Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

66th ASH Meeting 2024

San Diego & virtuell

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Expert:innen berichten zu Lymphomen & Leukämien

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Dr. med. Dr. med. univ. Stefan Habringer
Charité Universitätsmedizin Berlin

Primäre ZNS-Lymphome (PZNSL)

Offenlegung potentieller Interessenskonflikte

LymphomKompetenz KOMPAKT – ASH2024 wird in Kooperation mit sieben unterstützenden Firmen durchgeführt.
Meine persönlichen Disclosures betreffen:

Anstellungsverhältnis, Führungsposition	-
Beratungs-/ Gutachtertätigkeit	-
Besitz von Geschäftsanteilen, Aktien oder Fonds	Moonlight AI GmbH
Patent, Urheberrecht, Verkaufslizenz	Moonlight AI GmbH
Honorare	SERB, Incyte, Pentixapharm, Sanofi
Finanzierung wissenschaftlicher Untersuchungen	-
Andere finanzielle Beziehungen	-
Immaterielle Interessenkonflikte	-

Acalabrutinib + Durvalumab in R/R CNSL

985 Phase I Results of Acalabrutinib in Combination with Durvalumab in Primary Central Nervous System Lymphoma: Safety, Efficacy, and Central Nervous System Penetration

Imran A. Nizamuddin *Narendranath Epperla MS, Mary-Kate Malacek Brad S. Kahl Fei Wan Anne Fischer, BS, Chaz Moreno, Emily R. King, BA, Anna Krivenko, Nancy L. Bartlett and Neha Mehta-Shah*

Acalabrutinib + Durvalumab in R/R CNSL

Methods:

- **Design:**
  - Phase I, 3+3 dose-escalation study
- **Participants:**
  - n = 10 PCNSL, n = 3 SCNSL
- **Treatment:**
  - Acalabrutinib (100 mg or 200 mg BID) and
  - Durvalumab (1500 mg IV on day 1 of 28-day cycle)
- **Endpoints:**
  - Primary: Safety, tolerability, and RP2D
  - Secondary: Preliminary efficacy
  - Exploratory: CNS penetration of Acalabrutinib

Acalabrutinib + Durvalumab in R/R CNSL

Patient characteristics	
Median Age	74 years (range 38-83)
Female vs. Male	62 vs. 38%
PCNSL vs. SCNSL	10 PCNSL, 3 SCNSL
Ethnicity	White: 100%
GCB vs. Non-GCB	GCB: 23.1%, Non-GCB: 61.5%
Prior therapy lines	2 (1-3)

Acalabrutinib + Durvalumab in R/R CNSL

Efficacy	
ORR	4/10 PCNSL, **0/3 SCNSL**
CR/CRu	4/10 PCNSL

Acalabrutinib metabolites in CSF:

- Detectable ACP-196 in CSF 62.5%
- Detectable ACP-5862 in CSF 25%

Adverse Events:

- Pneumonia
- Diarrhea
- Transaminitis
- Hypertension

→ **RP2D 100mg BID**

Tirabrutinib in R/R PCNSL

572 Interim Analysis Data from Multi-Center Retrospective Observational Study of Effectiveness, Safety, and Treatment Status of Tirabrutinib in 161 Japanese Patients with Relapsed or Refractory Primary Central Nervous System Lymphoma: Rosetta Study

***Motoo Nagane**, Manabu Natsumeda , Fumiharu Ohka Ph, Fumiyuki Yamasaki , Hajime Yonezawa , Nobuyoshi Sasaki, Shigeru Yamaguchi , Kensuke Tateishi , Yoshitaka Narita , Yasukazu Kawai , Hiroyuki Sugahara , Jyunichiro Kuroda , Takeshi Okuda , Tomoo Matsutani , Manabu Kinoshita , Naoto Tomita , Keiichiro Hattori , Jun Muto , Noriaki Kitamura Keita Kinoshita, and Kazuhiko Mishima*

