NKGen Biotech

SNK Clinical Program Overview
Ex Vivo Activated/Expanded NK Cell Therapy

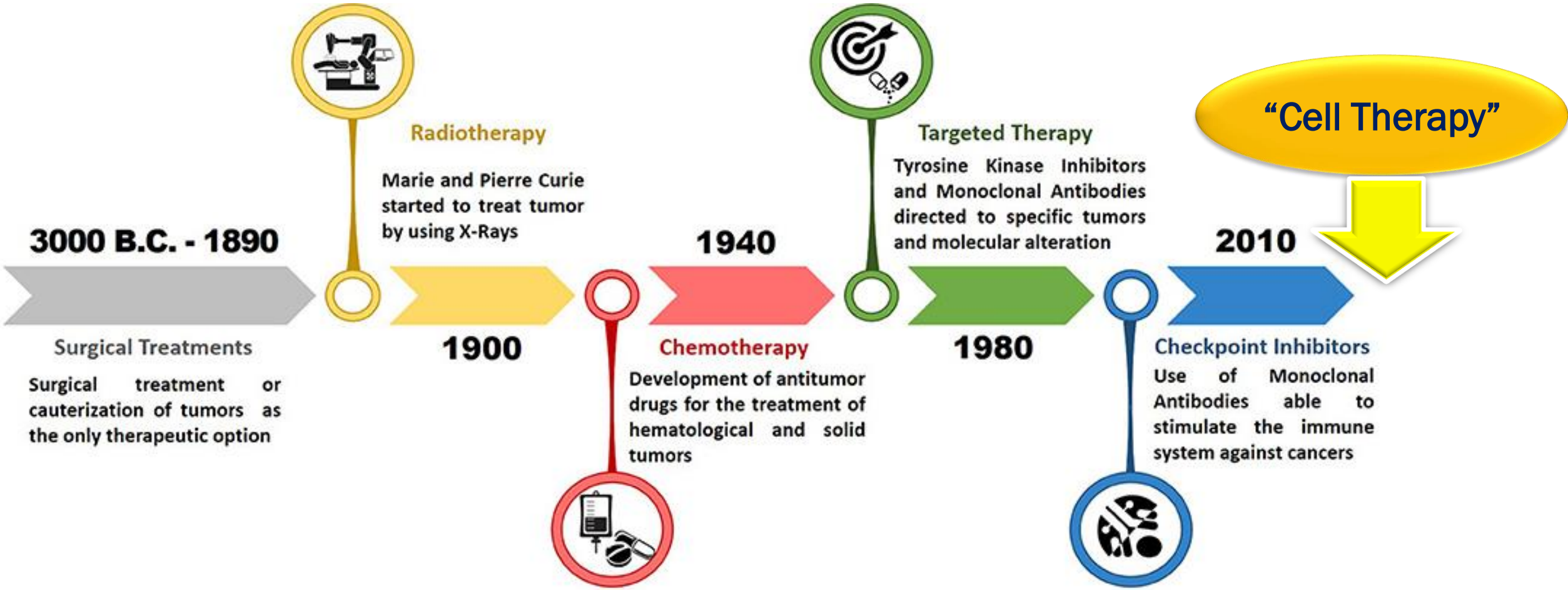
September 2021

Steven Cha, MD Chief Medical Officer – NKGen Biotech

NKGEN BIOTECH

July 2021

Evolution of Cancer Treatment



Falzone et al., 2018

Cell Therapy in Solid Tumors

Challenges

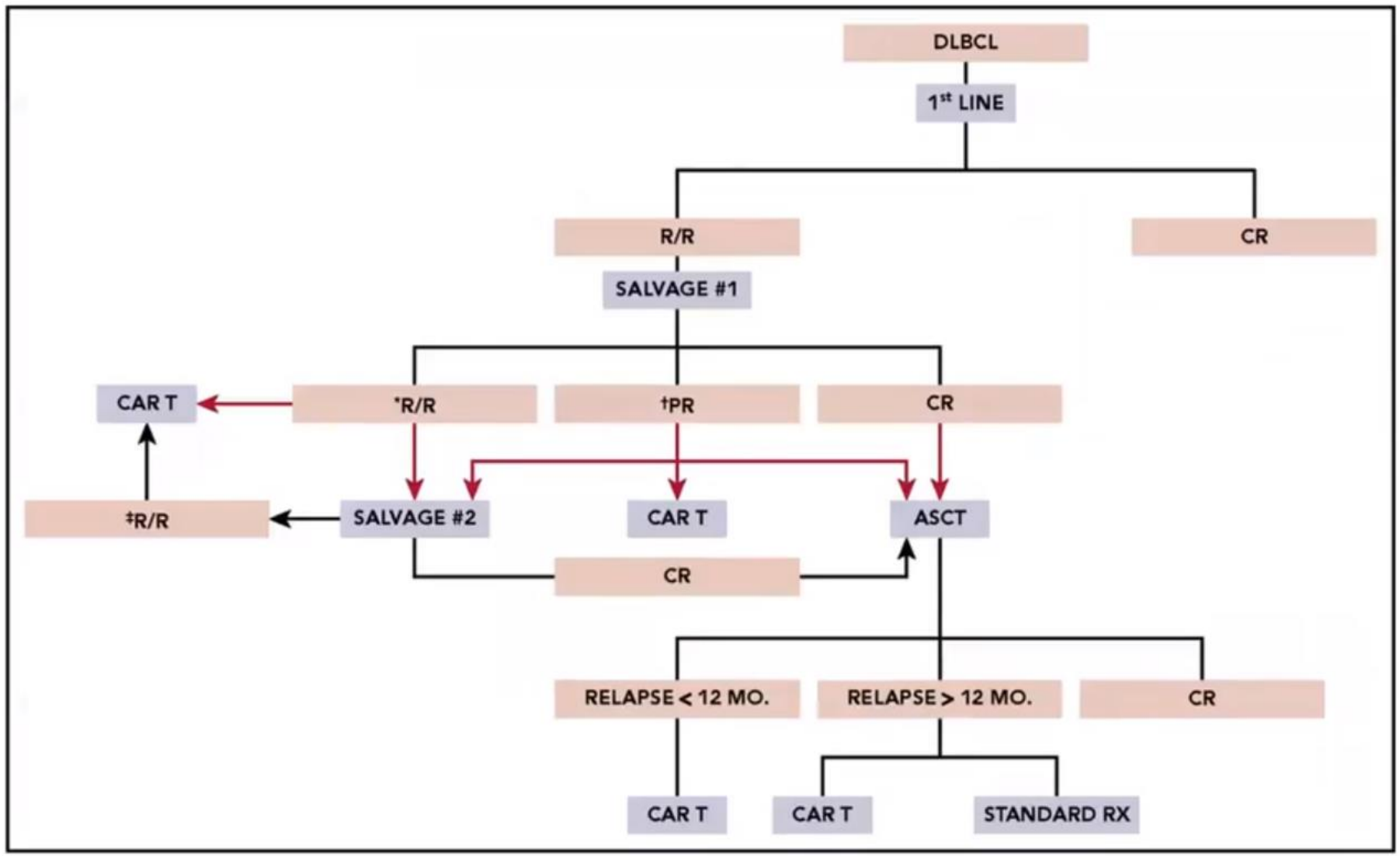
- Tumor Antigen Heterogeneity:
  - CAR Engineering: Tumor-associated antigens (TAA)
    - Diverse expression of TAA from different solid tumor cells → Huge barrier
  - Different levels of antigen expression at various tumor sites
    - May impair CAR-t function due to cancer cell antigen diversity
- Trafficking & Infiltration into Solid Tumor Tissue
  - CAR-t's return to bloodstream & lymphatics
  - Barriers to Migration into Solid Tumor cells:
    - Low/lack of chemokine expression
