7.29	137,900	171,700
Nilotinib → chemo/SCT	884,222	10.08	7.65	Weakly dominated	Weakly dominated
Dasatinib → chemo/SCT	912,367	10.02	7.61	Dominated	Dominated
Bosutinib → nilotinib → chemo/SCT	913,682	9.96	7.82	Dominated	Weakly dominated
Bosutinib → ponatinib → chemo/SCT	947,136	9.92	7.80	Dominated	Dominated
Imatinib → nilotinib → chemo/SCT	965,597	10.44	8.14	260,800	253,500
Imatinib → ponatinib → chemo/SCT	995,868	10.40	8.12	Dominated	Dominated
Imatinib → bosutinib → chemo/SCT	1,020,857	10.57	8.22	Weakly dominated	Weakly dominated
Bosutinib → dasatinib → chemo/SCT	1,062,220	10.45	8.14	Dominated	Dominated
Imatinib → dasatinib → chemo/SCT	1,099,065	10.88	8.43	Weakly dominated	Weakly dominated
Nilotinib → ponatinib → chemo/SCT	1,108,291	10.80	8.39	Dominated	Dominated
Dasatinib → nilotinib → chemo/SCT	1,111,549	10.79	8.38	Dominated	Dominated
Nilotinib → bosutinib → chemo/SCT	1,150,750	10.95	8.48	Weakly dominated	Weakly dominated
Dasatinib → ponatinib → chemo/SCT	1,139,314	10.75	8.35	Dominated	Dominated
Dasatinib → bosutinib → chemo/SCT	1,362,092	10.90	8.45	Dominated	Dominated
Nilotinib → dasatinib → chemo/SCT	1,200,921	11.23	8.67	299,800	445,100

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.

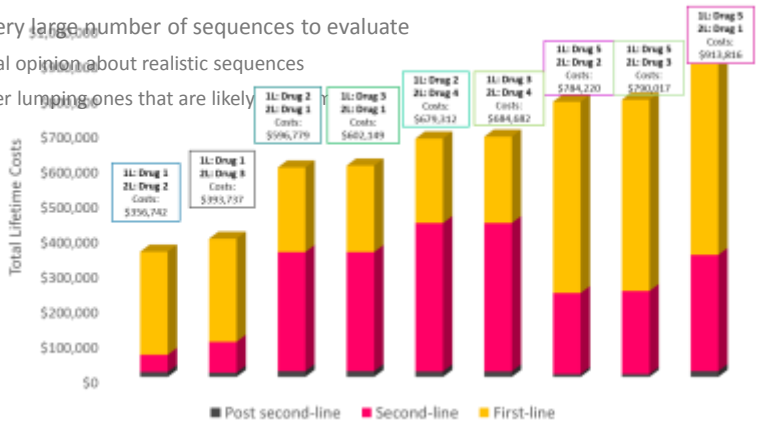
Presentation of Results



Rochau et al. 2015. CML.

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

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

Kohn et al. JCO 2017.

Sequential model in melanoma (1)

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

Sequences	First line	Second line	Third line
1.	Nivolumab	Ipilimumab	
2.	Nivo + Ipi	Carboplatin + paclitaxel	
3.	Pembrolizumab q2	Ipilimumab	
4.	Pembrolizumab q3	Ipilimumab	
5.	Ipilimumab	Nivolumab	
6.	Dacarbazine	Ipilimumab	Nivolumab

- 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)

