Case 2: Management of Neuroendocrine Carcinoma

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Neuroendocrine Carcinoma Epidemiology

- Rare! – 0.5-0.8/100,000
- Primary site in the digestive system
  - Colorectal 41%
  - Upper GI tract 23%
  - Pancreas 20%
- Risk factors are unknown (not strongly associated with smoking)

Dasari et al. Cancer 2018
Gatta G et al. Lancet Oncol 2017
Korse CM et al. *Eur J Cancer*. 2013

Neuroendocrine Neoplasms

Differentiation	Terminology	Grade	Mitotic Rate (mitosis/2 mm2)	Ki67 Index (Percent)
Well differentiated	NET G1	Low	<2	<3
	NET G2	Intermediate	2-20	3-20
	NET G3	High	>20	>20
Poorly differentiated	NEC, small cell type	High	>20	>20
	NEC, large cell type	High	>20	>20

Rindi et al.Endocrine Pathology. 2022.
Kawasaki et al., Nat Rev Clin Oncol. 2023

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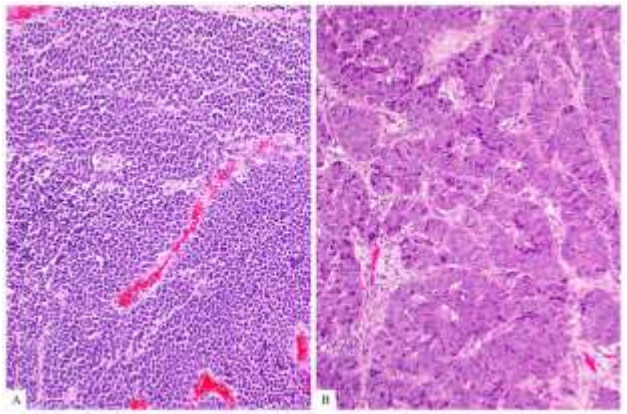
Pathology

- **Morphology:** poorly diff vs well diff
- **Grade:**
  - Ki67> 55% points to NEC
  - Small cell Ki67 typically > 90%

Small Cell Large Cell



- **Immunohistochemistry**
  - Majority positive for Synaptophysin, pankeratins (e.g. CAM5.2, AE1/AE3), CgA
  - Small cell: can lack CgA; 25% of NECs are negative for all traditional general neuroendocrine markers.
    - Insulinoma-associated protein 1 (INSM1) has 85% sensitivity. Expressed by up to 95% of NECs.
    - CXCR4 (diffuse, strong staining favors NEC)
- **Site of origin (Academic)**
  - IHC can facilitate NET site of origin assignment
  - Most occult primaries:
    - Midgut (CDX2)
    - Pancreas (islet 1, PAX6 or polyclonal PAX8, PR)
    - Rectum (SATB2)

WHO classification. International Agency for Research on Cancer 2022.
McHugh KE,. *Am J Clin Pathol*. 2020
Rooper et a. 2017

Management of Advanced NEC

First Line	Cisplatin (or Carbo) and Etoposide	Cisplatin (or Carbo) and Irinotecan	Trials	BSC if PS >2