    - Dense fibrotic matrix in solid tumors
  - Immunosuppresive Tumor Microenvironment

Cell Therapy in Hematological Malignancies

Challenges

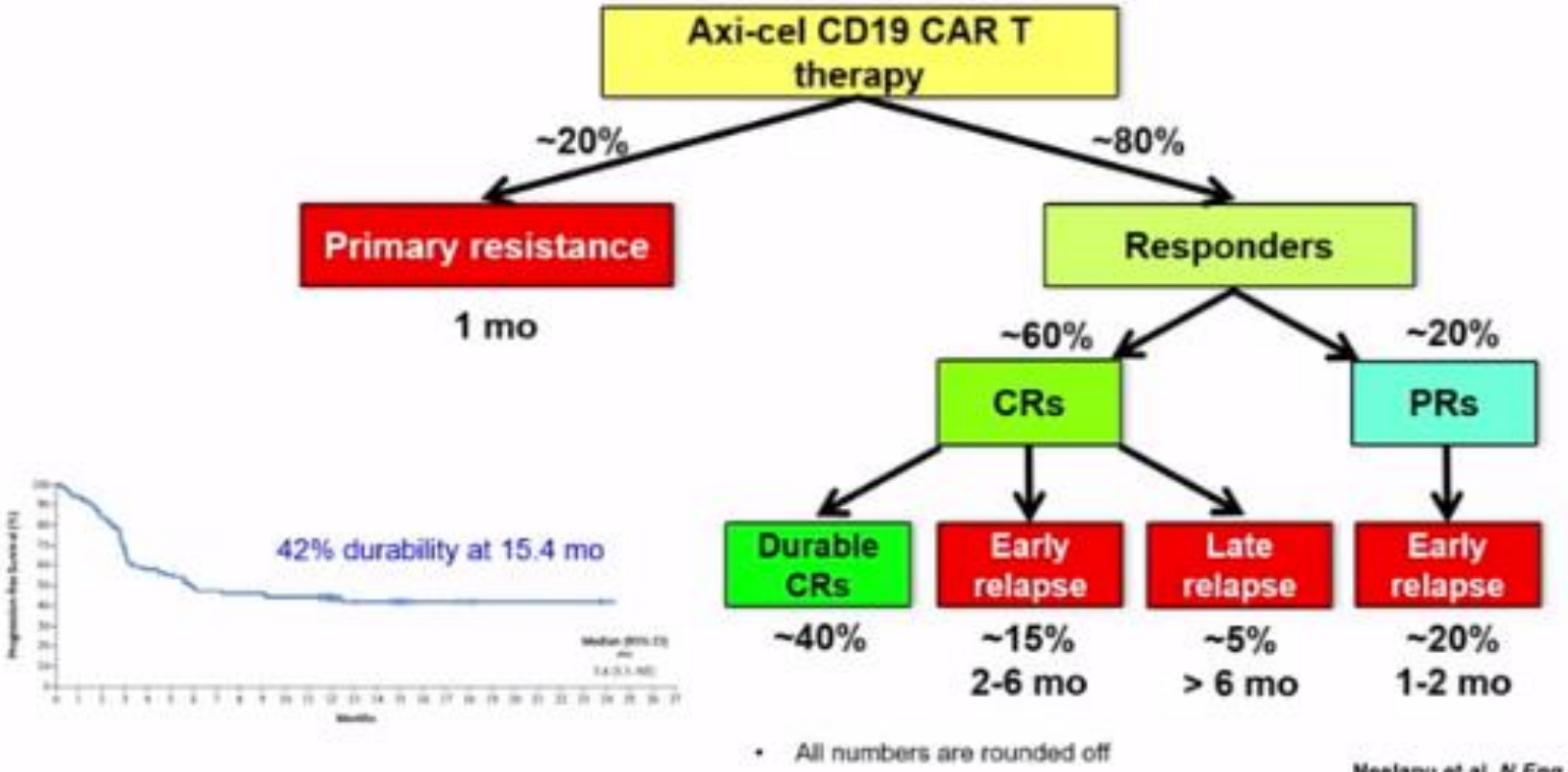
- Not suitable for all hematological malignancies
- CAR-t: successful in later line therapy in B-Cell malignancies
  - ❑ Not all CAR-t's have been successful:
    - ✓ "BELINDA" Trial (Novartis CAR-t) - Phase III in aggressive B-Cell NHL in 2nd line setting
      - ✓ Kymriah® vs SOC ("salvage chemotherapy" followed in responding patients by high-dose chemotherapy and bone marrow stem cell transplant)
      - ✓ No EFS benefit with Kymriah®
- Toxicities:
  - ❑ Lymphodepletion (conditioning chemo): in-patient
  - ❑ Cytokine Release Syndrome:
    - Can be fatal
    - In-patient observation
    - Limits accessibility of CAR-t to handful of sites in the US

