EUROPEAN HEMATOLOGY ASSOCIATION

Examples of Drug Development and Optimisation in Haematology

Diagnostics, Data and Policy Decisions

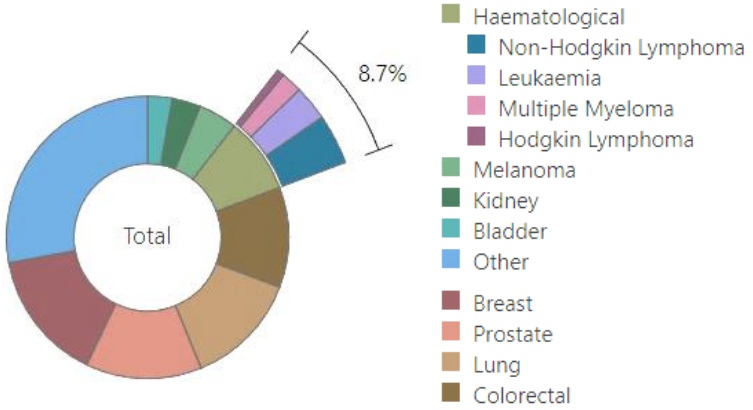
EMA/EORTC Cancer Medicines Forum Workshop

April 5, 2024

Haemato-oncology

Complex, diverse uncommon cancers

- Systemic cancers
- Systemic therapies
- Successes & challenges closely linked to regulatory policies
- Engine of innovation in medicinal treatment of cancer (selection)
  - Curative chemotherapies (ALL)
  - Mutation-specific therapy (CML)
  - Combination treatments (MM)
  - CAR-T therapy (ALL/NHL)
  - T-cell engagers/bispecific antibodies (ALL/NHL/MM)



https://hmrn.org/about/classification

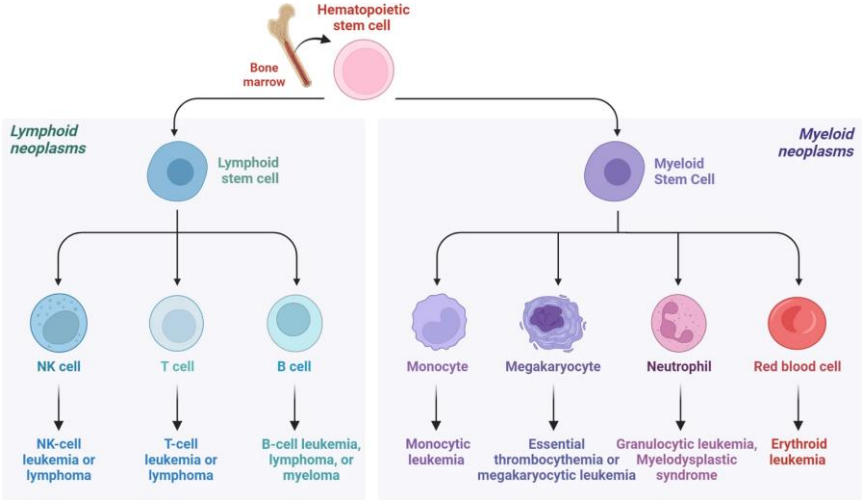
Haemato-oncology

Specialist diagnostics key for treatment

- Complex, multi-modal diagnostics
  - Morphology
  - Immunophenotyping
  - Genetics, molecular diagnostics
  - Immune system profiling

- Haemato-oncologists treat patients and perform diagnostics (in collaboration with pathology)

