Sequential Models
When Are They the Right Choice?

ISPOR HEOR Theatre | November 7, 2022

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AGENDA

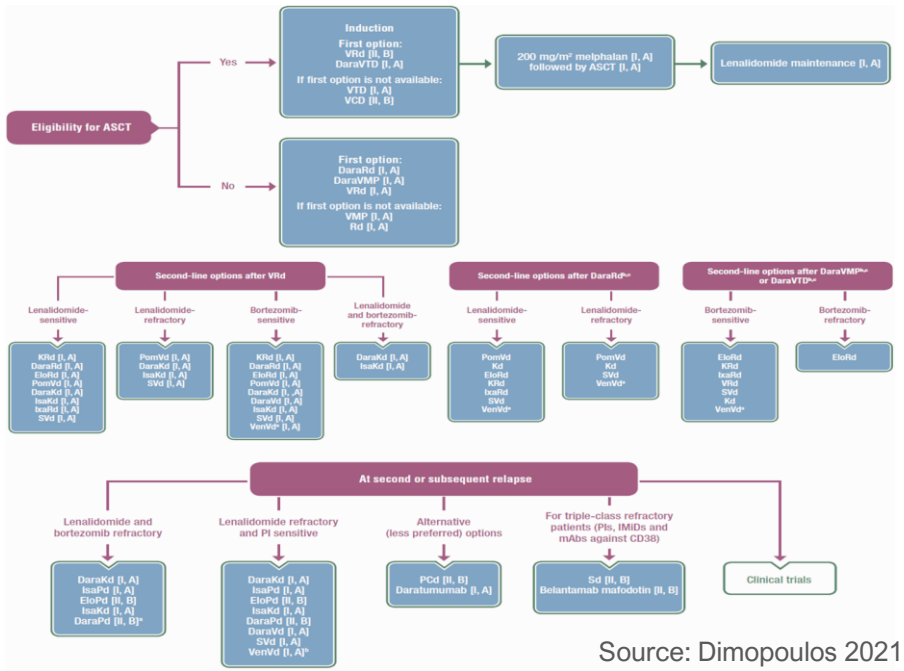
BACKGROUND & OBJECTIVE	• Why is there growing interest in sequential models?
SEQUENTIAL MODELS	• What are sequential models and how are they currently used?
STRATEGIC CONSIDERATIONS	• When sequential models should be considered?
TECHNICAL CONSIDERATIONS	• What model structures can be considered?
OTHER CONSIDERATIONS	• Interpretation of results, validation

BACKGROUND

Sequential Models Are Increasingly Being Considered Across Various Therapeutic Areas

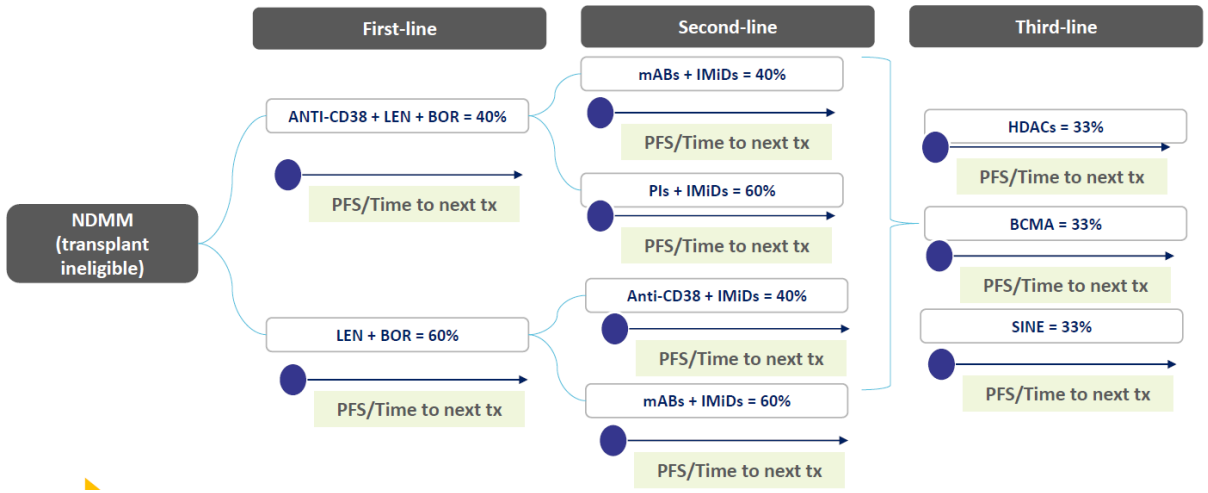
- Multiple disease areas are getting very crowded with numerous therapies
- Decisions are required about optimal sequencing of therapies for multiple stakeholders
- Computational capacity has grown
- Data is more readily available…

