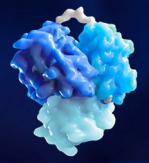
HARPOON Therapeutics

Spearheading Immunotherapies

DLL3 MARKET OPPORTUNITY AND KOL DISCUSSION OF HPN328

SEPTEMBER 15, 2023

Forward-looking Statements



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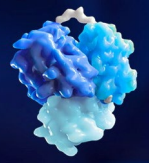
WELCOME AND INTRODUCTIONS

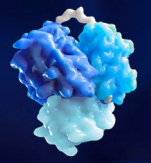
Julie Eastland
CEO

Agenda for Today



- 8:00 a.m.: Welcome
  - Julie Eastland, President and CEO
- 8:05 a.m.: DLL3 market opportunity – SCLC, NEC
  - Haibo Wang, SVP, Business Development
- 8:10 a.m.: HPN328 Phase 1/2 study overview
  - Luke Walker, M.D., Chief Medical Officer
- 8:20 a.m.: Treatment landscape, patient needs & experience with T Cell engagers, including HPN328 in SCLC
  - Erin Schenk, M.D., Ph.D., Assistant Professor of Medicine, Division of Medical Oncology, University of Colorado Anschutz Medical Campus
- 8:35 a.m.: Treatment landscape, patient needs & experience with HPN328
  - Himisha Beltran, M.D., Associate Professor, Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School
- 8:50 a.m.: Q&A
- 9:00 a.m.: Conclude

Advance Next-Generation T Cell Engagers



Program	Indication(s)	Stage of Development	Partner
HPN328 (DLL3)	SCLC / NEPC and other Neuroendocrine Tumors	Preclinical → Phase 1	Roche[1]
HPN217 (BCMA)	Multiple Myeloma	Preclinical → Phase 1	
HPN601 (EpCAM)	Multiple Solid Tumors	Preclinical → Phase 1	
Preclinical Candidates			
TriTAC (FLT3, undisclosed)	Oncology	Preclinical → Phase 1	
ProTriTAC (TROP2, Integrin-β6, undisclosed)	Oncology	Preclinical → Phase 1	
TriTAC-XR (Undisclosed)	Oncology / Non-Oncology	Preclinical → Phase 1	
TriTAC, ProTriTAC (Undisclosed)	Oncology	Preclinical → Phase 1	abbvie[2]

Phases: Preclinical | Phase 1 | Phase 2 | Phase 3

TriTAC **ProTriTAC** **TriTAC-XR**

(1) Roche supply agreement established for the use of atezolizumab in combination with HPN328
(2) Research collaboration with AbbVie to select a fixed number of targets from these platforms

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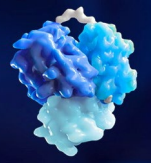
Today's Focus is on HPN328 (DLL3)



Program	Indication(s)	Stage of Development				Partner
		Preclinical	Phase 1	Phase 2	Phase 3	
HPN328 (DLL3)	SCLC / NEPC and other Neuroendocrine Tumors					Roche [1]

- Ongoing clinical program continues building on strength of prior HPN328 data which showed anti-tumor activity in SCLC at low dose levels while being well tolerated
- Dosed the first patients with SCLC in the ongoing Phase 1/2 trial with combination of HPN328 plus Roche's atezolizumab (Tecentriq®)
- Phase 1 interim monotherapy data to be presented at the European Society of Medical Oncology (ESMO) in October 2023

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(1) Roche supply agreement established for the use of atezolizumab in combination with HPN328

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DLL3 MARKET OPPORTUNITY
SCLC, NEC

Haibo Wang
SVP, Business Development

DLL3 Plays a Key Role in Neuroendocrine Cancer Biology

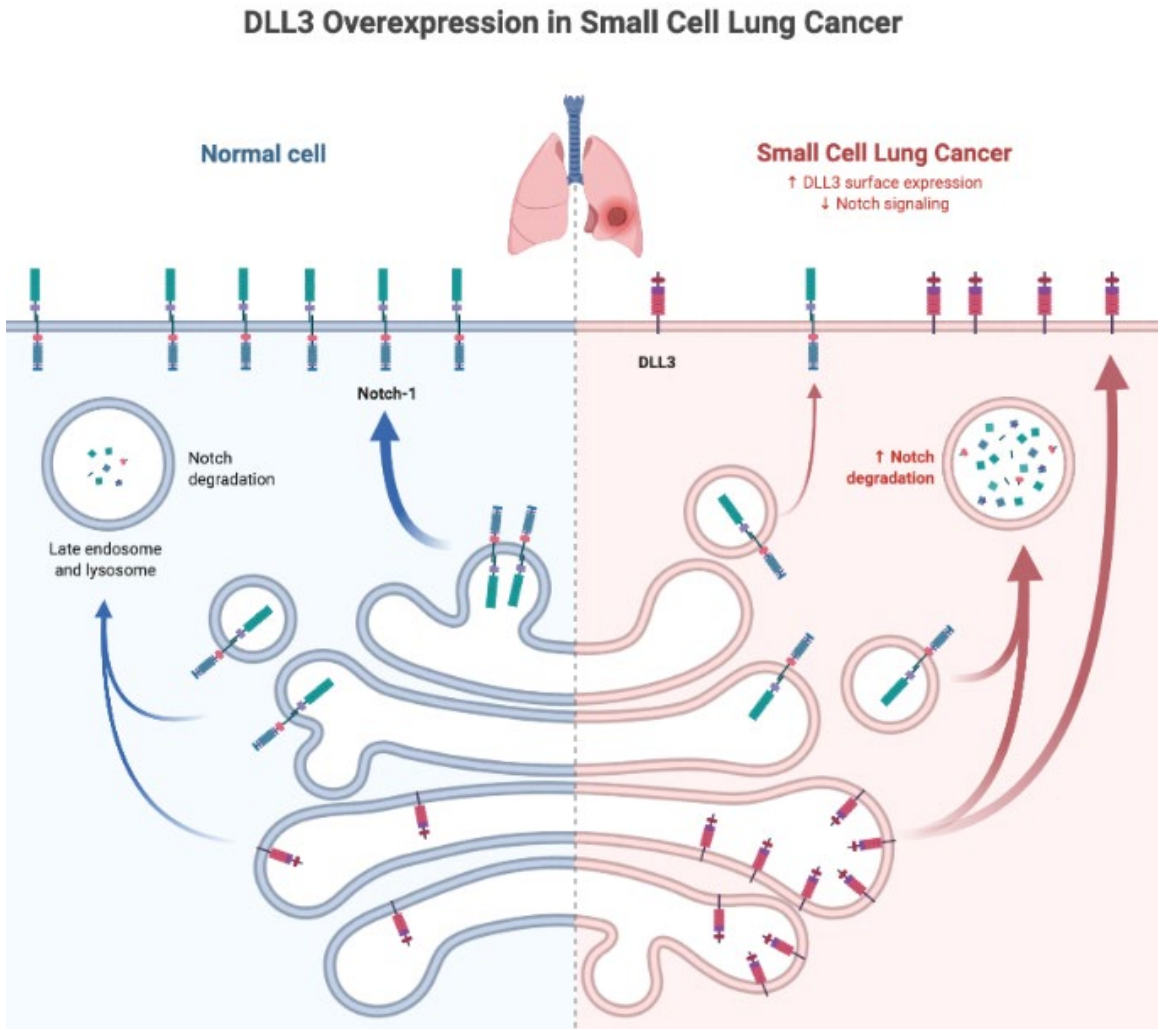
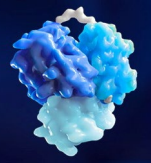


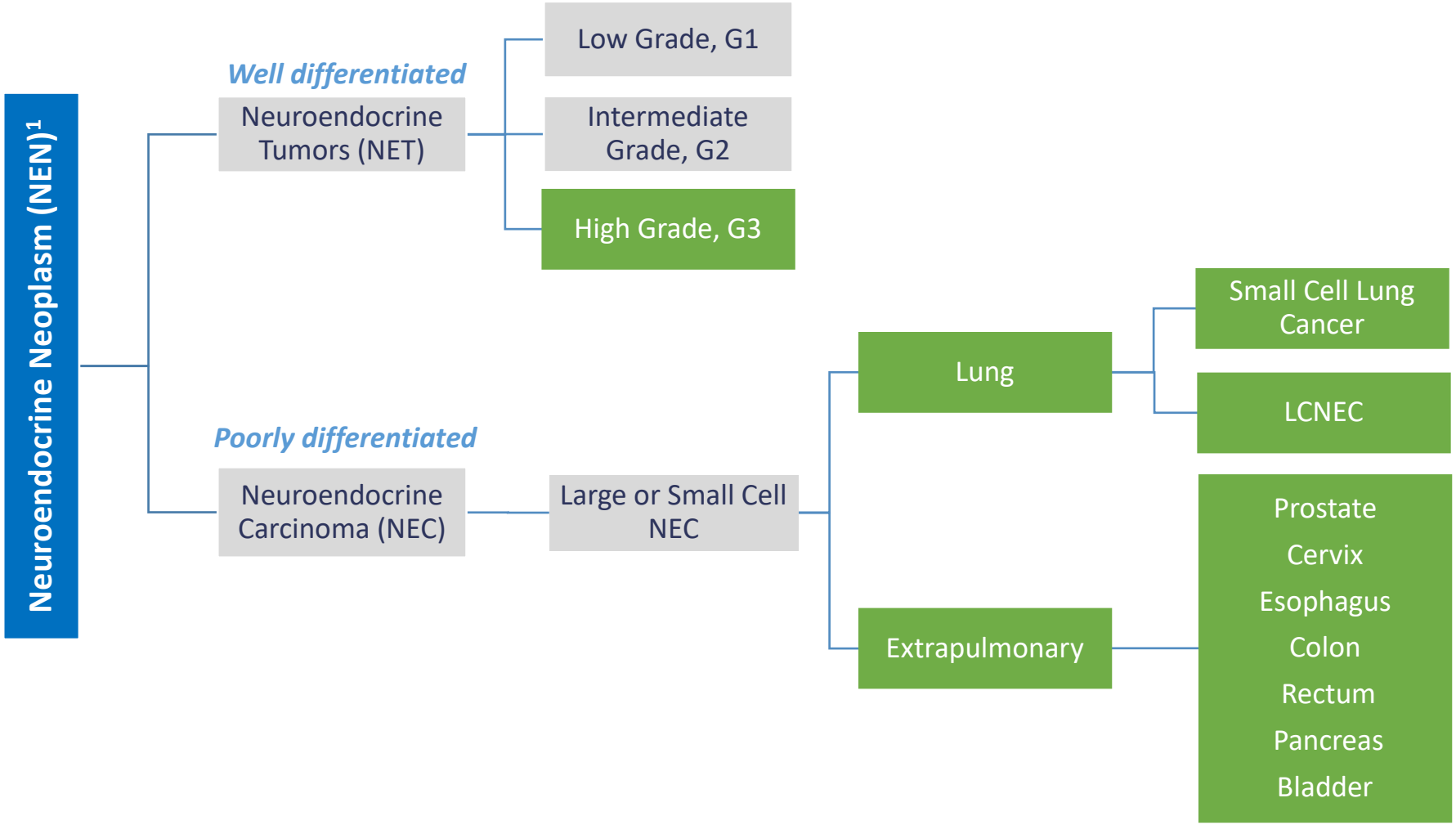
Figure 1: DLL3 and Notch pathway in SCLC[1]

- Delta-Like Ligand 3 (DLL3): a transmembrane protein and a ligand of the Notch receptor family
- Normally, DLL3 expression on cell surface is minimal.[2] However, in neuroendocrine cancer cells (e.g., SCLC), DLL3 **over expressed on cell surface** inhibits Notch signaling, driving cell differentiation into neuroendocrine phenotype and cell proliferation[3]
- The differential expression and localization profiles of DLL3 in normal and tumor cells make it an attractive therapeutic target[4]

1. Created by biorender (accessed Sept 7, 2023); 2. Chapman et al. *Hum Mol Genet* (2011); 3. Zhang et al. *Biomed Pharmacother.* (2023); 4. Rudin et al. *Journal of Hematology & Oncology* (2023)

NENs Encompass a Broad Spectrum of Cancer Types with Similar Histological Characteristics

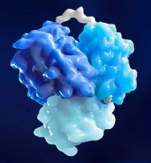




High grade NENs have poor prognosis and few treatment options

1. NCCN Neuroendocrine and Adrenal Tumors Version 2.2021

Large Addressable Population in SCLC and Other High Grade NENs with Significant Unmet Needs



	7 Major Market Incidence[1]	5-yr Survival	DLL3 Expression (>1%)
Small Cell Lung Cancer	~90,000	7%[2]	82%[3]
Neuroendocrine Prostate Cancer (NEPC)	~20,000[4]	14%[5,6]	77%[7]
NET, High Grade	~11,500	mOS 10 months[8]	Highly expressed
Extrapulmonary NEC, except NEPC	~2,600	Stomach 9%[9] Rectum 11%[9] Colon 15%[9] Pancreas 20%[9] Small Intestine 43%[9] Appendix 65%[9]	Cervix 81%[10] Gastroentero-pancreatic 77%[11] Pancreas 19-50%[12] Bladder 68%[13]
LCNEC, Lung	~1,300	21%[2]	82%[3]

High grade NENs have an estimated annual incidence >120K across 7 major markets, mostly with high DLL3 expression

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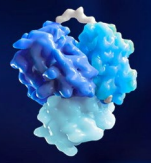
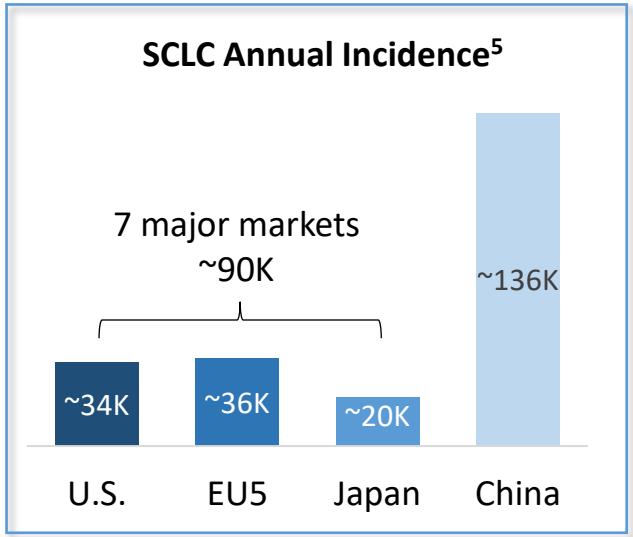
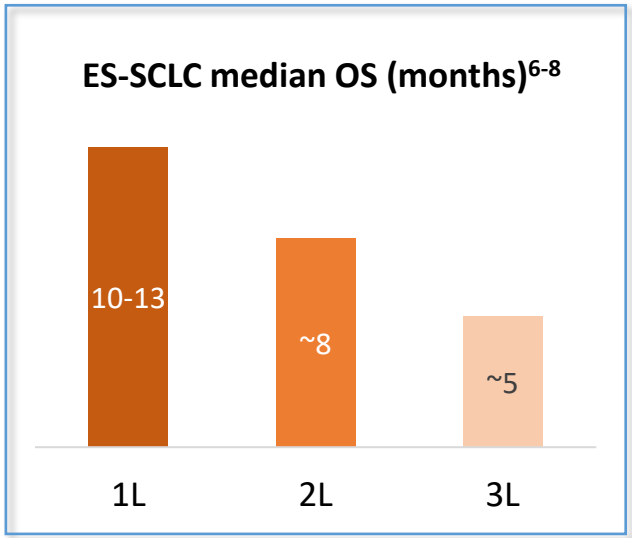
1. GlobalData Forecast 2023 incidence, 7 major markets (7MM) - US, Japan, France, Germany, Italy, Spain, UK; 2. SEER; 3. Lima et al. *Cancer Res* (2022); 4. Aparicio et al. *Cancer Discov* (2011); 5. Alabi et al. *Pharmacology & Therapeutics* (2022); 6. Bhagirath et al. *Sci Rep* (2021); 7. Puca et al. *Sci. Transl Med.* (2019); 8. Dasari, *JAMA Oncol.* (2017); 9. White, *Lancet* (2018); 10. Cimic, *Appl Immunohistochem Mol Morphol* (2021); 11. Liverani, *Endocr Pathol* (2021); 12. Yao, *Oncologist* (2022); 13. Koshin, *Clin Cancer Res* (2019)

Small Cell Lung Cancer: Large Opportunity for DLL3-targeting TCEs Across Line of Therapies







LARGE PATIENT POPULATION WITH AGGRESSIVE DISEASE

- **~330K** new cases worldwide annually[1]
- **>80%** SCLC express DLL3[2,3]
- **Long-term survival limited** with current therapies[4]: **5-year OS ~7%**

DLL3 T CELL ENGAGERS HAVE THE POTENTIAL TO IMPROVE OUTCOMES

- **Chemo-immunotherapy 1L** standard of care[9]: good responses, but often **early relapse (mPFS ~5m)[6]**
- Limited effective treatments for **relapsed disease with short duration and poor survival**
- **Unmet need across lines of therapy**: potentially addressable by DLL3-targeting TCEs

