Prevention of CNS Progression in Diffuse Large B-cell Lymphoma

19th International Ultmann Chicago Lymphoma Symposium
April 30, 2022

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Disclosures

- I have no personal financial relationships or interests with any proprietary entity producing healthcare goods/or services
- I have done consulting work for:
  - BeiGene: Clinical trial steering committee, Scientific Advisory Board
  - Janssen/Pharmacyclics: Scientific Advisory Board
  - Kite: Scientific Advisory Board
  - Morphosys: Advisory Board
  - TG Therapeutics: Advisory Board
- I have received grants from:
  - Lymphoma Research Foundation
  - V foundation
  - ORIEN Network
- I do have research funding from below:
  - AbbVie: investigator initiated trial
  - AbbVie/Roche/Genentech: Institutional PI on industry sponsored trial
  - Infinity: Institutional PI on industry sponsored trial
  - Acerta/AstraZeneca: Institutional PI on industry sponsored trial
  - TG therapeutics: Institutional PI on industry sponsored trial
  - BeiGene: Institutional PI on industry sponsored trial
  - Kite: Institutional PI on industry sponsored trial
  - Xencor: Institutional PI on industry sponsored trial
  - SeaGen: Institutional PI on industry sponsored trial

Outline

Review known risks of systemic DLBCL progression to CNS

Recent retrospective studies

Future directions

NOTE:
This talk is NOT about
Primary CNS lymphoma
OR
DLBCL presentations with concurrent systemic and CNS involvement
OR
Relapsed disease.

Audience Response

Case review

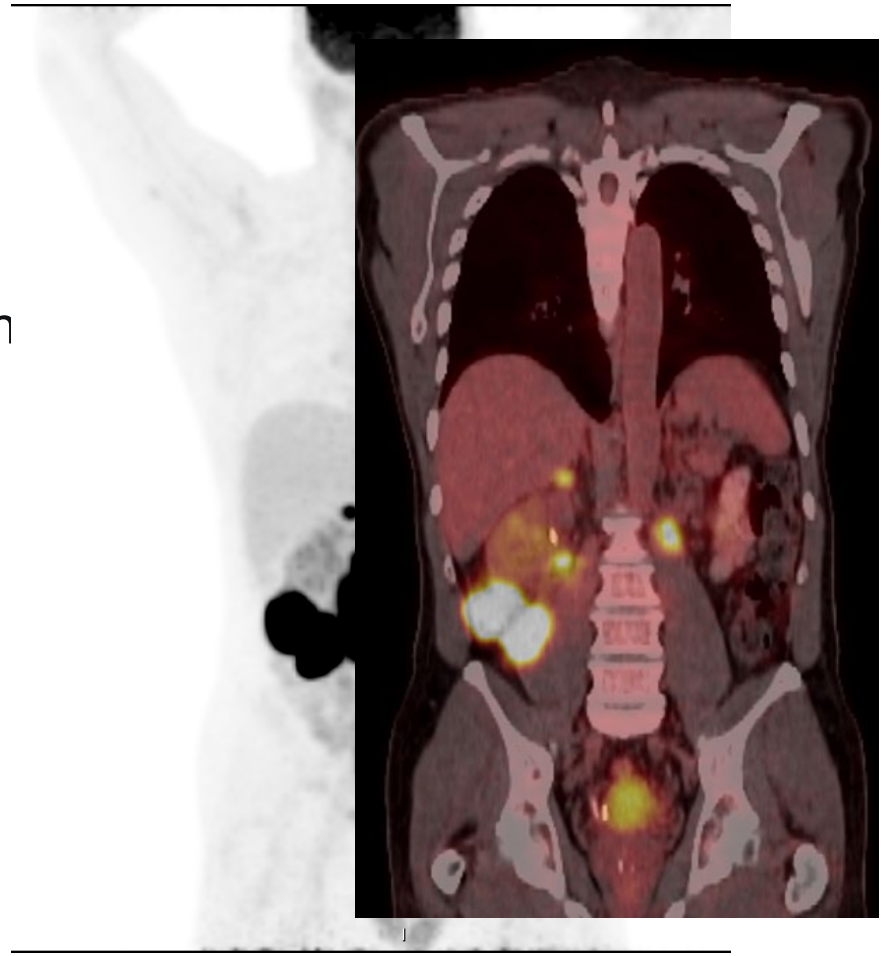
61 yo M with new diagnosis of DLBCL, non-GCB by immunohistochemistry presents with abdominal pain
PET shows bulky mesenteric mass with

- Soft tissue implants near duodenum
- Perinephric involvement
- Psoas muscle involvement which extends to kidney
- Ureteral obstruction

There are no alterations of myc or BCL6 or BCL2 translocation
Pt is planned for RCHOP. His CNS IPI is 5.

