Emerging Concepts in the Treatment of Neuroendocrine Carcinomas

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Disclosures

- Consultant: Exelixis, Crinetics, Ipsen, Boehringer Ingelheim
- Grant support: Ipsen and NETRF

- Board Member, NANETS

Learning Objectives

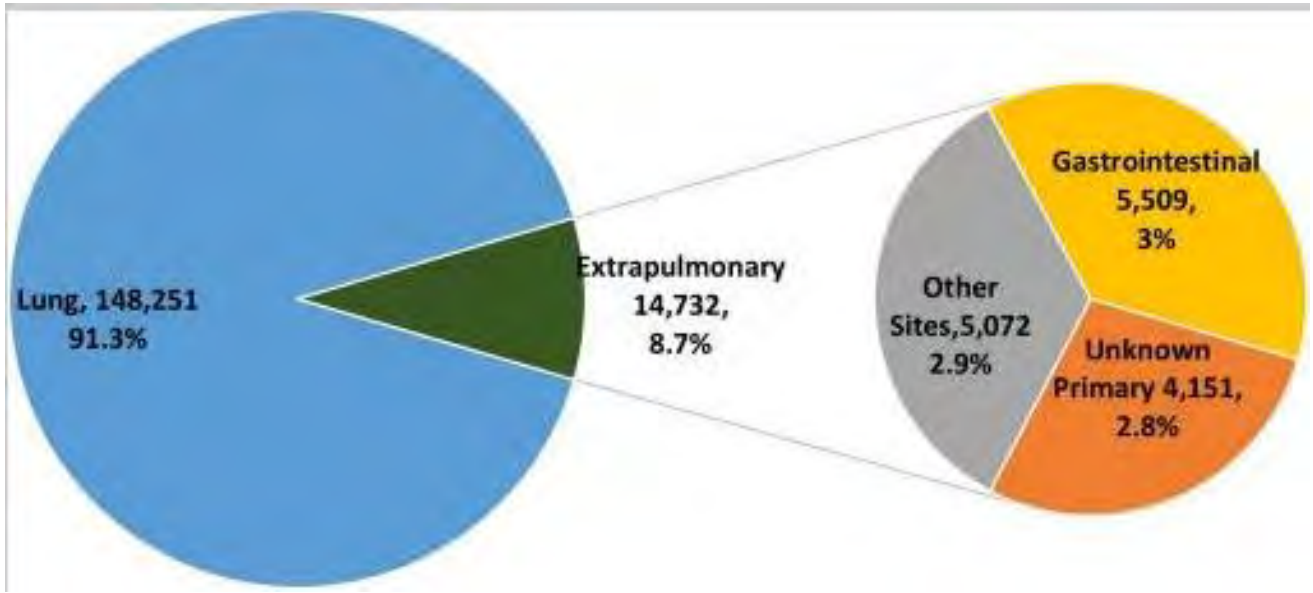
1. Targets for therapy in high grade neuroendocrine carcinoma

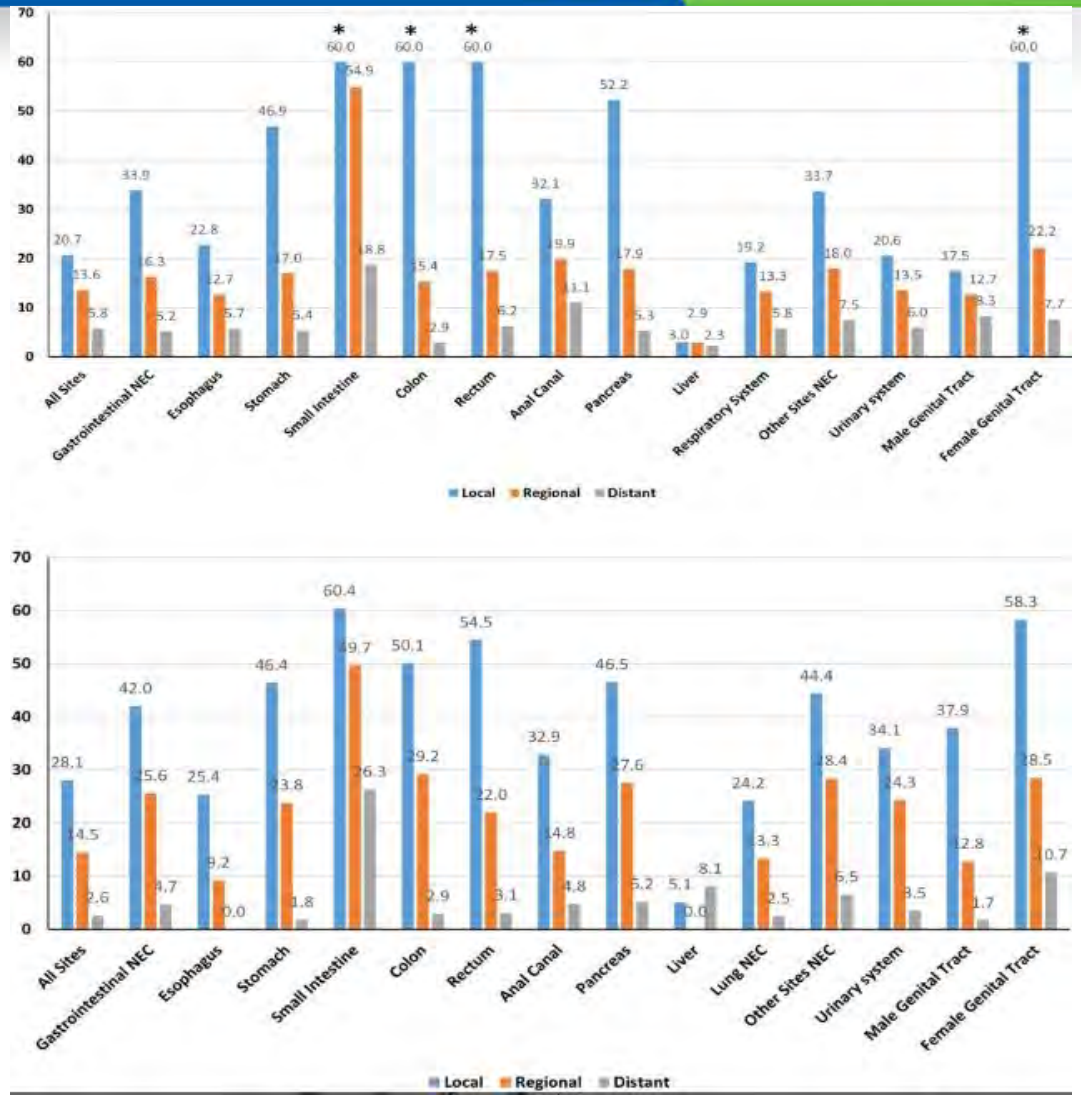
2. Ongoing trials

3. Future considerations for therapy

NEC- Incidence and Survival

- Incidence rate of NECs is 5.76 per 100,000
- Median survival of **all NECs – 7.7 months**
- Median survival: **Lung NECs - 7.6 months** vs **Extrapulmonary NECs -14.5 months,** with significant variability between sites
- 5-year survival: Lung NECs (5.6%) vs gastrointestinal NECs (13.1%)





(A) Median and (B) 5-year survival of poorly differentiated NECs

Dasari A, Mehta K, Byers LA, Sorbye H. Comparative study of lung and extrapulmonary poorly differentiated neuroendocrine carcinomas: A SEER database analysis of 162,983 cases.Cancer.2018;124(4):807-815.

High-Grade NECs are not a uniform entity

Site of origin, histology and mixed tumors

Table 1 Comparison of general characteristic of pulmonary and extrapulmonary (divided into GEP and urogenital tract locations) NECs