Tirabrutinib in R/R PCNSL

Methods

- **Study Design**
  - Multi-center, retrospective observational study, 51 Japanese centers
- **Participants**
  - 161 patients with R/R PCNSL
- **Treatment**
  - Tirabrutinib monotherapy
- **Outcomes**
  - ORR, CR/CRu, DOR, PFS, OS, and TRAEs

Tirabrutinib in R/R PCNSL

Patient characteristics	
Median Age	71 years (range: 38–89)
Female vs. Male	42.2 vs. 57.8%
Histology	69.6% DLBCL vs. 12.4% other vs. 18% unknown
Median KPS	70 (range: 20–100)
Prior HD-MTX	95.7 %
Prior WBRT	34.2 %
Prior ASCT	4.3 %

Tirabrutinib in R/R PCNSL

Efficacy	
ORR	77%
CR/CRu	55.5%
Median PFS	11.8 months
CR in BTKi-pretreated	22% (2/9 pts)
1-Year PFS	50%
1-Year OS	77%

Adverse Events	
Rash any grade	10%
Neutropenia any grade	9%
Grade 3 or higher	25%
Treatment discontinuation	20%

CSF-ctDNA in DLBCL

576 Clinical Implications of CSF-Ctdna Positivity in Newly Diagnosed Diffuse Large B Cell Lymphoma in a Large Cohort

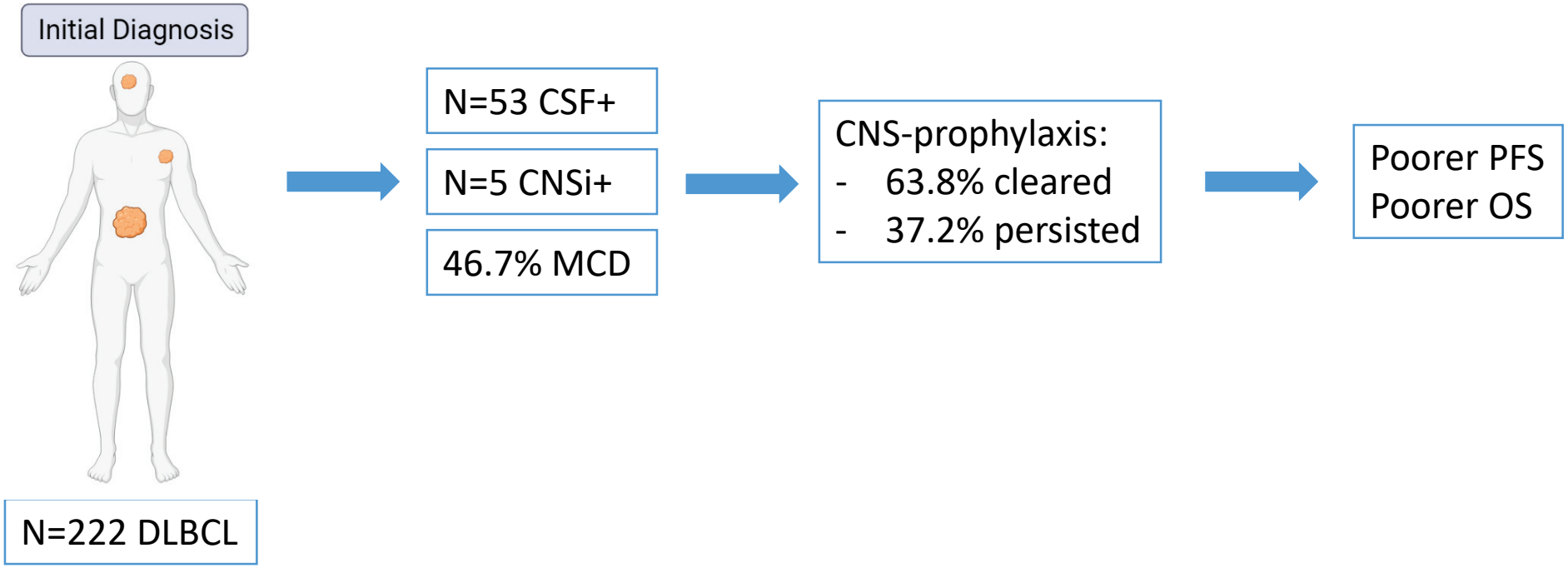
Jinhua Liang, *Yi-fan Wu, Jun-heng Liang, Yue Li, Xin-Yu Zhang, Hao-Rui Shen, Jiazhu Wu, Liu qing Zhu, Hua Yin, Li Wang, Jianyong Li and Xu Wei*