When to Consider CAR-t in DLBCL?



Chow Blood 2018

PATTERNS OF FAILURE IN DLBCL AFTER AXI-CEL

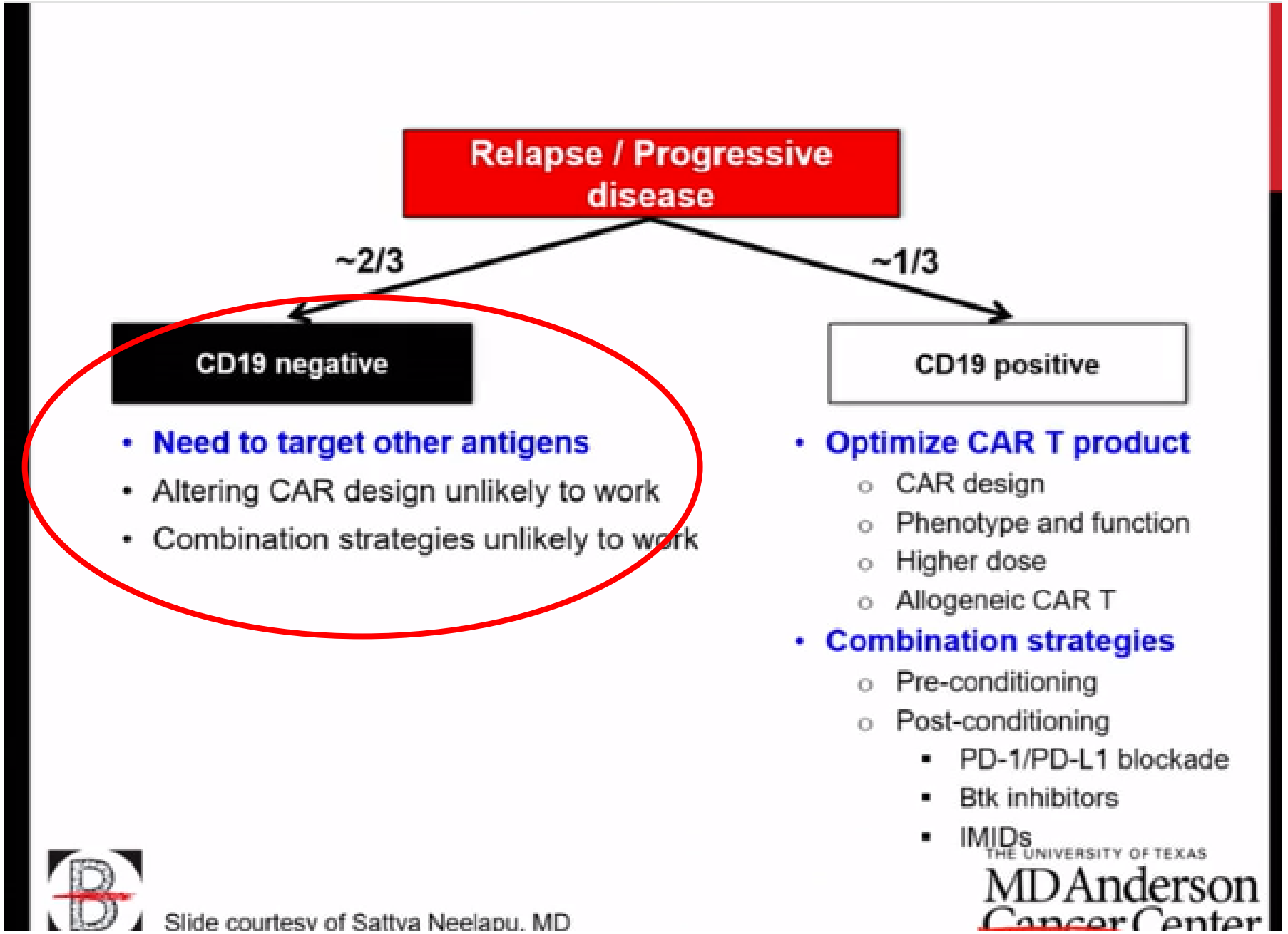


- All numbers are rounded off

Neelapu et al. *N Eng J Med* 2017

Slide courtesy of Sattva Neelapu, MD

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center


Relapse / Progressive disease
~2/3
~1/3
CD19 negative
CD19 positive
• Need to target other antigens
• Altering CAR design unlikely to work
• Combination strategies unlikely to work
• Optimize CAR T product
o CAR design
o Phenotype and function
o Higher dose
o Allogeneic CAR T
• Combination strategies
o Pre-conditioning
o Post-conditioning
▪ PD-1/PD-L1 blockade
▪ Btk inhibitors
▪ IMIDs
Slide courtesy of Sattva Neelapu, MD
THE UNIVERSITY OF TEXAS
MD Anderson
Cancer Center

NCCN Guidelines: Treatment of DLBCL

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2021
Diffuse Large B-Cell Lymphoma

NCCN Guidelines Index
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Discussion

SUGGESTED TREATMENT REGIMENS[a,b]

An FDA-approved biosimilar is an appropriate substitute for rituximab.

FIRST-LINE THERAPY

Preferred regimens
- RCHOP (rituximab,[c] cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)

Other recommended regimens
- Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab

FIRST-LINE THERAPY FOR PATIENTS WITH POOR LEFT VENTRICULAR FUNCTION[d,e,f]

Other recommended regimens (in alphabetical order)
- DA-EPOCH[g] (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab
- RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)
- RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine)
- RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone)
- RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, prednisolone)

FIRST-LINE THERAPY FOR VERY FRAIL PATIENTS AND PATIENTS >80 YEARS OF AGE WITH COMORBIDITIES[e,f]

Other recommended regimens (in alphabetical order)
- RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine)
- RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)
- R-mini-CHOP
- RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, prednisolone)

FIRST-LINE CONSOLIDATION (OPTIONAL)

- Lenalidomide maintenance (category 2B) for patients 60–80 y of age

CONCURRENT PRESENTATION WITH CNS DISEASE[h]

- Parenchymal: systemic high-dose methotrexate (≥3 g/m^2 or more of given on Day 15 of a 21-day RCHOP cycle that has been supported by growth factors)
- Leptomeningeal: IT methotrexate/cytarabine, consider Ommaya reservoir placement. Systemic high-dose methotrexate (3–3.5 g/m^2) can be given in combination with RCHOP or as consolidation after RCHOP + IT methotrexate/cytarabine

