INFECTIOUS COMPLICATIONS OF CAR T-CELL THERAPY AND BISPECIFIC ANTIBODIES

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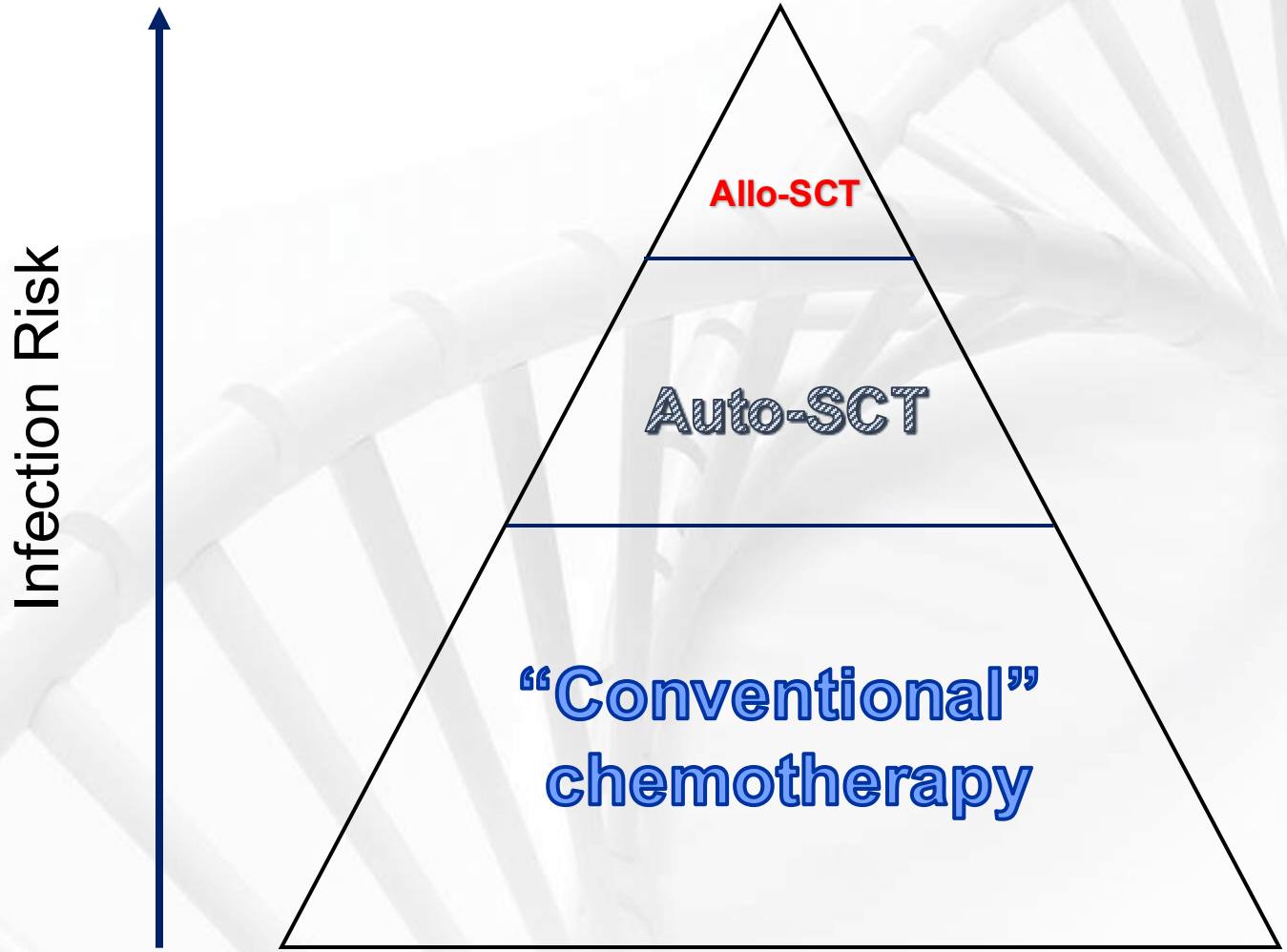
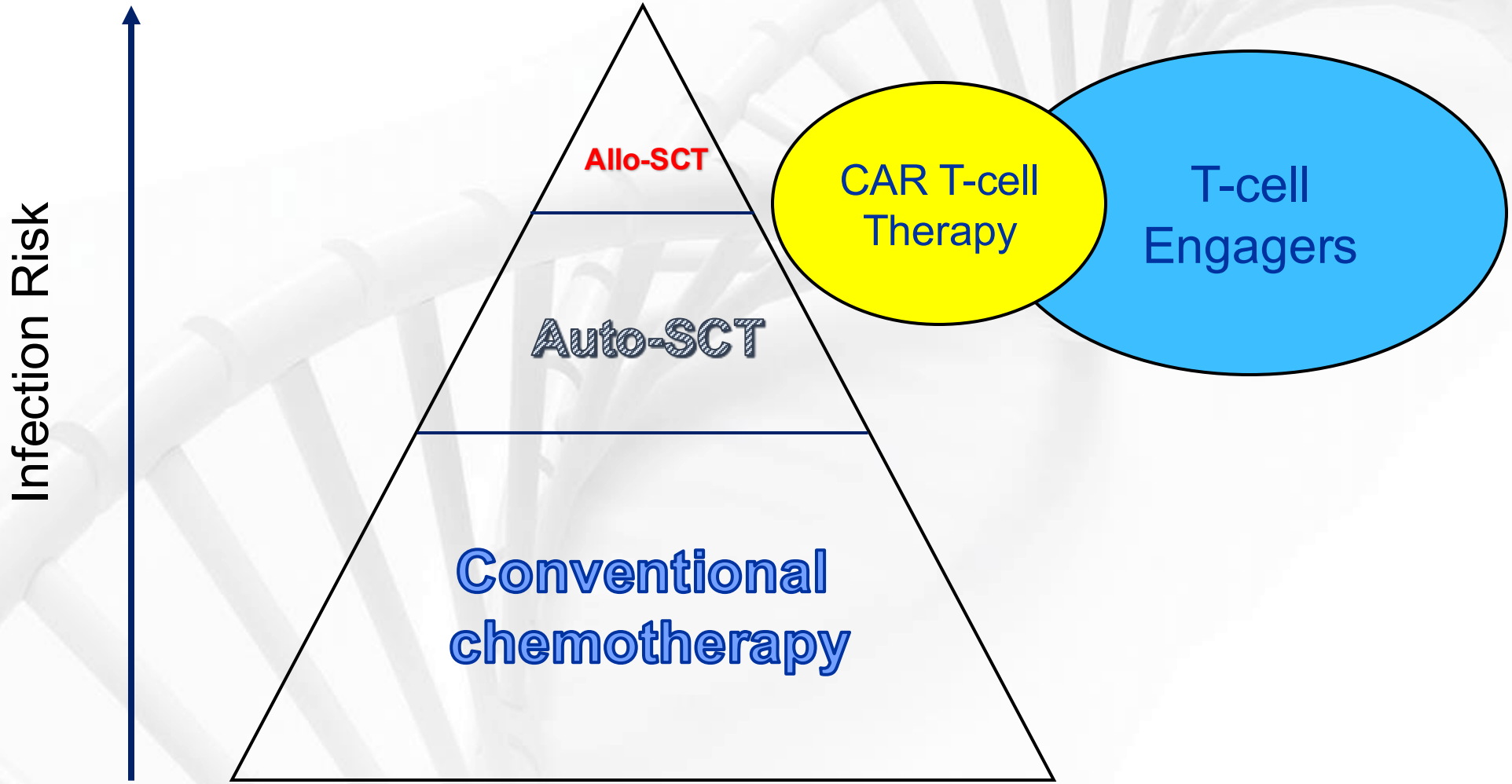
THE OLD WORLD OF INFECTIONS FOR CANCER PATIENTS