What would you recommend for CNS Prophylaxis:

A. High dose, IV MTX (3.5mg/m2) after intercalated between chemotherapy after C2, C4, and C6
B. Two doses of high dose MTX after C6
C. Intrathecal MTX with C2, C4, and C6
D. IT MTX with C2 and 4 and IV HD MTX after C6
E. No prophylaxis



The Problem:

Relapse into the CNS (brain and spinal cord) is a devastating event

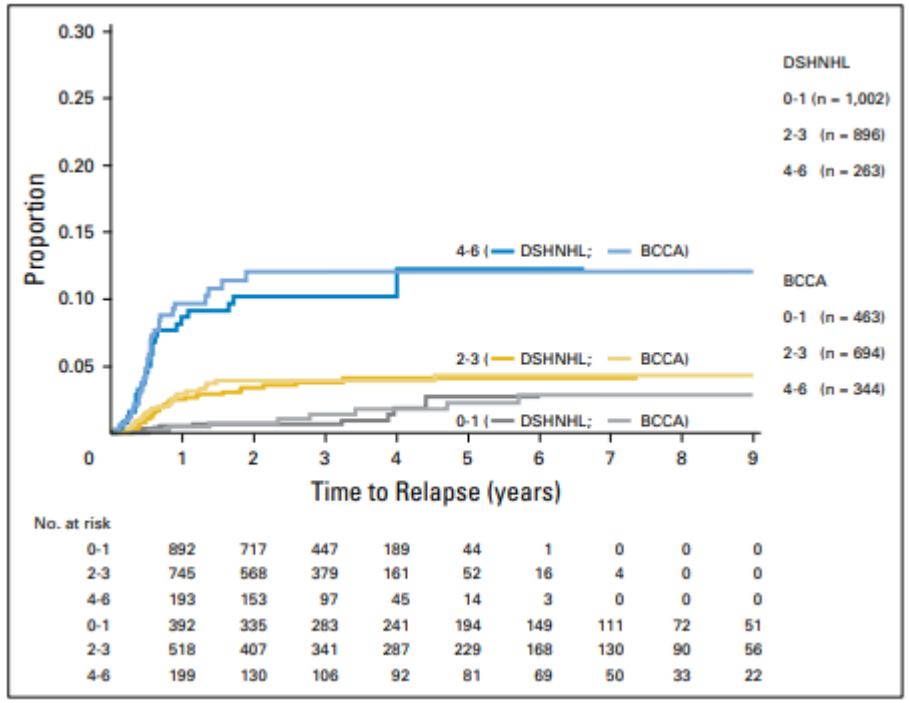
We know of risk factors for CNS progression

CNS-IPI

- Developed from German studies
- Validated by BCCA database
- Consists of:
  - Age >60
  - LDH > Normal
  - ECOG PS >1
  - Stage III/IV disease
  - 2 or more extranodal sites
  - Kidney/Adrenal involvement

Double Hit ? Double expresser

Testis also



Schmitz N, et al, JCO, 2016, 34(26):3150-3156

The Problem:

Use of MTX as a prophylaxis

RCHOP (or R-EPOCH) inadequately enters the CNS
(Rituximab does some)

Methotrexate is active in primary CNS lymphoma and is well known to cross the blood brain barrier

Multiple groups have recommend prophylaxis with MTX for high risk CNS-IPI patients

But when to give, how to give, and what dose to give is all a matter of debate.

And, Does it work?

