TARGETED AND IMMUNOTHERAPY FOR CANCER AND INFECTION RISK

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AGENDA

- Targeted therapies for Cancer
- Immunotherapies for Cancer
- General toxicities of targeted and immunotherapies for Cancer
- Infection Risks in targeted and immunotherapies for Cancer
- Immunotherapies in infection

Case

56-year-old man presented with two months of progressive fatigue; found to have WBC 83.5 with 65% blasts, AML with normal cytogenetics

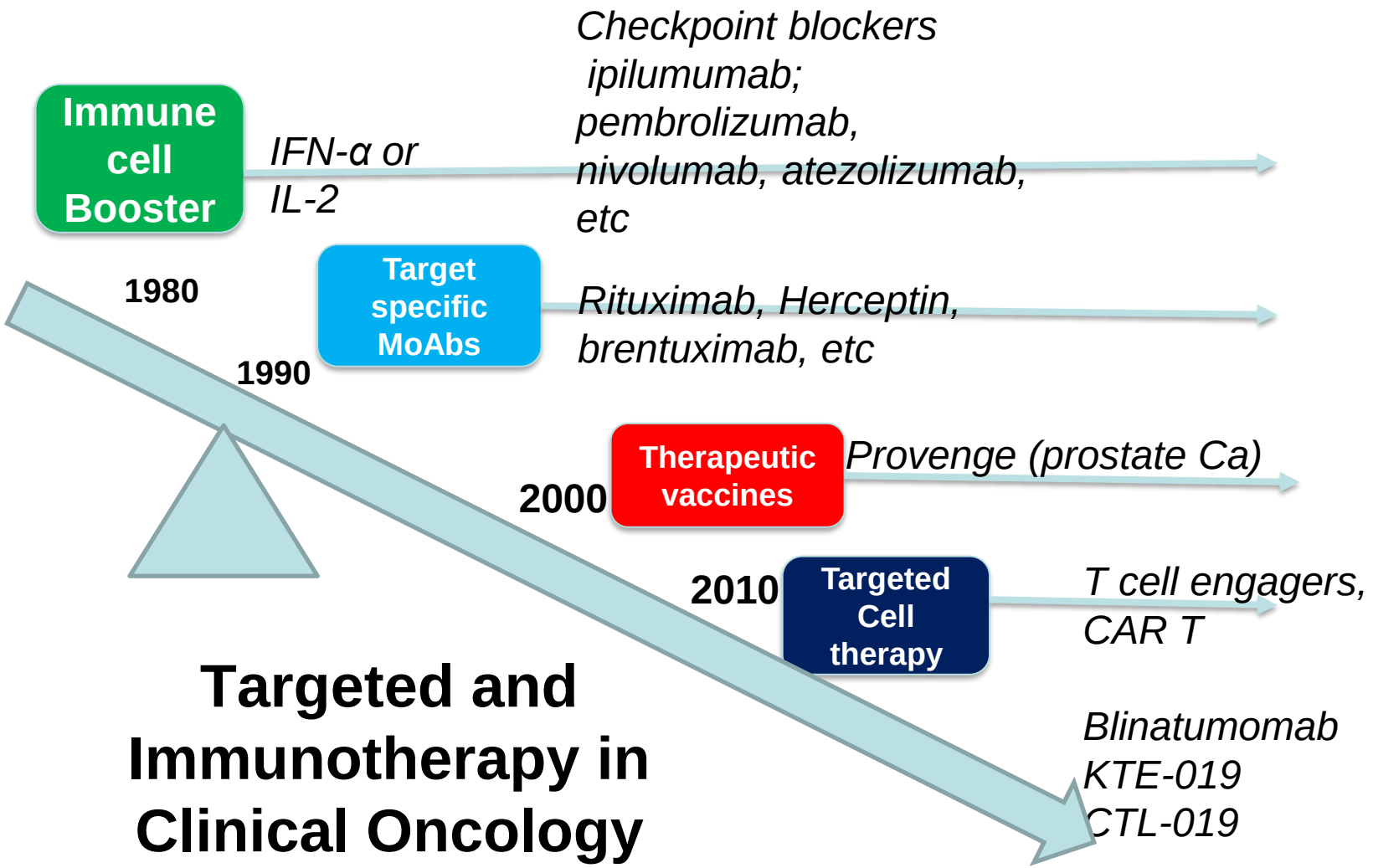
- 7+3 induction with cytarabine and daunorubicin, with levofloxacin, posaconazole and acyclovir as antimicrobial prophylaxis →remission
- At follow up 9 months later, the patient's laboratory tests showed pancytopenia.
- Bone marrow biopsy: 60% cellular marrow with 80% myeloid blasts.
- The next- generation sequencing hematologic malignancy panel showed NPM1-W290Sfs*10 (variant allele frequency, 25%) and IDH2-R140Q (variant allele frequency, 43%).
- Enasidenib was initiated
- Infectious Diseases was consulted to determine antimicrobial prophylaxis

Therapies for cancer

- Surgery, radiation, systemic anticancer therapy alone and in combination for many years
- Needed targeted, innovative therapy to try to decrease the off-target effects of chemotherapy on normally replicating cells

--targeted therapies and cancer immunotherapies are two novel treatment modalities that have recently begun to enter the hematology and oncology clinic to address these issues.

--often used in heavily pretreated patients and combine with other anticancer treatments



Courtesy of Dr. E. Budde, COH

What is Targeted Therapy in Cancer?

Targeted therapy

- **Small molecule drugs or monoclonal antibodies**

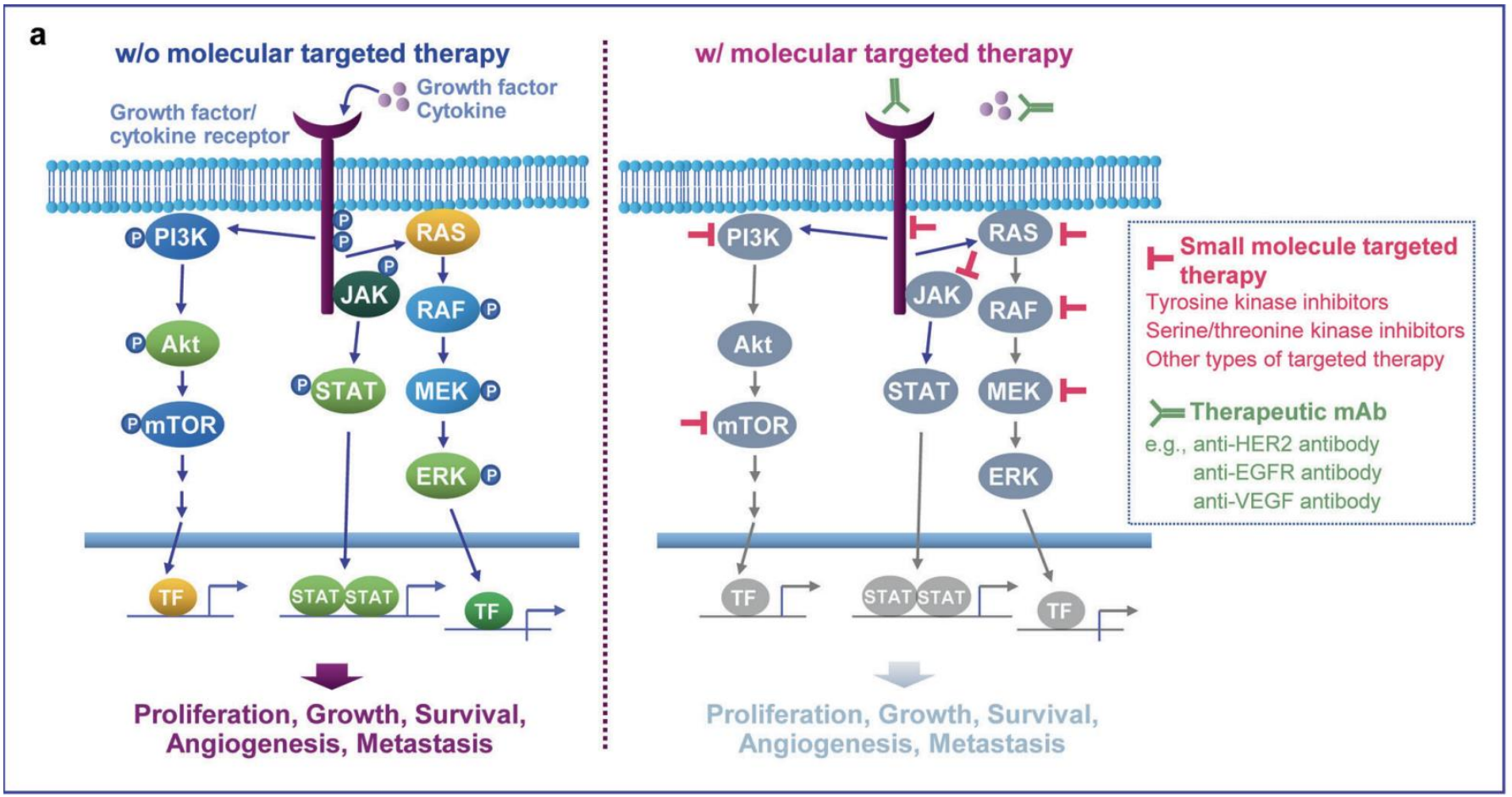
- Target specific genes and proteins. Only available for patients with tumors that have targetable driver mutations or aberrations, these agents may **interrupt growth of cancer cells by impairing signal transduction pathways involved in growth, proliferation or help the immune system destroy cells, deliver toxins, induce apoptosis**, etc.

- When based on genetic profiling of individual and tumor are the foundation of **precision medicine**

Also hampered by side effects/toxicities associated with cross-reactivity with normal cells and drug resistance

Ke et al. Frontiers in Laboratory Medicine 1 (2017) 69-75

Targeted therapies



Min and Lee, Exp and Molec Med (2022 54: 1670-1694)

Targeted therapy timeline (partial list)

From: Min and Lee, Experimental and Molecular Medicine, 2022

Targeted therapies for cancer

Where is the target normally expressed and what does inhibiting it do to normal cellular function, particularly, in the case of infectious diseases cells of the innate and adaptive immune system?

1. Trastuzumab – anti-HER2 monoclonal ab (treatment in HER-2+ breast CA)

2. Imatinib – small molecule tyrosine kinase inhibitor targeting BCR-ABL, an aberrantly activated ABL kinase that leads to production of an enzyme that causes normal myeloid cells to start behaving like cancer cells (treatment in PH+ CML)

3. Enasidenib - Mutations in isocitrate dehydrogenase IDH 1 or 2are found in 6-19% of patients with acute myeloid leukemia (AML). Mutated IDH alters normal DNA methylation and impairs differentiation. Enasidenib is a small molecule inhibitor of IDH.