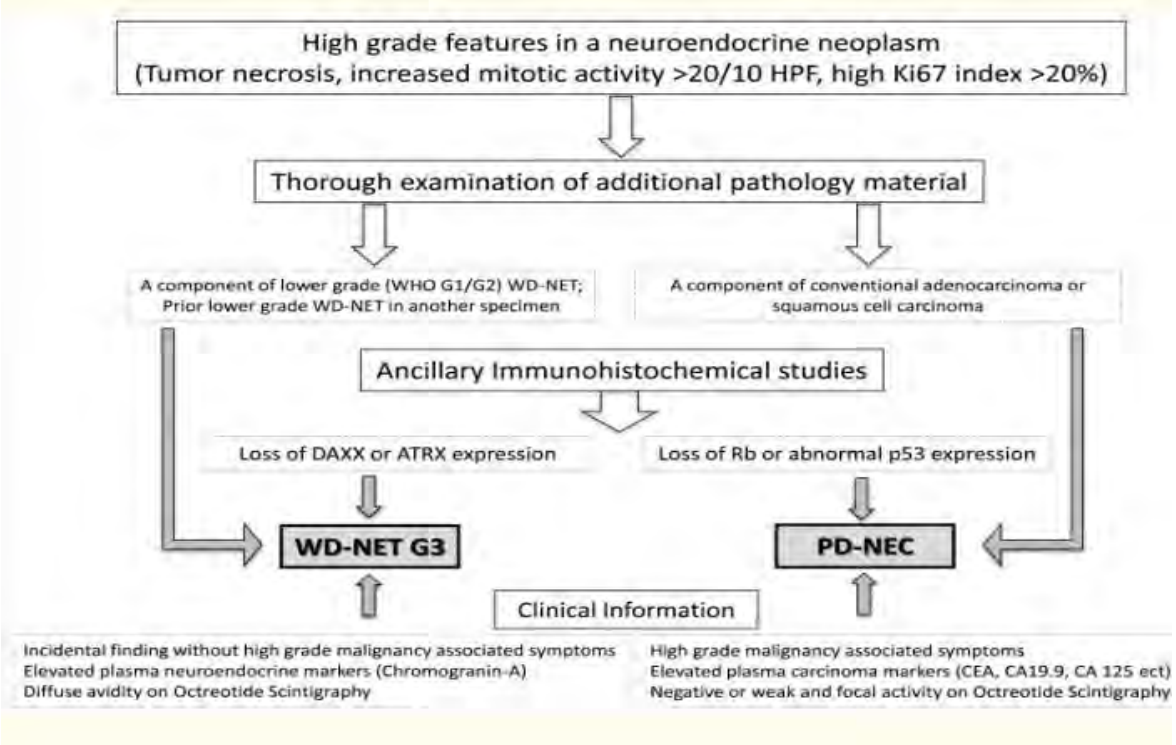
Location	Relative frequency as compared to NETs (carcinoids)	Most prevalent type (SCC *vs* LCNEC)	Frequency of mixed NE and non-NE features	Etiologic/ risk factors	Precursor lesions
Lung	More frequent	SCC	Very rare	Cigarette smoking	Unknown
GEP	Less frequent	LCNEC	Frequent	Unknown	Unknown (possibly divergent differentiation from adenocarcinoma)
Urogenital tract	More frequent	SCC	More than 50% of cases	Unknown	Unknown (possibly divergent differentiation from carcinoma subtypes)

Table 2 Review of reported small versus large cell EPNECs with Ki-67 index evaluation

Ref	No. of cases	Location	Ki-67 index (%) in different components	
			Small cell	Large cell
Nagao et al 2000 [27]	2	Parotid	-	55.3 (53.4-57.1)
Papotti et al 2000 [28]	2	Gallbladder	-	60.5 (50-71)
Crafa et al 2003 [29]	1	Rectum	-	50
Soriano et al 2004 [30]	10	Bladder	33 (15-70)	-
Sugawara et al 2004 [31]	1	Ampulla of Vater	54	-
Fernandez-Figueras et al 2005 [32]	23	Bladder/lung	64.7	-
Stachs et al 2005 [33]	1	Endometrium	50	-
Lee et al 2009 [34]	1	Bladder	-	40
Miyamoto et al 2006 [35]	1	Rectum	-	87.8
Malhotra et al 2008 [36]	1	Liver	90	-
Kozyrakis et al 2009 [37]	1	Bladder	70	-
Yamaguchi et al 2009 [38]	1	Breast	85	-
Lewis et al 2010 [39]	10	Larynx	-	64.2 (10-100)
Righi et al 2010 [40]	11	Breast	58 (40-75)	-
Stojsic et al 2010 [41]	1	Ampulla of Vater	-	41
Terada 2010 [42]	1	Endometrium	-	80
Terada 2011 [43]	1	Esophagus	100	-
Albisinni et al 2012 [44]	1	Prostate	100	-
Benkel et al2012 [45]	1	Gallbladder	70	-
Jianu et al 2012 [46]	1	Stomach	-	90
Samad et al 2012 [47]	1	Bile ducts	-	70
Yachida et al 2012 [10]	19	Pancreas	67 (n = 9) (55.1-85.8)	43.4 (n = 10) (20-68.4)
Yamamoto et al h2012 [48]	1	Pancreas	80	-
Mean values	93 cases		70.9	62

Molecular genomic signature

- Limited studies available on NECs
- Data on extrapulmonary is insufficient, often derived from mixed tumors



DLL3 expression is prominent in lung small cell carcinoma is > 95% and ~ 75% in EP NECS, and rare in lower grade (Poster C-11 Harsha Pattnaik)

1. Volante M, Birocco N, Gatti G, Duregon E, et al Extrapulmonary neuroendocrine small and large cell carcinomas: review of controversial diagnostic and therapeutic issues. Hum Pathol.2014 Apr;45(4):665-73.
2. Tang et al. Clin Cancer Res. 2016 Feb 15,22(4):1011-7

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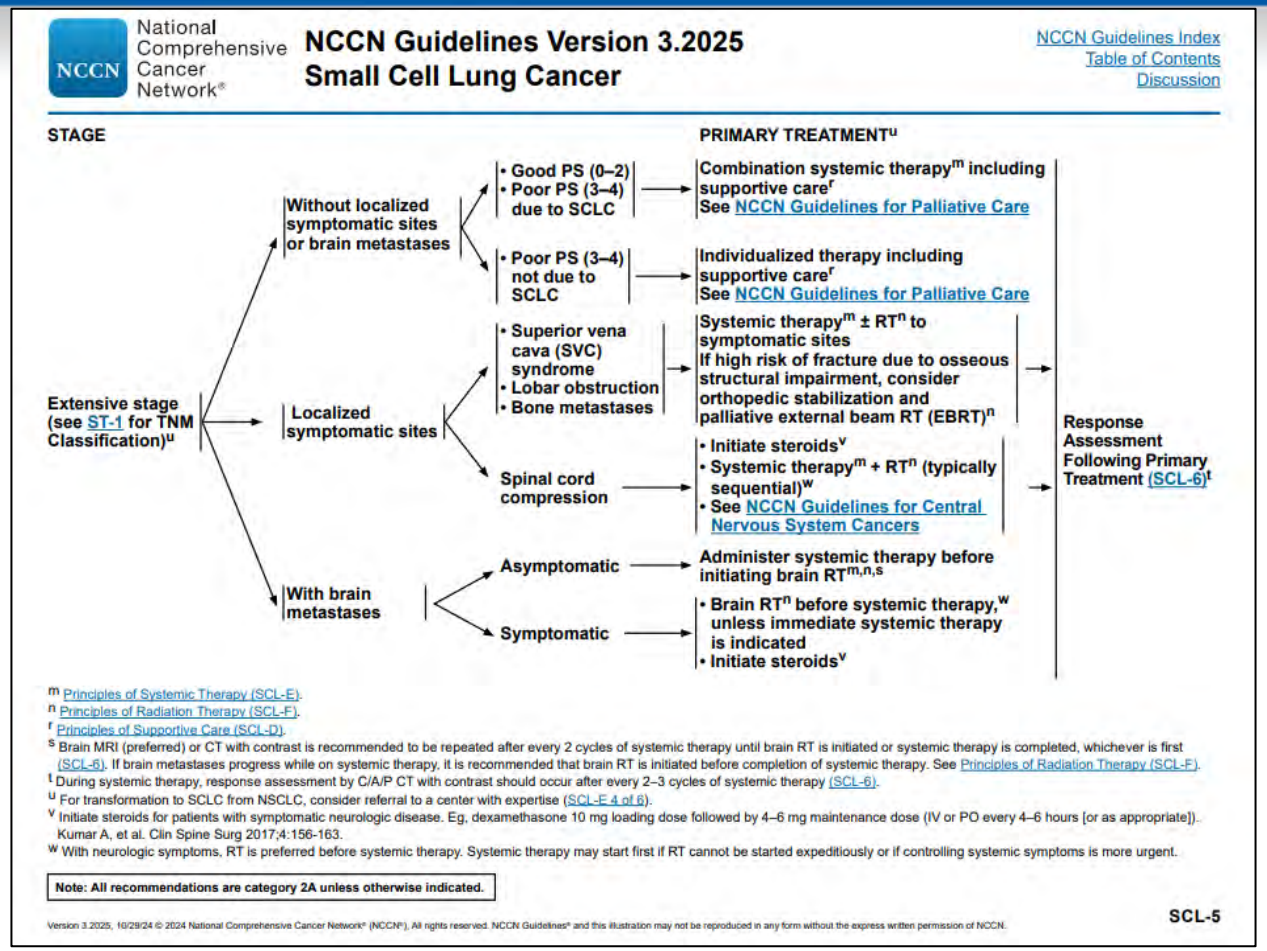
High-Grade NECs are not uniform entity

Clinical significance of Small Cell vs Large Cell and Ki-67

- Chemotherapy Response rate in small cell histology are similar in Lung SCLC vs EP-NEC but vary by location; worse in Hepatobiliary and Pancreatic NECs
- NORDIC study: Response to chemo differs with Ki-67 >55% vs <55%
- Limited prospective data available regarding chemo in EP-NECs exists (few small single arm studies)
- Given the differences in the clinical features of Lung NECs and EP-NECs, the management approach to EP-NECs should be different from Lung NECs guidelines still refer to small lung therapy algorithms

