# Bakteriyel ve Viral Enfeksiyonlarda İmmunoterapi

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HIV/AIDS Korunma ve Eğitim Derneği

# Sözün Özü

*Herkes dünyayı değiştirmeyi düşünür,*
*ama*
*kimse kendini değiştirmeyi düşünmez*

Lev Nikolayeviç Tolstoy (1828-1910)

# Niye İmmunoterapi?

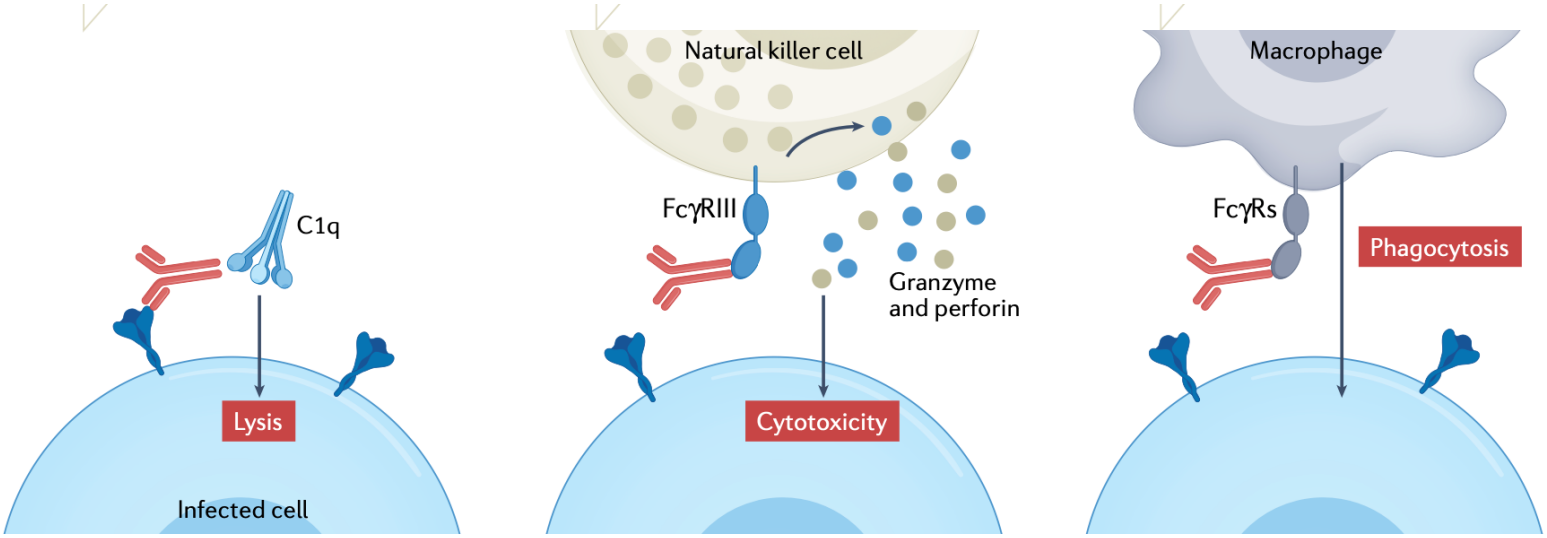
- Antibiyotik = antibiosis
  - İnsanın kibri
  - Daha çok antibiyotik – daha kötü bir dünya
- Pnömoni sonrası akciğer grafisinde iyileşme
  - Geç
- Bakteriyemi
  - Mikrobiyolojik küre rağmen halen daha uzun dönem mortalite

# Tarihte İlk Paralı Asker

- *10.000'ler*
- MÖ 401
- Cyrus, kardeşini (Pers kralı Artaxerxes II) tahttan indirmek için

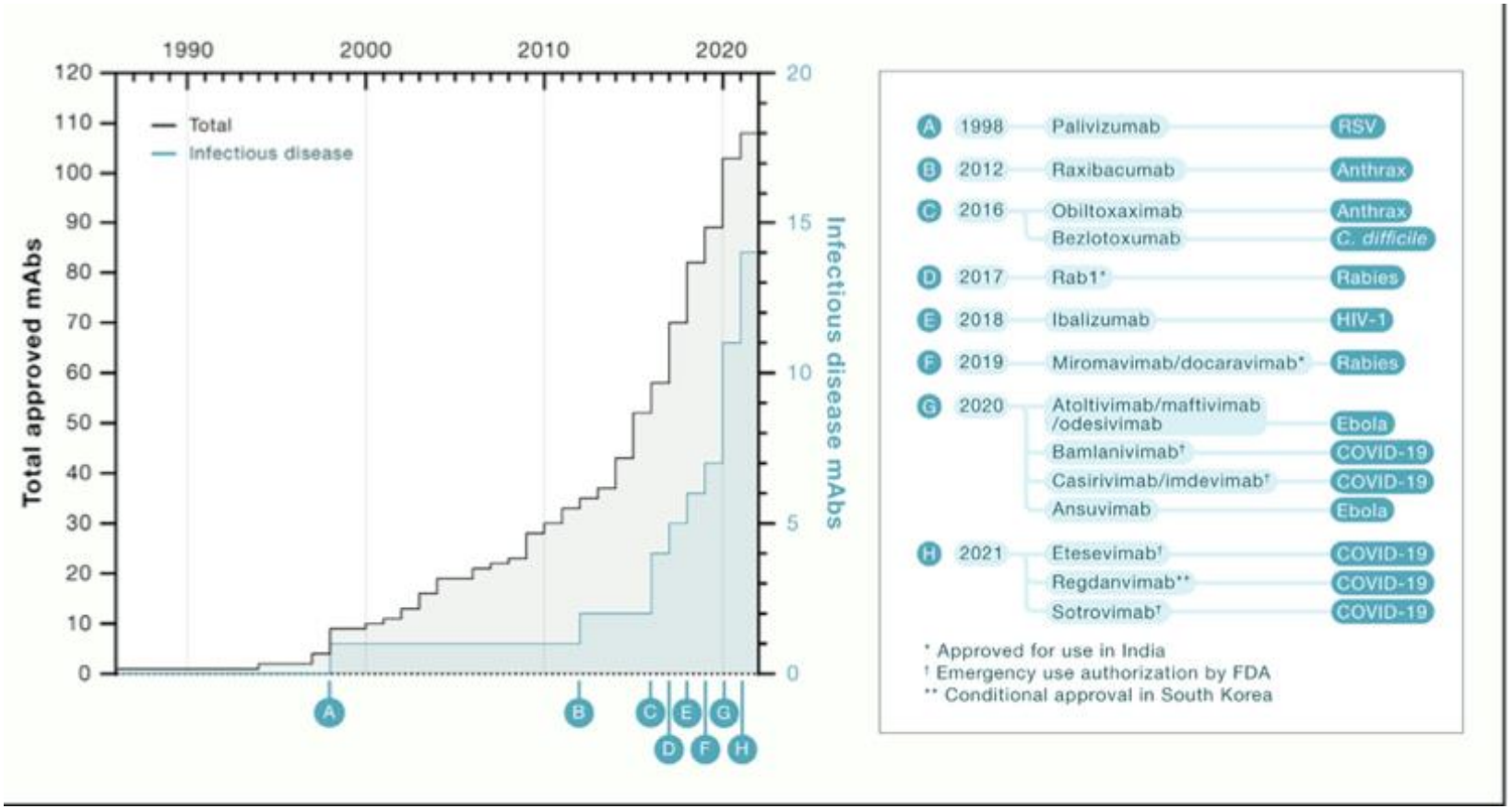
Anabasis Ksenophon *On Binler'in Dönüşü*, Çev. Ari Çokona, İş Bankası Kültür Yayınları, İstanbul, 2015, s. 7