4. Ibrutinib – Used in B cell malignancies such as CLL. cellular target of ibrutinib is Bruton tyrosine kinase (BTK) which is critical for B-cell proliferation and is important in macrophage function

Infection Risk in Targeted Therapies

- Evidence for an increased association between some agents and susceptibility to infection, whereas for others, clear correlation with infectious risk is lacking

- Complicating the picture, many agents are being used for a wide array of disease processes, often in combinations and in the setting of numerous prior chemotherapy regimens and relapse, various comorbidities

- In general, for infection risk, consider the **ON TARGET/OFF TUMOR EFFECTS (what cells are target expressed on)?**

Review article:

Davis et al Infections with Targeted Immunotherapies, Clin Micro Rev, 33; 3, pp 1-117

Case 2 -

- 77 y.o. male with stage IVB, double hit DLBCL with CNS, skin and lung involvement, relapsed after first clinical remission, received 3 cycles of R-EPOCH, 2 cycles of R-CHOP, IT methotrexate x7, and whole brain radiation therapy, MRI and PET scans in 2/2023 revealed refractory disease, who was admitted to undergo Breyanzi CAR-T cell therapy on 3/29/23 after fludarabine/cyclophosphamide lymphoid depletion

- Patient started to develop fevers on 3/27/23, with worsening fever curve worsened 4/2/23. His mental status started to deteriorate in late March, and by 4/2/23, patient developed more confusion and tremors
- started on dexamethasone on 3/30/23. He he received a dose of tocilizumab and mannitol on 4/3/23 and was started on Solu-Medrol

- 4/5/23 CT chest w/o: Bilateral pneumonia with a large consolidation in the right upper lobe extending to the apex. Trace bilateral pleural fluid. Increased subcutaneous edema across the body wall soft tissues

- Karius – aspergillus (no BAL)

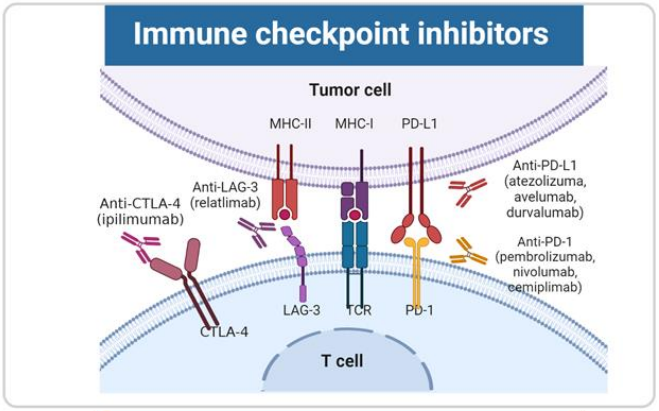
Case 3

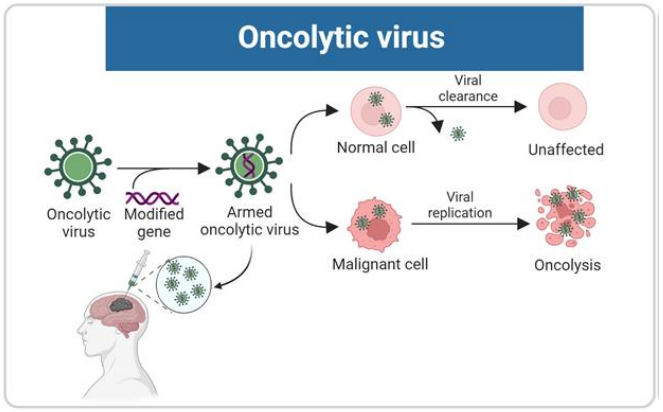
- 65 yo DLBCL Pt received Fly/Cy lymphodepletion for 3 days starting on 1/14 and received Yescarta CAR-T on 1/22/19. Her course was c/b elevated troponin, hypotension, respiratory distress due to pulmonary edema necessitating ICU transfer, transient pressor support and diuresis. Pt also developed restlessness/agitation and was unresponsive on 1/24 and she received Tocilizumab on 1/27 for CRS and then dexamethasone for encephalopathy. Pt on 1/31 underwent bronch and was placed on the vent thereafter. Bronch was pos for few Achromobacter xylosoxidans/denitrificans (sensitive to mero, levo, imi, ceftaz, pip/tazo, tmp/smx). She was treated with meropenem for this up until 2/12. She was converted to ceftazidime on 2/14. She also developed g-tube erythema/leaking and her g-tube required changing on 2/19. She was treated with 5 days of IV vancomycin from 2/14-2/18.
-
- On 2/20 worsening pulm sx and CT
- There appears to be interstitial and consolidative changes seen in the lungs with some mild FDG uptake. Inflammatory/infectious etiology should be considered.

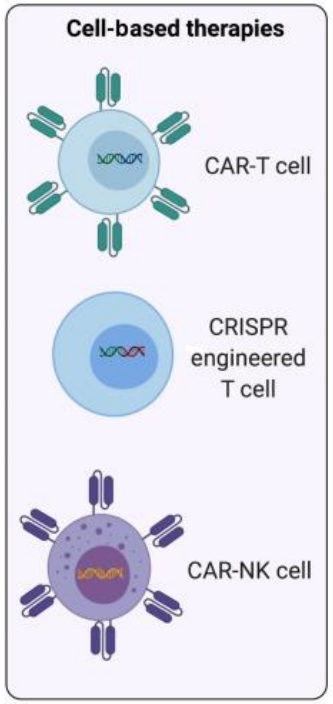
- CMV PCR serum 2.3 million copies/ml; BAL with shell vial pos and cytopathy c/w CMV pneumonitis; asp GM also positive at 1.4

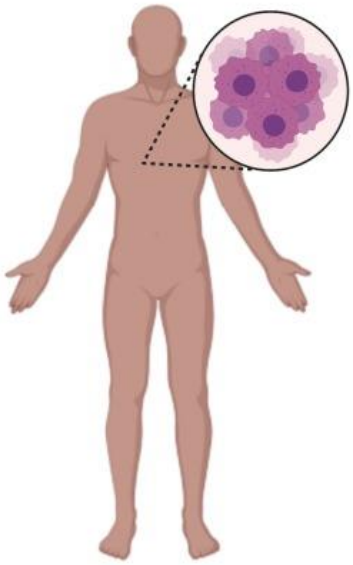
- Started on GCV and isavucon

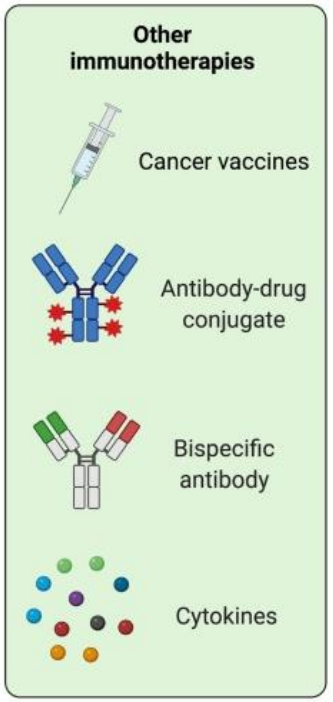
Cancer Immunotherapies (courtesy Dr. S. Ma, COH, adapted)





