Κλινικό Φροντιστήριο Νευροενδοκρινών Νεοπλασμάτων

Συστηματική θεραπεία LCNEC Πνεύμονα

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Lung Neuroendocrine Neoplasias (NEN): 20% of cases

NENs of pulmonary origin are grouped into:

- low-grade: typical carcinoid (TC)
- intermediate-grade: atypical carcinoid (AC)
- high-grade: small cell carcinoma (SCC), and large cell neuroendocrine carcinoma (LCNEC).
- All of the NETs demonstrate neuroendocrine differentiation, which is confirmed with IHC markers: synaptophysin, chromogranin A and CD56
- These diagnostic categories have different prognostic implications and require distinct treatment strategies

Lung NENs

- A carcinoid is a neoplasm that is characterized by neuroendocrine differentiation, and often by indolent clinical behaviour.
- TCs seldom metastasise, and patients with TC have an excellent prognosis even when regional lymph nodes are affected
- ACs are more likely to metastasise, and patients with this disease have a worse prognosis, particularly if mediastinal nodes are affected.
- Survival rates for patients with LCNEC are lower than those of patients diagnosed with non small cell lung cancer (NSCLC)
- LCNECs have similar survival rates as those of SCLC
- There is no standard treatment regimen for the treatment of LCNECs.

LCNECs vs SCLC

- Pulmonary LCNEC is a rare and aggressive tumor, diagnosed based on high grade features of greater than 10 mitotic figures in 2 mm2 and the presence of neuroendocrine markers
- Discriminated based on morphological features: large cells, abundant cytoplasm, prominent nuclei
- Its prognosis and treatment mirror that of small cell lung cancer (SCLC), with a 5-year survival rate for stage IV disease of less than 5%

LCNECs vs SCLC

- Compared with SCLC, however, LCNECs tend to present peripherally rather than centrally and are more likely to be early stage at diagnosis.
- Patients with LCNEC are often treated according to regimens typically used for SCLC
- Several recent studies have shown that LCNEC responds to cisplatin-based chemotherapeutic regimens similar to those used for SCLC. However, these are retrospective studies in small numbers of patients

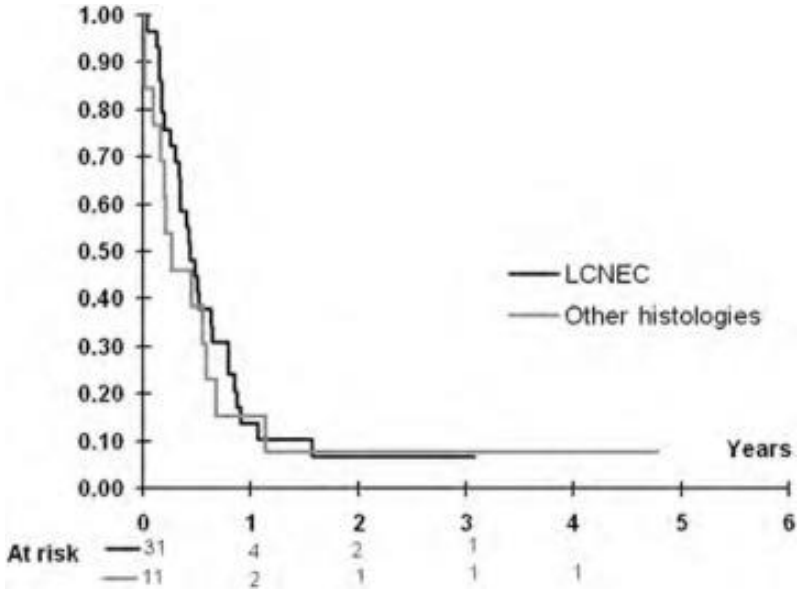
The GFPC 0302 study

- Prospective, multicentre (18), single-arm, phase II study with a centralised review of treatment-response and pathological data.
- 42 patients stage IV/IIIB LCNEC received cisplatin (80 mg/m2 d1) and etoposide (100 mg/m2 d1-3) every 21 days.
- PR in 34% of 29 pts with LCNEC diagnosis confirmed by the centralised pathology review
- Cisplatin and etoposide combination yielded similar outcome in LCNEC as in SCLC, with a median progression-free survival (PFS) of 5.2 months and overall survival (OS) of 7.7 months