Neuroendocrine Carcinoma
First-line

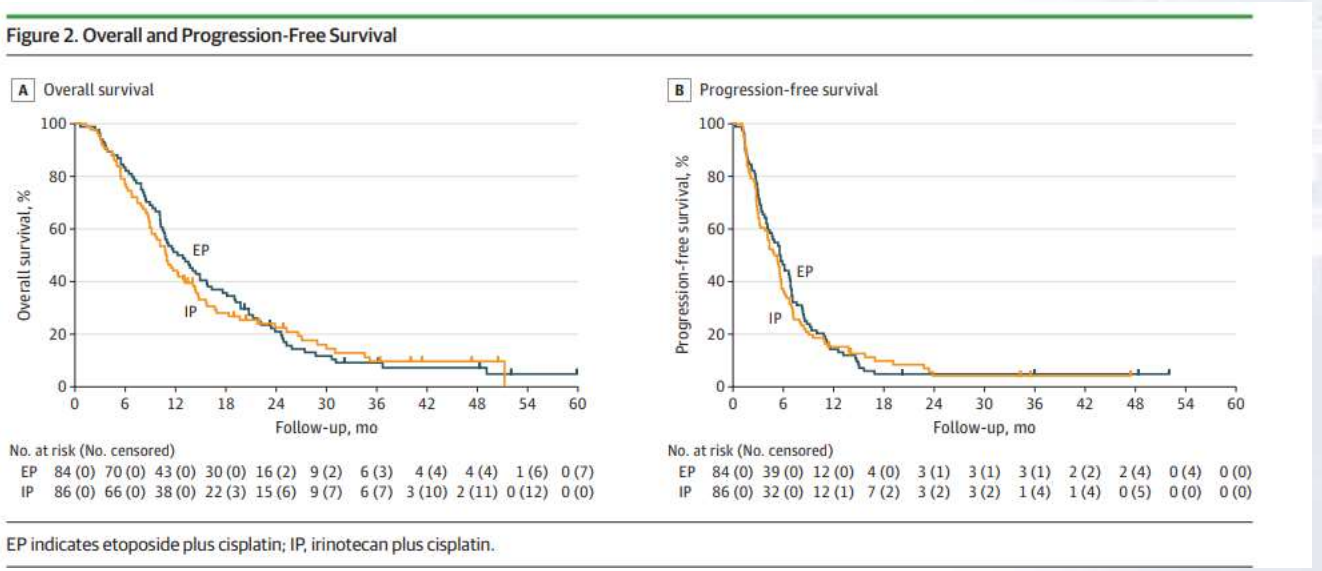
- **Platinum and Etoposide**
  - Response rate 30-50%; PFS 4-6 m; OS 11-12 m (OS only 7.6-8 m in colorectal)
  - Immediate progression with no benefit in 30% in digestive NEC, 60% in colorectal NEC

Reference	Design	Treatment	Number	Diff	ORR (%)	PD (%)	PFS (mo)	OS (mo)
Sorbye et al. Ann Oncol. 2013	Retrospective	Etoposide + Cisplatin or carboplatin	252	G3	31	36	4 mo	11 mo
Walter et al. Eur J Cancer. 2017	Retrospective	Platinum + Etoposide	152	Poorly	50	27	6.2	11.6
Zhang et al. Cancer. 2020	Phase II-R	Cisplatin + Etoposide or irinotecan	66	Poorly	42 vs 42	35 vs. 13	6.4 vs. 5.8	11.3 vs. 10.2
Morizane et al. JAMA Oncol. 2022	Phase III	Cisplatin + Etoposide or irinotecan	170	Poorly	55 vs. 53	13 vs. 15	5.6 vs 5.1	12.5 vs. 10.9

Neuroendocrine Carcinoma
First-line

- Irinotecan/cisplatin (TOPIC-NEC)
  - Randomized phase III trial 170 patients with advanced GI NEC. OS as primary endpoint
  - At least equivalent efficacy as cisplatin and etoposide (EP) in GI-NEC
  - No significant difference in mOS, PFS or responses
  - Grade 3 and 4 toxicity rates were higher with cisplatin plus etoposide for neutropenia (92 versus 54 percent), leukopenia (61 versus 31 percent), and febrile neutropenia (27 versus 12 percent)

OS
12.5 months in the EP arm
10.9 months in the IP arm



PFS
5.6 months in the EP arm
5.1 months in the IP arm

Morizane et al. 2022

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Trials comparing first line chemotherapy

Trial	Phase	Regimen	N	Endpoint	ORR (%)	PFS (mo)	OS (mo)	Reference
TOPIC-NEC (Asia)	III	EP IP	170	OS	54% 52%	5.6 5.1	12.5 10.9	Morizane JAMA Oncol 2022
EA2142 (USA)	II-R	EP CAPTEM	N = 67 EP 35 CAPTEM 32 57% PDNEC 33% G3NET 10%unknown	PFS (6→10 mo)	10% 9%	5.4 2.4	13.6 12.6	Eads et al., (2022), *ASCO*
FOLFIRINEC (France)	*II-Rand*	*EP mFFx*	*218 GEP-NEC*	*PFS (5→7.5 mo)*				*Ongoing*

