Multi-state Model for the Analysis of an Association between Safety and Efficacy Events Using R

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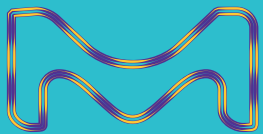


EMD SERONO

Motivation: Association of Safety and Efficacy

- Immunotherapy is a treatment that uses your body's own immune system to help fight cancer
- In chemotherapy, efficacy is generally associated with toxicity

How is the relationship for immunotherapy?

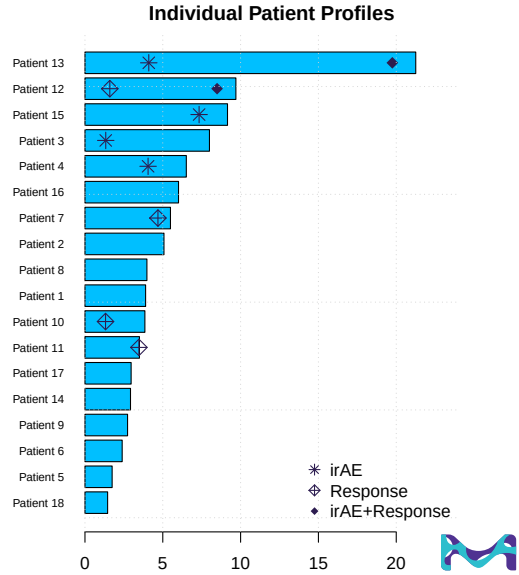
- Time-dependent Cox model identifies a survival benefit for immune-related adverse event (irAE) occurrence*
- Contradictory clinical considerations on causality◇

* von Pawel et al. (ESMO 2017): Association Between Immune-Related Adverse Events (irAE) and Atezolizumab Efficacy in Advanced NSCLC: Analyses from the Phase III Study OAK.

◇ Michot et al. (2016). Immune-related adverse events with immune checkpoint blockade: a comprehensive review. European Journal of Cancer, 54, 139-148.

Motivation: Statistical Challenges

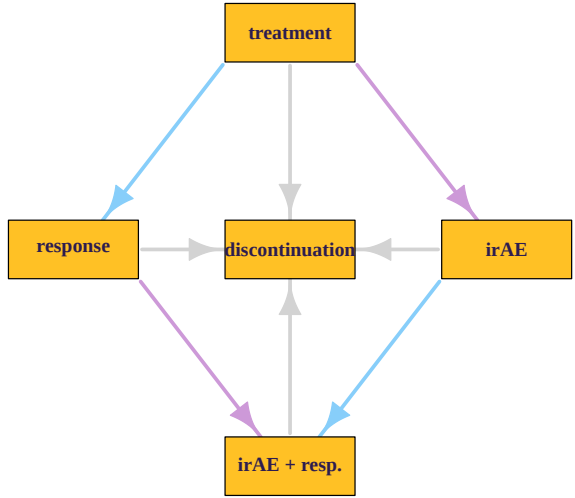
- Time-dependency:
  irAE occur throughout the treatment
- Spurious correlation:
  The longer the treatment duration, the higher the chance of irAE as well as the probability of response
- No fixed order:
  Response (and disease progression) can occur before or after irAE



Multistate Model Specification

Define possible progress of patients through different treatment states

```
require(mstate)
# define transition matrix
names = c("treatment","irAE","response",
"AE + resp.","discontinuation")
tmat <- transMat(x=list(c(2,3,5),c(4,5),
c(4,5),c(5),c()), names = names )
```



Compare the likelihood for

- Response given previous occurrence/absence of irAE
- irAE given previous non-/response