Le Treut J, *et al*. Ann Oncol 2013;24: 1548–52

The GFPC 0302 study

- The centralised pathologist review reclassified 11 of 40 (27.5%) patients: 9 as small-cell lung cancer, 1 as undifferentiated non-small-cell lung cancer, and 1 as atypical carcinoid.
- Survival data were not significantly changed by excluding the reclassified patients.
- **Conclusions:** The pathological diagnosis of LCNEC is difficult. The outcomes of advanced LCNEC treated with cisplatin-etoposide doublets are poor, similar to those of patients with advanced small-cell lung carcinoma (SCLC).



Le Treut J, *et al*. Ann Oncol 2013;24: 1548–52

Molecular Alterations of LCNEC

- LCNEC is made up of subgroups that resemble SCLC and NSCLC by their molecular profiles
- Rekhtman et al. performed an NGS analysis in 45 LCNEC and demonstrated alterations in TP53 (78%), RB1 (38%), STK11 (33%), KEAP1 (31%) and KRAS (22%)
- They identified two major and one minor subsets:
- SCLC-like LCNEC, characterized by TP53 + RB1 co-mutation/loss and MYCL amplification
- NSCLC-like LCNEC, characterized by the lack of co-altered TP53 + RB1 and almost universal occurrence of NSCLC-type mutations (STK11, KRAS and KEAP1)
- Carcinoid-like LCNEC, characterized by MEN1 mutations and low mutational burden.

Rekhtman, N. *et al* Clin. Cancer Res. 2016, 22, 3618–3629

Integrative and comparative genomic analyses identify clinically relevant pulmonary carcinoid groups and unveil the supra-carcinoids

- Integrative analyses on 257 lung neuroendocrine neoplasms stratify atypical carcinoids into two prognostic groups with a 10-year overall survival of 88% and 27%, respectively.

- Group of supra-carcinoids unveiled. A subgroup of atypical carcinoids with carcinoid-like morphology yet the molecular and clinical features of the deadly LCNEC!

  > high estimated levels of neutrophil infiltration

  > altered pathways related to neutrophil chemotaxis and degranulation

  > levels of immune checkpoint receptors and ligands (incl. PDL1 and CTLA4) =/> than LCNEC and SCLC

- Current classification only recognises existence of Grade 1 (typical) and Grade 2 (atypical) well differentiated lung NETs
- Grade 3 would only be associated with poorly differentiated SCLC and LCNEC
- Supra-carcinoids: The equivalent in the lung of the well-differentiated Grade 3 GEP NETs ?

Alcala N. *et al*, 2019, Nature Communications, **10**, 3407

Role for Immunotherapy?

- With regard to neuroendocrine tumors, most evidence comes from SCLC.
- The rationale for the use of immunotherapy in this setting derives from the fact that SCLC has one of the highest TMB among human cancers (median 8 mut/Mb), despite expressing PD-L1 in only 20% of the cases
- Usually, LCNEC patients are excluded from studies on SCLC, so data about immune checkpoint inhibition efficacy are derived mainly from case reports

Is there a role for Immunotherapy in LCNECs?

- The median tumor mutation burden (TMB) of LCNEC and SCLC are similar at 9.9 mut/Mb
- Reflecting that both disease entities are commonly associated with the higher mutational load seen in smoking induced malignancies

Chae YK, et al . 2017 J Clin Oncol 35, Abstr 8517

Immunotherapy in LCNECs

- multi-centre retrospective review
- patients with stage IIIB-IV LCNEC treated with nivolumab or pembrolizumab following 1st line platinum-based chemotherapy.
- 10 patients were treated with immune checkpoint inhibitors (9 with nivolumab and 1 with pembrolizumab).
- 6 of the 10 showed PR (60%), 1 demonstrated SD (10%)
- mPFS 57 weeks
- median no of doses of immune checkpoint inhibitor therapy received 16.