CSF-ctDNA in DLBCL

Methods:

- **Study Population**
  - 222 ND DLBCL patients with matched tissue, plasma, and CSF samples
- **Criteria for CSF-ctDNA Positivity (CSF+)**
  - Shared mutants between CSF-ctDNA and tissue
  - Canonical driver mutation in CSF-ctDNA when tissue unavailable
- **Treatment Regimens**
  - RCHOP-like or R-CGVP regimens, CNS prophylaxis per NCCN guidelines
- **Endpoints**
  - Prevalence of CSF+, genomic landscape, clinical correlations, and survival outcomes

CSF-ctDNA in DLBCL



→ CNS Relapse Prediction Sensitivity: 100%, Specificity: 78.2%

VIPOR in PCNSL/SCNSL

1724 A Pilot Study of Venetoclax, Ibrutinib, Prednisone, Obinutuzumab, and Lenalidomide (VIPOR) for Diffuse Large B-Cell Lymphoma Involving the Central Nervous System

Disha Dalela, *Rahul Lakhotia, Christopher Melani Stefania Pittaluga , James D. Phelan, Jagan R. Muppidi, Sarah Evans, Amynah Pradhan, Atekelt Tadese, Candis Morrison, Seth M. Steinberg, Elaine S. Jaffe, Louis M. Staudt, Wyndham H. Wilson and Mark Roschewski*

