Regulatory considerations in the design, development and quality of monoclonal antibodies and related novel antibody-based products.

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CMC Summer Strategy Forum
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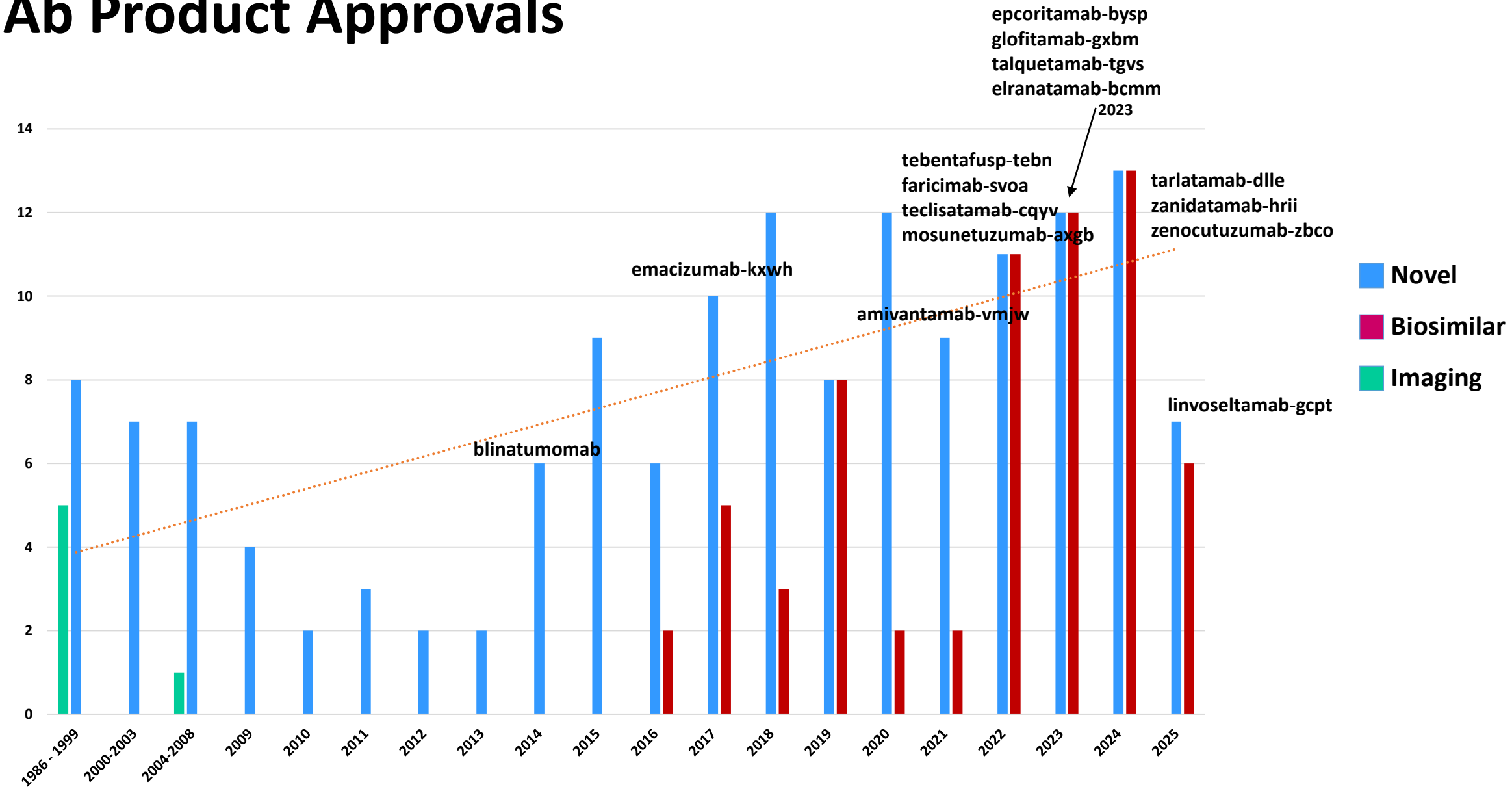
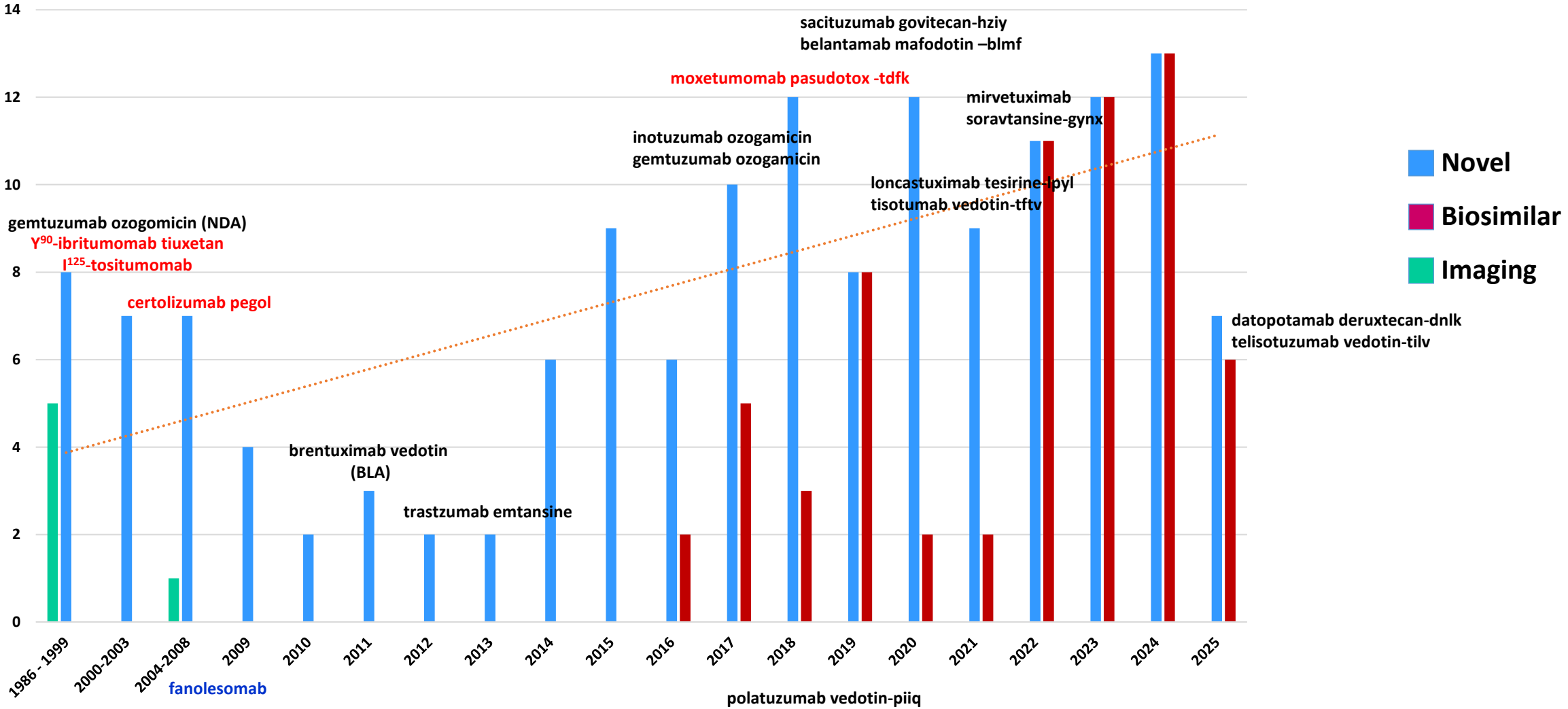
mAb Product Approvals



