Fred Hutch
Cancer Center

Insights and Lessons Learned in Developing a Research Career within the NCI Cooperative Groups

David Zhen, MD
Assistant Professor
GI Medical Oncology

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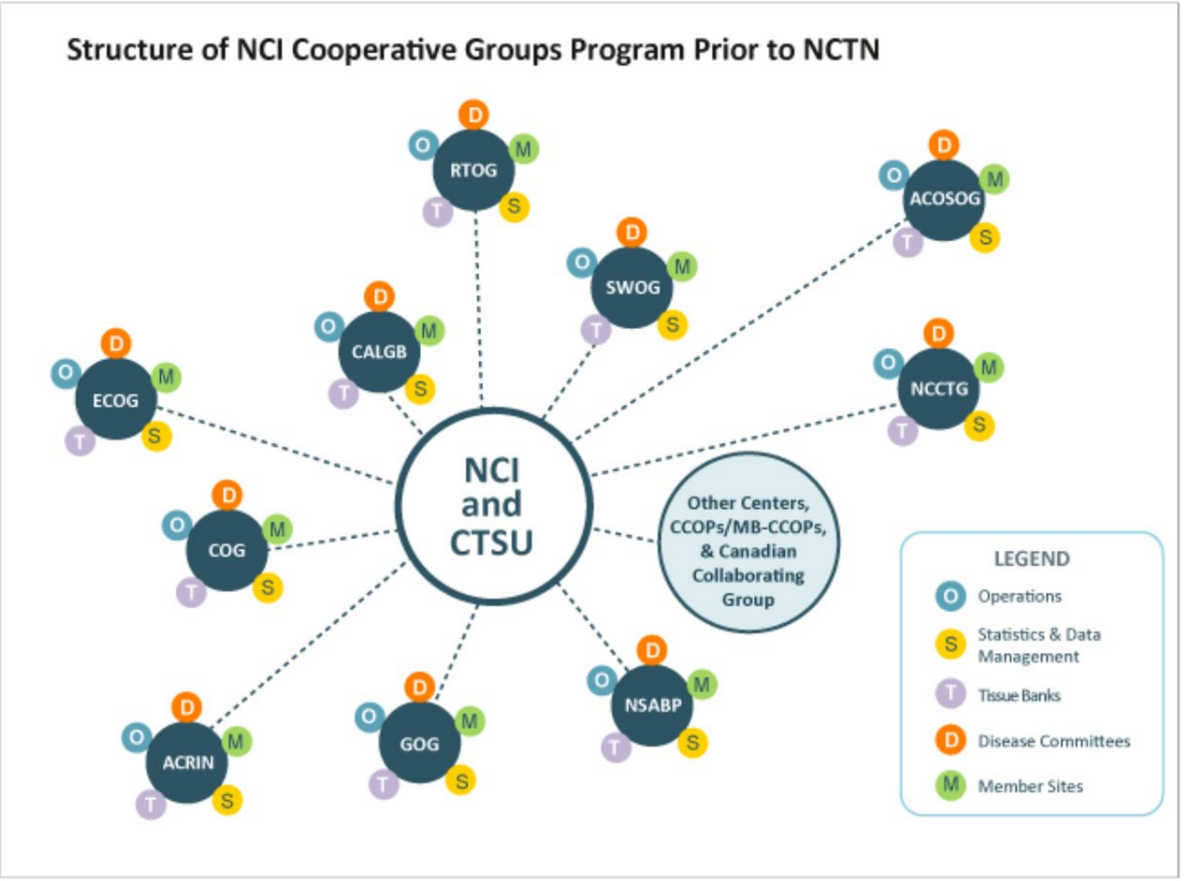
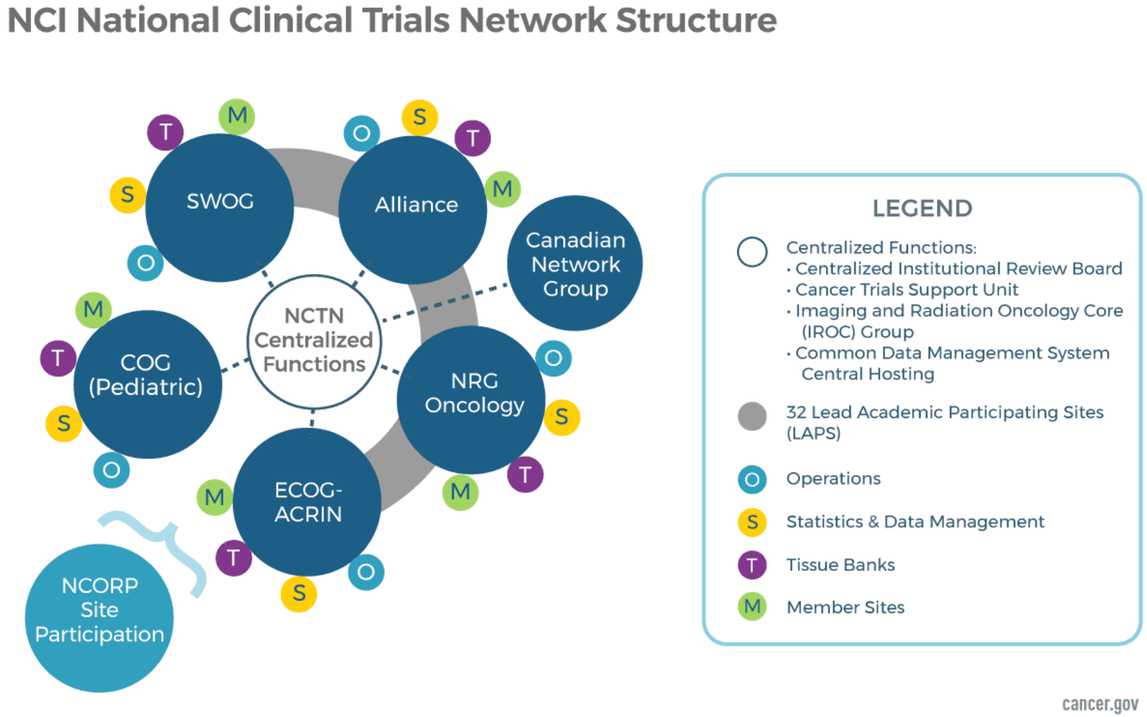
Outline

- Overview of NCI National Clinical Trials Network (NCTN) and cooperative groups
- Personal experiences and my journey of developing a trial in the NCTN
- Insights and lessons learned for conducting research in the NCTN