# Antikor Etki Mekanizması



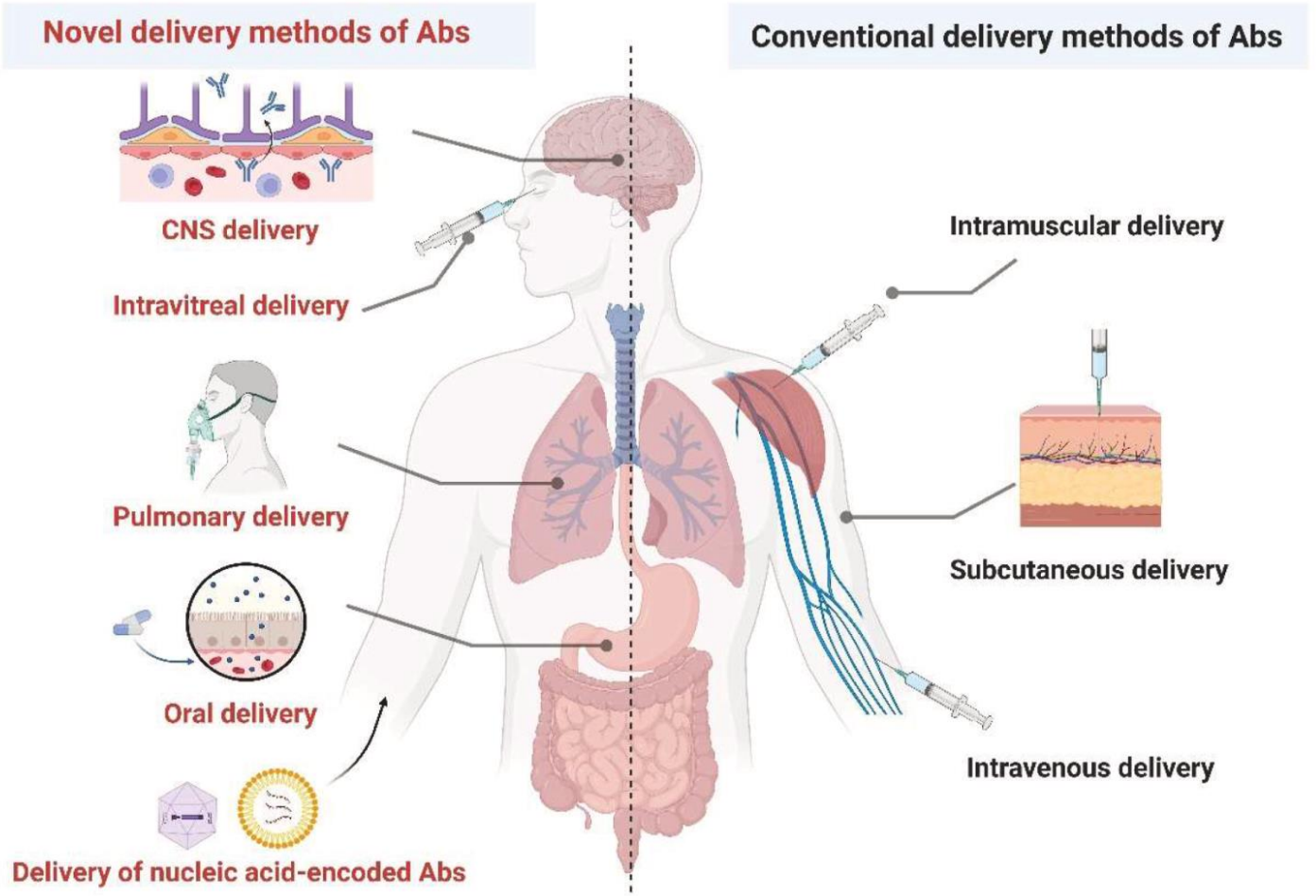

Pantaleo G etal 2022 *Antibodies to combat viral infections: development strategies and progress* Nat Rev Drug Discov

# Monoklonal Antikorlar: Tarihsel Gelişim



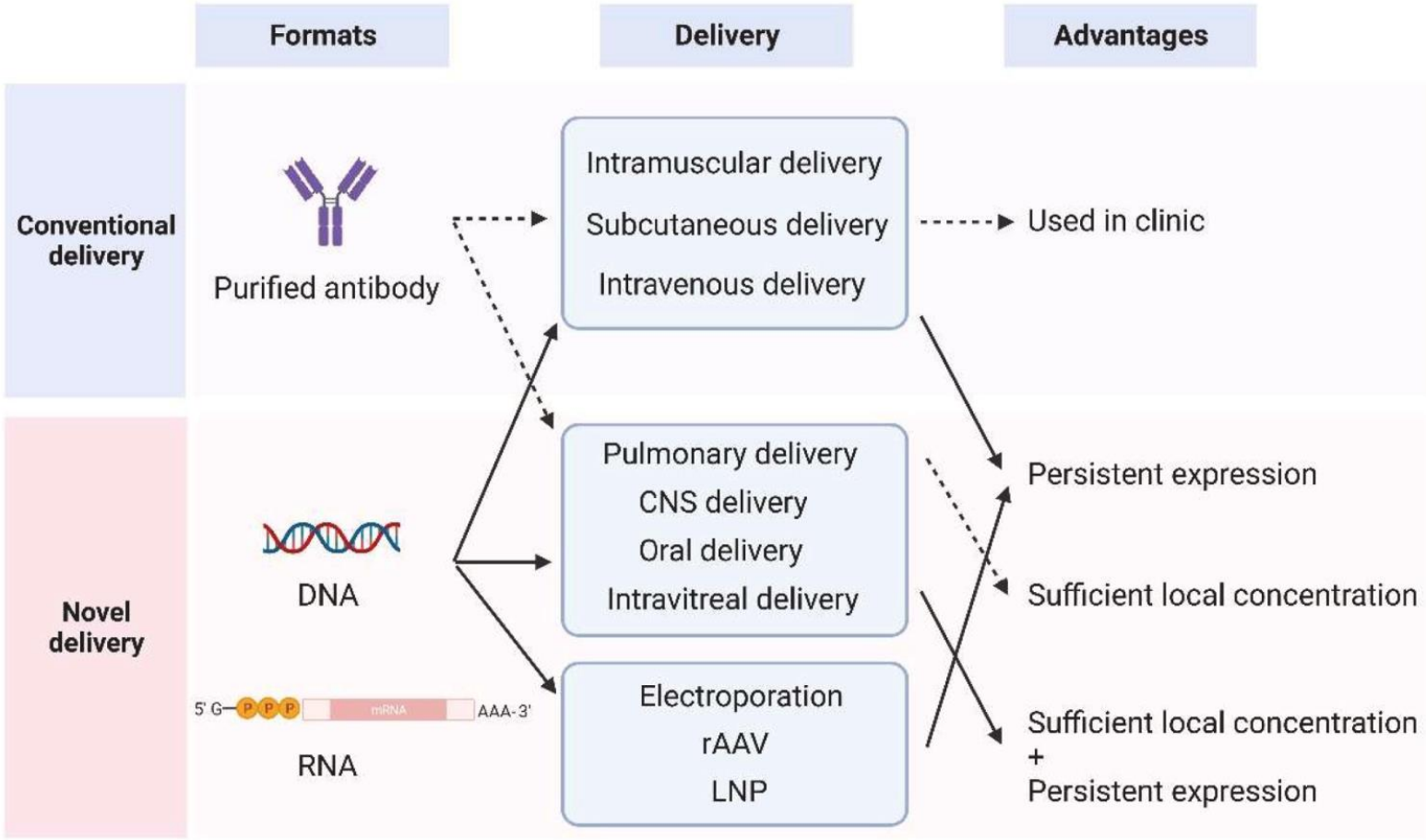

Corti D etal 2021 *Tackling COVID-19 with neutralizing monoclonal antibodies* Cell

# Monoklonal Antikorlar: Yenilikler



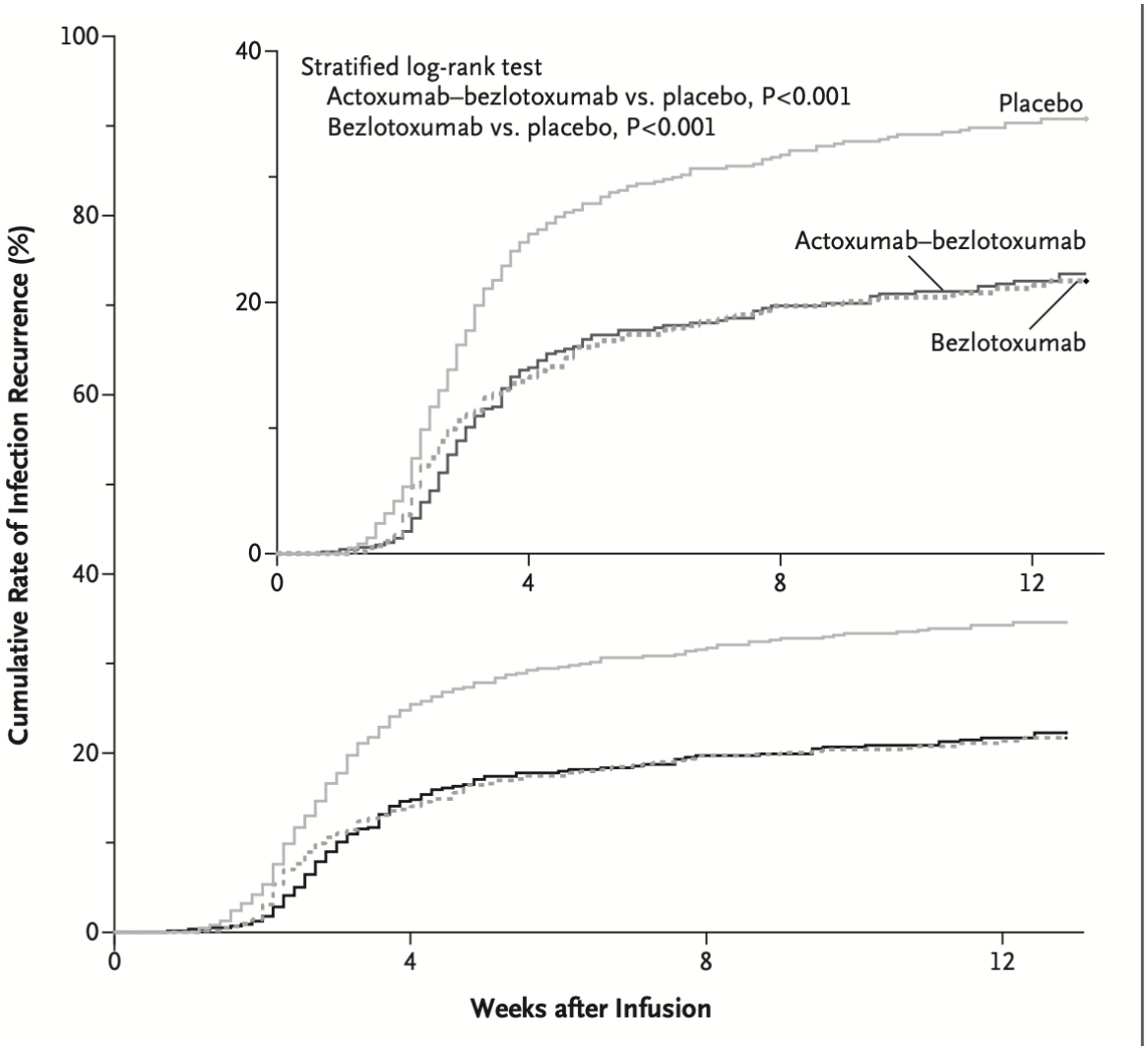

Sun W etal 2024 *Progress in novel delivery technologies to improve efficacy of therapeutic antibodies* Antiviral Res