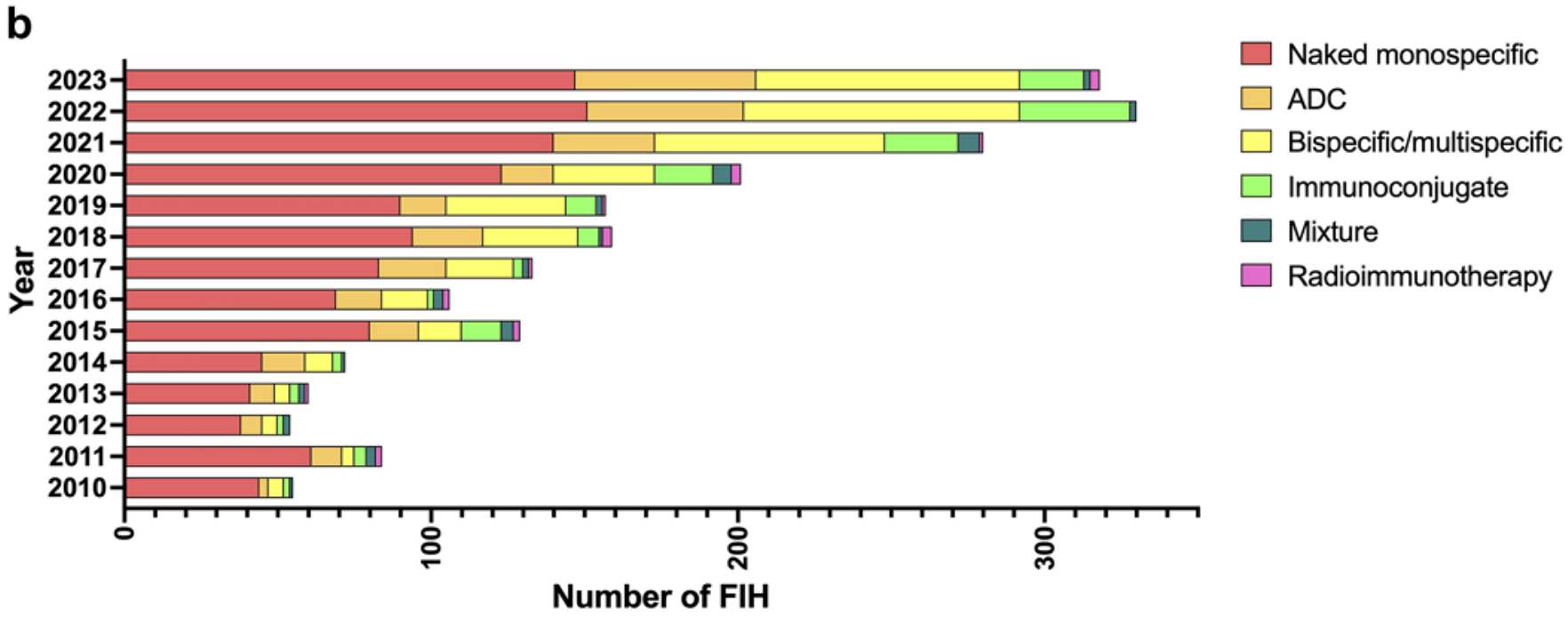
mAb Product Approvals



satumomab pedetide, imciromab pentetate
nofetumomab merpentan, arcitumomab
capromab pentetate

