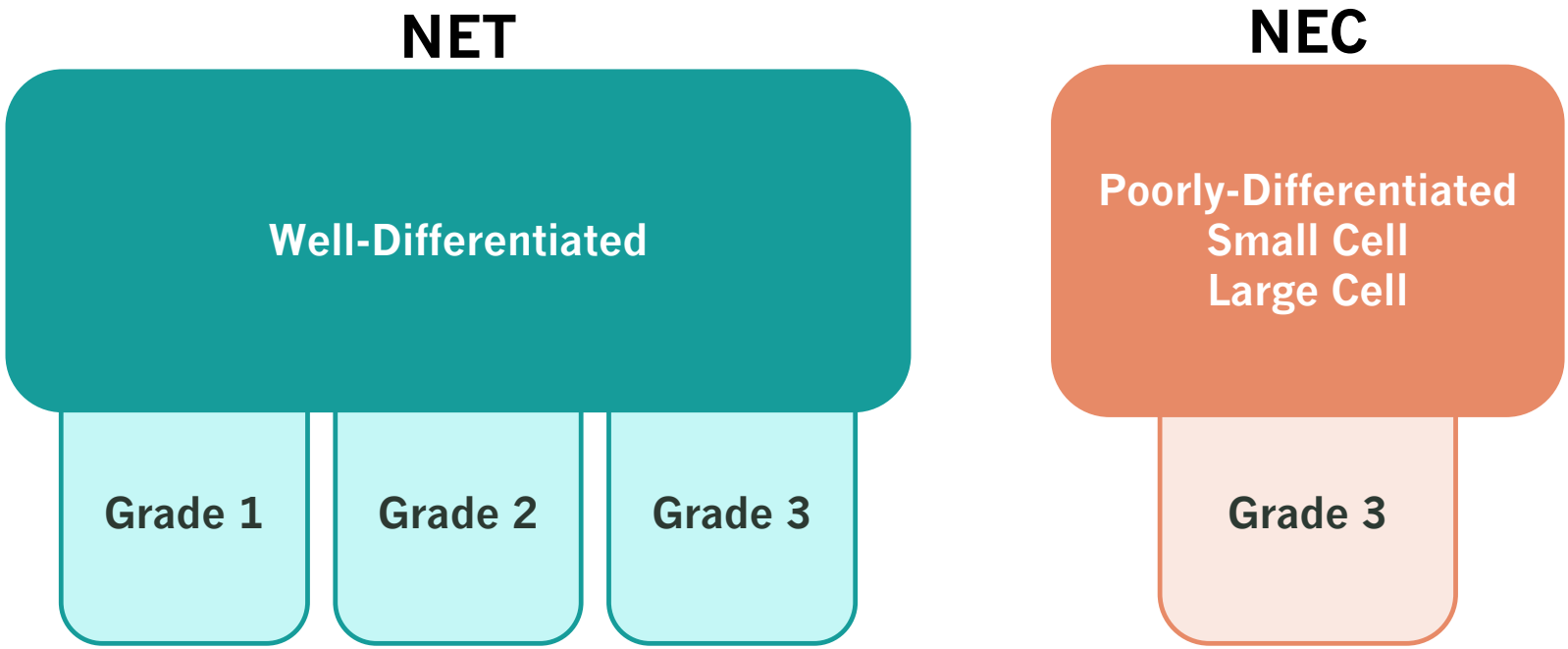
Latest in Immunotherapy for Neuroendocrine Cancers

Aman Chauhan, MD

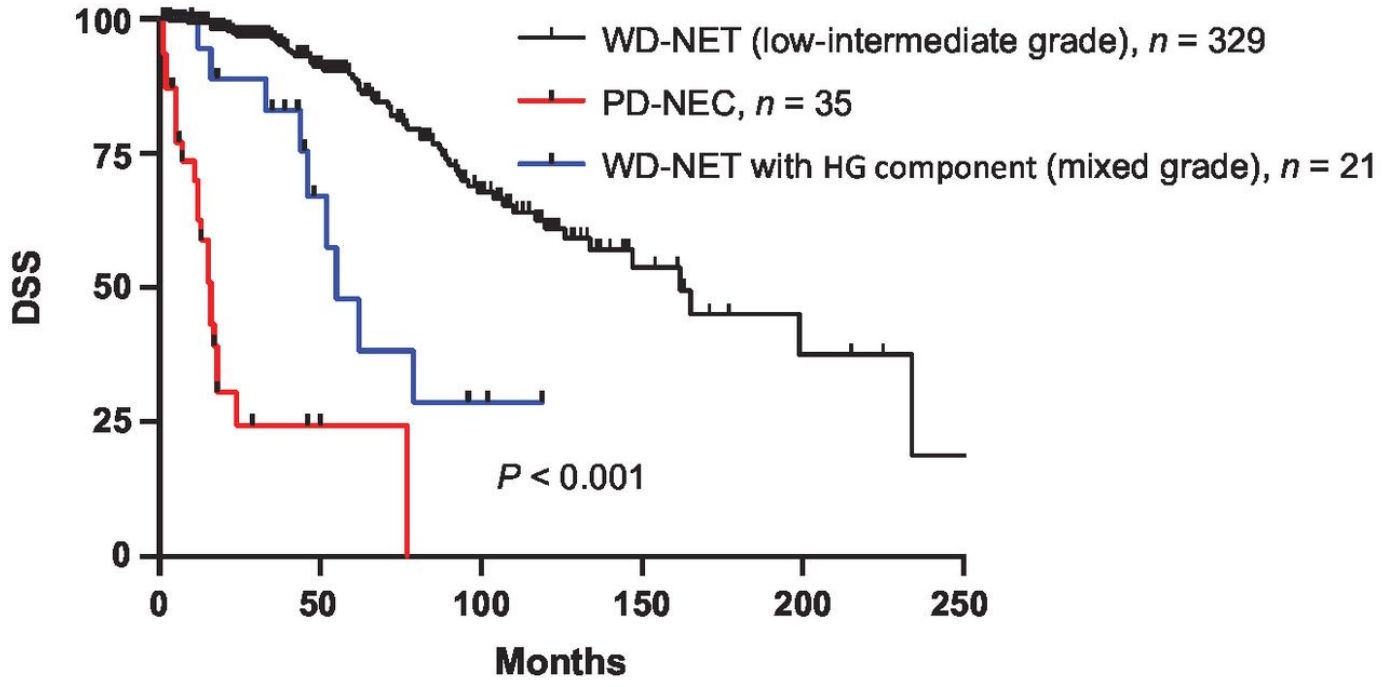
Neuroendocrine Neoplasm Classification



NEC = neuroendocrine carcinoma.

Chauhan et al, CA Jr of Clin 2024.

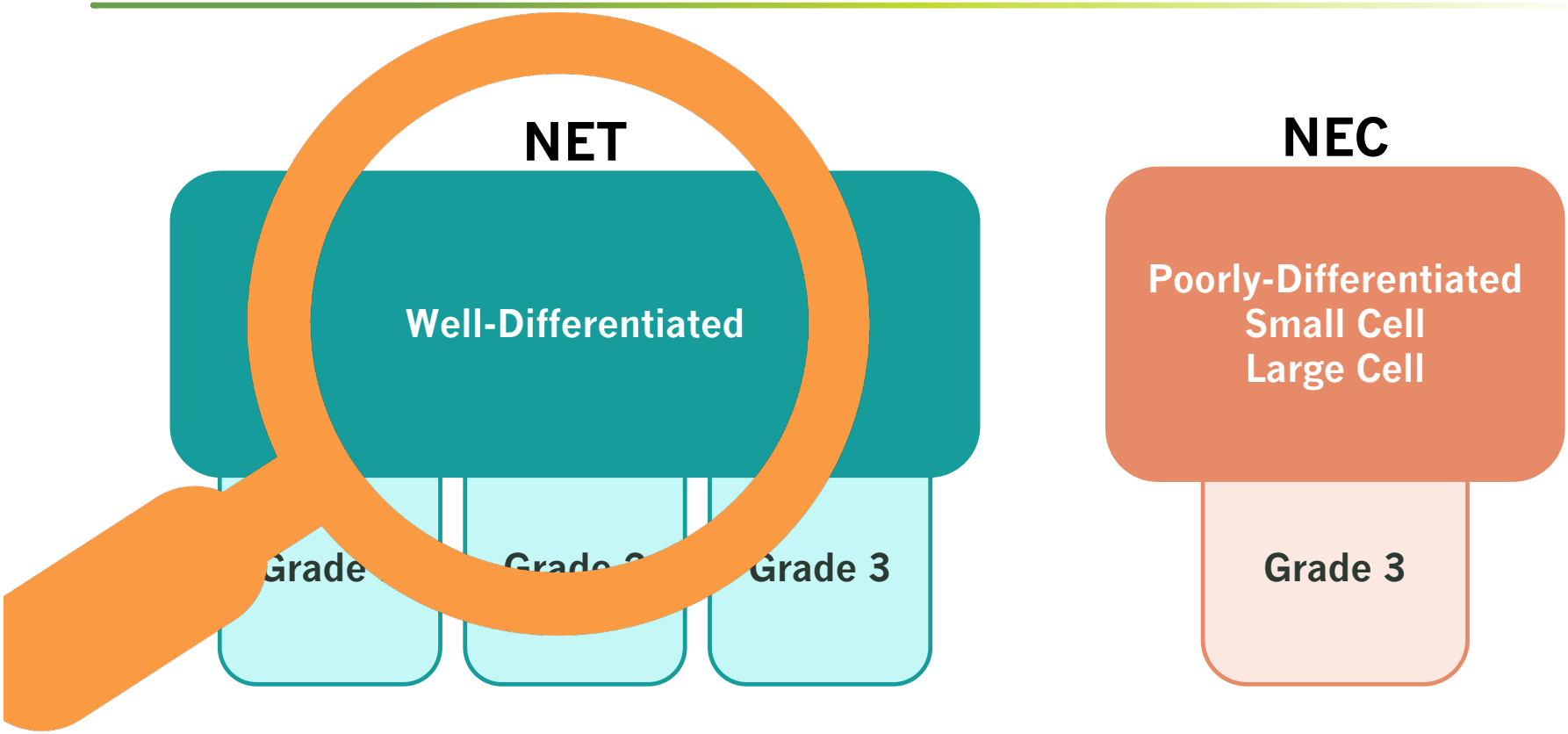
Survival by Grade and Differentiation



DSS = disease-specific survival; PD = poorly-differentiated; HG = high-grade.

Tang et al, 2016.

Neuroendocrine Neoplasm Classification



NEC = neuroendocrine carcinoma.

Chauhan et al, CA Jr of Clin 2024.

