Targeting IRAK4 as Novel Therapy in Primary CNS Lymphoma

Christopher D'Angelo, MD
Assistant Professor, Hematology/Oncology
Fred and Pamela Buffett Cancer Center
University of Nebraska Medical Center

University of Nebraska Medical Center℠

Disclosures

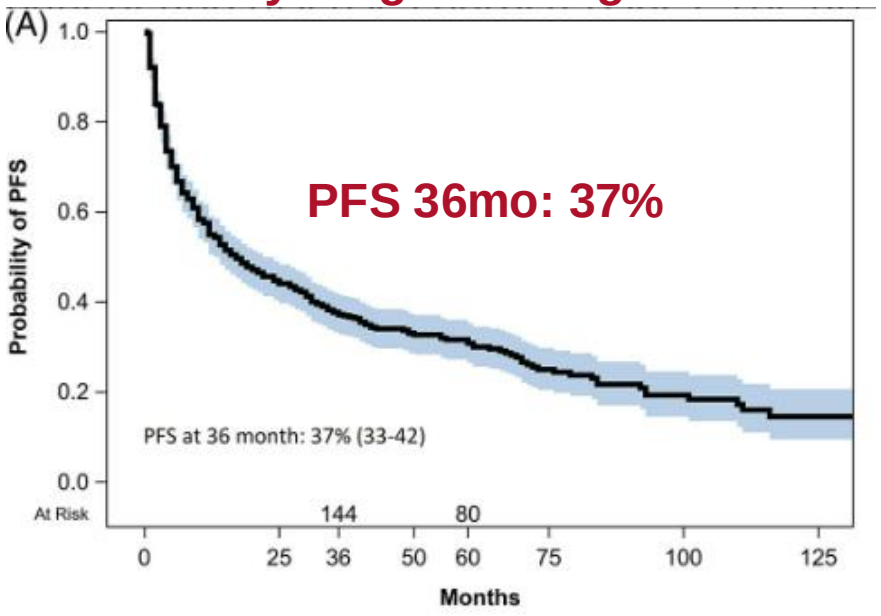
- Consulting: Abbvie, Genmab, Bristol Myers Squibb, Curis Inc
- Research: Bristol Myers Squibb, Abbvie, Genmab, Fate Therapeutics, Curis Inc

Objectives

- Discuss IRAK4 and the rationale for targeting IRAK4 in treating PCNSL
- Describe preliminary data on safety and efficacy for emavusertib + ibrutinib in r/r PCNSL resistant to BTKi