MULTIPLE MYELOMA GUIDELINES



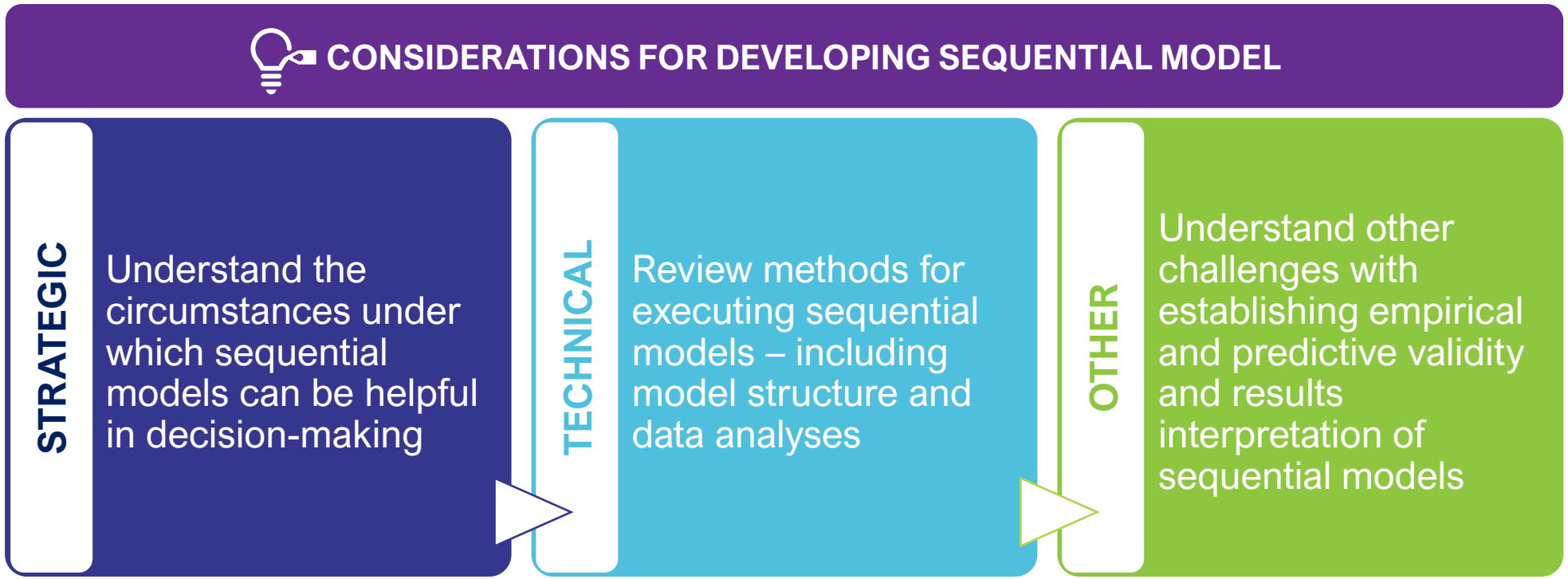
Source: Dimopoulos 2021

MULTIPLE OPTIONS FOR TX SEQUENCES



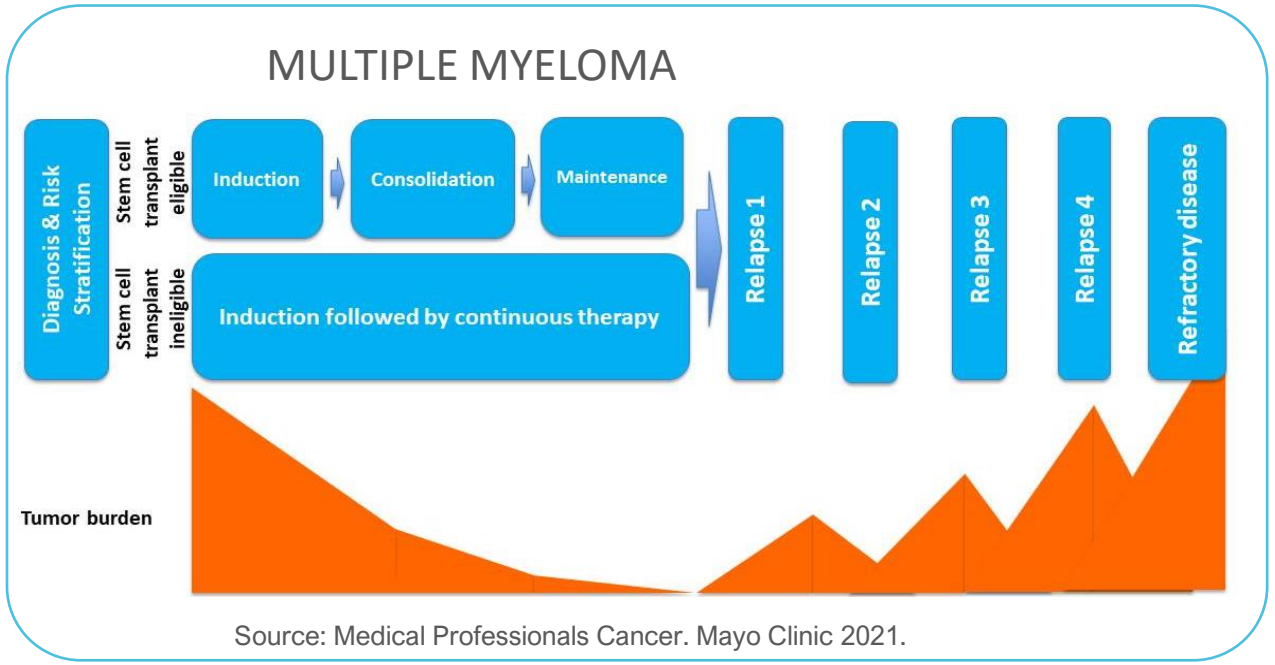
OBJECTIVES OF TODAY's TALK

Present circumstances when consider and develop sequential models for various stakeholders and discuss best practices
Illustrated with multiple recent applications



WHAT ARE SEQUENTIAL MODELS?

1. Compares among treatment sequences (not a particular drug)
2. Tracks outcomes on each line of treatment individually and cumulatively
3. Tracks patterns of clinical progression along the treatment pathway
4. Incorporates impact of prior therapy and possibly other factors



Source: Medical Professionals Cancer. Mayo Clinic 2021.

ILLUSTRATIONS

Cost-effectiveness of Diabetes Treatment Sequences to Inform Step Therapy Policies

March 10, 2020
Anna Hung, PharmD, PhD, Bhavna Jois, BS, Amy Lugo, PharmD, Julia F. Slejko, PhD
The American Journal of Managed Care, March 2020, Volume 26, Issue 03

This study assesses the cost-effectiveness of adding a sodium-glucose cotransporter 2 inhibitor vers receptor agonist in patients with diabetes on metformin and a dipeptidyl peptidase-4 inhibitor.

ABSTRACTObjectives: Cost-effectiveness estimates are useful to a health plan when they are specif To help inform a step therapy policy decision, this study assessed the 3-year cost-effectiveness of a inhibitor versus switching to a glucagon-like peptide-1 receptor agonist (GLP-1 RA) in patients with t dipeptidyl peptidase-4 (DPP-4) inhibitor from both private and public payer perspectives in the Unite

Study Design: Cost-effectiveness analysis.

Methods: A decision-analytic model was built incorporating goal glycated hemoglobin (A1C) achieve adverse effect and discontinuation rates from clinical trial data. One-way, scenario, and probabilistic

Results: In a cohort of 1000 patients, adding an SGLT2 inhibitor led to $3.9 million more in spending compared with switching from a DPP-4 inhibitor to a GLP-1 RA. This resulted in an incremental cost- to achieve goal A1C from the private payer perspective. Using a public payer perspective led to an IC sensitive to changes in drug costs and the proportion of patients achieving A1C goal or discontinuin