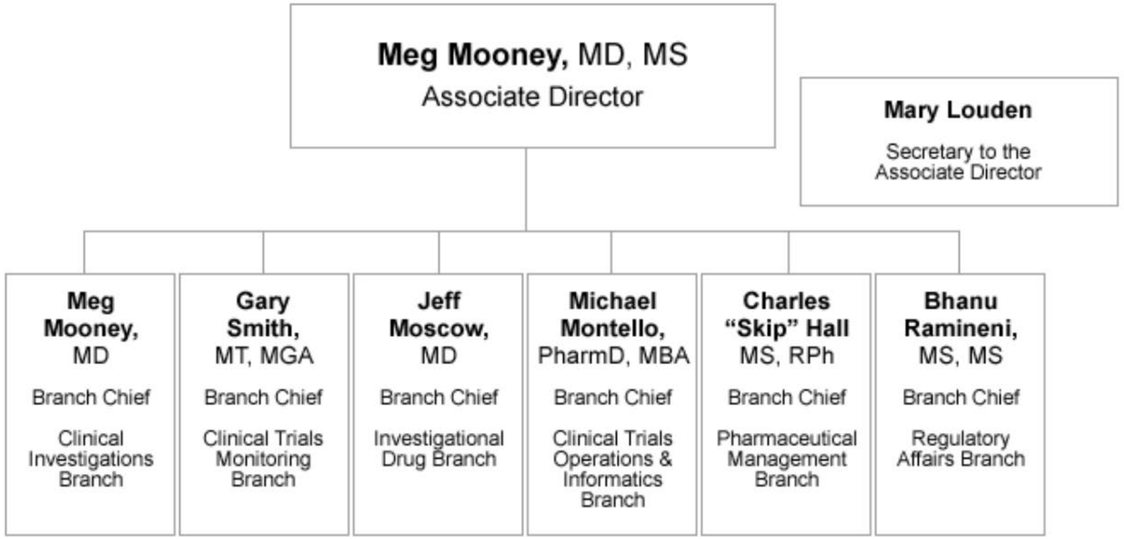
NCTN Structure: Past and Present

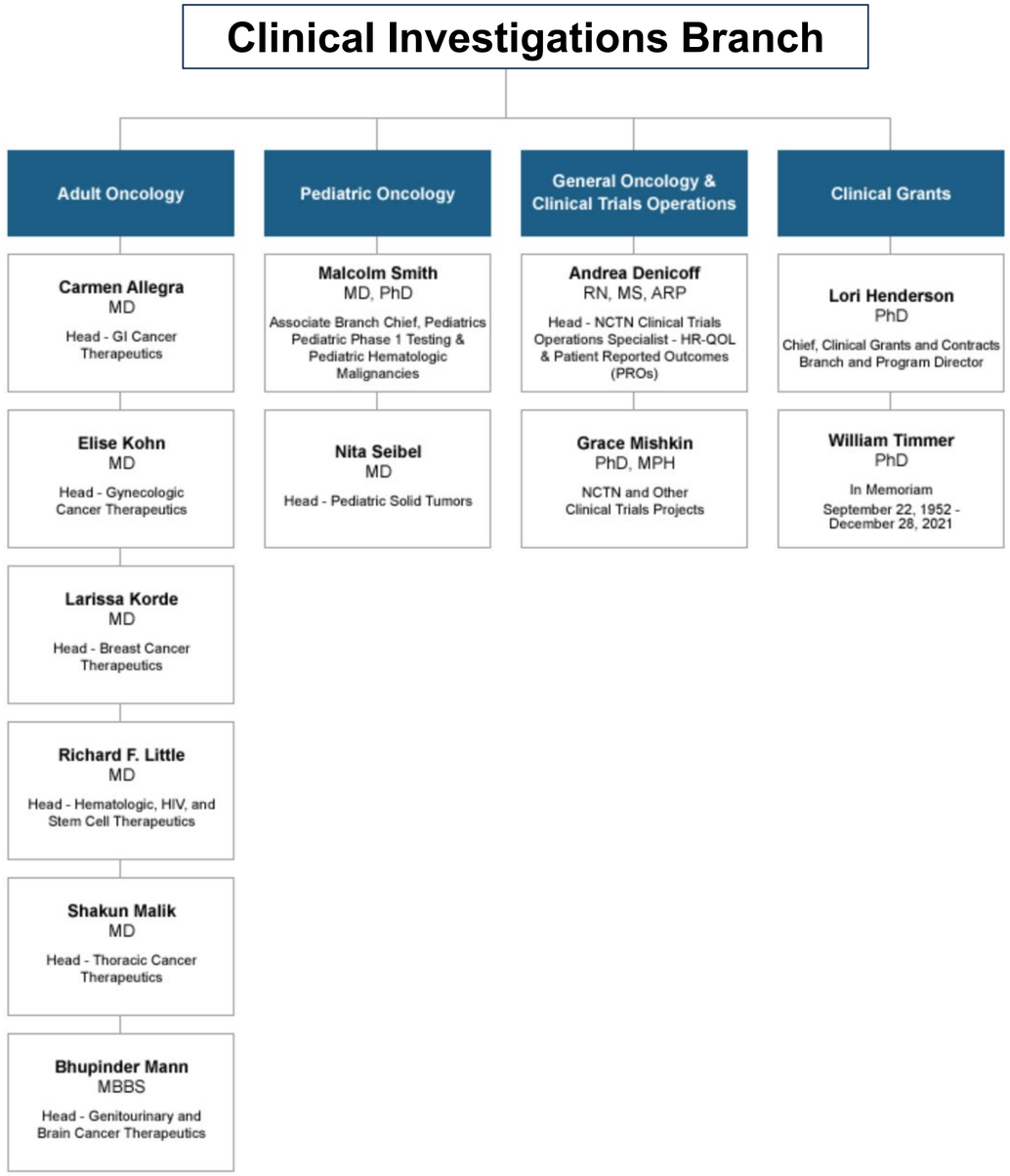




NCI Cancer Therapy Evaluation Program (CTEP)

CTEP Organization Chart





NCI Steering Committees

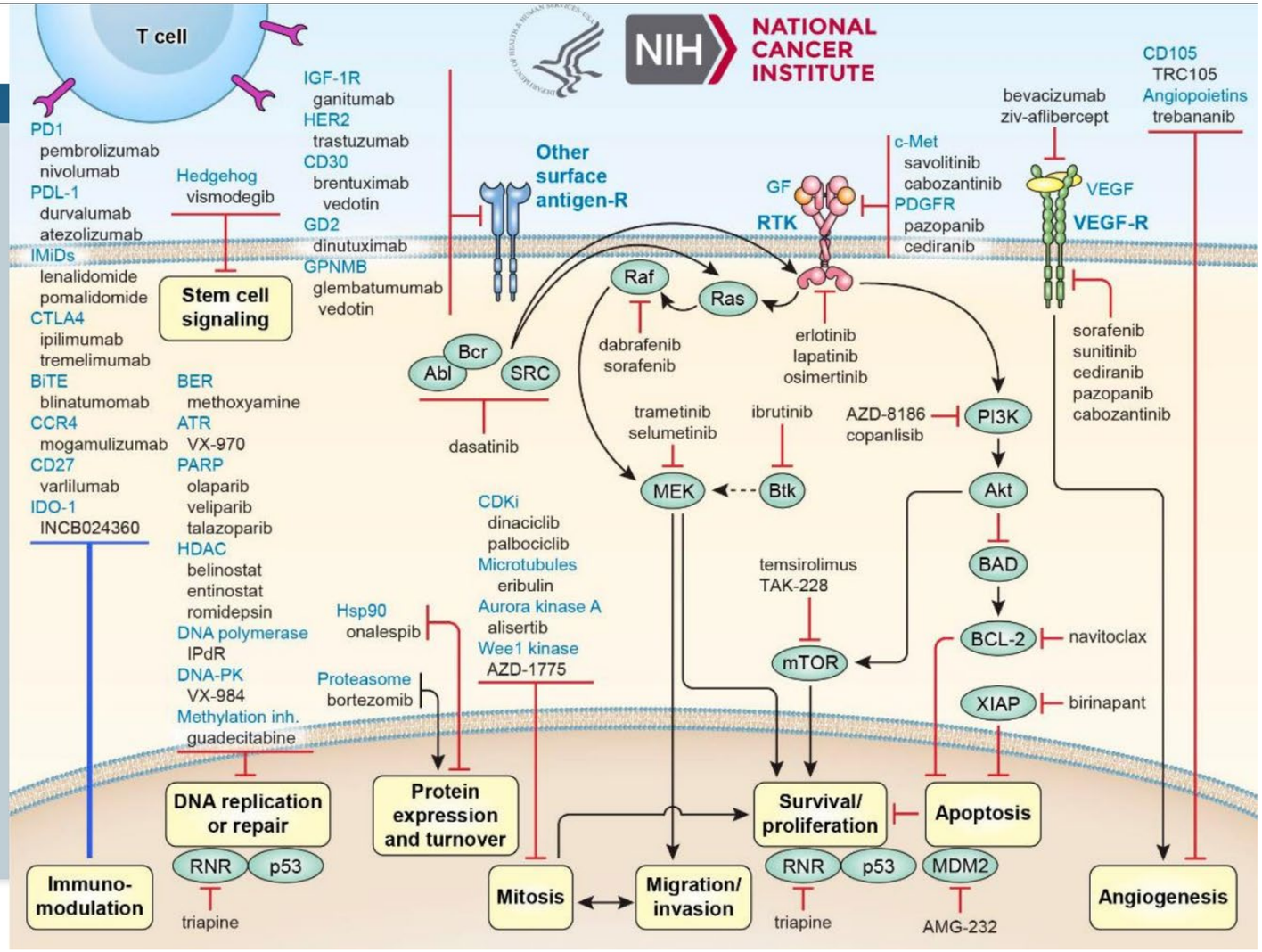
- Brain Malignancies
- Breast Cancer
- Gastrointestinal
- Genitourinary
- Gynecologic Cancer
- Head and Neck
- Leukemia
- Lymphoma
- Myeloma
- Pediatric and Adolescent Solid Tumor
- Pediatric Leukemia and Lymphoma
- Thoracic Malignancy