- Diagnosis of disease and intra-disease molecular and risk stratification



https://doi.org/10.1186/s13045-023-01460-2

Haemato-oncology

Substantive progress in previously intractable cancers

Curative treatment for some entities

- Acute leukaemia, High-grade lymphoma

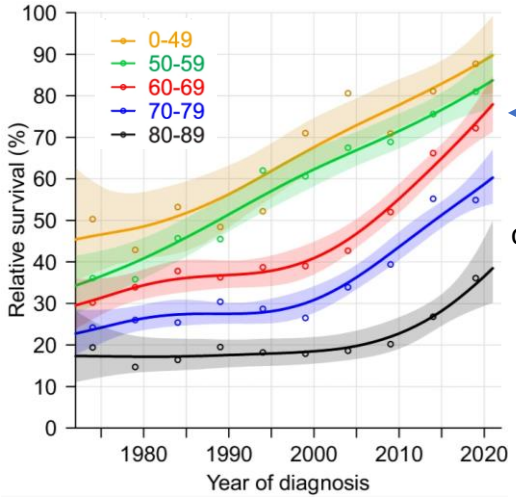
Highly successful disease modification in many incurable entities through drug (combination) treatment strategies

- Chronic myeloid leukaemia
- Low-grade lymphoma
- Chronic lymphocytic leukaemia
- Multiple myeloma

Disease modifying drugs consistently in top cancer drug spend lists

→ Treatment optimisation key topic in haemato-oncology >10 years

Example
Multiple myeloma
5-year survival



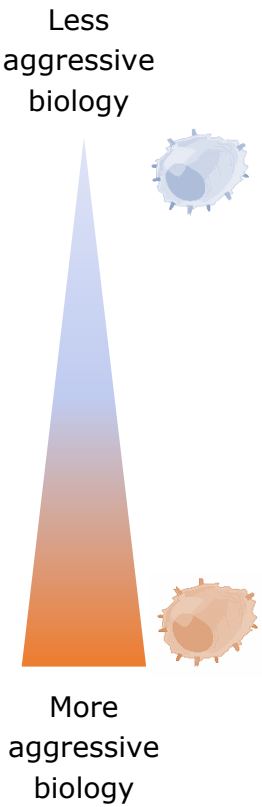
25% early deaths

Still incurable
All patients still relapse
Huge heterogeneity in outcomes

https://doi.org/10.1038/s41408-024-01026-6

Treatment optimisation

Inter-patient tumour heterogeneity – consequences for treatment optimisation



Potential for de-escalation

- Slow-growing tumours
- More predictable
- Still responding to drugs at relapse

Persistent unmet need

- Fast-growing tumours
- Less predictable, quickly evolving
- Not responding well to drugs at relapse

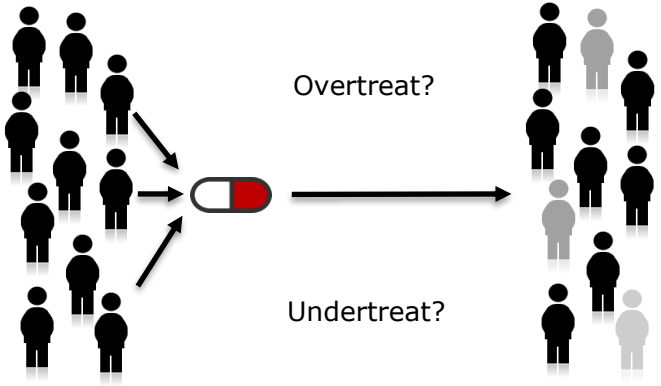
To stratify patients in the clinic:

- Complex specialist diagnostics required
- Not typical companion diagnostics
    - Product-independent
- Often combination of tests
- Qualitative and quantitative biomarkers

Stratified treatment optimisation

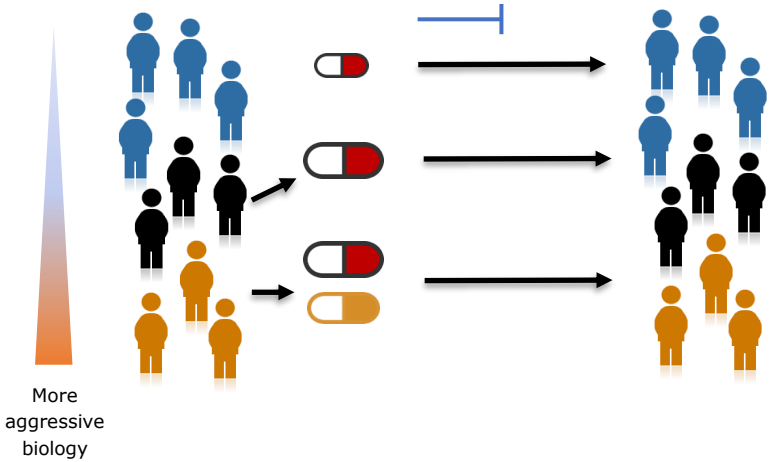
High potential for improving value proposition across patient population