1. International Agency for Research on Cancer – estimated 2.2 million new lung cancer diagnoses globally in 2020, with 15% being SCLC (https://gco.iarc.fr/today/home); 2. Saunders et al. *Sci Trans Med* (2015); 3. Tanaka et al. *Lung Cancer* (2018); 4. SEER data Available from: (https://seer.cancer.gov/archive/csr/1975_2012/browse_csr.php?sectionSEL=15&pageSEL=sect_15_table.13); 5. GlobalData, Harpoon internal data; 6. Horn et al. *NEJM* (2018); 7. Reck M, et al.: results from Checkmate 331; 8. Coutinho AD et al. *Lung Cancer* (2019); 9. NCCN guidelines

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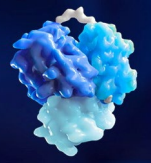
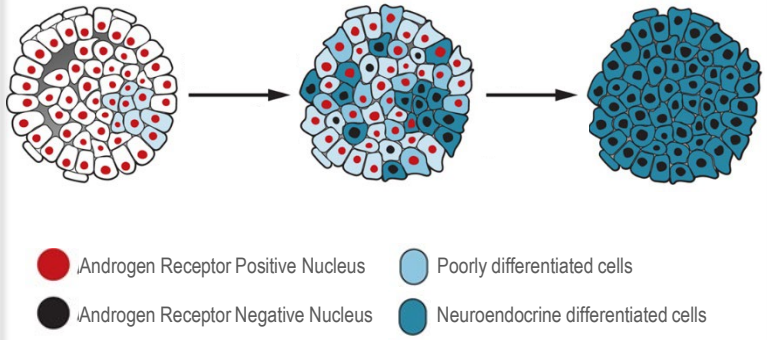
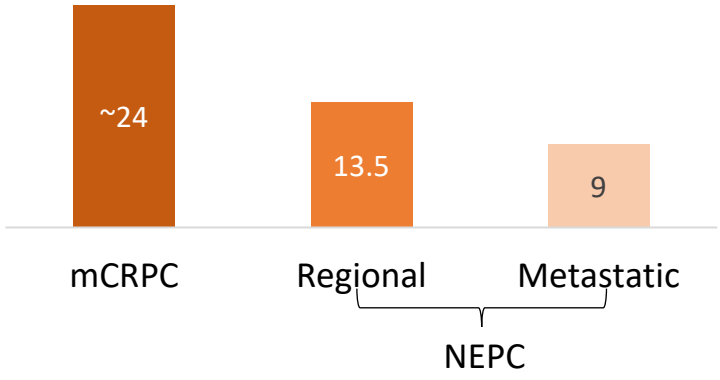
Neuroendocrine Prostate Cancer: Increasing Incidence due to Wide Adoption of Androgen Pathway Inhibitors



~25% mCRPC Differentiate into NEPC Post Treatment[1,6]



Median Overall Survival (months)[4,8]



NEPC IS A GROWING CANCER TYPE WITH POOR PROGNOSIS

- ~81K mCRPC new cases annually across 7 major markets[5]
- **~25%[1] of mCRPC, ~20K,** become treatment-emergent NEPC (t-NEPC), resistant to androgen deprivation therapy and androgen signaling inhibitors[7]
  - 17%[2] of mCRPC become NEPC with small cell histology
- Rising t-NEPC incidence likely due to earlier and longer treatment with androgen signaling inhibitors[3,7]

DLL3 TCE MAY TRANSFORM THE CHEMO-ONLY TREATMENT LANDSCAPE

- Chemotherapy is recommended as 1L treatment option and best supportive care as subsequent treatment option[9]
- **~77%** NEPC patients express DLL3[10]

1. Aparicio et al. *Cancer Discov* (2011); 2. Aggarwal et al. *J Clin Oncology* (2018); 3. Wang et al. *J Clin Oncology* (2014); 4. Zhu et al. *Medicine Baltimore* (2021); 5. GlobalData Forecast 2023 incidence, 7 major markets - US, Japan, France, Germany, Italy, Spain, UK; 6. Kelly et al. *Science* (2017); 7. Beltran et al. *Clin Cancer Res* (2015); 8. Freedland et al. *J Clin Oncology* (2022); 9. NCCN guidelines; 10. Puca et al. *Sci. Transl Med.* (2019)

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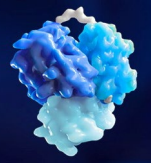
DLL3 Market Opportunity Takeaways



- **Large addressable population**
  - 120K+ annual incidence in high grade NENs, including SCLC, across 7 major markets
  - Opportunity across lines of therapy

- **Poor prognosis with limited treatment options**, mostly chemotherapy
  - Despite anti-PD-L1s approved for 1L SCLC, mPFS ~5 months, mOS ~12 months
  - Lack of non-chemo, durable treatment options for NEPC and other neuroendocrine cancer

- **Clinically validated, T cell engager against DLL3 has the potential to improve outcomes for patients with various high grade NENs**

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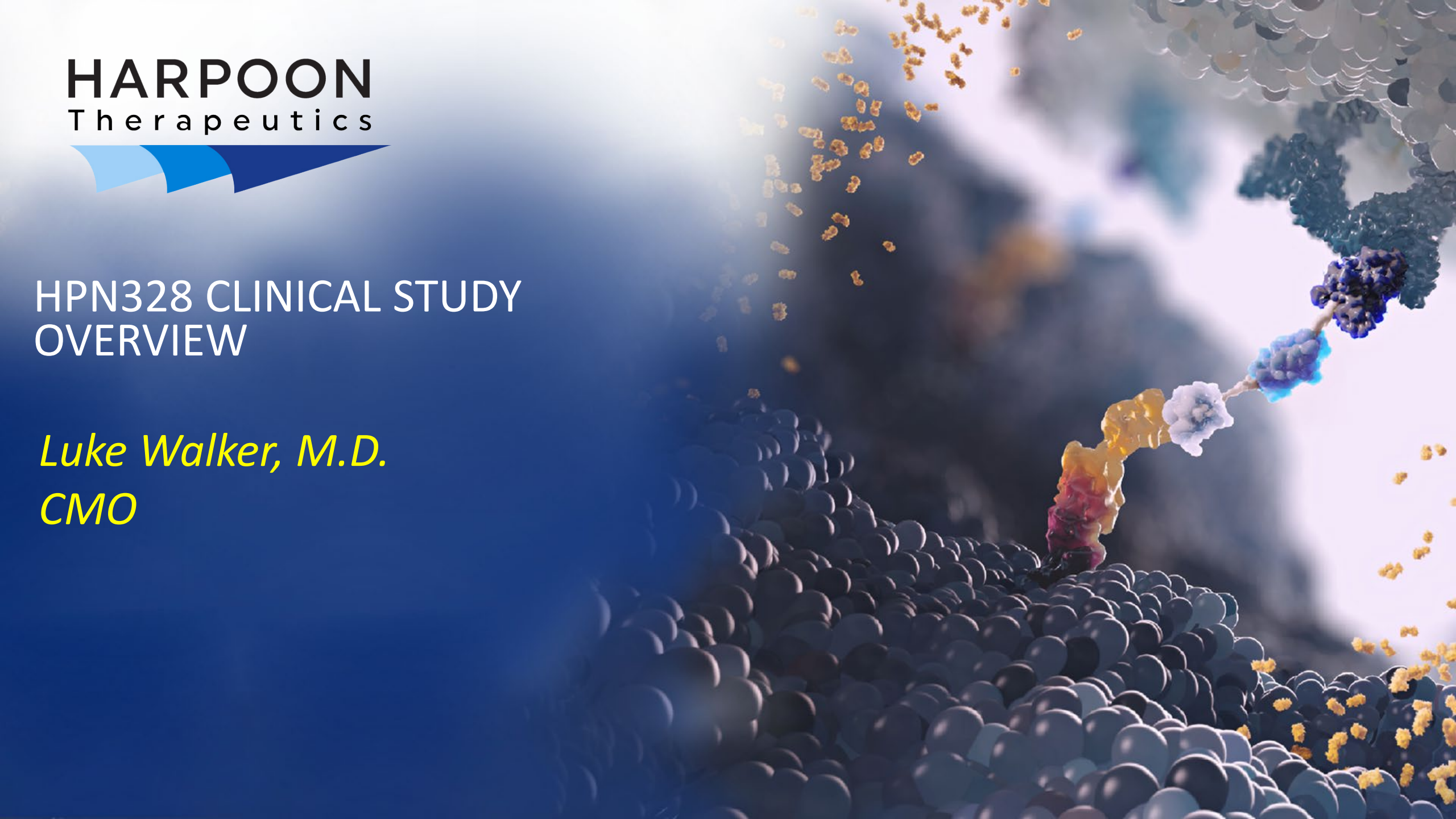
HPN328 CLINICAL STUDY OVERVIEW

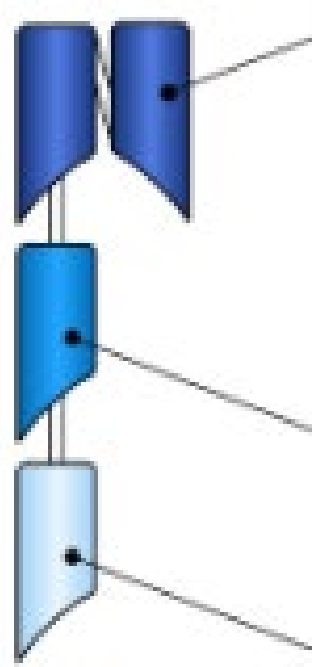
Luke Walker, M.D.
CMO



HPN328: A DLL3-targeted TriTac T Cell Engager

- DLL3 is significantly expressed in SCLC and other neuroendocrine tumor types
- HPN328 is DLL3-targeting T cell engager derived from the TriTAC platform
  - Redirects T cells to kill DLL3-expressing cancer cells
  - Small protein (~50kDa) to potentially enable efficient solid tumor penetration with prolonged half-life
  - Designed to minimize non-specific T cell activation and Fc receptor engagement, intended to increase therapeutic window

HPN328

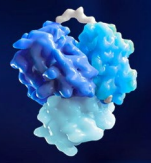


Anti-CD3 scFV
(T cell engagement)

Anti-albumin single domain antibody
(half-life extension)

Anti-DLL3 single domain antibody
(tumor targeting)

HPN328 Phase 1 Trial Description



Target Population

- Extensive stage SCLC relapsed after platinum chemotherapy
- Neuroendocrine prostate cancer and other DLL3 expressing tumors with high grade neuroendocrine features relapsed/refractory to standard therapy

Trial Design

- Assess safety and tolerability at increasing dose levels
- PK and pharmacodynamic data
- Evaluate preliminary anti-tumor activity

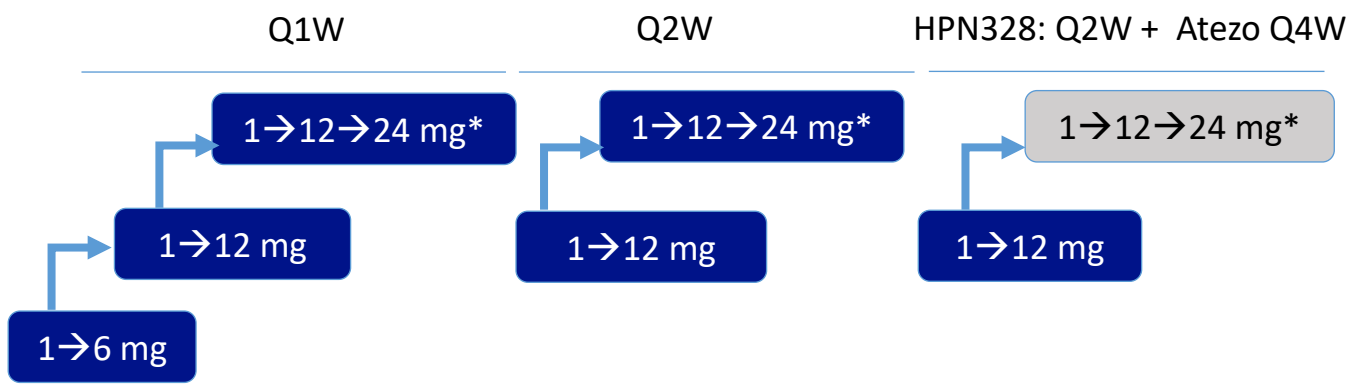
Dosing & Administration

- IV infusion with weekly and Q2W administration schedules
- Monotherapy cohorts for all tumor types, and combination cohorts with atezolizumab for SCLC
- Premedication and step dosing to manage cytokine release syndrome (CRS)

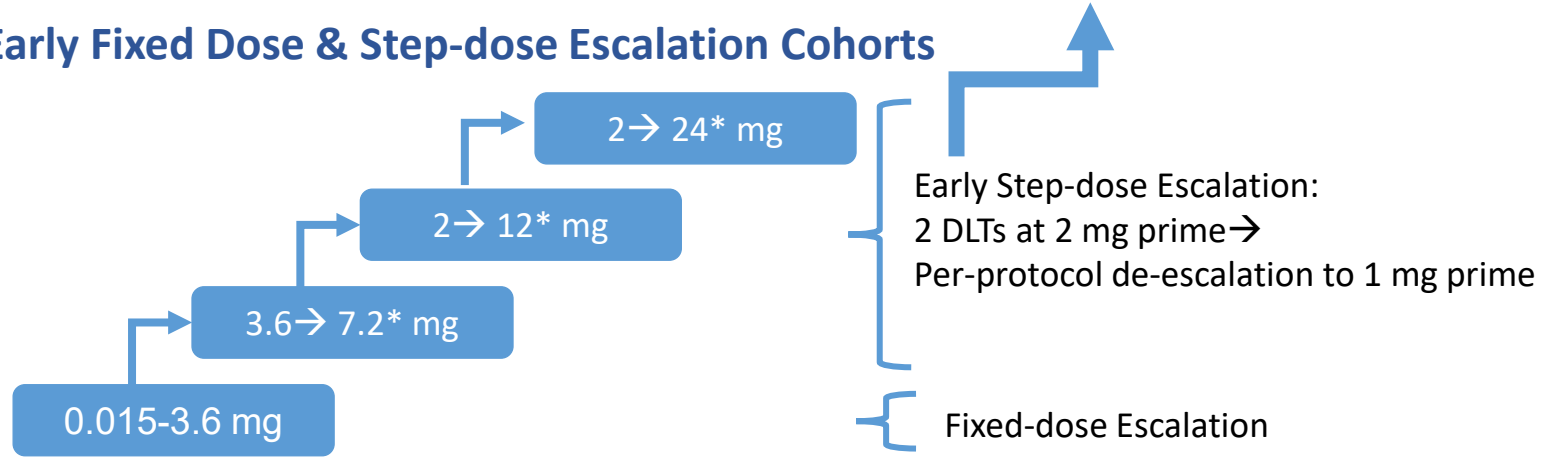
HPN328 Trial Design: Dose Escalation and Optimization

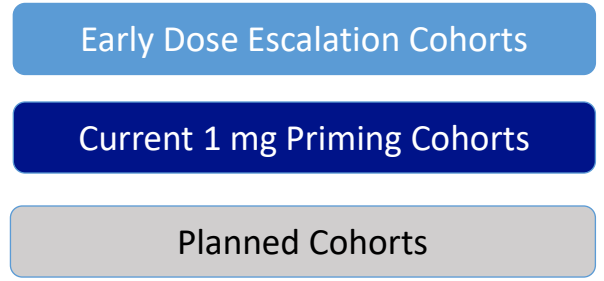
Dose Escalation 3+3 Design Including Fixed & Step-dose Cohorts and Dose Optimization

Ongoing 1 mg priming Step-dose Escalation and Optimization Cohorts (Focus of ESMO 2023)



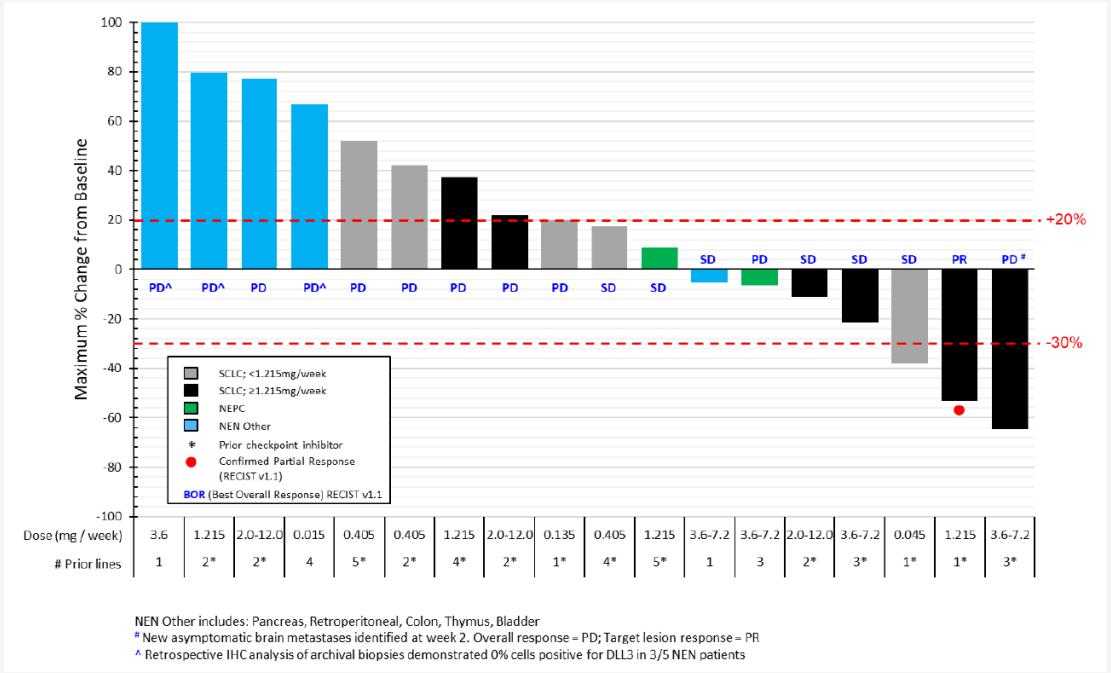
Early Fixed Dose & Step-dose Escalation Cohorts