- Disease specific committees who review and approve/disapprove proposed concepts along with CTEP
- Consists of investigators, statisticians, patient advocates, other NCI representatives
- Mainly review phase 2 and phase 3 studies (often studies with ≥100 pts– i.e. some studies may not require steering committee review)
- NCI Steering Committees may have Task Forces (TF) with sub-disease specialization (e.g. GI Steering Committee has Neuroendocrine TF, Colorectal TF, Pancreas TF, etc; GU has TF for bladder, prostate, renal)
- While part of the larger disease steering committee, TF mainly provide input on concepts of their respective sub-disease area during development and/or provide support letters to the larger steering committee but ultimately do not approve studies

CTEP CRADA Agreements: Access to Drugs for NCTN Trials

CTEP: Current Portfolio

- 72 active agents under cooperative research and development agreement (CRADA)
- https://ctep.cancer.gov/industryCollaborations2/agreements_agents.htm



- CTEP CRADA provides direct access to drugs for NCTN Trials
- Even if available, some drugs still require support/sign-off by pharma
- Drugs not available through CTEP CRADA will require external commitment and agreements to provide drugs via CTEP

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Advantages/Disadvantages of Participation in NCTN Cooperative Groups

- Publicly funded clinical trials research
- Address tough clinical questions (things often pharma don't want to do)
- Networking opportunities w/ national leaders
- Regarded with high academic prestige

- Trial development may take longer
- Rigorous review by multiple committees
- Concepts often turned down at NCI level (frustrating for early investigators)
- Funding limited mainly to conduct of study (need additional funds for translational work; few monetary reimbursement to PI/institutions)

My journey through the NCTN……

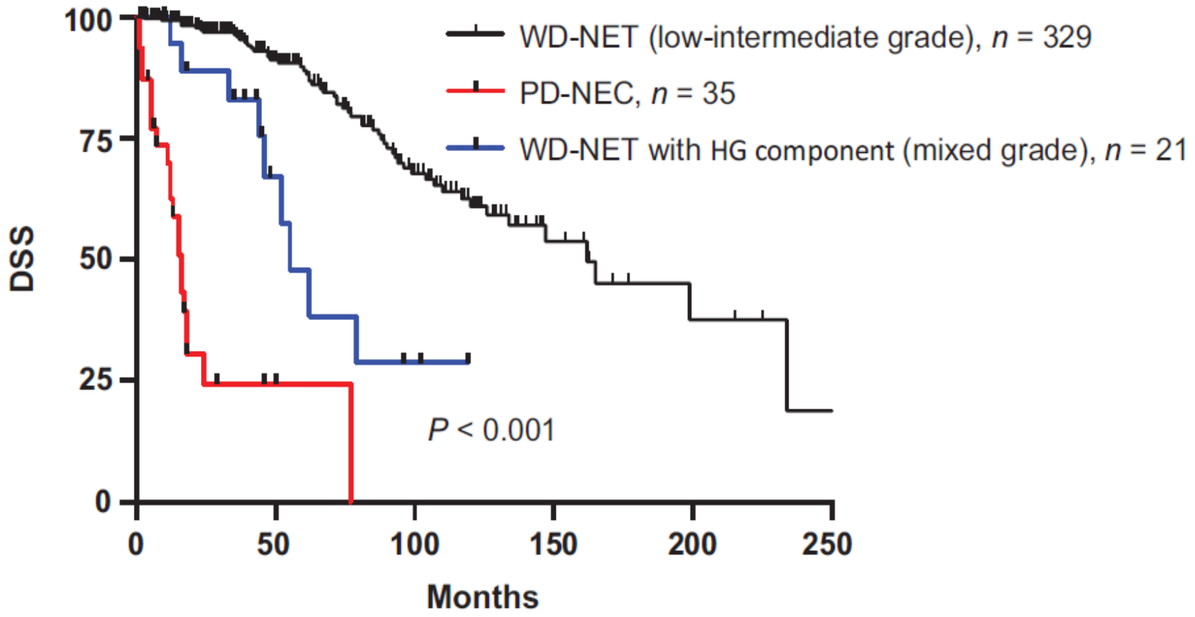
Starting in **2018**

2017 (now 2022) WHO Pathological Classification of GI Neuroendocrine Neoplasms (NEN)

Differentiation	Proliferation Indices	Designation
Well differentiated Neuroendocrine tumor (NET)	Ki-67 <3% Mitotic index <2/HPF	Low grade/ Grade 1
	Ki-67 3 – 20% Mitotic index <2-20/HPF	Intermediate grade/ Grade 2
New category compared to prior WHO classifications →	Ki-67 >20% Mitotic index >20/HPF	High grade/ Grade 3
Poorly Differentiated Neuroendocrine carcinoma (NEC)	Ki-67 >20% Mitotic index >20/HPF	High grade by default Subclassified by histology • Small Cell • Large Cell

Adapted from Rindi G et al. *Mod. Pathol.* 2018; **31**; 1770 – 1786.

Relevance of WHO Pathological Criteria



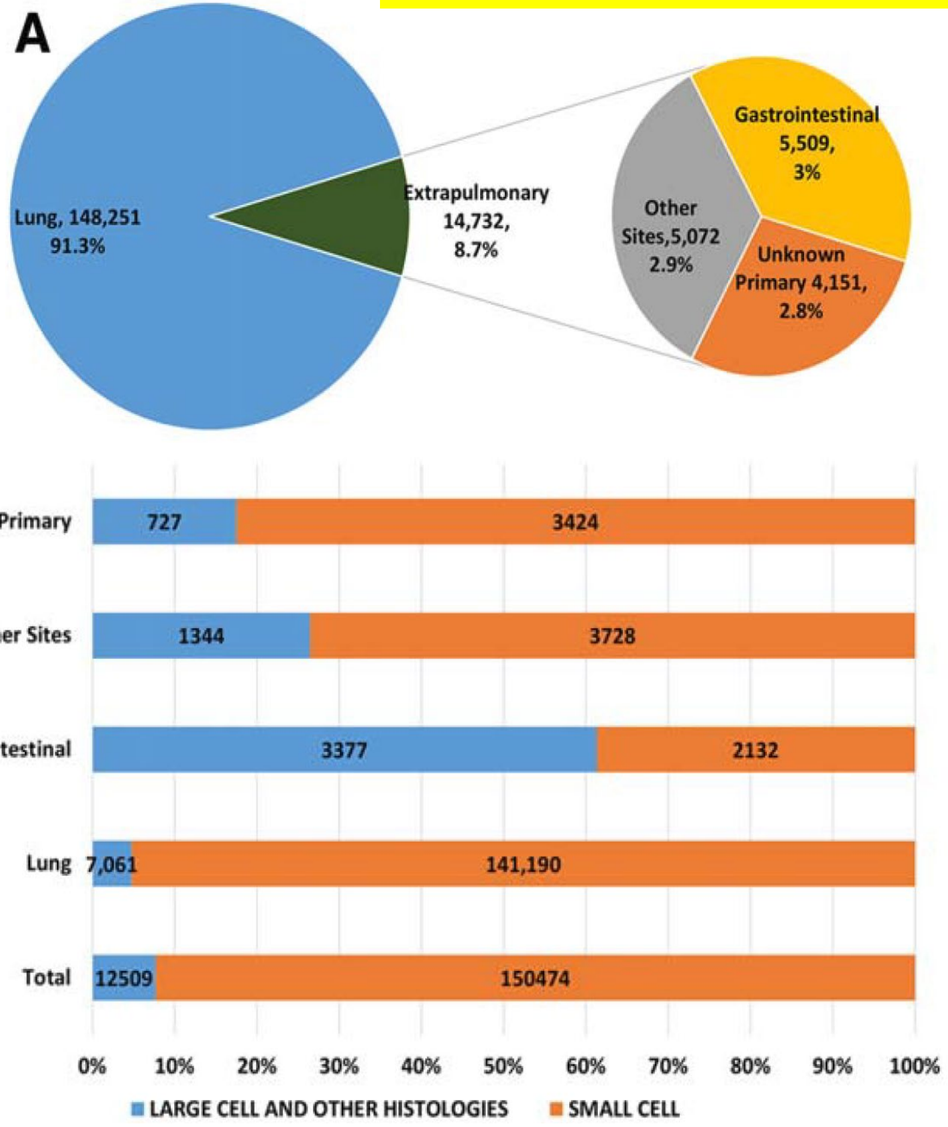
Tang et al. Clin Cancer Res 2015; 22:1011.