Currently immunotherapy is not routinely used in well differentiated NETs

Interferon Alpha and NETs: Historical but largely obsolete therapy

Clinical Effects:

- • Disease stabilization in 40–60% (older studies)
- • Limited ORR (~0–10%)
- • Helps refractory carcinoid syndrome

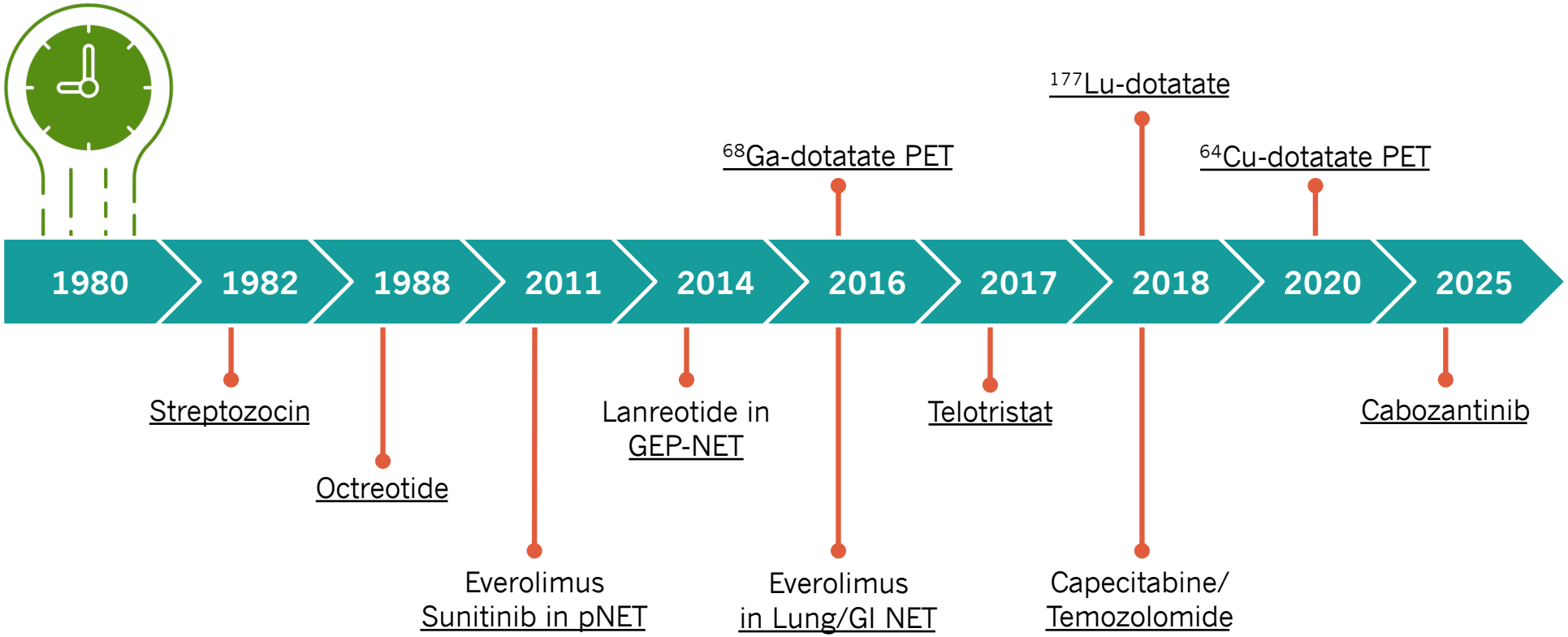
Limitations:

- • Fatigue, flu-like symptoms, mood changes
- • Cytopenias, thyroid dysfunction, hepatotoxicity

Current Role:

- • Rarely used; niche option for refractory syndrome or limited settings

Advances in Neuroendocrine Tumors



Lu = lutetium; pNET = pancreatic neuroendocrine tumor.

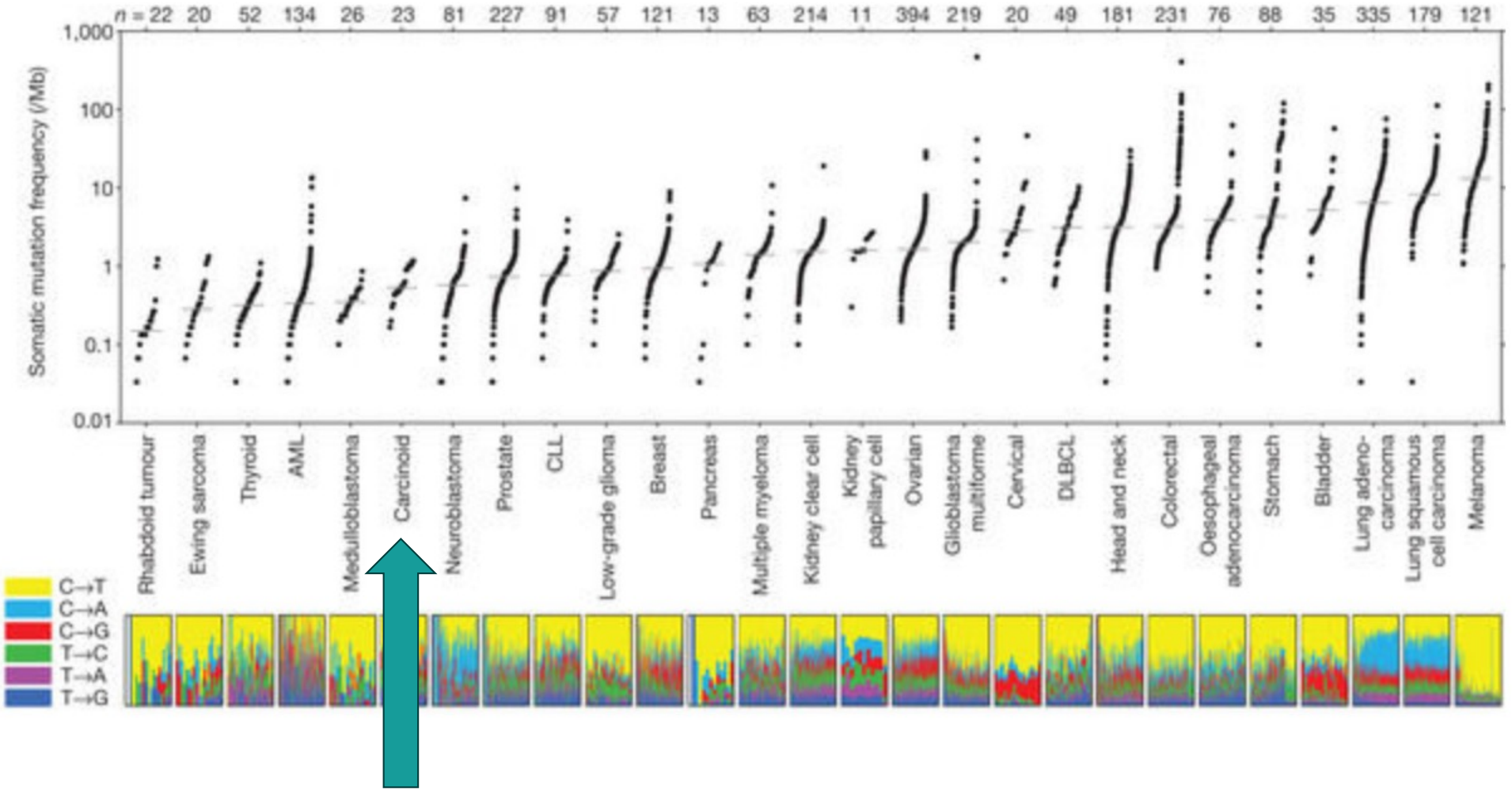
Chauhan et al, CA Jr of Clin 2024.

No approved immunotherapies for use in well differentiated NETs

Several negative studies evaluating immune checkpoint inhibitors in NETs

Immune Checkpoint Inhibitors in Well-Differentiated NETs (G1–2)

Study	Agent(s)	Population	N	ORR	Key Findings
KEYNOTE-028	Pembrolizumab	PD-L1+ carcinoid & pNET	41	12% (carcinoid) / 6.3% (pNET)	Modest activity; some durable responses; mostly stable disease
KEYNOTE-158	Pembrolizumab	Previously treated NETs (all GEP + lung)	107	**3.7%**	Essentially negative; rare deep durable PRs
Spartalizumab (PDR001)	Anti-PD-1	GI-, pNET-, thoracic NETs	116	3–7% (best in thoracic NET)	Minimal activity in GEP NET, small signal in lung NETs
Avelumab (G2–3 NEN)	Anti-PD-L1	G2–3 NEN (mixed)	27	0%	Limited monotherapy activity; some stable disease



Lawrence, M., Stojanov, P., Polak, P. *et al.* Mutational heterogeneity in cancer and the search for new cancer-associated genes. *Nature* **499**, 214–218 (2013).

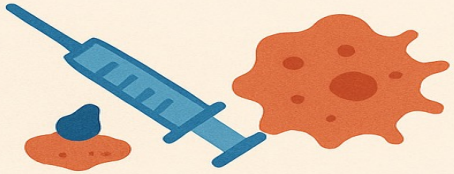
CANCER IMMUNOTHERAPY

BOOSTING THE IMMUNE SYSTEM TO FIGHT CANCER

Immune Checkpoint Inhibitors

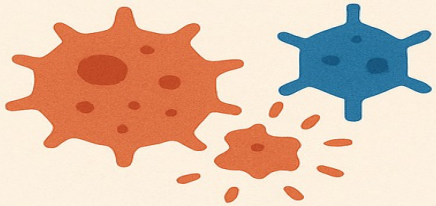
REMOVING BRAKES SO YOUR IMMUNE SYSTEM CAN FIGHT CANCER AGAIN

Cancer Vaccine



TEACHING YOUR IMMUNE SYSTEM WHAT THE CANCER LOOKS LIKE

Oncolytic Virus



A VIRUS THAT SELECTIVELY INFECTS AND DESTROYS CANCER CELLS

T-Cell Engagers

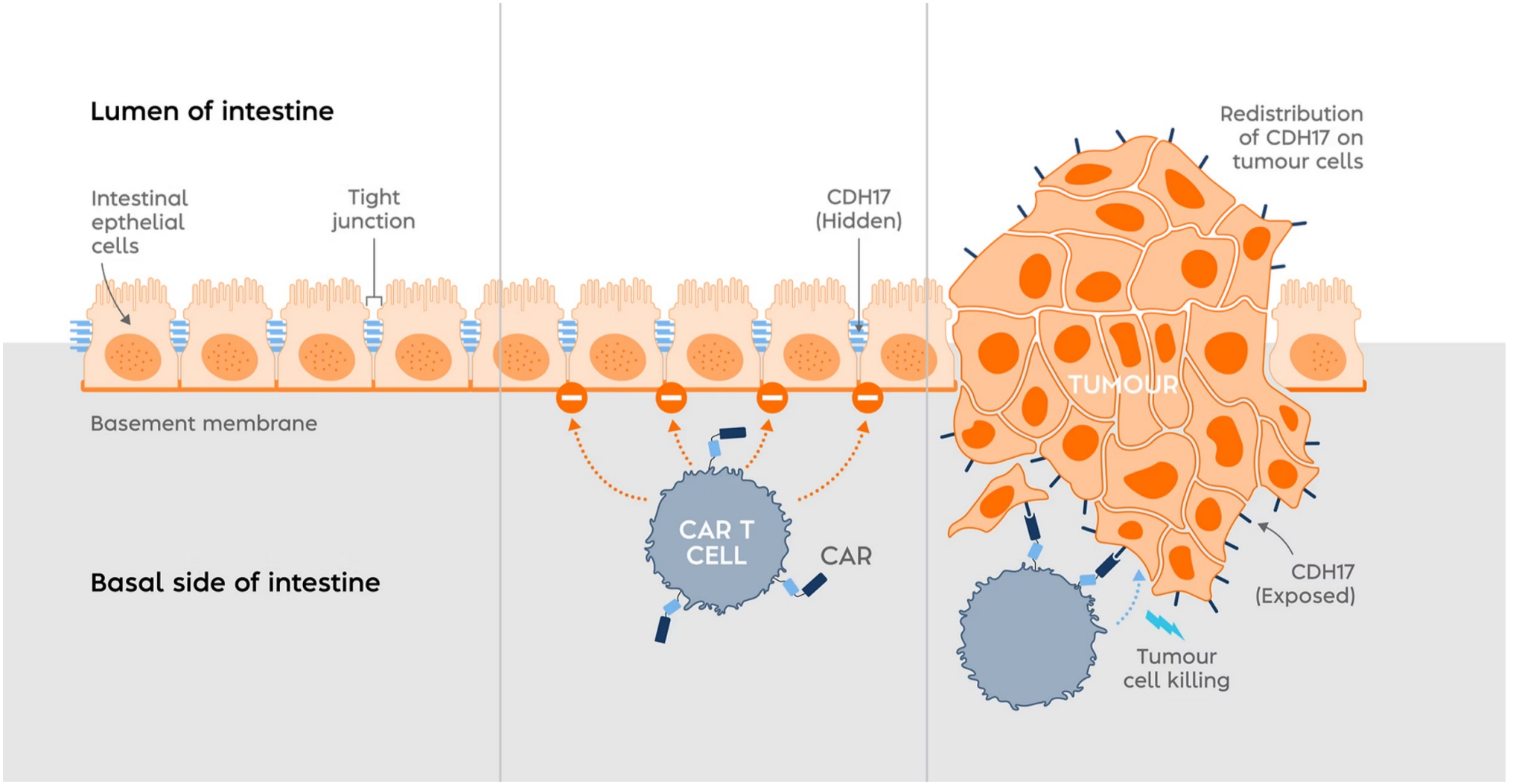
FORCING T CELLS AND CANCER CELLS TOGETHER SO KILLING CAN HAPPEN

REMOVING BRAKES SO YOUR IMMUNE SYSTEM CAN FIGHT CANCER LOOKS LIKE

- CAR-T
- Cancer Vaccine
- Oncolytic Virus

A Phase 1 / 2 Study to Evaluate CHM-2101, an Autologous Cadherin 17 Chimeric Antigen Receptor (CAR) T Cell Therapy