Part 1 of clinical protocol allows up to 162 patients to be enrolled
Further escalation, combination cohorts and Q2W schedules dependent on safety data from previous cohorts
* 1 mg to 24 mg cohorts use a 12 mg intermediate step up prior to moving to 24 mg target

Prior Data from HPN328 Phase 1: ASCO 2022



NEN Other includes: Pancreas, Retroperitoneal, Colon, Thymus, Bladder

New asymptomatic brain metastases identified at week 2. Overall response = PD; Target lesion response = PR

^ Retrospective IHC analysis of archival biopsies demonstrated 0% cells positive for DLL3 in 3/5 NEN patients

Initial Phase 1 Efficacy Data at ASCO 2022

- 18 patients mostly in low-dose escalation cohorts
- Showed promising early signs of clinical activity

Upcoming interim update at ESMO:

- More patients treated in efficacious dose range
- Focus on 1 mg prime with 6 mg, 12 mg and 24 mg target doses

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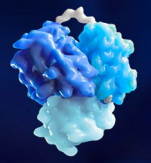
HPN328: Current Status and Near-Term Milestones



Current Status

Monotherapy and combination cohorts enrolling patients with multiple DLL3 expressing tumor types

- Includes SCLC, NEPC, other neuroendocrine carcinomas
- Cohorts exploring step-dose escalation at 1 mg priming and up to 24 mg target doses
- Multiple schedules being explored
- >70 pts in monotherapy cohorts enrolled, including >45 pts in 1 mg prime cohorts
- Combination cohorts (HPN328 + atezolizumab) recently initiated

Upcoming Milestones

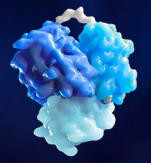
Interim data update planned at ESMO in October 2023

- Will report ongoing efficacy and safety evaluations including 1 mg priming step-dose cohorts

Completion of Phase 1 monotherapy dose escalation and selection of RP2D anticipated by end of 2023

Data from existing cohorts expected to enable regulatory discussions regarding further development options for HPN328 in SCLC and other neuroendocrine tumors

HPN328 Phase 1 Study Takeaways



- HPN328 being evaluated in areas with high unmet medical need
- Encouraging data seen previously at ASCO 2022 at initial low doses in escalation; ESMO 2023 presentation to provide more robust data set at efficacious dose range
- Progress in study enrollment and dose escalation have enabled expected selection of RP2D by end of 2023
- Combination cohorts with atezolizumab to provide data to support potential further development in earlier lines of therapy
- Goal to quickly pivot to regulatory engagements and initiate late-stage development

Erin Schenk, M.D., Ph.D.

Assistant Professor of Medicine,
Division of Medical Oncology,
University of Colorado Anschutz Medical Campus

University of Colorado **Anschutz Medical Campus**

HPN328 in Small Cell Lung Cancer

Erin Schenk M.D., Ph.D.
Assistant Professor of Medicine
University of Colorado

Thoracic Oncology Research Initiative

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Disclosures

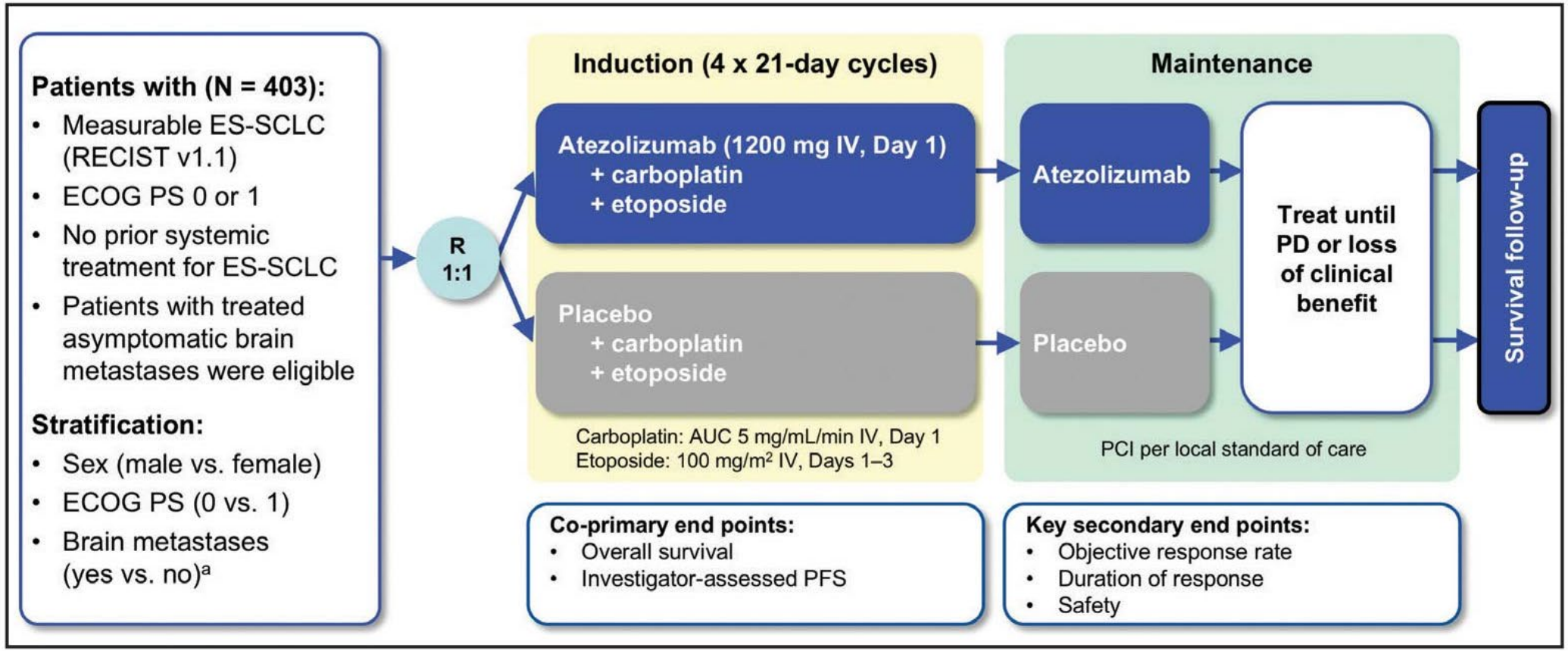
- Consulting or Advisory Role: Guidepoint Global, Regeneron, Bionest Partners, Actinium Pharmaceuticals, Prescient Healthcare Group, G1 Therapeutics, Regeneron, ClearView Healthcare Partners, BioAtla, The Scienomics Group, AstraZeneca

- Honoraria: Takeda, Ideology Health, Horizon CME, OncLive, Regeneron, MJH Life Sciences, MECC Global Meetings, Janssen, Horizon CME, BeiGeneius

Small Cell Lung Cancer

- 30,000 to 35,000 cases diagnosed annually in the US
- Clear association with cigarette smoking
- Emerging population of never smokers with lung cancer
  - SCLC transformation as a resistance mechanism for TKI
- 75% of patients are diagnosed with metastatic disease
- Remarkable response to chemotherapy but near inevitable recurrence even in early stages
- Only 50% of patients are alive 1 year after diagnosis

IMpower133
The 1st SCLC Treatment Advance in 20 years



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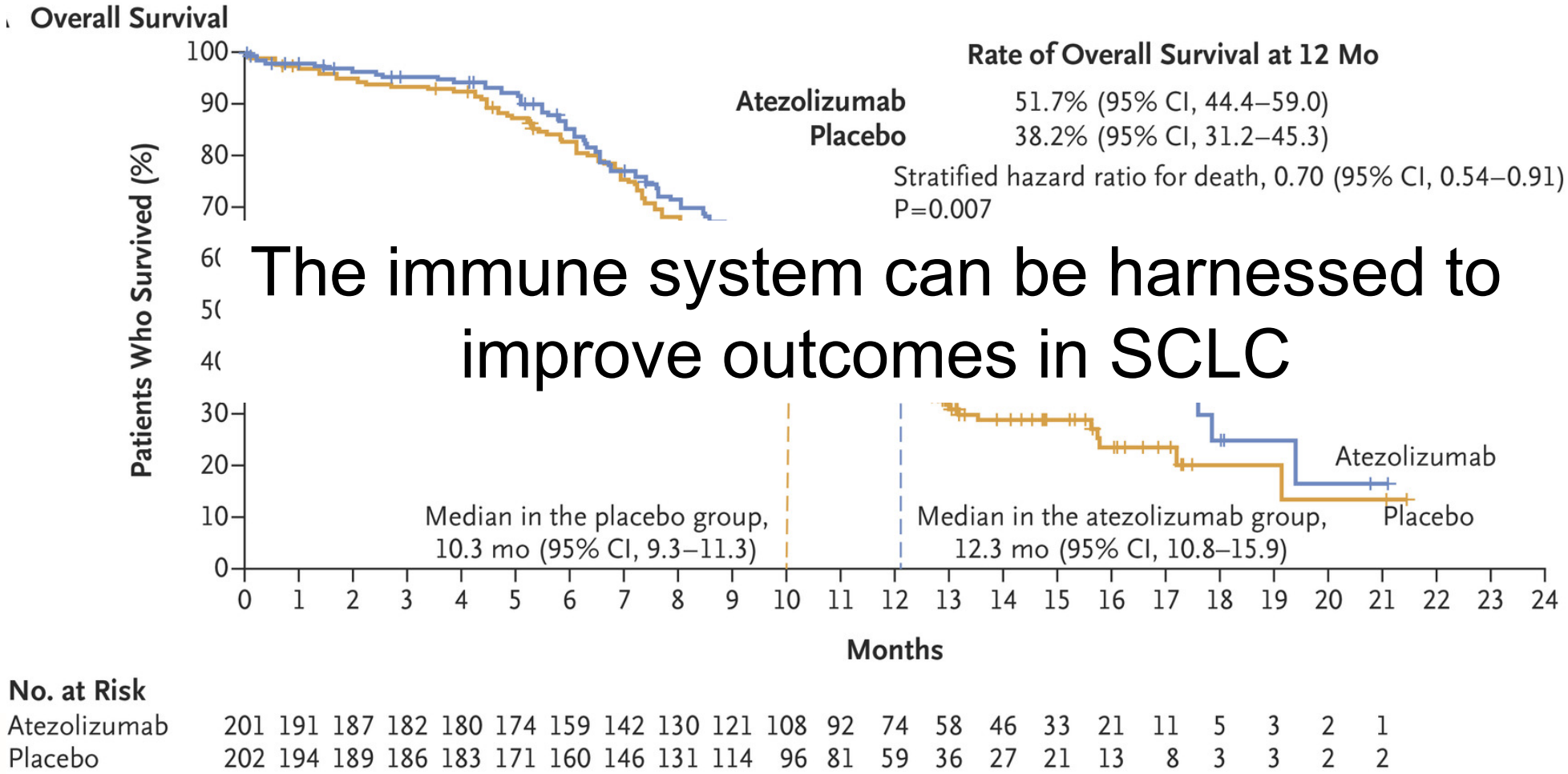
Horn L *et al.* N Engl J Med. 2018 Dec 6;379(23):2220-2229

IMpower133
The 1st SCLC Treatment Advance in 20 years



The immune system can be harnessed to improve outcomes in SCLC

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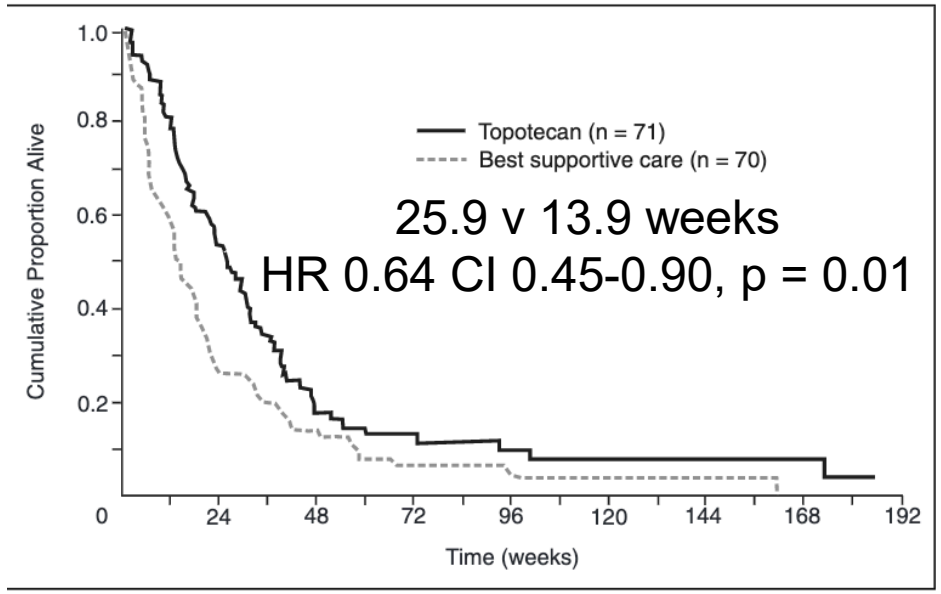
Horn L *et al.* N Engl J Med. 2018 Dec 6;379(23):2220-2229