# Monoklonal Antikorlar: Yenilikler



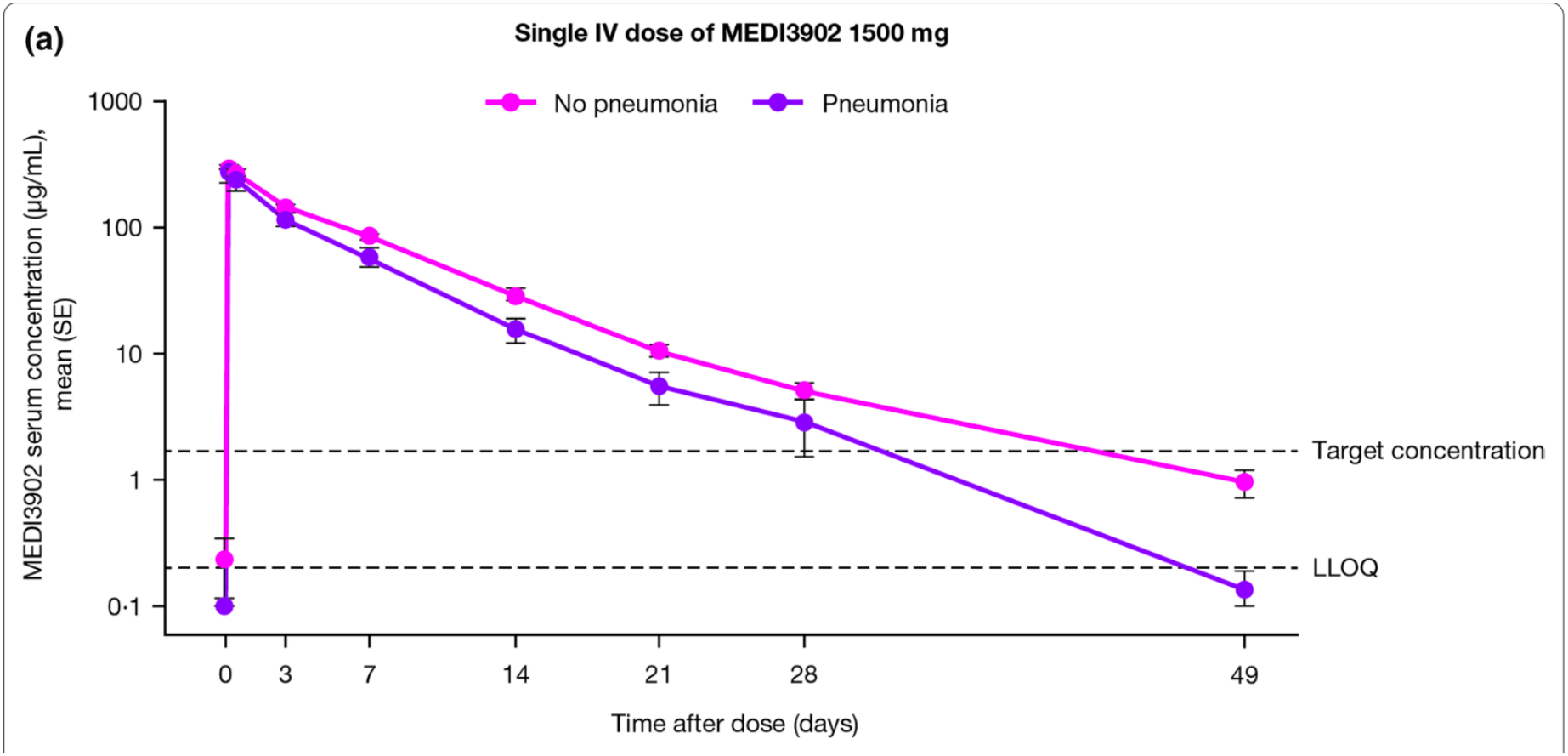

Sun W etal 2024 *Progress in novel delivery technologies to improve efficacy of therapeutic antibodies* Antiviral Res

# MAb:
# *C.difficile* Nüksünü Engeller mi?




Wilcox MH etal 2017 *Bezlotoxumab for Prevention of Recurrent Clostridium difficile Infection* N Engl J Med

# MAb Pseudomonas Kolonize Kişilerde Pnömoniyi engeller mi?




Chastre J etal 2022 *Safety, efficacy, and pharmacokinetics of gremubamab (MEDI3902), an anti-Pseudomonas aeruginosa bispecific human monoclonal antibody, in P. aeruginosa-colonised, mechanically ventilated intensive care unit patients: a randomised controlled trial.* Crit Care

# FDA Onayı Alan Antiviral Antikor Tedavileri

| Drug (brand name; company) | Target | Format | Technology | Indication | Year of FDA approval |
|---|---|---|---|---|---|
| Palivizumab (Synagis; MedImmune/AbbVie) | RSV | Humanized IgG1 | Hybridoma | Prevention of RSV infection | 1998 |
| Raxibacumab (ABthrax/ Anthrin; GlaxoSmithKline/ Human Genome Sciences) | *Bacillus anthrasis* PA | Human IgG1 | Human scFv phage display library | Anthrax infection | 2012 |
| Bezlotoxumab (Zinplava; Merck & Co.) | *Clostridioides difficile* enterotoxin B | Human IgG1 | Transgenic mice | Prevention of *C. difficile* infection recurrence | 2016 |
| Obiltoxaximab (Anthim; Elusys Therapeutics) | *B. anthrasis* PA | Chimeric IgG1 | Hybridoma | Prevention of inhalational anthrax | 2016 |
| Ibalizumab[a] (Trogarzo; TaiMed Biologics) | CD4 receptor (domain 2) | Humanized IgG4 | Mice | Treatment of HIV-1 infection | 2018 |
| Ansuvimab (Ebanga; MedImmune/Ridgeback Biotherapeutics) | Ebola glycoprotein | Human IgG1 | Human | Prevention and treatment of Ebola infection | 2020 |
| Atoltivimab, maftivimab and odesivimab (Inmazeb; Regeneron Pharmaceuticals) | Ebola glycoprotein | Human IgG1 | Transgenic mice | Prevention and treatment of Ebola infection | 2020 |

Pantaleo G etal 2022 *Antibodies to combat viral infections: development strategies and progress* Nat Rev Drug Discov