NCCN Guidelines: DLBCL – 2nd line and beyond

National Comprehensive Cancer Network®

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Diffuse Large B-Cell Lymphoma

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SUGGESTED TREATMENT REGIMENS[a,b]

An FDA-approved biosimilar is an appropriate substitute for rituximab.

SECOND-LINE AND SUBSEQUENT THERAPY[d,i,j] (intention to proceed to transplant)

Preferred regimens (in alphabetical order)
- DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab
- DHAX (dexamethasone, cytarabine, oxaliplatin) ± rituximab
- GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab
- ICE (ifosfamide, carboplatin, etoposide) ± rituximab

Other recommended regimens (in alphabetical order)
- ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab
- GemOx (gemcitabine, oxaliplatin) ± rituximab
- MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± rituximab

SECOND-LINE AND SUBSEQUENT THERAPY[d,i,j] (non-candidates for transplant)

Preferred regimens (in alphabetical order)
- GemOx ± rituximab
- Polatuzumab vedotin ± bendamustine ± rituximab[k,l]

Other recommended regimens (in alphabetical order)
- CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± rituximab - PO and IV
- CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab
- DA-EPOCH ± rituximab
- GDP ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab
- Gemcitabine, vinorelbine ± rituximab (category 3)
- Rituximab
- Tafasitamab[m] + lenalidomide

Useful in certain circumstances
- Brentuximab vedotin for CD30+ disease
- Bendamustine[k] ± rituximab (category 2B)
- Ibrutinib[n] (non-GCB DLBCL)
- Lenalidomide ± rituximab (non-GCB DLBCL)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

See First-line Therapy on BCEL-C 1 of 5.

[a] See references for regimens on BCEL-C 4 of 5 and BCEL-C 5 of 5

NCCN Guidelines: 3rd line and beyond

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2021
Diffuse Large B-Cell Lymphoma

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SUGGESTED TREATMENT REGIMENS[a]

CONSOLIDATION AFTER ALTERNATE SECOND-LINE THERAPY

- Allogeneic hematopoietic cell transplant (nonmyeloablative or myeloablative) for CR/PR following alternative second-line therapy

THIRD-LINE AND SUBSEQUENT THERAPY

- Anti-CD19 CAR T-cell therapy (only after ≥2 prior chemoimmunotherapy regimens)[p]
  - Axicabtagene ciloleucel
  - Lisocabtagene maraleucel
  - Tisagenlecleucel[q]
- Loncastuximab tesirine[m,r] (only after ≥2 lines of systemic therapy)
- Selinexor (only after at least two lines of systemic therapy; including patients with disease progression after transplant or CAR T-cell therapy)[o]