Conclusions: Assuming a $50,000 willingness-to-pay threshold, adding an SGLT2 inhibitor was cost- inhibitor to a GLP-1 RA from a private payer perspective but not from a public payer perspective. This reimbursement rates for medications can lead to contrasting results.

Am J Manag Care. 2020;26(3):e76-e83. *https://doi.org/10.37765/ajmc.2020.42639*

Future Medicine Ltd
Immunotherapy
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Research Article

Immunotherapy

Clinical and economic outcomes associated with treatment sequences in patients with *BRAF*-mutant advanced melanoma

Ahmad Tarhini[1], David McDermott[2], Apoorva Ambavane[3], Komal Gupte-Singh[4], Valerie Aponte-Ribero[3], Corey Ritchings[4], Agnes Benedict[5], Sumati Rao[4], Meredith M Regan[6] & Michael Atkins[7]

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Aim: The cost–effectiveness of treatment sequences in *BRAF*-mutant advanced melanoma **Materials & methods:** A discrete event simulation model was developed to estimate total costs and health outcomes over a patient's lifetime (30 years). Efficacy was based on the CheckMate 067/069 trials and a matching-adjusted-indirect comparison between immuno-oncology and targeted therapies. Safety, cost (in US dollars; US third-party payer perspective) and health-related quality-of-life inputs were based on published literature. **Results:** Estimated survival gain was higher for sequences initiating with anti-PD-1 + anti-CTLA-4 than for anti-PD-1 monotherapy or BRAF+MEK inhibitors. The incremental cost–effectiveness ratio per QALY gained for first-line anti-PD-1 + anti-CTLA-4 was US$54,273 versus first-line anti-PD-1 and $79,124 versus first-line BRAF+MEK inhibitors. **Conclusion:** Initiating treatment with anti-PD-1 + anti-CTLA-4 was more cost–effective than initiation with anti-PD-1 monotherapy or BRAF+MEK inhibitors.