Therefore, recently, multiple groups have evaluated various aspects of CNS prophylaxis for DLBCL including:

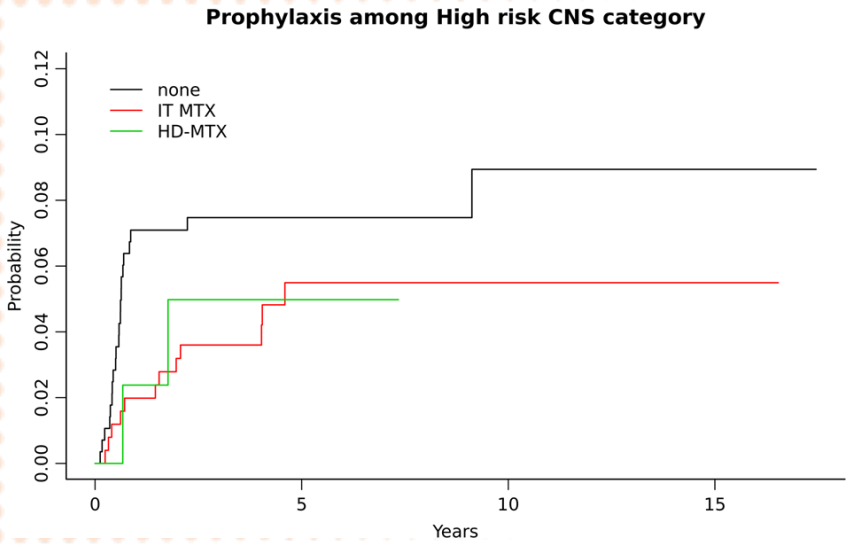
- Intravenous high dose vs. Intrathecal
- Intercalated vs. end of treatment
- Older patients
- Historical data
- Prophylaxis vs. no Prophylaxis

Retrospective analysis

Single institution comparisons

Memorial Sloan Kettering

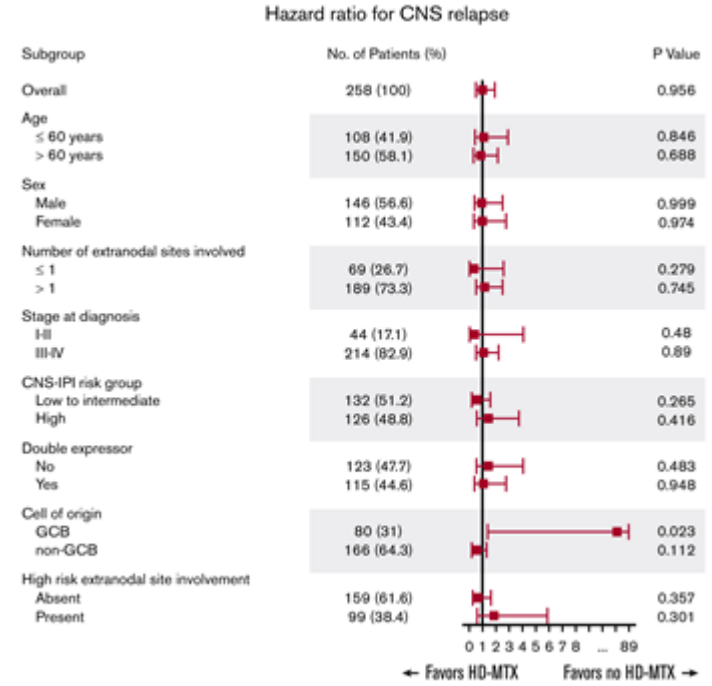
- Retrospective with RCHOP
- 585 high risk patients included
  - IT MTX n=253
  - HD MTX n=42
  - No prophy n=290
- Differences between groups
  - Older, poor PS



Bobillo S, et al. Blood Cancer J 2021

Asan Medical Center (Korea)

- Retrospective with RCHOP
- 258 high risk patients included
  - HD MTX n=128
  - No prophy n=130
- Not a lot of differences between groups



Jeong H et al, Blood Adv 2021

Retrospective analysis

During chemotherapy or after?