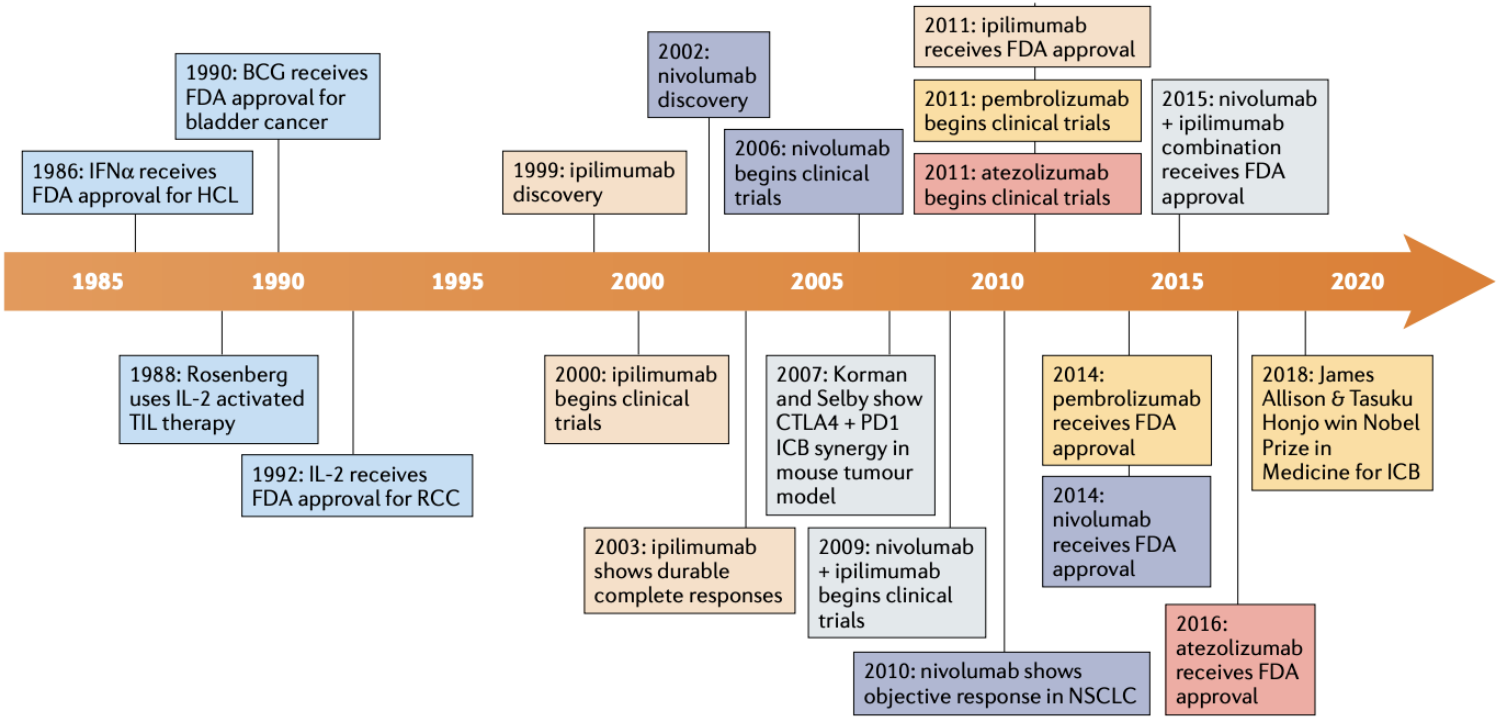






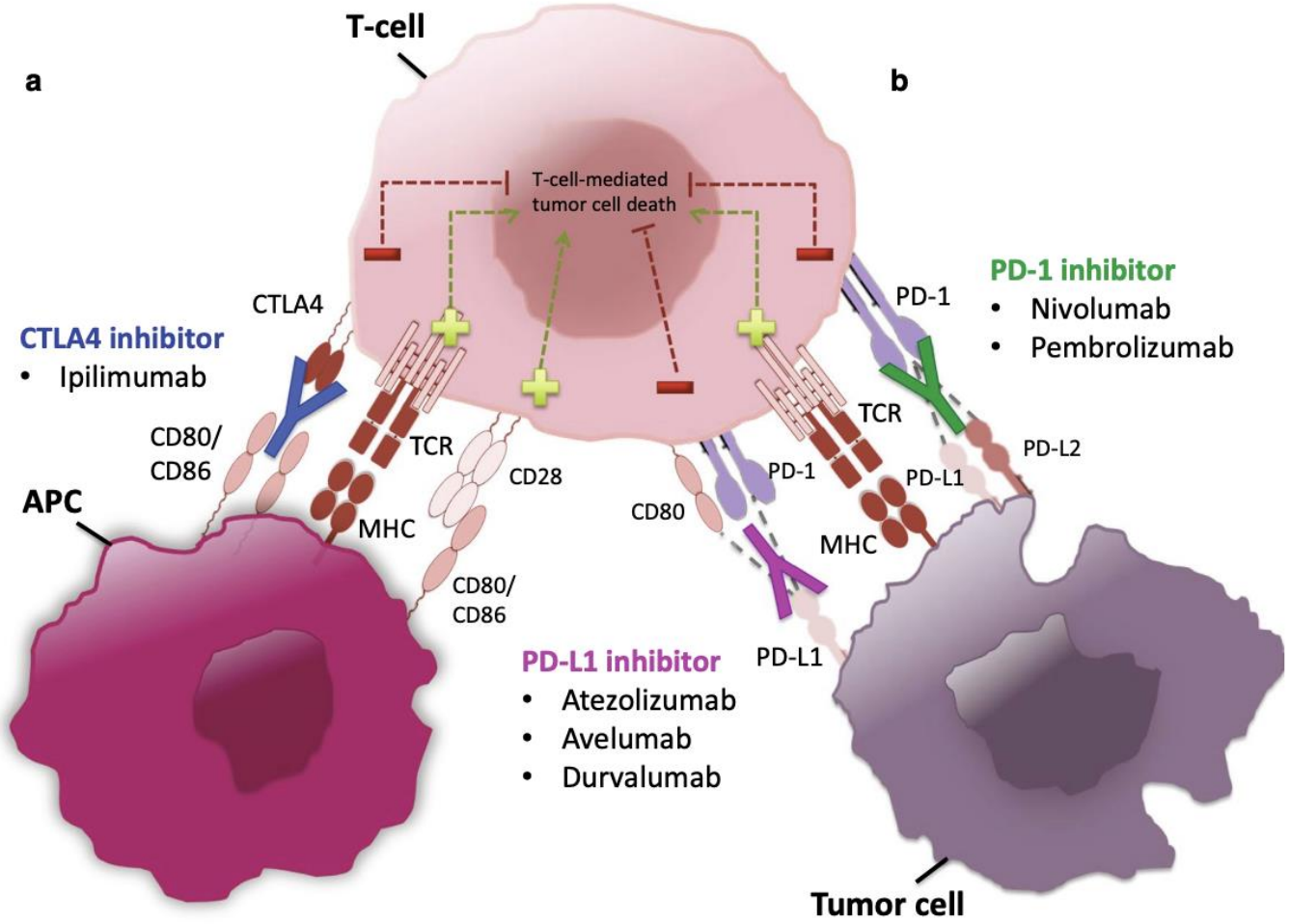
Adoptive cell therapy

Immunotherapy



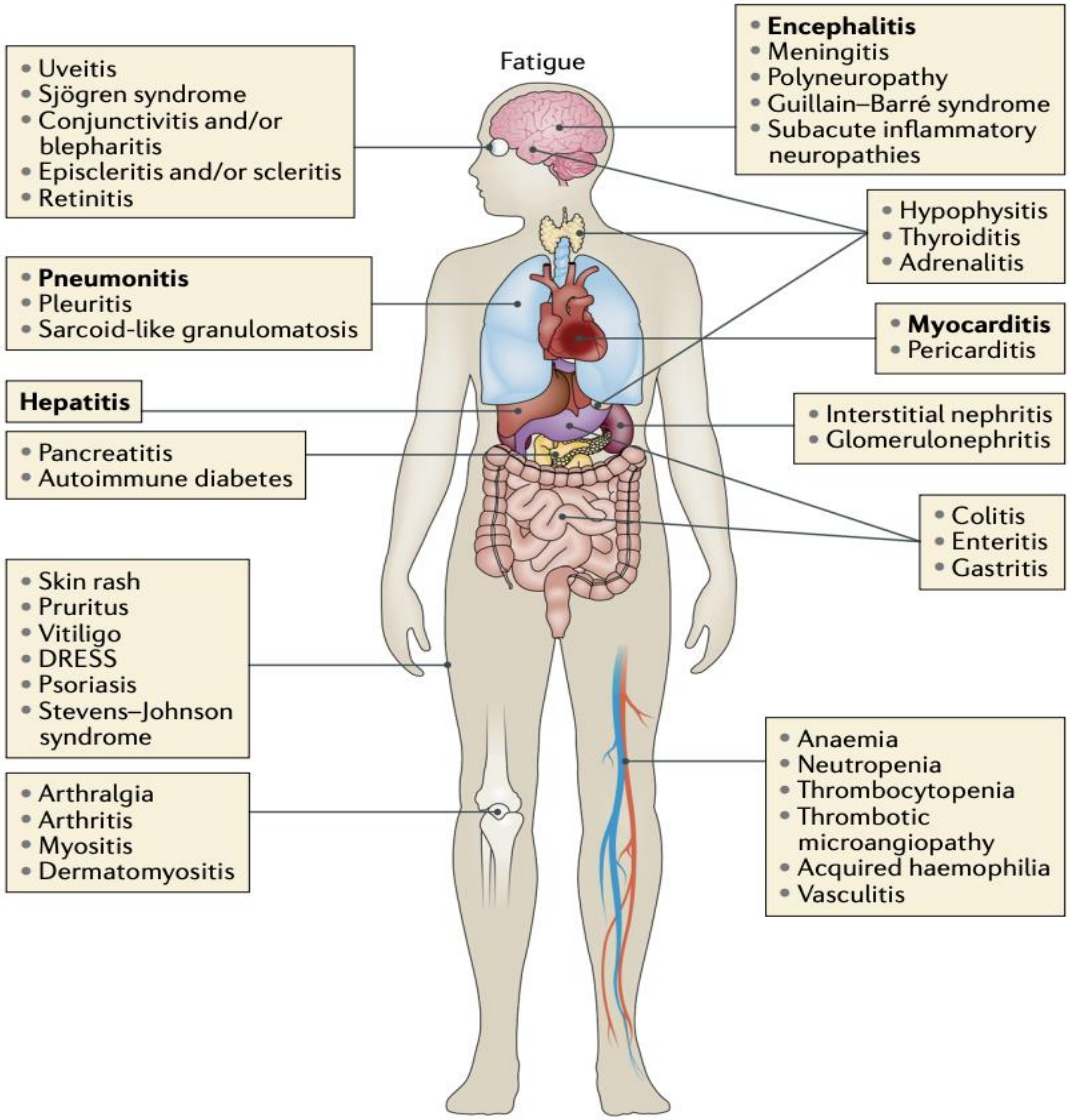
Korman et al. Nature Reviews July 2022 | volume 21