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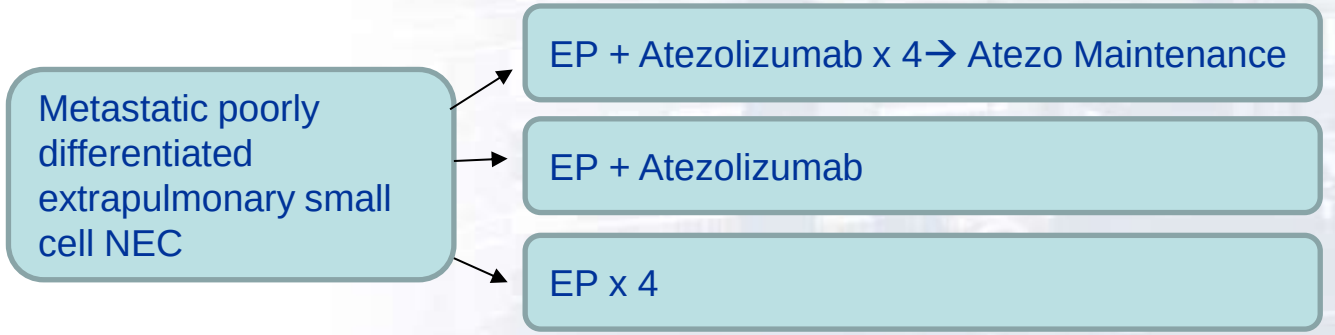
Should we add immunotherapy first line?

- NICE-NEC (Spain, ESMO 2022)
- PE-Nivolumab then Nivolumab
- Phase II, n=38 G3 NEN (29% NET-G3)
  - OS at 12 months 54%
  - ORR 54%
  - PFS 6 mo
  - OS 14 mo

- SWOG Phase II/III trial is evaluating platinum/etoposide with or without atezolizumab in NEC



Riesco-Martinez MC. Ann Oncol. 2022

NCT05058651

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NGS

- **Variants with Potential Targeted Therapies**
  - KRAS p.G12C
  - TMB:High 13 Mt/Mb
  - TP53 p.C176F
  - APC p.E1059* and p.E1374*,
  - JAK1 p.S1043I