Levra, M.G *et al* J. Thorac. Oncol. 2017, 12: S702–S703.

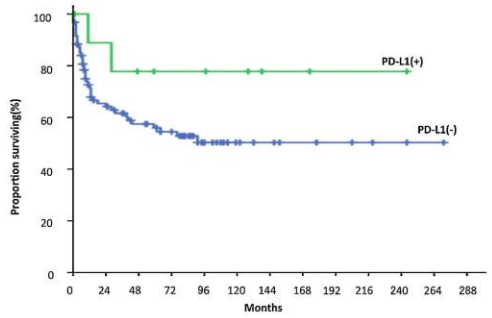
PD-L1 expression in neuroendocrine tumors of the lung

- single centre institutional review of surgical specimens
- 227 patients with neuroendocrine tumors of the lung (106 LCNECs)
- to assess the frequency of PD-L1 expression in patients
- PDL-1 expression was apparent in 10.4% of LCNECs, 5.8% in SCLC
- PDL-1 expression was NOT observed in carcinoid tumours

Tsuruoka K *et al*. Lung Cancer. 2017;108:115-120

Relationship between survival and PD-L1 expression in SCLC and LCNEC with expression of PD-L1.

(A) Disease-free survival of LCNEC patients with positive or negative for PD-L1 expression

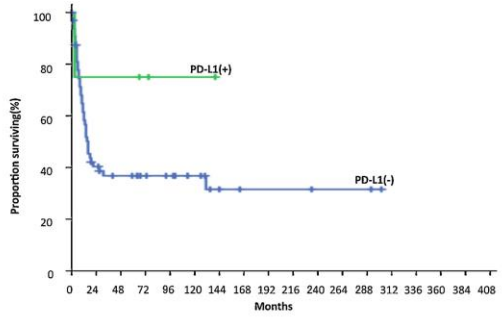


	No. of events / Total No. of Patients	Median Disease-Free Survival (months) (95%CI)
PD-L1 (-)	41 / 95	(-)
PD-L1 (+)	2 / 11	(-)

※Estimation is limited to the largest survival time if it is censored.
HR, 0.373 (95% CI, 0.090-1.543), P=0.173

Abbreviations: LCNEC, large cell neuroendocrine carcinoma.

(B) Disease-free survival of SCLC patients with positive or negative for PD-L1 expression

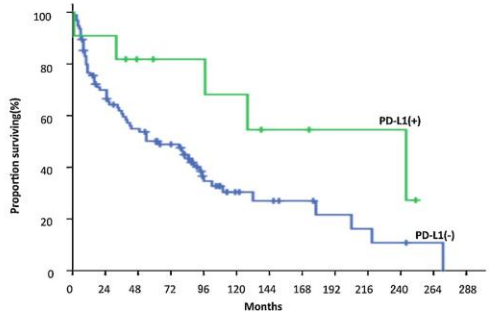


	No. of events / Total No. of Patients	Median Disease-Free Survival (months) (95%CI)
PD-L1 (-)	40 / 65	16 (11.2-20.8)
PD-L1 (+)	1 / 4	(-)

※Estimation is limited to the largest survival time if it is censored.
HR, 0.318 (95% CI, 0.044-2.321), P=0.259

Abbreviations: SCLC, small cell lung cancer.