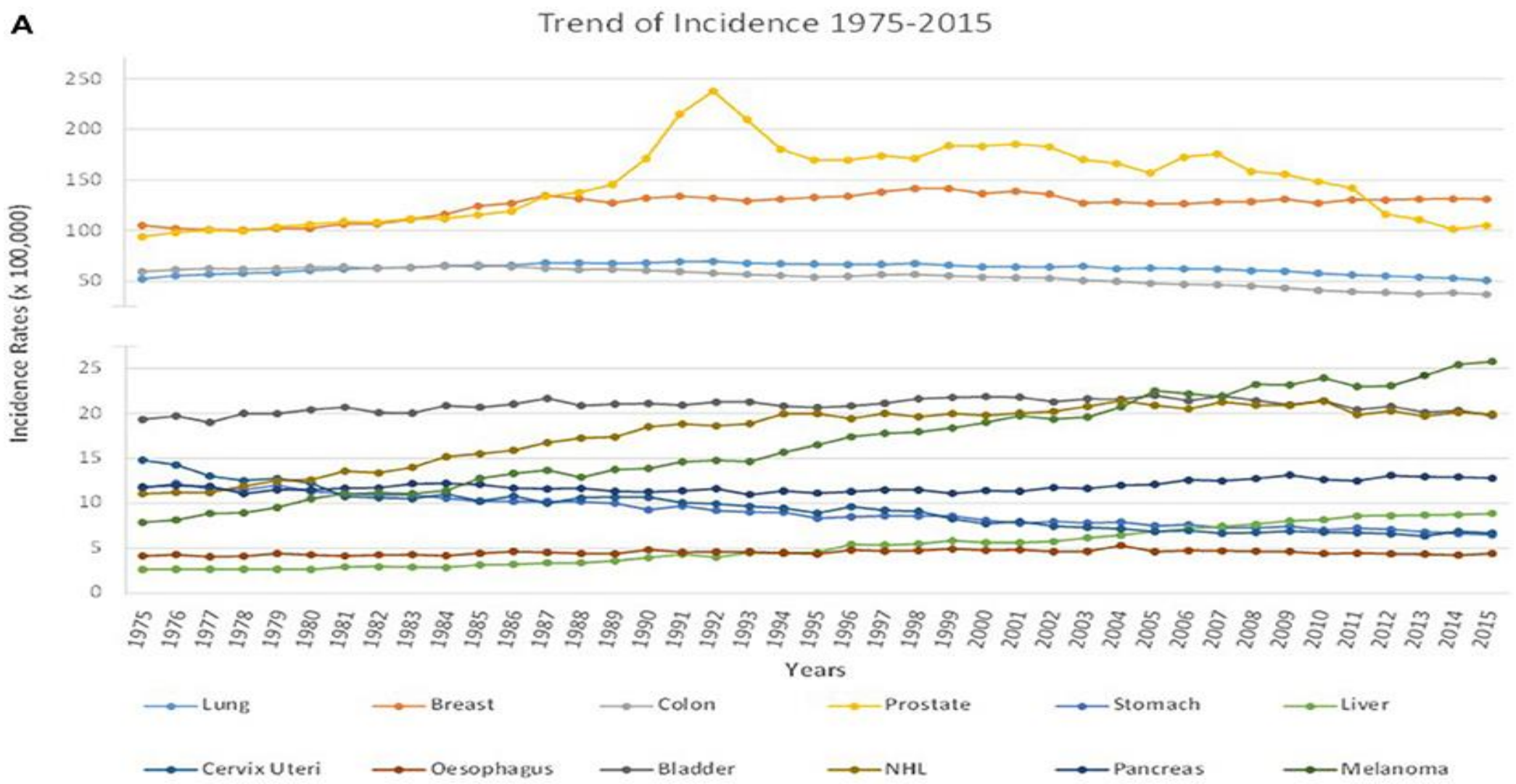
Response in Patients with Refractory DLBCL

- SCHOLAR-1 (International, Multicohort Retrospective NHL Research Study):
  - Data from 2 phase 3 clinical trials
    - Lymphoma Academic Research Organization-CORAL and Canadian Cancer Trials Group LY.12
    - 2 observational cohorts (MDACC & University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence)
  - 636 Patients with Refractory Disease