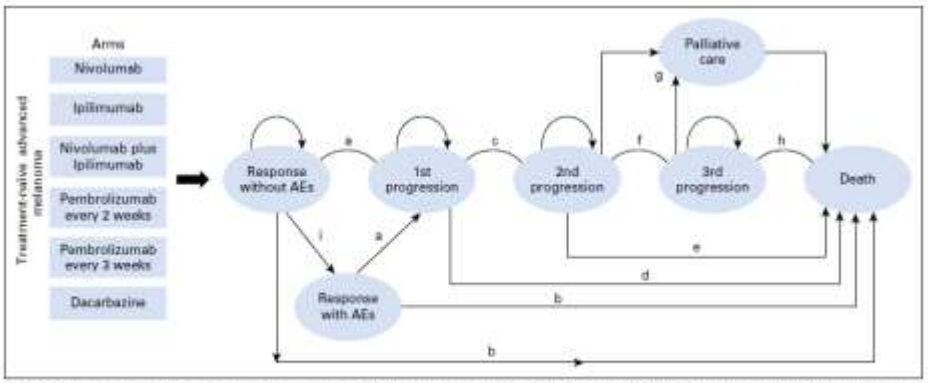


Fig A1. Markov model depicting the treatment arms seen in CheckMate-066, CheckMate-067, CheckMate-037, KEYNOTE-006, and NCT00094653. (a) First-line progression-free survival; (b) first-line overall survival; (c) progression-free survival after first progression; (d) overall survival after first progression; (e) overall survival after second progression; (f) progression-free survival after second progression; (g) progression-free survival after third progression; (h) overall survival after third progression; and (i) drug discontinuation rate. AE, adverse event.

Kohn et al. JCO 2017.

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

Table 3. Base-Case Results

Treatment Arm	Cost, Arm Total	Cost, Therapy	QALY, Arm Total	QALY, Therapy
Chemotherapy (dacarbazine)				
Response	$148,775	$3,199	0.26	
Ipilimumab (second-line)		$95,938		
Nivolumab (third-line)		$47,638		
Ipilimumab				
Response	$152,403	$94,357	0.34	
Nivolumab (second-line)		$8,046		0.20
Pembrolizumab every 3 weeks				
Response	$127,626	$54,301	0.38	0.28
Ipilimumab (second-line)		$73,326		
Pembrolizumab every 2 weeks				
Response	$164,871	$92,343	0.43	
Ipilimumab (second-line)		$72,528		
Nivolumab				
Response*	$172,219	$100,106	0.54	0.44
Ipilimumab (second-line)		$72,113		0.11
Nivolumab plus ipilimumab				
Response	$206,435	$200,734	0.56	0.37
Chemotherapy* (second-line)		$5,701		0.19

NOTE. This table reports b
which to calculate multiple
ipilimumab, is the dominan
Abbreviations: ICER, incre
*Response indicates a re

~ 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?

Kohn et al. JCO 2017.

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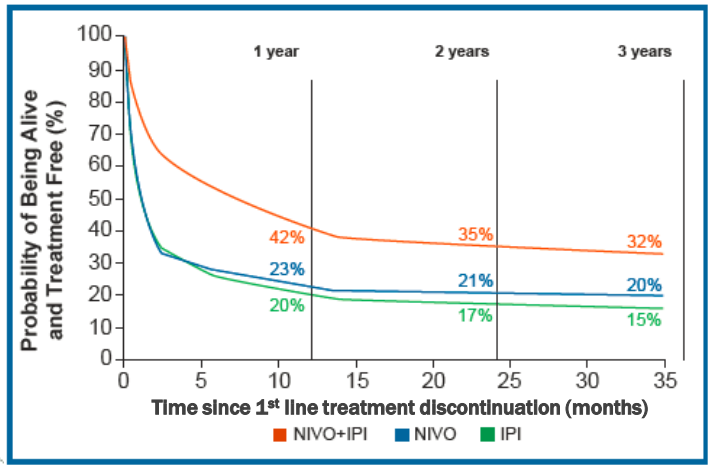
Was everything captured?

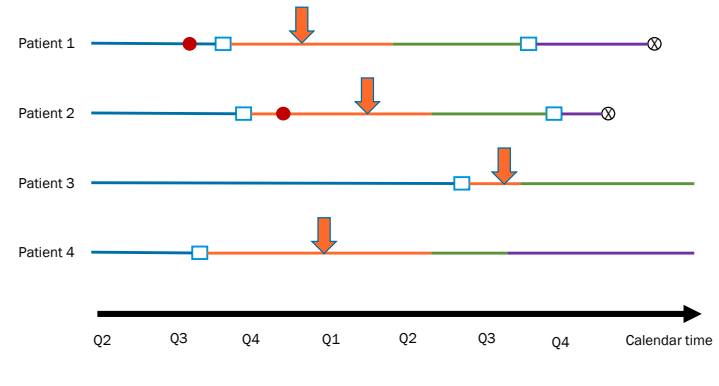
Figure 4. KM curves from the simulation model for time to subsequent treatment initiation



Source: Tarhini, McDermott, Benedict et al. 2017.