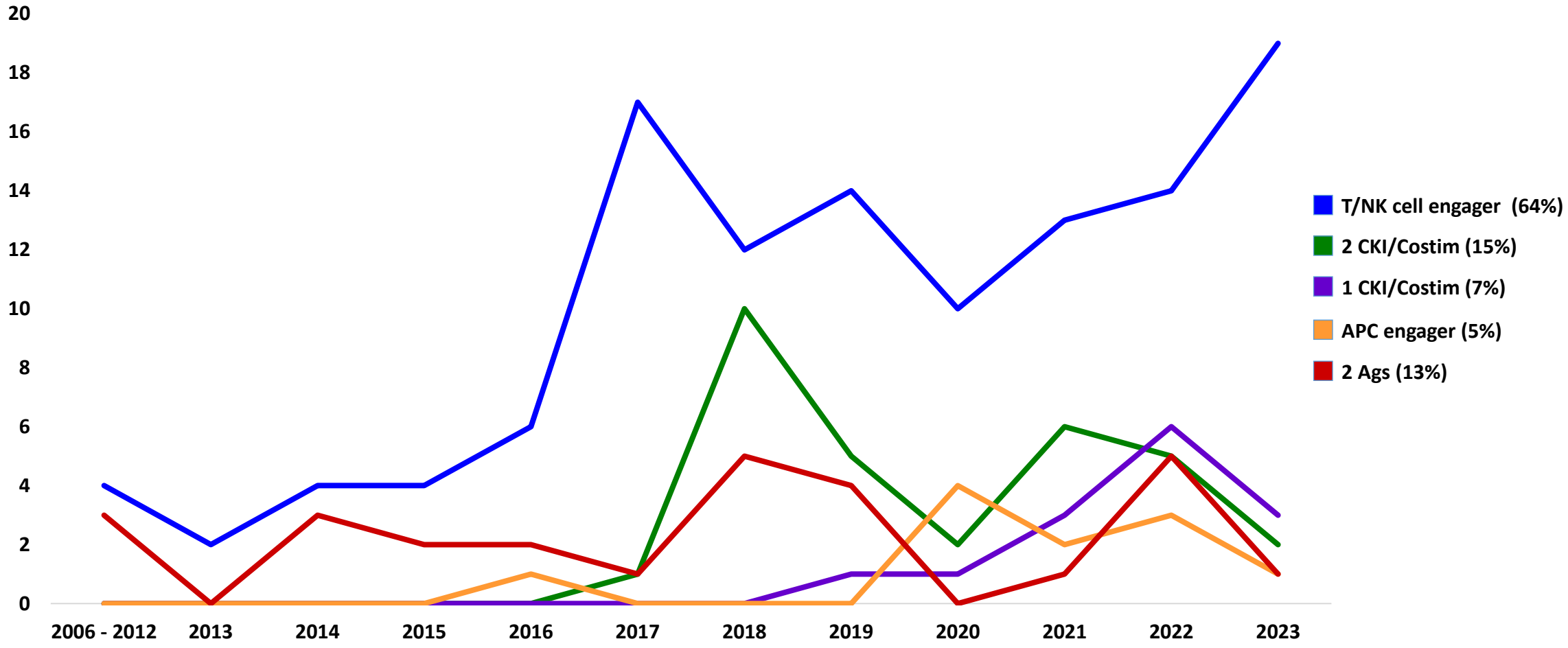
polatuzumab vedotin-piiq
enfortumab vedotin-ejfv
fam-trastuzumab deruxtecan-nxki