# MAb Ufukta Neler Var?

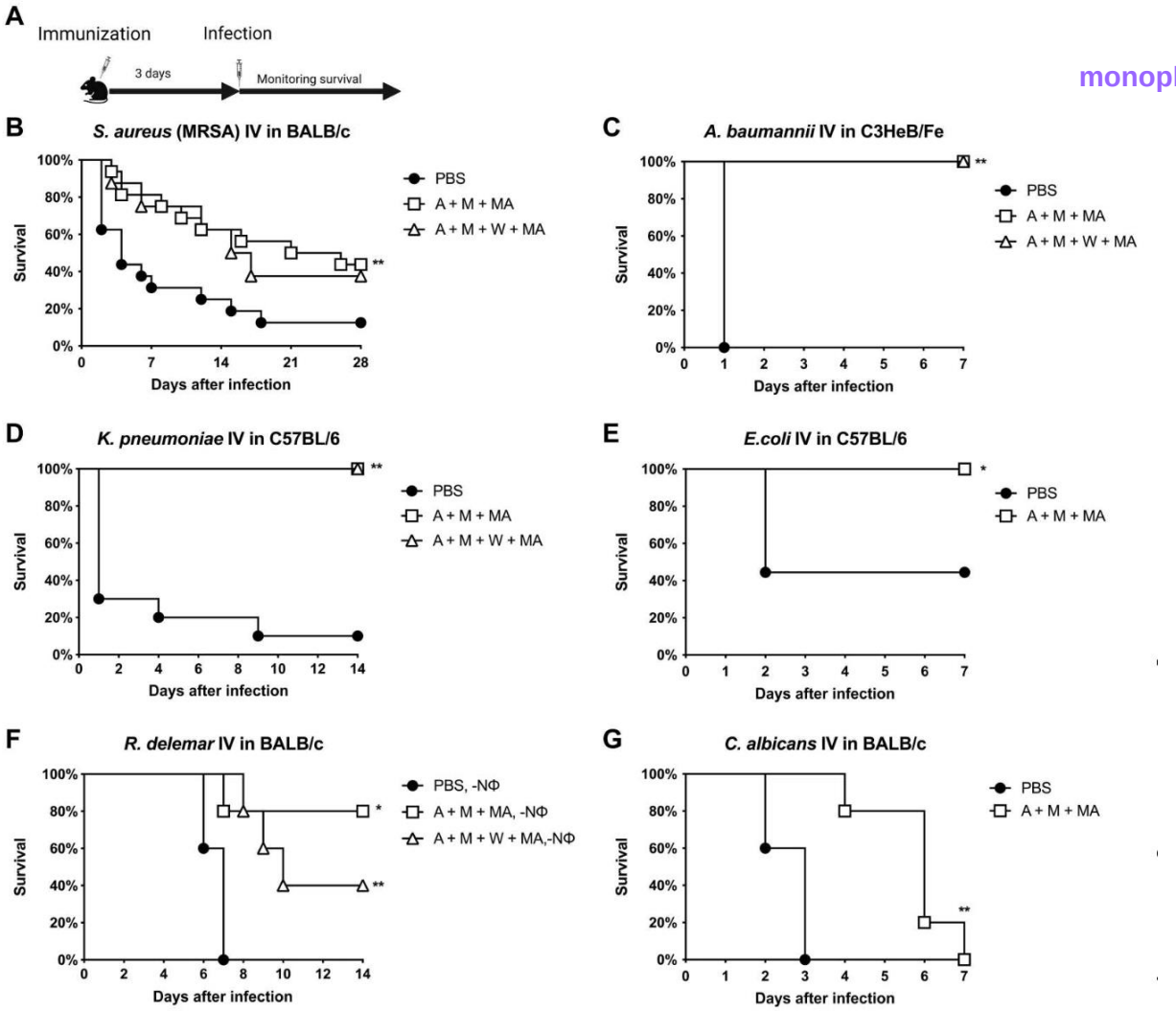
| Bacterial species | Drug | Type | Target | Phase | Clinical trial ID |
|---|---|---|---|---|---|
| Bacillus anthracis | Obiltoxaximab | Humanized IgG1 | Protective antigen (toxin) | IV | NCT03088111 |
| | Thravixa | Human IgG1 | | I | NCT01202695 |
| | Valortim | Human IgG1 | | I | NCT00964561 |
| | Raxibacumab | Human IgG1 | | IV | NCT02016963 |
| Clostridium botulinum | XOMA 3ab | Mix of 3 humanized IgG1 | Botulinum neurotoxin type B (toxin) | I | NCT01357213 |
| | NTM-1632 | Mix of 3 humanized IgG1 | | I | NCT02779140 |
| Clostridium difficile | Actoxumab | Human IgG1 | *C. difficile* toxin A (toxin) | III | NCT01241552 |
| | Bezlotoxumab | Human IgG1 | *C. difficile* toxin B (toxin) | III | NCT05304715 |
| Escherichia coli | Edobacumab | Mouse IgM | LPS lipid A | III | / |
| | Nebacumab | Human IgM | | III | / |
| | MAB-T88 | Human IgM | | III | / |
| STEC* | Shiga toxin MAbs, cαStx1 & 2 | Mix of 2 humanized IgG1 | *E. coli* Stx1 & Stx2 | II | NCT01252199 |
| Pseudomonas aeruginosa | Aerucin | Human IgG1 | *P. aeruginosa* alginate | II | NCT02486770 |
| | Panobacumab | Human IgM | *P. aeruginosa* LPS O11 | II | NCT00851435 |
| | KB001 | Human PEGylated Fab | *P. aeruginosa* PcrV | II | NCT01695343 |
| | MEDI3902 | Bispecific human IgG1 | *P. aeruginosa* PcrV and Psl | II | NCT02255760 |
| Staphylococcus aureus | Salvecin, AR-301 | Human IgG1 | *S. aureus* alpha-hemolysin | II | NCT03816956 |
| | ASN100 | Mix of 2 human IgG1 | Bi-component toxins & alpha-hemolysin | II | NCT02940626 |
| | Tefibazumab | Humanized IgG1 | S. aureus ClfA | II | NCT00198289 |
| | MEDI4893 | Human IgG1 modified | *S. aureus* alpha-hemolysin | II | NCT02296320 |
| | 514G3 | Human IgG3 | *S. aureus* protein A | II | NCT02357966 |
| | Pagibaximab | Chimeric IgG1 | Lipoteichoic acid | II | NCT00646399 |
| | Aurograb | scFv | GrfA (lipoprotein) | III | NCT00217841 |
| Multiple species | F598 | Human IgG1 | Poly-N-acetylglucosamine | II | NCT03222401 |

*STEC, Shiga toxin-producing Escherichia coli.

Troisi, M etal 2022 *A new dawn for monoclonal antibodies against antimicrobial resistant bacteria* Frontiers in Microbiology

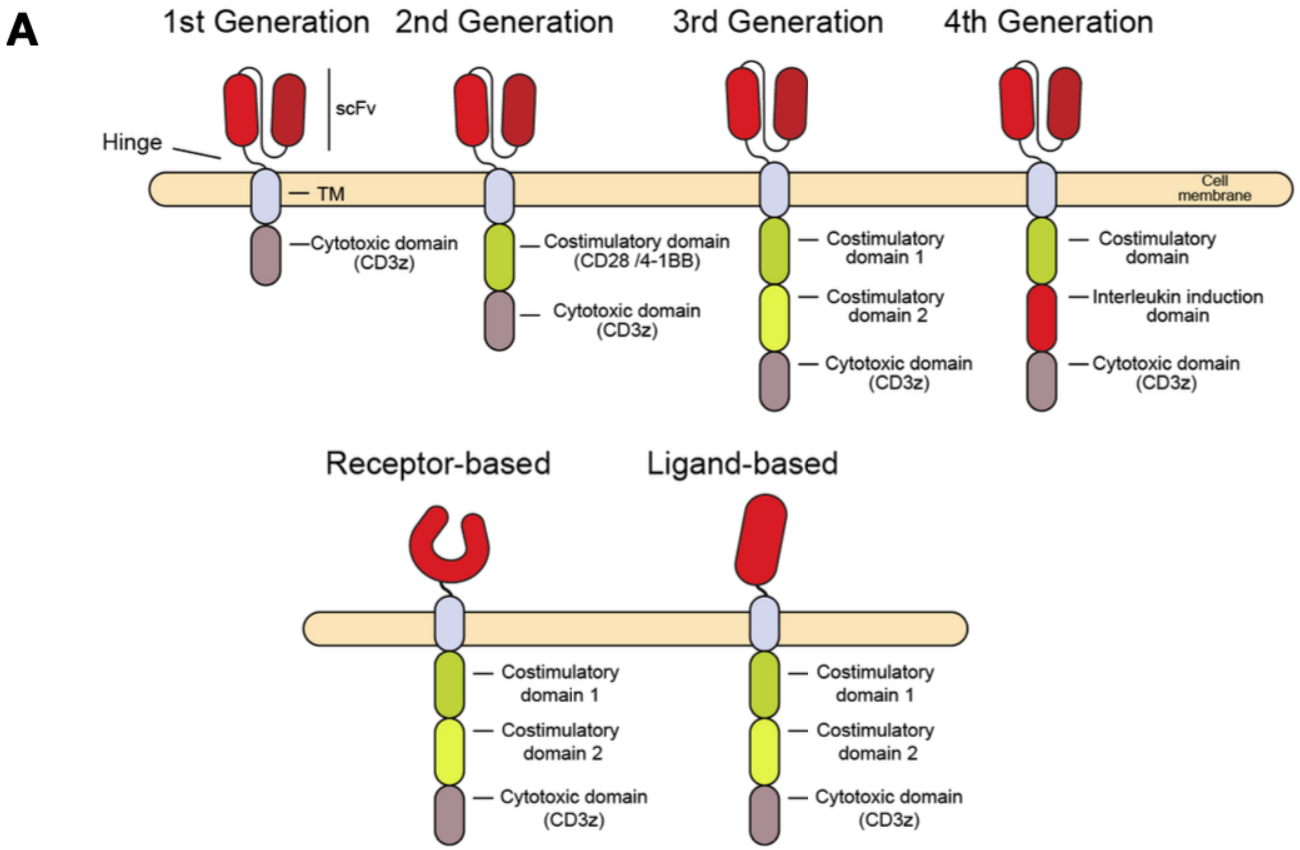
# Eğitilmiş İmmünite

Al(OH)3,
monophosphoryl lipid A (MPL),
glucan(WGP)
mannan




Yan J etal 2023 *A protein-free vaccine stimulates innate immunity and protects against nosocomial pathogens*. Sci Transl Med