(C) Overall survival of LCNEC patients with positive or negative for PD-L1 expression

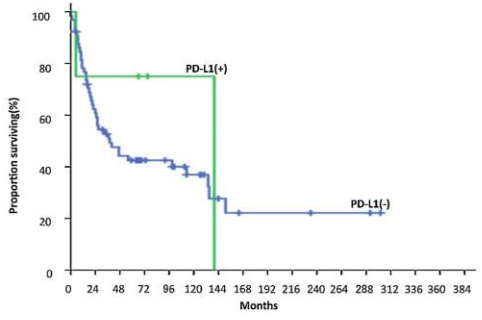


	No. of deaths / Total No. of Patients	Median Overall Survival (months) (95%CI)
PD-L1 (-)	64 / 95	64 (27.7-100.3)
PD-L1 (+)	5 / 11	244 (94.8-393.2)

HR, 0.421 (95% CI, 0.167-1.063), P=0.067

Abbreviations: LCNEC, large cell neuroendocrine carcinoma.

(D) Overall survival of SCLC patients with positive or negative for PD-L1 expression



	No. of events / Total No. of Patients	Median Overall Survival (months) (95%CI)
PD-L1 (-)	41 / 65	38 (15.9-60.1)
PD-L1 (+)	2 / 4	140 (-)

※Estimation is limited to the largest survival time if it is censored.
HR, 0.652 (95% CI, 0.157-2.709), P=0.557

Abbreviations: SCLC, small cell lung cancer.

Tsuruoka K *et al*. Lung Cancer. 2017;108:115-120

Single case of pulmonary LCNEC with an exceptional response to a first dose of pembrolizumab despite being PD-L1 protein expression negative by IHC.

- Patient with stage IB LCNEC > right upper lobectomy and LN dissection
- pT2aN0M0
- IHC staining negative for TTF-1, Napsin, p40, CK5/6, and the androgen receptor but positive for CK7, synaptophysin and CD56, consistent with a large cell neuroendocrine carcinoma of pulmonary origin
- >20 mitosis per 10 HPF
- Pt received 4 cycles of cisplatin-docetaxel adjuvant chemo
- PD with bone, lung and pancreatic mets within 4 months of adjuvant chemotherapy

Wang VE *et al*. Journal for immunotherapy of cancer 2017 vol. 5,1 75

Molecular profiling performed on the original surgical specimen

- TMB high at 24.76 mut/Mb
- PD-L1 negative (Initial PD-L1 staining using the SP142 antibody was negative and independent confirmatory testing with a second 22C3 antibody also showed <1% PD-L1 expression on the tumor cells)
- Positive for PD-L1 amplification
- PD-L1 amplification has been reported in only 2–4% of lung cancer based on The Cancer Genome Atlas and is usually concordant with PD-L1 protein expression, although this is not the case for this patient!

Wang VE *et al*. Journal for immunotherapy of cancer 2017 vol. 5,1 75

–Genomic alterations identified

Gene Alteration	Loss or Gain of Function	Predictor of Response to Pembrolizumab
CD274 (PD-L1) amplification	Gain	Yes
STK11 S216F and LOH	Loss	Negative predictor
MYC amplification	Gain	No
APC E2516	Loss	No
RB1	Loss	No
TP 53 R158 L	Loss	No

Genomic profiling suggested that the patient's tumor more closely resembles the SCLC type with high mutation burden, TP53 and RB1 loss, and MYC amplification.