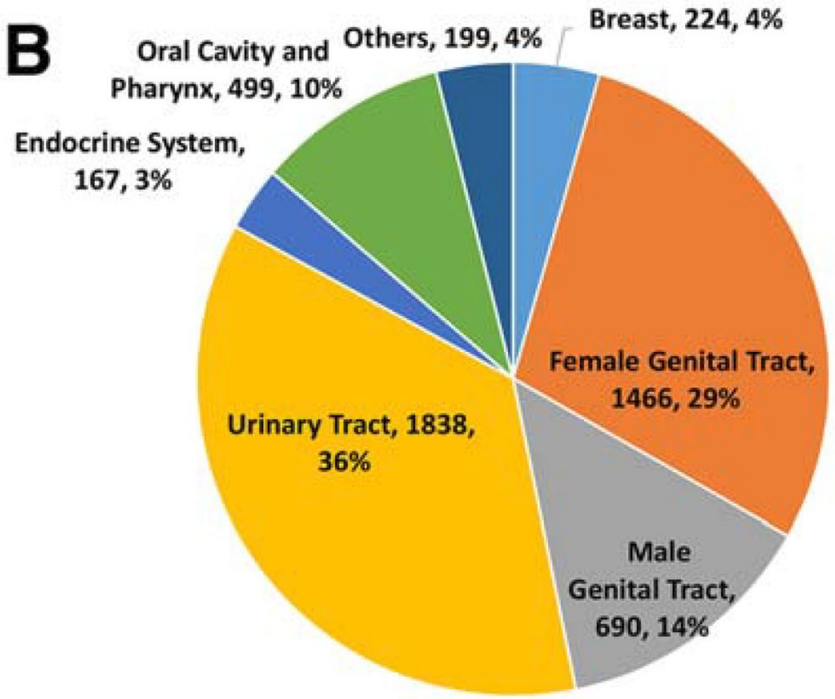
WD: Well differentiated, PD: Poorly differentiated
Gr: Grade; HG: High grade

- Prognosis:
  - WD-Gr1/2 NET: Years (Median ~12 years)
  - PD-NEC: <12 months
  - WD-Gr 3 NET: In between the above
- WD-Gr3 NET mutational profiles more similar to WD-Gr1/2 NET
  - NET: *MEN1, DAXX, ATRX*
  - NEC: *TP53, RB1*
- WD-Gr3 NET less responsive to platinum/etoposide compared to PD-NEC
- Hence differentiating from WD-Gr3 from PD-NEC is important for prognostic and treatment considerations

NEC Prevalence (SEER Database 1973-2012)

Extrapulmonary NEC is a rare disease = 1/100,000





Dasari A et al. Cancer 2018

Current Treatment Paradigm in NEC

- Extrapolated from small cell lung cancer (SCLC) with use of platinum (cisplatin or carboplatin)/etoposide
- Data from restrospective series

Study	N	Histology (%)	Ki-67 Proportion	OS	PFS	RR
NORDIC-NEC[1] (GI)	305	Small Cell: 38% Non-small cell: 49% Unknown: 13%	**≥55%:** 54%	11 mo	4 mo	**Overall:** 31% **Ki-67 ≤ 55%:** 15% **Ki-67 ≥55%:** 42%
FFCD-GTE[2] (GI & unknown primary)	Total: 253 GI-NEC: 189	Small Cell: 39% Large Cell: 61%	**51-80%:** 47% **>80%:** 18%	11.6 mo	6.2 mo	50%
Mackey JR et al.[3] (GU)	Total 180 (106 bladder, 60 prostate, 8 renal, 6 ureter)	42.7% with mixed histology (adeno+ small cell);	Not reported	**Overall:** 10.5 mo Prostate: 7 mo Bladder: 13 mo	?	?
Margolis B et al.[4] (Cervix)	1,896	Not reported	Not reported	~10 mo	?	?

[1]Sorbye H et al. Ann Oncol 2013 [2]Walter T et al. Eur J Cancer 2017 [3]Mackey J et al. J Urol 1998 [4]Margolis B et al. Gynecol Oncol 2016

Monotherapy PD-1/PD-L1 Studies in SCLC

Study	Agent	N	Phase	Line of Therapy	ORR	SD	PFS (mo)	OS (mo)	Notes
IFCT-1603[a] (Non-comparative study against chemo)	Atezolizumab	43	2	2nd line	2.3%	20.9%	1.4	9.5	No efficacy vs chemo (i.e. negative study)
CheckMate 032[b]	Nivolumab	98	2	≥2nd line (56% w/ 2-3 prior therapies)	10%	22%	1.4	4.4	
CheckMate 331[c] (Randomized against 2nd line chemo)	Nivolumab	569	3	2nd line	14%	?	1.4	7.5	No efficacy vs chemo (i.e. negative study)
KEYNOTE 028[d]	Pembrolizumab	24	1b	≥3rd line	33%	4.2%	1.9	9.7	
KEYNOTE 158[e]	Pembrolizumab	107	2	≥2nd line	18.7%	?	2.0	9.1	

[a]Pujol JL et al. J Thorac Oncol 2019; 14(5): 903-13 [b]Antonia SJ et al. Lancet Oncol 2016; 17:883-95 [c]Reck M et al. ESMO 2018, Abstract LBA5.
[d]Ott PA et al. J Clin Oncol 2017; 35:3823-29 [e]Chung HC et al. ASCO 2018, Abstract 8506

Monotherapy PD-1/PD-L1 Studies in Extrapulmonary NEC

Study	Agent	N	Histologic Characteristics	Phase	Line of Therapy	ORR	SD	PFS (mo)	OS (mo)
Vijayvergia N et al[a]	Pembrolizumab	**21** • 14 GI • 1 kidney • 6 unknown	**Small cell:** Unknown **Ki-67:** 48% ≥ 55%	2	≥2nd	4.7%	14.2%	2.3	3.9
Mulvey C et al[b]	Pembrolizumab (Part A Results)	**14** • 6 GI • 4 GU • 4 Other	**Small Cell:** 79% **Ki-67:** Median 80%	2	≥2nd	7%	14%	1.9	4.8
AVENEC[c]	Avelumab	**29** • 21 GI • 2 ENT • 2 Lung • 4 GU	**19 NEC, 10 NET** **Small Cell:** Unknown **Mean Ki-67:** 73%	2	≥2nd	6.9%	20.7%	3.9	4.7