1. Volante M, Birocco N, Gatti G, Duregon E, et al Extrapulmonary neuroendocrine small and large cell carcinomas: review of controversial diagnostic and therapeutic issues. Hum Pathol.2014 Apr;45(4):665-73.
2. Tang et al. Clin Cancer Res. 2016 Feb 15,22(4):1011-7

Treatment of Small Cell Lung Cancer



National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2025
Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

STAGE | **PRIMARY TREATMENT[u]**

Extensive stage (see ST-1 for TNM Classification)[u]

- **Without localized symptomatic sites or brain metastases**
  - • Good PS (0–2) • Poor PS (3–4) due to SCLC → Combination systemic therapy[m] including supportive care[r] See NCCN Guidelines for Palliative Care
  - • Poor PS (3–4) not due to SCLC → Individualized therapy including supportive care[r] See NCCN Guidelines for Palliative Care
- **Localized symptomatic sites**
  - • Superior vena cava (SVC) syndrome • Lobar obstruction • Bone metastases → Systemic therapy[m] ± RT[n] to symptomatic sites If high risk of fracture due to osseous structural impairment, consider orthopedic stabilization and palliative external beam RT (EBRT)[n]
  - Spinal cord compression → • Initiate steroids[v] • Systemic therapy[m] + RT[n] (typically sequential)[w] • See NCCN Guidelines for Central Nervous System Cancers
- **With brain metastases**
  - Asymptomatic → Administer systemic therapy before initiating brain RT[m,n,s]
  - Symptomatic → • Brain RT[n] before systemic therapy,[w] unless immediate systemic therapy is indicated • Initiate steroids[v]

→ **Response Assessment Following Primary Treatment (SCL-6)[t]**

[m] Principles of Systemic Therapy (SCL-E).
[n] Principles of Radiation Therapy (SCL-F).
[r] Principles of Supportive Care (SCL-D).
[s] Brain MRI (preferred) or CT with contrast is recommended to be repeated after every 2 cycles of systemic therapy until brain RT is initiated or systemic therapy is completed, whichever is first (SCL-6). If brain metastases progress while on systemic therapy, it is recommended that brain RT is initiated before completion of systemic therapy. See Principles of Radiation Therapy (SCL-F).
[t] During systemic therapy, response assessment by C/A/P CT with contrast should occur after every 2–3 cycles of systemic therapy (SCL-6).
[u] For transformation to SCLC from NSCLC, consider referral to a center with expertise (SCL-E 4 of 6).
[v] Initiate steroids for patients with symptomatic neurologic disease. Eg, dexamethasone 10 mg loading dose followed by 4–6 mg maintenance dose (IV or PO every 4–6 hours [or as appropriate]). Kumar A, et al. Clin Spine Surg 2017;4:156-163.
[w] With neurologic symptoms, RT is preferred before systemic therapy. Systemic therapy may start first if RT cannot be started expeditiously or if controlling systemic symptoms is more urgent.

Note: All recommendations are category 2A unless otherwise indicated.

SCL-5

DLL3 – Tarlatamab: FDA granted accelerated approval for extensive stage SCLC with disease progression on or after platinum-based chemotherapy based on promising RR ~40^ and PFS data
Main AE: CRS

Four cycles of cytotoxic chemotherapy are recommended, but some patients may receive up to 6 cycles based on response and tolerability after 4 cycles.

Preferred Regimens

- **Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and atezolizumab 1200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1200 mg day 1, every 21 days (category 1 for all)[d,e,k,6]**

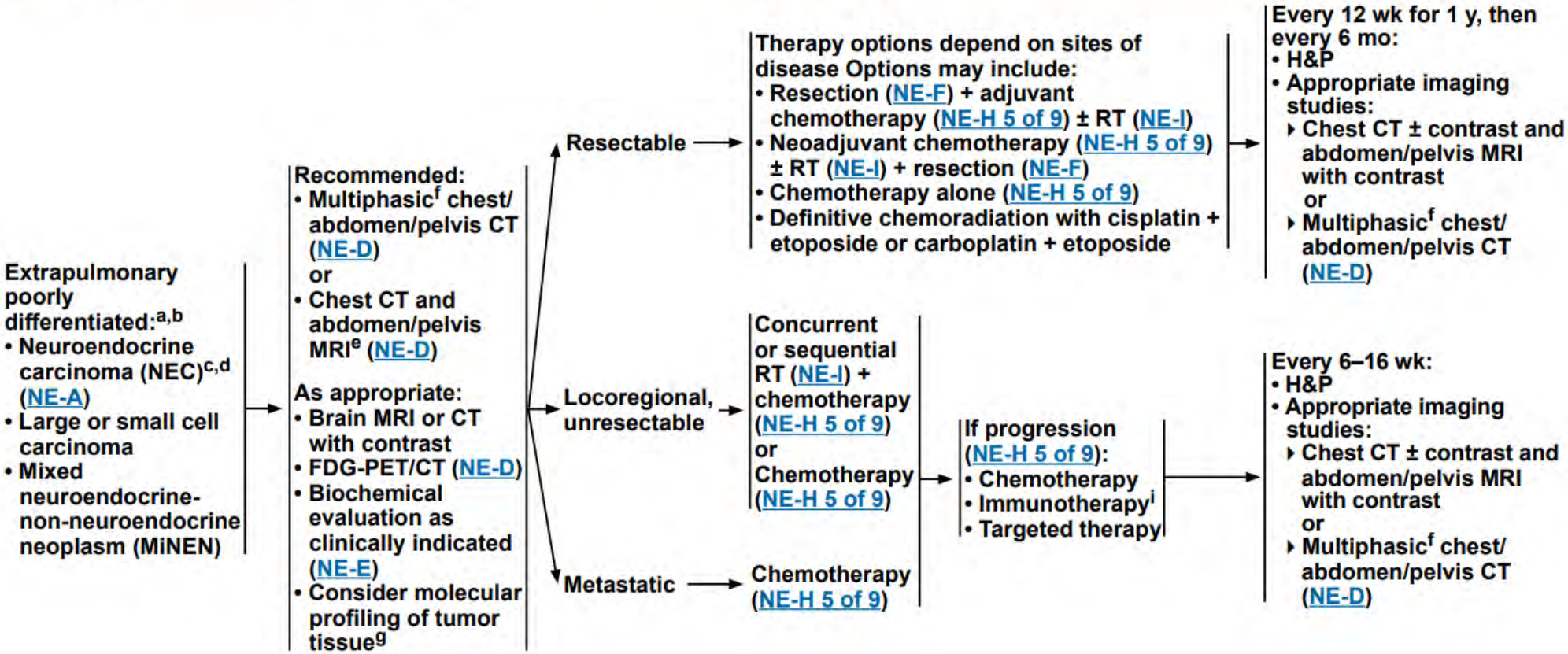
Treatment of Extrapulmonary Neuroendocrine cancers