Inflammatory Bowel Diseases, 2022, **XX**, 1–16
https://doi.org/10.1093/ibd/izac160
Advance access publication 9 August 2022
Original Research Articles - Clinical

CROHN'S & COLITIS FOUNDATION

Cost-effectiveness Analysis of Subcutaneous Infliximab for Inflammatory Bowel Diseases in Sequential Biologic Treatment

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Background: Inflammatory bowel disease (IBD) guidelines recommend tumor necrosis factor-α inhibitors (TNFis) for patients who have not responded to conventional therapy, and vedolizumab in case of inadequate response to conventional therapy and/or TNFis. Recent studies have shown that vedolizumab may also be effective in the earlier treatment lines. Therefore, we conducted cost-effectiveness analyses to determine the optimal treatment sequence in patients with IBD.

Methods: A Markov model with a 10-year time horizon compared the cost-effectiveness of different biologic treatment sequences in patients with moderate to severe ulcerative colitis (UC) and Crohn's disease (CD) from the UK and French perspectives. Subcutaneous formulations of infliximab, vedolizumab, and adalimumab were evaluated. Comparative effectiveness was based on a network meta-analysis of clinical trials and real-world evidence. Costs included pharmacotherapy, surgery, adverse events, and disease management.

Results: The results indicated that treatment sequences starting with infliximab were less costly and more effective than those starting with vedolizumab for patients with UC in the United Kingdom and France, and patients with just CD in France. For patients with CD in the United Kingdom, treatment sequences starting with infliximab resulted in better health outcomes with incremental cost-effectiveness ratios (ICERs) near the threshold.

Conclusions: Based on the ICERs, treatment sequences starting with infliximab are the dominant option for patients with UC in the United Kingdom, and patients with UC and CD in France. In UK patients with CD, ICERs were near the assumed "willingness to pay" threshold. These results reinforce the UK's National Institute for Health and Care Excellence recommendations for using infliximab prior to using vedolizumab in biologics-naïve patients.

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DECISION PROBLEMS

SEQUENCING MODEL

	For Payers	For Clinicians	For Company
GOAL	• Minimize budget per patient • Coverage/access to various treatment regimens • Optimize lifetime patient outcomes	• Identify treatment selection drivers • Optimize lifetime patient outcomes	• Maximize revenue generation • Achieve regulatory and market access success • Establish clinically effective treatment pathway / optimizing lifetime patient outcomes • Understand value of therapy
ANALYSIS TO SUPPORT	• Budget impact analyses • Cost-effectiveness analyses • Disease and treatment modeling	• Disease and treatment modeling	• Disease and treatment modeling • Revenue optimization • Strategic decision making

Can apply to any disease area with several therapy options: oncology, immunology, mental health/neurology, infectious diseases, cardiovascular disease

STRATEGIC CONSIDERATIONS

Pathway Uncertain — **Is there uncertainty about the best sequence?**

- E.g. there are large number of therapies with different mechanism of action & licenced in multiple lines
- If **YES** – there may be an interest in developing a sequential model

Pathway Different in Guideline vs Trial — **Is a country/HTA recommended pathway different that clinical trial's enrolment/ disposition?**

- E.g. A country may primarily use Tx A followed by B and C. However, clinical trial of Z included patients with a different prior treatment mix and subsequent treatments.
- If **YES** – there maybe interest in developing a sequential model

New decision node in treatment strategy ? — **Is a decision node based on patient outcomes introduced to guide treatment strategy?**

- E.g. in cancer a maintenance therapy option enters a space with previously no maintenance option
- If **YES** - sequence is disrupted – it is a truly sequential problem and may require a sequential model

Disruptive subsequent therapy? — **Is there a need to capture efficacy of subsequent therapy explicitly?**

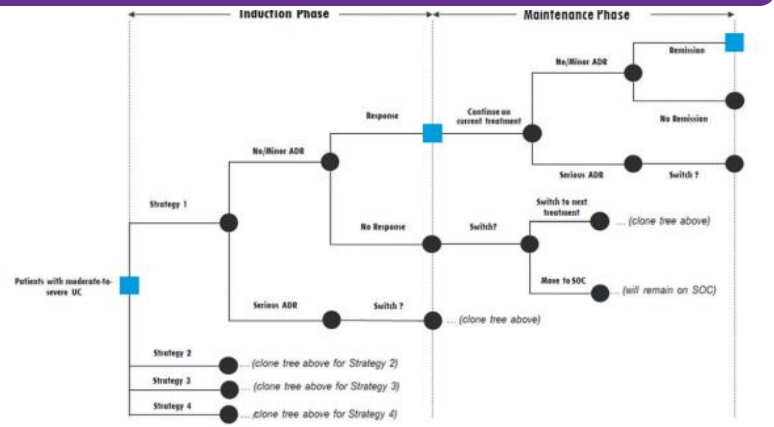
- E.g. in cancer area a specific later line of therapy becomes available that extends survival - however, is not captured in trial
- If **YES** - new efficacious treatment would need to be modelled and may require a sequential model