PCNSL Outcomes: Room for Improvement

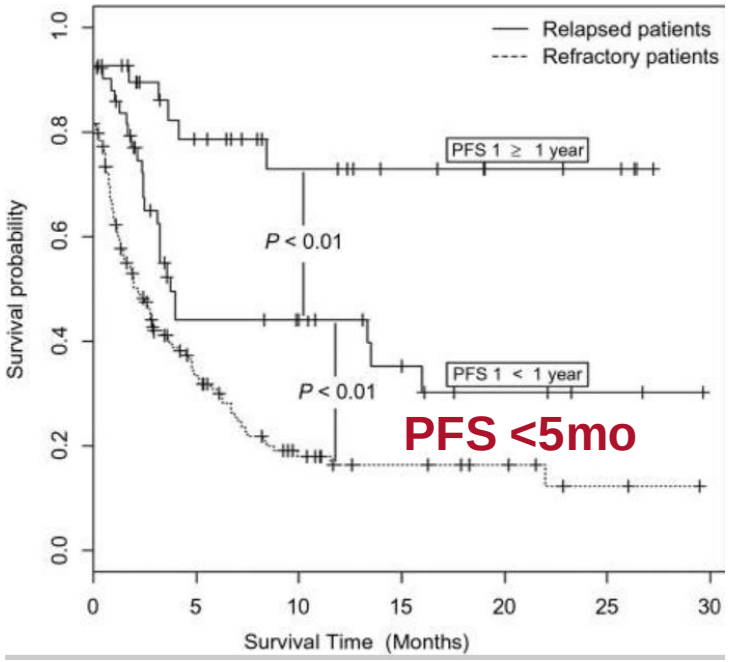
Newly Diagnosed Age >60



PFS 36mo: 37%

David et al, *AJH* 2023

Relapsed/Refractory



PFS <5mo

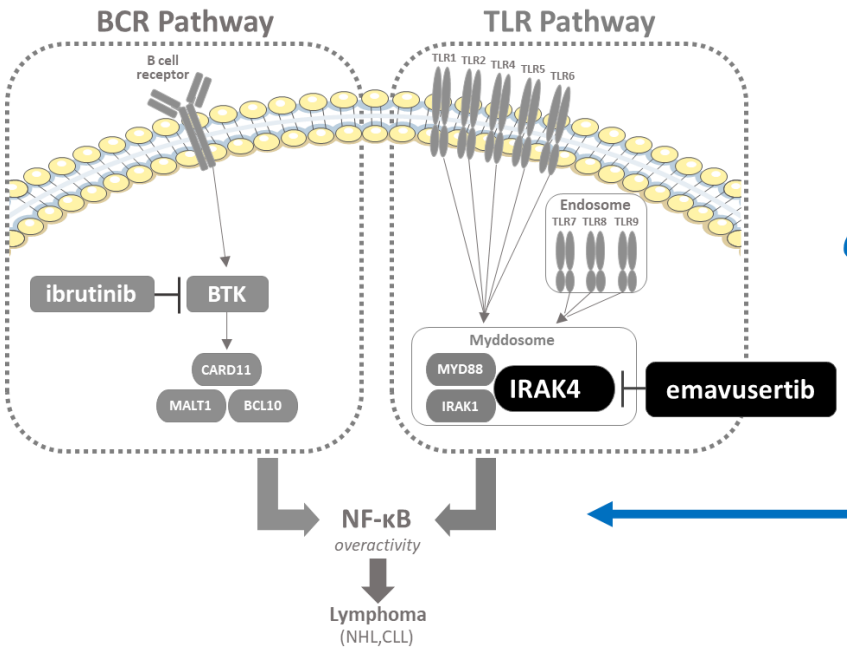
Lagner-Lemercier, Neuro Oncol, 2016

Relapsed/Refractory PCNSL Trials

Drug	ORR (CR)	PFS
Ibrutinib[1]	77% (39%)	4.6mo
Pomalidomide/dex[2]	48% (32%)	5.3mo
Temozolomide[3]	31% (25%)	2.8mo
revlimid-rituximab[4]	35% (25%)	7.8mo

[1]Grommes et al, *Cancer Discovery* 2017, [2]Tun et al, *Blood* 2019, [3]Reni et al, *Br J Cancer* 2007, [4]Ghesquieres et al, *Annal Oncology,* 2019

IRAK4 Signaling in Lymphoma



Two pathways drive NF-κB
(which drives B-cell lymphomas)

IRAK4i + BTKi
enables dual blockade of NF-κB

The“myddosome”: activates NF-kB and present in PCNSL
TME beyond cancer cells: astrocytes and immune cells