Multicenter, US collaboration of 47 centers

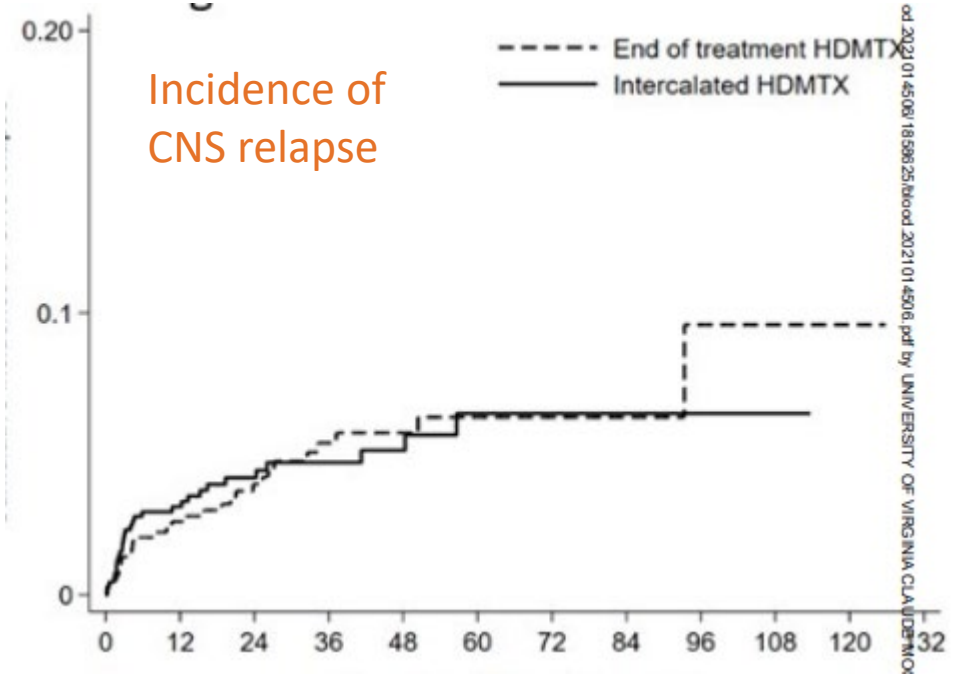
All patients received RCHOP and HD MTX and compared where MTX was administered

- Intercalated vs. end of treatment

1384 patients identified (intercalated 749; EOT 635)

- CNS-IPI 4-6: 44.2%
- CNS-IPI 2-3: 40.9%
- CNS-IPI 0-1: 14.9%
- NOTE: IT MTX was allowed and EOT had more IT MTX

Utilized a landmark analysis to account for those patients in the EOT group that would not have seen HD MTX



Also found more toxicity with intercalated and more RCHOP delays

OS was better for EOT (in non-landmark analysis) ? Due to ineffective RCHOP delivery

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Wilson, M et al Blood 2022

Retrospective analysis

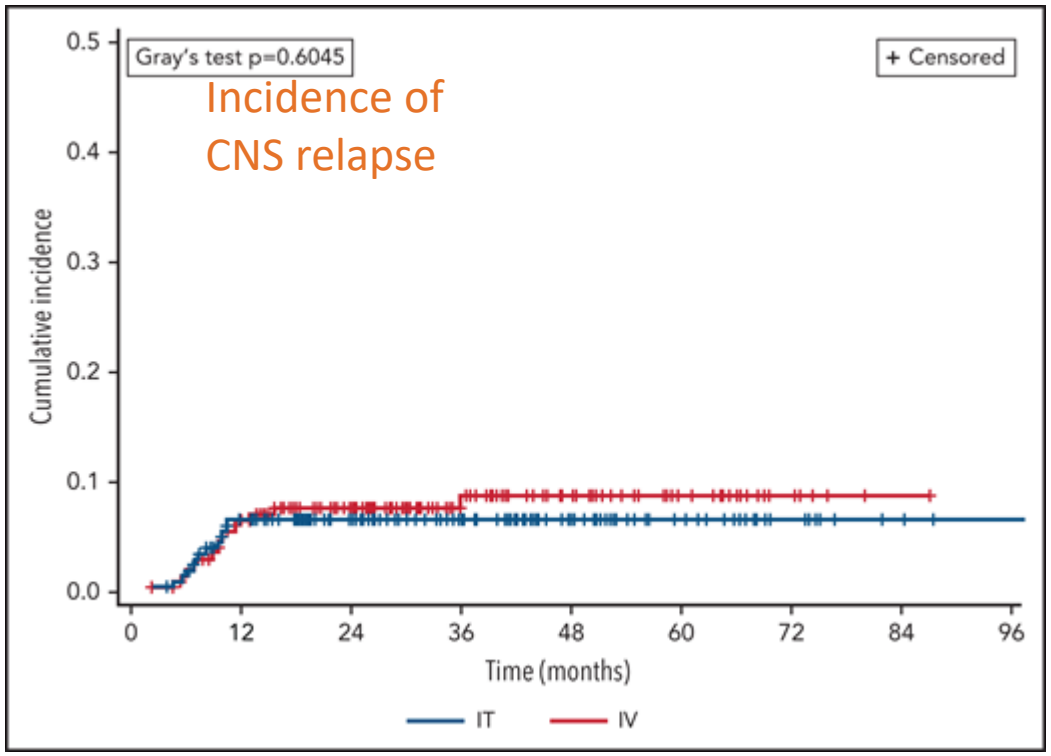
Intrathecal vs. HD MTX?