- ORR 26% (CR 7%)
- mOS: 6.3 months
- 20% 2-year OS

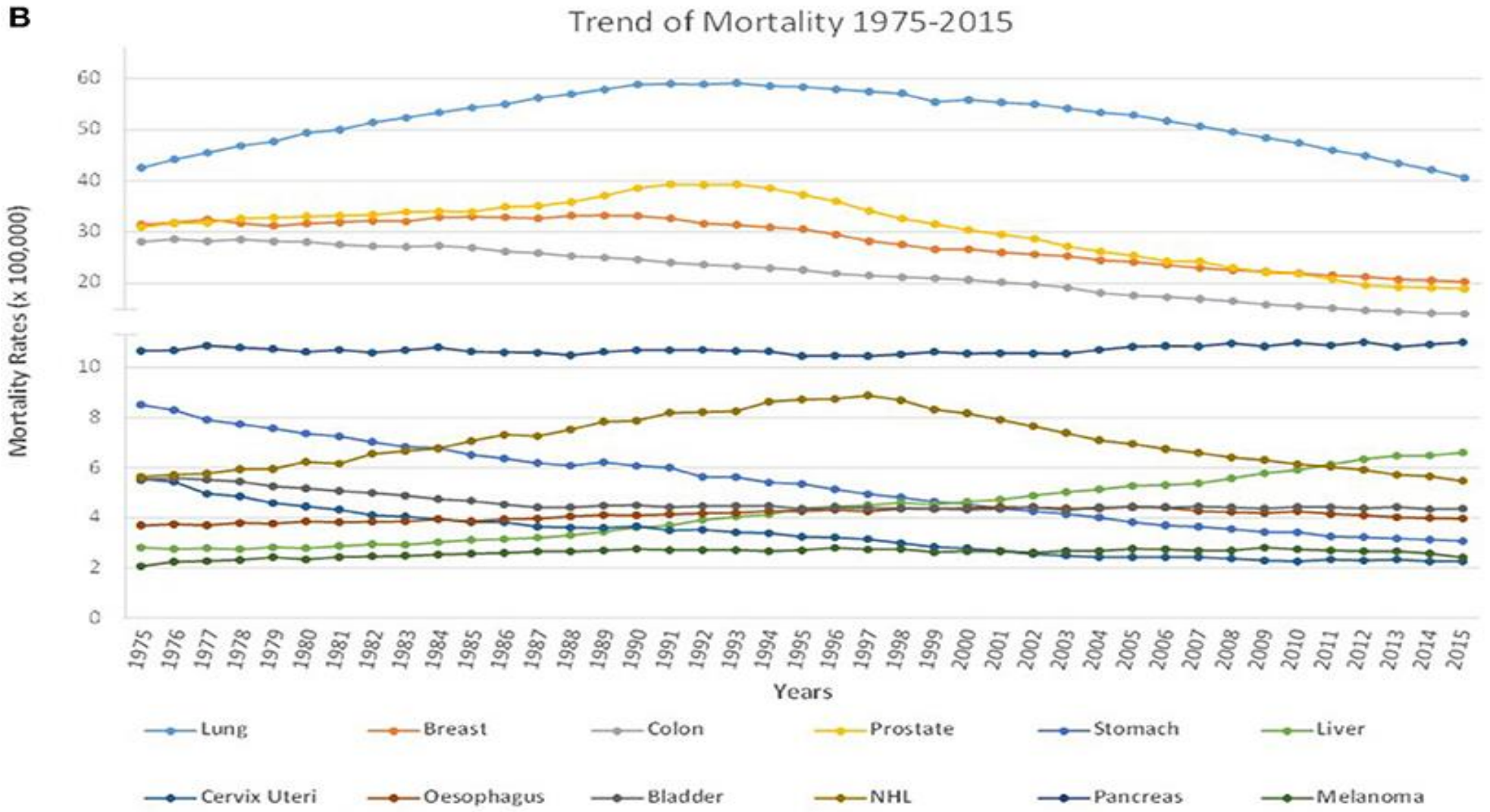
- Not unusual to see patients with CR & PR in salvage therapy setting
- Survival benefit is key in oncology drug development

Cancer Incidence: 1975 - 2015



Falzone et al., 2018

Cancer Mortality Rates: 1975 - 2015



Falzone et al., 2018

Pioneering NK Cell Therapy in Solid Tumor Settings

Historically, blood and bone marrow transplant experience showed infusion of **non-activated/non-expanded donor NK cells** into patients did not confer much clinical benefit

Factors Needed to "Build" Successful NK Cell Therapy	NKGEN BIOTECH	OTHERS
CYTOTOXICITY NK cells need proper "training" to effectively kill cancer cells ***Multiple distinct proprietary feeder cell lines + cytokine cocktail***	✓	⊘
POTENT, SAFE AUTOLOGOUS NK CELLS ▪ True outpatient procedure for large number of patients ▪ No lymphodepletion required ▪ Zero risk of GVHD ▪ Repeat dosing without interruption, discontinuation, modification	✓	⊘
SOLID TUMOR CLINICAL DATA Convincing and promising as single agent & combination approach	✓	⊘
HIGHEST ACHIEVABLE QUANTITY Dosing 4+ billion active cells per infusion in clinic	✓	⊘
CRYOPRESERVATION Retain viability and cytotoxicity	✓	?

SNK Cells: Highly Cytotoxic Activity

Superior “Educated” NK Cells leading to superior cytotoxicity across multiple solid tumor indications