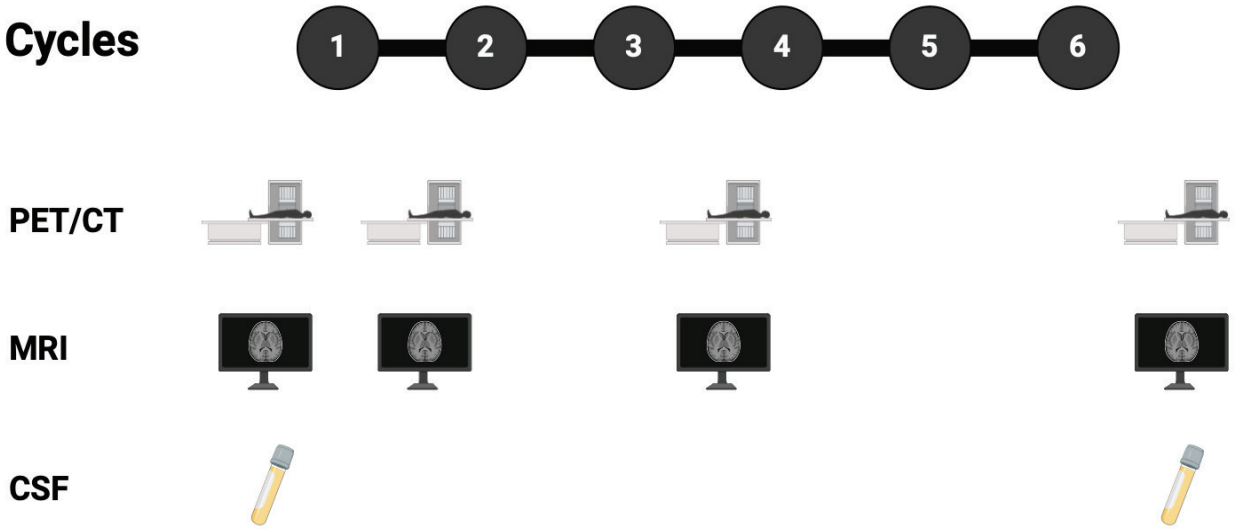
VIPOR in PCNSL/SCNSL

Key inclusion criteria

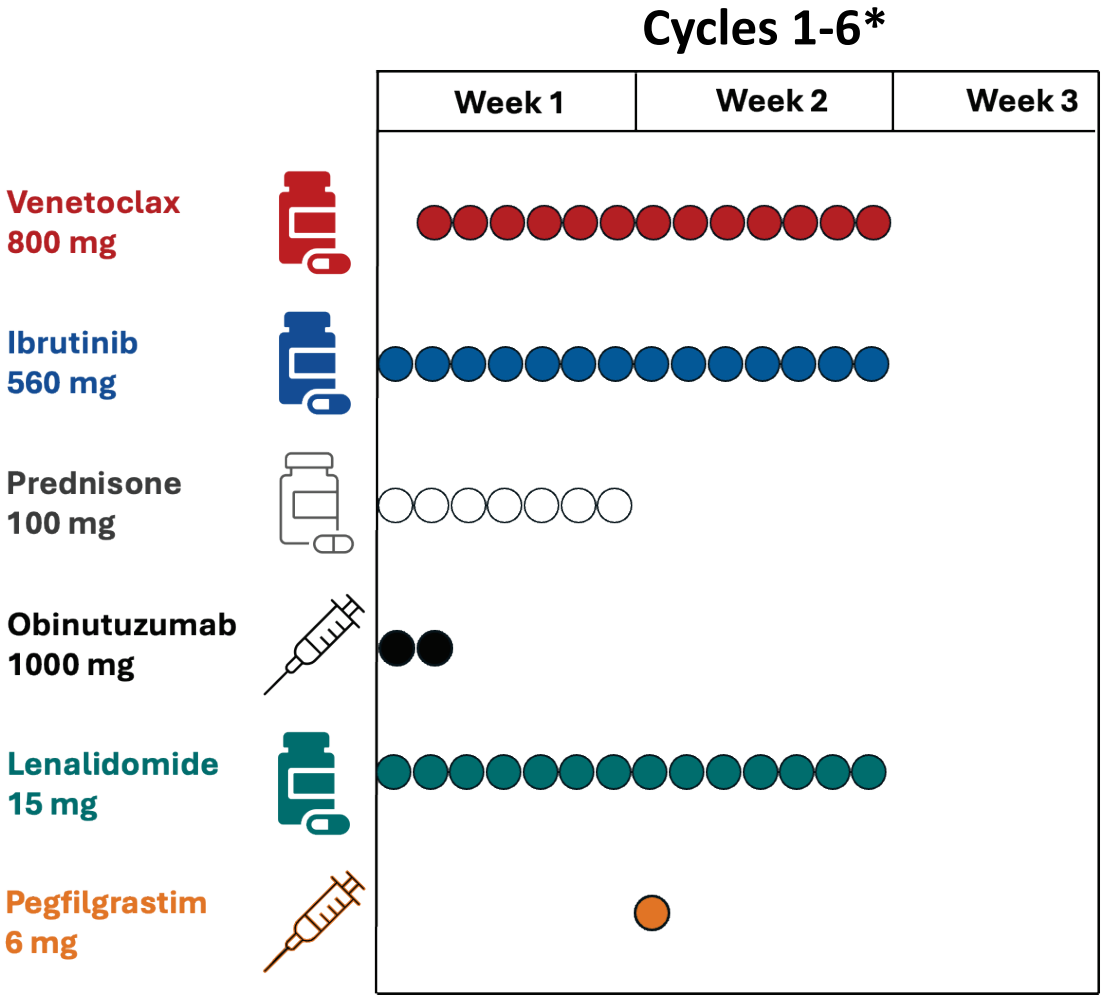
PCNSL or NonGCB DLBCL with CNS involvement

- Relapsed or refractory
- Untreated allowed if ineligible for methotrexate (age ≥70, effusions, renal dysfunction)

Prior BTKi use allowed



No maintenance or consolidation



*First 4 patients received nivolumab and lenalidomide in a 3-week window, followed by nivolumab on D1 of Cycles 1-6.