Immune Checkpoint Inhibitors (ICI) Mechanism of action

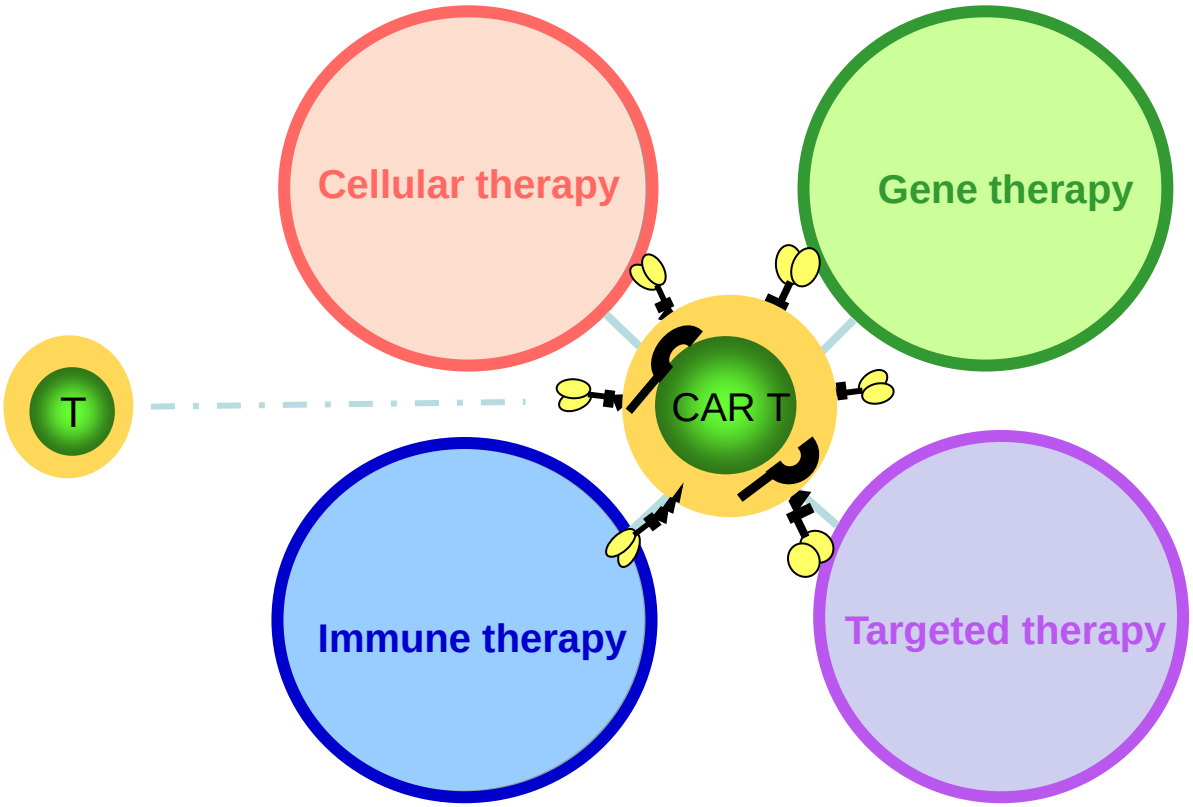


Centanni et al, Clinical Pharmacokinetics (2019) 58:835–857

Immune checkpoint inhibitors

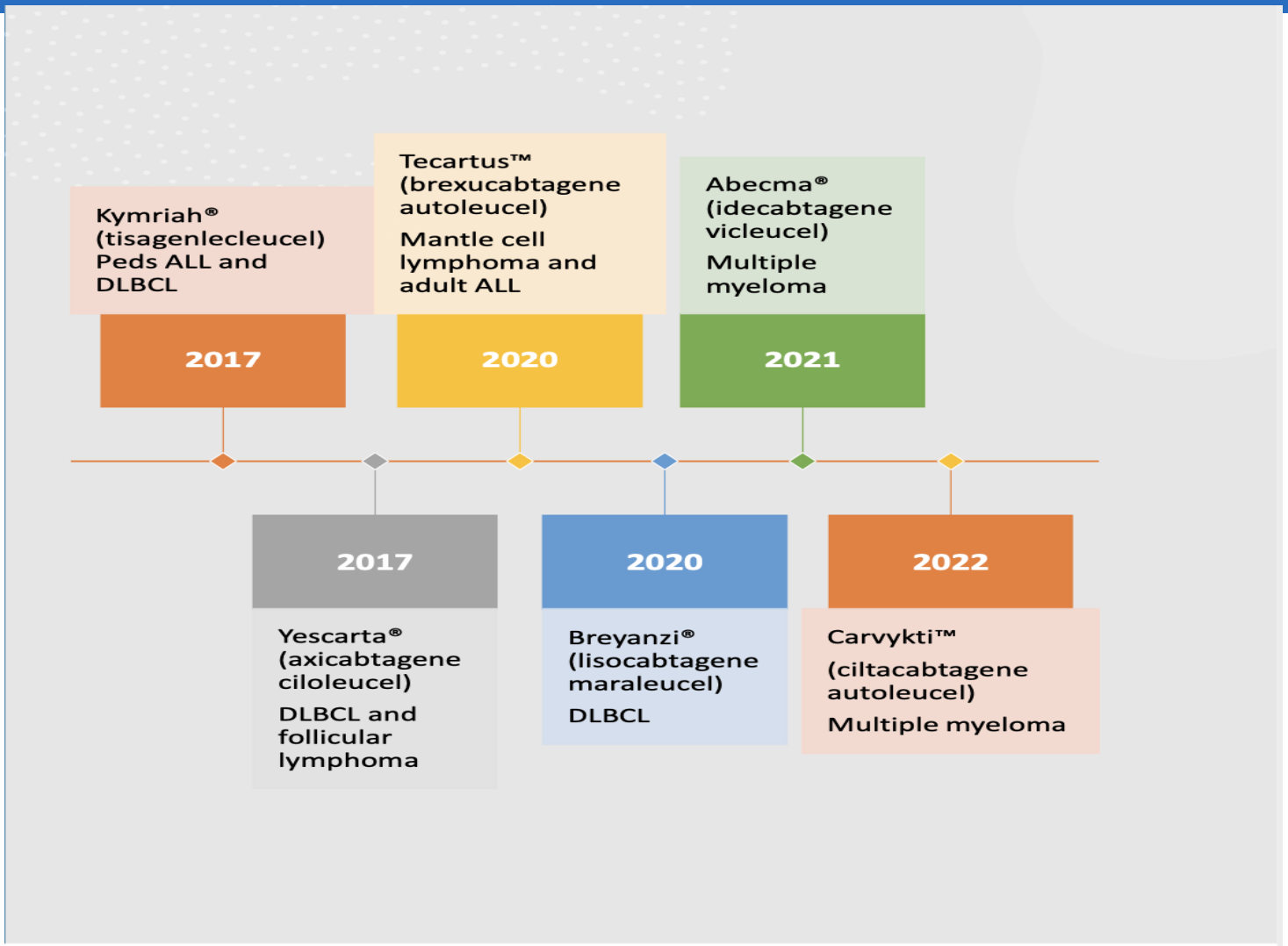


What is CAR T Cell Therapy

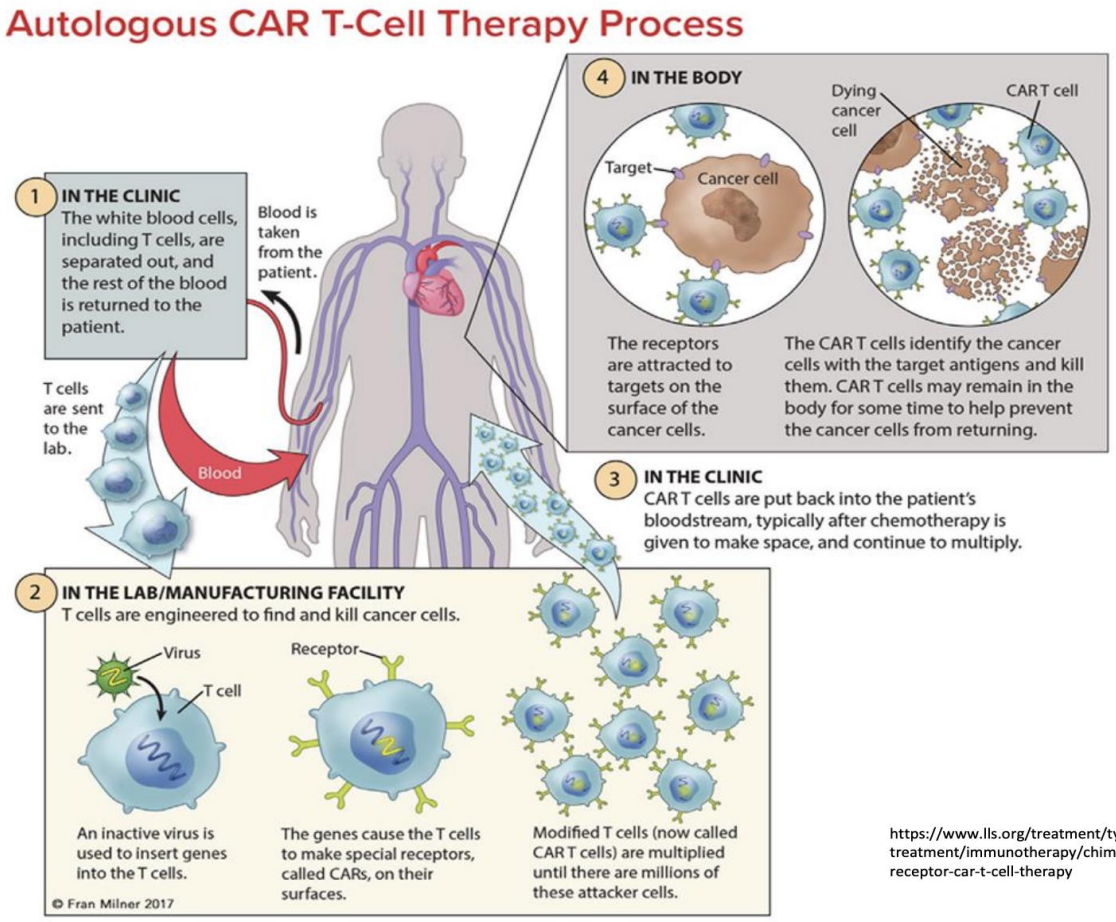


Courtesy E. Budde, COH

CAR-T

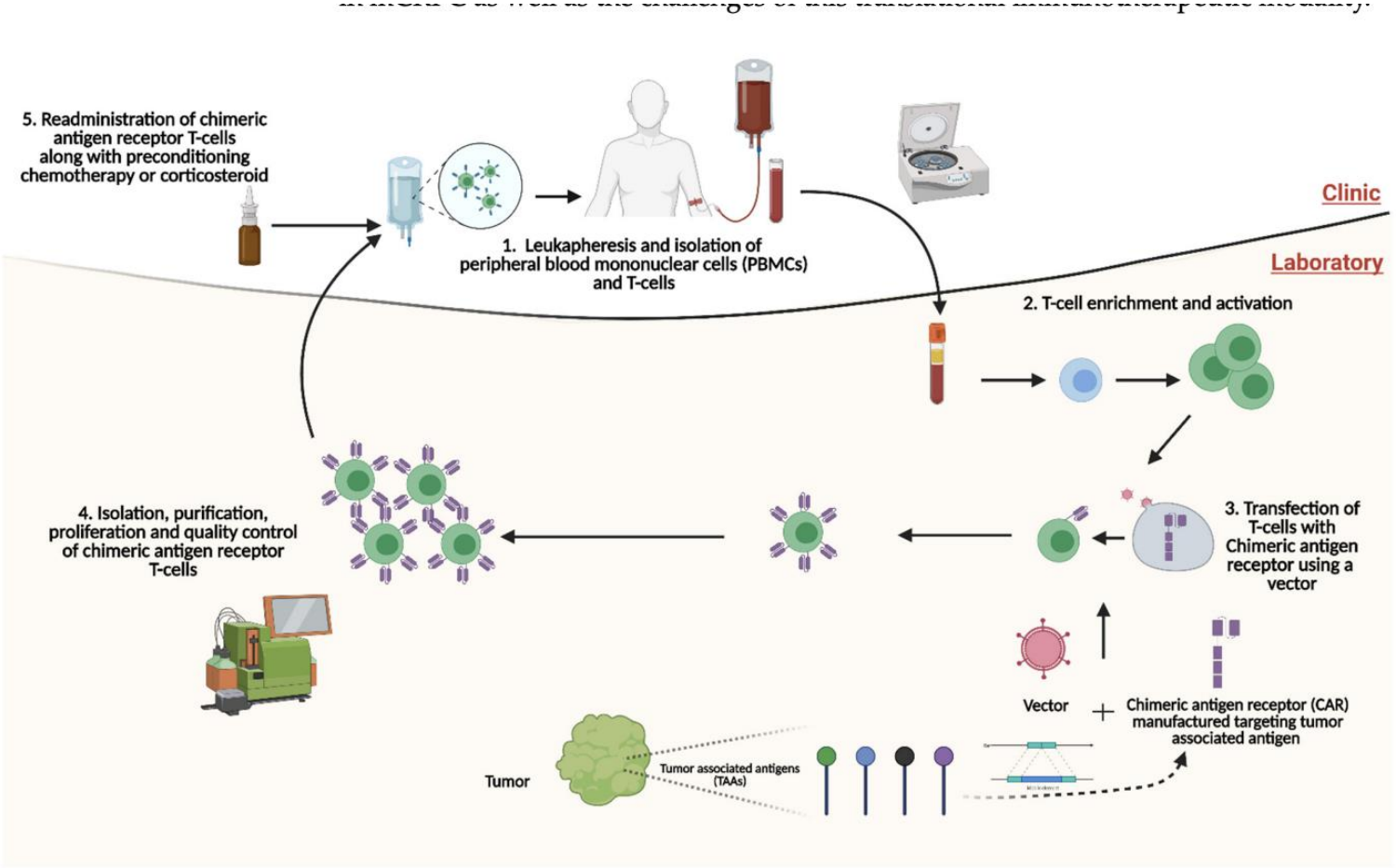

Kymriah® (tisagenlecleucel) Peds ALL and DLBCL
Tecartus™ (brexucabtagene autoleucel) Mantle cell lymphoma and adult ALL
Abecma® (idecabtagene vicleucel) Multiple myeloma
2017
2020
2021
2017
Yescarta® (axicabtagene ciloleucel) DLBCL and follicular lymphoma
2020
Breyanzi® (lisocabtagene maraleucel) DLBCL
2022
Carvykti™ (ciltacabtagene autoleucel) Multiple myeloma

CAR-T



https://www.lls.org/treatment/types-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy

CAR-T – adapted to prostate Cancer



Perera et al, *Cancers* **2022**, *14*, 503

CAR-T Toxicity

- CAR T-cells can cause several unique adverse events including
  - cytokine release syndrome (CRS),
  - immune effector cell-associated neurotoxicity syndrome (ICANS),
  - hypogammaglobulinemia,
  - and prolonged cytopenia
- In addition, due to on-target effects,
  - CD19 CAR T-cells result in depletion of B cells and a subset of CD19 + plasma cell
  - BCMA-targeted CAR T-cells lead to plasma cell aplasia

  - **As a result of underlying immune system dysregulation and further disruption by CAR T-cells, patients who undergo CAR T-cell therapy are predisposed to infections. In addition, underlying hematologic malignancies and immunosuppressive treatment for CAR T-cell-associated toxicities also contribute to the cumulative immunosuppressive state of CAR T-cell recipients**.