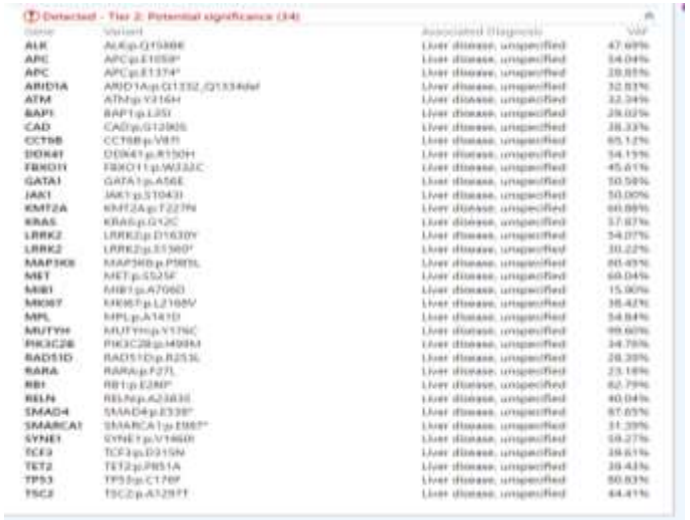

TABLE 1. VARIANTS WITH POTENTIAL TARGETED THERAPIES

Gene / Biomarker	Alteration	%VAF	FDA-approved / NCCN-recommended Drug for this Indication	FDA-approved / NCCN Recognized Resistance for this Indication	FDA-approved / NCCN-recommended Drug for another Indication	Clinical Trials (Number of Trials)
APC	p.E1059* & p.E1374*	54.04 28.85	None	None	None	phase 1 (1)
JAK1	p.S1043I	50.00	None	None	None	phase 1 (2)
KRAS	p.G12C	57.87	None	None	Adagrasib (Non-Small Cell Lung Carcinoma)	phase 1 (19) phase 1 or 2 (19) phase 2 (2)
TMB	TMB High	13.23 mutations/Mb	Pembrolizumab	None	None	phase 1 (34) phase 1 or 2 (24) phase 2 (7)
TP53	p.C176F	80.83	None	None	None	phase 1 (2)

*Please visit clinicaltrials.gov for the most up-to-date and detailed inclusion and exclusion criteria

The assay detected a high tumor mutation burden, as well as driver mutations in APC, KRAS, TP53, RB1, SMAD4, SMARCA1, and MUTYH. A high tumor mutation burden (TMB) strongly predicts response to treatment with immune checkpoint inhibitors, such as pembrolizumab.

The detected MUTYH variant has been reported as a pathogenic germline mutation associated with hereditary cancer predisposing syndromes, including MYH-associated polyposis. Genetic counseling and follow-up germline testing may be considered, if clinically indicated.

Please contact MolecularTumorBoard@jhmi.edu for additional consultation regarding these findings. For possible enrollment on biomarker-driven JHMI trials, contact Phase1trials@jhmi.edu.

Management of Advanced NEC

First Line	Cisplatin (or Carbo) and Etoposide	Cisplatin (or carbo) and Irinotecan	Trials	BSC if PS >2
Second Line	Tumor Agnostic Treatment	Relapse > 3mo Rechallenge EP	5FU based: FOLFOX FOLFIRI NalIRI	Immunotherapy-Dual

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Second Line: *Tumor Agnostic Molecular Targets*

Molecular Alteration	Therapy Options	Frequency	Reference
ALK Mutation, EML4-ALK fusion	ALK inhibitor (Alectinib)	Rare	Wang et al, The Oncologist 2017 Lei Xi et al, Transl Lung Cancer Res 2022 AkBoundova et al Front Oncol 2022
RET gene fusions	RET-inhibitor (Selpercatinib)	Rare	Ray et al J Prec Med 2018 Subbiah V. Lancet Oncol. 2022
NTRK gene fusions	Entrectinib, Larotrectinib	0.3%	Doebelle Lancet Oncol 2020 Sigai D J Natl Comp Canc Network 2017
KRAS G12C	Sotorasib	1.1% 6-40% (CRC)	Wang et al Front Mol Biosci 2022 Saiki et al JTO Clin Case Rep 2023
BRAFV600 Mutations	BRAFi + MEKi: Dabrafenib + Trametinib	20% mainly CRC	Ray et al J Prec Med 2018 Klempner et al Cancer Discov 2016
TMB high/MSI high/ MMR gene defects	Pembrolizumab Dostarlimab Nivolumab-Ipilimumab	<10% mainly high grade	Puccini et al Clin Cancer Res 2020 Marabelle et al. Lancet Oncol 2020 Yachida et al. 2012, Tang et al. 2016b, Girardi et al. 2017 Mohamed A ET AL. Cancers. 2022

Re-Treatment

- NORDIC NEC retrospective study
- Retreatment with the same platinum-based regimen
  - ORR 15%
  - SD 27%

Sorbye et al. Ann Oncol. 2013

Second Line: *Chemotherapy*

- 5FU-based chemotherapy regimens or site specific
  - FOLFOX
  - FOLFIRI
  - FOLFIRINOX

Bajetta et al. Cancer Chemother Pharmacol. 2007
Zhu et al. J Gastrointest Cancer. 2015
Hentic et al. 2012, Endocr Relat Cancer;
Hadoux et al. Endocr Relat Cancer. 2015
Walter et al. Eur J Cancer. 2017