Risk Factors

- Prior therapies (host)
- Neutropenia
- Lymphopenia
- Disrupted barriers
- Active immune suppression
- GVHD

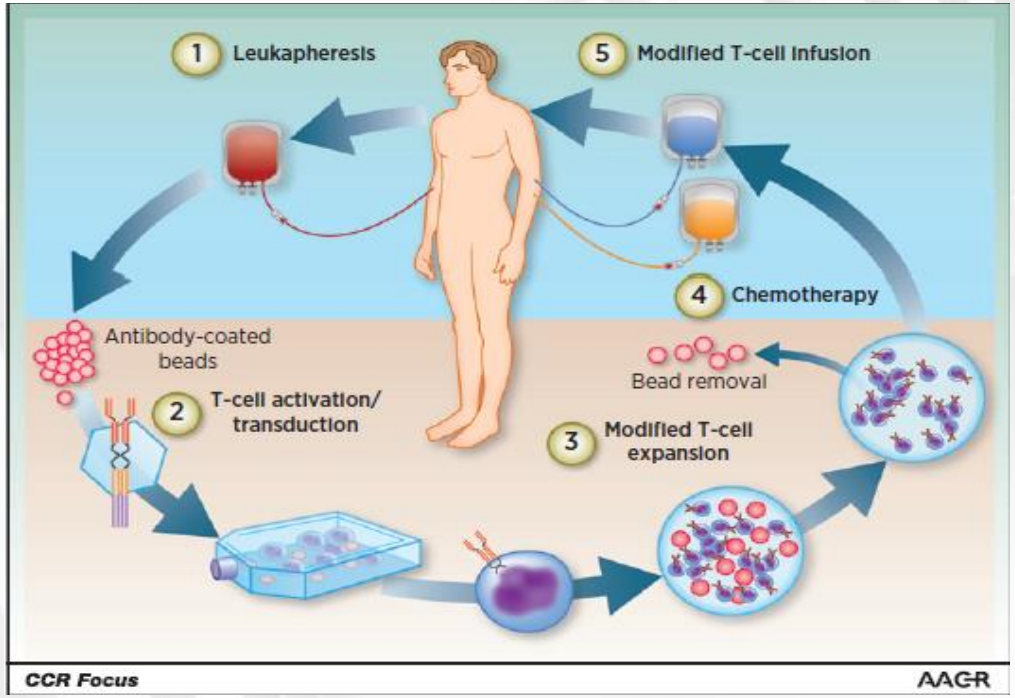
THE LANDSCAPE HAS BECOME MORE COMPLICATED



WHY IS THIS IMPORTANT?

- Different patient populations (lymphoma, myeloma, solid tumors, etc) that we aren't used to having to worry much about
- *Need for dynamic risk assessment*
- Role of community providers and need for education

Infections after CAR T-cell Therapy



From: Maus MV, June CH. *Clin Cancer Res.* 2016;22(8):1875-1884.

CAR T-CELL THERAPY IN A PATIENT WITH ADVANCED MYELOMA

- 48 yo woman with R/R myeloma—8 prior lines of therapy
  - Significant disease burden going into LD chemo
- Investigational GPRC5D-directed CAR T-cell product given after standard Flu/Cy LD chemo
- Gr 3 CRS and Gr 4 ICANS requiring several doses of Tocilizumab, prolonged steroids (>2 wks), and Anakinra
- Infectious complications
  - Multiple bacteremias
  - Invasive fungal sinusitis
  - High level CMV reactivation with suspected CMV enteritis

RISK FACTORS FOR INFECTION AFTER CAR T-CELL THERAPY

- **Host factors**
  - Prior lines of therapy
  - Prior infections, esp within 100 d
  - Lymphopenia and/or hypogammaglobulinemia prior to LD chemo (CAR)
  - Age and KPS
- **Therapy related factors**
  - Intensity of LD chemo
  - CAR target
- **Influence of post-therapy events and management**
  - Occurrence and severity of CRS, ICANS, IEC-HLH, late IEC-GI toxicity, late neurotoxicity, etc
  - Need for prolonged corticosteroids and other immunosuppressive agents for management
  - Prolonged cytopenias and hypogammaglobulinemia

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Expert Review of Anti-infective Therapy

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Risk of infection in patients with hematological malignancies receiving CAR T-cell therapy: systematic review and meta-analysis

Gülçin Telli Dizman, José María Aguado & Mario Fernández-Ruiz

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META-ANALYSIS: POPULATION

- Included 45 studies (34 RCTs); 3591 patients—through 2022
  - **B-cell malignancies: 77.8%**
    - B-cell NHL:57.8%
    - B-ALL: 6.7%
    - Both: 13.3%
  - **Myeloma: 13.3%**
  - **Mixed bag of malignancies: 8.9%**

META-ANALYSIS: RESULTS

- Pooled incidence rates
  - Overall infections 33.8%;
  - Severe (≥gr 3) infections 16.2%
  - Pooled estimate of infection-related mortality: 1.8%
  - Among studies reporting late infections (>d 28), infection incidence rate was 36%
- Most common sites of infection: URI, pneumonia, bloodstream infections/sepsis
  - Early: bacterial and viral infections predominate
  - Late: more varied, including opportunistic pathogens
- Risk factors for infection
  - Prior HSCT
  - # prior lines of therapy
  - Baseline neutropenia
  - CRS or ICANS requiring anti-IL-6 agents and/or prolonged corticosteroids (>3d)