Patient Flow – Diagram of Patient Experience

- Treatment –free interval….



Data requirements: What is needed for a sequential model?

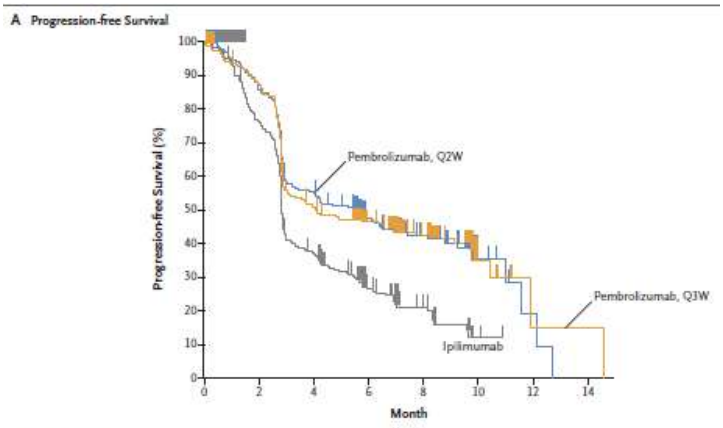
- Individual patient data
- Data source with long follow-up, large samples
  - Piecing separate studies together - difficult
- However, the absence of these ideal sources is not necessarily an argument not to do models sequentially:
  - Line specific models imply many assumptions
- Indirect comparisons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

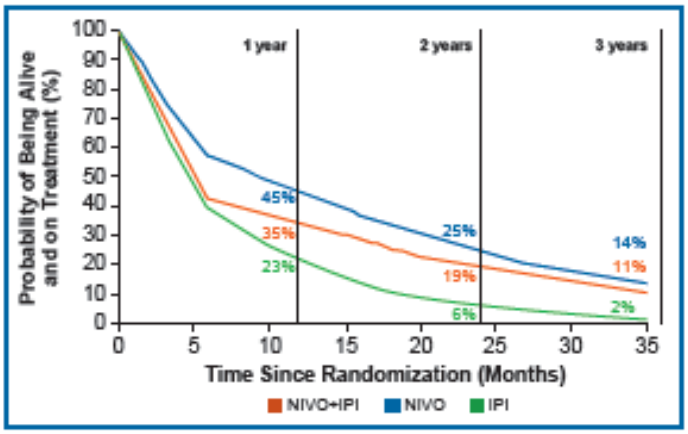
Appendix

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

	Time to first-line treatment discontinuation	Time to second-line treatment initiation	Time to death: treatment-free interval	ECOG PS at first-line treatment discontinuation	LDH level at first-line treatment discontinuation
Distribution	Weibull	Weibull	Weibull	Logistic	Linear
Placebo/no (Y/N)	Y	Y	Y	NA	NA
NIVO+IPI/NIVO/IPI	Y	Y	Y		
Interaction term between segments of survival curves and first-line treatment effect	Y	Y	Y		
BRAF status (mutant or wild type)		Y	Y		
PD-L1 status at 5% cutoff (+/–)	Y	Y			Y
Metastasis stage (M0/M1a/M1b/M1c)	Y	Y	Y		
Number of lesions (continuous)	Y	Y	Y	Y	
Age				Y	
Sex	Y				
Race (white, other)		Y		Y	
Region (Europe, USA, other)	Y	Y			
Weight			Y	Y	
Smoking	Y	Y			
Prior adjuvant therapy		Y			
Prior radiotherapy	Y				
Time since diagnosis					Y
ECOG score*	Y		Y	Y	Y
LDH*	Y		Y	Y	Y
Time to first-line treatment discontinuation		Y		Y	Y

*Y represents statistically significant covariates
*ECOG and LDH were based on baseline assessment for time to first-line treatment discontinuation and time to death while on first-line treatment. However, time to subsequent treatment initiation and time to death in treatment-free interval were based on estimates at first-line discontinuation
N, no; NA, not available; PD-L1, programmed death ligand 1; Y, yes

Source: Tarhini, McDermott, Benedict et al. 2017.