VIPOR in PCNSL/SCNSL

Characteristics	N = 14
Median Age (range)	66 (45-86)
Male sex	9 (64%)
Histology	
Primary CNS lymphoma	9 (64%)
HGBL-DH (*MYC*/*BCL6*)	1 (7%)
DLBCL, NOS (non-GCB)	4 (29%)
Prior lines of therapy, median	2 (1-6)
Prior BTK inhibitor	10 (72%)
Prior lenalidomide	2 (14%)
ECOG	
0 or 1	10 (72%)
2	3 (21%)
3	1 (7%)
Elevated lactate dehydrogenase	10 (72%)
IPI (N=5)	
0-1	0
2	2 (40%)
≥3	3 (60%)
IELSG risk (N=9)	
0-1 (low)	2 (22%)
2-3 (intermediate)	5 (56%)
4-5 (high)	2 (22%)
Leptomeningeal involvement	8 (57%)
Intraocular disease	1 (7%)

VIPOR in PCNSL/SCNSL

Adverse event category	Adverse event term	All grades (N [%])	Grade 3-4 (N [%])
General	Fatigue	4 [29]	1 [7]
	Headache	3 [21]	
Respiratory	Cough	2 [14]	
Gastrointestinal	Diarrhea	10 [71]	1 [7]
	Nausea and vomiting	4 [29]	
	Mucositis	3 [21]	
	Dyspepsia	3 [21]	
	Dehydration	2 [14]	1 [7]
	Drug induced liver injury	1 [7]	1 [7]
Hematologic	Thrombocytopenia	6 [43]	3 [21]
	Neutropenia	5 [36]	5 [36]
	Anemia	2 [14]	1 [7]
	Febrile neutropenia	1 [7]	1 [7]
Cardiovascular	Atrial fibrillation	2 [14]	
	Atrial flutter	2 [14]	
	Conduction disorder	1 [7]	1 [7]
	Syncope	1 [7]	1 [7]
Neurologic	Tremor	3 [21]	
	Fall	2 [14]	1 [7]
	Seizure	1 [7]	1 [7]
Dermatologic	Rash	4 [29]	
Infections	COVID-19	3 [21]	1 [7]
	Urinary tract infection	2 [14]	1 [7]
	Lung infection	1 [7]	1 [7]
	Sepsis	1 [7]	1 [7]
Metabolic	Hypokalemia	7 [50]	3 [21]