Multicenter, US collaboration of 21 centers

All patients received RCHOP or R-EPOCH

1130 patients identified (Intrathecal 894; HD IV 236)

- CNS-IPI >6: 30%
- CNS-IPI 4-5: 43%
- CNS-IPI 2-3: 18%
- CNS-IPI 0-1: 1%
- Differences in groups, Age, >2 EN sites, HGBCL, EPOCH admin, renal impairment



Matching using propensity score did not change outcomes

HD MTX more likely to have toxicity

Orellana-Noia, V et al Blood 2022

Retrospective analysis

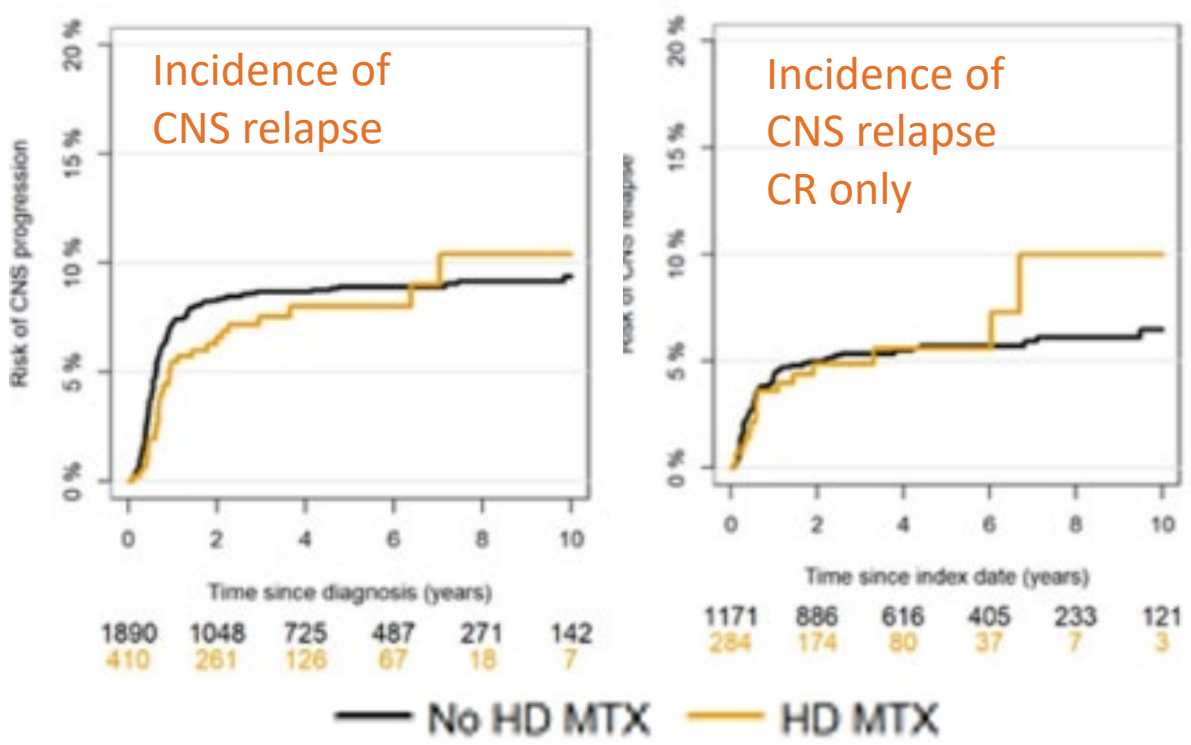
High dose MTX

Multicenter, international collaboration of 21 centers

All high risk patients with DLBCL (CNS-IPI 4-6, HGBCL, and testis/breast lymphoma)

2300 identified, 1455 achieved CR

- CNS-IPI 4-6: 87%
- HD MTX: 410 Pts (145 with IT MTX)
- IT MTX: 435
- No prophy: 1455



Lewis et al, ASH 2021, abstract 181

Retrospective analysis

Older patients?