Trends in First-in-Human Studies



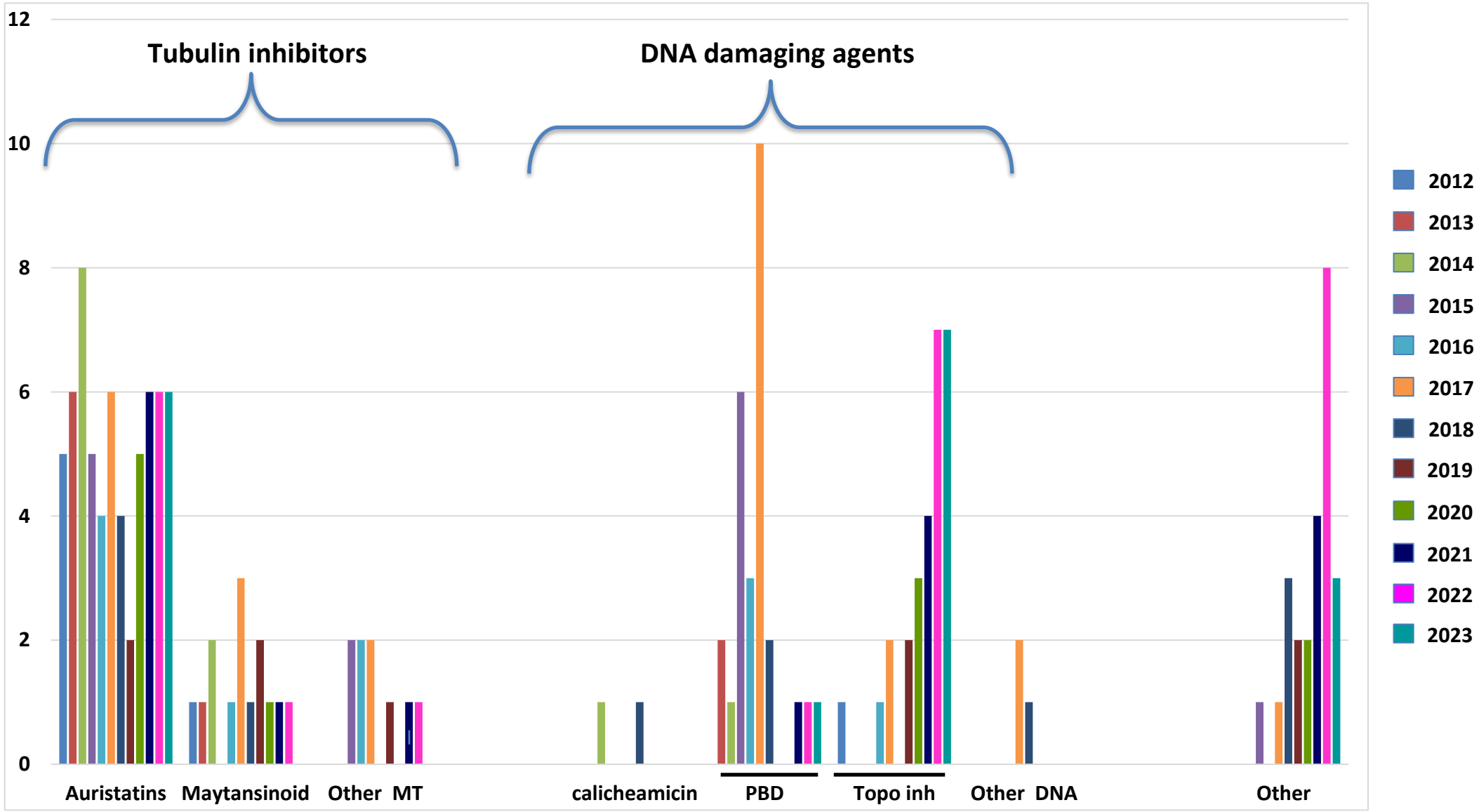
Crescioli et al. Antibodies to watch 2025. mAbs, 17:1 https://doi.org/10.1080/19420862.2024.2443538

Trends in BsAb IND Submissions



Shapiro. Regulatory considerations in the design, development and quality of monoclonal antibodies and related products for the diagnosis and treatment of cancer. Frontiers in Oncology 2024. https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2024.1379738/full

Trends in ADC Payloads



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Current and Next Generation mAb Conjugates and Multi-Specific Products

- Tri-specific TCE targeting two different antigens/epitopes
- Target NK cells instead of T cells
- Bispecific complement engagers
- Constructs that contain an anti-HSA domain or HSA itself to prolong half life
- Bispecific ADCs
- Prodrug BsAbs
- Fusion proteins/immunocytokines (prodrug)

- Protein degraders/molecular glues
- Radioimmunoconjugates – newer nuclides
- Optical imaging probes
- Dual cytotoxic drug payloads
  - Same or different linkers
- Dual cytotoxic and radionuclide payloads
- Prodrug ADCs
- Affinity tuning (all types of mAb products)

Rationale for newer constructs: broaden therapeutic window, overcome drug resistance in tumors, improve PK, improve tissue penetration, mitigate cytokine release for TCEs and other T-cell targeted products.

Regulatory considerations for novel mAb constructs – could it be a CQA?

BsAb, ADC and Immunocytokine Prodrugs should have no activity. Remove the mask to demonstrate expected activity. Consider release assay for both.

Bi/multi-specific abs and fusion proteins with gly-ser linkers. Characterize for O-glycosylation and other PTMs.

HSA and anti-HSA containing constructs - included for extended half-life. Characterize to ensure lot-to-lot consistency.

Novel antibody conjugate payloads may have different properties compared to traditional cytotoxic payloads and need different characterization/release methods (e.g., mAb-oligo constructs)

Mabs, even human mAbs, can be immunogenic. Pre-existing ADA in normal serum have been detected against parts of some novel constructs. Test the immunogenicity of your design early in development

Thanks for your attention!

References

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