VIPOR in PCNSL/SCNSL

VIPOR in PCNSL/SCNSL

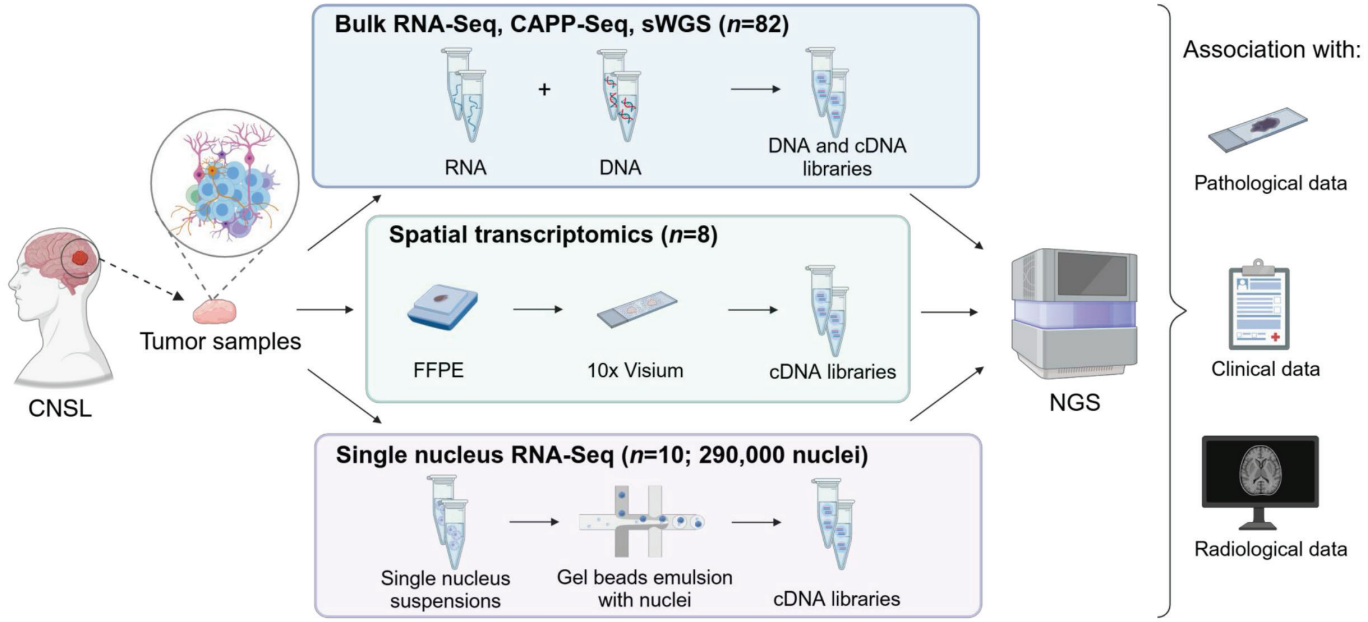
Bonus: Translationales Highlight

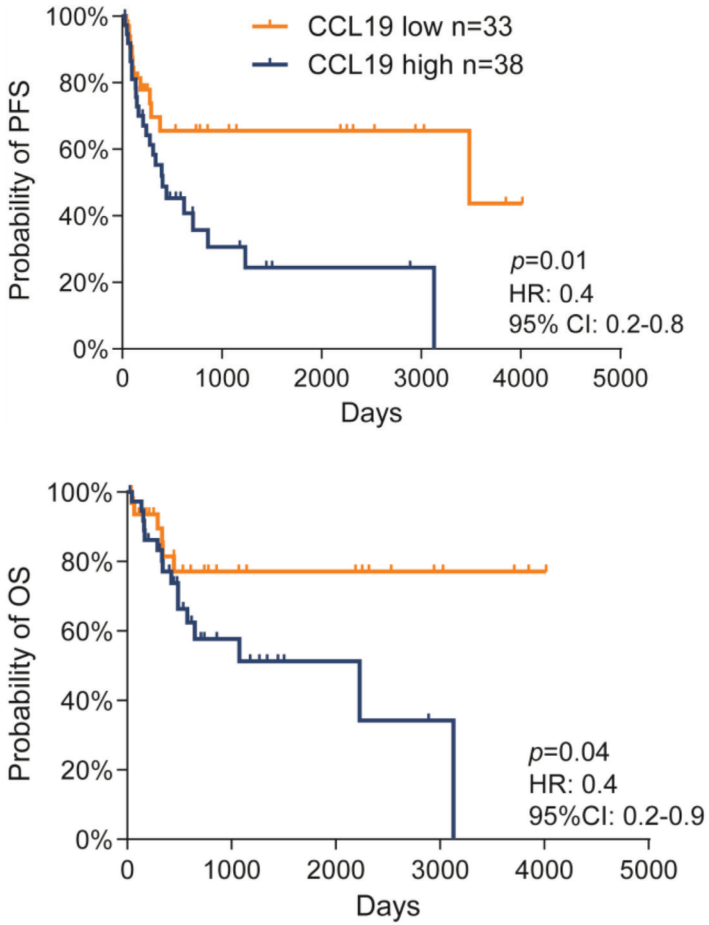
856 Modulation of the Tumor Microenvironment By CCL19 in Primary CNS Lymphomas