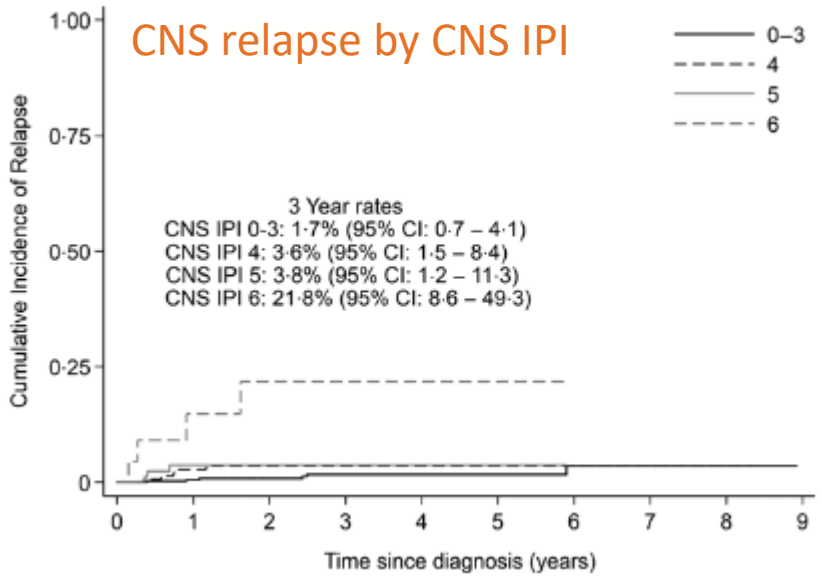
Multicenter, UK collaboration of 8 centers

All patients received RCHOP therapy and >70 yo

690 patients identified

- CNS-IPI 4-6: 39.7%
- CNS-IPI 2-3: 39.7%
- CNS-IPI 0-1: 12%

IT Prophy given 14.3%,
HD MTX given 4.5%,
no prophy 81.2%



No improvement in CNS relapse with IT MTX

WAS an increased risk of infection related admission with IT MTX

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Eyre TA et al, BJH 2019

Current State

Summary

Can we prevent CNS progression with Methotrexate?

- Single institution, retrospective studies comparing suggest no difference in CNS relapse rates between treatment and no treatment
- OLDER patients do not benefit from IT MTX and maybe harmed
- High dose Intravenous methotrexate is safer at the end of treatment
    - We don’t prevent early relapse.
- Intrathecal Methotrexte is safer and equally effective as High dose Methotrexate
- Is the incidence of CNS relapse any different than the original CNS-IPI that had limited use of prophylaxis???

Current State

My two cents (for what it's worth)

The role of Methotrexate to prevent CNS relapse is limited

We can predict a risk for CNS relapse but it is unclear if we prevent it

Prospective study is wrought with complications:

- Require high numbers of patients to power for low numbers of events, even if limiting to high risk
- High risk patients often need rapid treatment and are hard to enroll on study
- Competes with other more interesting study (novel agents)

I typically will use CNS prophylaxis only for testis or kidney/adrenal involvement AND if the Pt can tolerate it (not with chronic kidney disease and not if over 70 years)

- If giving high dose, intravenous MTX, would do at end of RCHOP treatment
- Intrathecal therapy is limited now

Future State

It's likely that methotrexate is not adequately preventing CNS recurrence

Better treatment of systemic disease is likely to improve CNS recurrence rates also

Other agents do enter the CNS and have been studied in DLBCL and with RCHOP

- Ibrutinib (PHEONIX)
- Lenalidomide (R2-CHOP)
- How does Polatuzumab-vedotin enter into this picture??????

Better classification and detection methods may help identify the highest risk patients

- DLBCL clusters (also direct therapy better?)
- Circulating tumor DNA
- Cerebral spinal fluid tumor DNA

QUESTIONS

Thank you!

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