CAR T cell therapy: toxicity overview

Target specific toxicities: on target off tumor effect

The immune-mediated recognition of TAAs in normal tissues

Target	tumor	off tumor concerns	outcome
CD19	B cell malignancies	Normal B cells	B cell aplasia
CD33	AML	Normal HSC	Myeloablation
Her2 (4D5)	Colon Cancer	lung epithelium	Serious Death reported
CEA	Colorectal Cancer	Colonic epithelium	Severe Colitis
carboxyanhydrase-IX	Renal cell carcinoma	bile duct epithelium	cholestasis

Morgan et al, Mol Ther, 18 (2010; Parkhurst et al. Mol. Therapy 2011; Lamers et al. Mol Ther, 21 (2013)

CAR T cell therapy: toxicity overview

- Target specific toxicities
  - On target off tumor event
- Lymphodepletion chemo related events

Myelosuppression
nausea/vomiting
Fever (fludarabine)
Hemorrhagic cystitis (cyclophspohamide)
tumor lysis syndrome
organ dysfunction (i.e. cardiac,liver, renal, plumonary)
Immunosuppression
Neurotoxicity (fludarabine, cyclophosphamide)
Hypersensitivities

- CAR T cell related/emergent events

CAR T Cell Therapy: toxicity overview

- Target specific toxicities
- Lymphodepletion chemo related events
- CAR T cell related/emergent events

Short term (within 8 weeks)

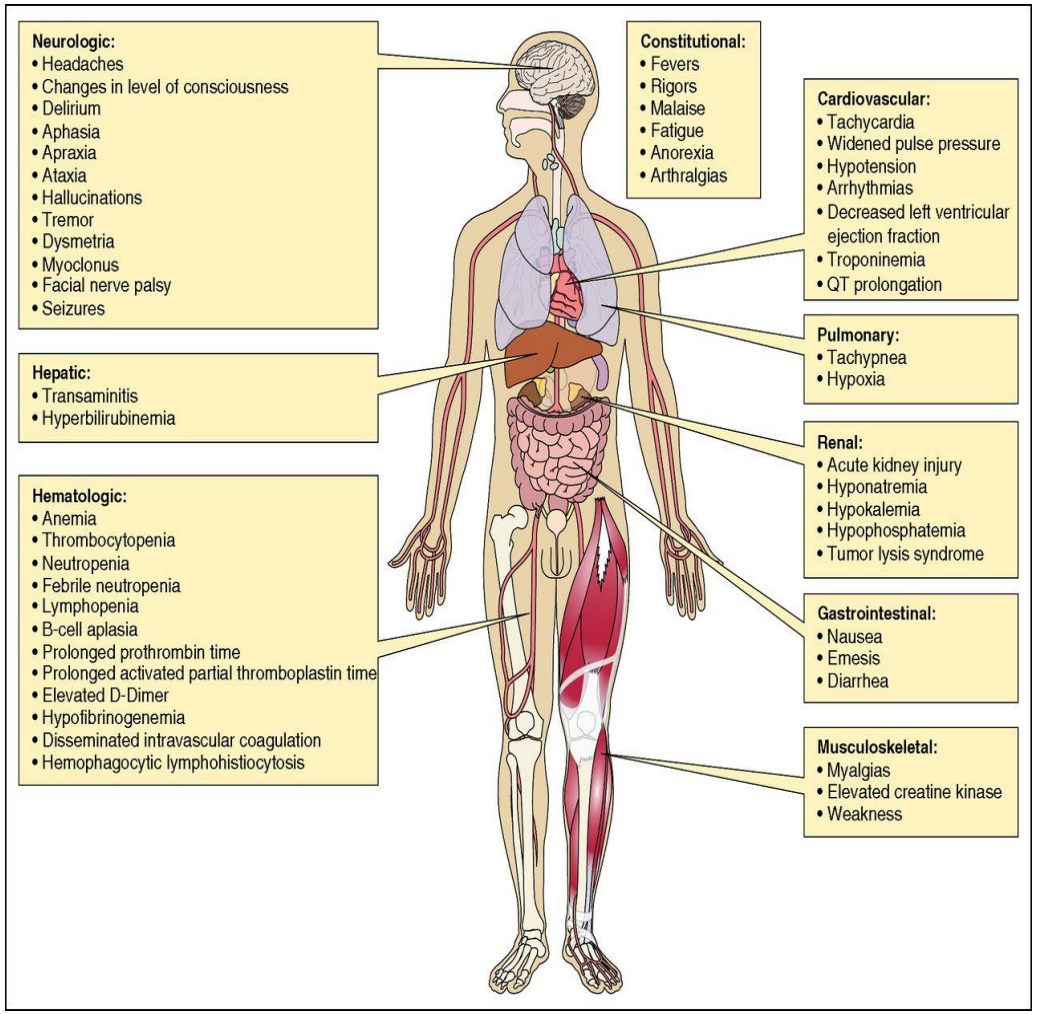
- Cytokine release syndrome (MUST CONSIDER INFECTION)
- Neurotoxicity
- Macrophage activation syndrome (HLH/MAS)
- Infection
- Coagulopathy
- Cardiac toxicity

Long term (>8 weeks)

- prolonged cytopenia
- Infection
- Secondary malignancy due to insertional mutagenesis
- Deconditioning

Cytokine Release Syndrome

- A common toxicity to CAR T cell therapy
- Not restricted to a particular antigen
- constellation of inflammatory symptoms from cytokine elevations.
- Association with T cell activation and proliferation
- Association with clinical benefit and toxicity in some CAR T product treatment.



Jennifer N. Brudno, and James N. Kochenderfer Blood 2016;127:3321-3330

CRS Grading System

TABLE 1 | American Society for transplantation and cellular therapy consensus grading of cytokine release syndrome (CRS).

CRS parameter*	Grade 1	Grade 2	Grade 3	Grade 4
Fever#†	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
		With either:		
Hypotension#	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or‡		
Hypoxia#	None	Requiring low-flow nasal cannula^ or blow-by	Requiring low-flow nasal cannula^, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP**, intubation and mechanical ventilation

*Organ toxicities associated with CRS may be graded according to Common Terminology for Adverse Events version 5.0, but these toxicities do not influence CRS grading.

#Not attributable to any other cause.

† In patients who have CRS and then receive tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity.

‡CRS grade is determined by the more severe event.

^Low-flow nasal cannula is ≤6 L/min and high-flow nasal cannula is >6 L/min.

**CPAP, continuous positive airway pressure; BiPAP, bilevel positive airway pressure.

Table adapted from (17).

CRS Management

Goal: reduce serious CRS symptoms and signs, and prevent life-threatening complications

- Tocilizumab is the first choice for CRS mitigation
- humanized IgG1 anti-hIL-6R mAb, FDA approved in 8/2017
  8 mg/kg iv over 1 hour x1, can repeat in 24 to 48 hours

What to do in tocilizumab refractory cases (no improvement after 2 doses of Tocilizumab)?

- Steroids, Methylpred 2mg/kg/d or Dex 0.5mg/kg max 10mg/dose, quick taper.
- Siltuximab, Etenercept, Roxilitinib, ibrutinib

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

TABLE 4 | American Society for Transplantation and Cellular Therapy consensus encephalopathy assessment tool.

Immune-effector cell-associated encephalopathy tool (ICE)

- **Orientation:** Orientation to year, month, city, hospital: 4 points
- **Naming:** Ability to name three objects (e.g., patient is asked to point to clock, pen, button): 3 points
- **Following commands:** Ability to follow directions (e.g., patient is asked to hold up two fingers or close their eyes and stick out their tongue): 1 point
- **Writing:** Ability to write a standard sentence (e.g., Our national bird is the bald eagle): 1 point
- **Attention:** Ability to count backwards from 100 by 10: 1 point

Treatment: steroids

Other!

- Although CD19 is expressed on most B-cell malignancies, it is also present on normal B-cells, creating an “on-target, off-tumor” of B-cell aplasia, which results in cytopenias and hypogammaglobulinemia.
  - Cytopenias typically occurs within the first 30 days after cell infusion but can take months or possibly longer to resolve.
  - Lymphodepleting chemotherapies are known to cause drops in blood counts initially, but the CAR T-cells can also cause immune-mediated pancytopenia.

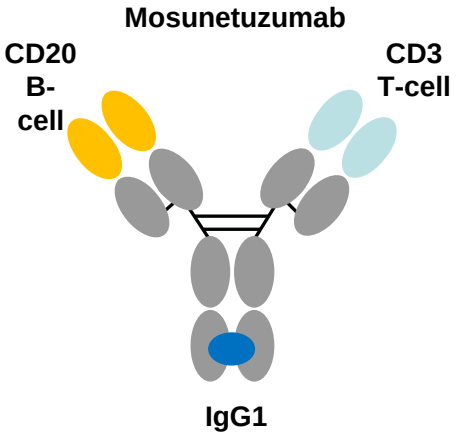
- BCMA CAR - associated with plasma cell aplasia

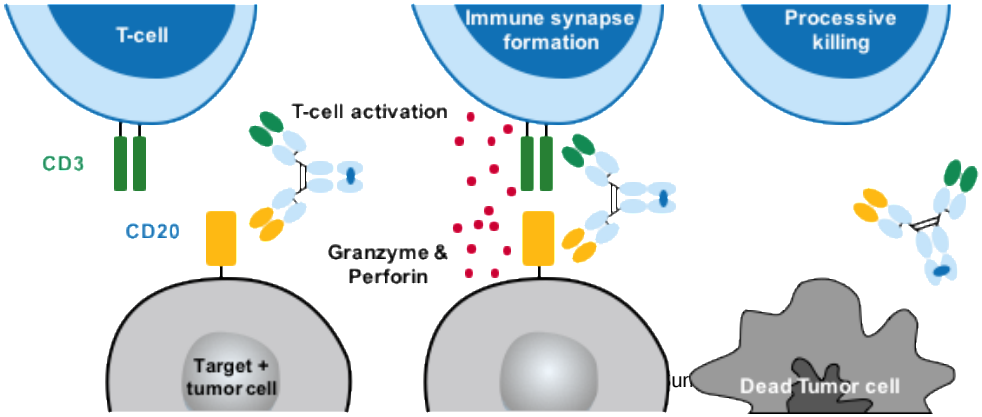
- CD33 – myeloid stem cells

- **Underlying heme malignancies and IS treatment for CAR-T cell associated therapies (steroids, toci) contribute to net state of immunosuppression.**

Mosunetuzumab: a bispecific antibody targeting CD3 and CD20

- **Full-length humanized IgG1 antibody**
  - Longer half-life than fragment-based drug formats
  - **Does not require *ex-vivo* T-cell manipulation**
  - **Off the shelf, readily available treatment**
- **Mechanism of action**
  - Redirects T-cells to engage and eliminate malignant B-cells





ADCC, antibody-dependent cell-mediated cytotoxicity

Infection Risk CAR-T

Incidence: 23% FHCRC trial; 27% JULIET trial; 38% ZUMA-1; 41% ELIANA

Pretreatment factors
- impaired immune function
- tissue damage from prior chemotherapy regimens

