Primary CNS Lymphoma

Las Vegas-- March 16, 2018
Disclosures

- Advisory Board: Forty-Seven, Inc. Celltrion
- I will discuss off-label use of temozolomide, lenalidomide and ibrutinib.
Outline

- Demographics
- What do we know about the unique markers/makeup of PCNSL?
- PCNSL -- prognosticating outcome
- Presentation
- Workup
- Treatment (usual vs. special circumstances)
- AutoSCTx in CR1 or not?
- Treatment of Relapsed disease
Demographics

- 3% of primary cerebral tumors
- 2-3% of all cases of NHL.
- SEER data show incidence may be increasing among patients >65, with pts >75 having the highest incidental risk.
- 1900 new cases per year in U.S.
- Limited prospective and/or randomized data to guide its therapy.
- Historically associated with a poor prognosis.
- Accumulation of recent prospective phase I/II results, and retrospective series demonstrate reproducible improvements in outcomes for patients with PCNSL and SCNSL.
Sites of PCNSL

Multiple lesions 34%

13% 14% <1% 44% 6%
Sites of PCNSL

- Multiple lesions: 34%
- Deep lesions: 40%
Sites of PCNSL

- Multiple lesions: 34%
- Deep lesions: 40%
- Sites:
  - 44%: Frontal region
  - 28%: Temporal region
  - 14%: Occipital region
  - 6%: Parietal region
  - <1%: Other regions
Risk Factors

- Acquired or congenital immunodeficiency states (WAS, AT, SCID, CVID—4% lifetime risk)
- Renal transplant 1-2% lifetime risk
- 2-7% cardiac, lung, liver transplant—association with T-cell specific immunodeficiency (mycophenolate)
- AIDS-defining illness, assoc. with very low CD4 count (<50cells/μL)—nearly 100% assoc w/EBV
Incidence Trend PCNSL 1980-2008

Rate by gender/race

Rate by age at dx

Rel. survival by age group

By gender/race for <50yo

By gender/race for >50
The changing incidence of primary central nervous system lymphoma is driven primarily by the changing incidence in young and middle-aged men and differs from time trends in systemic diffuse large B-cell non-Hodgkin's lymphoma.
The changing incidence of primary central nervous system lymphoma is driven primarily by the changing incidence in young and middle-aged men and differs from time trends in systemic diffuse large B-cell non-Hodgkin's lymphoma.
PCNSL must be considered a “whole brain disease”
Characteristic radiographic features of PCNSL on magnetic resonance imaging.

Histology

- DLBCL CD20+ 95%
- T-cell PCNSL 2%, Burkitt, LB, intraparenchymal MZL.
- 20% present with intra-ocular involvement.
  - IOL progresses to CNSL in 80% cases, mandating staging procedures commensurate with risk.
Schematic representation of our hypothesis, developed to explain the histogenesis of PCNSL, taking into consideration the time of B-cell arrest and the corresponding antigen expression.

<table>
<thead>
<tr>
<th>Germinal center</th>
<th>After GC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>Late</td>
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</tbody>
</table>

- **CD10**: Early 10-20%, Late 50-80%
- **Bcl-6**: Early 50-80%, Late 95%
- **MUM1**: Early 95%
- **CD138**: Late

**PCNSL**

**Systemic DLBCL**

Sophie Camilleri-Broët et al. Blood 2006;107:190-196

©2006 by American Society of Hematology
BCL6 expression influences outcome in patients treated on CALGB 50202
PCNSL

- Late germinal center or post-germinal center lymphoid cells that show very distinct characteristics that separate them from nodal DLBCLs.
ABC-like immunophenotype

- 95% stain for MUM-1, consistent with overlapping features of germinal center and activated B-cell phenotypes.
Comparison of overall survival rates for patients with PCNSL or systemic DLBCL expressing ABC phenotypes.

Camilleri PCNSL cohort 83 patients, OS compared to 240 patients with systemic DLBCL –96.4% ABC

(previously presented by Rosenwald et al, NEJM. 2002;346: 1937-1947.)