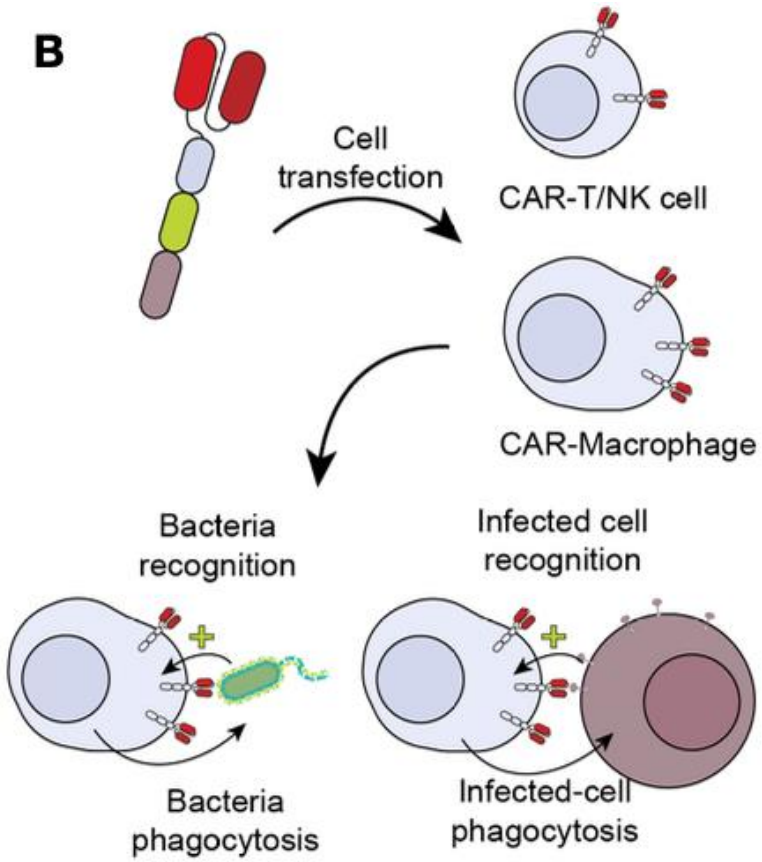
# Kimerik Antijen Reseptörü



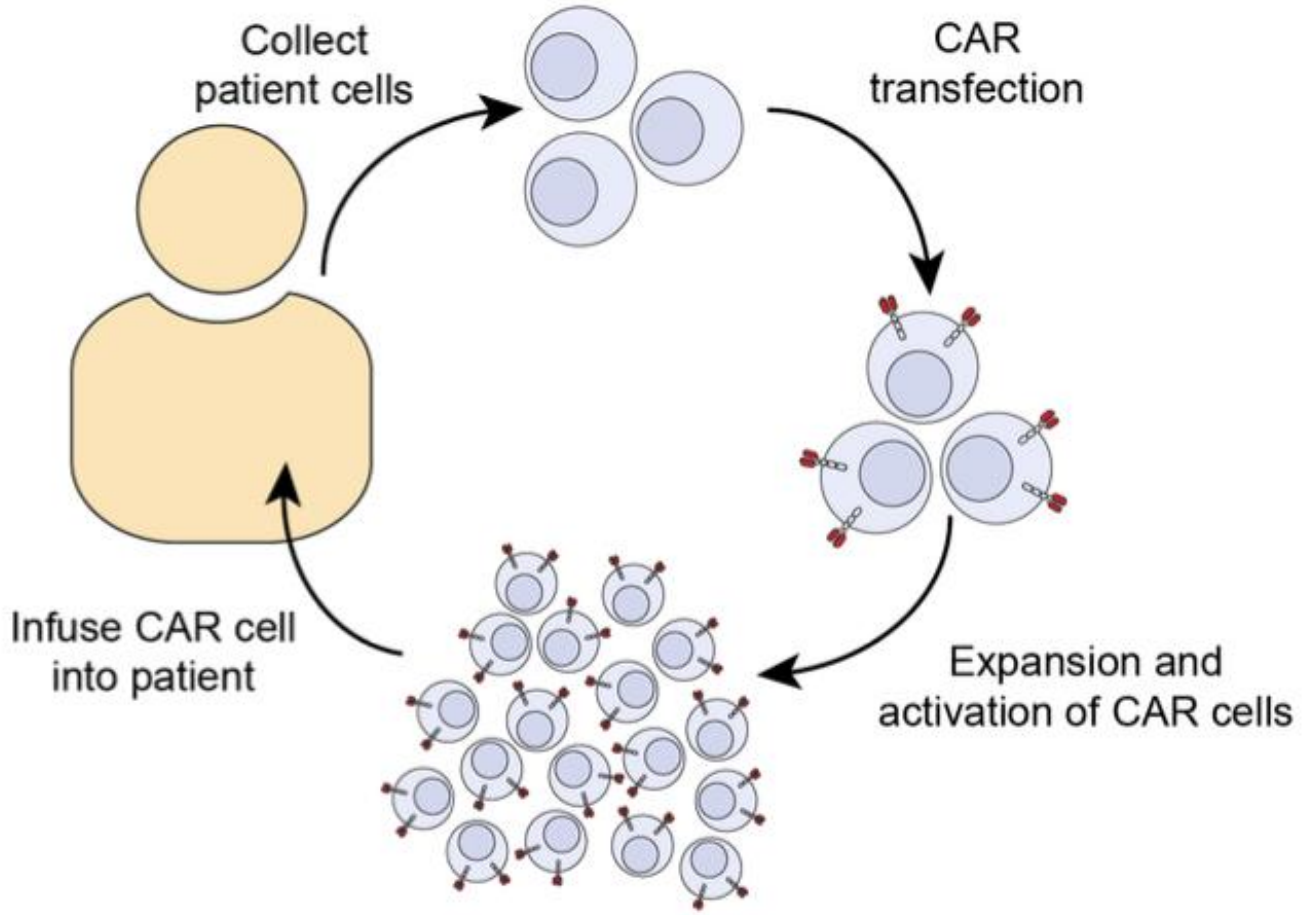

Morte-Romea E etal 2024 *CAR Immunotherapy for the treatment of infectious diseases: a systematic review* Front Immunol