- **IDENTIFIER (ClinicalTrials.gov)**: NCT06055439
- **SPONSOR**: Chimeric Therapeutics



Chimeric Therapeutics

- This is a Phase 1/2 open-label study to evaluate CHM-2101, an autologous CDH17 CAR T-cell therapy for the treatment of advanced gastrointestinal (GI) cancers that are relapsed or refractory to at least 1 standard treatment regimen in the metastatic or locally advanced setting.

- Eligible participants will undergo leukapheresis to collect PBMCs for product manufacturing, which comprises enrichment of T cells, lentiviral transduction, ex vivo expansion, and cryopreservation of the CHM-2101 cell product.

A Phase 1 / 2 Study to Evaluate CHM-2101, an Autologous Cadherin 17 Chimeric Antigen Receptor (CAR) T Cell Therapy

- **Sponsor** Anusha Kalbasi (Stanford)
- **IDENTIFIER (ClinicalTrials.gov)**: NCT04119024 (UCLA and Stanford)

- ***IL13Rα2 CAR T was originally investigated in Melenoma***
- Study is open to screening NET patients for target "***IL13Rα2 CAR T "***

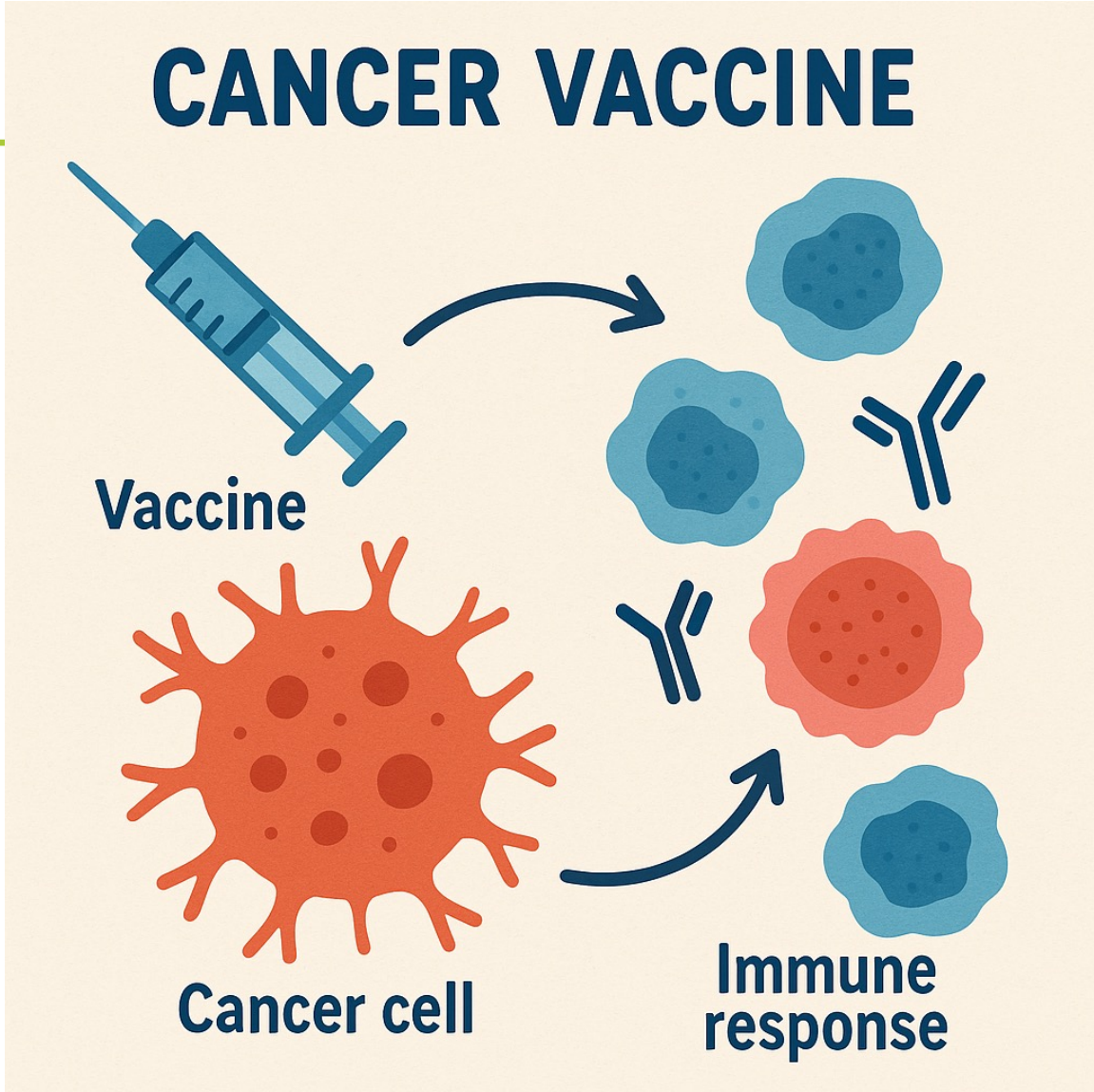
SVN53-67/M57-KLH peptide vaccine (SurVaxM) and octreotide acetate (Sandostatin LAR)