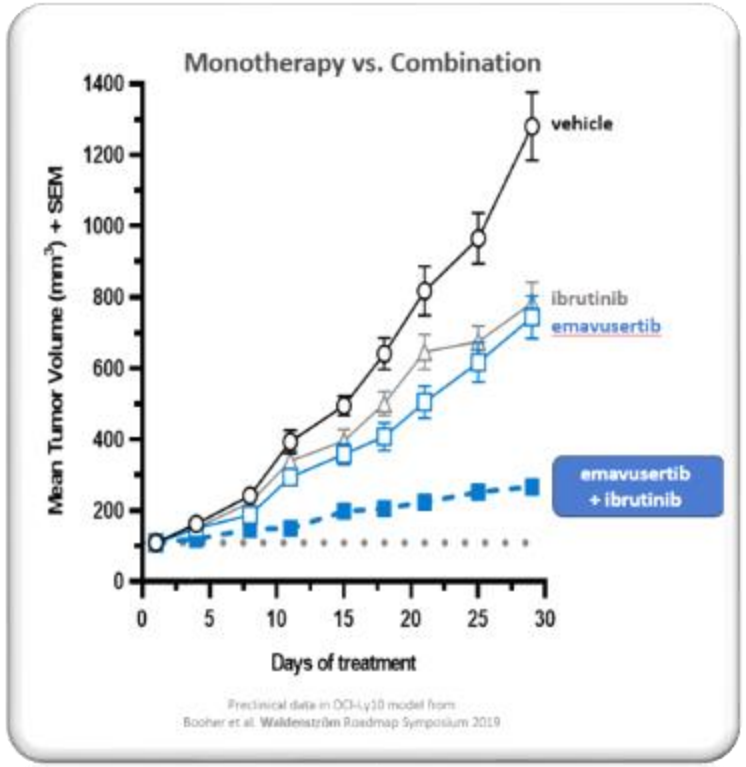
Von Roemling et al Clin Cancer Res 2023

IRAK4 is synergistic with BTKi

emavusertib + ibrutinib

blocking both BCR and TLR pathways has been demonstrated to be better than blocking either one alone

- IRAK4 inhibition synergizes with BTK inhibition to promote killing of **ABC-DLBCL**[1]
- Concurrent treatment with IRAKi and ibrutinib was significantly more potent in patient **CLL** cells than either drug alone[2]
- "Our data suggest IRAK4 as a novel treatment target for **CLL**; inhibition of IRAK4 blocks survival and proliferation of CLL cells" [3]

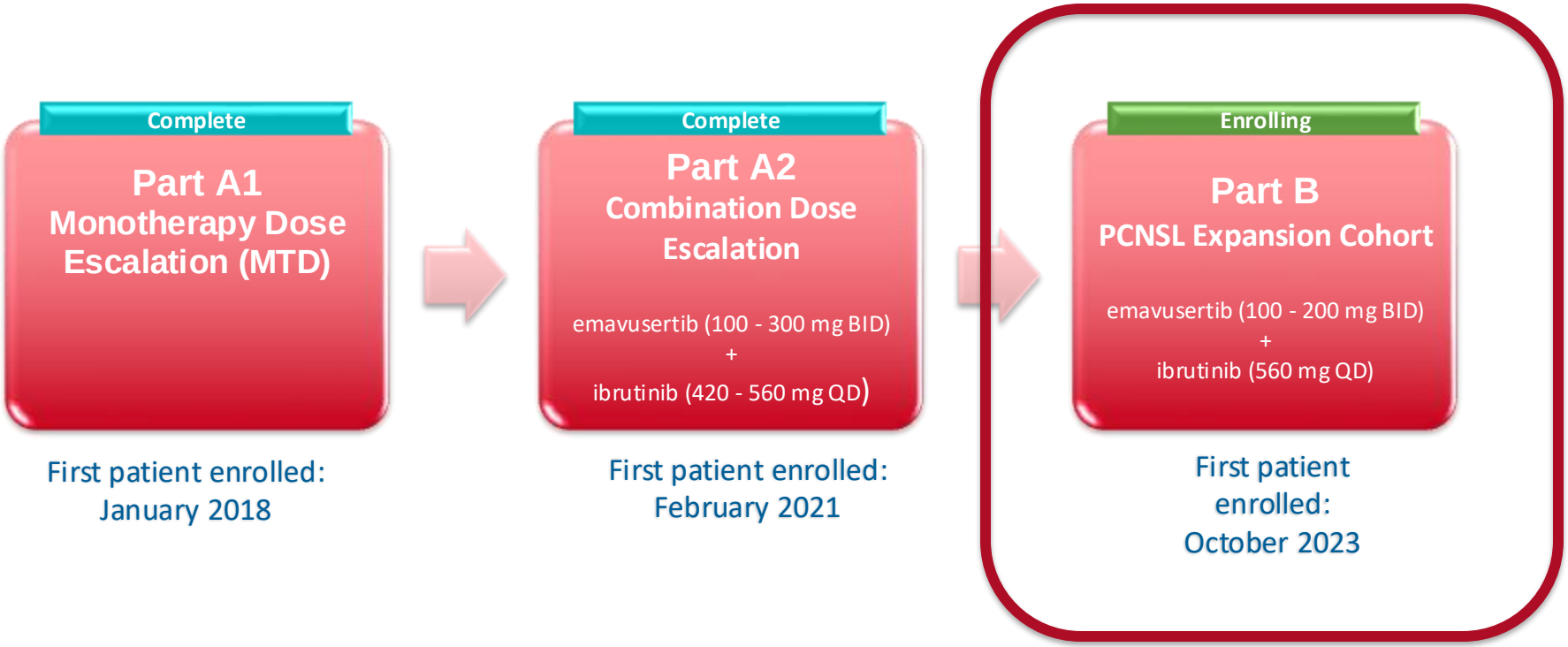


1) Kelly J Exp Med 2015, 2) Dadashian Ca Res 2019, 3) Giménez Leukemia 2020

TakeAim Lymphoma

Open-label expansion trial evaluating the safety, PK/PD, and clinical activity of emavusertib (CA-4948) + ibrutinib in R/R primary CNS lymphoma