# CAR Hücreler

- CAR-T
- CAR-NK
- CAR-M

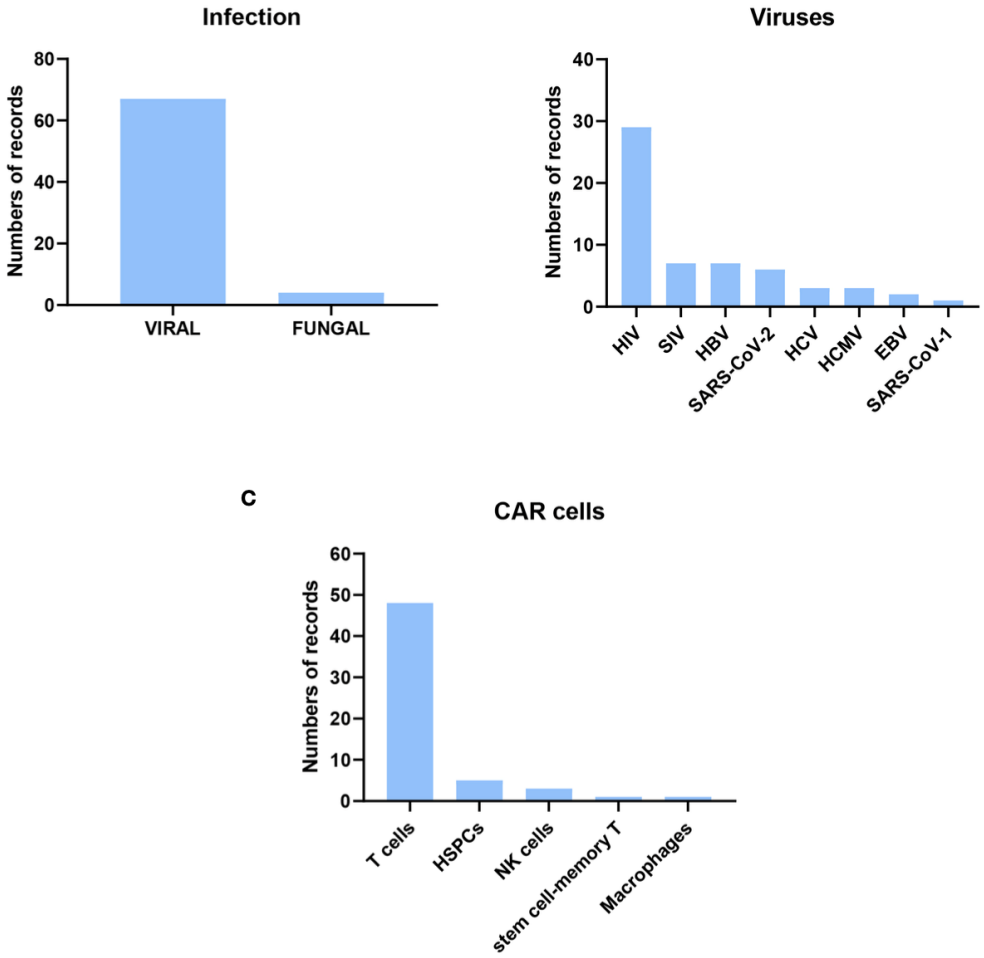


# CAR-Hücre Geliştirme



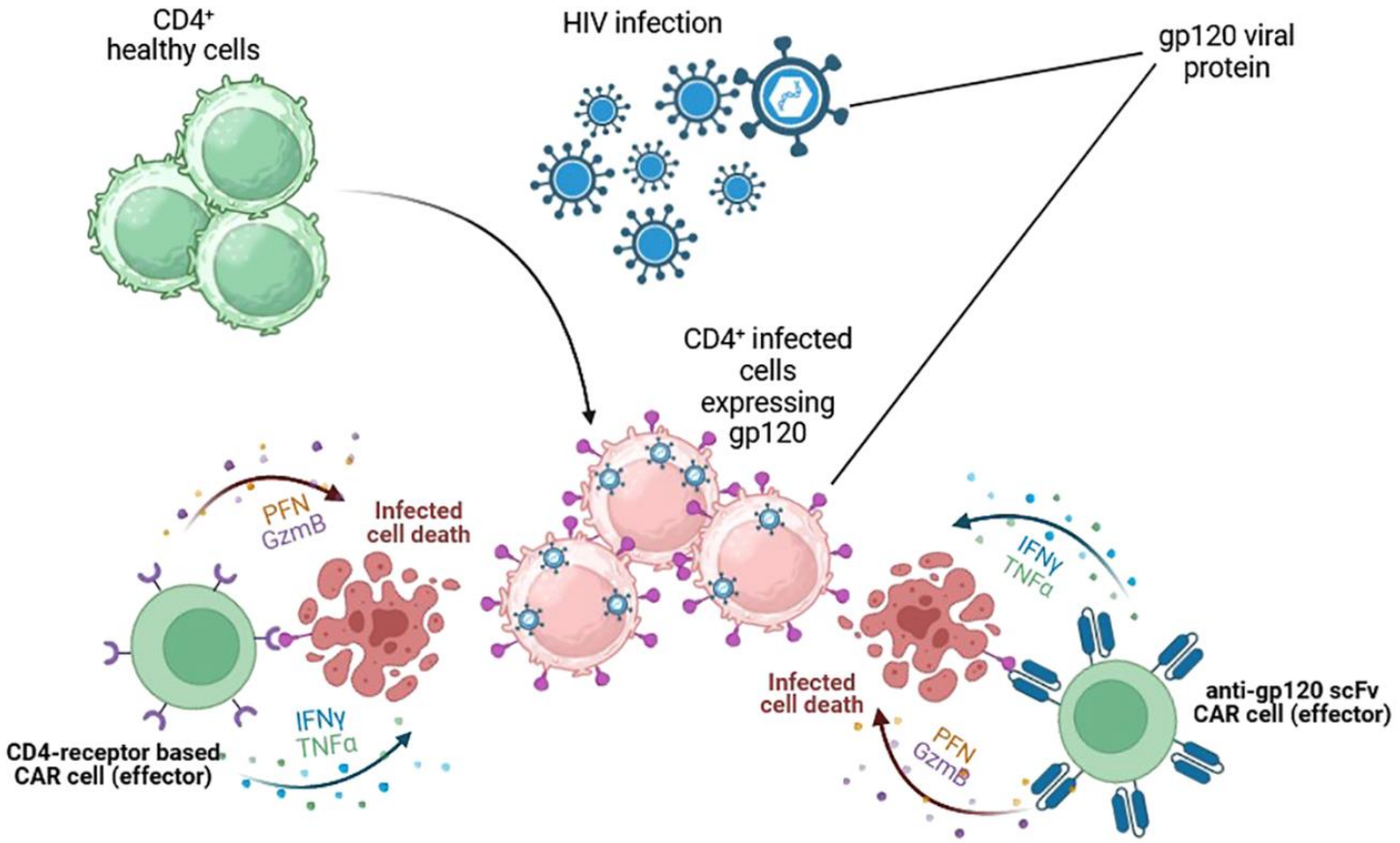

Morte-Romea E etal 2024 *CAR Immunotherapy for the treatment of infectious diseases: a systematic review* Front Immunol

# CAR-Hücre Kullanım



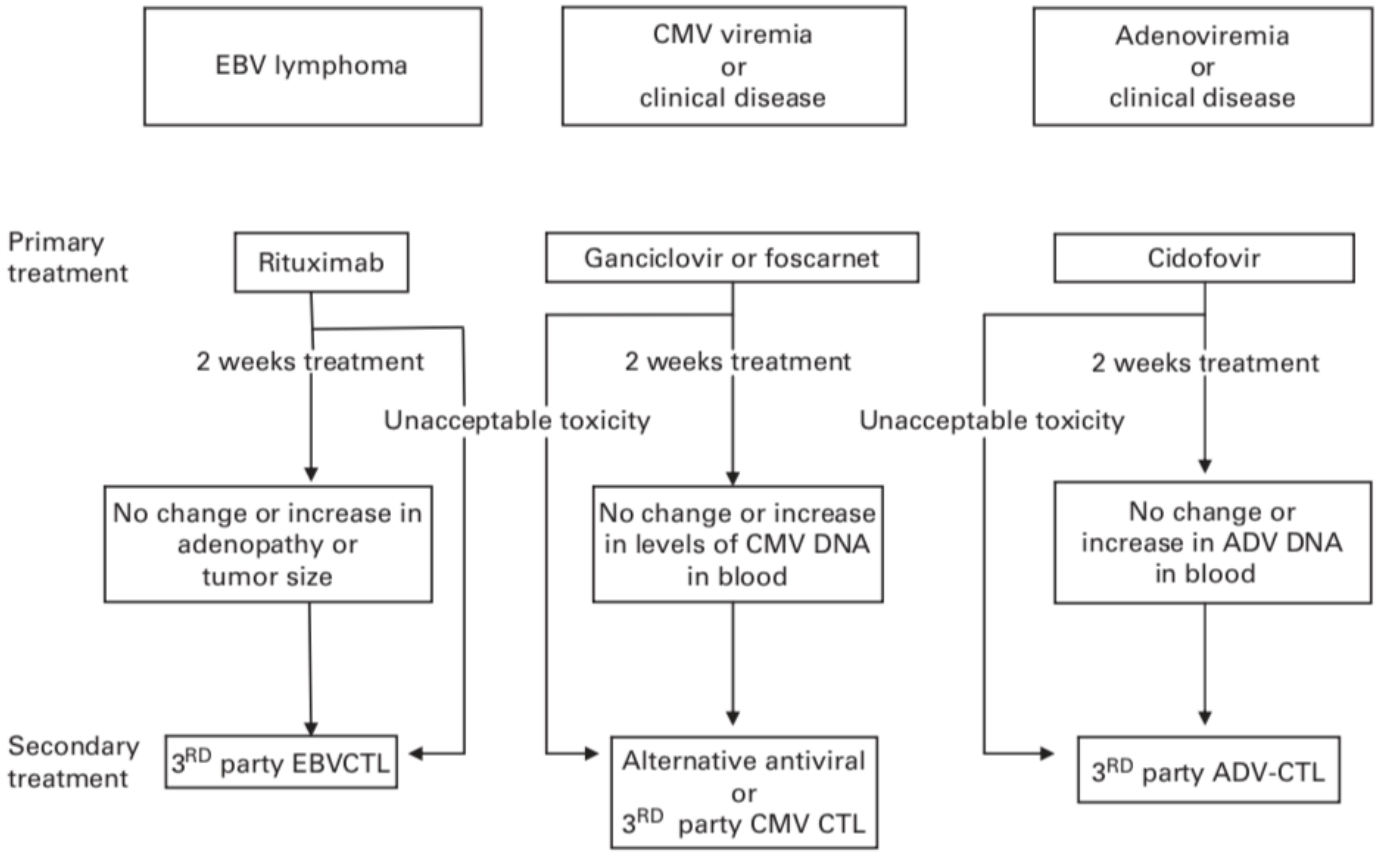

Morte-Romea E etal 2024 *CAR Immunotherapy for the treatment of infectious diseases: a systematic review* Front Immunol

# CAR-Hücre HIV




Morte-Romea E etal 2024 *CAR Immunotherapy for the treatment of infectious diseases: a systematic review* Front Immunol

# Virüs Spesifik T Hücre




Reilly RJ etal 2016 *Virus-specific T-cell banks for 'off the shelf ' adoptive therapy of refractory infections* Bone Marrow Transpl

# Virüs Spesifik T Hücre Hazırlanması

- Viral peptidler nasıl belirleniyor

  Viral proteinler => peptidlere ayrılma => APC sunumu

  Her HLA sadece belli peptidleri sunar

  HLA'ya uygun peptid

  Her hasta, her donör ve her virüs için değişken => belirlenmiş olan peptid havuzları

AdV5 Hexon
CMV pp65
EBV LMP2A
EBV EBNA-1
BKV VP1

Her biri 11 amino asitten oluşan dizilerdir.

Etiketleme

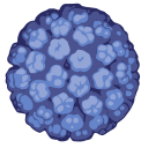
Paketleme

Transfer

Uygulama

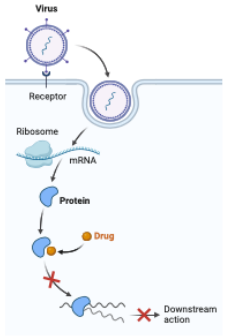
Kriyoprezervasyon


# PML Tedavi



## Human Polyomavirus (HPyV) Treatment Options

### Antivirals

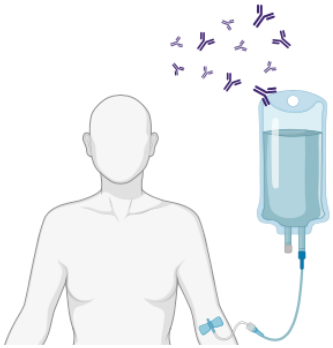



Drugs and drug-candidates have limited efficacy on the course of polyomavirus disease and their usage had limited effect on the disease outcome.

### Immunosuppression reduction

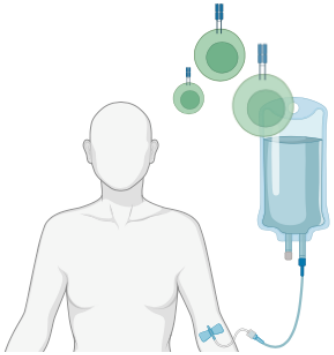
An approach to managing both BKPyVHC and BKPyVAN is the reduction of immunosuppression in transplant recipients.

### IVIG



Intravenous immunoglobulin (IVIG), sourced from pooled plasma of numerous donors, harbors limited amount of neutralizing antibodies against BKPyV

### VST



Virus specific T cells (VST) may be a promising and safe option for the treatment of devastating polyomavirus disease in immunocompromised patients.