Renuka V. Iyer, MD

CLINICALTRIALS.GOV IDENTIFIER

NCT03879694

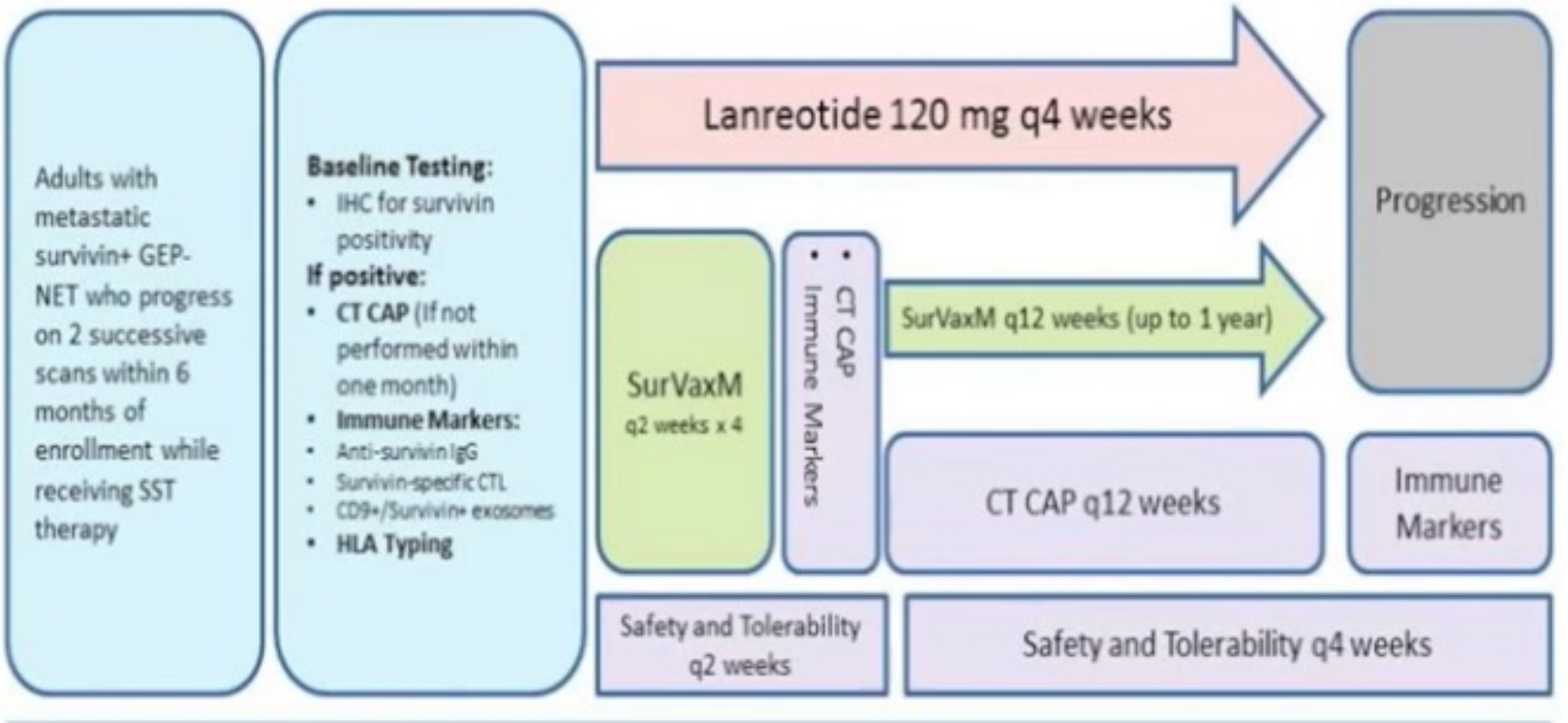
Roswell Park Cancer Institute



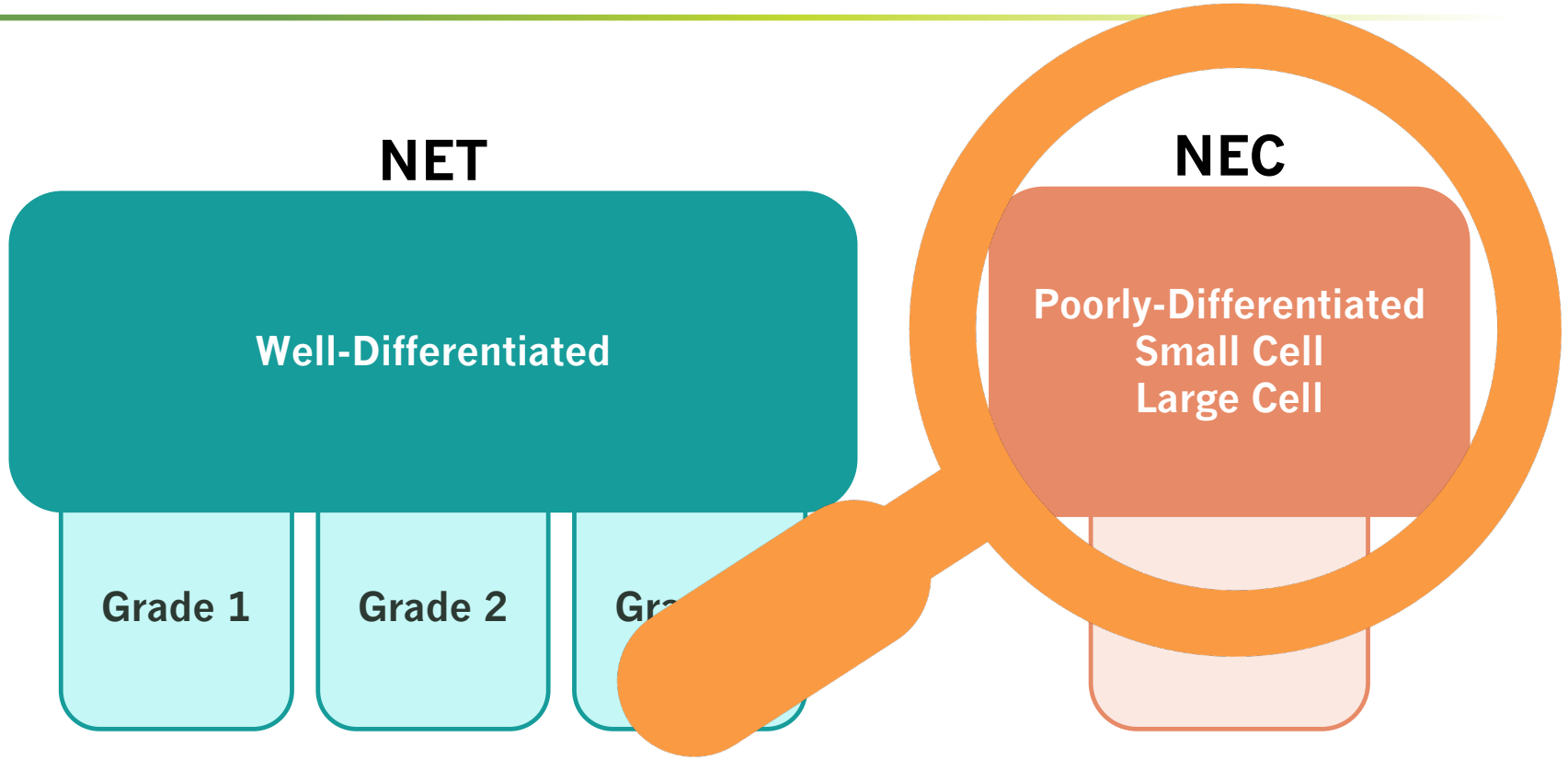
Rationale

- Survivin is an intracellular protein that alters cell division, function of cell death proteases and inhibits apoptosis. It is undetectable in adult cells and expressed in many tumors, making it an ideal target.
- SurVaxM is a 15 amino acid synthetic peptide vaccine. It stimulates antigen presentation via intracellular cell-surface target recognition and induces CD8+ & CD4+ T cells and IgG production. It was well tolerated in a phase I trial in recurrent glioma pts (Fenstermaker et al., Neurooncol; 2014). Prelim analysis from a phase II study in glioma pts showed its efficacy (Ahluwalia et al., Neurooncol; 2018).

Study Schema



Neuroendocrine Neoplasm Classification



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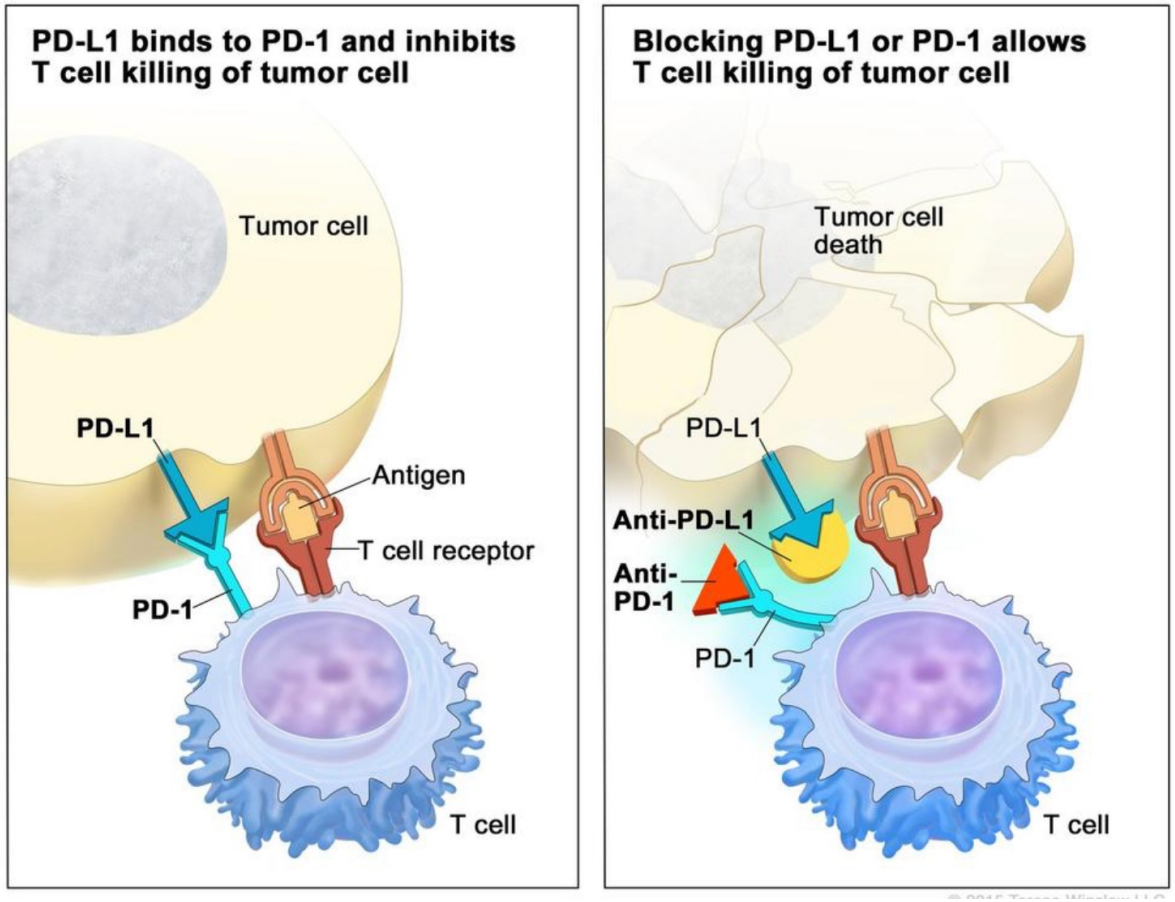
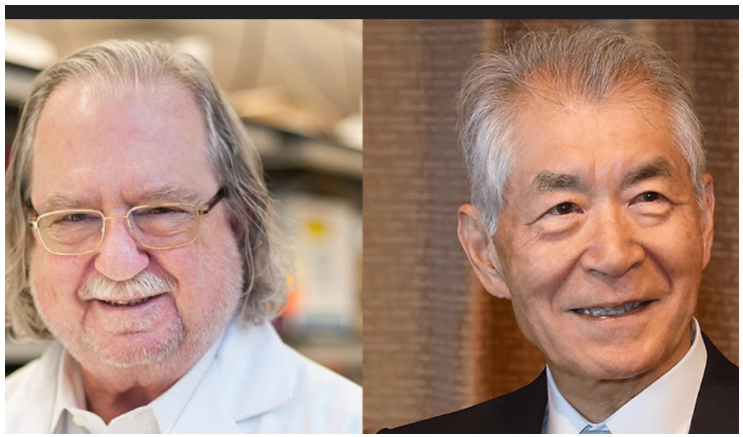
Chauhan et al, 2024.

Immune checkpoint Inhibitors

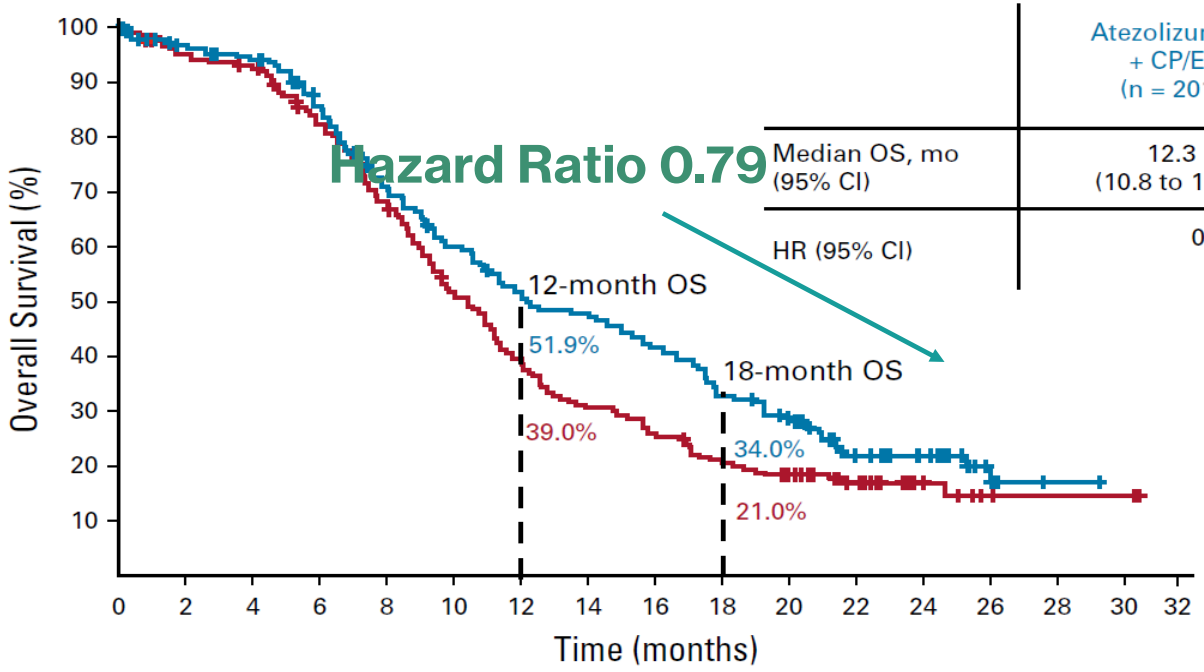




2018 Nobel Prize in Physiology or Medicine was awarded to James P. Allison and Tasuku Honjo

Immunotherapy 1st line advanced SCLC
Impower 133 Carbo+Etop +/- Atezo then Atezo maintenance: Overall Survival (Median F/U 22.9 mos)

A



	Atezolizumab + CP/ET (n = 201)	Placebo + CP/ET (n = 202)
Median OS, mo (95% CI)	12.3 (10.8 to 15.8)	10.3 (9.3 to 11.3)
HR (95% CI)	0.76 (0.60 to 0.95) *P* = .0154*	

No. of Patients at Risk

Atezolizumab + CP/ET	201	187	180	159	130	109	93	86	75	61	51	28	21	8	1
Placebo + CP/ET	202	189	183	160	131	97	74	58	49	39	33	20	8	3	2	2