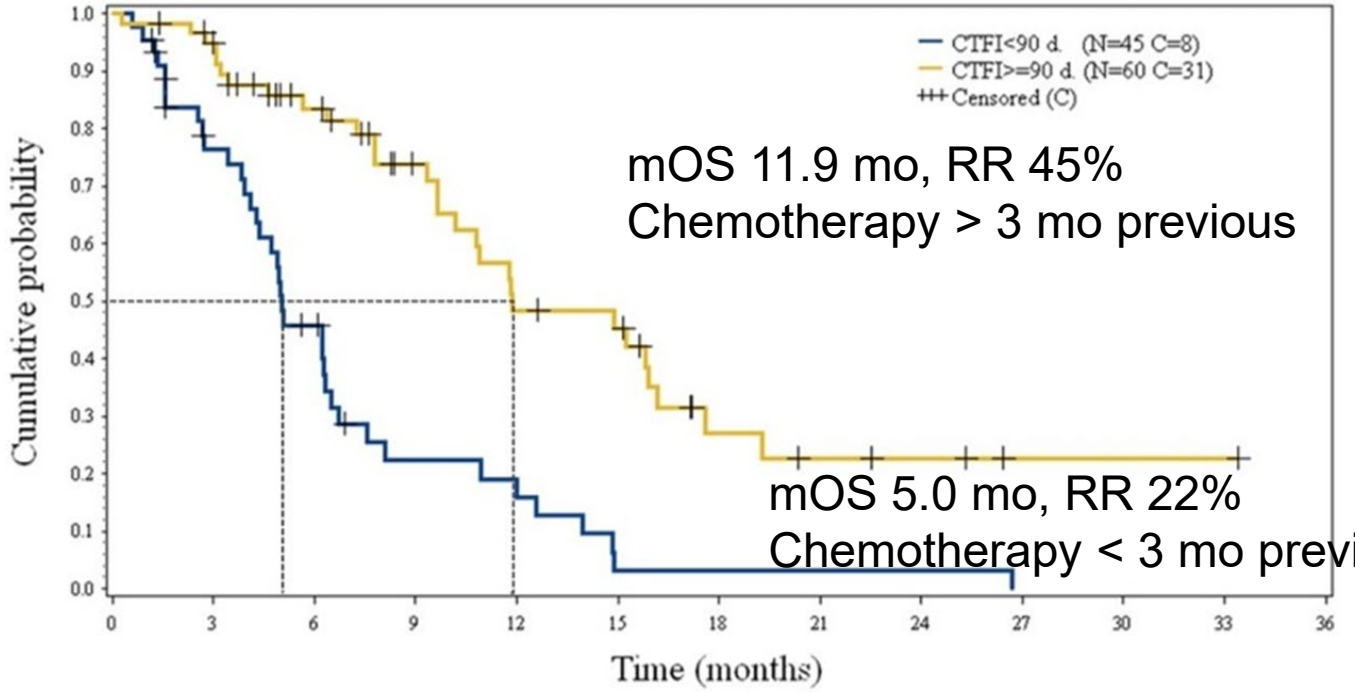
Small Cell Lung Cancer
2nd line Therapy

Topotecan



ORR ~7%

Lurbinectedin



ORR ~35%

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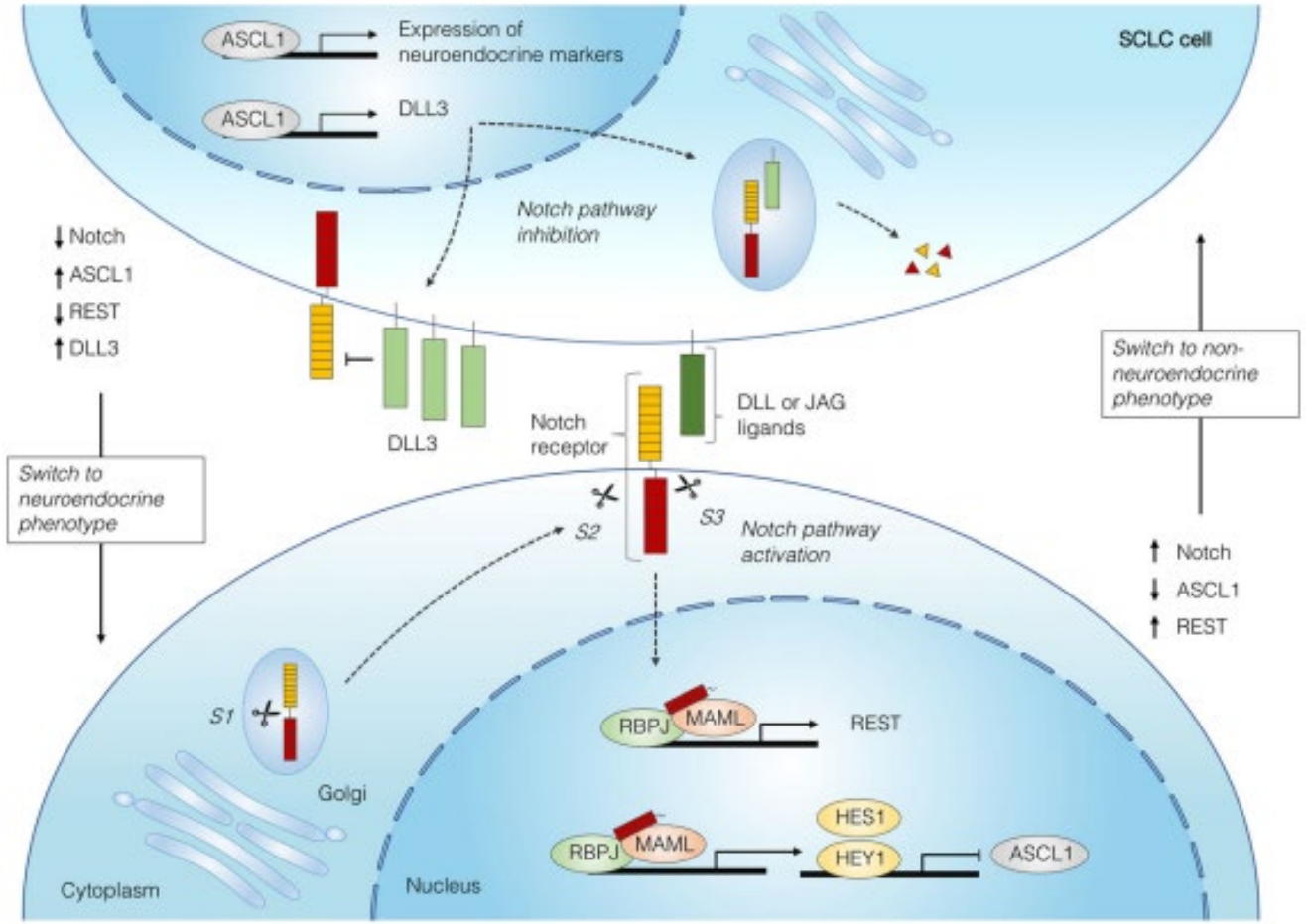
O'Brien *J Clin Oncol 2006 Dec 1;24(34):5441-7*
Paz-Ares LG et al. Meeting Abstract | 2019 ASCO Annual Meeting I
Trigo J *et al.* Lancet Oncol 2020; 21: 645–54

Patient Needs

- Unmet need for novel therapies in SCLC
- Effective therapies with a durable response
  - PFS IMpower133 5.2 v 4.3 mo
- Therapies with CNS penetrance
  - ~80% of patients with SCLC develop brain metastases

SCLC Targets Beyond PD-1/PD-L1



- High levels of ASCL1 in SCLC results in upregulation of DLL3
- DLL3 is usually retained intracellularly but in SCLC overexpression of DLL3 leads to cell surface expression
- ~85% SCLC express DLL3

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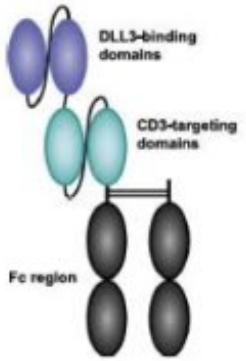
Leonetti A *et al.* Cellular Oncology (2019) 42:261–273

4. ENGAGING IMMUNITY

DLL3/CD3 TARGETED THERAPIES: T-CELL ENGAGERS

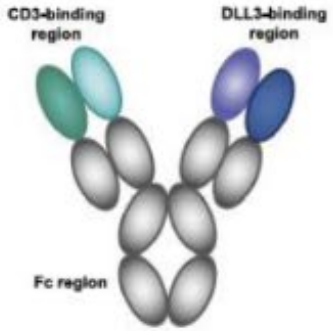
Tarlatamab
Bispecific mAb (BiTE®)
Amgen
(Phase 2-3)



Fc domain
(to extend half-life)

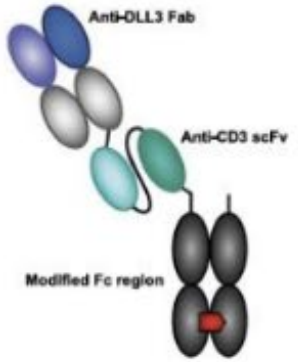
Dellphi-300 (first-in-human study)
Dellphi-301 (phase 2) ongoing
Dellphi-304 (phase 3) ongoing

BI 764532[2]
Bispecific mAb
Boehringer Ingelheim
(FIH)

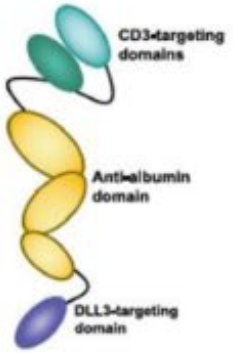


IgG-like
structure

QLS31904
Bispecific mAb
Qilu Pharmaceuticals
(Phase 1)



HPN328
Trispecific mAb (TriTAC®)
Harpoon Therapeutics
(Phase 1/2)

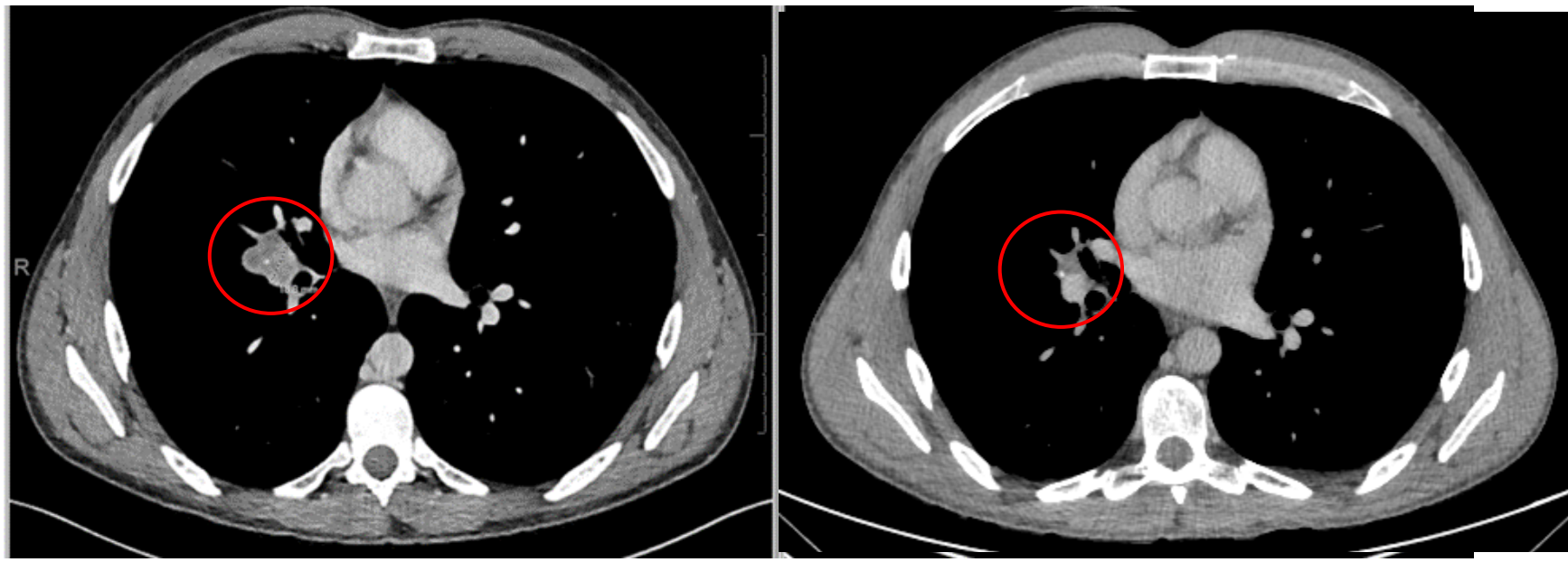


1.-Rudin C, et al. J Hematol Oncol 2023; 2.- Wermke M et al. ASCO 2023

Clinical Experience with HPN328

40 with ES-SCLC

- 1st line chemoIO x 4 cycles followed by IO maintenance x 2 cycles then experienced progression
- 2nd line HPN328



Baseline 28 x 18 mm perihilar mass 3/16/23 (left) and after 7 cycles 11 x 9 mm perihilar mass 8/7/23 (right)

Gr 1 CRS (fever)
Gr 1 dysgeusia/altered taste

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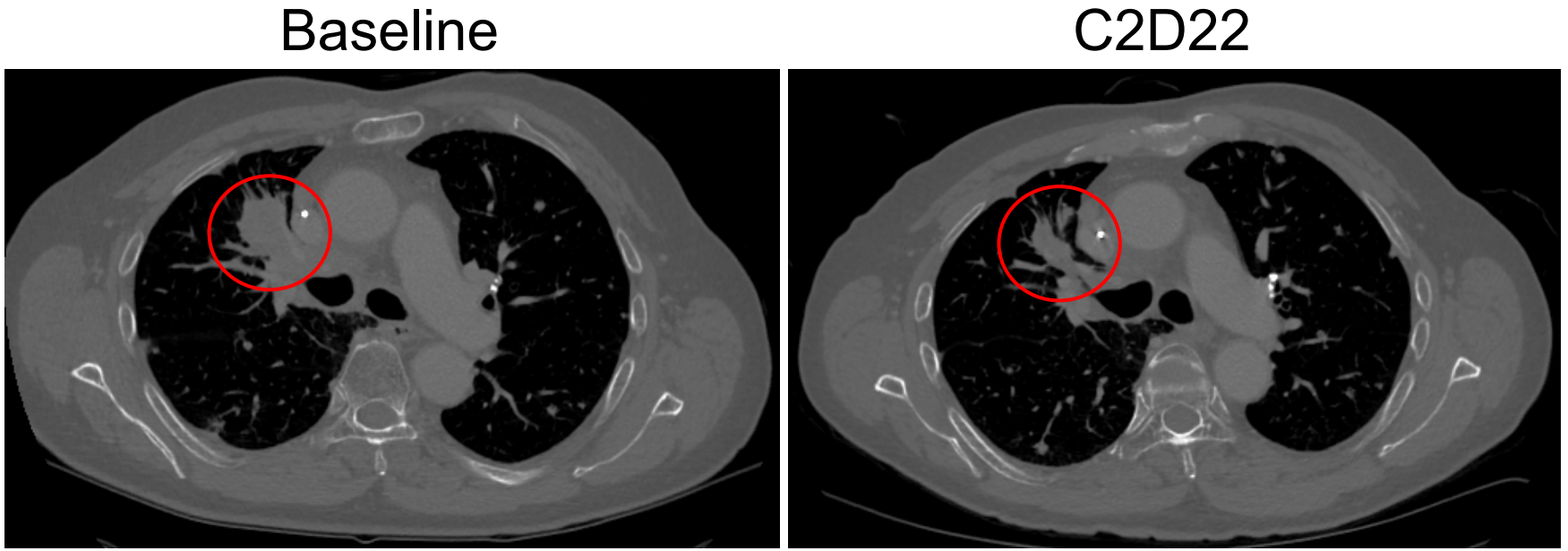
Clinical Experience with HPN328

74 with ES-SCLC

- 1st line chemoIO x 4 cycles followed by IO maintenance x 3 cycles then experienced progression
- 2nd line HPN328



Baseline 4 x 2.5 cm RML mass 6/23/23 (left) and after 2 cycles 3.5 x 1.3 cm RML mass 8/23/23 (right)

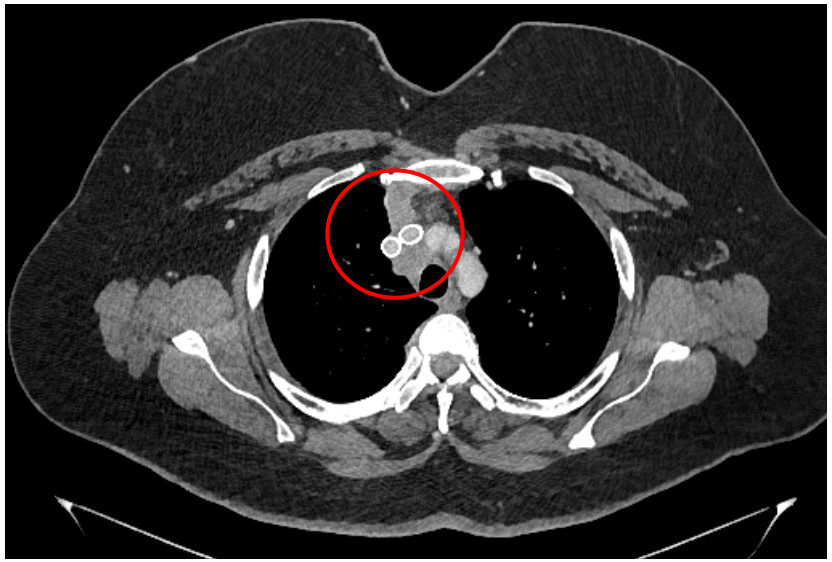
Gr 2 CRS
Gr 2 fatigue
Gr 2 altered taste

Clinical Experience with HPN328

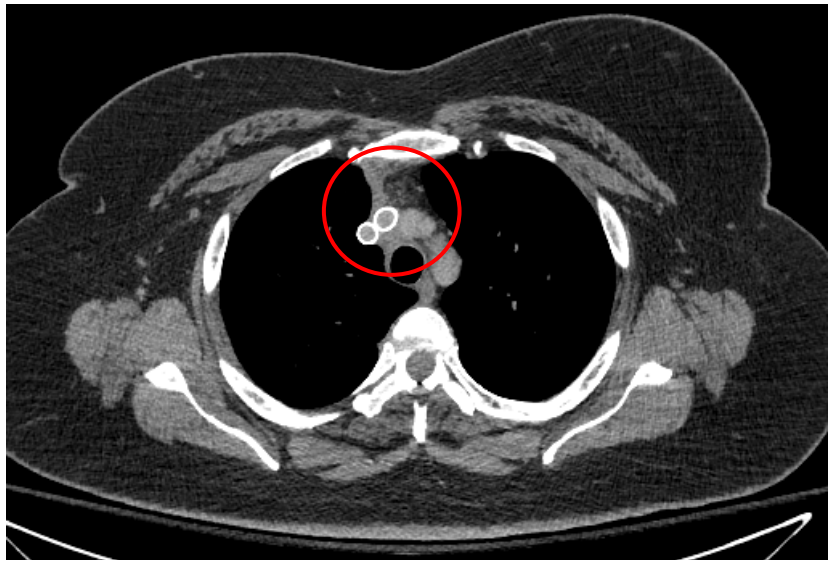
50 with ES-SCLC

- 1st line chemoIO x 4 cycles followed by IO maintenance x 3 cycles then experienced progression
- 2nd line HPN328

Baseline



C1D20



Baseline 1.5 mm mediastinal mass 7/21/23 (left) and after 2 doses 0.7 mm mediastinal mass 8/16/23 (right)

Gr 1 CRS

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DLL3 Agents in Development for SCLC