Julia C. Kuehn *Roman Sankowski Nicolas N. Neidert Elena Grabis, Jurik A. Mutter Stefan K. Alig Junyi Zhang, Christian Klingler Lavanya Ranganathan, Fabian Hummel, Sabine Bleul, Eliza M. Lauer Dieter Henrik Heiland Marco Prinz Katharina J. Müller Louisa von Baumgarten Justus Duyster Elisabeth Schorb Maximilian Diehn , Ash A. Alizadeh , Peter C. Reinacher, and Florian Scherer,*

CCL19 in CNSL

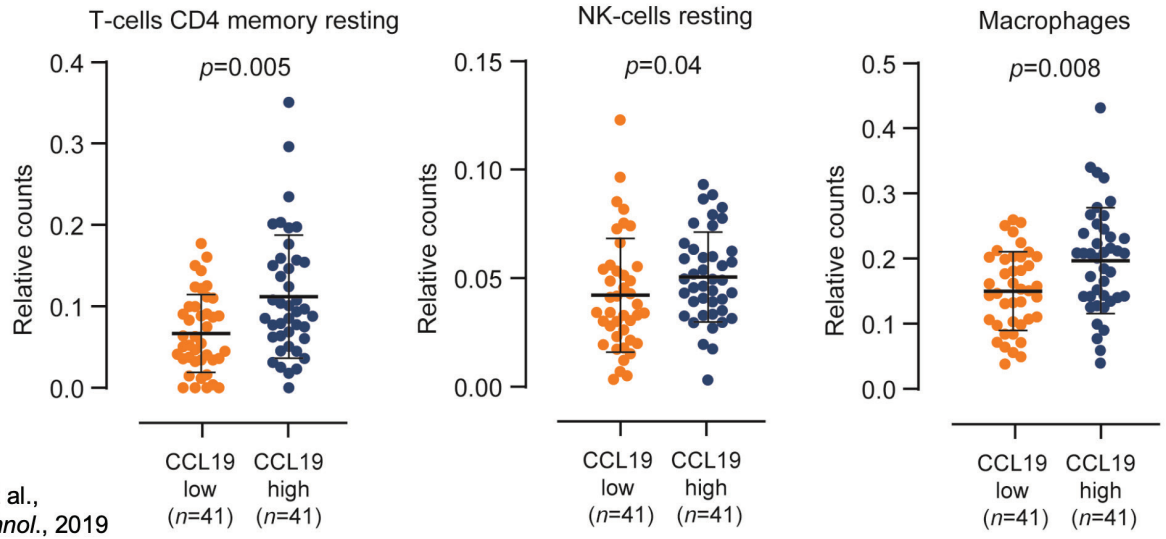
CCL19 expression is associated with adverse prognosis