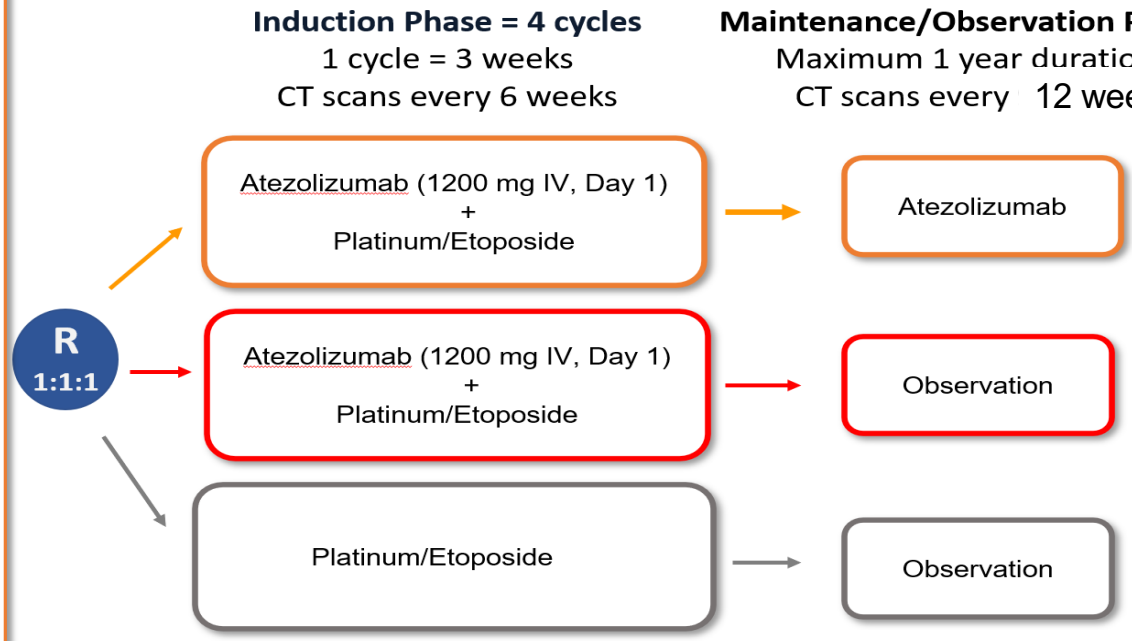
Liu. JCO 2021; 39:619-630

S2012: Randomized Phase II / III Study of First Line Platinum and Etoposide with or without Atezolizumab in Patients with Poorly Differentiated Extrapulmonary Neuroendocrine Carcinomas

N = 189

Key Eligibility:

- Metastatic poorly-differentiated extrapulmonary NEC with Ki-67≥55% (Ki-67 not needed for GU sites)
- Evaluable, measurable and non-measurable disease
- Zubrod PS 0-2
- No prior treatment EXCEPT one cycle of platinum/etoposide allowed
- Asymptomatic brain metastases eligible
- **Stratification factors:**
  - ❑1) PS 0-1 vs 2
  - ❑2) Known prostate vs GI vs other origin



David Zhen, MD

Gabriela Chiorean, MD

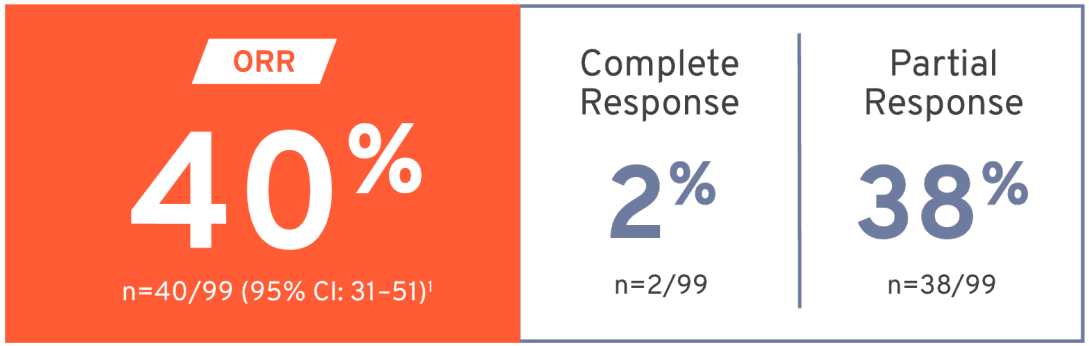
Primary Endpoint: OS (from time of randomization)
Secondary Endpoints: OS (from time of maintenance/observation), ORR, PFS, Toxicities, Duration of Response

The First and Only FDA Approved

DLL-3 targeting BiTE for ES SCLC

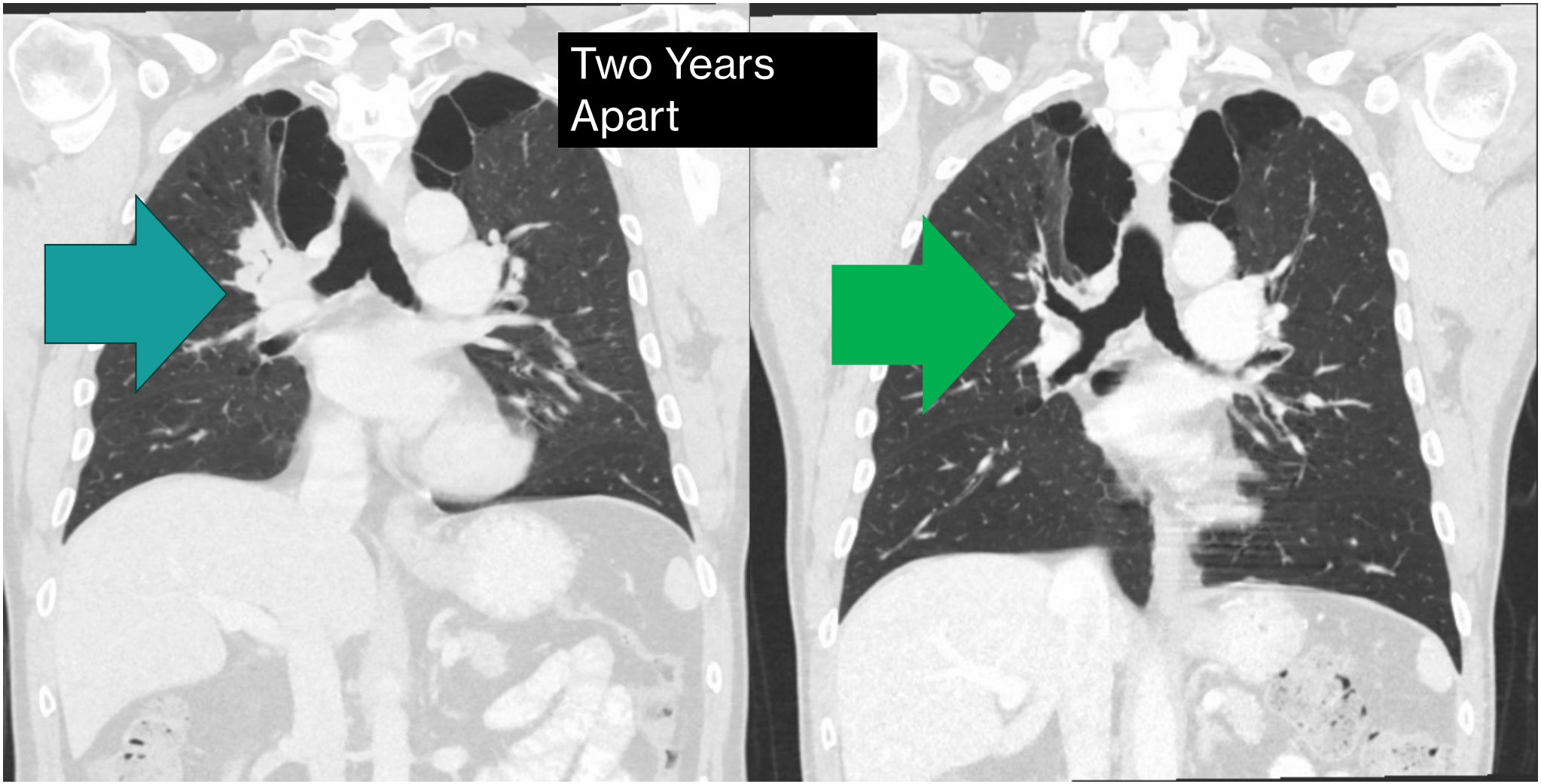
Tarlatamab in advanced SCLC

- Objective Response Rate of 40%
- Median Overall Survival of 14.3 Months in Patients with Advanced SCLC
- Accelerated approval in ES-SCLC with disease progression on or after platinum-based chemotherapy in May 2024

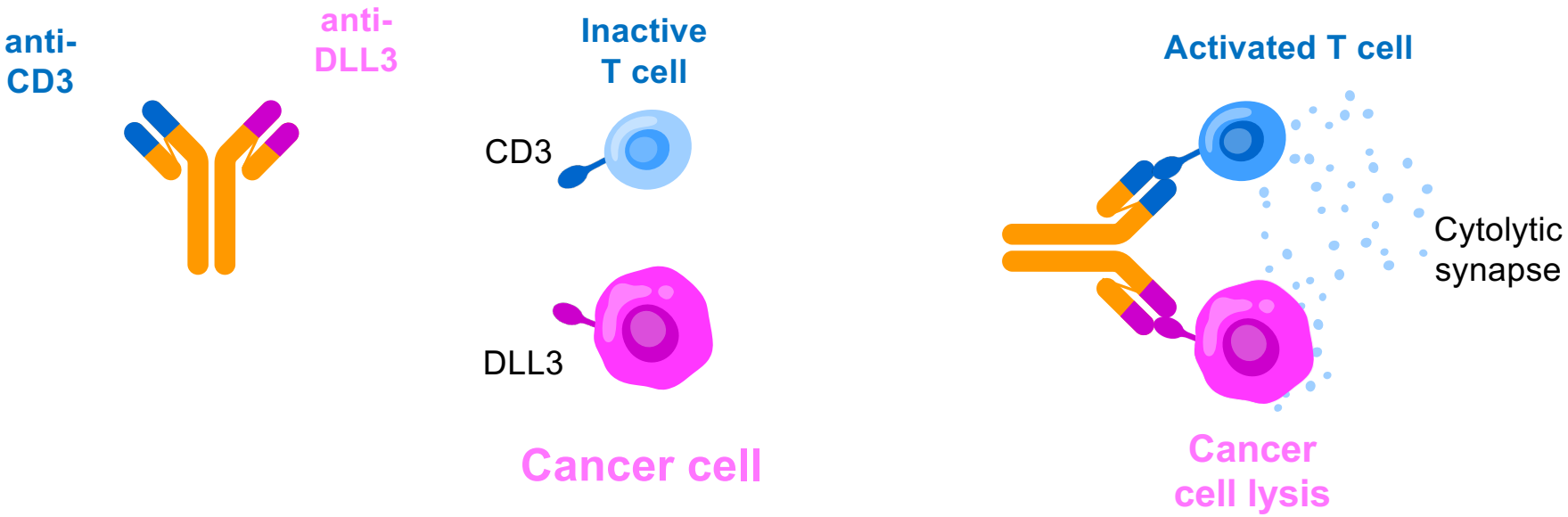


NEJM 2023; 389:2063-2075

What is a DLL-3 TcE and Why such optimism?