Default



Higher uncertainty
Higher tendency to overtreat
'More is better'

Aim – Disease and patient-centric

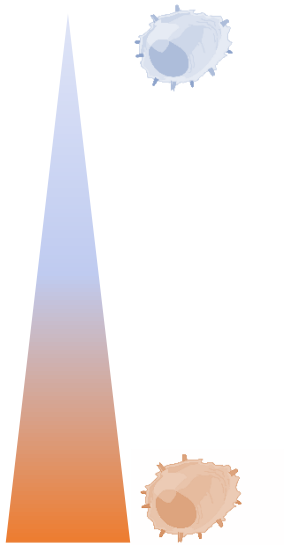


Better outcomes
Better patient experience
Better value
Patient-centric allocation of resources

Example chronic lymphocytic leukaemia

Genetically stratified optimisation

Less aggressive biology



More aggressive biology

No TP53 gene mutation (wt)

No MRD present

Treatment stopping trials, e.g. GAIA/CLL13

Stopping safe and efficacious

TP53 gene mutated

Ongoing unmet need

No stopping, intensification, Focus for novel clinical trials

Concept established through academic research and public (academic) clinical trials

MRD=measurable residual disease (by specialist diagnostics)

10.1056/NEJMoa2310063

Example multiple myeloma

Molecularly stratified optimisation based on combination of markers

Less aggressive biology

Risk mutations or gene expression markers absent

No MRD present

Treatment de-escalation trials (ongoing)

Risk mutations or gene expression markers present

gain(1q)

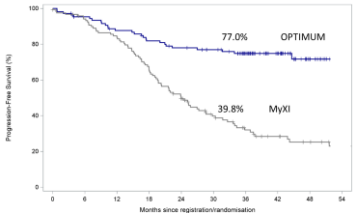
del(17p)

t(4;14)

GEP

Address unmet need, treatment intensification e.g. OPTIMUM trial

Treatment intensification in 1st improves long-term outcomes



More aggressive biology

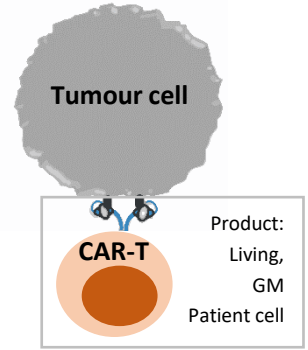
Concept established through academic research and public (academic) clinical trials

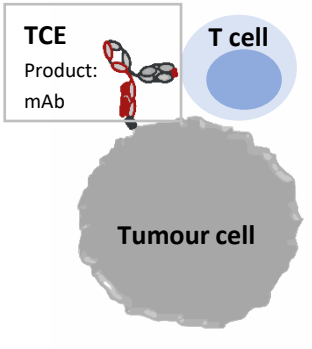
MRD=measurable residual disease (by specialist diagnostics)

https://doi.org/10.1038/s41408-024-01026-6

The next frontier for stratified treatment optimisation

Patient's own immune cell qualities are part of 'drug' characteristics





CAR-T

- Quality of patient T–cells going into genetic modification
- Quality of T-cells at return

T-cell engager (TCE) [bispecific antibody]