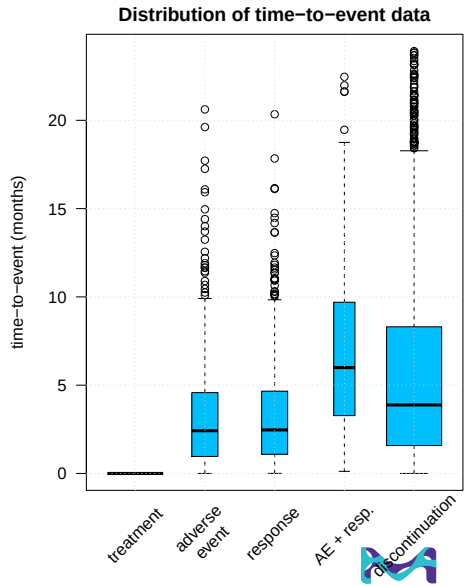
Reasons for discontinuation of treatment include withdrawal, lost to follow-up, progressive disease, adverse event or death

Data Simulation

- Simulation of $N = 2000$ patients from a general multistate model using *gems* package
- Convert to long data format using *mstate* package

```
msdat[msdat$id==12,]
```

```
## An object of class 'msdata'
##
## Data:
##    id from to trans Tstart Tstop time status
## 42 12    1  2     1    1.0   3.9 2.89      0
## 43 12    1  3     2    1.0   3.9 2.89      1
## 44 12    1  5     3    1.0   3.9 2.89      0
## 45 12    3  4     6    3.9   4.5 0.62      1
## 46 12    3  5     7    3.9   4.5 0.62      0
## 47 12    4  5     8    4.5   9.5 5.03      1
```

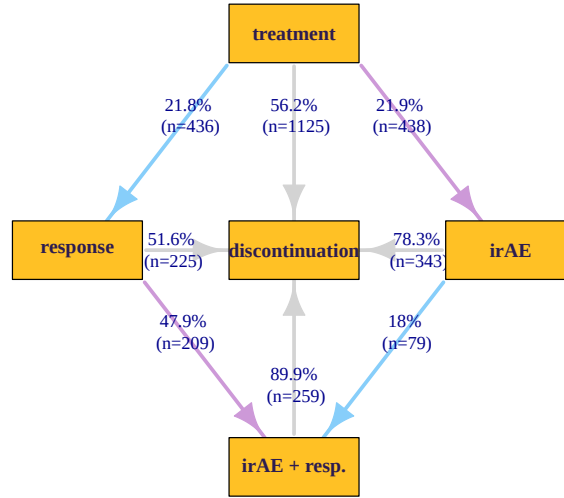


Crude Transition Probabilities

- Simple relative frequency of transitions given being in state

$$\frac{\text{no. of } i \to j \text{ transitions}}{n \text{ in state } i}$$

- No consideration of time immortality bias



Time-dependent Transition Probabilities

Given a patient is in state i at time t, the probability that a patient is in state j at time s is given by

$$P(X(s) = j | X(t) = i), s > t$$

Implementation using mstate

```
# fit cox model
coxM <- coxph(Surv(Tstart,Tstop, status) ~ strata(trans), data=msdat)
# estimate cum. transition hazards
cumHaz <- msfit(coxM, vartype="greenwood", trans = tmat)
# time-dependent transition probability
estPr <- probtrans(cumHaz, predt=5, method = 'greenwood')
```

Estimated Time-dependent Transition Probs I

Compare the likelihood for response given previous occurrence/absence of irAE.

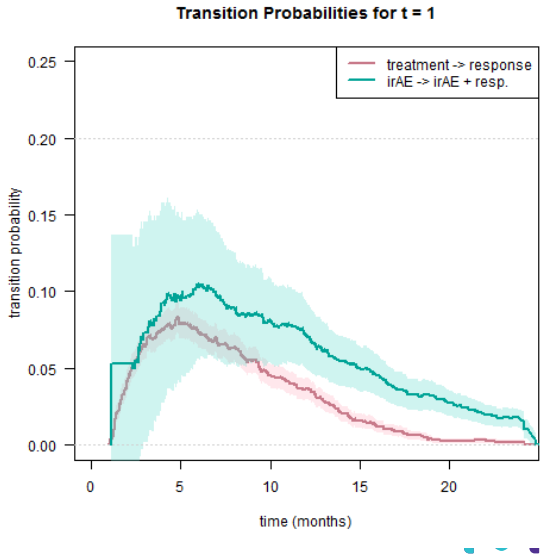
Thus, for $0 \leq t < s$:

$$Pr(X(s) = \text{'response'} \mid X(t) = \text{'no irAE'})$$

and

$$Pr(X(s) = \text{'response'} \mid X(t) = \text{'irAE'})$$

$\Rightarrow$ Similar chance of transition to response with/without irAE, i.e. occurrence of irAE cannot predict response.