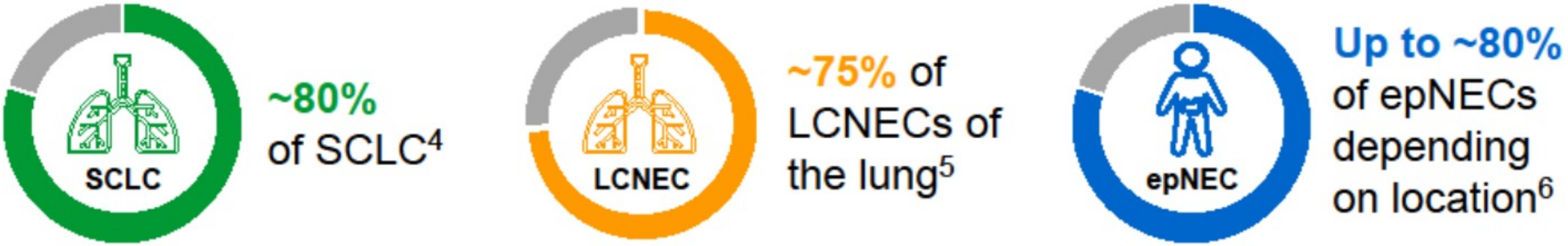

Two Years
Apart

DLL3-targeting T cell engager



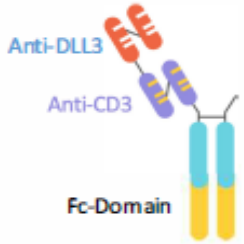
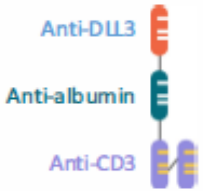
DLL3: Notch ligand selectively expressed on the cell surface of SCLC, and epNECs

DLL3 expression in SCLC and NECs



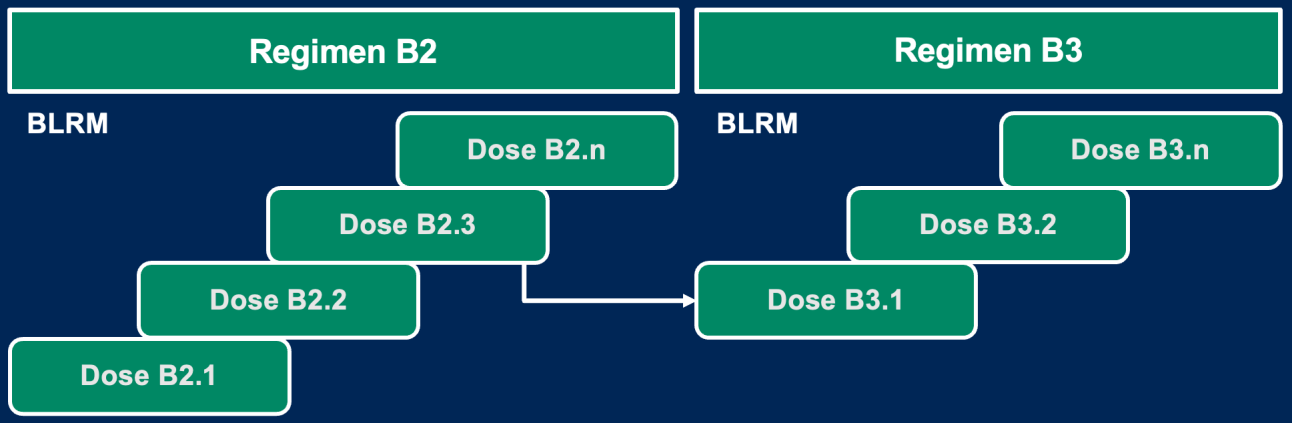
Ref:
Hermans BCM, et al. Lung Cancer 2019;138:102–108;
Lima CF, et al. Abstract 5305 at AACR; Apr8–13, 2022; New Orleans

Other DLL3-targeting TcEs under investigation, with varying molecular structures, target indications and stages of development

Drug (sponsor)	AMG-757/Tarlatamab (Amgen)	HPN-328/MK-6070 (Harpoon Therapeutics/MSD)	RO7616789 (Roche)
Structure and administration	***Q2W HLE-BiTE****[1,2]*	***TBC TriTAC****[3]*	***TBC***
Structure diagram[4]			Not yet known
Latest-phase ongoing trials[5] *(click links for trial summary)*	Phase III DeLLphi program:* 2L+ LS-SCLC (-306); relapsed SCLC (-304)	Phase I/II: DLL3-expressing tumors (NCT04471727)	Phase I: SCLC/NEC (NCT05619744)

*AMG-757 is also under investigation for prostate NEC (Phase I) and II SCLC (not yet recruiting for Phase 111).5BiTE, bispecific T-cell engager; CD3, cluster of differentiation 3; DLL3, delta-like protein 3; Fe, fragment crystallizable; HLE, half-life extended; lgG, human immunoglobulin G; L, line;NEC/NEN, neuroendocrine carcinoma/neoplasm; SCLC, small cell lung cancer; TBC, to be confirmed; TcE, T-cell engager; TriTAC, Tri-specific T cell-activating construct. I. IMDELLTRA™ (tarlatamab) prescribing information; 2. Giffin MJ et al. Clin Cancer Res 2021;27:1526-1537; 3. Merck Press Release: Merck Completes Acquisition of Harpoon Therapeutics, Inc. (Mar 2024; accessed Apr 2024); 4. Voynov Vet al. Antibodies 2020;9:65; 5. Clinicaltrials.gov (accessed Apr 2024).

First-in-human dose-escalation trial of obrixtamig in patients with SCLC, epNEC, or LCNEC-L: NCT04429087



All patients received 90–1080 µg/kg (active dose range)

IV QW → **Additional IV Regimen**

Four regimens were assessed; two with step-up dosing

Primary endpoints:
- MTD
- DLTs in the MTD evaluation period

Secondary endpoints:
- Objective response (RECIST v1.1)
- Pharmacokinetic parameters

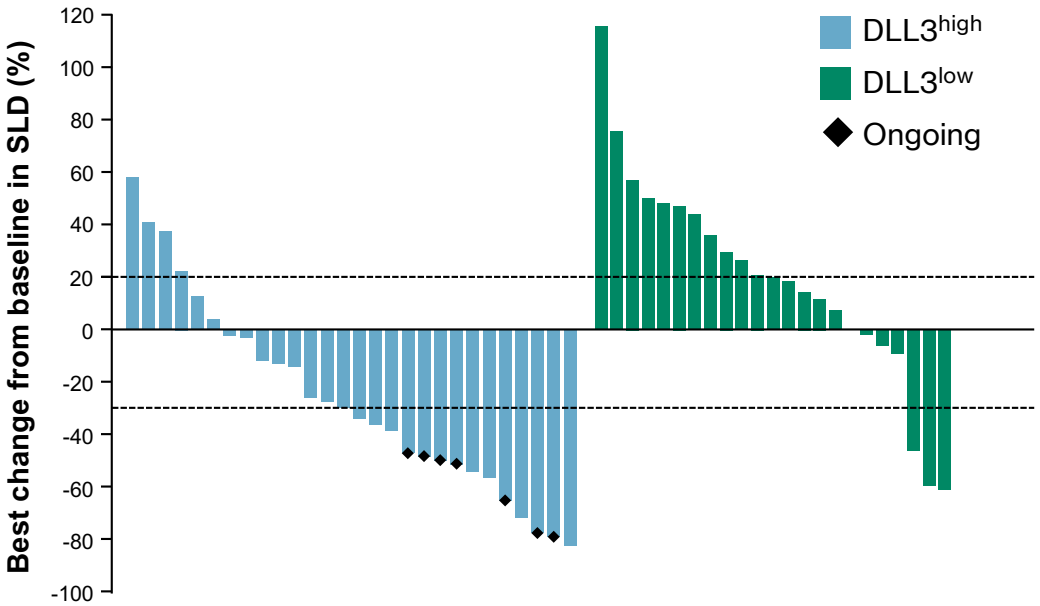
Patients with epNEC treated with Regimens B2 and B3 are reported here

Key inclusion criteria:
- Advanced SCLC, **epNEC**, or LCNEC-L
- DLL3-positive* according to central review
- Failed/ineligible for available standard therapies
- Adequate liver, bone marrow, and renal function

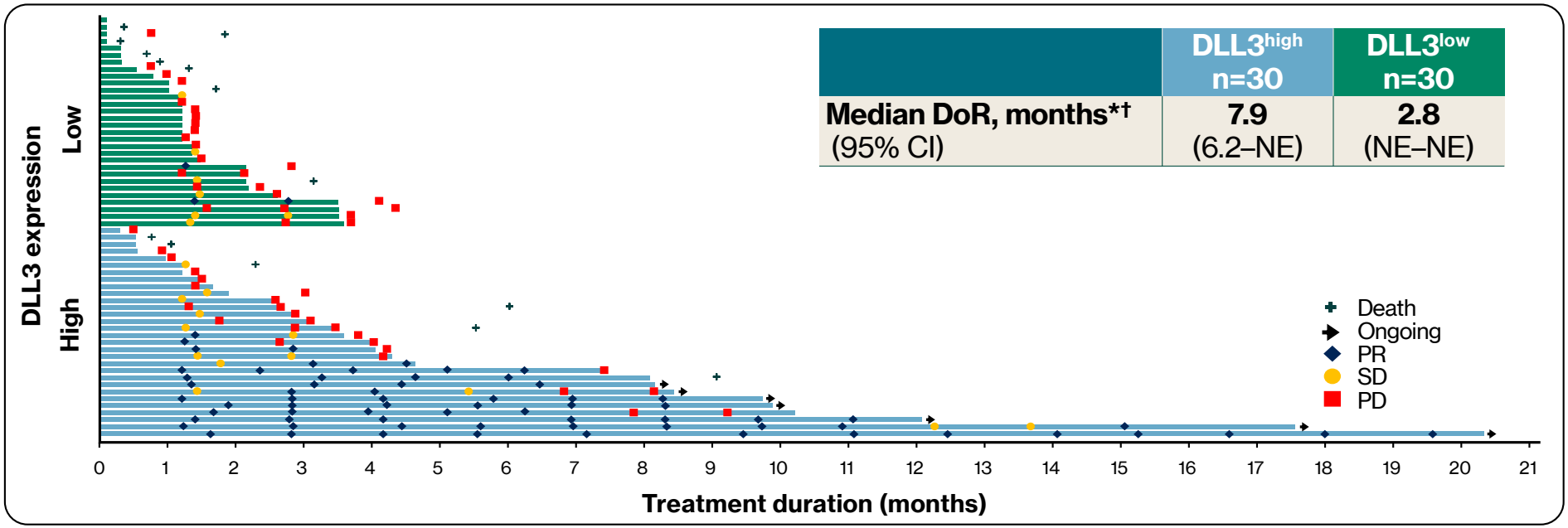
*DLL3-positive defined as any >0% TC staining at moderate and/or strong intensity
BLRM, Bayesian Logistic Regression Model; DLL3, delta-like ligand 3; DLTs, dose-limiting toxicities; epNEC, extrapulmonary neuroendocrine carcinoma; IV, intravenous; LCNEC-L, large cell neuroendocrine carcinoma of the lung; MTD, maximum tolerated dose; QW, every week; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria In Solid Tumours version 1.1; SCLC, small cell lung cancer; TC, tumor cell

Patients with DLL3^{high} tumors had a high ORR and DCR

Confirmed response	All N=60	DLL3^{high} n=30	DLL3^{low} n=30
ORR, % (95% CI)	22 (13–34)	40 (25–58)	3 (1–17)
PR, n (%)	13 (22)	12 (40)	1 (3)
DCR, % (95% CI)	47 (35–59)	67 (49–81)	27 (14–44)
SD, n (%)	15 (25)	8 (27)	7 (23)
PD, n (%)	23 (38)	8 (27)	15 (50)
NE, n (%)*	9 (15)	2 (7)	7 (23)



Obrixtamig demonstrated durable efficacy in patients with DLL3^{high} epNEC

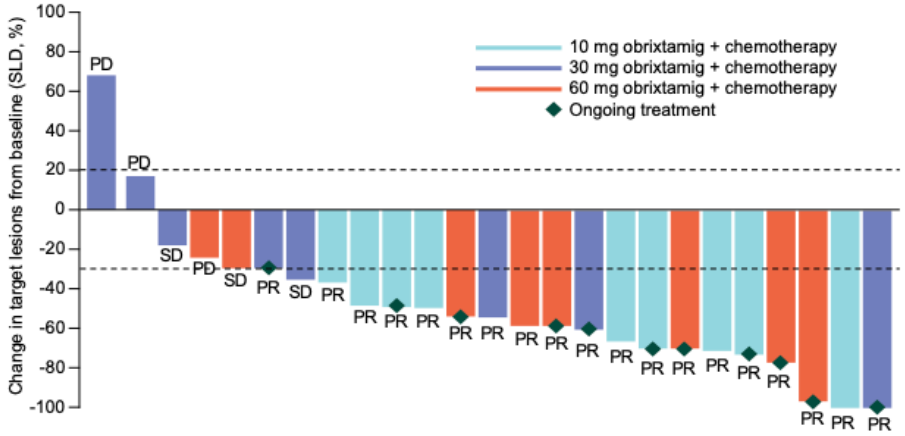


	DLL3^{high} n=30	DLL3^{low} n=30
Median DoR, months*† (95% CI)	**7.9** (6.2–NE)	**2.8** (NE–NE)

DAREON®-7: Phase I open-label dose-escalation/-expansion study of first-line obrixtamig (BI 764532) plus platinum-doublet chemotherapy in patients with DLL3-positive neuroendocrine carcinomas

DAREON 7

Efficacy (cont.)