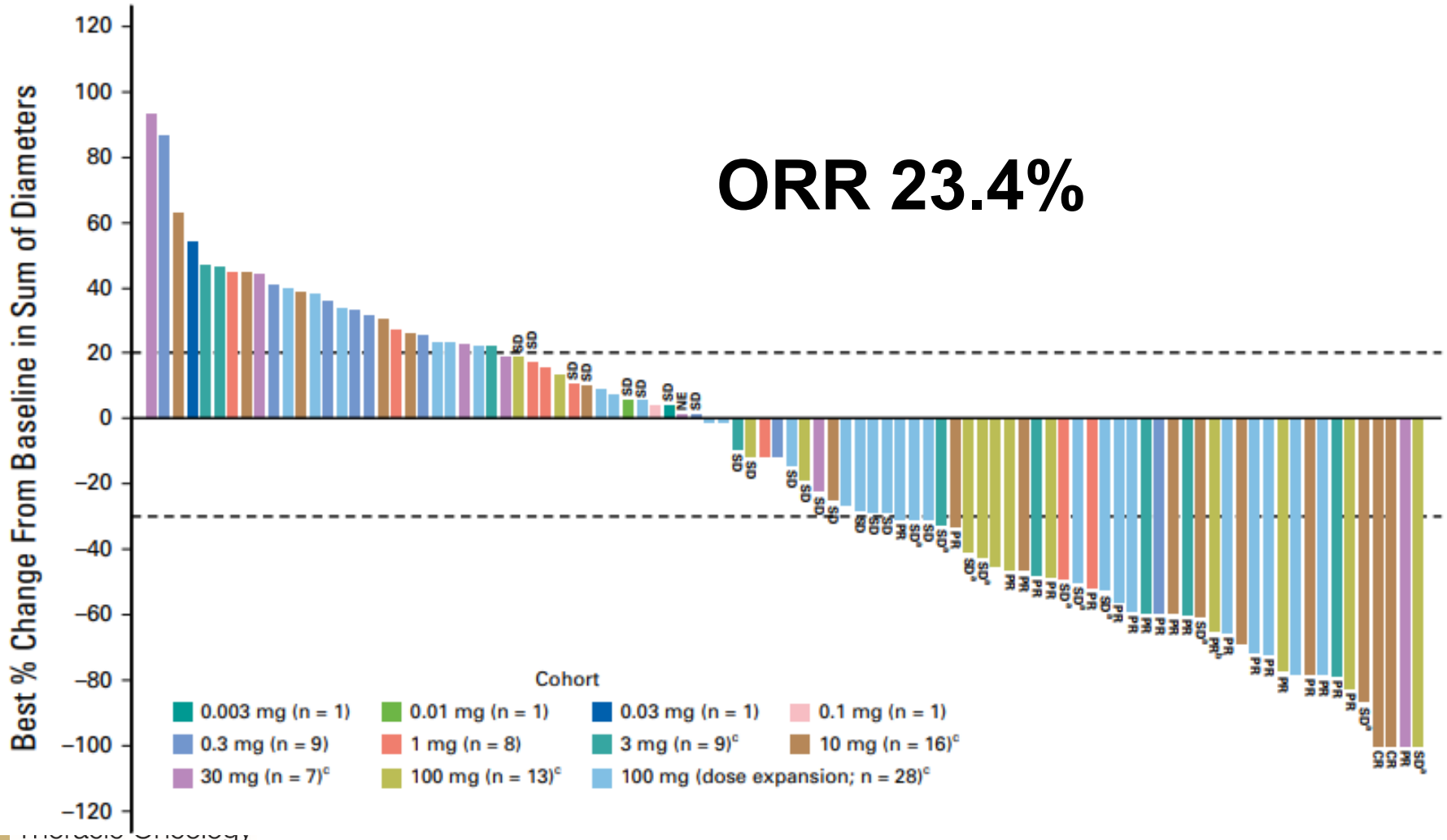
ADCs	
Rovalpituzumab tesirine	ADC targeting DLL3
SC-002	ADC targeting DLL3
CAR therapies	
DLL3-CAR-NK cells	Anti-DLL3–transduced NK cells
AMG 119	Anti-DLL3–transduced autologous T cells

T-cell engagers	
Tarlatamab	Half-life–extended DLL3 x CD3 bispecific T-cell engager
BI 764532	DLL3/CD3 T-cell–engaging bispecific antibody
HPN328	Tri-specific recombinant protein construct
RO7616789	DLL3 x CD3/CD137 multispecific antibody
PT217	Anti-DLL3 x anti-CD47 bispecific antibody
QLS31904	Anti-DLL3 x anti-CD3 bispecific antibody

Modified from: Rudin CM *et al.* Journal of Hematology & Oncology volume 16, Article number: 66 (2023)

Tarlatamab: DLL3 BiTE (Amgen)

DeLLphi-300 Phase I Dose Escalation and Expansion



ORR 23.4%

Dose Cohorts

- 0.3 mg (1/9) 11%
- 1 mg (1/8) 12%
- 3 mg (4/9) 44%
- 10 mg (6/16) 38%
- 30 mg (1/7) 14%
- 100 mg (12/41) 29%

Research Initiative
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Paz-Ares L. *et al.* J Clin Oncol 41:2893-2903. © 2023

Tarlatamab

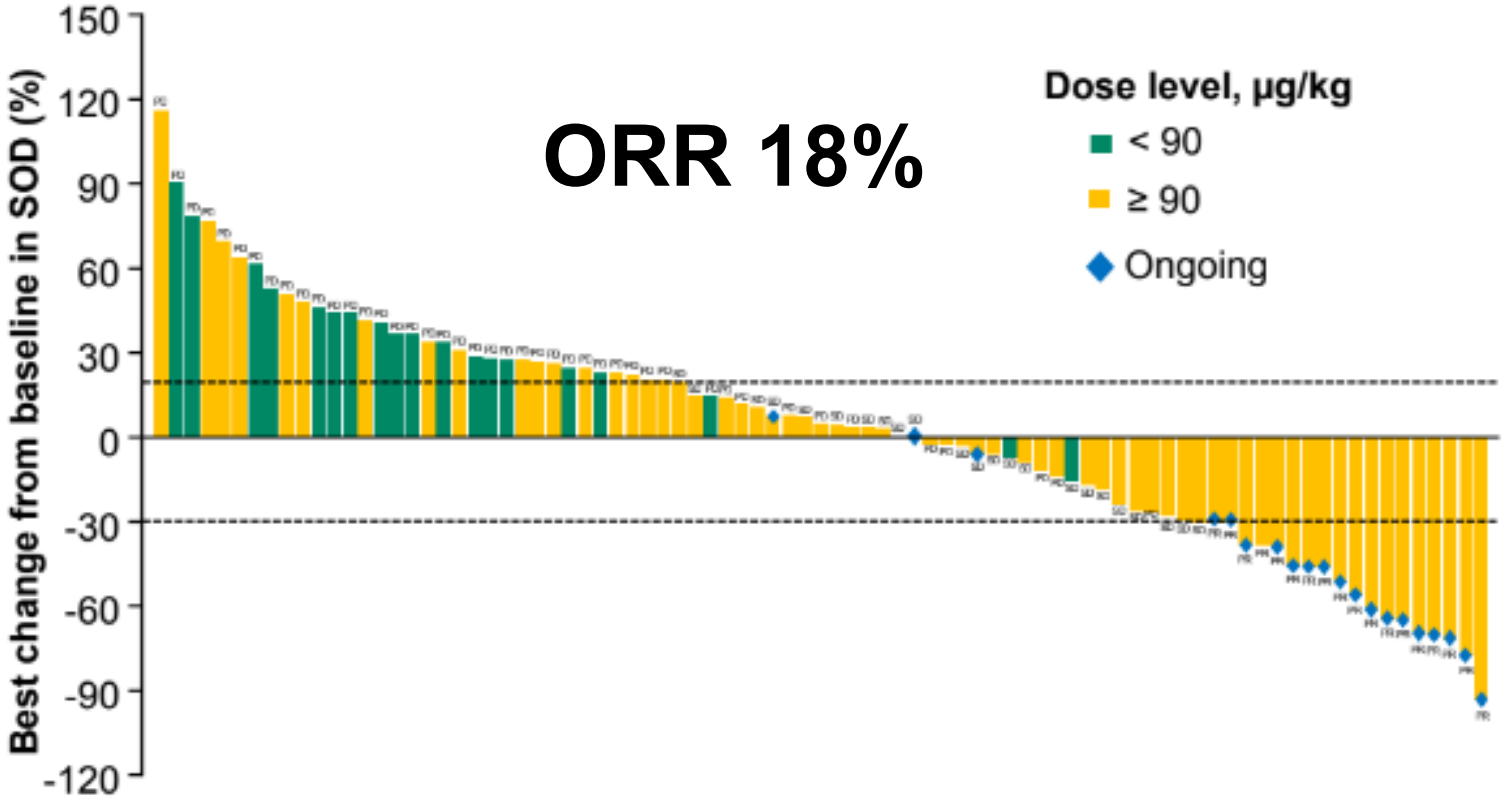
TABLE 2. AEs (preferred term and AMQ for selected terms)

AE	All Patients (N = 107)				
	Any Grade, No. (%)	Grade 1-2, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)	Grade 5, No. (%)
AEs of any cause that occurred during treatment[a]					
Any	107 (100)	46 (43)	48 (45)	12 (11)	1 (1)
Serious	55 (51)	25 (23)	23 (21)	6 (6)	1 (1)
Resulting in discontinuation	4 (4)	1 (1)	3 (3)	0 (0)	0 (0)
Treatment-related AEs	97 (91)	64 (60)	23 (21)	9 (8)	1 (1)
Treatment-related AEs occurring in > 10% of patients or grade ≥ 3 in > 1%)[a]					
CRS	56 (52)	55 (51)	1 (1)	0	0
Pyrexia	40 (37)	38 (36)	2 (2)	0	0
Dysgeusia	24 (22)	24 (22)	0	0	0
Fatigue	23 (22)	20 (19)	3 (3)	0	0
Nausea	21 (20)	21 (20)	0	0	0
Decreased appetite	14 (13)	14 (13)	0	0	0
Vomiting	13 (12)	13 (12)	0	0	0
AEs of interest[b]					
CRS					
Any cause	56 (52)	55 (51)	1 (1)	0	0
Related	56 (52)	55 (51)	1 (1)	0	0
Neurologic events					
Any cause	75 (70)	63 (59)	11 (10)	1 (1)	0
Related	53 (50)	46 (43)	6 (6)	1 (1)	0

Paz-Ares L. *et al.* J Clin Oncol 41:2893-2903. © 2023

BI 764532 (Boehringer Ingelheim)

Overall efficacy (all patients)



n, (%)	All tumors (n=99)*	SCLC (n=54)*	LCNEC (n=8)*
PR	18 (18)	10 (19)	3 (38)
SD	23 (23)	11 (20)	3 (38)
PD	45 (45)	23 (43)	2 (25)
DCR	41 (41)	21 (39)	6 (75)
NE†	13 (13)	10 (19)	0

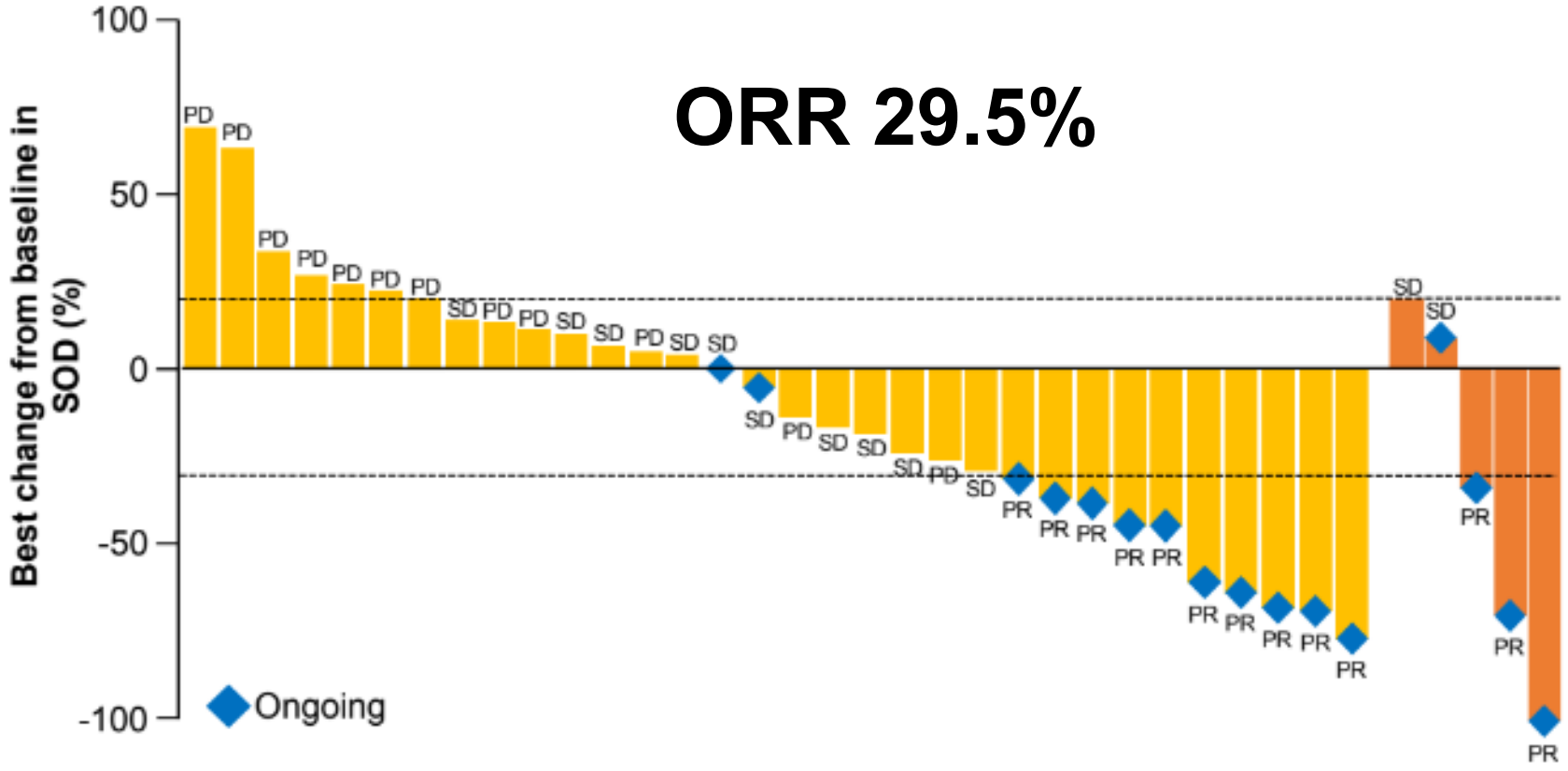
*Efficacy population: ≥1 post-baseline tumor assessment or permanently discontinued prior to tumor assessment; responses evaluated per RECIST v1.1 criteria;
†Discontinued prior to tumor assessment

- **Efficacy, i.e. tumor shrinkage, observed at doses ≥ 90 µg/kg**

DCR, disease control rate; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; SOD, sum of diameters

BI 764532 (Boehringer Ingelheim)

Efficacy in patients with SCLC and LCNEC (doses ≥ 90µg/kg)



n, (%)	SCLC (n=39)*	LCNEC (n=5)*
PR	10 (26)	3 (60)
SD	10 (26)	2 (40)
PD	12 (31)	0
DCR	20 (51)	5 (100)
NE†	7 (18)	0

*Efficacy population: ≥1 post-baseline tumor assessment or permanently discontinued prior to tumor assessment; responses evaluated per RECIST v1.1 criteria; †Discontinued prior to tumor assessment

Most common all-cause AEs in pts with SCLC and LCNEC (>15% patients)

AE, n (%)	Patients (n=66)* All grade	Grade 1–2	Grade 3–5
Number of pts with ≥1 AE	**66 (100)**	**31 (47)**	**35 (53)**
CRS	32 (48)	31 (47)	1 (2)
Asthenia	21 (32)	19 (29)	2 (3)
Dysgeusia	18 (27)	18 (27)	0
Constipation	18 (27)	18 (27)	0
Lymphocyte count decreased	16 (24)	4 (6)	12 (18)
Nausea	15 (23)	14 (21)	1 (2)
Fatigue	13 (20)	12 (18)	1 (2)
Malignant neoplasm progression†	13 (20)	0	11 (17)
Decreased appetite	12 (18)	10 (15)	2 (3)
AST increased	12 (18)	11 (17)	1 (2)
Headache	12 (18)	12 (18)	0
Pyrexia	11 (17)	11 (17)	0

- **CRS managed with supportive care, corticosteroids, and/or anti-IL-6R antibodies**
- **Patients with AEs/TRAEs leading to discontinuation: 15 / 6%**

*Safety population: ≥1 dose of BI 764532; †Two patients with malignant neoplasm progression had a missing CTCAE grade. AE, adverse event; AST, aspartate aminotransferase; IL-6R, interleukin 6 receptor; TRAE, treatment-related AE

SCLC Second Line Landscape

	Topotecan n=71	Lurbinectedin n=105	Lurbinectedin 3mo+ CFI n=60	Tarlatamab n=107	Tarlatamab 100mg n=41	BI 764532 n=99	BI 764532 90ug/kg n=44
ORR	~7%	35%	45%	23.4%	29%	18%	29.5%
mPFS	4.1 mo	3.5 mo	4.6 mo	3.7 mo			
mOS	6.5 mo	9.3 mo	11.9 mo	13.2 mo			
DoR		5.3 mo	6.2 mo	12.3 mo			
TRAE Gr 3+		15%		30%		53%*	

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*All cause AEs.
TRAE not yet reported

Opportunities in SCLC
How to Get Noticed

#1 Be a novel agent with a rational design

- For decades have attempted various chemotherapy regimens with no improvement
- Addition of PD-L1 therapy is an improvement, but modest
- Targeting DLL3 with a T cell engager is an exciting combination of a known target with a novel immunotherapy – investigators are primed for a bold change

Opportunities in SCLC
How to Get Noticed

#2 Report ‘smart’ outcomes

- ORR/PFS/OS are all cornerstones
- Duration of response

- **<u>Intracranial efficacy</u>**
  - HPN 328 has extracranial efficacy
  - Aggressively generate CNS efficacy data and LEAD THE FIELD

Opportunities in SCLC
How to Get Noticed

#3 Identify responders with biomarkers

- DLL3 expression
- Molecular subtypes of SCLC
- Chemotherapy free interval

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Opportunities in SCLC
How to Get Noticed