No Data on Overall Sequence Benefit/Cost — **Is there data about overall benefit / cost of treating patients**

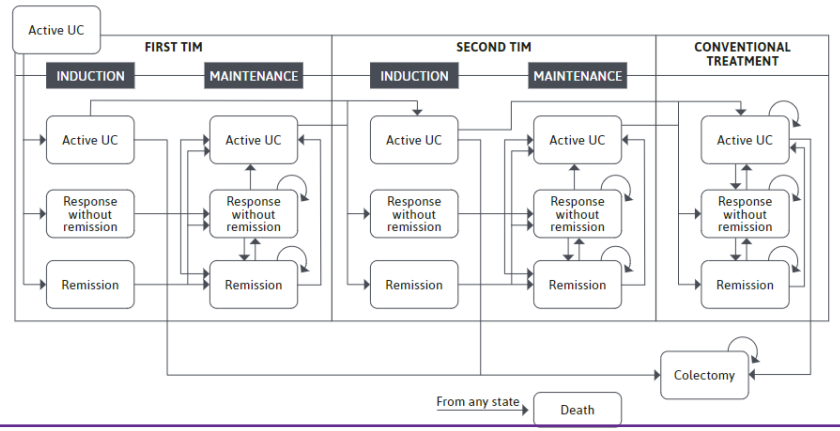
- E.g. in ulcerative colitis only 1-2 year-long trial is available, no good understanding of overall cost of treating patients with multiple lines of therapy
- If **NO** – there may be an interest in developing a sequential model

TECHNICAL CONSIDERATIONS
Model Structure

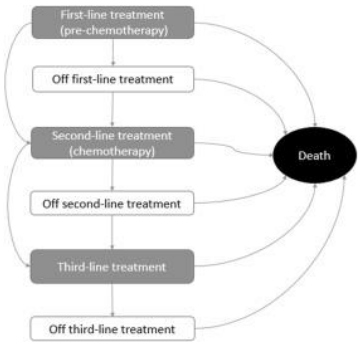
DECISION TREE
Milev 2019: Ulcerative Colitis



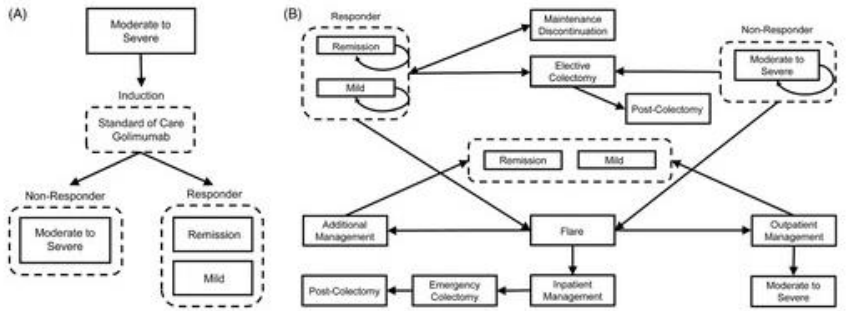
MARKOV COHORT MODEL
Bloudek 2021: Ulcerative Colitis



DISCRETE EVENT SIMULATION
Pan 2018: Prostate Cancer



MARKOV PATIENT LEVEL MODEL
Stern 2017: Ulcerative Colitis

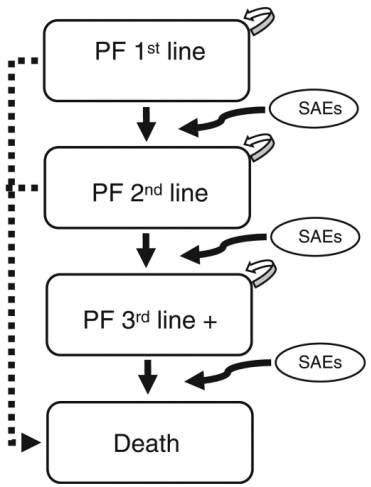


Model structure can vary in complexity, even within the same disease area.
Regardless of the structure, the key challenge is to capture the impact of prior history on the subsequent lines of therapy

TECHNICAL CONSIDERATIONS
'Data Stitching'

Just focus on treatment-specific outcomes, for each line, to parametrise the sequential model

BREAST CANCER



Clinical trials used for individual patient data reconstruction organized by treatment line.