Trials comparing second line chemotherapy

Trial	Regimen	Phase	N	Population	ORR (%)	PFS (mo)	Survival	Reference
PRODIGE 41-BEVANEC	FOLFIRI-BEV FOLFIRI	II-R	150	Second line EP first line in advanced NEC	25% 18%	3.7 3.5	OS 7 vs 9 months	Walter T. Lancet Oncology 2023
NET-02	nalIRI/5FU or Docetaxel	II-R Non comparative	58	second line PD epNEC	11% 10%	3 2	6 months PFS 30% 14%	McNamara MG. EClinicalMedicine. 2023
SENECA (Italy)	CAPTEM vs. FOLFIRI	II-R	53/112 Stopped futility	2nd line in PDNEC		12w-DCR FOLFIRI 39.1% CAPTEM 28%	12 mo OS FOLFIRI 28.4% CAPTEM 28.4%	Bongiovanni et al., (2024), *European Journal of Cancer*

Ongoing
TENEC (Italy) NCT04122911-Temozolomide P2
NCT04042714 (USA)- TAS-102

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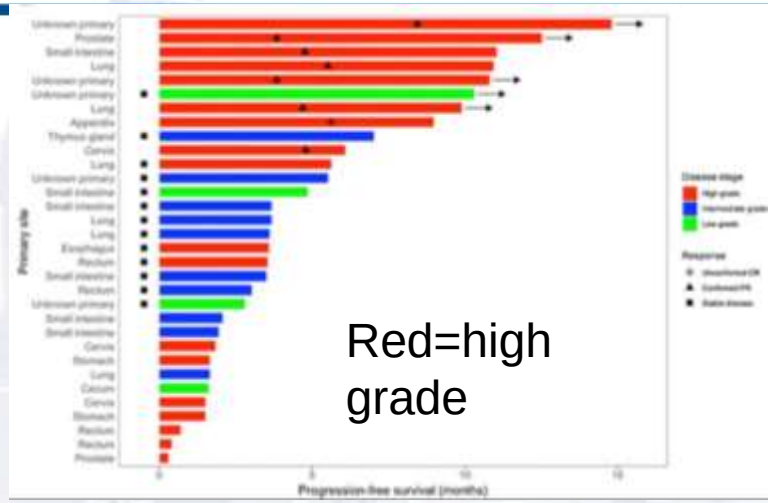
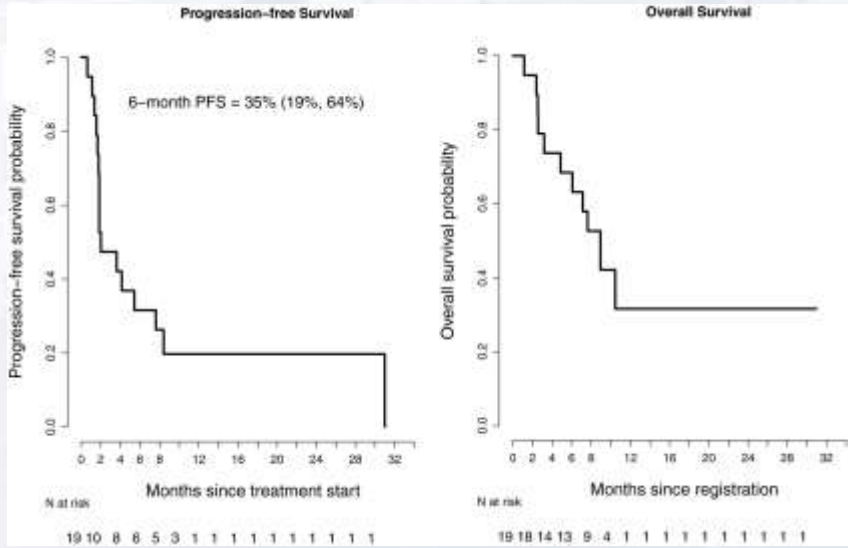
Second line: Immunotherapy