#4 Develop combination strategies that reflect practice needs

- Transformed SCLC (resistance mechanism to NSCLC TKIs) is a feared complication with even worse outcomes
- Develop safety and early efficacy data with TCE + TKI
  - PD-1/PD-L1, RT, chemotherapy, etc
- Other DLL3 positive cancers

Conclusions

- Patients with SCLC have had few breakthroughs over the decades
- No TCE has emerged the clear winner
- HPN 328 can come to the forefront:
  - Efficacy
    - **Intracranial response rates**
  - Identification of biomarkers/patient factors that enrich for response
  - Addressing patient populations with unmet needs (tSCLC)
  - Generating safety data with drug combinations that reflect clinical practice


Question and
Discussion
University of Colorado
Anschutz Medical Campus

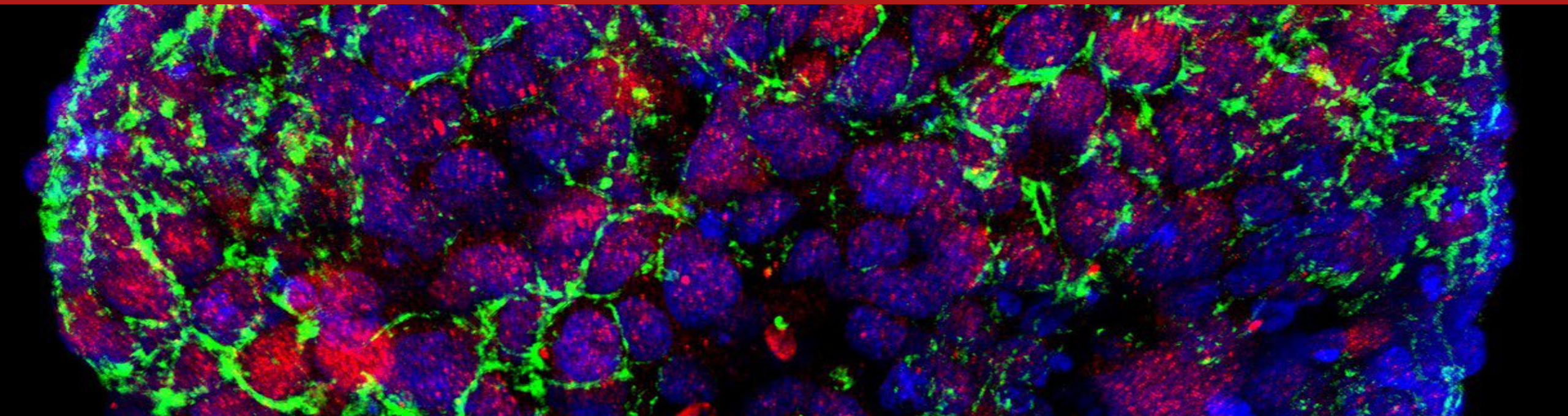
Himisha Beltran, M.D.

Associate Professor, Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School

Neuroendocrine Prostate Cancer: An Emerging Prostate Cancer Subtype

Himisha Beltran, MD

Dana Farber Cancer Institute
Harvard Medical School



Prostate Cancer in the United States

Estimated New Cases

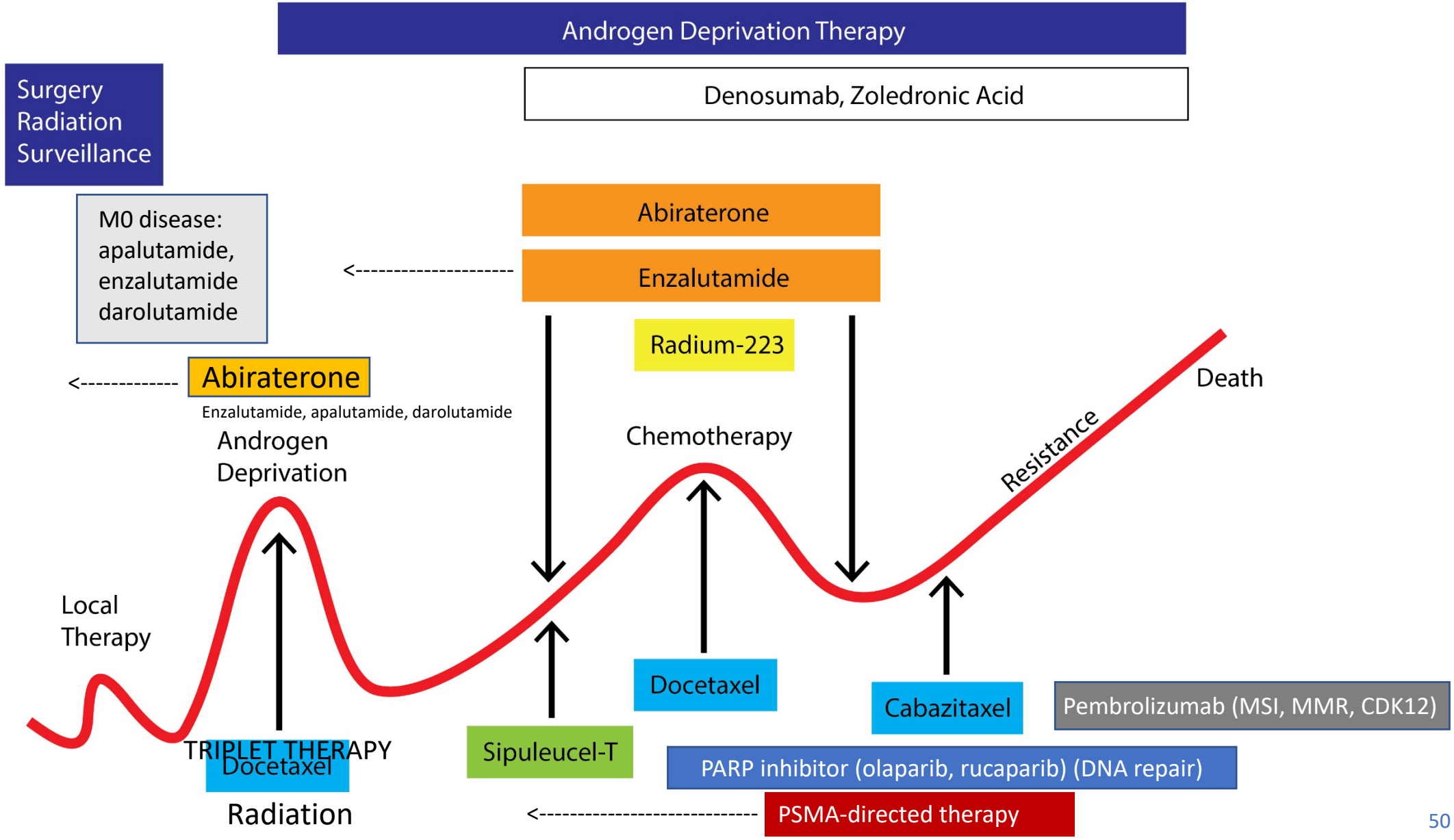
Males				Females		
Prostate	288,300	29%		Breast	297,790	31%
Lung & bronchus	117,550	12%		Lung & bronchus	120,790	13%
Colon & rectum	81,860	8%		Colon & rectum	71,160	8%
Urinary bladder	62,420	6%		Uterine corpus	66,200	7%
Melanoma of the skin	58,120	6%		Melanoma of the skin	39,490	4%
Kidney & renal pelvis	52,360	5%		Non-Hodgkin lymphoma	35,670	4%
Non-Hodgkin lymphoma	44,880	4%		Thyroid	31,180	3%
Oral cavity & pharynx	39,290	4%		Pancreas	30,920	3%
Leukemia	35,670	4%		Kidney & renal pelvis	29,440	3%
Pancreas	33,130	3%		Leukemia	23,940	3%
All Sites	**1,010,310**	**100%**		**All Sites**	**948,000**	**100%**

Estimated Deaths

Males				Females		
Lung & bronchus	67,160	21%		Lung & bronchus	59,910	21%
Prostate	34,700	11%		Breast	43,170	15%
Colon & rectum	28,470	9%		Colon & rectum	24,080	8%
Pancreas	26,620	8%		Pancreas	23,930	8%
Liver & intrahepatic bile duct	19,000	6%		Ovary	13,270	5%
Leukemia	13,900	4%		Uterine corpus	13,030	5%
Esophagus	12,920	4%		Liver & intrahepatic bile duct	10,380	4%
Urinary bladder	12,160	4%		Leukemia	9,810	3%
Non-Hodgkin lymphoma	11,780	4%		Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	11,020	3%		Brain & other nervous system	7,970	3%
All Sites	**322,080**	**100%**		**All Sites**	**287,740**	**100%**

Siegel et al, CA Cancer J Clin 2023

<--- EARLIER AND MORE POTENT INHIBITION OF THE AR



What does resistant prostate cancer look like?

Group 1 (80%):

- Gradually progressive: bone, LN metastases, rising PSA
- Initially responsive to potent AR therapies

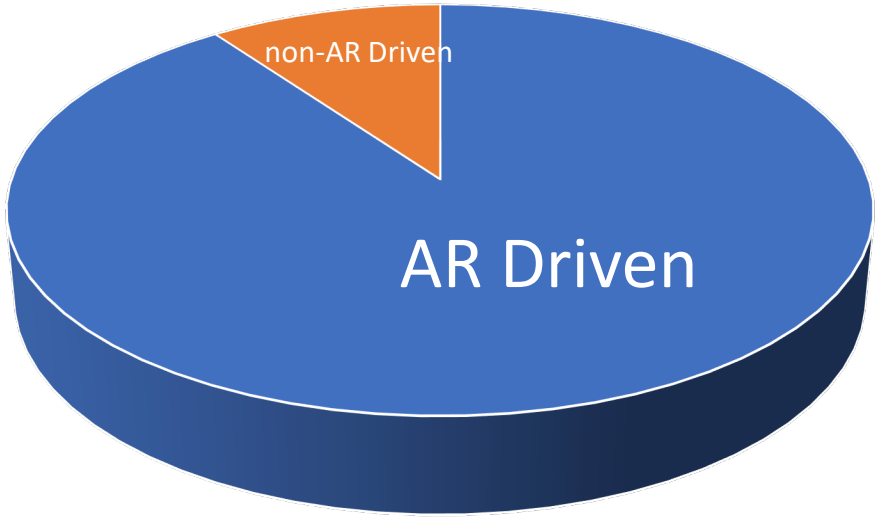
Group 2 (15-20%):

- Resistant/refractory to potent AR therapies
- Rapidly progressive: liver, brain mets, low or non-rising PSA

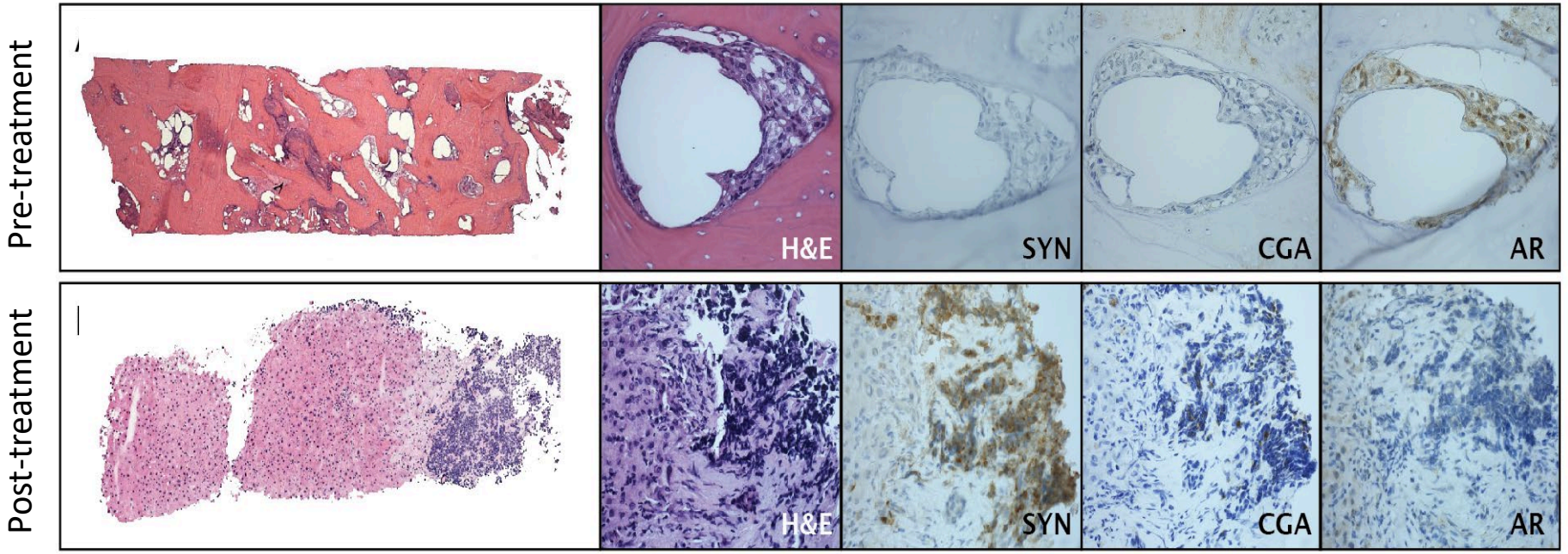
Treatment Resistant Prostate Cancer

Most prostate cancers are driven by androgen receptor (AR) signaling

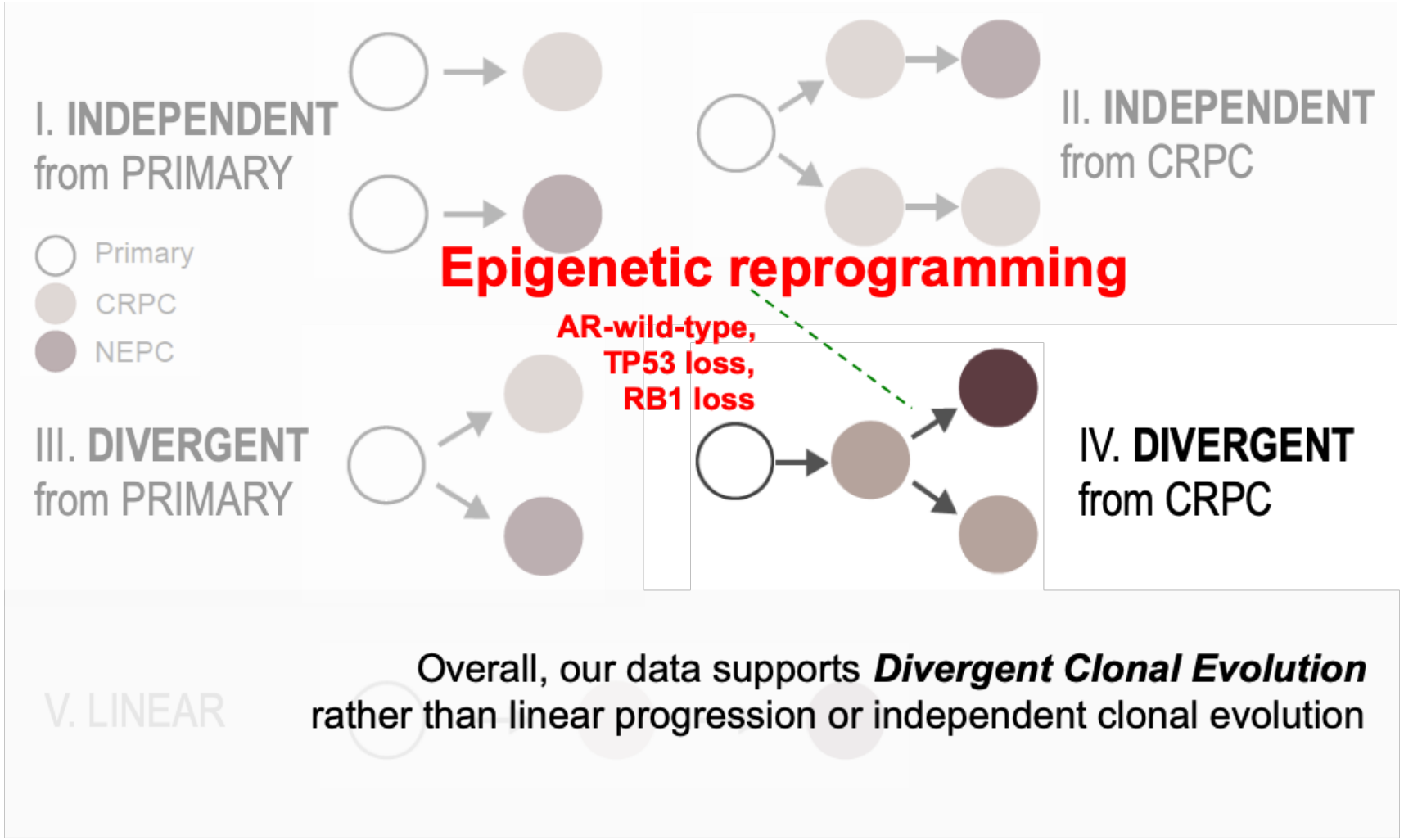
Non AR-driven prostate cancer occurs in approx. 15-20% of patients, higher in later stages of the disease (and after potent AR therapies)



In prostate cancer, therapeutic pressure may lead to small cell/neuroendocrine prostate cancer transformation