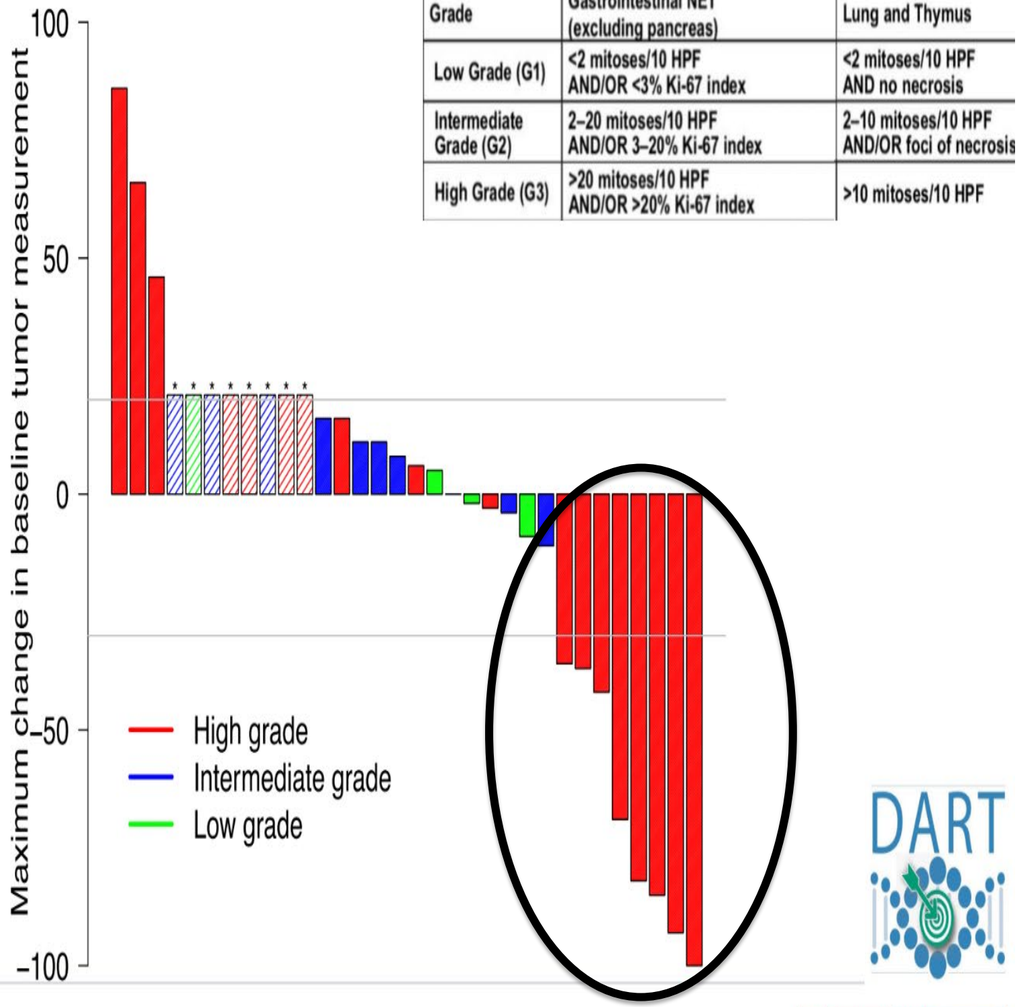
Similar lack of activity with single agent anti PD-1/PDL1 in SCLC and high-grade NEC
RR 5-10%
PFS 1.4-2 months

[a]Vijayvergia N et al. ASCO 2018: Abstract 4104
[b]Mulvey C et al. GI ASCO 2019: Abstract 363
[c]Fottner C et al. ASCO 2019: Abstract 4103

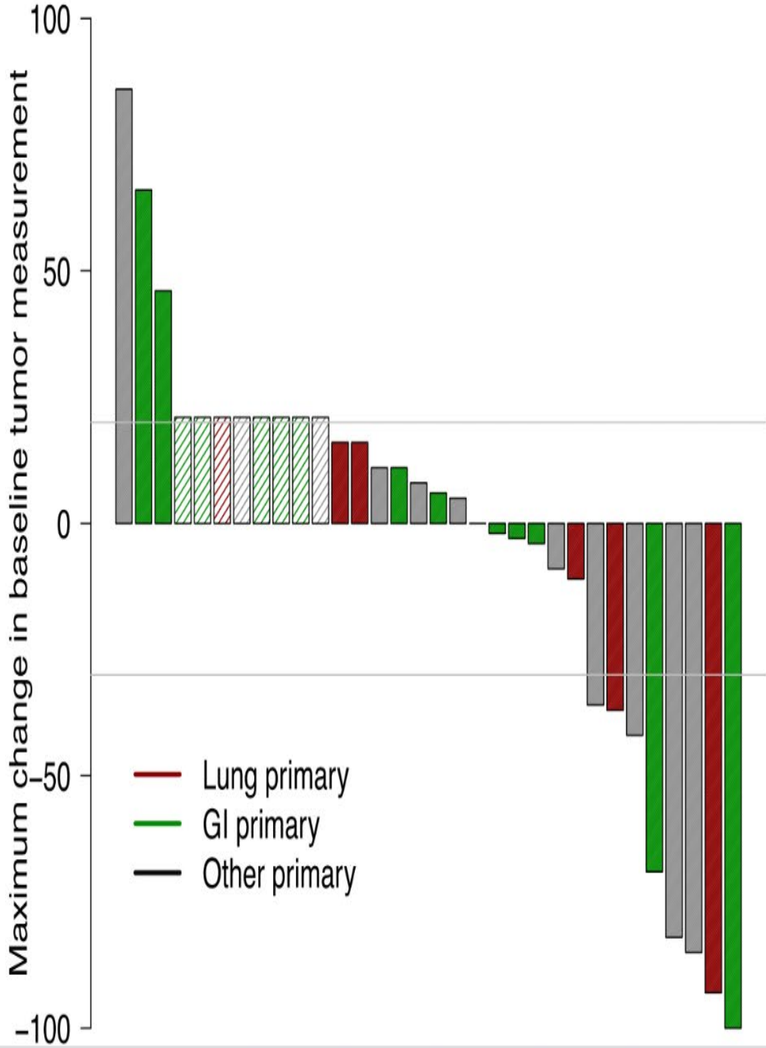
SWOG S1609 (DART Study): Nivolumab (PD-1) + Ipilimumab (CTLA-4) in Rare Cancers: Neuroendocrine Cohort

Response Rate by Tumor Grade of Neuroendocrine Neoplasm

Grade	Gastrointestinal NET (excluding pancreas)	Lung and Thymus
Low Grade (G1)	<2 mitoses/10 HPF AND/OR <3% Ki-67 index	<2 mitoses/10 HPF AND no necrosis
Intermediate Grade (G2)	2–20 mitoses/10 HPF AND/OR 3–20% Ki-67 index	2–10 mitoses/10 HPF AND/OR foci of necrosis
High Grade (G3)	>20 mitoses/10 HPF AND/OR >20% Ki-67 index	>10 mitoses/10 HPF

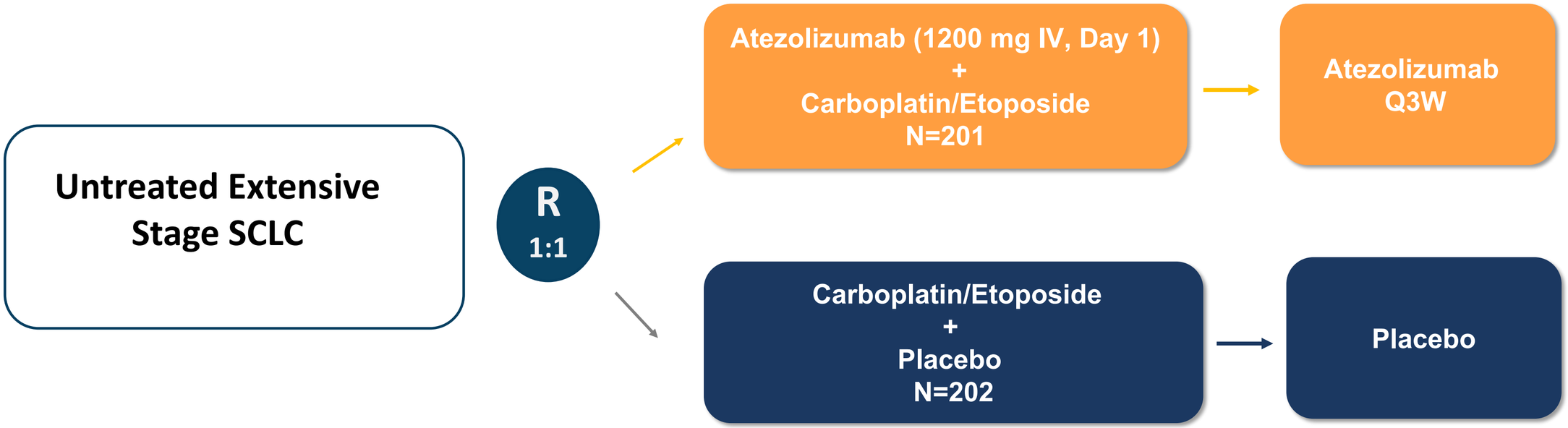


Response Rate by Primary Site of Neuroendocrine Neoplasm



Patel SP, Othus M, Chae YK, et al. Clin Cancer Res 2020; 26: 2290-6

IMpower133: Ph1/3 study of 1L carboplatin/etoposide ± atezolizumab in extensive-stage SCLC