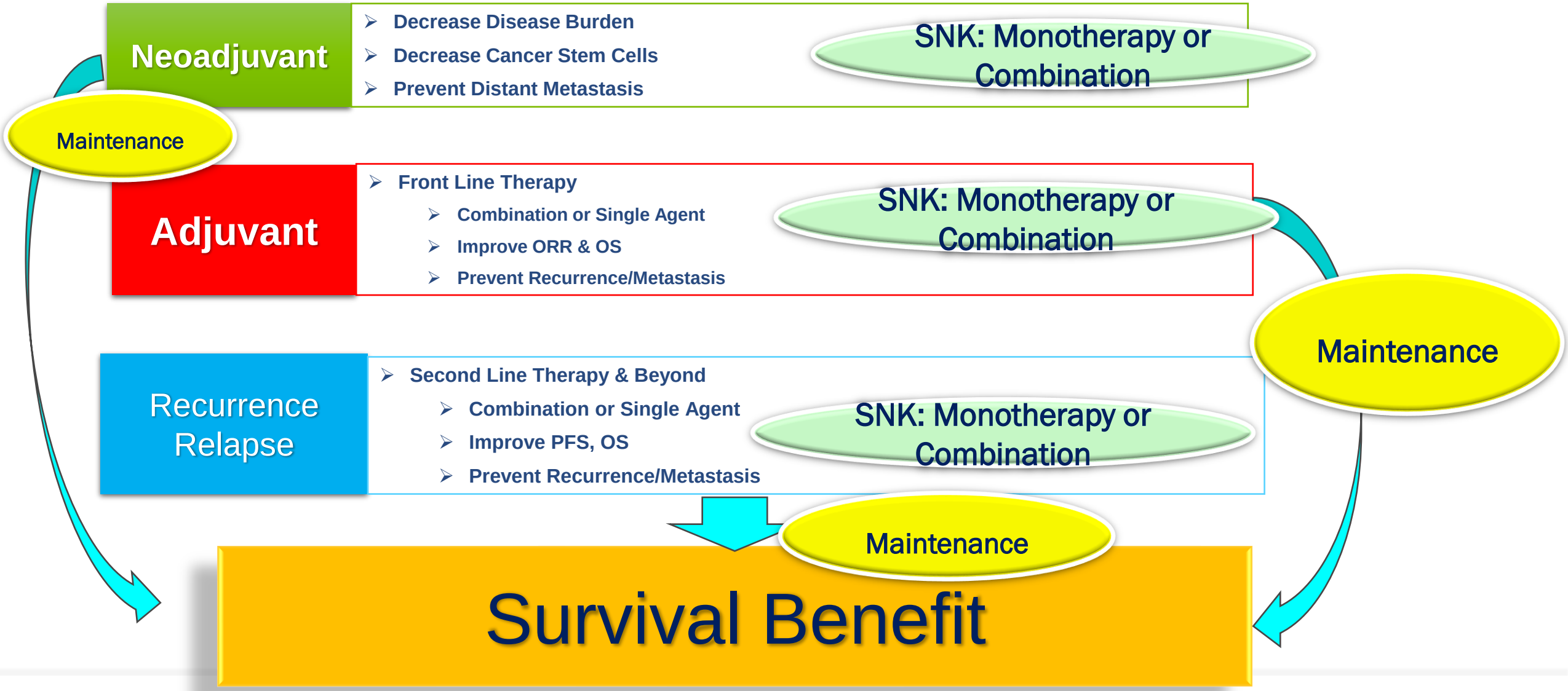
- Direct Antitumor Effects (lysis)
- Enhances ADCC Activity
- Anti-Cancer Stem Cell Activity → Prevents Distant Metastasis
- Potentially recruit and activate immune cells to tumor environment

SNK01 Cells: Safe & Well Tolerated with long term dosing

Autologous Platform:

- Not Engineered
  - ✓ iPSC may need long term (10-15 years) safety study in Clinical Trials
- Patients own cells
  - ✓ Zero risk of GvHD, even with multiple, repeat, chronic dosing
- Lymphodepletion not required
  - ✓ No “conditioning chemo” needed
  - ✓ Most NK Cell Therapy programs require full or partial conditioning chemo (e.g., fludarabine (25 mg/m2, d1–d3) and cyclophosphamide (500 mg/m2 d2–d3)
    - Cases of Cytokine Release Syndrome already seen with other platform
    - Cases of bone marrow suppression (e.g., neutropenic fever) observed with other platform

Oncology: Strategic Treatment with SNK



NK cell infiltration and outcome

TUMOR TYPE	NK cells infitration	NOTES
CRC	POOR	Pre-operative low NK level is associated with higher risk of recurrence
Melanoma	POOR	High NK level in tumor infiltrated LNF. High expression of NKG2D and NKp30 correlates with low number of cancer cells
Breast	YES	Positive corelation NK – response to neoadjuvant therapy [illegible] biomarker for
Head [illegible]		[illegible]
Kidney	YES	[illegible] favourable prognosis
NSCLC	POOR	No impact on outcome (but NK cells do not infiltrated tumor nests and remain in the stroma – NK exclusion)

SNK 01

Highly Promising Clinical Data in patients with NSCLC and Sarcoma, especially in heavily pre-treated settings

Habif G et al, Cell Molecular Immunol 2019

SNK01 + pembrolizumab in NSCLC

Clinical Trial Initiated 2/2019

Title	A phase 1/2A, randomized, open, single-center trial evaluating the safety and anti-tumor activity of SNK01 (Natural Killer cells) plus pembrolizumab in patients with Non-Small Cell Lung Cancer who failed first-line platinum-based chemotherapy
Indication	Stage IV Non-Small Cell Lung Cancer patients who failed platinum-based chemotherapy
Investigational Product (IP)	SNK01 (Super Natural Killer cells; Autologous Natural killer cells)
Estimated Enrollment	More than 18 subjects: • Cohort 1 (3 + 3): 2 x 10^9 NK cells/dose , 6 times injection with one-week intervals plus Keytruda (pembrolizumab) 200 mg, injection with three-week intervals • Cohort 2 (3 + 3): 4 x 10^9 NK cells/dose , 6 times injection with one-week intervals plus Keytruda (pembrolizumab) 200 mg, injection with three-week intervals • Cohort 3 (6): Control – Keytruda (pembrolizumab) 200 mg, injection with three-week intervals
Administration Schedule	See table below
Outcome Measures	F/U period: 52 weeks after enrollment • Safety Evaluation variables: Adverse events (NCI CTCAE V5.0), physical examination, Clinical laboratory test, ECG • Efficacy Evaluation variables: - Potential efficacy: progression-free survival (PFS), overall survival rate (OS), time to progression (TPP), objective response rate (ORR), QoL (EORTC QLQ-C30, EORTC QOL-LC13) • Others: Change of immune cell population (T-cell, B-cell, Treg, NK cell) & cytokines (chemokines)