NCT03328078



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TakeAim Lymphoma

Study Design: PCNSL Expansion

Patient Population

- R/R PCNSL exposed/refractory to BTKi
- Absence of residual grade ≥2 toxicity from prior therapy

Study Treatment
28-day Cycle

Emavusertib
100-200 mg BID

+

Ibrutinib
560 mg QD

Endpoints

Primary:

- Safety (AEs)

Secondary:

- ORR, DOR, DCR, PFS, OS, PK

Grommes, C. (2024). American Society of Clinical Oncology (ASCO) Annual Meeting, 2024.

TakeAim Lymphoma

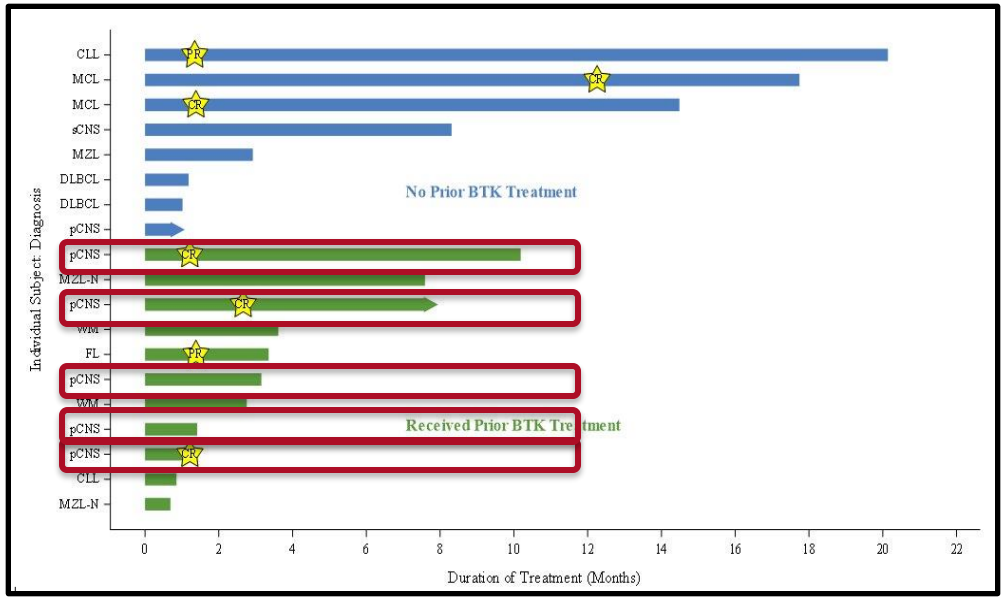
Well-tolerated and Manageable Adverse Event Profile at Multiple Dose Levels

Grade 3+ Treatment-Related Adverse Event Ocurred in >1 Patient	100 mg BID+IBR	200 mg BID+IBR	300 mg BID+IBR	Total
N (%)	**(N=2)**	**(N=10)**	**(N=7)**	**(N=19)**
# patients having grade 3+ TRAEs	1 (50)	7 (70)	6 (86)	14 (74)
Platelet count decreased		2 (20)	1 (14)	3 (16)
Alanine aminotransferase increased		1 (10)	1 (14)	2 (11)
Aspartate aminotransferase increased		1 (10)	1 (14)	2 (11)
Fatigue		1 (10)	1 (14)	2 (11)
Hyponatraemia		2 (20)		2 (11)
Lipase increased	1 (50)	1 (10)		2 (11)