LIMITATIONS

- Time bias…
  - **COVID pandemic**
- Heterogeneity of practice
- Under-representation of myeloma patients
- Limited granularity and heterogeneity of data
- Under-reporting of later events (including mortality) in most studies

INFECTION RISK AFTER CAR T-CELL THERAPY IN MYELOMA

- Cartitude-1 Study (Cilta-cel)
  - 97 treated subjects
  - Infection incidence: 58%
  - Gr 3-4 infection: 20%
  - 3 deaths (3%) attributable to infection (all >30 d post infusion--sepsis, PNA)

JG Berdeja, et al. Lancet 2021

- Real-world data for Ide-cel vs Cilta-cel—infection incidence
  - Ide-cel: 36%
  - Cilta-cel: 47%

DK Hansen, et al. JCO 2025

LATE EVENTS ARE MAJOR DRIVERS OF INFECTION RISK

- Target effects (B cell and plasma cell depletion)
  - Prophylaxis: esp VZV and PJP
  - Hypogammaglobulinemia
  - Immunizations---yes, but when?
- Prolonged neutropenia in a subset of pts
- Complications →additional immune suppression
  - IEC enterocolitis, late neurotoxicities, etc
  - Lymphoproliferative disorders/lymphomas

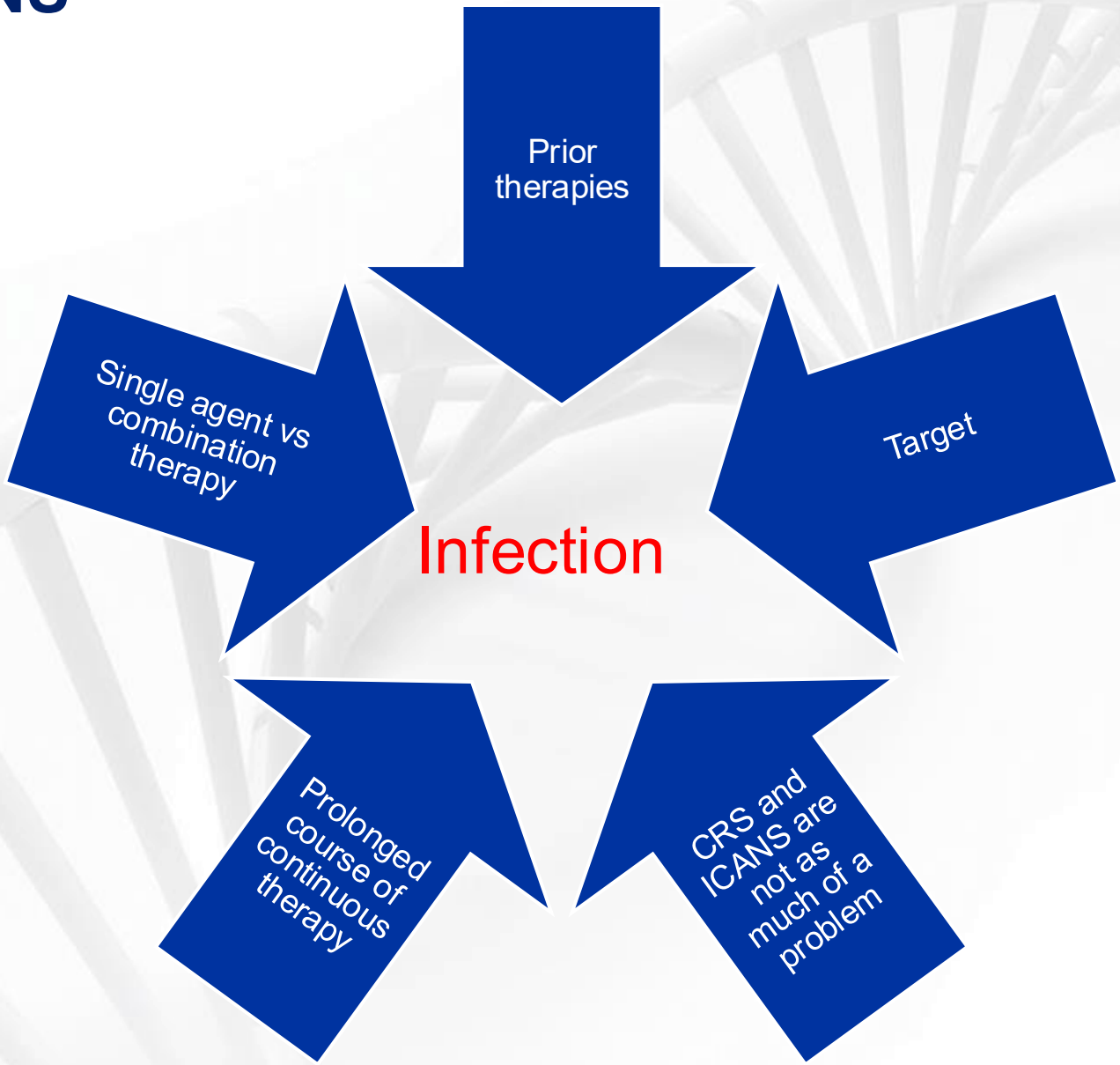
WHAT ABOUT INFECTION RISK AFTER T-CELL ENGAGERS?