- As of August 28, 2025, 18 patients had a confirmed PR; 11 patients were still receiving treatment
- Tumor shrinkage in target lesions was observed in 23 out of 25 evaluable patients

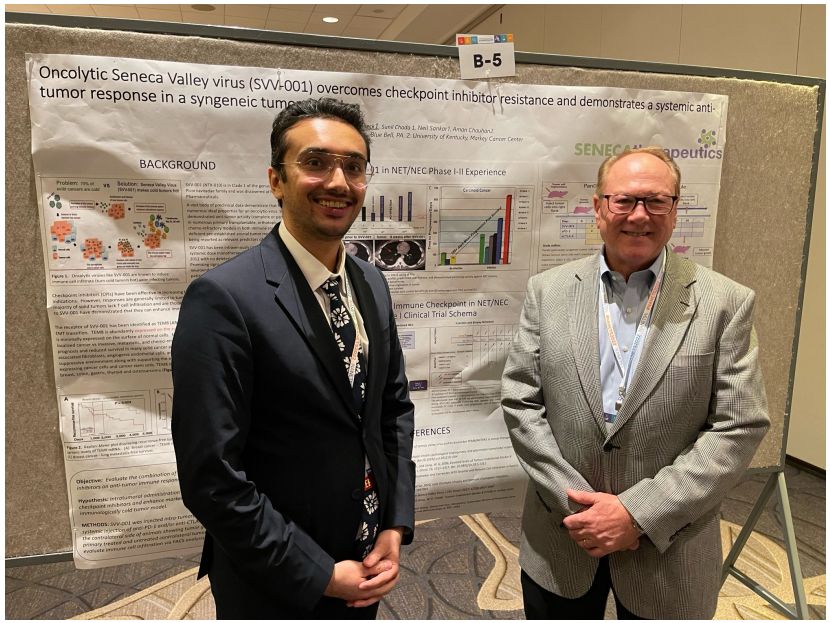
Key Findings and Conclusions

- The combination of obrixtamig with carboplatin and etoposide demonstrated a safety profile consistent with individual standard treatments, reinforcing its favorable tolerability in combination with platinum-doublet chemotherapy
- In patients with epNEC and LCNEC, encouraging efficacy was observed in the 1L setting (6-month PFS rate of 64%; median DoR of 8.8 months), warranting prioritized development of obrixtamig in combination with platinum-doublet chemotherapy regimens in these settings of high unmet need

Chauhan A. et.al NANETS 2025

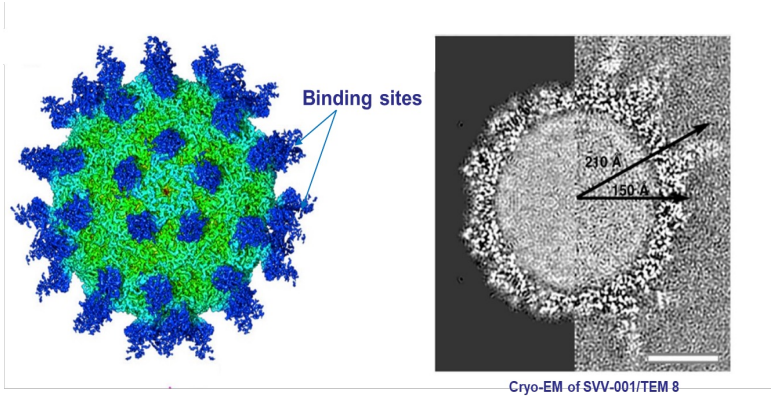
A Phase 1 Trial of the Oncolytic Virus SVV-001 in Combination with Nivolumab and Ipilimumab for high grade neuroendocrine cancers

- Sponsor: Seneca Therapeutics and University of Miami
- PI: Aman Chauhan



SVV-001 is an oncolytic piconavirus that targets the tumor endothelial marker 8 (TEM8)

- SVV-001 is an oncolytic picornavirus discovered as a contaminant of a laboratory adenovirus preparation (Reddy et al, 2007; Venkataraman et al, 2008a; Venkataraman et al, 2008b).
- SVV-001 demonstrates remarkable activity against tumors that are highly permissive for viral replication. SVV-001 has a replication cycle of under 12 hours, promoting productive infection within tumors before the development of an immune response.
- TEM8 appears to be a negative prognostic marker for patients with various malignancies



Seneca Therapeutics' SVV-001 targets TEM8

(Rudin et al, 2011; Molina et al, 2013).

Sample Cancer Antigens & Drugs Targeting Them

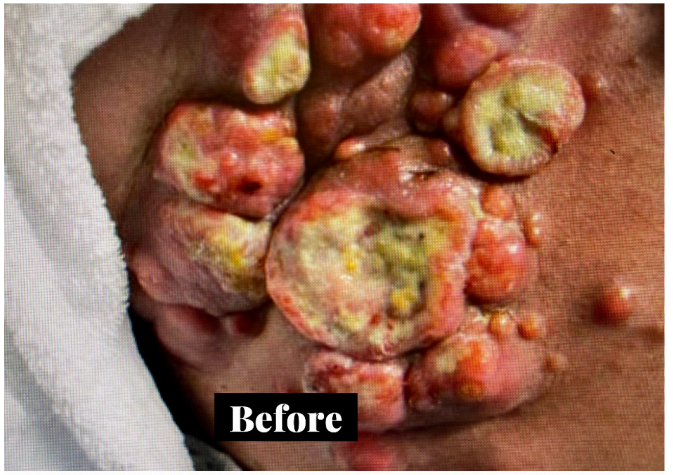
PSA	Pluvicto
HER-2	Herceptin
PD-L1	Keytruda
EGFR	Erbitux
VEGF	Avastin
TEM8	Historically considered "undruggable"

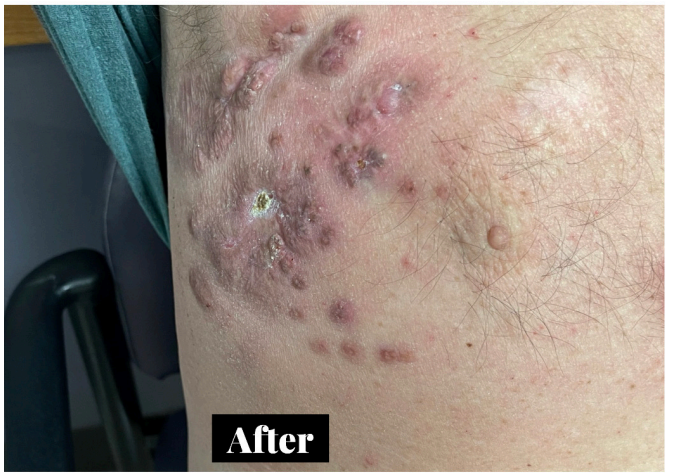
SVV-001 Safety Profile in Humans from Prior IV study is Excellent

- SVV-001 was delivered via single systemic intravenous dose in 76 patients in three clinical trials
  - Phase I/II in NET/NEC Patients (2010)
  - Phase I/II in Pediatric Patients (2014)
  - Phase II in ES SCLC Patients (2014)
- **Studies done before TEM8 was the known target of SVV-001**

Deep Durable Responses with Immunotherapy in NEC

"However very few patients respond to immune checkpoint alone"

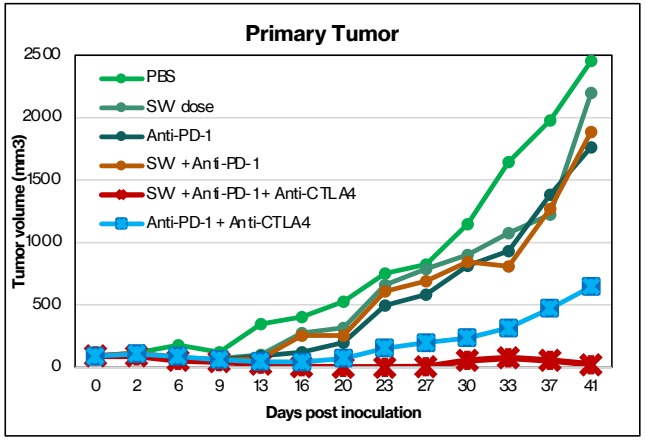


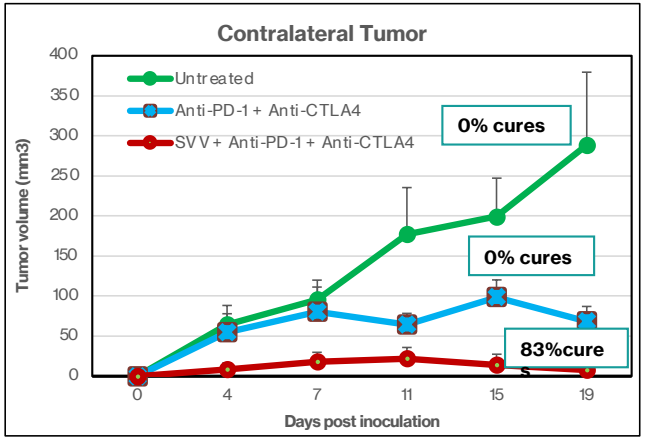


Immune Checkpoint Inhibitors in High-Grade NEN / NEC (G3)

Study	Therapy	Population	N	ORR	Key Findings
Spartalizumab (NEC cohort)	Anti-PD-1	Metastatic GEP-NEC	30	4–5%	Minimal monotherapy activity
AveNEC (Avelumab)	Anti-PD-L1	Progressive NEN-G3 & NEC	60	**5%**	Some durable SD/PR; overall low response rate
NIPINEC Trial	Nivolumab vs Nivo + Ipi	GEP-NEC	85	7% vs 15%	Combo superior to monotherapy; still short PFS
DART SWOG S1609	Nivo + Ipi	High-grade NEN (basket trial)	~32	**~26%**	Strongest ICI signal in HG-NEN; responses mostly in NEC
Al-Toubah (Retrospective)	Nivo + Ipi	Real-world NEC	34	15%	Responses almost exclusively in NEC; PFS ~1 mo

SVV-001 in Combination with Checkpoint Inhibitors Showed Complete Tumor Ablation AND Systemic Immunity in Syngeneic Mice