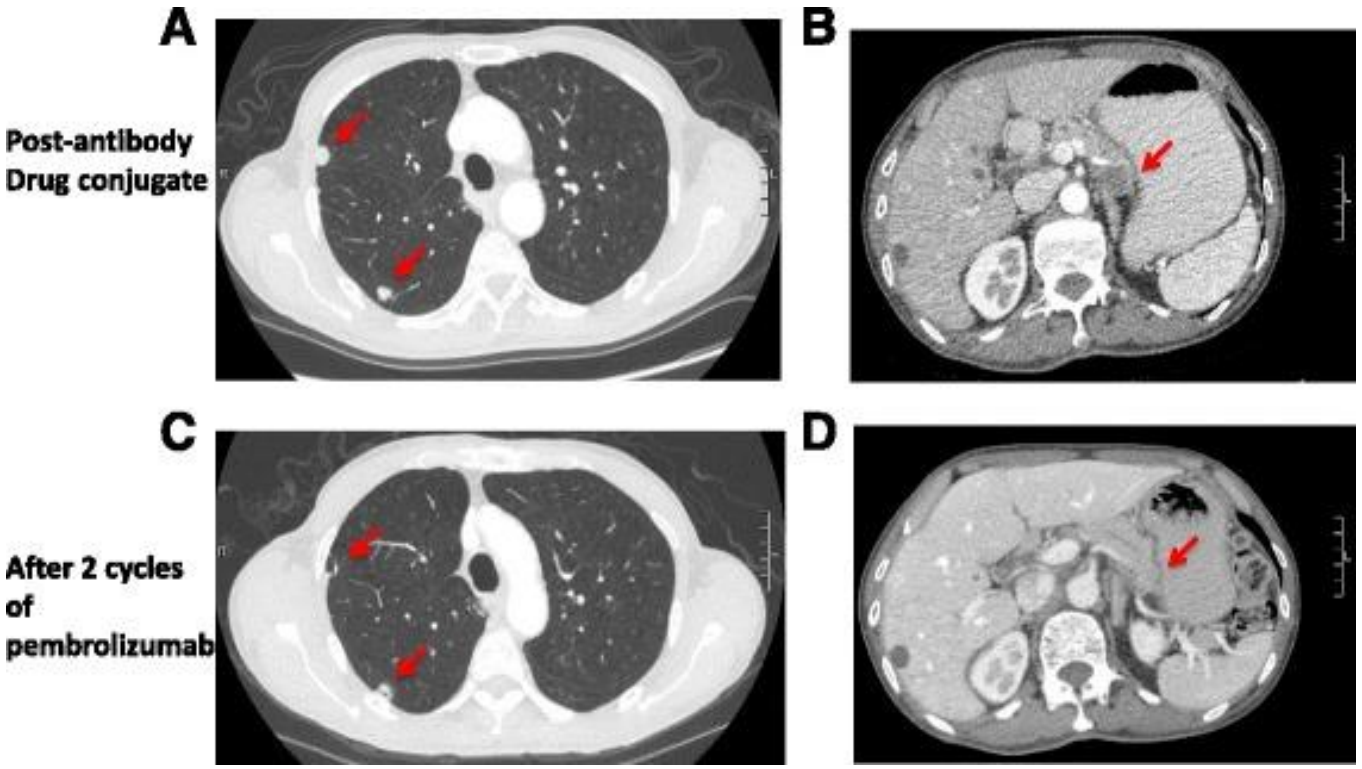
However, the presence of STK11 mutation in this patient's tumor is more commonly associated in LCNECs that resemble NSCLC

Wang VE *et al*. Journal for immunotherapy of cancer 2017 vol. 5,1 75

- The tumor was positive for a neuroendocrine specific cell surface marker so patient received palliative RT to the right hip and was enrolled in a phase I/II study of an antibody drug conjugate targeting this specific cell surface protein.
- PD with a new pancreatic lesions after 1 cycle with the experimental drug
- Patient stopped the trial and started on pembrolizumab.

Wang VE *et al*. Journal for immunotherapy of cancer 2017 vol. 5,1 75

CT findings



After 1 cycle of experimental drug: increase in both the size and number of pulmonary nodules. Two new pancreatic lesions

After 2 cycles of pembrolizumab, all visible lesions shrunk and no new lesions were seen

Patient remains on pembrolizumab with continued improvement of the disease 6 months after.