Sobering data

Lots of agents and targets

Community administration and prolonged course of treatment

CONSIDERATIONS



Incidence, timing, and management of infections in patients receiving teclistamab for the treatment of relapsed/refractory multiple myeloma in the MajesTEC-1 study

Ajay K. Nooka MD[1] | Cesar Rodriguez MD[2] | María Victoria Mateos MD, PhD[3] | Salomon Manier MD, PhD[4] | Katherine Chastain MD[5] | Arnob Banerjee MD, PhD[6] | Rachel Kobos MD[5] | Keqin Qi PhD[7] | Raluca Verona PhD[6] | Margaret Doyle MSc[8] | Thomas G. Martin MD[9] | Niels W. C. J. van de Donk MD, PhD[10]

Cancer 2024; 130:886-900

MajesTEC-1 STUDY- PATIENT POPULATION

- Triple-class-exposed R/R myeloma
- Standard ramp-up and administration schedule of Teclistamab , with continuation of therapy until progression or intolerance
- N=165 pts
  - Median age 64 (33-84)
  - Median 5 prior lines of therapy (2-14), and 78% were triple-class refractory
  - Median treatment duration: 8.5 mos (0.2-24.4)
  - Median follow-up for this analysis: 22.8 mos

MajesTEC-1 STUDY--OUTCOMES

- Hypogammaglobulinemia in 71% of pts
  - IVIg given in 46% of pts
- Gr 3-4 neutropenia in 65% of pts
- Infections
  - All grades: 80%
  - Gr 3-4: 55.2%
  - Infectious death: 12.7%
    - *18 of the 21 infectious deaths due to COVID-19*

DIGGING INTO INFECTIONS in MajesTEC-1

- Viral infections (excluding COVID-19)
  - Overall: 12.1%
    - About half within 6 mos
  - Gr 3-4: 4.2%
    - Adenovirus, HBV, CMV (2), PML
    - One death from PML
- Fungal
  - Aspergillosis in 1 pt, and Candida in 4 pts
- PJP
  - 4.2% overall—all gr 3-4, but no deaths
- Respiratory infections (excluding COVID-19 and PJP)
  - Overall: 57.6%; gr 3-4: 19.4%
  - Deaths: 1.2%

Comparative infection risk in CAR T vs bispecific antibodies in B-cell lymphoma: a systematic review and meta-analysis

Herman van Besien,[1,*] Neela Easwar,[1,*] Michelle Demetres,[2] Michelle Pasciolla,[3] Tsiporah Shore,[1] John Leonard,[1] Juliet Barker,[1] Peter Martin,[1] and Samuel Yamshon[1]

- 25 prospective studies (3202 subjects)
  - 15 CAR T and 10 BsAb studies
  - Included studies of agents FDA approved at the time of analysis
  - Excluded combination regimens
  - Median of 3 prior regimens for both cohorts

blood advances

9(23): 6063-75, 2025

INFECTION INCIDENCE

	CAR T	BsAb	p
All grades infection	0.44	0.54	0.18
Infection/pt month	0.0167	0.0397	0.0012
Gr 3+ infection	0.16	0.22	0.08
Gr 3+ infection/pt month	0.0069	0.0165	0.0003
Infection-related mortality	0.04	0.03	0.26

Real-world evidence on infection risk in multiple myeloma treated with BiTEs and CAR-T cells: a meta-analysis

Federico Spataro[1,2], Vanessa Desantis[1], Giuseppe Dicuonzo[2], Stefano Molica[3], Hermann Einsele[4], Angelo Vacca[2], Roberto Ria[2] and Antonio Giovanni Solimando[2*]

- 16 retrospective real-world studies
  - 2097 BITEs and 495 CAR T subjects
  - Included BCMA-directed CAR T constructs and BCMA and GPRC5D-directed BITEs
  - Median age 66 yrs
  - Mean of 6.1 prior lines of therapy

Exp Hematology & Oncology, 2026.