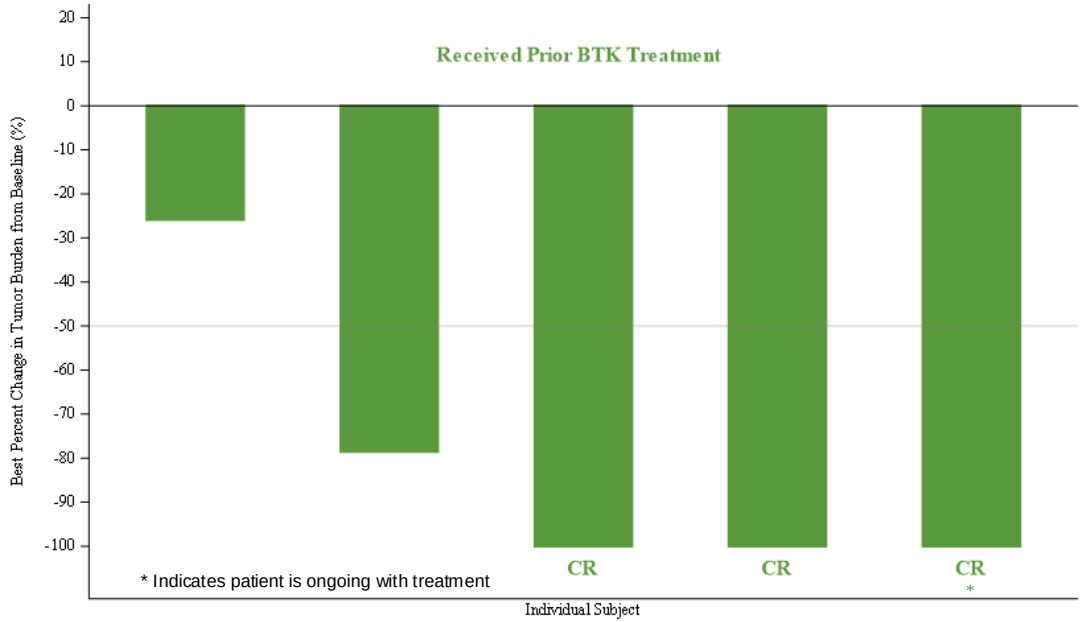
Grommes, C. (2024). Emavusertib (CA-4948) in Combination with Ibrutinib in Relapsed/Refractory Primary Central Nervous System Lymphoma (R/R PCNSL) Patient. Poster presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, 2024.