National Comprehensive Cancer Network®

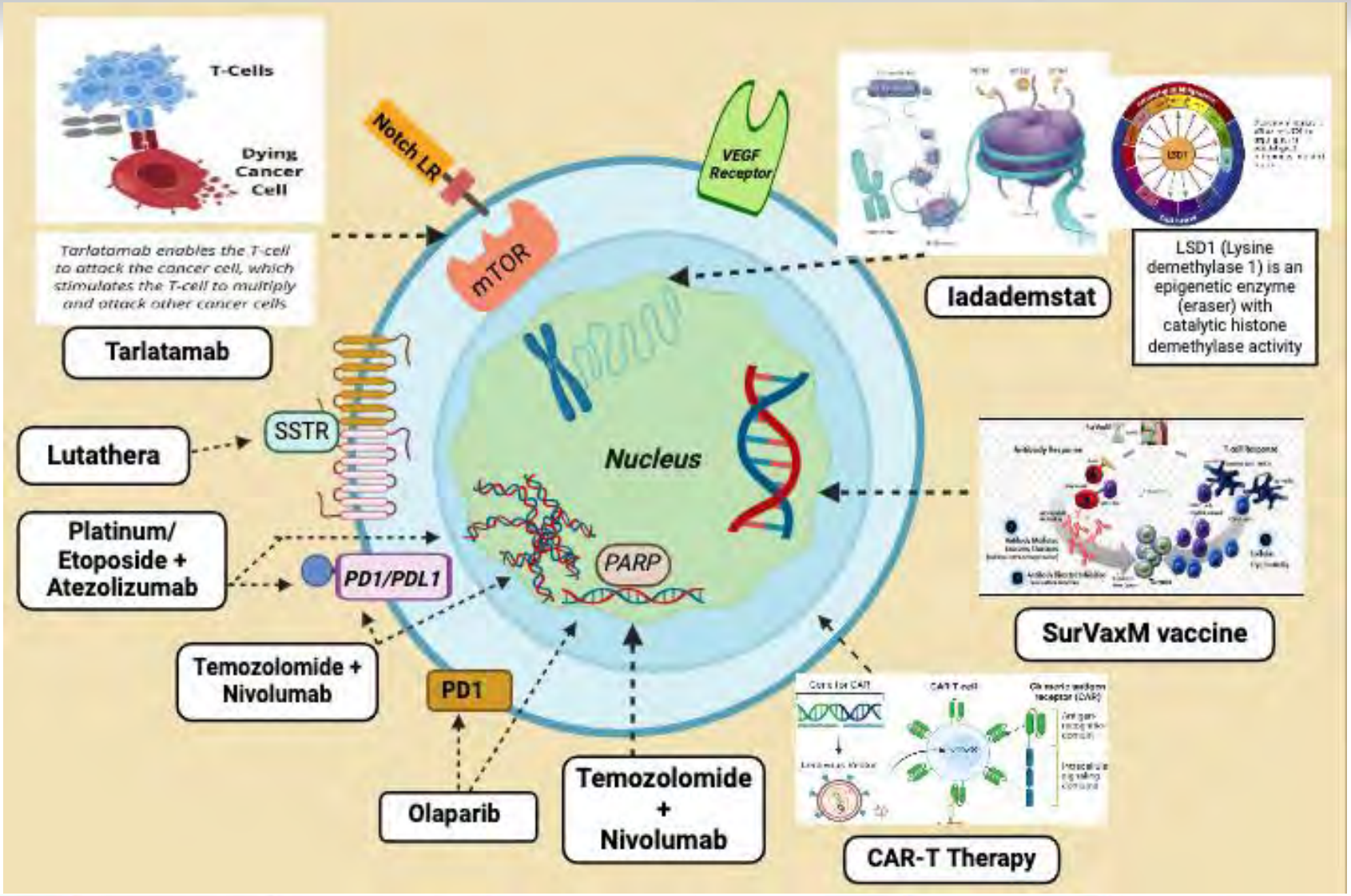
NCCN Guidelines Version 2.2024

Extrapulmonary Poorly Differentiated: Neuroendocrine Carcinoma/ Large or Small Cell Carcinoma/Mixed Neuroendocrine-Non-Neuroendocrine Neoplasm

NCCN Guidelines Index
Table of Contents
Discussion



Overview of IO and other targets in NEC



Overview trials – IO and novel targets

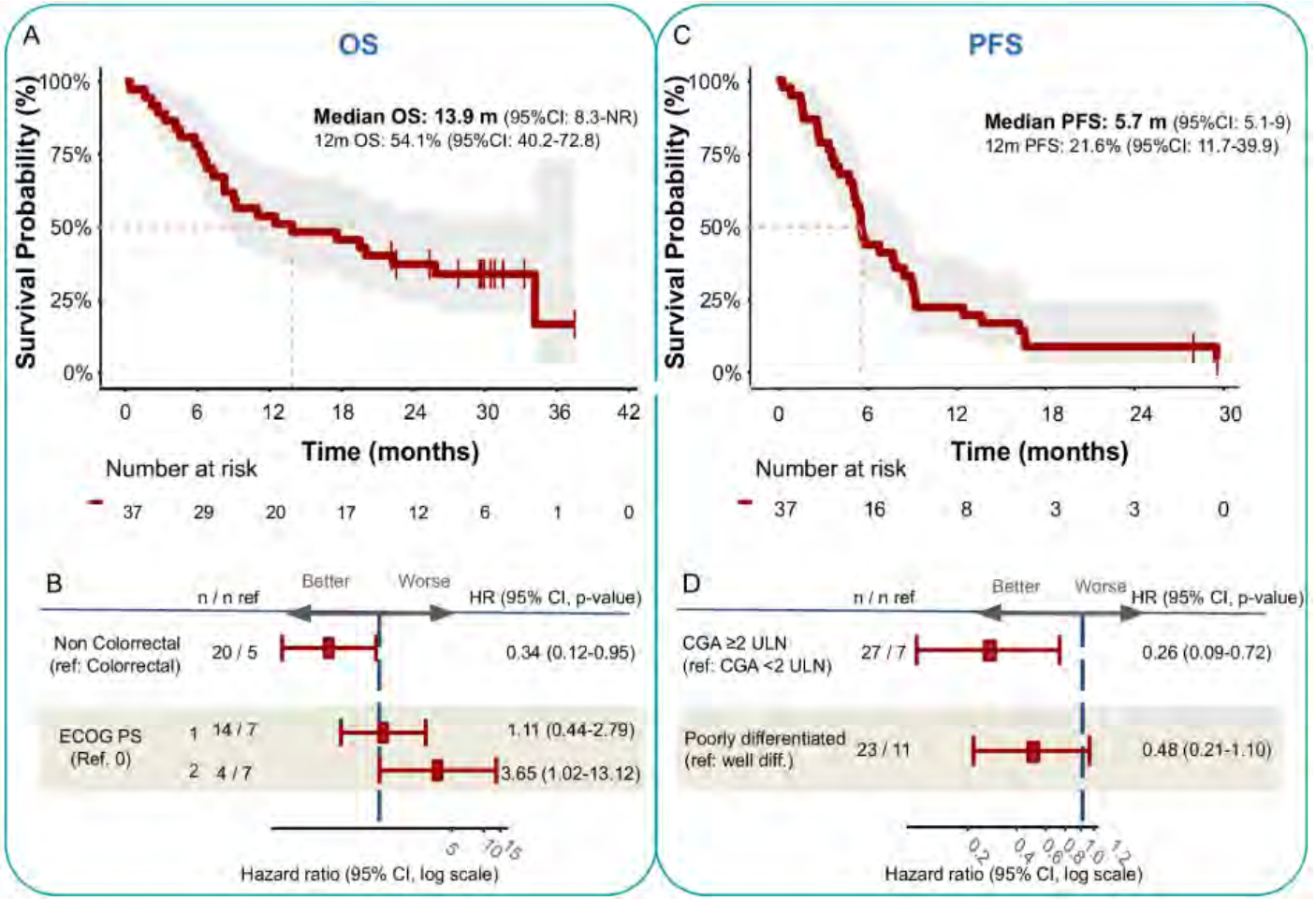
Chemotherapy + other agents	Immuno-Oncology targets	Radiopeptide
• Carbo-Etoposide + Nivolumab • Platinum/Etoposide + Atezolizumab • Temozolomide + Nivolumab • Iadademstat + Paclitaxel • Temozolomide + Olaparib	• Checkpoint inhibitors ➢ Ipi+Nivo • Vaccines ➢ SurVaxM* • ADCs targeting DLL3 ➢ Rovalpituzumab tesirine • T cell engagers ➢ Tarlatamab ➢ BI 764532, HPN328, RO7616789, PT217, QLS31904 • CAR-T cells- ➢ Autologous Cadherin 17, ➢ DLL3-CAR-NK cells ➢ AMG 119 (anti-DLL3 autologous T cell) ➢ DLL 3 armored CAR-T secreting Il-18*	• PRRT

Chemotherapy + PD-1 inhibitor

Phase II trial of Carboplatin + Etoposide + Nivolumab for G3 GEP or Unknown Primary NEN (NICE-NEC)

- Single arm phase 2 trial of Carboplatin + Etoposide + Nivolumab –upto 6 cycles followed by maintenance Nivolumab in chemo-naïve advanced G3 NEN of GEP/unknown origin
- Enrolled 38 patients (68% NEC and/or Ki-67>55%)
- ORR 57%
- Median PFS 5.7 mo
- Median OS 13.9 mo

1 year OS rate of 54% -> did not meet primary endpoint – although 38% of the patients had OS > 2 years

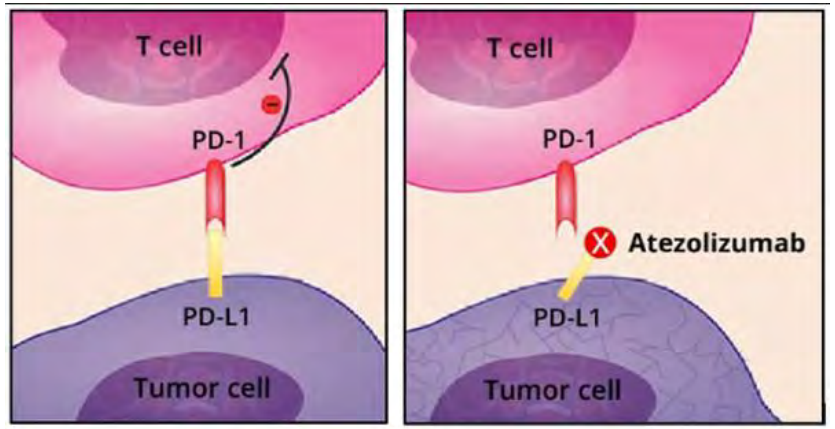


Riesco-Martinez *et al.* Nivolumab plus platinum-doublet chemotherapy in treatment-naive patients with advanced grade 3 Neuroendocrine Neoplasms of gastroenteropancreatic or unknown origin: The multicenter phase 2 NICE-NEC trial (GETNE-T1913). *Nat Commun* **15**, 6753 (2024).