Week	W1	W4	W5	W6	W7	W8	W9	W10	W13	...	W52	Follow-up every 3 months
Pembrolizumab	●	●			●			●	●	Every 3 weeks	End of Study Visit	
SNK01		●	●	●	●	●	●					

Comparable Patient Population to Keynote-001 Trial

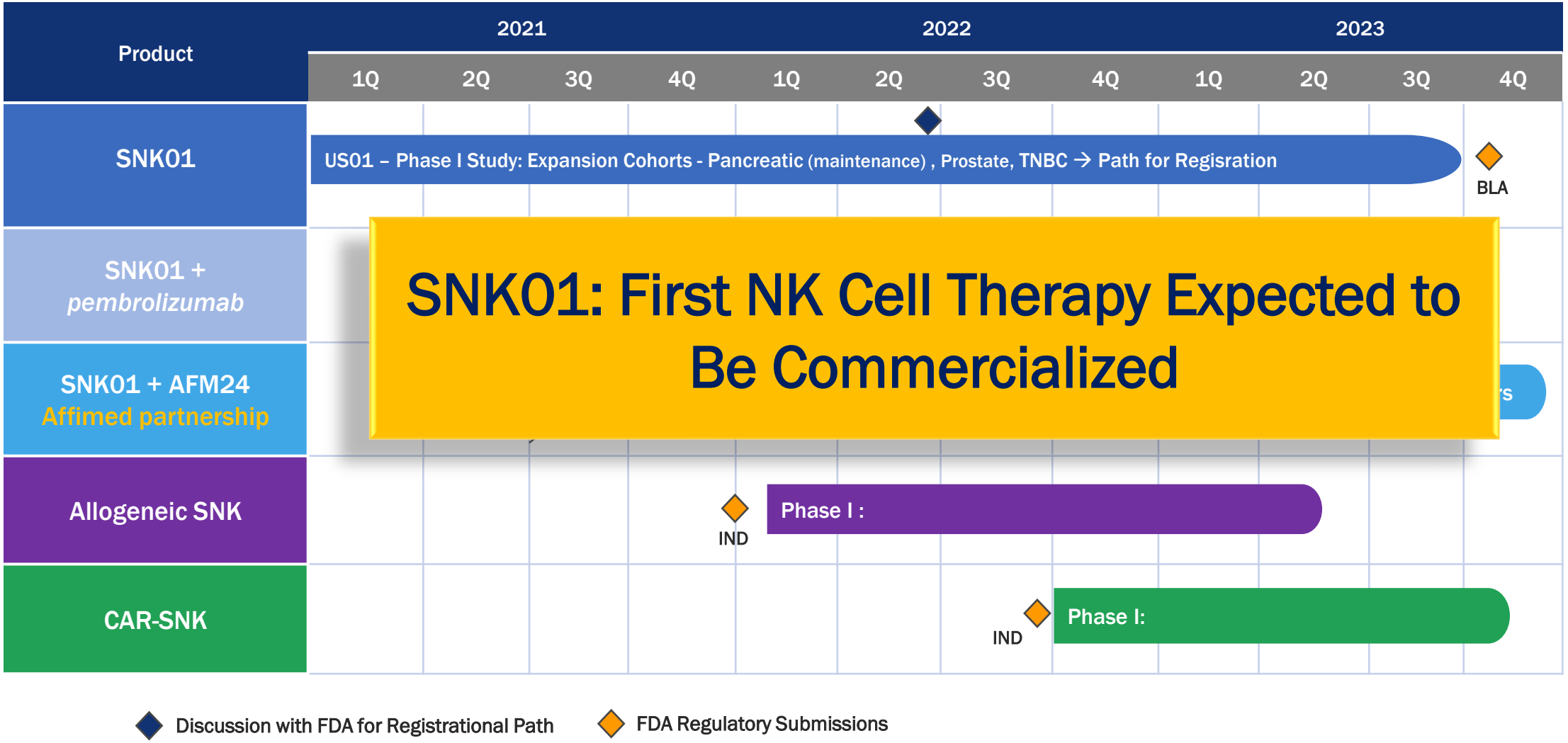
Study Data: SNK01 + pembrolizumab in NSCLC

	ASCO 2020 Presentation	
	pembrolizumab only (Cohort 3)	SNK01 + pembrolizumab
ORR	0/8 (0 %)	4/9 (44.4 %)
Median PFS	1.6 months	8.0 months
Median OS	6 months	Not reached

Final Data – Completed Study

- Compelling final data to be submitted for publication. Planning to present data at SITC 2021 if publication has not been accepted by the time of the SITC meeting.
- Final data set shows maintenance of trend on interim efficacy data from ASCO 2020.
- Treatment cohorts containing SNK + pembrolizumab reported robust, superior ORR and PFS than the cohort receiving pembrolizumab alone.
- Statistically significant PFS ($p < 0.05$).

SNK Oncology Clinical Development Timeline - Path to Approval & Commercialization



Maximizing NK Cell Therapy Potential

Multiple Therapeutic Indications

- Clinical benefit as monotherapy
- Increased PFS with SNK01+ pembrolizumab vs pembrolizumab alone in NSCLC
- Targeted therapy with CAR-NK: EGFR, HER2 settings

Safety

- Safe, well-tolerated, without dose modifications, interruptions, or discontinuations
- Safe to combine with pembrolizumab
- Potential to combine with other agents

Maximizing SNK Potential

- Precision/Personalized Medicine
- Harness potential for NK Cell Therapy
- Ability to position in Front Line Therapy, Maintenance Therapy, Combination Therapy