Treatment factors
- cytopenia from lymphodepletion,
- immunosuppressive drugs such as toci/dex
- ICU stay
- hypogammaglobulinemia

Other risk factors
- ALL patients
- >= 4 lines of prior therapies
- Higher CAR dos
- Severe CRS

Hill et al.Blood 2017
Wudhikarn et alBMT 2022
Budde & Zaia Blood 2017

Infection Risk - CART

FHCRC cohort, N=133

Incidence: 23%
Median Time to onset: 6

Bacterial 17% (N =22)
Viral 11% (N = 11)
Fungal 5% (N = 6)
Fatal infection 4% (n=5)

ZUMA-1 cohort, N=108

Incidence: 38%
Median Time to onset: 6

Bacterial 9%
Viral 4%
Unspecified 16%
Severe infection 23%

ID prophylaxis is recommended –- lack of standard approach

Hill et al.Blood 2017;
Yescarta.com

ELIANA (Tisagenlecleucel in ALL; target CD19): Safety

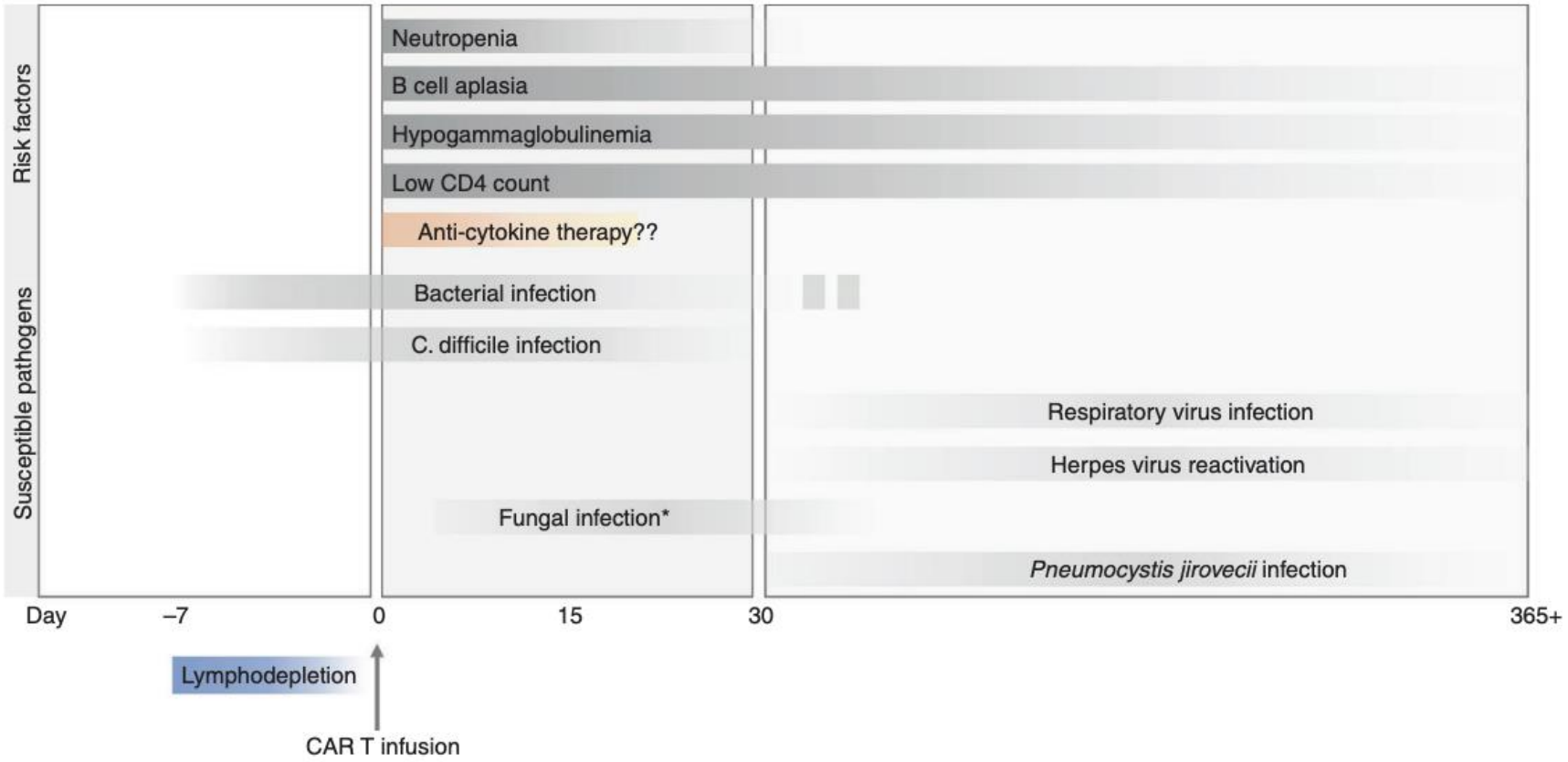
Table 3. Adverse Events of Special Interest within 8 Weeks after Infusion, Regardless of Relationship to Tisagenlecleucel.*

Type of Event	Any Grade (N=75)	Grade 3 (N=75)	Grade 4 (N=75)
	number of patients (percent)		
Any adverse event of special interest	67 (89)	26 (35)	30 (40)
Cytokine release syndrome	58 (77)	16 (21)	19 (25)
Neurologic event	30 (40)	10 (13)	0
Infection	32 (43)	16 (21)	2 (3)
Febrile neutropenia	26 (35)	24 (32)	2 (3)
Cytopenia not resolved by day 28	28 (37)	12 (16)	12 (16)
Tumor lysis syndrome	3 (4)	3 (4)	0

ICU admission 47% (35 of 75) with median stay of 7 days (range, 1-34)
10% mechanical ventilation
25% high dose vasopressors

SL Maude et al. N Engl J Med 2018;378:439-448.

Infection Risk in CAR-T cell therapy



Wudhikarn et al, BMT (2022) 57: 1477-1488

Infection Risk CAR-T and BiTE

Key points

- Do not assume fever is due to CRS
- Do not assume neurologic changes are due ICANS
- Could be bacterial, viral, or fungal infection
- Could be fatal

Overall approach to Infectious risk in targeted and immunotherapy

Evolving practices in prevention and management of infectious risk in patients treated with targeted and immunotherapy

Patients should be managed based on a comprehensive risk assessment taking into account the **net state of immunosuppression** and including disease status and prior and current therapies to ensure best prophylaxis and management of infections with an eye toward antimicrobial stewardship

ID consultation and pharmacy involvement as needed is strongly encouraged

NCCN guidelines

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2022
Prevention and Treatment of Cancer-Related Infections

NCCN Guidelines Index
Table of Contents
Discussion

Table 1. Targeted Therapies

IMMUNE AND TARGETED TREATMENTS[a,b]

Mechanism of Action	Agents	Major Uses	Infection Concerns	Recommendations and Comments[c,d,e]
Ubiquitin-proteasome pathway inhibitors[1]	Bortezomib	MM, MCL	• Respiratory tract infection • VZV • HBV • PML	• Recommend VZV prophylaxis • VZV vaccination in VZV-seronegative patients at least 1 month prior to initiation • Consider HZ vaccination in VZV-seropositive patients • Drug-induced neutropenia and pneumonitis • QTc prolongation can occur
	Carfilzomib	MM		
	Ixazomib			
Bruton tyrosine kinase (BTK) inhibitors[2]	Acalabrutinib	CLL, MCL	• VZV • HBV • Opportunistic fungal infections • PJP	• Consider HSV/VZV and PJP prophylaxis in patients with additional risk factors • Drug-induced neutropenia
	Ibrutinib	CLL, MCL, WM, MZL, GVHD		
	Zanubrutinib	MCL, MZL, W		
BCR-ABL tyrosine kinase inhibitors[2,3,5]	Bosutinib	CML	• CMV (dasatinib) • VZV • HBV	• Second-generation agents are associated with greater risk of drug-induced pancreatitis and hepatotoxicity • QTc prolongation can occur • Drug-induced neutropenia • Drug-induced pleural effusion (most frequently dasatinib)
	Nilotinib			
	Imatinib	CML, ALL, GIST, aggressive SM,DMSP, hypereosinophilic syndrome and/or chronic eosinophilic leukemia, MDS, MPD		
	Dasatinib	CML, ALL		
	Ponatinib			
Phosphatidylinositol-3-kinase (PI3K) inhibitors[3]	Copanlisib	FL	• CMV • VZV • PML • Opportunistic fungal infections • PJP	• Consider CMV surveillance in CMV-seropositive patients • Consider PJP prophylaxis • QTc prolongation can occur • Drug-induced neutropenia • Drug-induced pneumonitis, colitis, and hepatitis
	Idelalisib	CLL		
	Duvelisib			
	Alpelisib	Breast cancer		
	Umbralisib	FL, MZL		
	Rigosertib	CML		

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

References

INF-A
1 OF 13

IMMUNE AND TARGETED TREATMENTS[a,b]

Table 1. Targeted Therapies (continued)

Mechanism of Action	Agents	Major Uses	Infection Concerns	Recommendations and Comments[c,d,e]
mTOR inhibitors[2]	Everolimus	Breast cancer, NET, RCC	• VZV • HBV • HCV • PML • PJP • TB	• Screen for latent TB, treat as indicated • Consider PJP prophylaxis in patients with additional risk factors • Drug-induced pneumonitis and stomatitis • Associated with impaired wound healing
	Temsirolimus	RCC		
	Sirolimus	GVHD		
Histone deacetylase inhibitors	Vorinostat	CTCL	• HBV • HIV	• May reverse HIV and HBV latency • QTc prolongation can occur
	Romidepsin			
	Belinostat	PTCL		
Janus kinase (JAK) inhibitors[2,3,5]	Fedratinib	Myelofibrosis	• CMV • HBV • HSV • Opportunistic fungal infections • PJP • PML • TB • VZV	• Screen for latent TB and HBV, treat as indicated • Consider PJP prophylaxis (depending on additional risk factors) and HSV/VZV prophylaxis • Monitor for drug withdrawal syndrome with taper or discontinuation • Fedratinib can be associated with serious and sometimes fatal Wernicke-like encephalopathy • Drug-induced neutropenia
	Ruxolitinib	GVHD, myelofibrosis, PV		
Isocitrate dehydrogenase 1 (IDH1) and isocitrate dehydrogenase 2 (IDH2) inhibitors	Enasidenib	AML	No significantly increased infectious risks	• Monitor for differentiation syndrome[f] • QTc prolongation can occur
	Ivosidenib	AML, cholangiocarcinoma		
BRAF kinase inhibitors[2]	Dabrafenib	Melanoma, NSCLC, thyroid cancer	No significantly increased infectious risks	• Drug-induced rash (including serious hypersensitivity reactions), fever, arthralgias, neutropenia, and lymphopenia • Drug-induced pneumonitis and interstitial lung disease reported with single and combination therapies (eg, BRAF kinase + MEK kinase inhibitors) • Drug-induced hepatotoxicity, especially with vemurafenib • Adverse effect profile impacted by combination MEK kinase inhibitor therapy • QTc prolongation can occur
	Encorafenib	CRC, melanoma		
	Vemurafenib	Melanoma		

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

References

Table 1. Targeted Therapies (continued)