Chemotherapy + PD-L1 inhibitor

Randomized Phase II/III Trial of First Line Platinum/Etoposide with or without Atezolizumab in Patients with Advanced or Metastatic Poorly Differentiated Extrapulmonary Neuroendocrine Carcinomas

- Treatment: Platinum/etoposide +/- Atezolizumab
  - Study is randomized 1:1:1
- Main eligibility: Poorly differentiated NEC, treatment-naïve, unresectable/metastatic disease
  - Patients may have 1 cycle of platinum/etoposide prior to registration



Arm 1 (Experimental Arm)	Arm 2 (Experimental Arm)	Arm 3 (Control Arm)
Atezolizumab + Platinum/ Etoposide	Atezolizumab + Platinum/ Etoposide	Platinum/ Etoposide

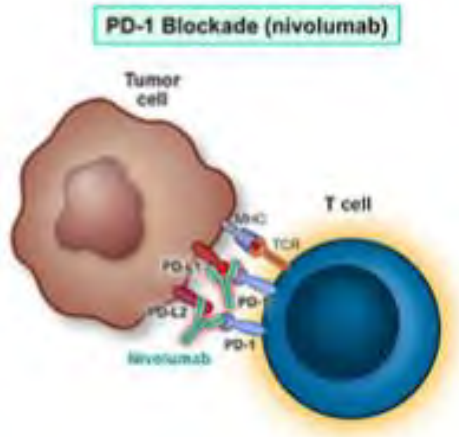
NCT05058651

David Bing Zhen et al., SWOG S2012: Randomized phase II/III trial of first line platinum/etoposide (P/E) with or without atezolizumab (NSC#783608) in patients (pts) with poorly differentiated extrapulmonary small cell neuroendocrine carcinomas (NEC).. JCO 40, TPS4179-TPS4179(2022). DOI:10.1200/JCO.2022.40.16_suppl.TPS4179

Chemotherapy + PD-1 inhibitor

CLO20-054: A Phase 2 Trial of Nivolumab and Temozolomide in Advanced Neuroendocrine Tumors (NETs) NCT03728361

- Non-randomized, two-cohort, open-label phase 2 study
- 28 patients with advanced or metastatic NEN of any grade or primary site and recurrent/refractory SCLC will be recruited
- accrual ongoing
- Interim analysis was performed after 15 patients, with a median follow up time of 6.9 months - PFS & OS data are not mature
- 12/15 were evaluable.
- Of the patients with PR, 1 had pancreatic (Ki-67: 80%), 1 had ampullary (Ki-67: 70%), and 1 had bronchial (Ki-67: 15%) NET



Ki-67%	
<3%	1 (8%)
3-20%	8 (67%)
>20%	3 (25%)

Best Response per RECIST v1.1	
Partial Response	3 (25%)
Stable Disease	8 (67%)
Progressive Disease	1 (8%)

Owen DH, Wei L, Goyal A, et al. A phase 2 trial of nivolumab and temozolomide in advanced neuroendocrine tumors (NETs): interim efficacy analysis. JNCCN. 2020;18(3.5):CLO20-054.

Chemotherapy + PARP inhibitor

Testing the Addition of an Anticancer Drug, Olaparib, to Temozolomide for Advanced Neuroendocrine Cancer

NCT04394858 - enrolling

- Phase II trial to study efficacy of adding olaparib to the standard treatment, temozolomide, in patients with advanced neuroendocrine cancer (pheochromocytoma or paraganglioma) that are metastatic or unresectable

- Poly (adenosine diphosphate [ADP]-ribose) polymerases (PARPs) are proteins that help repair deoxyribonucleic acid (DNA) mutations. PARP inhibitors, such as olaparib, inhibit DNA repair tumor cells. Giving olaparib with temozolomide may shrink or stabilize the cancer in patients with pheochromocytoma or paraganglioma better than temozolomide alone

- No prior treatment with temozolomide, dacarbazine, or a poly ADP ribose polymerase (PARP) inhibitor

https://www.cancer.gov/research/participate/clinical-trials-search/v?id=NCI-2020-03379&r=1

Chemotherapy + LSD1-inhibitor

A Phase 2 Study of iadademstat in Combination with Paclitaxel in Relapsed or Refractory Small Cell Lung Cancer and Extrapulmonary High Grade Neuroendocrine Carcinomas - enrolling

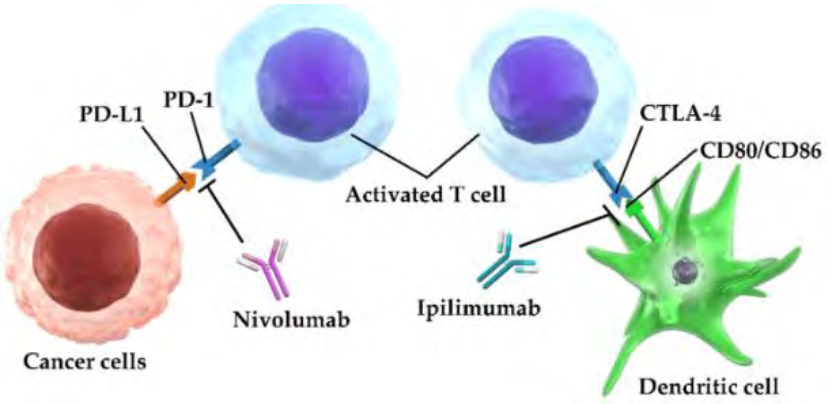
- Non-randomized single-arm, two cohorts, phase II study of **iadademstat** in combination with weekly **paclitaxel**
- A total of 42 patients with SCLC (21 patients) and G3 NEC (21 patients) will be enrolled
- Treatment: **Iadademstat + Paclitaxel**
  - Iadademstat is a small oral molecule, which acts as a covalent and highly selective inhibitor of the epigenetic enzyme Lysine Specific Demethylase-1, LSD1

- Main eligibility: patients with **refractory SCLC** or **extrapulmonary G3 NECs** who have refractory or relapsed disease after platinum-based chemotherapy

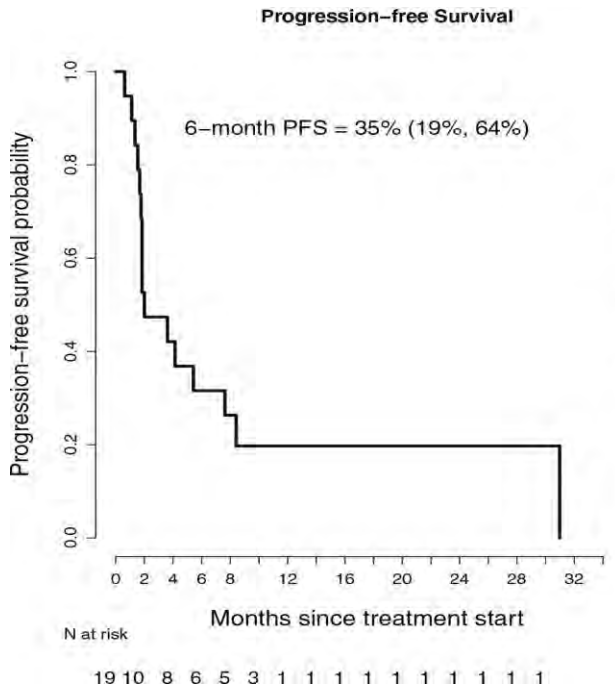
Immuno-Oncology: Dual Anti–CTLA–4 and Anti–PD–1 Blockade

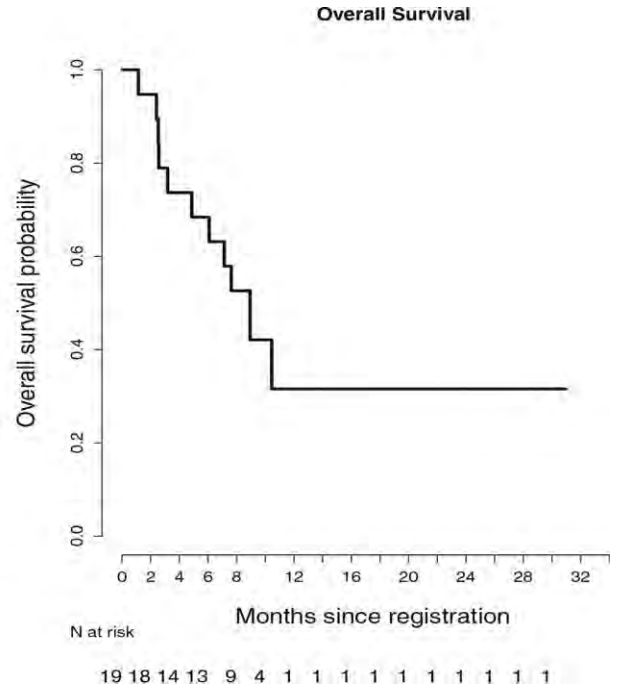
A Phase II Basket Trial of Dual Anti–CTLA–4 and Anti–PD–1 Blockade in Rare Tumors (DART) SWOG S1609: High-Grade Neuroendocrine Neoplasm Cohort

- Prospective, open-label, multicenter, phase 2 clinical trial of ipilimumab plus nivolumab



Best RECIST Response	No. (%)
Confirmed partial response	5 (26)
Clinical benefit (stable disease for ≥6 mo)	1 (5)
Stable disease for <6 mo	5 (26)
Progression	7 (37)
Not assessed[a]	1 (5)





- 6-month PFS rate = 32% (16%–61%)
- Median PFS = 2.0 months
- Median OS of 8.9 months

Patel SP, Mayerson E, Chae YK, Strosberg J, Wang J, Konda B et al. A phase II basket trial of Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (DART) SWOG S1609: High-grade neuroendocrine neoplasm cohort. Cancer. 2021 Sep 1;127(17):3194-3201.