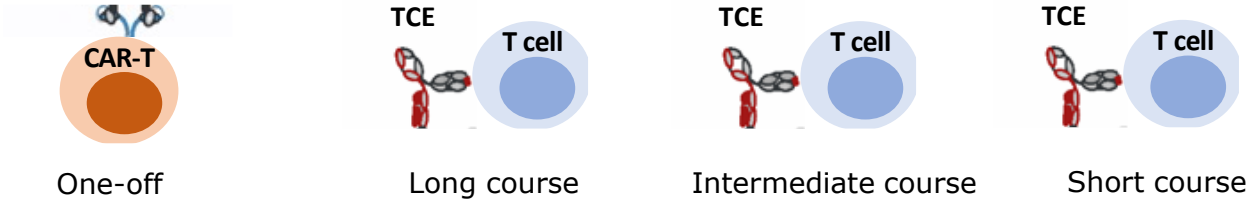
- Quality of patient T-cells at time of each infusion
- Frequency and length of TCE infusions (e.g. T-cell exhaustion)
- **Less treatment may be more for some patients**

Challenge for biomarker development:

- **Product profile**
- **Immune profile**
- **Tumour profile**

Improved diagnostics as incentives for more patient-centric clinical development

Example T-cell based therapies for multiple myeloma



Current status

One-size-fits-all incentive

Aspiration, informed by advanced diagnostics and Enhanced, stratified definition of clinical need

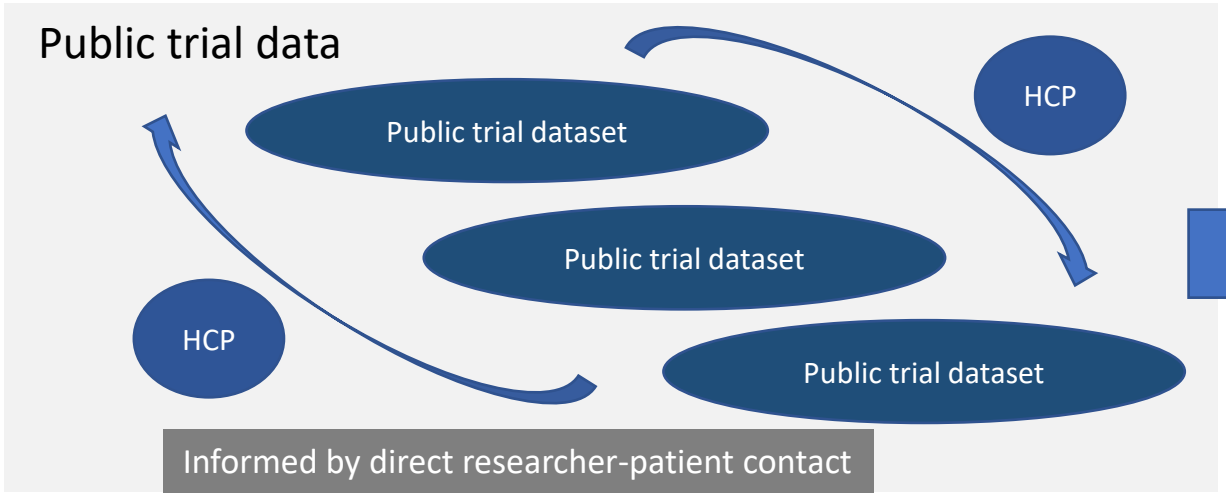
Incentives defining specific value for patient sub-groups

Product profile + Immune profile + Tumour profile +Patient characteristics

Public/academic trials hallmark for biomarker development in haemato-oncology

Enabled by interconnectedness of public data beyond a single product

Source: Martin Kaiser



- Cross-trial
- Product-independent
- Definition of unmet need and clinically relevant sub-groups

Main challenge: funding of public trials with independent data utilisation

Specialist diagnostics for stratified treatment optimisation

Need for improved strategy and policy

Currently multiple challenges for diagnostics (selection)

Policy challenges

- Not part of standard licensing evaluation process
- Not part of standard reimbursement evaluation process
- IVD regulation

Practical challenges

- Outside core expertise of most drug manufacturers
- Relatively under-funded / limited commercial incentive
- Funding of diagnostic services detached from drug budgets

Conclusions

- Treatment optimisation should be patient-centric
- Specialist diagnostics can provide opportunities for more patient-centricity in drug optimisation
- Potential to reduce uncertainty for regulators, payers and industry
- Currently, diagnostics are under-represented in regulatory and reimbursement review and under-utilised and under-funded in research