INFECTIOUS OUTCOMES

- Gr 3-4 infections: BITEs 0.26 (0.23-0.3) vs CAR-T 0.19 (0.12-0.27)

- For BITEs
  - Trend toward more infections with BCMA-directed therapy
  - Trend toward lower risk of infections associated with prior BCMA-directed therapy (likely selection bias)

WHAT ABOUT COMBINATION REGIMENS AND INCLUSION IN EARLIER LINES OF THERAPY?

- Efficacy results are generally impressive in NHL and MM
  - Cautious optimism in solid tumors
- Safety signals are generally manageable, but…
  - Expect more cytopenias, hypogammaglobulinemia and serious infections with combinations than expected with backbone chemo regimens
  - Predisposition to respiratory infections is a common theme
  - Most studies have had safety lead-ins

HOW DO WE MITIGATE RISKS OF INFECTION?

- **Pre-treatment screening**
  - Hep B (incl. HBcAb), HepC, HIV
- **Prophylaxis**
  - Antibacterial (+/-) if/when ANC < 500
  - Antifungal
    - Mold-active prophylaxis *if prolonged steroids, prolonged neutropenia or other immunosuppressives*
  - Antiviral
    - Acyclovir/valacyclovir – until appropriate for VZV vaccination
    - BITE pts should receive continuous prophylaxis
  - PJP
    - Until at least 6-12 mos post CAR T-cell infusion or completion of bispecific therapy
    - Look at CD4 count and subsequent therapies

N Tabbara, et al. ASH Education Program 2024
Z Shahid, et al. Transplant & Cell Therapy 2024

YES TO REVACCINATION, BUT WHAT AND WHEN?

- Seasonal Flu and COVID-19 are safe and generally somewhat effective after 3 months post infusion
- Do not depend on efficacy of any vaccines before 6 mos post therapy
- Standard post-transplant vaccine schedules similar to HSCT guidelines are appropriate
  - Live vaccines (e.g. MMR) generally not safe until at least 1 yr post infusion or completion of therapy
  - Consider immune reconstitution data in timing of any live vaccines

N Tabbara, et al. ASH Education Program 2024
Z Shahid, et al. Transplant & Cell Therapy 2024

MONITORING?

- CMV
  - PCR monitoring at least q 1-2 wks is appropriate if requiring ongoing steroids or h/o CMV reactivation
  - Pts presenting with later GI sx should have CMV PCR and full GI evaluation, as CMV enteritis can occur and can mimic late IEC GI toxicity
- EBV and HHV6
  - Rare, but check if unexplained problems
- Absolute CD4 and CD19 counts in blood
  - When to stop PJP prophylaxis—CD4 >200 is reasonable
  - When to vaccinate—monitor B cell numbers and immunoglobulin levels

N Tabbara, et al. ASH Education Program 2024
Z Shahid, et al. Transplant & Cell Therapy 2024

CONCLUSIONS

- CAR T-cell therapy and T-cell engagers are clearly a step forward in managing B-cell and plasma cell disorders as well as an increasing number of solid cancers
- Progress comes at a price…
  - Lots of factors predispose to infectious complications
  - Escalated risk in setting of CRS, ICANS, HS, IEC-EC, etc
- *The more complicated the post-treatment course, the more mindful we must be*
  - *Screening*
  - *Prophylaxis*
  - *Surveillance*
  - *Index of suspicion*

CONCLUSIONS

- Opportunistic pathogens such as CMV, PJP, fungi, etc remain threats to success of these novel and effective therapies
- Infection prophylaxis and monitoring are crucial during and after these therapies
- Please call us when unexplained problems—infections are common and may not be obvious


Bacteria
Microbe
Varicella
Vaccination
Contagious
Inflammation
Influenza
Calicivirus
Germ
Symptoms
Microbiology
Incubation
Infection
Immune
Candida
Fever
Pathogen
Antibiotics
Cytomegalovirus
Immunity
Disease
Disinfection
Antibiotic
Infection
Virus
Hygiene
Quarantine
Herpes
Antiviral
Vector
Host