Immuno-Oncology – SurvaxM vaccine

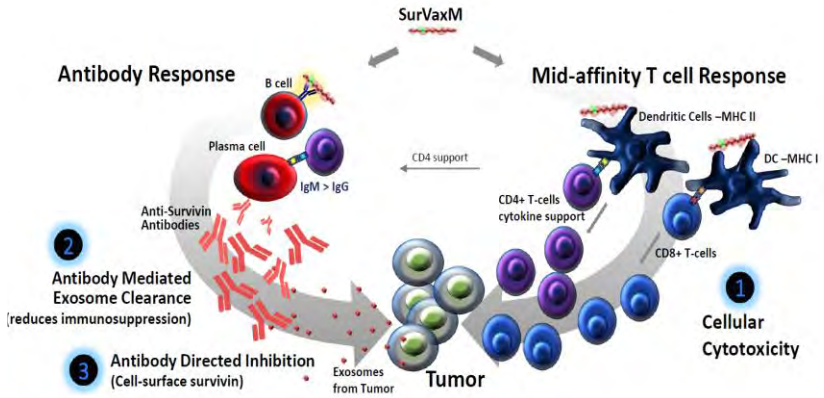
- Survivin is a ubiquitous protein associated with increased resistance to therapy through inhibition of apoptosis
- Survivin was present (≥ 1% or higher) in 51.5% of all NETS, and 58% of NECs

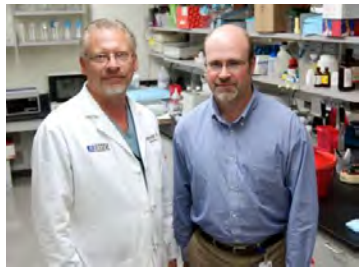
		Negative n (%)	Positive n (%)	Overall n (%)	P-value
Overall	N	64 (48.5)	68 (51.5)	132 (100)	
Age	< 60	18 (28.1)	36 (52.9)	54 (40.9)	0.005
	> 60	46 (71.9)	32 (47.1)	78 (59.1)	
Sex	Male	21 (32.8)	26 (38.2)	47 (35.6)	0.59
	Female	43 (67.2)	42 (61.8)	85 (64.4)	
Smoking Status	Never	32 (50.0)	11 (16.2)	43 (32.6)	< .001
	Former	18 (28.1)	30 (44.1)	48 (36.4)	
	Active	14 (21.9)	27 (39.7)	41 (31.1)	
Primary Site	Lung	22 (34.4)	40 (58.8)	62 (47.0)	0.003
	Pancreas	14 (21.9)	5 (7.4)	19 (14.4)	
	Small Intestine	18 (28.1)	11 (16.2)	29 (22.0)	
	Other	7 (10.9)	12 (17.6)	19 (14.4)	
	Unknown	3 (4.7)		3 (2.3)	
Grade	I	36 (61.0)	17 (26.2)	53 (42.7)	< .001
	II	12 (20.3)	10 (15.4)	22 (17.7)	
	III	11 (18.6)	38 (58.5)	49 (39.5)	

Treatment

Patients will receive 4 priming doses of SurVaxM (500 mcg) + 100µg GM-CSF, emulsified in Montanide ISA 51 VG every 2 weeks.

Maintenance SurVaxM (500 mcg) + 100µg GM-CSF, emulsified in Montanide ISA 51 VG every 12 weeks until progression

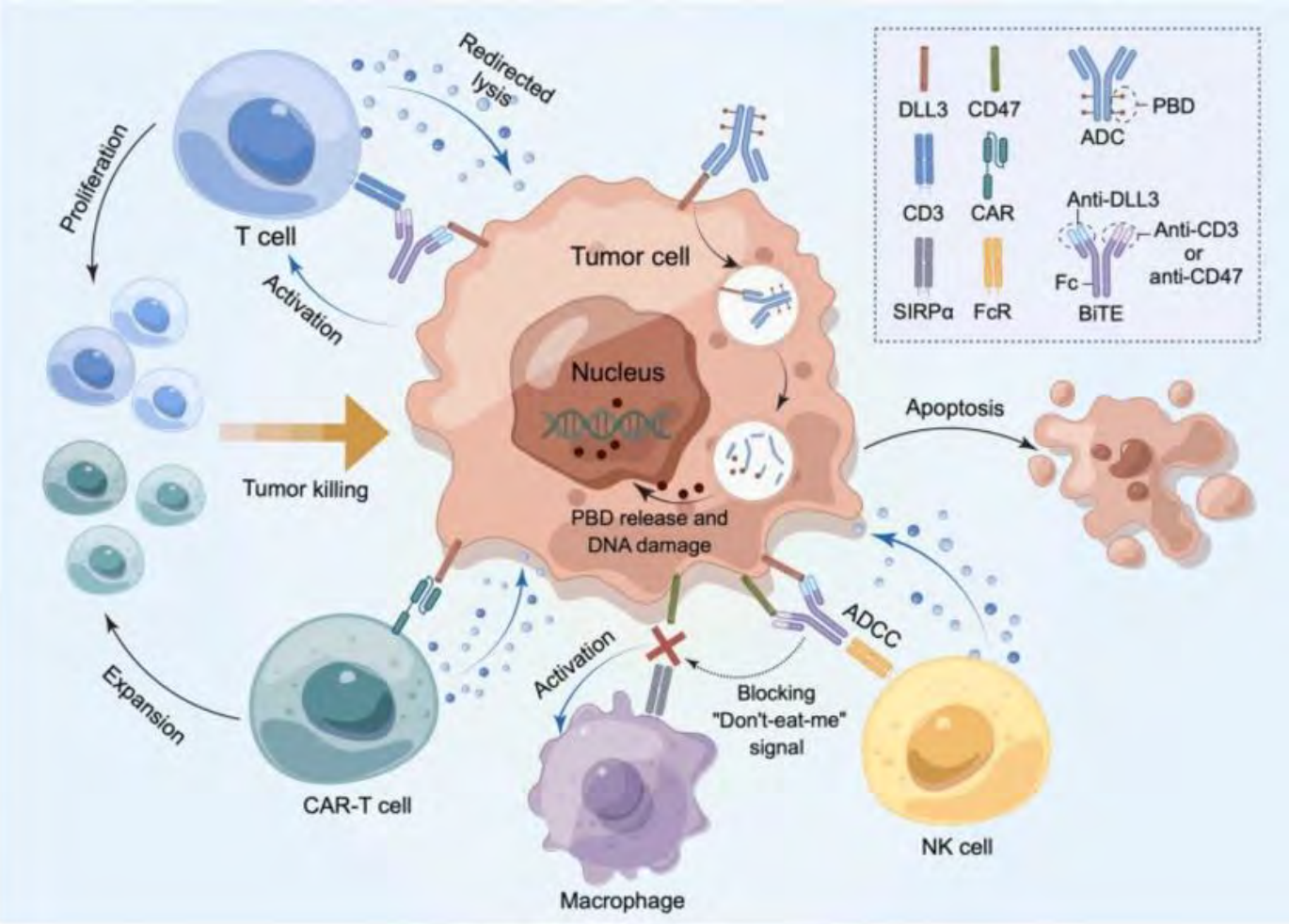




1. A Phase I Study of Safety and Immunogenicity of Survivin Long Peptide Vaccine (SurVaxM) in Patients with Metastatic NETs
   Open, NCT03879694
2. A Phase II Study of Temozolomide and Survivin Long Peptide Vaccine (SurVaxM) in Patients with Progressing Metastatic NETs.
   Will open soon, NCT06202066

Hanif A, Lee S, Gupta M, et al. Exploring the role of survivin in neuroendocrine neoplasms. Oncotarget. 2020;11(23):2246-2258.