Trial	Regimen	Phase	n	Population	ORR (%)	mPFS (mo)	mOS	Reference
NIPINEC (France)	Ipi-Nivo vs Nivolumab	II-R (Non Comp)	185	GEP-NEC (n=93)	14.9 7.2	1.9 1.8	5.8 7.2	Girard N, Mazieres J, Otto J , et al Ann Oncol. 2021;32S:S1283
NCT03136055	Pembro vs Pembro-Chemo (Paclitaxel or Irinotecan)	II-not R	14 22	Ep-NEC	7 5	1.8 2	7.8 4.8	Raj, (2023), *Br J Cancer*
DART	Ipi-Nivo	II	18 NEC	Ep-NEC	44	6mo PFS -44%	11	Patel SP. Cancer. 2021
DUNE	Durva-Treme	II	18/123	Cohort 4 G3 NET-18 NEC	3/18 (17%)	2.5 (all cohort 4)	5.9	Capdevila. Nature Comm. 2023
AveNEC	Avelumab	II	38/60	60- G3 38- NEC	2/38 (5%)	1.5	4.6	Fottner et al. CCR. 2024

DART SWOG 1609
A phase II basket trial of Dual Anti-CTLA-4 and Anti-PD-1 blockade in Rare Tumors in patients with nonpancreatic neuroendocrine tumors

- Included all histologic grades
- 32 eligible patients received therapy
  - **18 (56%) had high-grade carcinoma**
  - **15 (47%) were gastrointestinal**
- Overall response rate 25% (1CR, 7 PR)
- **Of those with high-grade, ORR was 44% (8/18) versus 0% in low/intermediate grade tumors**
- 6 month PFS 31%
- Median OS 11 months



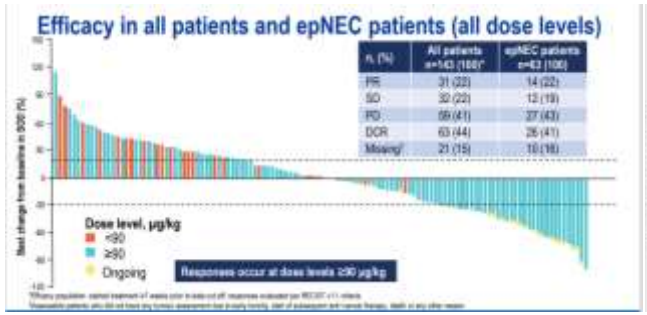


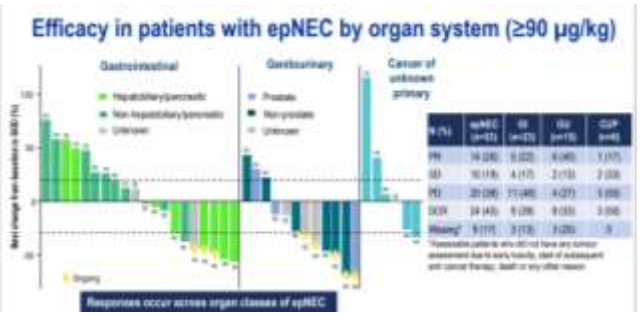
Patel SP. Cancer. 2021

Novel (Experimental) Targets

DLL3

- Notch ligand selectively expressed on the cell surface of SCLC, and epNECs
- Expressed >50-80% NEC depending of location
- DAREON-5 BI 764532 (NCT05882058)
  - Single arm phase II dose selection trial of BI764532, a DLL3 Targeting T cell engager in patients with SCLC or extra-pulmonary NEC DLL3+





- Other phase II trials in DLL3 + NEC
  - HPN328 (NCT04471727, anit-DLL3/CD3)
  - Tarlatamab (anti-DLL3/CD3)
  - DLL3 CAR-T cell

Other targets:

- -Lurbinectedin (RNA polymerase II, NCT05126433)
- -PARP, HDAC, ATR, SSTR, XPO1, BCL-2) among others

Capdevila. ENETS 2024

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Conclusions

- Systemic treatment options in first line setting include platinum/etoposide and platinum/irinotecan.
- Consider NGS testing to identify tumor agnostic molecular targets.
- Clinical trials indicated at any line of treatment.

THANK YOU!