IMMUNE AND TARGETED TREATMENTS[a,b]

Mechanism of Action	Agents	Major Uses	Infection Concerns	Recommendations and Comments[c,d,e]
MEK kinase inhibitors[2]	Binimetinib	Melanoma	No significantly increased infectious risks	• Drug-induced rash (including serious hypersensitivity reactions) and fever • Drug-induced hepatotoxicity, neutropenia, and lymphopenia • Drug-induced pneumonitis and interstitial lung disease reported with single and combination therapies (eg, BRAF kinase + MEK kinase inhibitors) • Adverse effect profile impacted by combination BRAF kinase inhibitor therapy • QTc prolongation can occur
	Cobimetinib			
	Trametinib	Melanoma, NSCLC, thyroid cancer		
Bcl-2 (B-cell lymphoma 2) inhibitors[2]	Venetoclax	AML, CLL/SLL	No significantly increased infectious risks	• Drug-induced neutropenia and lymphopenia
FLT3 (FMS-like tyrosine kinase 3) inhibitors	Gilteritinib	AML	No significantly increased infectious risks	• Monitor for differentiation syndrome with gilteritinib[f] • Drug-induced neutropenia • Drug-induced pneumonitis • QTc prolongation can occur
	Midostaurin	AML, mast cell leukemia, SM		
Nuclear export inhibitor	Selinexor	DLBCL, MM	No significantly increased infectious risks	• Drug-induced gastrointestinal (GI) side effects (nausea, vomiting, and diarrhea) and neutropenia
Multi-target protein kinase inhibitors[6]	Lenvatinib	Endometrial cancer, HCC, RCC, thyroid cancer	No significantly increased infectious risks	• Toxicities vary with agent but include drug-induced neutropenia, lymphopenia, skin rash, hepatotoxicity, and GI effects including perforation • Associated with impaired wound healing • QTc prolongation can occur
	Pazopanib	RCC, soft tissue sarcoma		
	Regorafenib	CRC, GIST, HCC		
	Sorafenib	HCC, RCC, thyroid cancer		
	Sunitinib	GIST, pancreatic cancer, RCC		
	Tivozanib	RCC		
Rho-associated coiled-coil–containing protein kinase 2 (ROCK2) inhibitor	Belumosudil	GVHD	No significantly increased infectious risks	• Drug-induced neutropenia and lymphopenia • Associated with impaired wound healing

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References

IMMUNE AND TARGETED TREATMENTS[a,b]

Table 1. Targeted Therapies (continued)

Mechanism of Action	Agents	Major Uses	Infection Concerns	Recommendations and Comments[c,d,e]
ALK inhibitors[3]	Alectinib	NSCLC	No significantly increased infectious risks	• Drug-induced pneumonitis and hepatotoxicity • Development of renal cysts with potential secondary infection seen with crizotinib • QTc prolongation can occur
	Brigatinib			
	Ceritinib			
	Crizotinib	Anaplastic large cell lymphoma, NSCLC		
	Lorlatinib	NSCLC		
CDK4/6 inhibitors	Abemaciclib	Breast cancer	No significantly increased infectious risks	• Drug-induced neutropenia, hepatotoxicity, and rash • QTc prolongation can occur
	Palbociclib			
	Ribociclib			

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CMV, cytomegalovirus;CRC, colorectal cancer; CTCL, cutaneous T-cell lymphoma; DFSP, dermatofibrosarcome protuberans; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GIST, gastrointestinal stromal tumor; GVHD, graft-versus-host disease; HBV, hepatitis B virus; HCC, hepatocellular cancer; HIV, human immunodeficiency virus; HSV, herpes simplex virus; MCL, mantle cell lymphoma; MDS, myelodysplastic syndrome; MM, multiple myeloma; MPD, myeloproliferative disease; MZL, marginal zone lymphoma; NET, neuroendocrine tumors; NSCLC, non-small cell lung cancer; PJP, *Pneumocystis jiroveci* pneumonia; PML, progressive multifocal leukoencephalopathy; PTCL, peripheral T-cell lymphoma; PV, polycythemia vera; RCC, renal cell carcinoma; SLL, small lymphocytic lymphoma; SM, systemic mastocytosis; TB, tuberculosis; VZV, varicella zoster virus; WM, Waldenström macroglobulinemial;

[a] The information in this table is continuously evolving and is not an exhaustive list. Refer to the FDA-approved labeling for these agents for further information on the appropriate use and further details on potential toxicities and drug interactions. The infection risk of these agents should be weighed according to the cancer being treated, the patient's relative medical comorbidities, and other antineoplastic therapies used during treatment.

[b] Additional agents in these and other categories have been FDA-approved, but their infection risk profile has not been fully established.

[c] All patients anticipating systemic anticancer therapy should be tested for HBV prior to the start of therapy. Risk assessment, including the need for HBV-directed treatment and prophylaxis, should be undertaken in patients with findings of chronic or past HBV infection (see INF-5).[7]

[d] TB screening should at minimum be performed in those with risk factors (eg, individuals [or caregivers and household members] from high-incidence TB countries, recent exposure, health care workers, and residents and employees of homeless shelters/correctional facilities) and with planned use of agents associated with an increased risk for TB infection.

[e] Vaccination history should be assessed and updated (when relevant) in all patients (see INF-7 and INF-8).

[f] Clinical features of differentiation syndrome can include fever, shortness of breath, rapid weight gain, pleuro-pericardial effusions, lung infiltrates, hypoxia, and hypotension.

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References

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2022
Prevention and Treatment of Cancer-Related Infections

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IMMUNE AND TARGETED TREATMENTS[a,b]

Table 2. Monoclonal Antibodies and Fusion Proteins

Mechanism of Action	Agents	Major Uses	Infection Concerns	Recommendations and Comments[c,d,e]
Bispecific CD19-directed CD3 T-cell engager (BiTE)[8]	Blinatumomab	ALL	• Bacterial infection • CMV • HSV/VZV • PML • Opportunistic fungal infections • PJP	• Consider PJP and HSV/VZV prophylaxis • Monitor for cytokine release syndrome • Drug-induced neurotoxicity, leukoencephalopathy, pancreatitis, hepatoxicity, neutropenia, and hypogammaglobulinemia
CD19 target and alkylating agent conjugate	Loncastuximab tesirine	Large B-cell lymphoma	Limited data on specific infections	• Drug-induced pleural effusion, pericardial effusion, ascites, and myelosuppression (ie, neutropenia, lymphocytopenia)
CD20 target[8]	Obinutuzumab	CLL, FL	• HBV (high risk) • HCV • HSV/VZV • PML	• Screen for HBV[c], treat as indicated • Consider prophylaxis for VZV/HSV • Consider prophylaxis for PJP, especially if concomitant therapy further increases PJP risk • Drug-induced neutropenia, lymphocytopenia, and hypogammaglobulinemia
	Ofatumumab	CLL		
	Rituximab	CLL, NHL		
CD22 target[9]	Inotuzumab ozogamicin	ALL (B-cell)	Limited data on specific infections	• Risk for capillary leak syndrome (moxetumomab) and VOD/hepatotoxicity (inotuzumab) • QTc prolongation can occur
	Moxetumomab pasedotox	HCL		
CD30 target[9]	Brentuximab vedotin	CD3+ Hodgkin-lymphoma, anaplastic large T-cell lymphoma	• PML • CMV • PJP • HSV/VZV	• Consider CMV monitoring in CMV-seropositive patients • Consider PJP and HSV/VZV prophylaxis • Drug-induced neutropenia and lymphocytopenia
CD33 target[9]	Gemtuzumab ozogamicin	AML	• Bacterial infections • Opportunistic fungal infections • PJP	• Drug-induced VOD/hepatotoxicity, neutropenic colitis, and interstitial pneumonitis • QTc prolongation can occur
CD38 target[9]	Daratumumab	MM	• *Listeria* • HBV • HSV/VZV • CMV • PJP • *Cryptococcus*	• Recommend HSV/VZV prophylaxis • Consider PJP prophylaxis • Drug-induced neutropenia
	Isatuximab			

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References

IMMUNE AND TARGETED TREATMENTS[a,b]

Table 2. Monoclonal Antibodies and Fusion Proteins

Mechanism of Action	Agents	Major Uses	Infection Concerns	Recommendations and Comments[c,d,e]
CD52 target[8]	Alemtuzumab	CLL, aplastic anemia, MF/SS, T-cell prolymphocytic leukemia, T-cell large granular lymphocytic leukemia	• *Nocardia* • TB • *Listeria* • HSV/VZV • CMV • ADV • BKV • PML • Opportunistic fungal infections	• Consider CMV monitoring in CMV-seropositive patients • Recommend PJP prophylaxis if CD4 <200 • Recommend VZV/HSV prophylaxis • Risk for prolonged lymphocytopenia
CD319 (SLAMF-7) target[9]	Elotuzumab	MM	VZV	• Recommend HSV/VZV prophylaxis • CCR4 target[9]; drug-induced interstitial pneumonitis
CCR4 target[9]	Mogamulizumab	MF/SS	• *Mycobacterium* spp. • CMV • HSV/VZV • HBV • *Candida* • PJP	• Consider CMV monitoring in CMV seropositive patients • Recommend PJP and HSV/VZV prophylaxis • Drug-induced dermatological toxicity
Complement C5 inhibitor[10]	Eculizumab Ravulizumab	Paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome associated thrombotic microangiopathy	• *Neisseria* spp (e.g. *N. meningitides, N. gonorrhoeae)* • Opportunistic fungal infections in neutropenic patients	• Screen for gonorrhea in high-risk patients • Consider prophylaxis with PCN (ciprofloxacin or azithromycin if allergic to PCN) in addition to vaccination. Duration of prophylaxis is to be guided by drug half-life, sC5b-C9/sMAC levels, sC5a, and CH50 complement activity recovery[11] • Vaccinate with both MenACWY and MenB vaccines at least 2 weeks prior to use of drug (if possible) • Risk for other encapsulated bacterial infections (*Streptococcus pneumoniae* and *Haemophilus influenzae*) is lower. Unvaccinated patients should be immunized according to ACIP recommendations. • Non-groupable *Neisseria meningitides* infection can occur despite vaccination

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IMMUNE AND TARGETED TREATMENTS[a,b]

Table 2. Monoclonal Antibodies and Fusion Proteins

Mechanism of Action	Agents	Major Uses	Infection Concerns	Recommendations and Comments[c,d,e]
IL-6 inhibitor[10]	Tocilizumab	CAR T-cell–induced cytokine release syndrome	• Bacterial infections • Mycobacteria (TB, non-TB) • VZV • HBV • Opportunistic fungal infections • PJP	• Screen for latent TB when combined with other immunosuppressive agents in high-risk patients and if epidemiologically indicated • Monitor closely for signs of infection as fever and CRP can be blunted • Drug-induced hepatotoxicity
	Siltuximab	Non-HIV and non–HHV-8 Multicentric Castleman disease		
Vascular endothelial growth factor (VEGF) inhibitor[6]	Bevacizumab	Cancers of cervical, colorectal, ovarian; RCC, NSCLC, glioblastoma	No significant increased infection risk	• Drug-induced neutropenia, bowel perforation, and GI hemorrhage • Associated with impaired wound healing
	Aflibercept	CRC		
VEGF receptor inhibitor[6]	Ramucirumab	Cancers of colorectal, gastric, liver; NSCLC		
Bispecific EGFR and MET receptor-directed antibody (with exon 20 mutation)	Amivantamab	NSCLC		• Drug-induced skin rash including acneiform dermatitis, and interstitial pneumonitis
Epidermal growth factor receptor (EGFR/ HER1) inhibitor[6]	Cetuximab	Cancers of colorectal, head/ neck		• Avoid sun exposure; use sunscreen • Dermatology consultation for severe rash • Drug-induced neutropenia, severe rash, and acneiform eruptions
	Panitumumab	CRC		
	Necitumumab	NSCLC		
HER2 inhibitor[6]	Pertuzumab	Breast cancer	Bacterial infections	• Risk for skin and nail infections • Drug-induced rash including acneiform dermatitis

