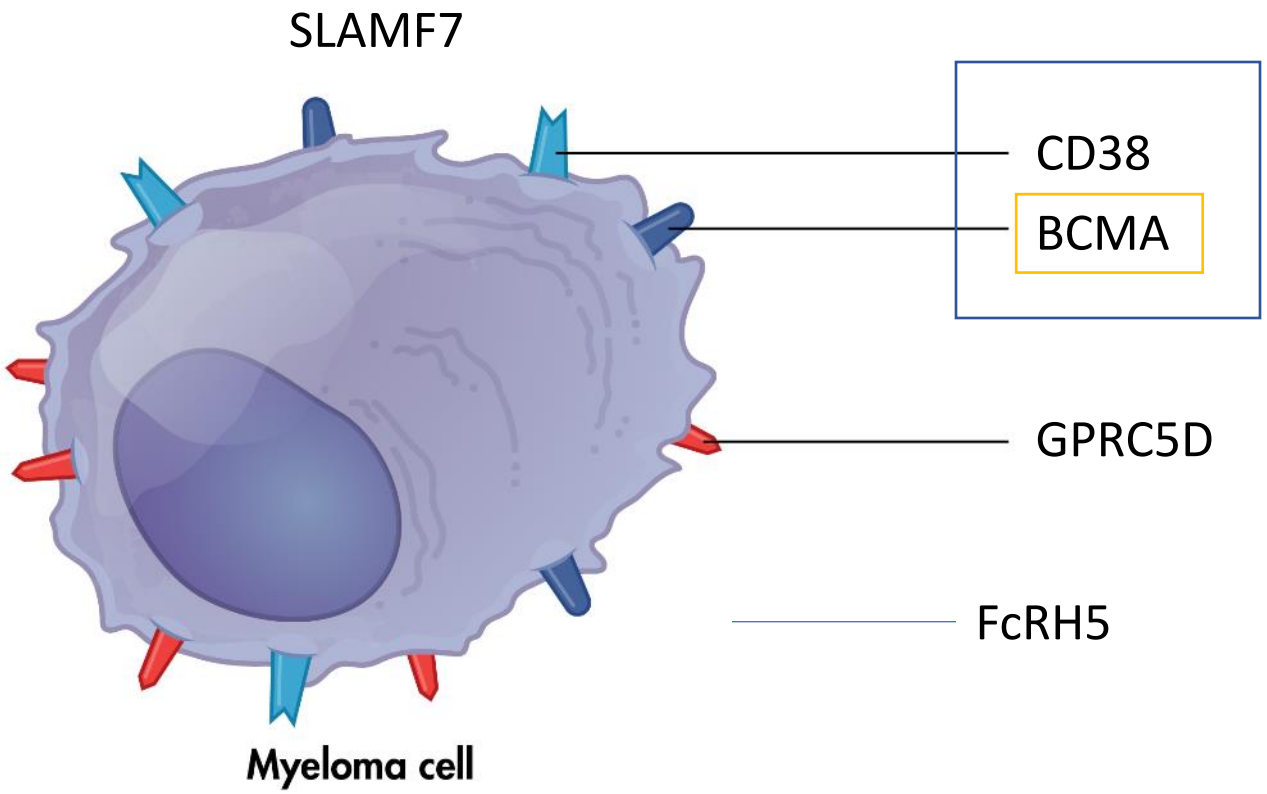
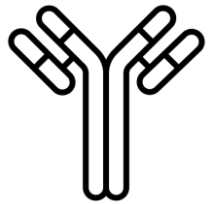
If a drug works ‘too well’
Challenges in dose finding of innovative drugs

EMA Cancer Medicines Forum
European Hematology Association (EHA)

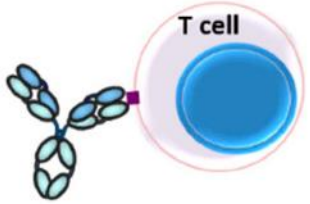
June 29, 2023

Immunotherapy for myeloma
From ‘immune cloaked’ to prime target

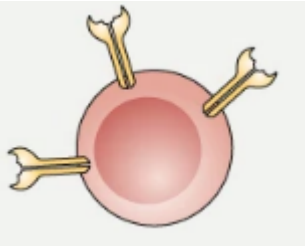




‘Naked’ mAb

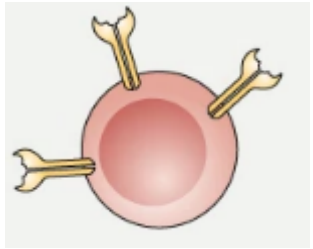


T-cell engager



CAR-T

T-cell based therapy for myeloma
Truly new field with many uncertainties (Unknown Unknowns)
Potential historical considerations that influenced development