DLL3 (delta-like ligand 3) targeting strategies



Agent	Targets
BI 764532	Bi-specific Ab DLL/CD3
HPN328	Tri-specific Ab DLL/CD3/Albumin
PT217	Bi-specific Ab DLL/CD47
LB2102	DLL-CAR T-cell

Zhang et al, Biomed Pharmacother 2023

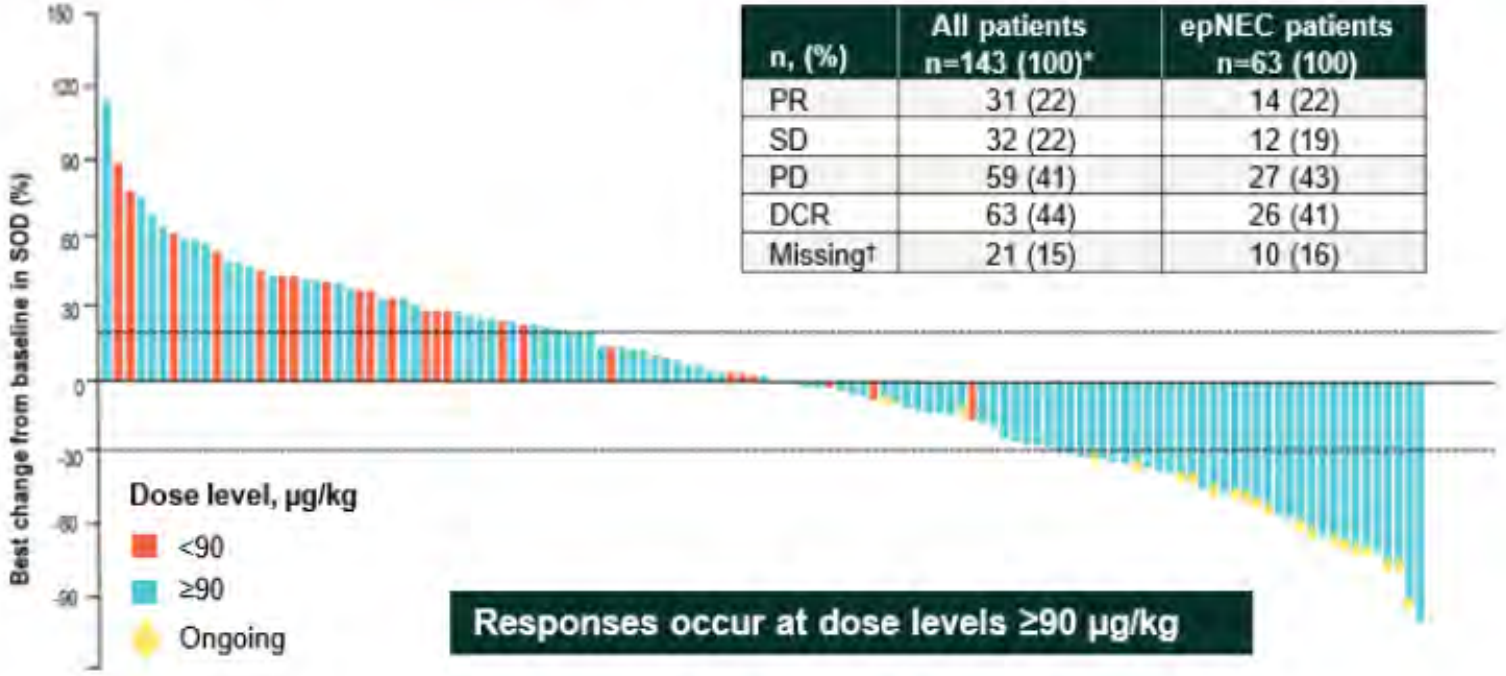
DLL3 (delta-like ligand 3) targeting strategies

DLL3/CD3 IgG-like T-cell engager BI 764532 in patients with DLL3-positive tumours: focus on extrapulmonary neuroendocrine carcinomas- NCT04429087

- Phase I, first-in-human, open-label, dose-escalation trial of obrixtamig in locally advanced or metastatic DLL3-positive SCLC, epNEC, or LCNEC-L who progressed on prior treatment
- 154 patients

Posters C 12 and T7 Dareon
7 chemo + BI764532

EFFICACY IN ALL PATIENTS AND EPNEC PATIENTS (ALL DOSE LEVELS)

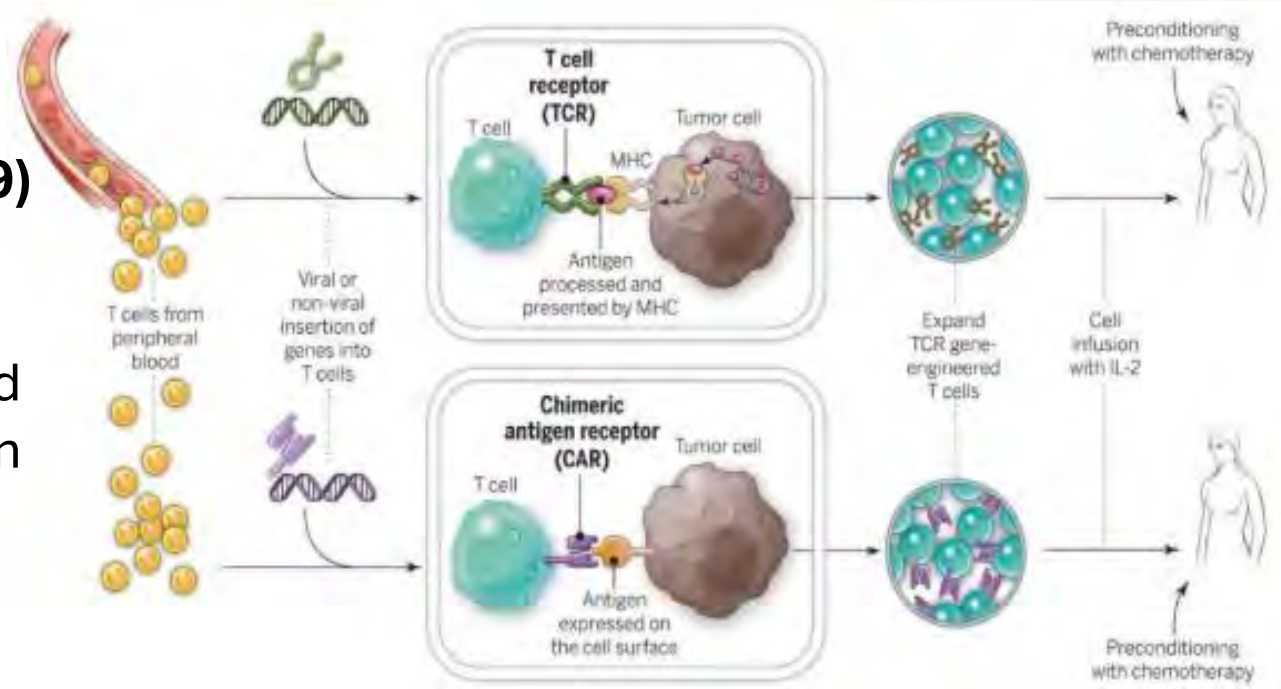


n, (%)	All patients n=143 (100)*	epNEC patients n=63 (100)
PR	31 (22)	14 (22)
SD	32 (22)	12 (19)
PD	59 (41)	27 (43)
DCR	63 (44)	26 (41)
Missing†	21 (15)	10 (16)

Jaume Capdevila, Valentina Gambardella, Yasutoshi Kuboki et al. Phase I trial of the delta-like ligand-3 (DLL3)/CD3 IgG-like T-cell engager obrixtamig* (BI 764532) in patients with DLL3-positive tumors: updated data. (presented at ENETS 2024 and poster C12 NANETS 2024

Immuno-Oncology - CAR T cell therapy

A Phase 1/2 Study to Evaluate CHM-2101, an Autologous Cadherin 17 Chimeric Antigen Receptor (CAR) T Cell Therapy (NCT06055439)



- CAR T cells are T cells engineered to target and kill cancer cells. While CAR T cells have shown success in blood cancers, their use in solid tumors is yet to be explored.

- Newly developed CDH17 CAR T cell therapy-> CHM 2101.