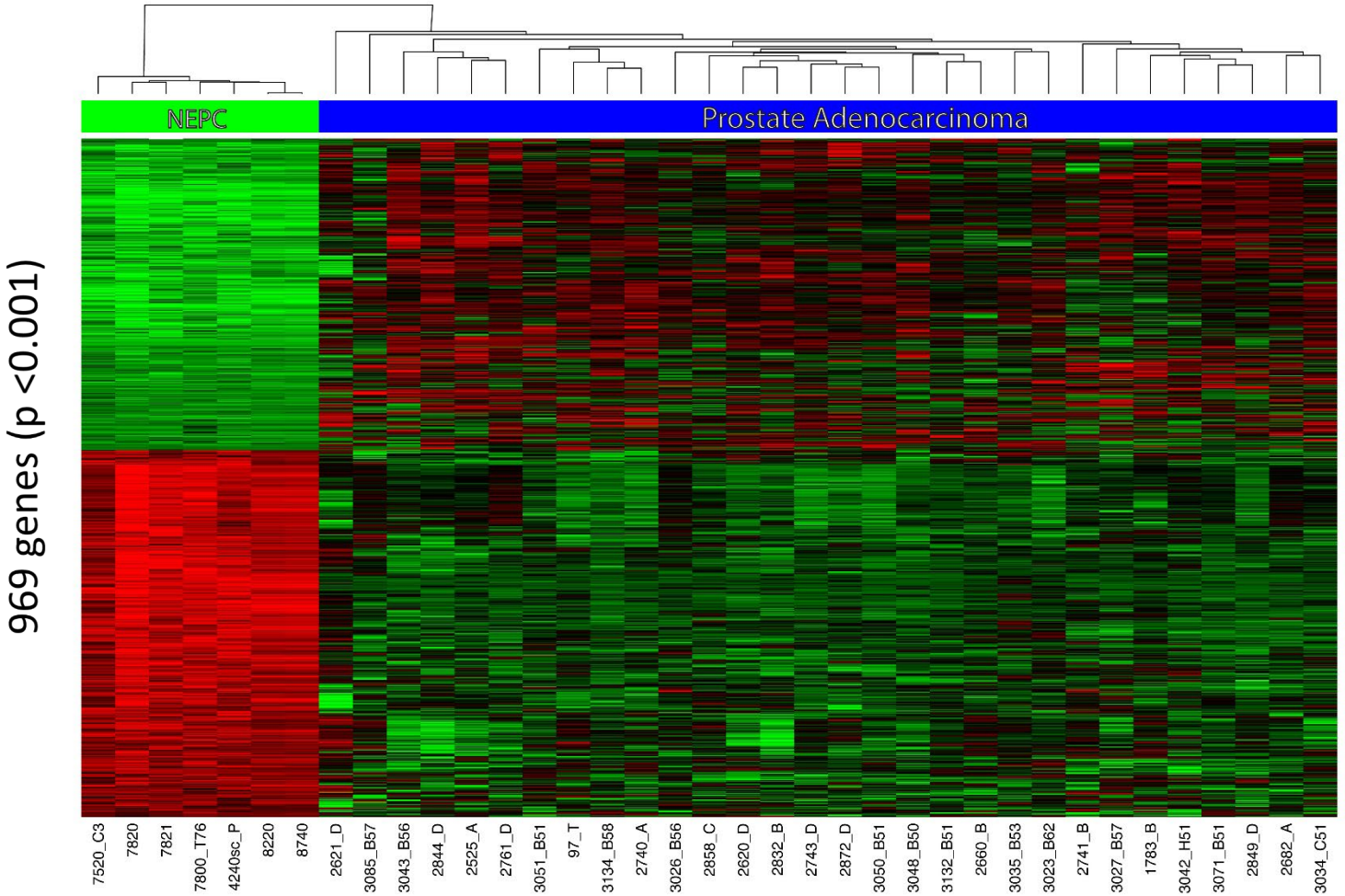


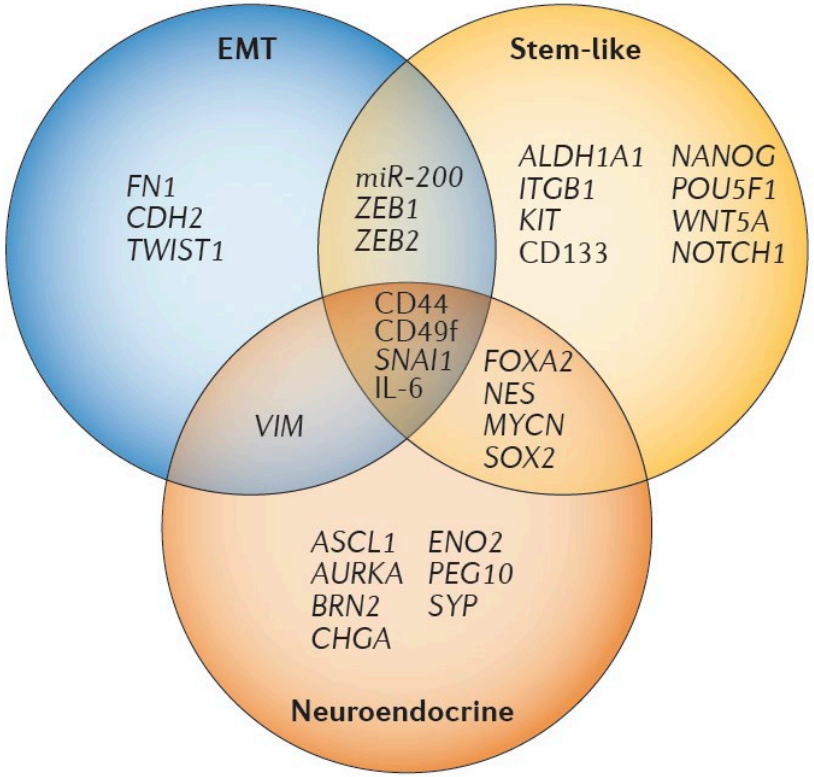
Evolution of castration resistant prostate adenocarcinoma to neuroendocrine prostate cancer



Beltran et al Nat Med 2016

Transcriptome Analysis: NEPC vs prostate adenocarcinoma





DLL3

Red= High Expression

Green= Low Expression

Beltran et al Cancer Discov 2011

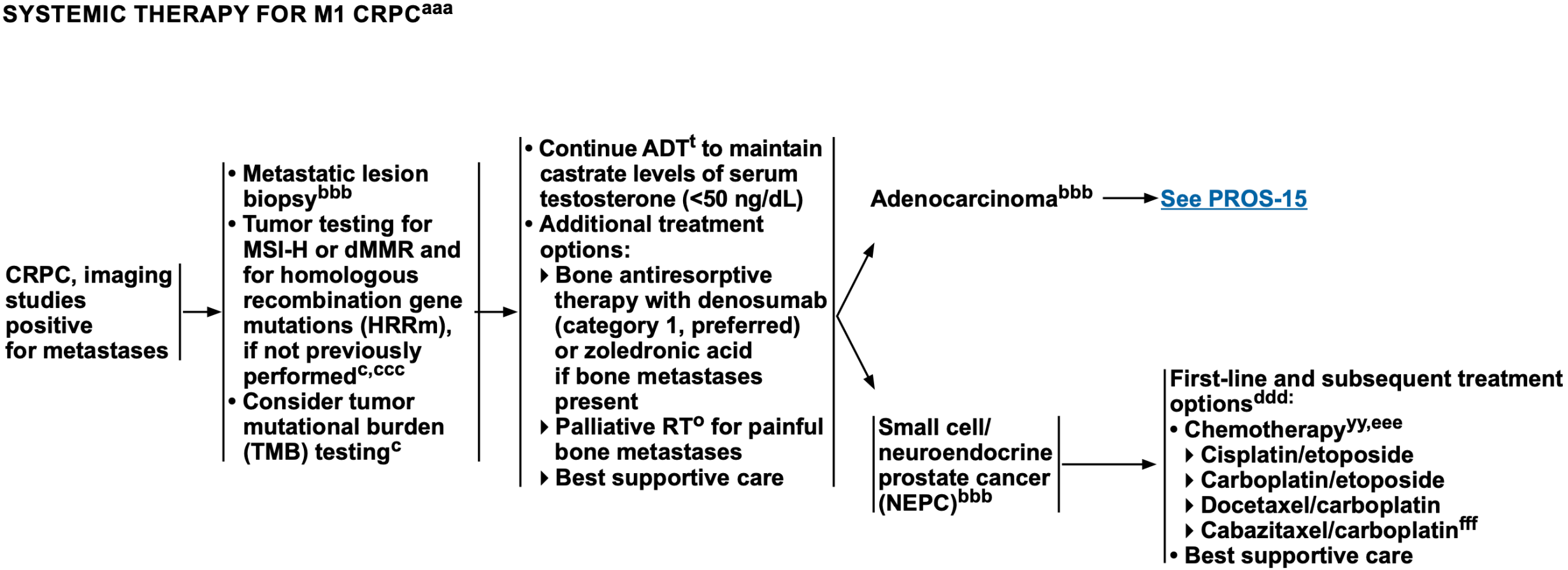
Beltran et al Nature Medicine 2016

How can we better treat or co-target neuroendocrine prostate cancer?

There are no approved therapies for NEPC

- Platinum chemotherapy
- Targeted therapies?
- Co-targeting AR and non-AR pathways?
- Immunotherapies?
- Other approaches?

NCCN Guidelines (May 2022)

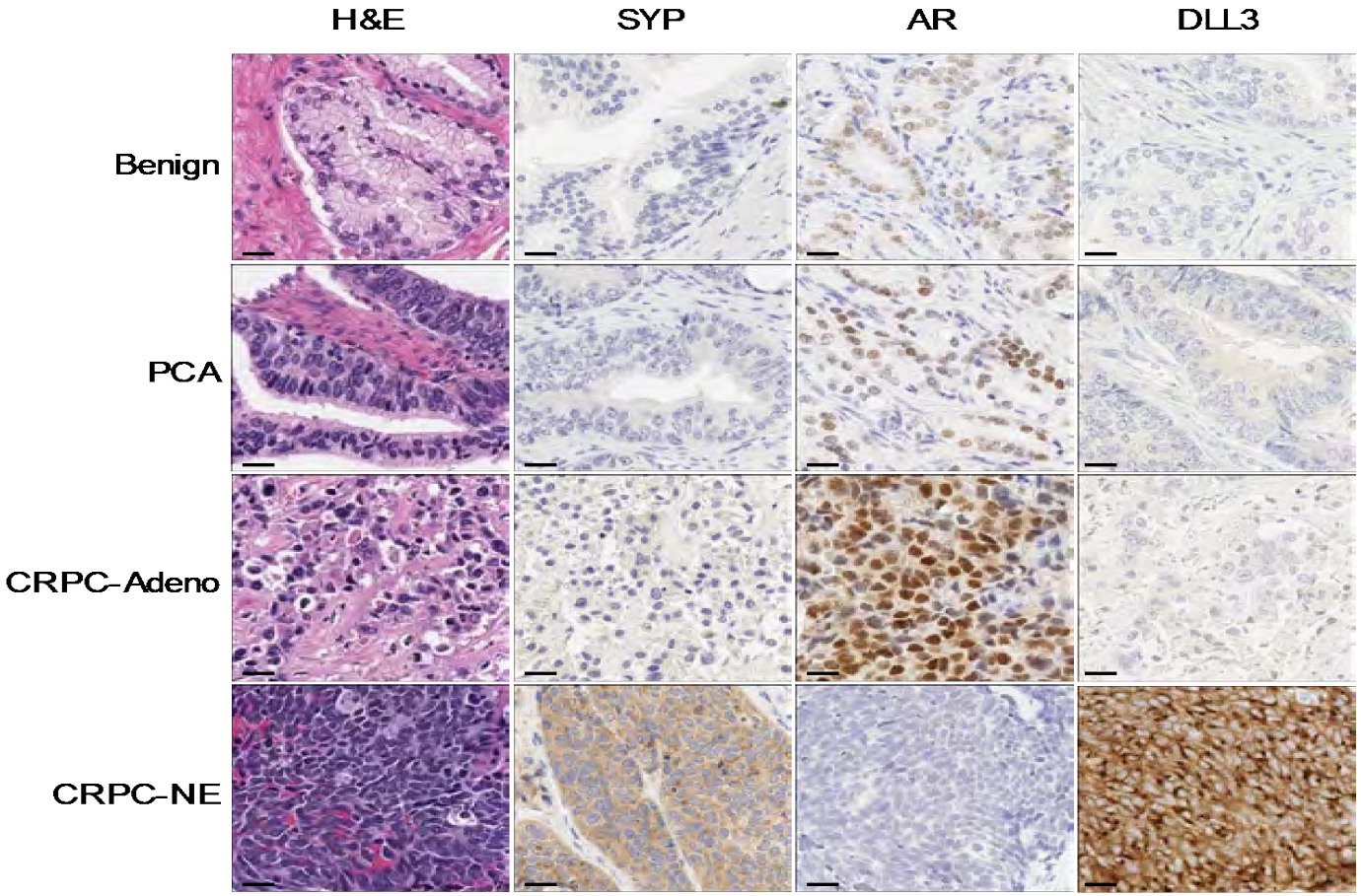


What to give next line?

- What is dominant pathology? Associated clinical features?
- Small cell lung cancer regimen
  - Lurbinectedin
  - Topotecan
  - Ipi/Nivo– limited data supporting IO in NEPC
- CRPC regimen
- Molecularly-driven therapy – eg., PARPi for BRCA2
- **Consider a clinical trial whenever possible**

CANCER

Delta-like protein 3 expression and therapeutic targeting in neuroendocrine prostate cancer



DLL3+ (%)

0% (0/103)

0.52% (1/194)

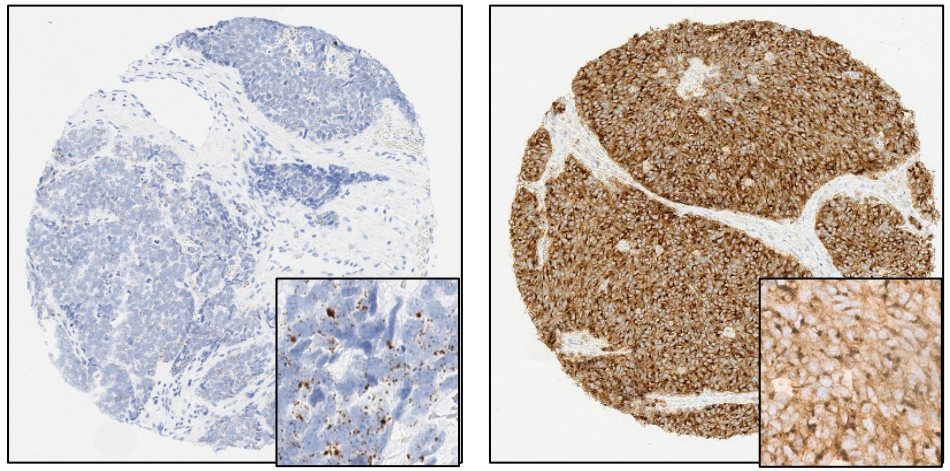
12.5% (7/56)

76.6% (36/47)

Puca L et al., Sci. Transl. Med. (2019)

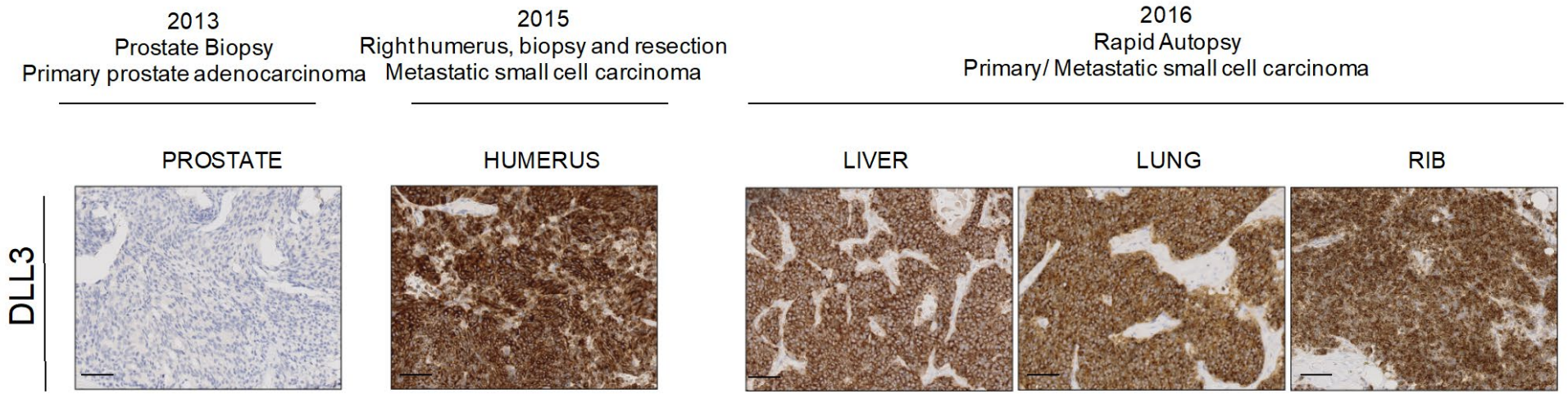
DLL3 is highly expressed in neuroendocrine prostate cancer patient cohort

(high DLL3 by IHC and Nanostring)