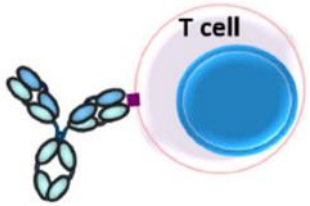
CAR-T

Development influenced by lymphoma experience:

Curative ‘one-off’ treatment

Proliferates post-infusion

Technically only 1 dose feasible, ‘one dose is enough’



T-cell engager (TCE)

Development influenced by leukaemia experience:

Permanent infusion in ALL

Only works if ‘much drug around’

→ Dose-response relationship

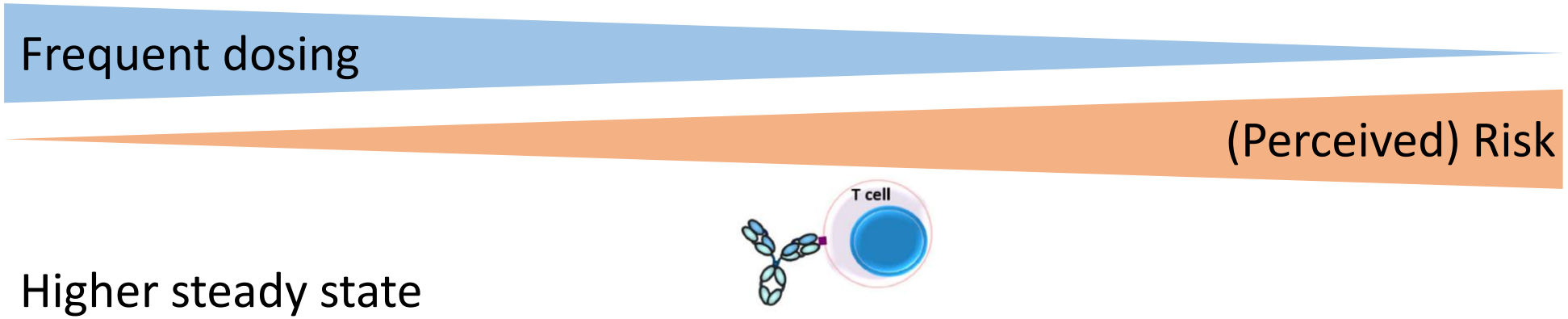
CRS risk when stopping-restarting

→ Frequent dosing = more steady-state

Seeking Accelerated Approval

Incentive to **reduce risk** as much as feasible in terms of **1) Early tox 2) Efficacy**

When actually very little is known



Higher steady state
= putative lower CRS recurrence risk

Higher concentration
= putative higher efficacy

Potential economic considerations

Accelerated Approval successful – true innovation
Teclistamab (Tecvayli) – BCMA TCE

- ~60% response rate as single agent drug in RRMM, 11 months median PFS
  - Unprecedented in RRMM as single agent – patient-friendly (no steroids etc)
  - True innovation, first-in-class
- Accelerated approval for RRMM granted
  - **Weekly dosing sc – economic model/price set for weekly dosing**

Emerging anti-BCMA TCE evidence
Required time to emerge
Benefited from wider patient access as different than expected

- CRS very manageable - very rarely recurring – this could not have been anticipated (!)

- BCMA TCE wipe out most humoral immunity (BCMA on healthy plasma cells)

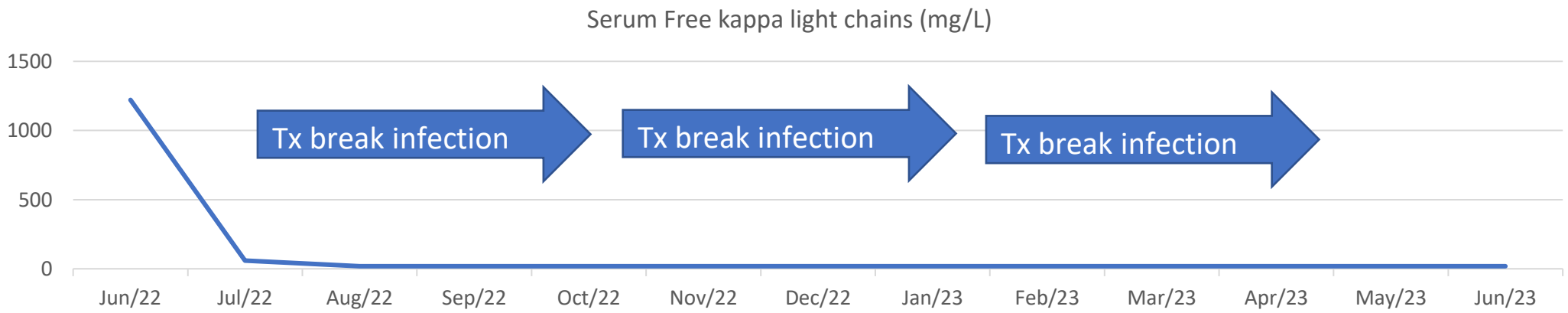
  - Infections

  → instrumental and beneficial for rapidly gaining experience with less frequent dosing