Wang VE *et al*. Journal for immunotherapy of cancer 2017 vol. 5,1 75

2 LCNEC patients treated with ICIs at Markey Cancer Center, University of Kentucky

Patient	Prior treatment	Current treatment	Response
57 Y/O with metastatic LCNEC of lung with brain metastasis	Resection of brain metastasis followed by radiation, carboplatin and etoposide X 4 cycles, intolerance to further platinum doublet. Switched to maintenance pemetrexed X 21 cycles, developed toxicity to pemetrexed. Switched to off label nivolumab.	Nivolumab discontinued post 4 doses due to lack of measurable radiological disease. Currently on observation.	Complete response. Off therapy for 15 months now.
39 Y/O F with metastatic LCNEC of lung. Positive for following mutations; STK11, AURKA, AXL, MYC, CCNE1, GNAS, KEAP1, MCL1, RUNX1, TP53. High tumor mutation burden and PD-L1 positive.	Carboplatin and etoposide X 5 cycles. Radiological disease progression. Switched to nivolumab based on molecular tumor board recommendation.	Currently on nivolumab q 2 weeks Status post 15 doses	Radiological and clinically stable disease.

Chauhan A. *et al* Oncotarget 2018, 9(18): 14738–14740.

Case Report: CR of a locally advanced LCNEC after palliative thoracic RT & nivolumab

- 41-year-old woman diagnosed with an unresectable locally advanced L-LCNEC
- Ki67 80%, **PDL1 expression 1-5%**
- TNM based on CT & FDG PET: cT4cN2cM0
- Cisplatin-etoposide x3 > PD
- Palliative thoracic RT > nivolumab 3mg/kg every 2 weeks
- PR after 4 cycles- significant decrease in L- lung mass & mediastinal LNs
- Further tumour regression after 8 and 14 cycles
- Restaging including PET & MRI brain > ycT2a ycN0 ycM0
- Salvage surgery was then performed 7 months after initiation of nivolumab
- Histological analysis of the resected lung and LNs showed absence of residual viable tumor cells > ypT0ypN0 (R0)
- No adjuvant Rx
- Disease-free and treatment free 8m post op.

Mauclet C. *et al*, Lung Cancer 2019, 128:53-56

Case Report: CR of a locally advanced LCNEC after palliative thoracic RT & nivolumab

- Impressive tumor response to immunotherapy with nivolumab after non-curative thoracic radiotherapy
- Analysis of pts tumour by NGS revealed a G105C mutation in TP53 while there was no mutation in STK11 and Rb1 **compatible with a NSCLC subtype**
- The absence of Rb1 mutation is a possible explanation for the poor response to cis-etop.
- Retrospective analysis of patient's tumour revealed high TMB 27.74mut/Mb and 33.86mut/Mb in two different labs > may explain good response to nivolumab
- **Immunotherapy may be effective in Lung LCNECS even if PDL1 tumour expression is low**

Mauclet C. *et al*, Lung Cancer 2019, 128:53-56

IO + RT rationale

- combination of immune checkpoint inhibitors with radiation therapy can create synergistic anti-tumor activity, eliciting a stronger immune response.
- The rationale for the use of radiotherapy lies in the so-called “abscopal effect”. This is an immune-mediated effect triggered by a localized radiation treatment at one site that recruits reactive cells that elicit a response on a distant site outside of the irradiated field

DART: Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors

- The **DART study** is a currently ongoing phase II basket trial of double blockade with nivolumab 240 mg every 2 weeks plus ipilimumab 1mg/kg every 6 weeks
- continuous schedule until disease progression or unacceptable toxicity, across multiple rare tumor types.
- Recently, data from the neuroendocrine cohort (excluding pNET) were reported. Of the 32 patients, 18 had high-grade neuroendocrine carcinoma.
- The most common primary sites were gastrointestinal (N = 15) and lung (N = 6)
- median number of prior lines of therapy was 2.
- Primary end point was ORR, which was 25% in the entire cohort, but up to 44% (8/18) in high-grade neuroendocrine carcinoma vs. 0% in low/intermediate grade tumors.
- mPFS was 4 months
- mOS was 11 months.
- irAEs were reported in 72% of patients: the most common were hypothyroidism (31%) and AST increase (25%), while the most common Grade 3–4 irAEs (38%) were ALT increase (9%) and AST increase (6%), lipase increase (6%), and encephalopathy (6%)