Alkan B, underreview

# Polyoma Virüs Hastalığı Tedavide MVST

85 hemorrhagic cystitis, 27 BKPyV viremia, 2 patients with BKPyV nephritis, 14 hemorrhagic cystitis and BKPyV viremia, and 32 PML treated with virus specific T cells

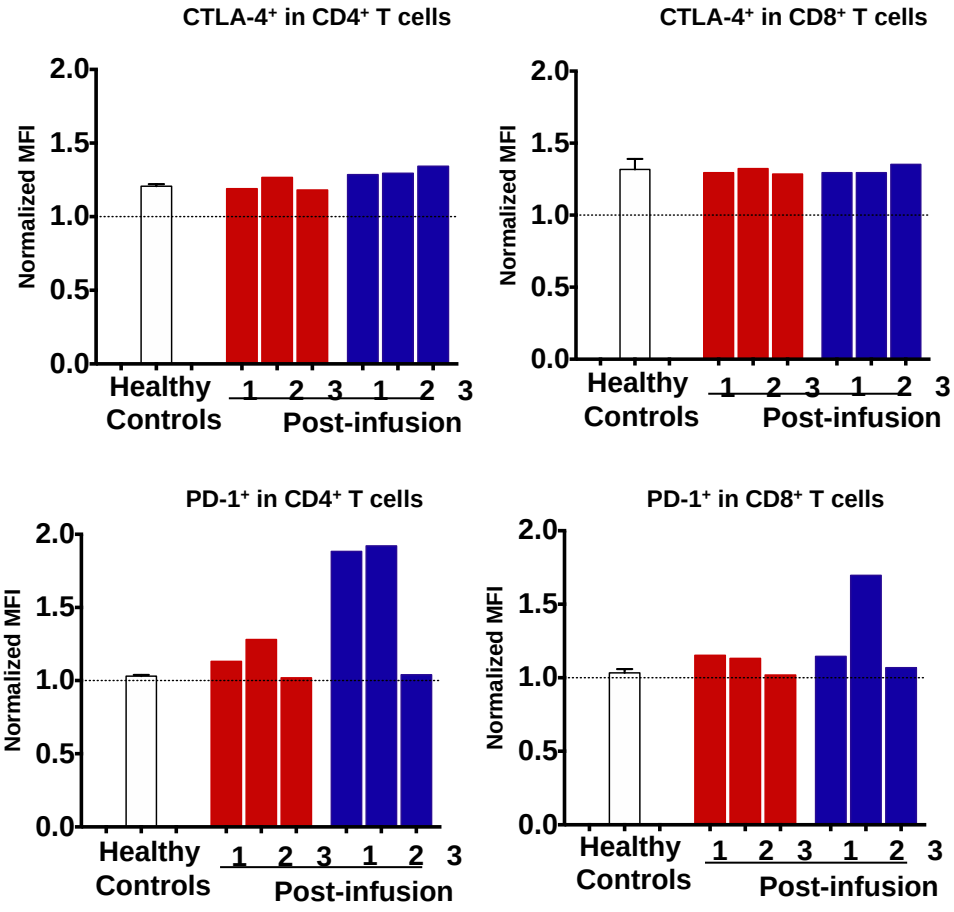
Here, we reviewed the case reports and case studies published on HPyV targeted T cell therapies

| | BKPyV n = 128 | JCPyV n = 32 |
|---|---|---|
| Complete Response | 73 | 9 |
| Partial Response | 25 | 8 |
| No Response | 20 | 15 |

**Overall response rate:** 82% complete, 33% partial, 35% non-response. (Not available=10)

Alkan B, underreview

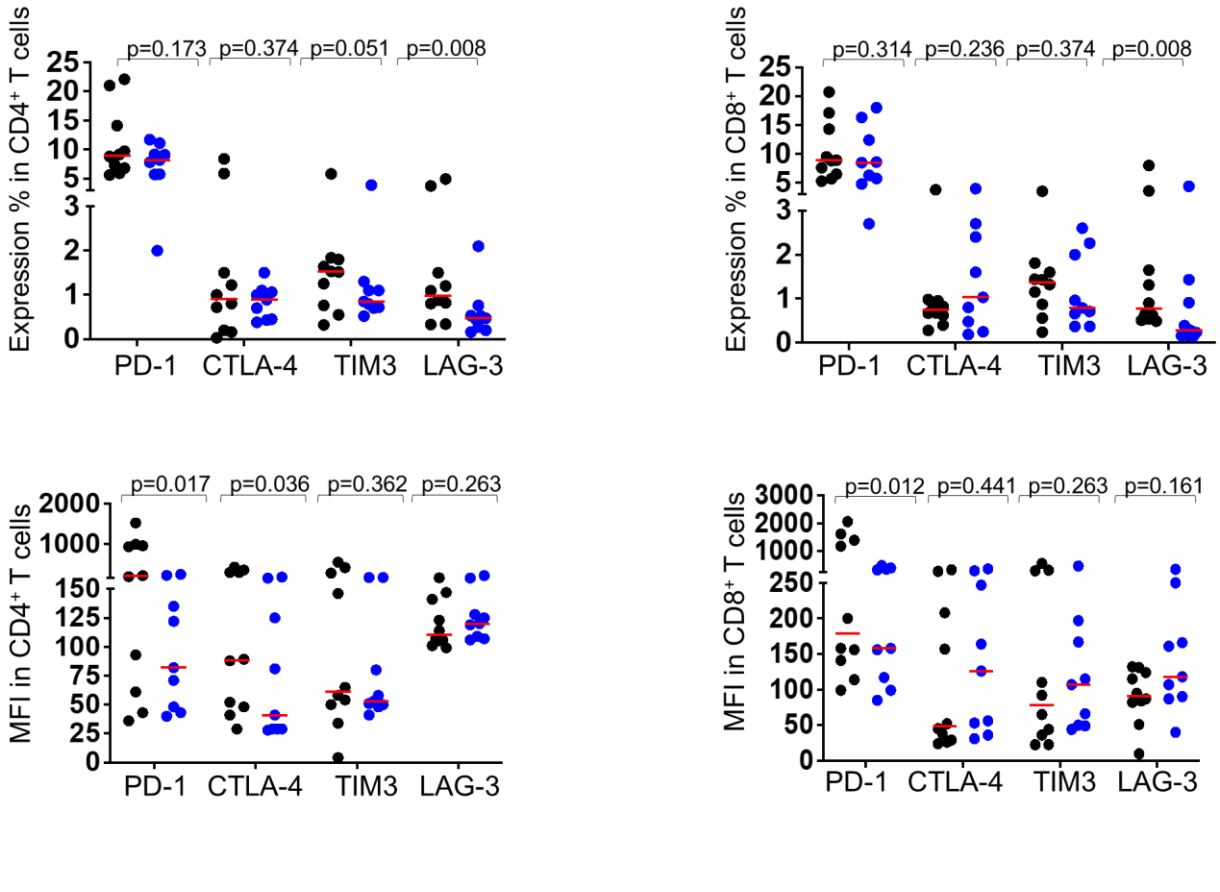
# CD4⁺ ve CD8⁺ T hücrelerde CTLA-4




İnkaya AC, Esendağlı G, Göçmen R, Tuncer A unpublished

# CD4:CD8 Oranından Ötesi T Hücre Yorulması

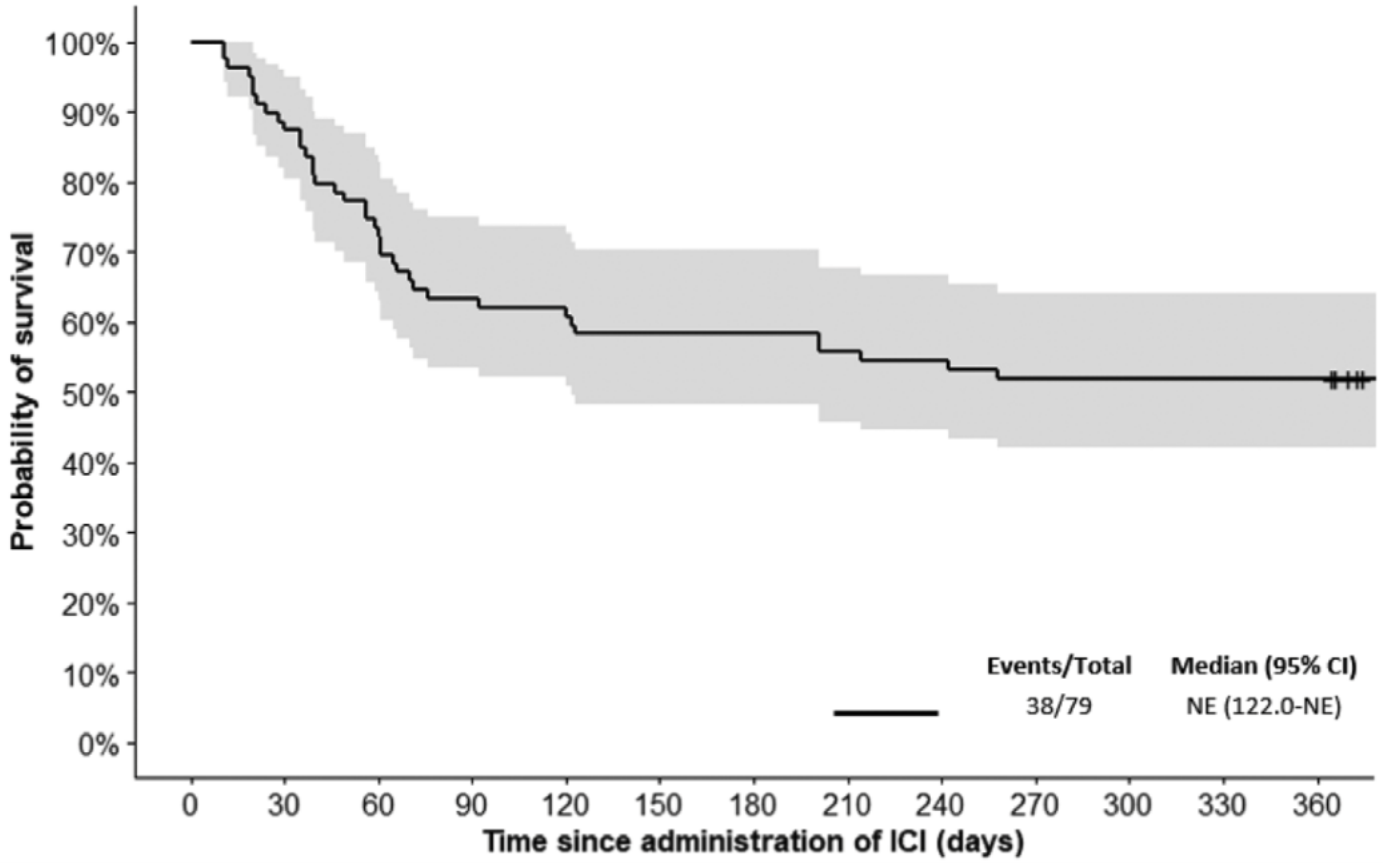
**GROUP A**
**ART-NAÏVE PLWH**




*All p-values were calculated using Wicoxon Signed-Rank test.