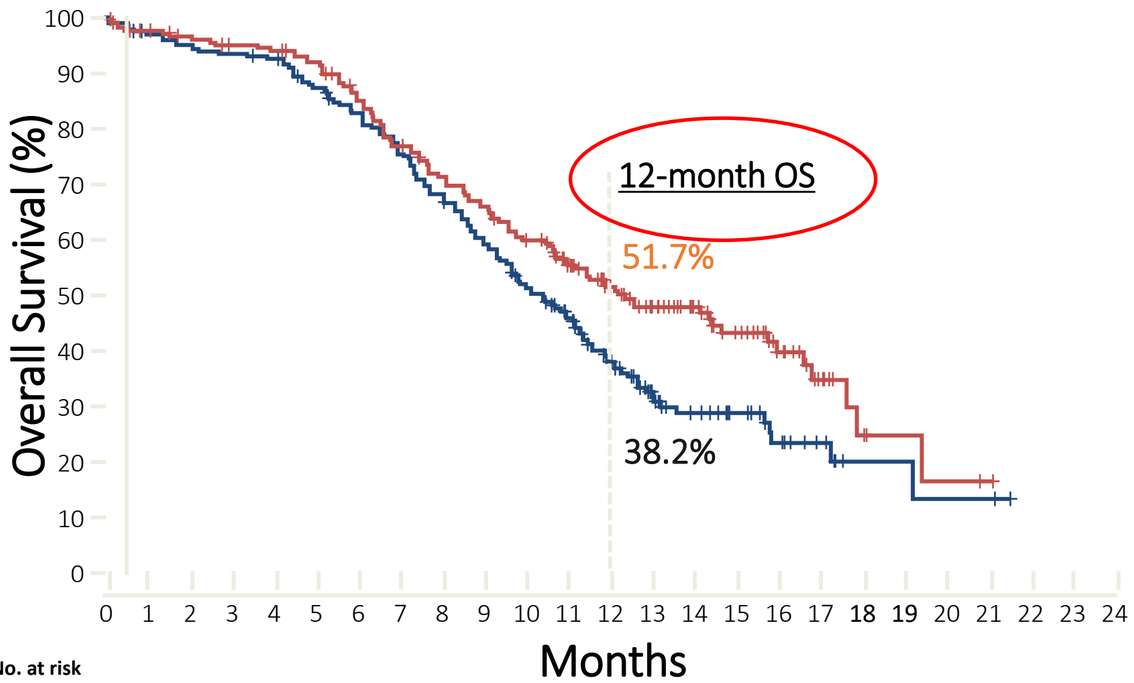


Primary Endpoints: Overall survival (OS) and Progression Free Survival (PFS)

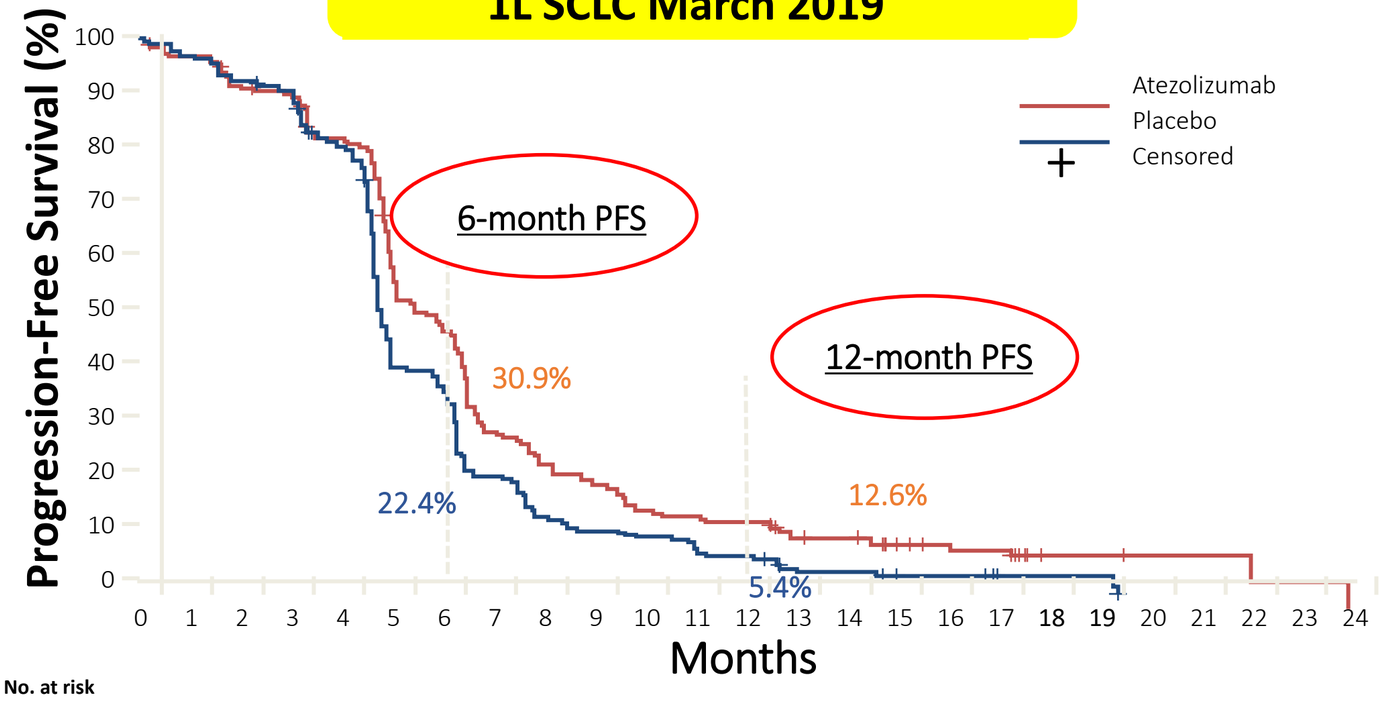
Secondary Endpoints: Objective Response Rate (ORR) and Duration of Response (DOR)

Horn L et al. N Engl J Med 2018

IMpower133: 1L Carboplatin/Etoposide ± Atezolizumab in Extensive-Stage SCLC



FDA approval of Atezolizumab in 1L SCLC March 2019



	Atezolizumab (N=201)	Placebo (N=202)
OS events, n (%)	104 (51.7)	134 (66.3)
Median OS, months (95% CI)	12.3 (10.8, 15.9)	10.3 (9.3, 11.3)
HR (95% CI)	0.70 (0.54, 0.91) *P* = 0.0069	
Median follow-up, months[a]	13.9	

	Atezolizumab (N=201)	Placebo (N=202)
PFS events, n (%)	171 (85.1)	189 (93.6)
Median PFS, months (95% CI)	5.2 (4.4, 5.6)	4.3 (4.2, 4.5)
HR (95% CI)	0.77 (0.62, 0.96) *P* = 0.017	
Median follow-up, months[a]	13.9	