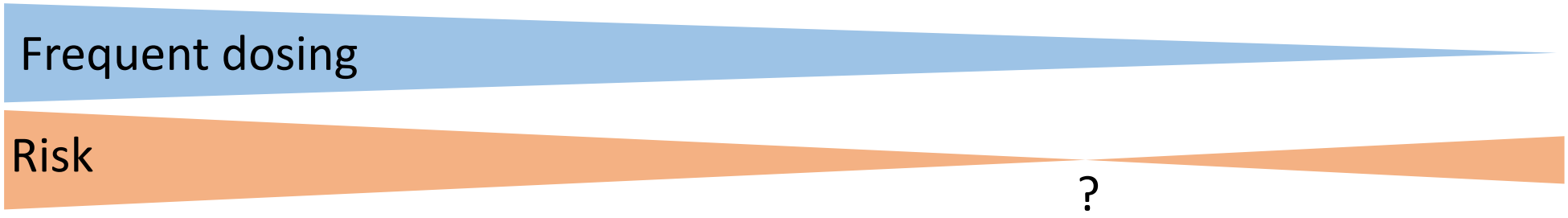
Emerging anti-BCMA TCE dosing experience

Representative, purely hypothetical patient avatar: >60 years old, diagnosed >10 years ago, 8th line RRM
Started BCMA TCE mid 2022
Went into CR within 2 months – best response ever
Had to interrupt Tx due to prolonged non-serious viral infection multiple times
Received only 1 dose TCE every 3 months on average
Remains in CR ever since, very good quality of life

Patient avatar is informed & active – asks why give more frequently than q3mo in those in CR?



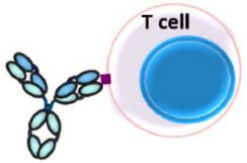
Novel T-cell based therapy in myeloma
Emerging long-term use risks



More serious infection risk

Potentially more other side effects

Potentially less efficacy (!): T-cell exhaustion



Accelerated approval and dosing in highly innovative medicines
Potential scenario: Risk to innovation

A highly innovate product has been developed, taking considerable risks due to many uncertainties
Policy incentives for accelerated approval were followed as intended
Most available early indicators indicated lower development risk with more frequent dosing
MA granted and price set for frequent dosing
Emerging evidence indicates dosing at small fraction of licensed indication (maybe 1/10) may suffice

→ Truly innovative first-to-market drug – but price tied to dosing
→ No incentive for innovator/risk-taker to reduce dosing – it would be economic self-harm
→ If market uses only 1/10 of drug, price is set wrong and incentive for innovation diminished
→ Disadvantage for the first-to-market innovator – who wants to take risk?
→ Might incentivise less innovation/risk taking on commercial side over time
→ Particular risk for less common cancers/cancers with busy markets

→ Problem is: myeloma is still incurable – this may become a problem for multiple cancers in the future!

Accelerated approval and dosing
Potential scenario: how to mitigate this risk?

Slower development?
Less accelerated approval if first-in-class?

→ Against patient preference/voice
→ Higher costs for development overall – risk of less activity overall, esp for uncommon cancers?

Opportunity to re-visit MA label within 1st year, especially regarding dosing?

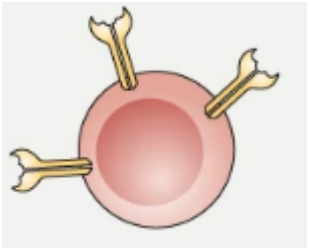
→ Not feasible or useful for all medications
→ But could be limited to highly innovative medicines, First-in-class – but who would decide?

Other options? Multiple prices?

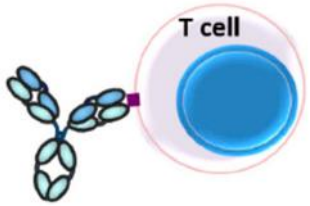
→ C**ommercially attractive incentives could be biggest lever for patient-centricity!**

Novel T-cell based therapy in myeloma
Hypothetical considerations

Photo: @graham74GC



CAR-T



T-cell engager

One-off treatment

Difficult manufacturing process

Highly efficacious

Very high price perceived as justified by society

What if effect size will be very similar to CAR-T, i.e. highly efficacious?

Effect mechanism in MM may be very similar to CART effect with optimal dosing?

Could a higher price ever be incentivised for development as one-off/2-3 doses treatment **and how?**