Sophie Camilleri-Broët et al. Blood 2006;107:190-196
Molecular genetics

- 3 genome wide analyses using whole genome sequencing
- Identify alterations of NF-kB pathways, especially through somatic mutations of MYD88 (leu265pro 38-50%) and CD79B (20%)
  - Bruno et al. Oncotarget 2014;5:5065-5075
  - Vater et al. Leukemia 2014
Oncogenic survival signaling components in PCNSL

Activation of TLR/MYD88 pathway may directly contribute to pro-survival signaling directly via NFkB as well as via the enhanced production of IL-10 which itself contributes to survival signals via the JAK/STAT pathway.
Presentation

- Neuroanatomic lesion location determines clinical presentation
  - >60% have cognitive, motor or constitutional sx
  - 30% have visual sx at presentation
  - 20% have seizures.
  - Concomitant leptomeningeal disease 15-20% typically asx.
CT/MRI findings suspicious for PCNSL

Withhold corticosteroids
Chest x-ray, CT: chest, abdomen, pelvis, testicular ultrasound
CBC, HIV, LDH

SLE and lumbar puncture with cytology and flow cytometry

+ Cells in vitreous
  Vitrectomy
  - Lymphoma
    Brain biopsy
    - PCNSL
      Diagnosis - appropriate therapy
  + Lymphoma
  + PCNSL

+ CSF lymphoma

- CSF and SLE
  Brain biopsy
  + PCNSL
  - PCNSL
  Diagnosis - appropriate therapy

Liver function tests
Creatinine clearance
Spinal MRI
Assess cognitive function (MMSE)

Corticosteroids if necessary for symptom control
Definitive treatment of PCNSL
Prognosis

- IELSG parameters:
  - Age >60*
  - ECOG >1
  - LDH > ULN
  - High CSF protein
  - Tumor location in BG, periventricular, brainstem/cerebellum

<table>
<thead>
<tr>
<th># RF</th>
<th>2Y OS</th>
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<tr>
<td>0-1</td>
<td>80%</td>
</tr>
<tr>
<td>2-3</td>
<td>48%</td>
</tr>
<tr>
<td>4-5</td>
<td>15%</td>
</tr>
</tbody>
</table>
Therapy and outcomes of primary central nervous system lymphoma in the United States: analysis of the National Cancer Database

by Jaleh Fallah, Lindor Qunaj, and Adam J. Olszewski

BloodAdv
Volume 1(2):112-121
December 13, 2016
Survival of patients with PNCSL, stratified by treatment modality

Use of chemotherapy and radiation for management of PCNSL. (A) Matrix plot illustrating proportions of patients receiving chemotherapy and/or radiation therapy; percentages indicating cases treated with unspecified chemotherapy were omitted for clarity.

OS outcomes in PCSNL. (A) Survival in the entire cohort (2004-2012).

Whole Brain Irradiation

Utility is limited by

- Insufficient local control of disease
- Dissemination of cells within the CSF circulation (outside radiation field)
- Detrimental effects of XRT on brain function.

- Single agent therapy with WBRT ORR 90%, but OS 11.6 mo with >60% of patients with progression within the irradiated field.
Neurotoxicity

- **Risk Factors:** age >60, WBRT or WBRT + chemotherapy
- **Four domains are most sensitive to disease and treatment**
  - Attention
  - Executive functions
  - Memory
  - Psychomotor speed
  - IPCG Cognitive Battery has been developed for incorporation into prospective clinical trials.
- **Lower doses— prophylactic WBRT at 30Gy also produces significant neurotoxicity.**
Radiation Toxicity

- Acute Adverse Effects- alopecia, erythema and dry desquamation of the scalp. Some experience fatigue, headache and inflammation of the external auditory canal or middle ear.
- Patients requiring treatment of the eye are likely to experience conjunctival irritation and dry eye.
- These acute effects typically resolve within 6 – 8 weeks of completion of WBRT.
Radiation Toxicity

- Late adverse effects: neurocognitive decline, sensorineural hearing loss, permanent alopecia
- Those whose eyes are treated- cataracts, chronic dry eye
- The risk of neurocognitive dysfunction increases with age, total RT dose and co-administration of chemotherapy
Can we lower the dose of WBRT?