ICIs + chemo combination clinical trials

- only a few prospective trials specifically designed for the combination of immunotherapy and chemotherapy in LCNEC.
- Two phase II trials of pembrolizumab in combination with platinum (carboplatin or cisplatin) and etoposide chemotherapy (NCT03901378) and of nivolumab plus ipilimumab (NCT03591731) in metastatic or unresectable relapsed LCNEC or GEP–NEC in progression after one or two lines of treatment, including a platinum-based regimen, are ongoing.
- the combination of VEGF and immune checkpoint inhibition is being tested in a phase II trial of cabozantinib, a multikinase inhibitor also targeting VEGF and c-MET, combined with nivolumab and ipilimumab in patients with poorly differentiated NEN (including small and large cell morphology), regardless of the primary site, progressed on one previous line of treatment (NCT04079712).
- The combination therapy of nivolumab with temozolomide is being tested in patients with recurrent or refractory SCLC, LCNEC, or advanced G1-G3 well-differentiated NETs (NCT03728361).

Activity & safety of spartalizumab (PDR001) in patients (pts) with advanced neuroendocrine tumors (NET) of pancreatic (Pan), gastrointestinal (GI), or thoracic (T) origin, & gastroenteropancreatic neuroendocrine carcinoma (GEP NEC) who have progressed on prior treatment (Tx)

Annals of Oncology 29 (Supplement 8): viii467–viii478, 2018

Confirmed Overall Response Rate by BICR

Variable	Well-diff NET				Poorly-diff GEP NEC N=21
	Thoracic cohort N=30	Pancreatic cohort N=33	GI cohort N=32	Overall N=95	
PR, n (%)	6 (20)	1 (3)	0	7 (7)	1 (5)
SD, n (%)	16 (53)	17 (52)	19 (59)	52 (55)	3 (14)
PD, n (%)	5 (17)	13 (39)	11 (34)	29 (31)	14 (67)
Unknown, n (%)	3 (10)	1 (3)	2 (6)	6 (6)	3 (14)
Confirmed ORR, n (%)	6 (20)*	1 (3)	0†	7 (7)	1 (5)
DCR, n (%)	22 (73)	19 (58)	19 (59)	60 (63)	4 (19)

Median follow-up, months (range): 8 (6.0-10.9) for NET and 6 (4.7-6.9) for NEC

*Among 6 responders in thoracic cohort, all were in patients with atypical carcinoids, 4 responses were ongoing with duration of response of 2-6 months. 2 other patients died after confirmation of response due to respiratory failure (not treatment-related) and myasthenia gravis (treatment-related). †1 PR in the GI cohort with time to response of approx. 7 months was unconfirmed at the time of the cut-off date.

Abbreviations: BICR, blinded-independent central review; DCR, disease control rate; diff, differentiated; GEP NEC, gastroenteropancreatic neuroendocrine carcinoma; NET, neuroendocrine tumors; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

MUNICH 2018 ESMO congress

Conclusions: These preliminary results suggest clinical activity of spartalizumab in pts with **well-diff** nonfunctional NET of **T origin**.

Further studies are needed to explore the role of immunotherapy combinations, identifying predictive biomarkers for immunoncology (IO) response or strategies to increase response to IO in this pt population.

Conclusions

- LCNEC is a biologically heterogeneous group of tumours
- 2 main subsets based on genomic signatures: SCLC-like and NSCLC-like
- Treating all LCNECs with SCLC regimens might be suboptimal
- 60% of pulmonary LCNECs do not exhibit the small cell hallmark signature (p53 and Rb1 co-mutation)
- Chemo selection may not be possible by histology only- must incorporate molecular analysis

Conclusions

- This may explain the large percentage of LCNEC patients who are platinum –refractory or rapidly progress on a platinum doublet.
- Promising data supporting a role for ICIs in some LCNEC patients- prospective data warranted
- lack of concordance amongst current biomarkers for predicting responses to checkpoint inhibitor therapies
- Prospective randomised clinical trials are required to guide the treatment of lung LCNECs according to genomic subtypes.