Study (year)	Treatment(s)	Treatment line	Reference
Swain *et al.* (2013)	Pertuzumab + trastuzumab + docetaxel	First	9
Swain *et al.* (2013)	Trastuzumab + docetaxel	First	9
Verma *et al.* (2012)	T-DM1	Second	10
Blackwell *et al.* (2010)	Trastuzumab + lapatinib	Second	13
Geyer *et al.* (2006)	Capecitabine + lapatinib	Third	12
von Minckwitz *et al.* (2009)	Trastuzumab + capecitabine	Third	11
Blackwell *et al.* (2010)	Trastuzumab + lapatinib	Third	13

T-DM1: trastuzumab emtansine.

Source: Diaby 2016

Data

- Line specific data often available across comparators from literature

Implementation

- Easy to implement and communicate
- Easy to adapt

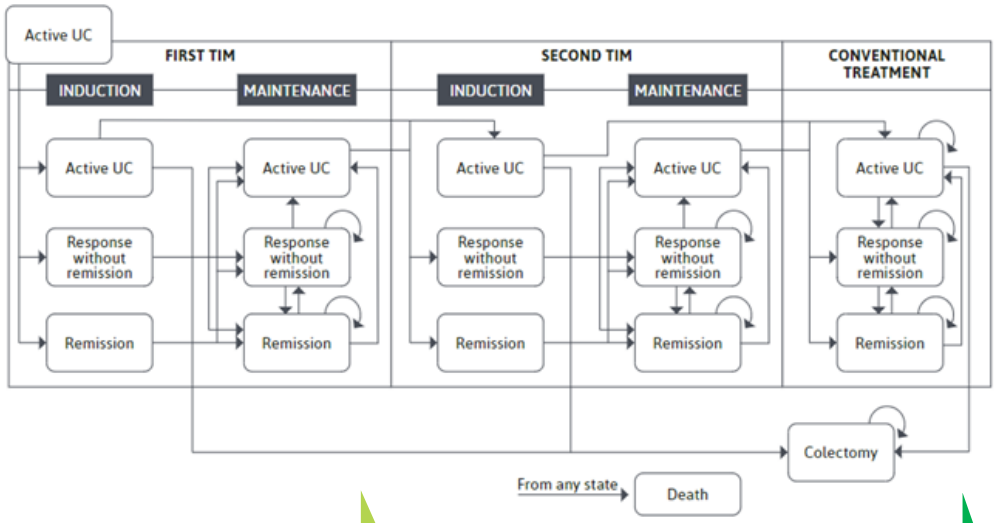
Attention!

- Impact of earlier lines outcomes on later lines not captured
- Available data not reflective of modeling needs
- May result in counterintuitive results due to misalignment in populations

TECHNICAL CONSIDERATIONS
'Data Stitching' Stratified by Prior History

Use treatment-specific outcomes stratified by prior exposure, to parametrise the sequential model

ULCERATIVE COLITIS



Use biologic-naïve clinical outcomes

Use biologic-exposed clinical outcomes

Source: Bloudek 2021

Data

- Data across comparators more challenging but manageable
- Captures the impact of treatment exposure on subsequent treatments