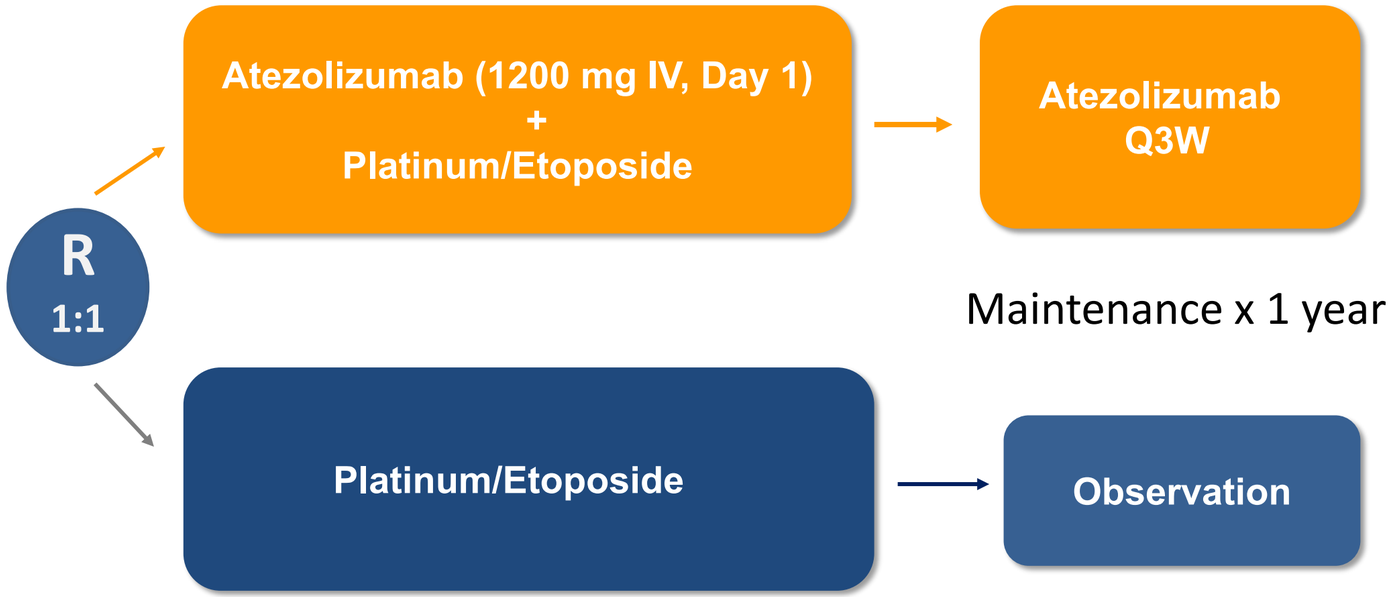
Horn L et al.
New Engl J Med 2018

Original Study Proposal

Phase 2 Randomized Trial

Key Eligibility:

- Metastatic poorly differentiated, grade 3 **GEP NECs (small cell or large cell Ki67>50%)**
- Known or suspected GI origin
- Measurable disease (RECIST v1.1)
- ECOG PS 0-2
- No prior treatment EXCEPT one cycle of platinum/etoposide allowed
- Treated asymptomatic brain metastases eligible



PFS improvement from 4 to 7 months
n=33 patients/arm
2 yrs accrual

Primary Endpoint:

- PFS

Secondary Endpoints

- ORR
- DOR
- OS

Exploratory Biomarkers

- Ki-67
- PD-L1
- TMB

In archival tumor tissue

Initial Feedback from SWOG GI Committee in 2018

- Mixed but overall favorable reviews
- Accrual major concern
  - Although DART study enrolled ~3 pts/month
  - Competing with another ECOG neuroendocrine study (enrolled WD-Gr3 and large cell; excluded small cell)
- What is the relevant endpoint (PFS or OS)?
  - PFS would keep pt # low but might not be as meaningful
- Approve to discuss at the NCI Neuroendocrine Task Force

Several Presentations to NCI Neuroendocrine Task Force--2019

- Majority felt clinical question was important; OS should be primary endpoint

- Accrual was major concern
  - ? How to design a study w/ quick read out but also get meaningful answer (i.e. design as phase 2/3 study)
  - Avoid any barriers (no central pathology read, 1 prior cycle therapy allowed)
  - With all that said, final recommendation was to RESTRICT to small cell only AND broaden to all extrapulmonary sites (ie GU/Gyn) to avoid competition with other NCTN neuroendocrine study

- In late 2019, SWOG leadership decided study would be primarily ran through Early Therapeutics/Rare Cancers Committee with GI as a secondary committee

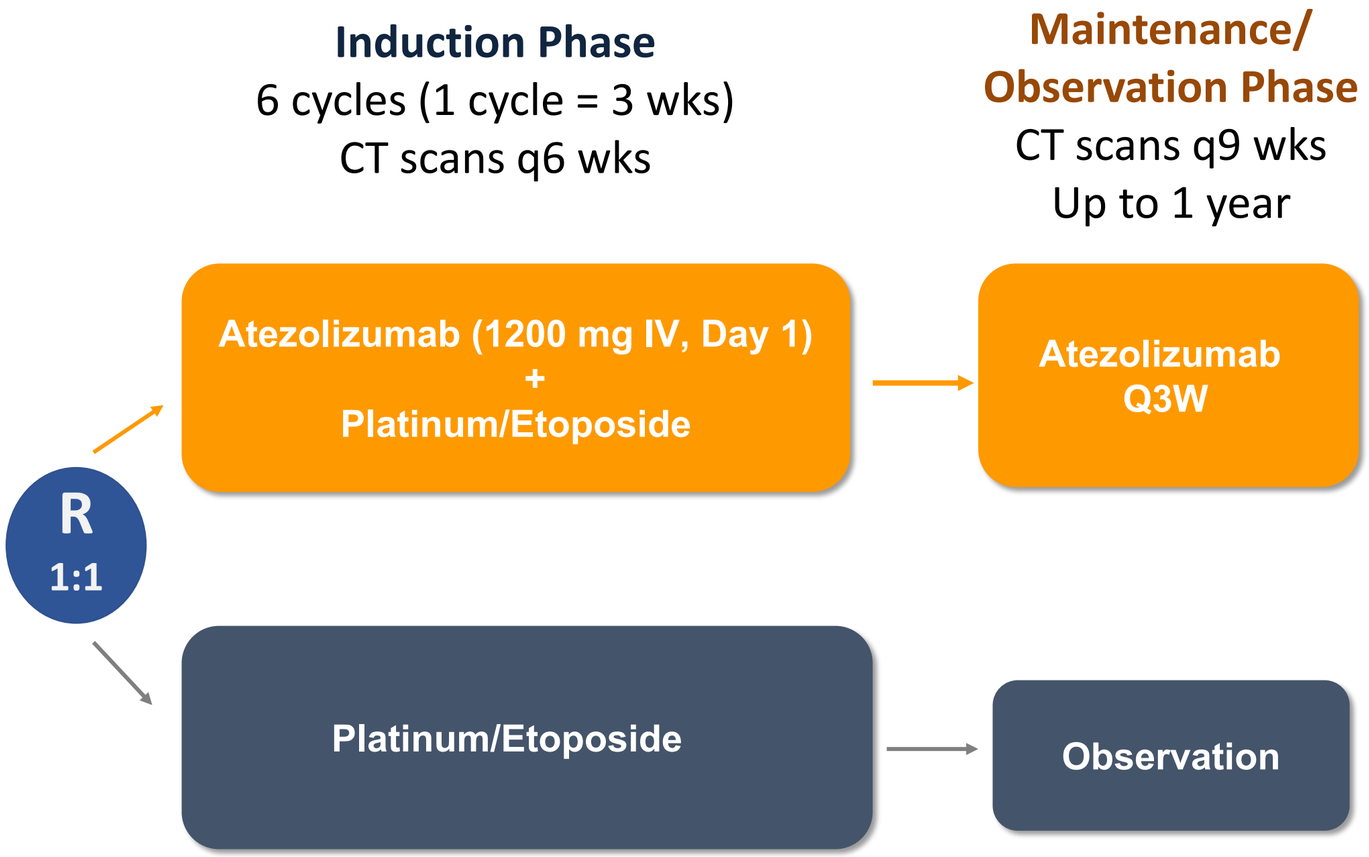
Updated Study Schema

Phase 2 Randomized Trial

N=134 pts

Key Eligibility:

- **Metastatic poorly-differentiated extrapulmonary (i.e. exclude lung) small cell NEC of any origin**
- Measurable disease (RECIST v1.1)
- ECOG PS 0-2
- No prior treatment EXCEPT one cycle of platinum/etoposide allowed
- Treated asymptomatic brain metastases eligible
- Stratification factors:
  - ❑ 1) Received (Y/N) one cycle of therapy prior to randomization
  - ❑ 2) Known pancreatic origin vs other GI origin vs non-GI origin



Primary Endpoint:

- OS

Secondary Endpoints

- PFS
- ORR
- Clinical benefit rate
- Duration of response

Exploratory:

- Banking archival tumor tissue and blood for future research (e.g. Ki-67 index, PD-L1, TMB, cell-free DNA)

Roller coaster ride in 2020-2021

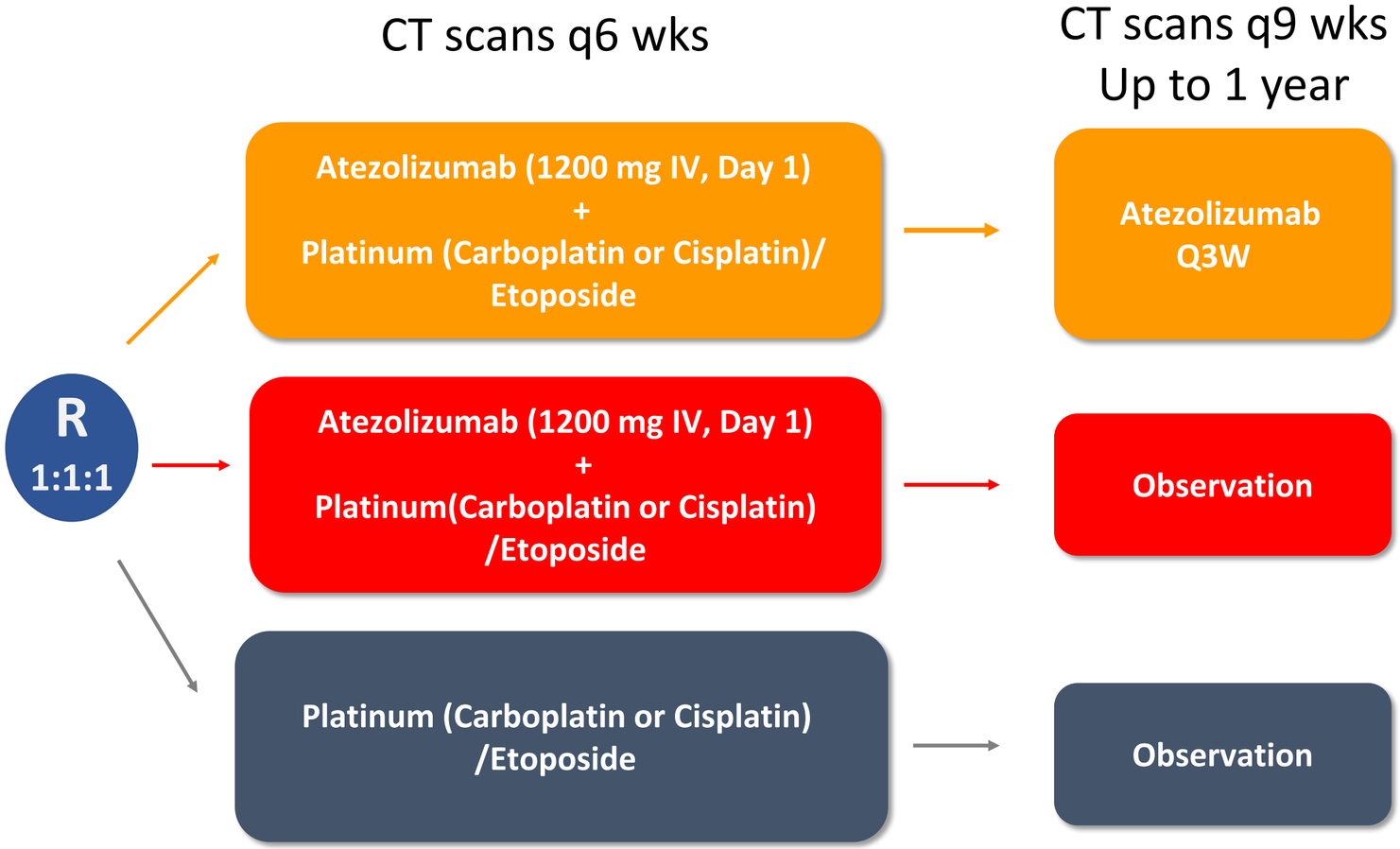
- SWOG leadership approves the study Feb 2020 - S2012 name given!!
- Study undergoes formal review at NCI GI Steering Committee and CTEP
  - All felt clinical question important, but accrual is concern
  - And yet, concern raised about lack of prospective data for the maintenance checkpoint inhibitor
  - Study rejected and needs to be modified to include another treatment arm of chemoimmunotherapy induction and no maintenance therapy (so more patients????)
- Roche/Genentech will not support 3 arm study
- CTEP will not approve 2 arm study
- Study seemed like it was going to fail
- Multiple meetings with CTEP and Genentech (including intervention from my mentor)
- After much debate lasting for close to 1 year, ultimately all parties agreed to 3 arm study

SWOG S2012: Randomized Ph 2/3 Trial of First Line Platinum/Etoposide +/- Atezolizumab for Extrapulmonary Small Cell NEC

Activated Dec 2, 2021

Key Eligibility: **N=189**

- Metastatic poorly-differentiated extrapulmonary (i.e. exclude lung) small cell NEC with Ki-67≥55%
- 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



Primary endpoint: OS (from time of randomization)

Secondary endpoints: OS (from time of maintenance/observation), PFS, ORR, DOR

Translational analyses: Banking tissue and blood for future biomarker analyses

Zhen DB, Chiorean EG, et al. Abstract TPS4179. ASCO 2022 Annual Meeting

Status of SWOG S2012

- As expected, accrual was slow with restriction of small cell histology only (3 pts in 1 year)
- Ultimately the other study closed in 2021, providing opportunity to amend S2012 to allow enrollment of all NEC subtypes (ie small and large cell)
- NCI initially disapproved amendment regarding over GU NEC (wanting de-novo cases and not mixed cases, which is rare and will hinder accrual)
- With support from other members at NCI, SWOG and NCI NET committees, GU investigators, and patient advocates, ultimately CTEP agreed to approve amendment, activated 1/2023

Career Development as a Result of My NCTN Trial

- Invited to be SWOG Champion for 2 other NCTN cooperative group trials
- Elected to be an Early Career Member of the NCI Neuroendocrine Task Force
- Elected to be FHCC representative on NCCN Neuroendocrine and Adrenal Guidelines Panel
- Developed a NET Tumor Board in 2019 and now co-lead our neuroendocrine program
- Providing mentorship to other investigators proposing trials

Lessons Learned for Developing Trials in NCTN Cooperative Groups

- **MENTORSHIP IS KEY!!!!—Need advocate(s)**
- Be prepared (know your stuff, anticipate feedback)
  - Scientific rationale (Scientific basis, current treatment outcomes, relevant qxn being asked?)
  - Trial design (Endpoints, Eligibility Criteria, Randomization, Stratification Factors, Trial Phase)
  - Feasibility (Anticipated accrual, competing and ongoing trials)
  - Future impact (Next steps based on trial results; will the question be irrelevant?)
  - How are you going to get drug? (CTEP CRADA agreement?; support from pharma)
  - Involve your patient advocates early in trial design
- Be thorough and succinct in presentations
- Be ready to handle critiques (do not take things personally!!!)
- Be patient (it's a very long process)
- Take ownership (respond to requests promptly)
- Be persistent but flexible (have less control over some things)
- Even if your trial doesn't happen, people will recognize your effort and could open other opportunities (help with other studies, serve on committees)

Conclusions

- Would I do it all over again---interestingly, YES! (and I will)
- Grew personally and professionally through this experience
- Gained significant knowledge and skills that have helped me in all my clinical trials research
- Many networking opportunities (even outside of my GI area)
- Even though it's hard, the payoff is getting to be involved in national practice changing research that could affect the lives of many cancer patients