CCL19 in CNSL

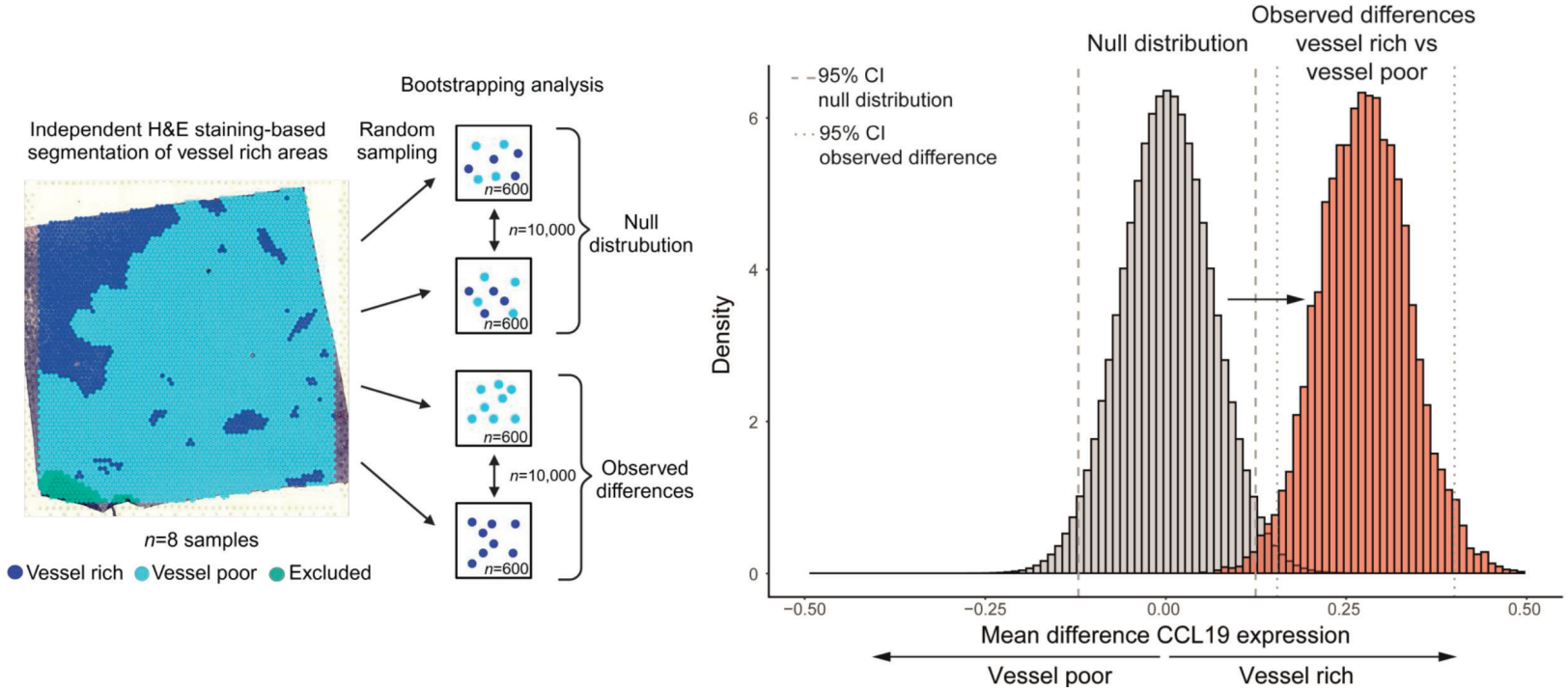
CCL19 is associated with a resting immune environment and derived from vessel-rich areas



Newman et al., *Nat Biotechnol.*, 2019

CCL19 in CNSL

CCL19 is associated with a resting immune environment and derived from vessel-rich areas



Take-Home-Messages

- Daten zu Wirksamkeit diverser BTK-Inhibitoren und Kombinationen
- Optimaler Einsatz von Checkpoint-Inhibitoren noch unklar (SCNSL vs PCNSL?)
- ZNS-Wirksamkeit von VIPOR
- ctDNA für Diagnostik und Therapiesteuerung
- Mechanistische Erkenntnisse für Entwicklung neuer Therapien (CCL19, TLR-pathway)

→ Keine Ergebnisse großer prospektiver Studien, dafür innovative Phase I/II Konzepte

Die Kurzpräsentationen sind online unter

www.lymphome.de/ash2024

Für den Inhalt verantwortlich:

Dr. med. Dr. med. univ. Stefan Habringer

Charité Universitätsmedizin Berlin

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Expert:innen berichten zu Lymphomen & Leukämien

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