Implementation

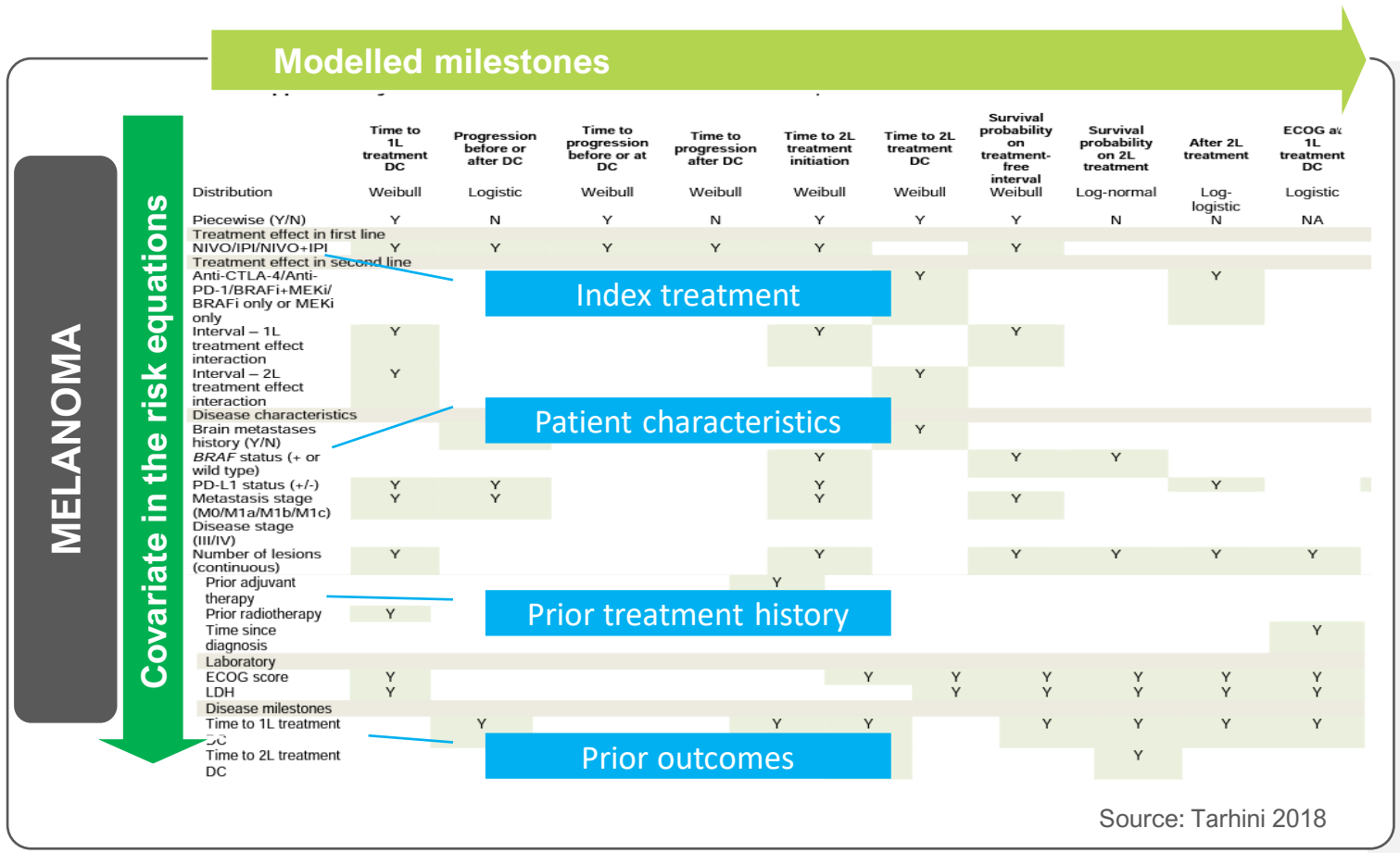
- Impact of earlier lines outcomes on later lines is captured

Attention!

- May be difficult to get data for all type of prior treatment classes across all comparators

TECHNICAL CONSIDERATIONS
Multivariate Risk Equations

Use multivariate risk equations to capture impact of patient characteristics, index treatment, prior treatment history, and prior outcomes on clinical outcomes



	Time to 1L treatment DC	Progression before or after DC	Time to progression before or at DC	Time to progression after DC	Time to 2L treatment initiation	Time to 2L treatment DC	Survival probability on treatment-free interval Weibull	Survival probability on 2L treatment	After 2L treatment	ECOG at 1L treatment DC
Distribution	Weibull	Logistic	Weibull	Weibull	Weibull	Weibull	Weibull	Log-normal	Log-logistic	Logistic
Piecewise (Y/N)	Y	N	Y	N	Y	Y	Y	N	N	NA
Treatment effect in first line NIVO/IPI/NIVO+IPI	Y	Y	Y	Y	Y		Y			
Treatment effect in second line Anti-CTLA-4/Anti-PD-1/BRAFi+MEKi/ BRAFi only or MEKi only						Y			Y	
Interval – 1L treatment effect interaction	Y				Y		Y			
Interval – 2L treatment effect interaction	Y					Y				
Disease characteristics										
Brain metastases history (Y/N)						Y				
BRAF status (+ or wild type)					Y		Y	Y		
PD-L1 status (+/-)	Y	Y			Y				Y	
Metastasis stage (M0/M1a/M1b/M1c)	Y	Y			Y		Y			
Disease stage (III/IV)										
Number of lesions (continuous)	Y				Y		Y	Y	Y	Y
Prior adjuvant therapy				Y						
Prior radiotherapy	Y									
Time since diagnosis										Y
Laboratory										
ECOG score	Y					Y	Y	Y	Y	Y	Y
LDH	Y						Y	Y	Y	Y	Y
Disease milestones										
Time to 1L treatment DC		Y			Y	Y		Y	Y	Y	Y
Time to 2L treatment DC									Y		

Source: Tarhini 2018

Data

- Detailed longitudinal data required that captures the impact of multiple factors: patient & disease characteristics, prior treatments, relationships between disease milestones
- Only published data for comparators may be limiting

Implementation

- Requires implementation of patient-level simulation to capture heterogeneity
- Experienced statistical team to generate risk equations

Attention!