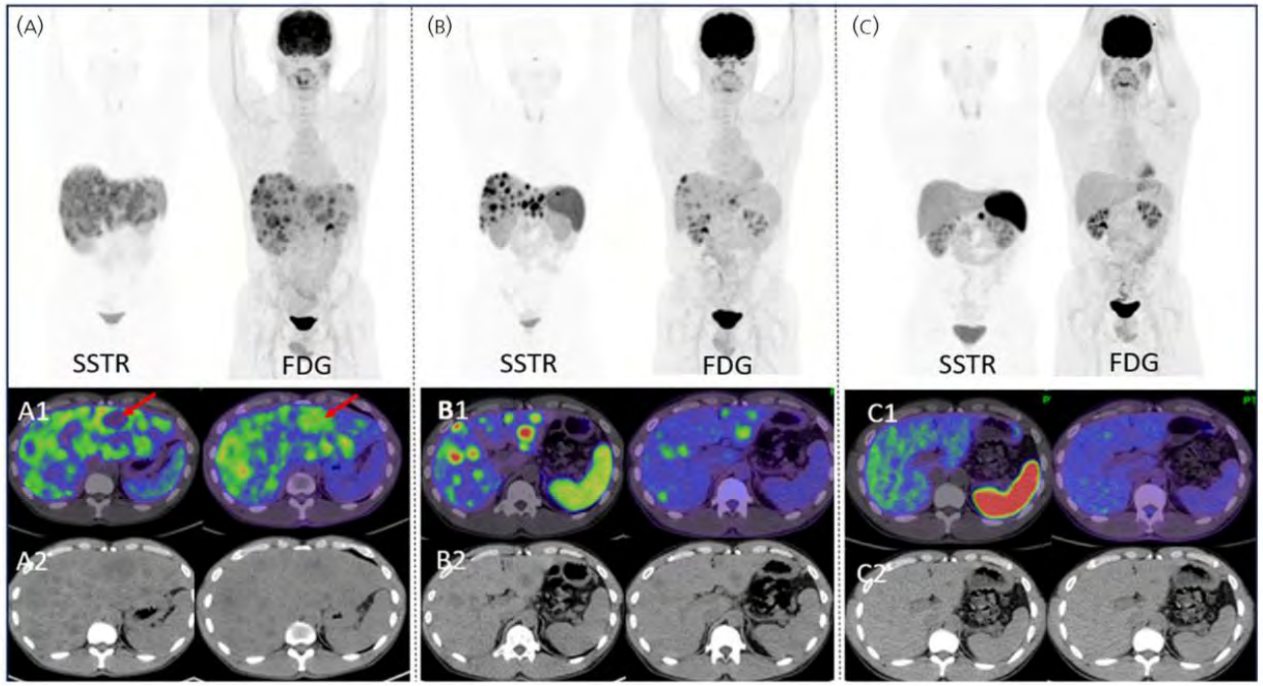
- In October, the FDA approved a trial of CHM 2101 will begin patient enrollment in 2024. This trial will investigate the safety and efficacy of CHM 2101 therapy in G1, G2, and well-differentiated G3 neuroendocrine tumors of the midgut and hindgut (with ≤ 55% Ki67 expression)

https://clinicaltrials.gov/study/NCT06055439

Peptide Receptor Radionuclide Therapy

G3 NETs and some NECs that express SSTR may benefit from PRRT

Study	Pat no	Subgroup	RR	DCR	PFS	OS
Carlsen et al.[28]	43	NET G3	42%	93%	19 m	44 m
	51	NEC	41%	66%	8 m	19 m
	39	NEC Ki-67 < 55%	44%	75%	11 m	22 m
	11	NEC Ki-67 > 55%	45%	54%	4 m	9 m
	99	NEN Ki-67 < 55%	42%	83%	16 m	31 m
	14	NEN Ki-67 > 55%	43%	57%	6 m	9 m
Zhang et al.[29 a]	53	NEN Ki-67 < 55%	35%	82%	11 m	22 m
	11	NEN Ki-67 > 55%	0%	40%	4 m	7 m
Thang et al.[30 b]	22	NEN Ki-67 < 55%	35%	80%	12 m	46 m
	6	NEN Ki-67 > 55%	33%	33%	4 m	7 m
Mitjavila et al.[31]	42	NET G3	38%	76%	12.9 m	
	10	NEC	40%	70%	17.1 m	
Nicolini et al.[32] NEN Ki-67 15–70%	23	NEN Ki-67 < 35%	9%	87%	26.3 m	52.9 m
	10	NEN Ki-67 > 35%	0%	30%	6.8 m	12.6 m
Raj et al.[33]	19	NET G3	28%	72%	13.1 m	
Trautwein et al.[34] NET Ki-67 15–55%	10	NET PRRT+chemo	70%	90%	26 m	NR
	10	NET PRRT	20%	60%	12 m	51 m
Singh et al.[35]	52	NET G3	48%		22.2 m	



-Pathological distinction of NEC vs. NET G3 is challenging when Ki-67 < 55%.
-PRRT may be considered for refractory NEC with high SSTR uptake, Ki-67 < 55%, and no rapid progression

Sorbye H, Kong G, Grozinsky-Glasberg S, Strosberg J. PRRT in high-grade digestive neuroendocrine neoplasms (NET G3 and NEC). J Neuroendocrinol. 2024; e13443

Conclusions/Takeaway

- Ep-NECs are a heterogenous group based on site, histology and ki67, as well as molecular characteristics
- G3 NET and NEC with Ki 67 up to 55% are difficult to distinguish and tailoring therapy based on tumor growth rate, SSTR expression should be considered
- Limited treatment modalities are available for NECs, especially extrapulmonary NECs
- I/O space has many options in development- DLL-3, checkpoint inhibitors, vaccines and CAR-T cells
- Prospective studies and molecular characterization to identify response signatures and new targets are needed

Community Referrals are key: DART Trial and Rural vs urban outcomes

SWOG / News & Events / News / **DART Trial Shows Early Enrollment Success**

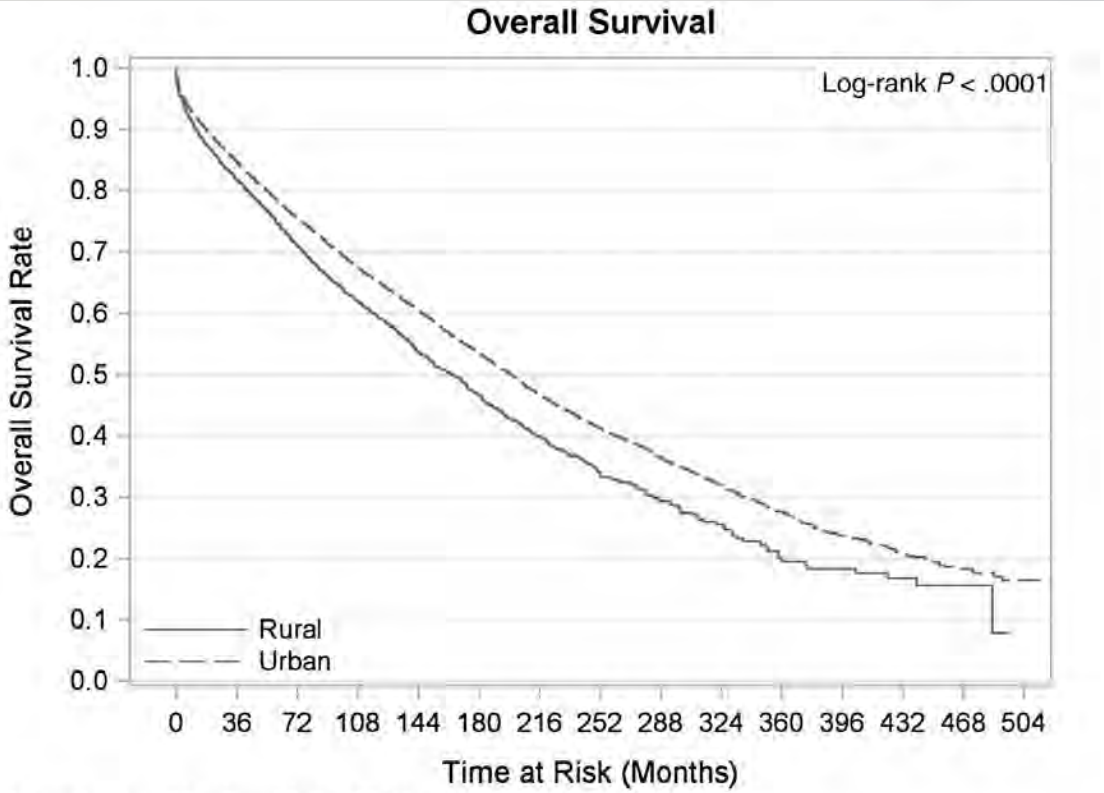
DART Trial Shows Early Enrollment Success

February 22, 2018
Communications Manager

Share

SWOG's rare cancers clinical trial has hit the halfway mark for patient enrollment in its initial phase, averaging two new registered patients each day. Called DART, short for Dual Anti-CTLA-4 & Anti-PD-1 blockade in Rare Tumors, the trial is a unique federally funded immunotherapy trial devoted to rare cancers.

- **62% enrolled in community setting**
- **32% with NETS enrolled in just 3 months**



Unadjusted Kaplan-Meier Estimates

Strata	3-y Survival Rate (95% CI)	5-y Survival Rate (95% CI)	Median Survival (95% CI)	Median Follow-up (Range)	Sample
Total	0.84 (0.84, 0.85)	0.78 (0.78, 0.78)	195.0 (191.0, 199.0)	94.0 (0.0, 514.0)	E=16403 C=36247 T=52650
Rural	0.82 (0.81, 0.83)	0.75 (0.73, 0.76)	163.0 (153.0, 173.0)	94.0 (0.0, 495.0)	E=1946 C=3524 T=5470
Urban	0.85 (0.84, 0.85)	0.79 (0.78, 0.79)	199.0 (194.0, 203.0)	93.0 (0.0, 514.0)	E=14457 C=32723 T=47180

Gosain R et al, Cancer 2019

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