ACIP, Advisory Committee on Immunization Practices; ADV, adenovirus, ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; BKV, BK virus, CAR T-cell; chimeric antigen receptor; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; CRC, colorectal cancer, CRP, C-reactive protein; FL, follicular lymphoma; HBV, hepatitis B virus; HCL, hairy cell leukemia; HCV, hepatitis C virus; HIV; human immunodeficiency virus; HHV-8; human herpesvirus 8; HSV, herpes simplex virus; MF/SS, mycosis fungoides/ Sézary syndrome, MM, multiple myeloma; NHL, non-Hodgkin lymphome, NSCLC, non-small cell lung cancer; PCN, penicillin; PJP, *Pneumocystis jiroveci* pneumonia; PML, progressive multifocal leukoencephalopathy; RCC, renal cell carcinoma; TB, tuberculosis; VOD, veno-occlusive disease, VZV, varicella zoster virus.

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References

IMMUNE AND TARGETED TREATMENTS[a,b]

Table 3. Checkpoint Inhibitors (Monoclonal Antibodies)[1]

Mechanism of Action	Agents	Major Uses	Infection Concerns	Recommendations and Comments[c,d,e]
Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitor	Ipilimumab	Cancers of colorectal, liver; NSCLC, RCC, melanoma, mesothelioma	Increased infection risks from CPIs are thought to be mostly due to immunosuppressive treatment of irAEs (eg, with corticosteroids and/or TNF-alpha antagonists), but emerging data suggest that dysregulated immunity from CPIs can directly increase infection risks.	• Examples of irAEs: colitis, hepatitis, pneumonitis, thyroiditis, myositis, myasthenia gravis, rash, and many others. See NCCN Guidelines for Management of Immunotherapy-Related Toxicities. • Reactivation of latent TB and HBV, and invasive fungal infections have been reported with or without additional immunosuppression for treatment of irAEs • Screen for HBV and latent TB, treat as indicated • Based on epidemiologic factors, screening for *Coccidioides* and *Strongyloides* may be indicated • PJP prophylaxis if high-dose steroid use (≥20 mg per day of prednisone x4 weeks).
Programmed death-1 (PD-1) inhibitors	Nivolumab	Cancers of colorectal, squamous cell of head/neck, liver, urothelial, esophageal, gastric; NSCLC, RCC, melanoma, Hodgkin lymphoma		
	Pembrolizumab	Cancers of cervical, gastric, head/neck, urothelial, colorectal, breast, cutaneous squamous cell, esophageal, endometrial, Merkel cell, liver; NSCLC, RCC, Hodgkin lymphoma, thymic LBCL, melanoma; other solid tumors		
	Cemiplimab	Cutaneous squamous cell cancer, basal cell cancer, NSCLC		
	Dostarlimab	Mismatch repair deficient (dMMR) endometrial cancer and solid tumors		
PD ligand-1 (PD-L1) inhibitor	Atezolizumab	Cancers of lung (small cell), urothelial, liver, breast; NSCLC, melanoma		
	Durvalumab	Small cell lung cancer, NSCLC		
	Avelumab	Merkel cell cancer, RCC, urothelial cancer		

CRC, colorectal cancer; CPI, checkpoint inhibitor; HBV, hepatitis B virus; irAEs, immune-related adverse events; LCBL, large B-cell lymphoma; NSCLC, non-small cell lung cancer; PJP, *Pneumocystis jiroveci* pneumonia; RCC, renal cell carcinoma; TB, tuberculosis; TNF, tumor necrosis factor.

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References

IMMUNE AND TARGETED TREATMENTS[a,b]

Table 4. Chimeric Antigen Receptor-Engineered T-Cell (CAR T-Cell) Therapy[13]

Mechanism of Action	Agents	Major Uses	Infection Concerns	Recommendations and Comments[c,d,e]
CD19-directed	Axicabtagene ciloleucel	Large B-cell lymphoma, FL	Risk factors for infections: • Pre-infusion: underlying malignancy, prior chemotherapy +/- hematopoietic cell transplant (HCT) • Post-infusion: neutropenia, CRS and treatment (eg, high-dose corticosteroids, IL-6 inhibitors), lymphopenia, and hypogammma-globulinemia Within 30 days: • Neutropenia; CRS • Highest infection risks • Bacterial infections predominate Beyond 30 days: • B-cell aplasia, hypogammaglobulinemia • Lower incidence of infection • Respiratory tract viral infections more common Fungal and herpesvirus infections reported but infrequent	• Screen for and treat HBV as indicated • Recommend PJP and HSV/VZV prophylaxis • Consider antibacterial and antifungal prophylaxis while neutropenic • Consider mold prophylaxis if additional risk factors such as prolonged neutropenia or IST for CRS • Monitor for CRS, which may mimic sepsis. See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
	Brexucabtagene autoleucel	ALL (B-cell), MCL		
	Tisagenlecleucel	ALL (B-cell), DLBCL		
	Lisocabtagene maraleucel	Lymphoma (large B-cell)		
B-cell maturation antigen (BCMA)-directed	Idecabtagen vicleucel	MM		
	Ciltacabtagene autoleucel			

ALL, acute lymphocytic leukemia; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HBV, hepatitis B virus; HSV, herpes simplex virus; MCL, mantle cell lymphoma, MM, multiple myeloma; PJP, *Pneumocystis jiroveci* pneumonia; VZV, varicella zoster virus.

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References

The use of newer targeted therapies and immunotherapy for infection

- While immunotherapy in Cancer is a relatively new field, not so for ID (eg Jenner and smallpox in 1796)
- Monoclonal antibodies for infection (RSV, C. diff, anthrax, ebola, COVID – more to come)
- “new age” immunotherapy for infection – toward restoration of immune function
  - Checkpoint inhibition
  - Cytokine therapies
  - Cellular therapy

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Adoptive immunotherapy for infections in cancer (VST's)

- Selection or in vivo expansion of donor PBMC's (for instance, from stem cell donor) or off the shelf, third party healthy donors.
- Many CMV and EBV treatment studies
- Treatment adenovirus BK virus and viral hemorrhagic cystitis
- Multivirus prevention studies (allo-Tx, SOT) - Prevention of adenovirus (AdV), BK virus (BKV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6), JC virus (JCV)
- Treatment of hMPV, Flu, PIV, RSV in allo/auto or high risk general population

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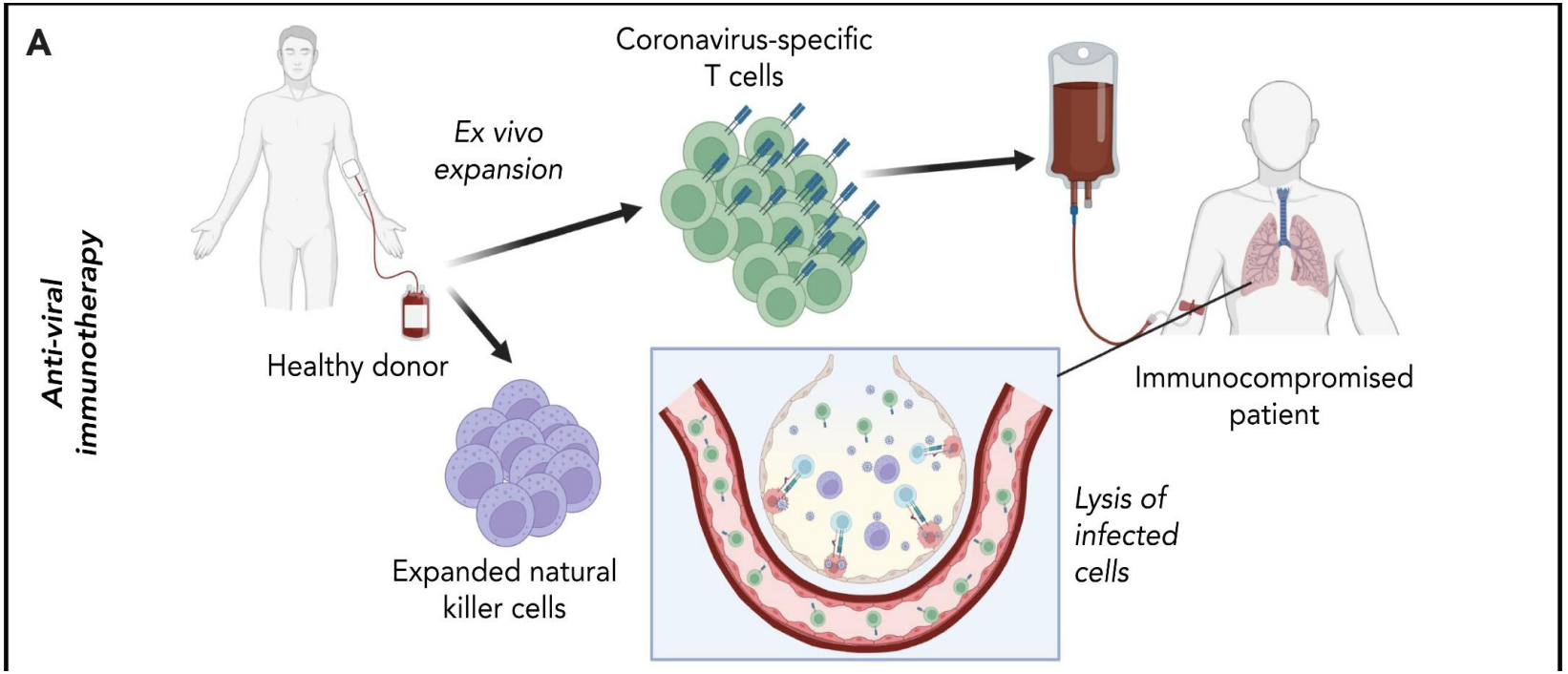
SARS-CoV-2-specific T cells for Adoptive T-cell therapy.



Conway et al. *Blood* (2022) 140 (3): 208–221

Summary

- Targeted and immunotherapies are a growth field in Cancer therapy
- Infections with targeted therapies and immunotherapies in cancer occur, and vary in incidence depending on multiple factors including host, therapeutic target, ancillary treatments
- Vigilance for infection is critical, since other AE's may also be common (such as CRS) and be infection mimics
- Awareness of the risks is critical, and access to updated guidance important given the rapid expansion of these products
- Harnessing immunotherapeutic products to treat infection is not new, but is also a reemerging and growing field

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