- Data availability, especially for comparators
- Complex statistical analyses and validation
- Complex model development and validation

OTHER CONSIDERATIONS

RESULTS PRESENTATION

Results can be difficult to present, especially for value differentiators, with a large number of sequences

Table 3 Results for the sequences not fully dominated by ETB-ABA-INF.*

Sequence	Life-Years	Time Weak Activity	Failures, N/pt	Total Cost	Total QALY	ICER (€/QALY)
ETB>ABA>INF	16.58	10.28	2.34	€116 912	11.166	0
ETA>ABA>INF	16.58	10.30	2.16	€128 131	11.171	2 006 494
ETB>ABA>CER	16.58	10.30	2.33	€128 292	11.170	2 525 533
ETB>ABA>ADA	16.58	10.29	2.34	€129 332	11.167	13 739 085
ETB>ABA>GOL	16.58	10.30	2.33	€129 773	11.170	2 854 210
ETB>ABA>TOC	16.58	10.35	2.29	€138 356	11.182	1 314 782
ETA>ABA>CER	16.58	10.32	2.15	€138 594	11.172	3 585 508
ETA>ABA>ADA	16.58	10.31	2.16	€139 381	11.172	3 407 964
ETA>ABA>GOL	16.58	10.32	2.15	€139 937	11.172	3 807 688
ETA>CER>ABA	16.58	10.28	2.21	€145 871	11.168	12 312 214

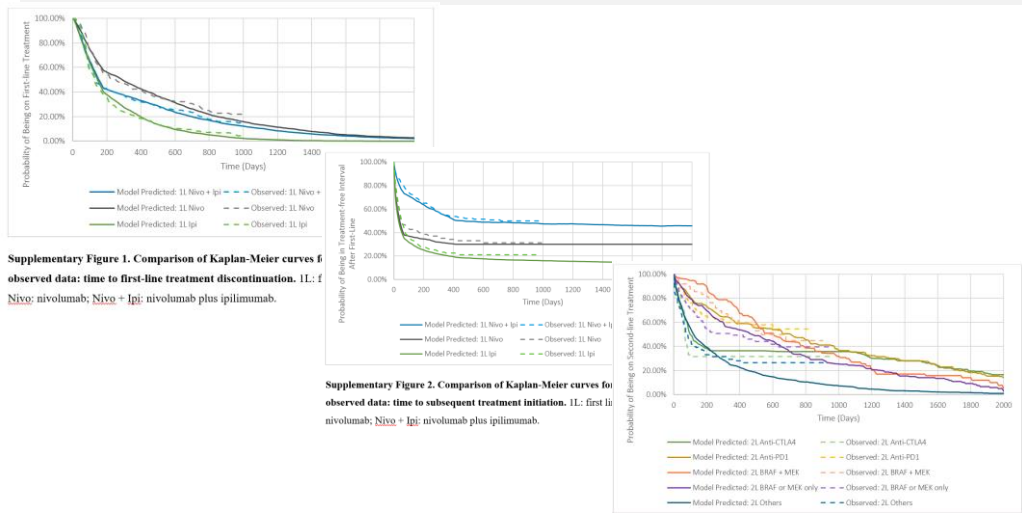
Source: Ghabri 2020

RESULTS INTERPRETATION

Understanding and interpreting results may be more involved due to richness of analyses

VALIDATION

…a project on its own for sequence models and can be challenging



Supplementary Figure 1. Comparison of Kaplan-Meier curves f observed data: time to first-line treatment discontinuation. 1L: f Nivo: nivolumab; Nivo + Ipi: nivolumab plus ipilimumab.

Supplementary Figure 2. Comparison of Kaplan-Meier curves fo observed data: time to subsequent treatment initiation. 1L: first li nivolumab; Nivo + Ipi: nivolumab plus ipilimumab.

Source: Tarhini 2018

TIMELINE & BUDGET

Longer and likely more expensive project

CONCLUSIONS

1 SHOULD I CONSIDER A SEQUENTIAL MODEL?

2 DO I HAVE ENOUGH BUILDING BLOCKS?

3 GO – NO GO ?

SEQUENTIAL MODEL TO BE CONSIDERED

Decision Problem	Busy treatment landscape with treatments with different mechanism of action allowing many choices	**Data**	Enough data to model: RCTs from a therapy portfolio or large EMR data on many active therapies but with remaining questions
Strategic Considerations	Unclear strategy, with significant questions about positioning	**Statistical analysis**	Dependencies between disease milestones across the treatment pathway can be properly established

SEQUENTIAL MODEL MAY NOT PROVE VALUABLE

Decision Problem	Little uncertainty about best sequence, not many treatment classes	**Data**	Available data (trials, RWE) not enough to capture impact of treatment choices across key lines of therapy
Strategic Considerations	Clear strategy and positioning	**Statistical analysis**	Dependencies between disease milestones across lines of therapy cannot be established

Timelines

Budget

CONCLUSIONS

EXECUTION

Similar to any other modeling project: solid conceptualization, implementation, statistical analysis, and validation is a very large part of the project

WHERE TO START ?

Key to start with a feasibility assessment before diving into a sequencing model development

FEASIBILITY ASSESSMENT

- Decision Problem
- Strategic Considerations
- Data For Treatment & Comparators

GO-NO GO DECISION

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