Preliminary Efficacy Results in PCNSL Population

NHL Population: Duration

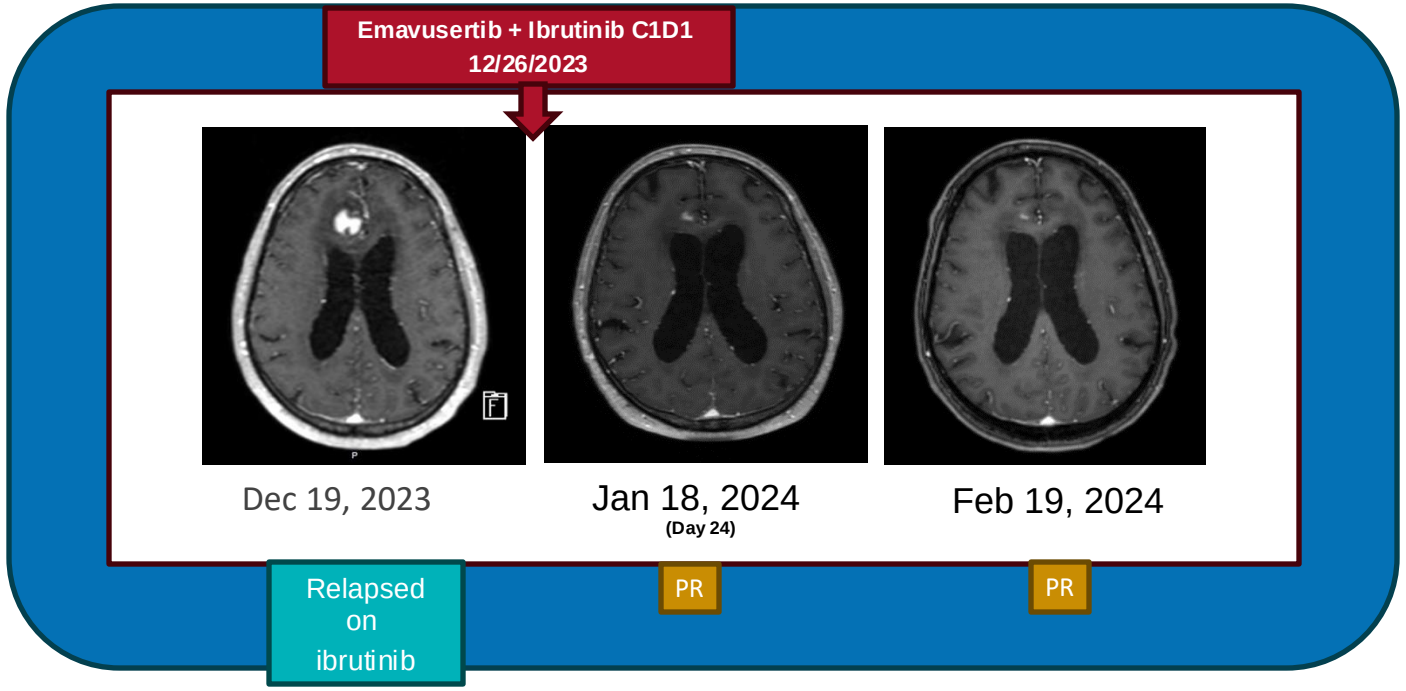


PCNSL Population



Grommes, C. (2023). American Society of Hematology (ASH) Annual Meeting, 2023.

PCNSL patient achieved 95.3% PR on ibrutinib + emavusertib



as of April 1, 2024

Conclusions

- R/R PCNSL carries a poor prognosis
- IRAK4 signaling is increased in PCNSL, targeted inhibition with emavusertib + ibrutinib shows strong preclinical efficacy
- Preliminary data of combo IRAK4 + BTKi demonstrates safety, with encouraging responses in BTKi exposed/refractory
- Study is actively enrolling in PCNSL-specific expansion

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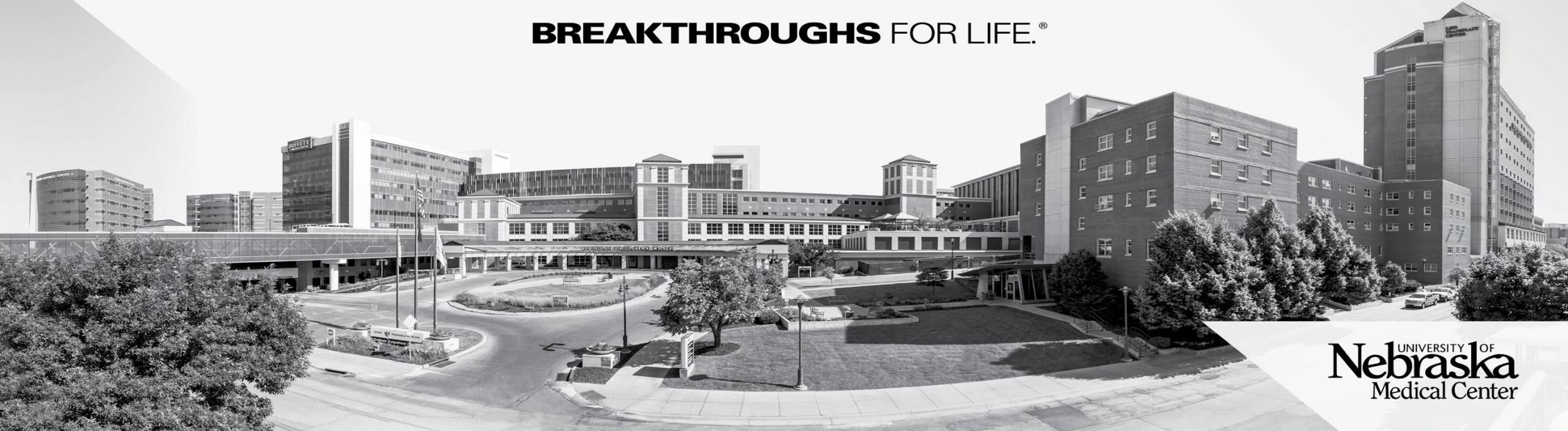

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