Estimated Time-dependent Transition Probs II

Compare the likelihood for irAE given previous non-/response.

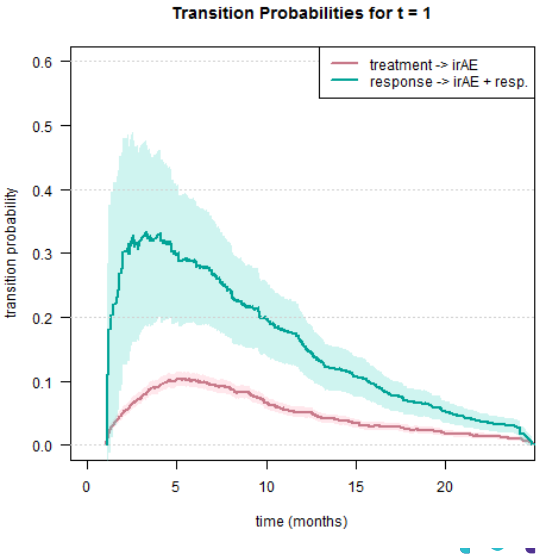
Thus, for $0 \leq t < s$:

$$Pr(X(s) = \text{'irAE'} \mid X(t) = \text{'non-response'})$$

and

$$Pr(X(s) = \text{'irAE'} \mid X(t) = \text{'response'})$$

$\Rightarrow$ More likely to develop an irAE given response



Summary

- Multi-state model provides meaningful insights to the underlying mechanisms of action in immunotherapy
- Informs on the risk of irAE and so allows their adequate management
- Can be easily implemented using the R package *mstate*

References

- Blaser et al. (2015). gems: An R Package for Simulating from Disease Progression Models. Journal of Statistical Software, 64(10), 1-22.
- Liesbeth et al. (2011). mstate: An R Package for the Analysis of Competing Risks and Multi-State Models. Journal of Statistical Software, 38(7), 1-30.

Thanks!

for your interest and the support of my colleagues

Multi-state Model: Statistical Representation I

Statistical Representation as Time-Inhomogeneous Markov Processes with Finite State Space

- Consider a *stochastic process* $(X_t)_{t\geq 0}, X_t \in 0, 1, 2, \ldots, J$ that denotes the state of an individual at time t, where transient and absorbing states are differentiated
- Events are modelled as *transitions* $i \rightarrow j, i \neq j, i, j \in 0, 1, 2, \ldots$ between the states of model
- Transition probabilities for time s assume *Markov property*, i.e. depend on the past only via the previous time
  $P(X(s) = j|X(t) = i, past) = P(X(s) = j|X(t) = i), s > t$
- Note that the transition probabilities depend on time t, which means the process is *time-inhomogeneous*

Multi-state Model: Statistical Representation II

Nested series of competing risk experiments/time-dynamic perspective

- Consider an individual is in state $j \in 0, 1, 2, \ldots$ at time t, which is not absorbing
- A waiting time in state I is generated with hazard $\alpha_{i\cdot}(t) = \sum_{j=0, i \neq j}^{J} h_{ij}(t'), t' > t$, where the transition hazards $h_{ij}(t)$ can be envisaged as momentary forces of transition between states i and j
- Given waiting time s, the next state entered is determined in a multinomial experiment, which decides with probability $P(X(s) = j | X(t) = i) = \frac{h_{ij}(s)}{h_{i\cdot}(s)}$ on state $j, i \neq j, s > t$.