Özcan BB etal *Antiretroviral therapy causes a reduction in T-cell exhaustion, which is preserved after switching to a new therapy regimen* EACS2021

# PML: İmmün Checkpoint İnhibitörleri




Boumaza X etal 2023 *Immunotherapy for PML Study Group. Progressive Multifocal Leukoencephalopathy Treated by Immune Checkpoint Inhibitors* Ann Neurol

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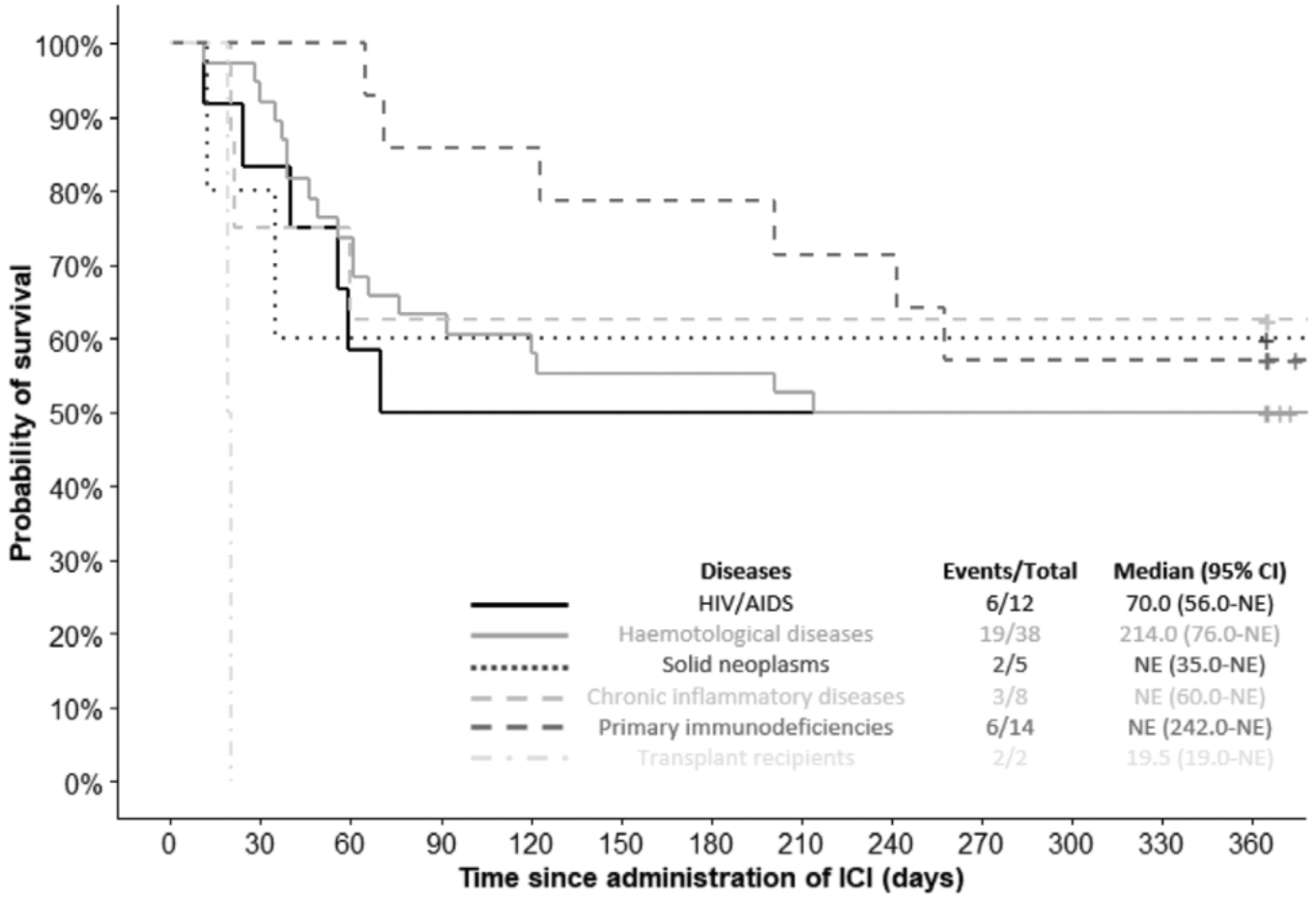
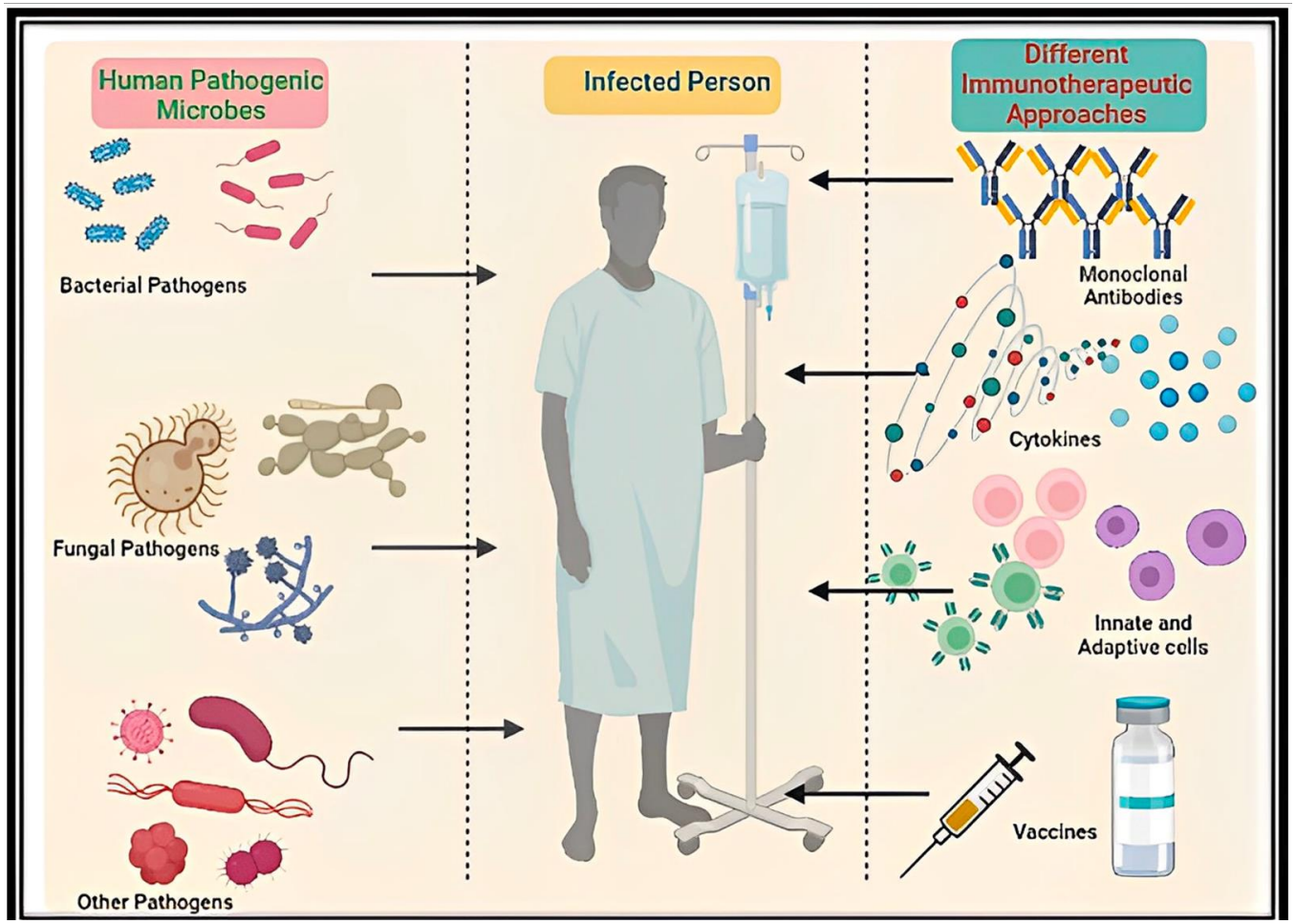



Boumaza X etal 2023 *Immunotherapy for PML Study Group. Progressive Multifocal Leukoencephalopathy Treated by Immune Checkpoint Inhibitors* Ann Neurol

# İmmünoterapi




Qadri H etal 2023 *Immunotherapies against human bacterial and fungal infectious diseases: A review.* Front Med (Lausanne)