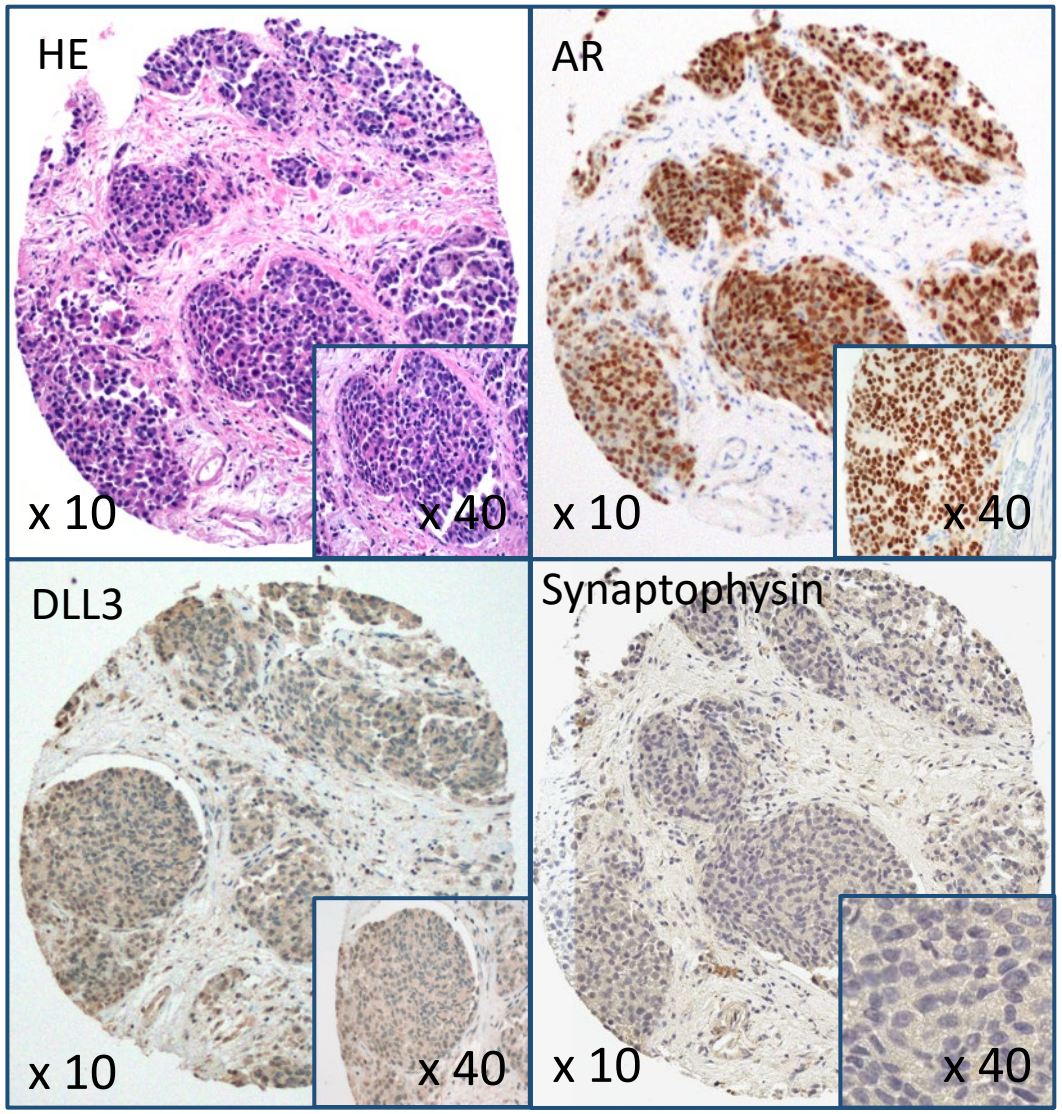
RNAish IHC

Development of RNAish assay



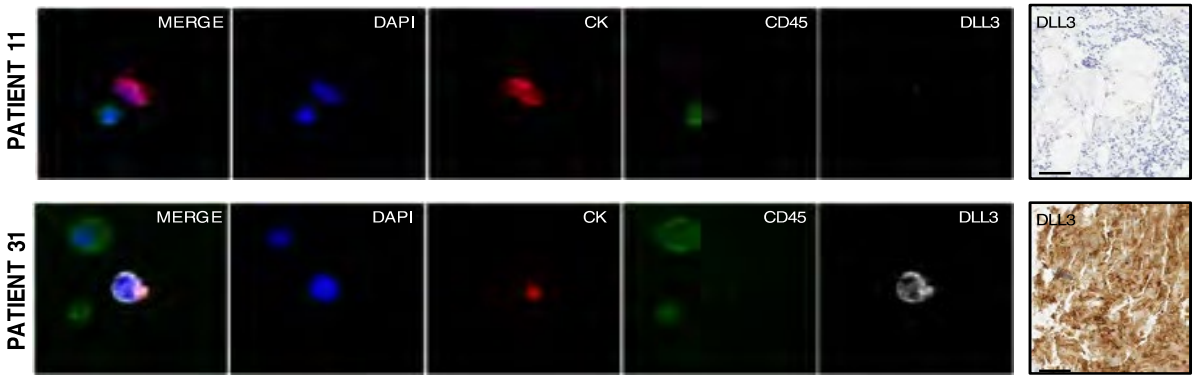
Puca L et al., Sci. Transl. Med. (2019)

Example of CRPC case (AR+) expressing NE-Markers and DLL3

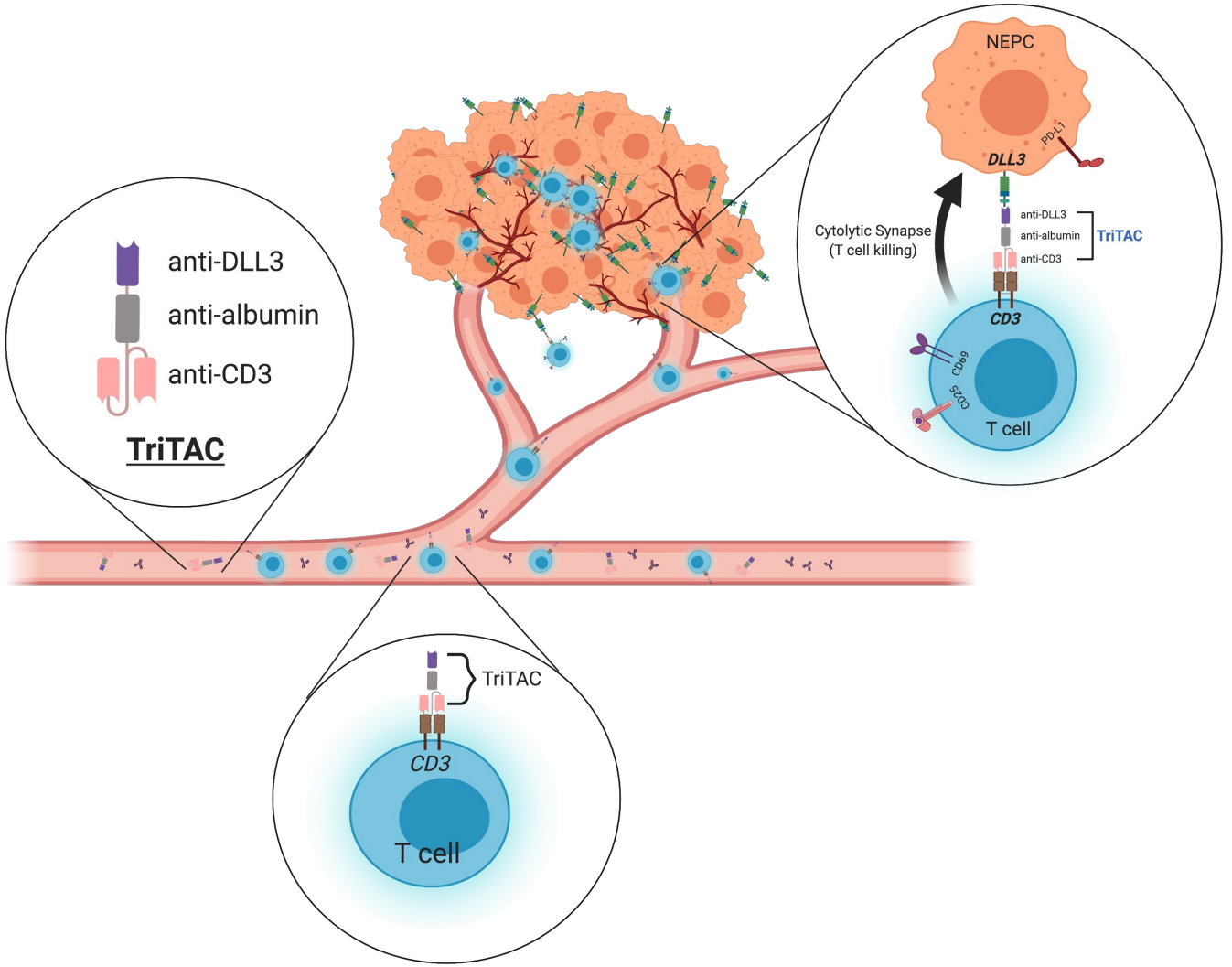


Puca L et al., Sci. Transl. Med. (2019)

DLL3 expression in CTCs (Epic)



HPN328 - DLL3 T cell engager



Phase 1/2 trial of HPN328 for NEPC and SCLC

First 15 pts treated on ongoing Phase 1 trial (Johnson et al, ASCO 2022):

- 40% had decrease size of target lesions (4 SCLC, 1 NEPC, 1 other NE tumor)
  - 33% SCLC pts across all doses had > 30% decrease
- 25% had stable disease: 2 SCLC, 1 NEPC, 1 NEN

Our Site Experience (we have now enrolled 15 patients at DFCI)

- Adverse events transient, manageable, and no ≥ Grade-3 immune related side effects
- NEPC patients (n=9)= clinical improvement even when mixed responses and manageable toxicities

NEPC patient 1

70 yo diagnosed in with metastatic prostate adenocarcinoma with bone metastases, PSA 35 ng/ml. Treated with androgen deprivation therapy + abiraterone/prednisone

3 years later-- developed progression in setting of PSA 0.08 including new liver metastases.

Pathology: NEPC

Treated with carboplatin+ cabazitaxel X 10=> POD

cisplatin+ etoposide+ durvalumab x 1 (stopped due to poor tolerance)

Started HPN328 study in 12/2022

Scans at 2 months-- decreased size of liver mets and other lesions

Scans at 5 months– mixed response – decreased size liver mets but 2 new small lesions

Continues on therapy and doing well (now 9 months)

NEPC patient 2

65 yo with metastatic prostate cancer with mixed features

- Liver biopsy: High grade poorly differentiated NE carcinoma
- Progressed after ADT + 3 cycles of cisplatin + etoposide
- Progressed after CAV (cyclophosphamide + Adriamycin + vincristine) x 3
- Progressive prostate /pelvic /RP LN disease (requiring catheter), liver, lung, and bone mets
- Enrolled on HPN328– significant clinical improvement
- Scans: decrease lung mets, LN, prostate mets, increase liver mets
- Felt so well, he continued past progression x 6 months (flew weekly from Chicago)

HPN328 Patient Case 3: Relapsed ES-SCLC

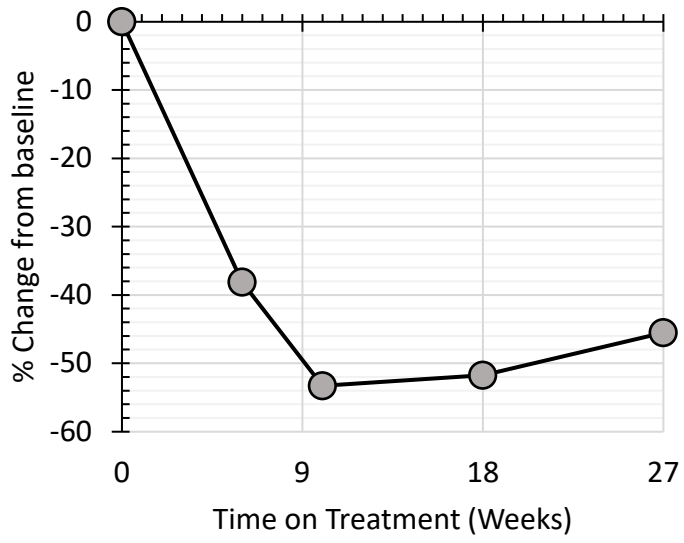
53% Reduction in Sum of Target Lesion Diameters at Week 10: Confirmed PR

Patient History

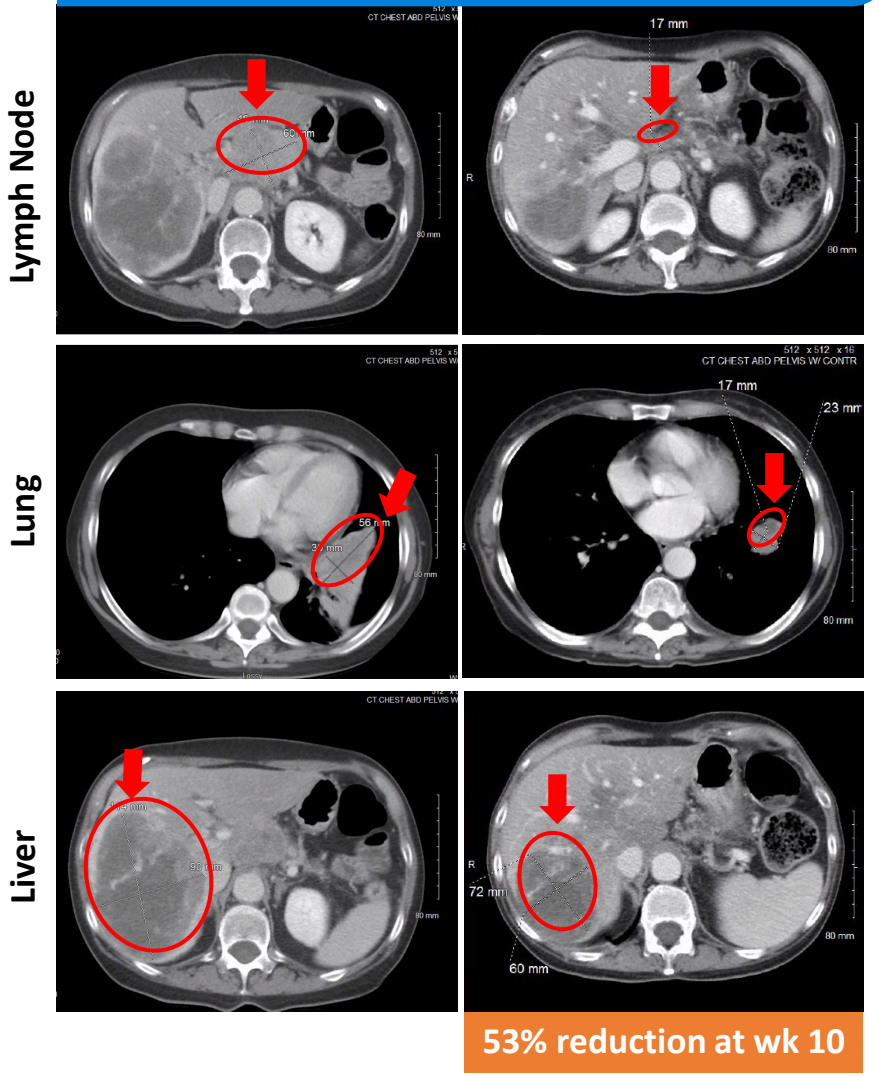
- 61-year-old female
- Diagnosed Jan 2021 with extensive-stage SCLC
- Location of metastases:
  - TLs: lung, liver x2, lymph nodes x2
  - Non-TLs: lung x2, liver
- Prior systemic treatment:
  - carboplatin + etoposide + atezolizumab
- Time on most recent prior systemic treatment: 20.1 weeks
- Upon study entry, **stable disease as best response** to most recent prior systemic treatment

Results

- **Initiated HPN328 at 1.215mg/week, later dose escalated**
- **Confirmed PR at week 10**
- **Continued treatment with HPN328 for 33 weeks**



Week 10 On Treatment



Unaudited patient data based on entries provided in open clinical database as of 10/10/2022 (subject to change)

Summary

- Aggressive subtypes of advanced prostate cancer exist that are not responsive to AR pathway inhibitors due to loss of tumor dependency on AR signaling (15-20% of late stage prostate cancers) Incidence of lineage plasticity and neuroendocrine prostate cancer is increasing.

- Often share pathologic, clinical, molecular (eg., RB1, TP53, **DLL3**) features with small cell lung cancer but arise clonally from prostate adenocarcinoma during CRPC progression.

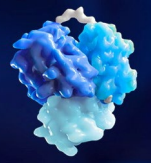
- There are no approved therapies for men with NEPC and development of novel therapies is a pressing unmet need. Targeting DLL3 with HPN328 is a promising approach.

HARPOON Therapeutics

CLOSING REMARKS

Julie Eastland
CEO

Capitalizing on the DLL3 Opportunity with HPN328



- HPN328 is a clinically validated, T cell engager with the potential to address a large patient population currently facing poor prognosis and limited treatment options
- Ongoing clinical program continues building on strength of prior HPN328 data which showed anti-tumor activity in SCLC at low dose levels while being well tolerated
- Dosed the first patients with SCLC in the ongoing Phase 1/2 trial with combination of HPN328 plus Roche's atezolizumab (Tecentriq®)
- Phase 1 interim monotherapy data to be presented at the European Society of Medical Oncology (ESMO) in October 2023