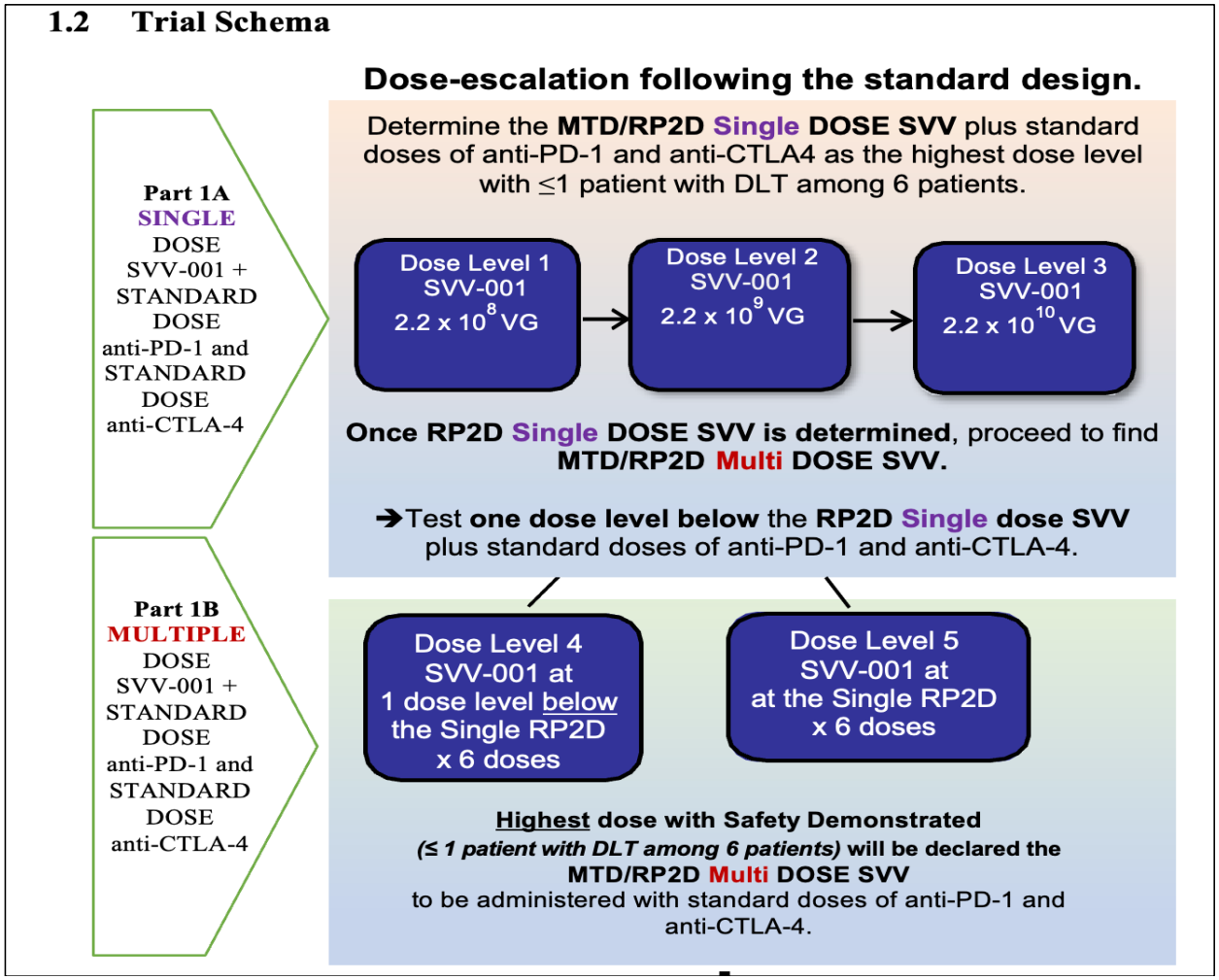
- **SVV + Checkpoint Inhibitors:**
  - Caused cold tumors to turn hot (CD8 influx and CXCL10 expression)
  - Eradicated established PAN02 tumors in syngeneic mice
  - Induced a systemic anti-tumor immune response.

Study Objectives and Schema

- To determine the RP2D of SVV-001 when administered intratumorally as single or multiple doses, in combination with nivolumab and ipilimumab in patients with high-grade neuroendocrine cancers
- To evaluate progression-free survival (PFS) with SVV-001 in combination with nivolumab and ipilimumab in patients with high-grade neuroendocrine cancers
- To evaluate the kinetics of viral release and viral load in plasma
- To evaluate objective response rate (ORR) with TEM8 expression

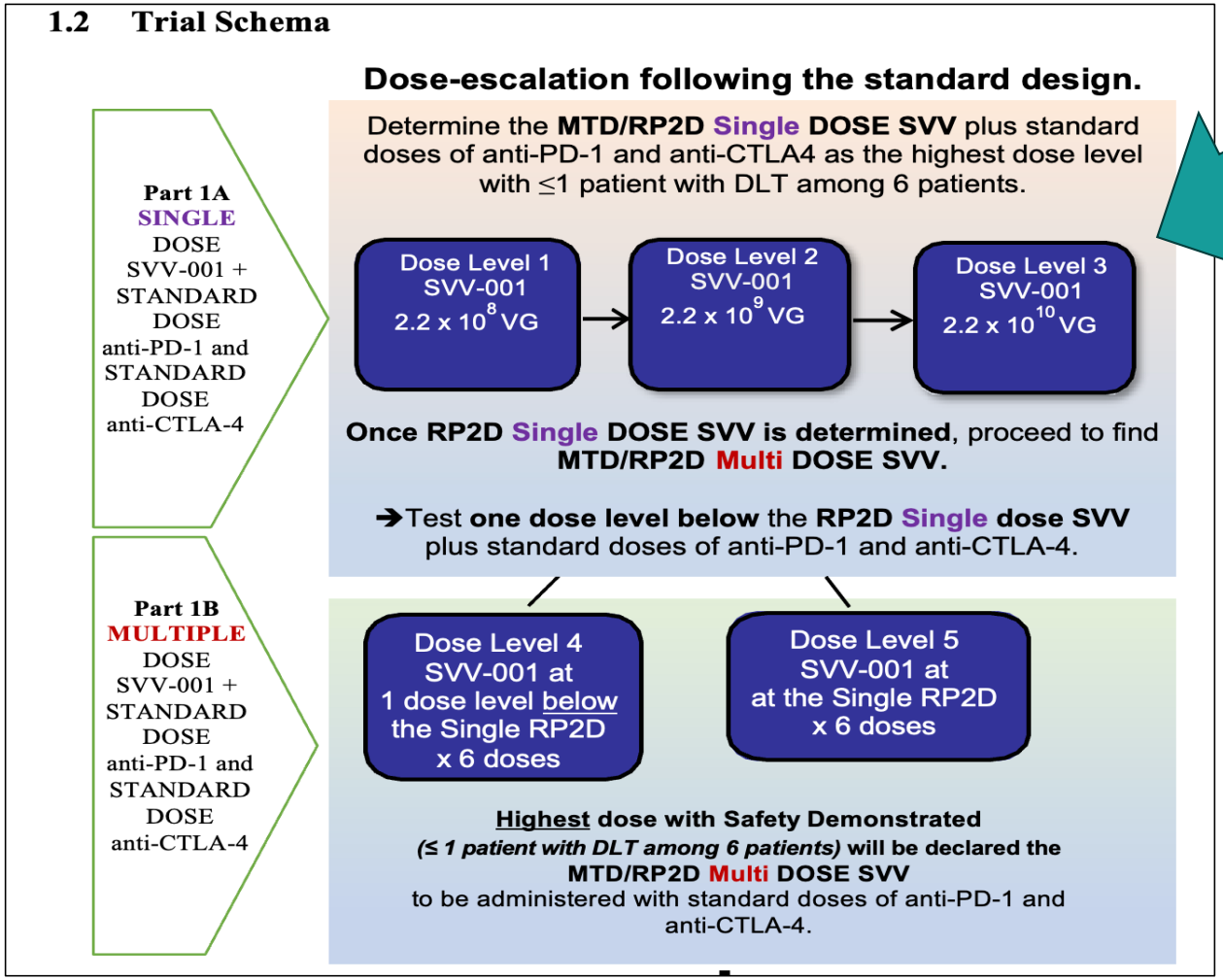
PI: Aman Chauhan (Currently Enrolling)

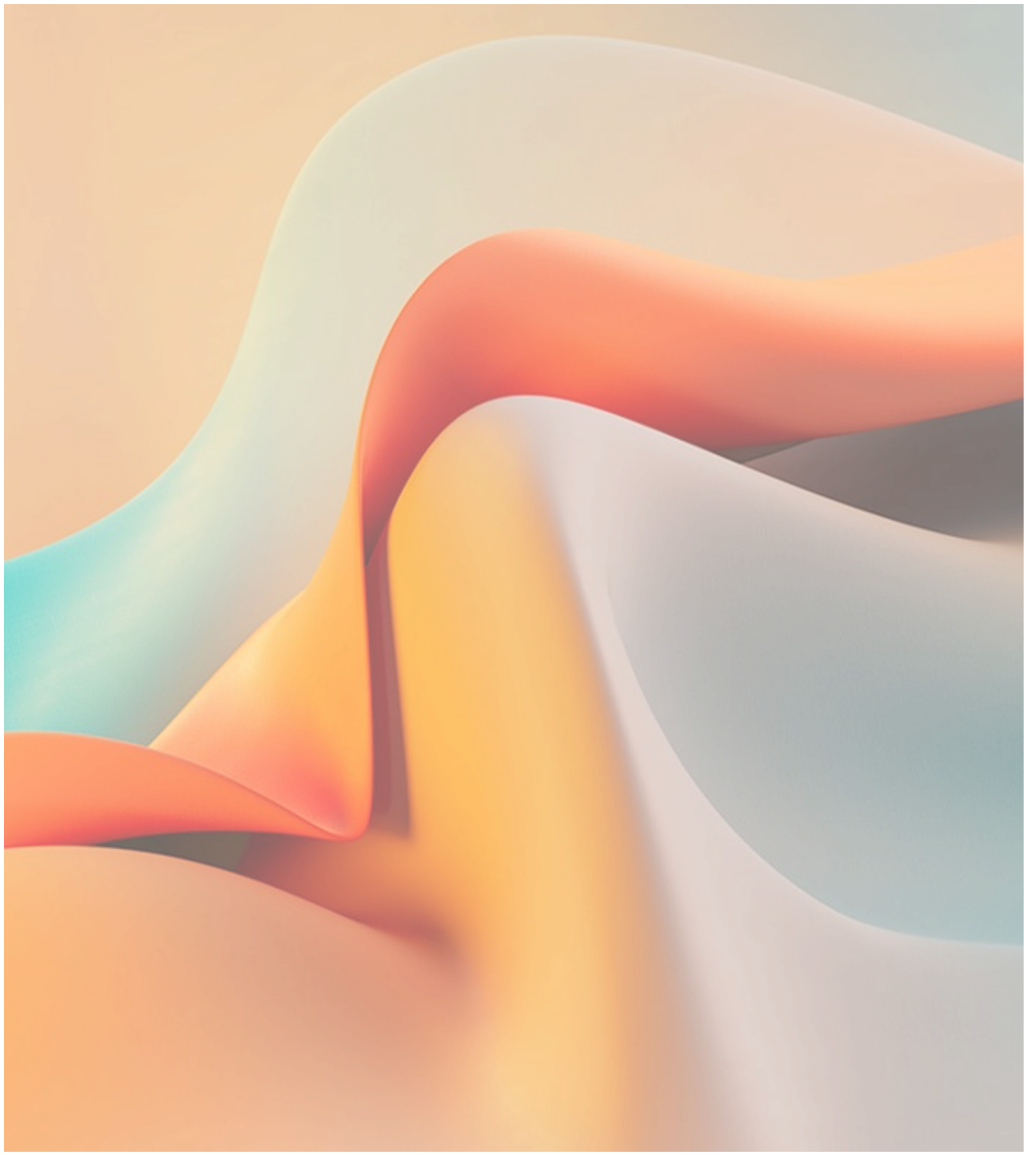
Study Schema



Abbreviations: DLT = dose-limiting toxicity; MTD = maximum tolerated dose;
NEC = neuroendocrine carcinoma;
NET = neuroendocrine tumor;
RP2D = recommended Phase 2 dose;
VG = viral genome.

Study Schema





Thank You