- Combined modality therapy with reduced WBRT
  - Multicenter, phase 2
  - N=52
  - Median age = 60
  - MTX 3.5mg/m2; vincristine;procarbazine+ rituximab (R-MPV) followed by WBRT (23.4Gy if CR or 45 Gy if <CR followed by Ara-C for 5-7 cycles
  - CR = 60%
  - 2 yr PFS = 77%; median PFS = 3 years; median OS = 6.6 years
  - Neuropsychological function “relatively stable”
  - Randomized trial (RTOG 1114) completed

Can we Eliminate WBRT?

Randomisation

First-line chemotherapy based on high-dose methotrexate

- Complete response: Consolidating whole brain radiotherapy
- No complete response: Rescue whole brain radiotherapy
- Complete response: Watch and wait
- No complete response: High-dose cytarabine
# Treatment Regimens for PCNSL

<table>
<thead>
<tr>
<th>Study (#pt)</th>
<th>Regimen</th>
<th>ORR</th>
<th>Median PFS (mo)</th>
<th>Median OS (mo)</th>
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<tbody>
<tr>
<td>WBRT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelson et al, 1992 (n=14)</td>
<td>WBRT 40GY +20Gy boost</td>
<td>100%</td>
<td>MA</td>
<td>12.2</td>
</tr>
<tr>
<td>MTX monotx</td>
<td></td>
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<td></td>
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<tr>
<td>Batchelor, 2003 (N=23)</td>
<td>MTX 8gm/m2</td>
<td>74%</td>
<td>12.8mo</td>
<td>&gt;23</td>
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<tr>
<td>Herrlinger, 2005</td>
<td>Mtx 8gm/m2</td>
<td>35%</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Combined modality</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ferreri 2009</td>
<td>Mtx 3.5gm/m2 +WBRT</td>
<td>41%</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Ferreri 2009</td>
<td>Mtx 3.5gm/m2 +HIDAC +WBRT</td>
<td>69%</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>DeAngelis 2002</td>
<td>MPV + Itmtx +WBRT (45Gy)+HIDAC</td>
<td>94%</td>
<td>24</td>
<td>37</td>
</tr>
<tr>
<td>Shah, 2007</td>
<td>R-MPV+HIDAC+WBRT (23Gy)</td>
<td>93%</td>
<td>&gt;37</td>
<td>40</td>
</tr>
<tr>
<td>Intensive chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illerhaus, 2008</td>
<td>Mtx 8gm/m2 +HIDAC+BCNU/TT(ASCT)</td>
<td>85%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Rubenstein, 2013</td>
<td>MT-R +EA</td>
<td>77%</td>
<td>52</td>
<td>NR</td>
</tr>
</tbody>
</table>
Progress in the treatment of PCNSL. Comparison of outcomes for newly diagnosed PCNSL in 2 multicenter cooperative group clinical trials.

Mtx 2.5mg/m2, vcr, procarb, IT mTX, Dex, hyperfractionated WBRT 45Gy, HIDAC x 2

What dose of MTX to use?

- Optimal doses have not been defined
  - Doses > 1gm/m2 achieve tumoricidal levels of mtx in brain parenchyma. (Skarin et al, BLOOD 1977)
  - Retrospective analysis of PCNSL outcomes at MSKCC demonstrate that elimination of IT MTX did not affect outcome in pts treated at a target dose of 3.5g/m2. (Khan et al, J Neuro-oncol, 2002)
  - 8gm/m2 produces higher cytotoxic levels in serum and csf than IT mtx (Glantz et al, JCO 1998)
Progress in the treatment of PCNSL. Comparison of outcomes for newly diagnosed PCNSL in 2 multicenter cooperative group clinical trials.

PFS for pt rec induction + consol

RTOG 9310 (2002)

CALGB 50202 (2012)

Mtx 2.5mg/m2, vcr, procarb, IT mTX, Dex, hyperfractionated WBRT 45Gy, HIDAC x 2

Protocol schema.

Remission Induction Therapy: MT-R (14-day cycle)
Day 1  Methotrexate 8 grams/m² IV over 4 hrs
Day 2  Leucovorin 100 mg/m² every 6 hrs, until methotrexate < 0.05 mM
Day 3  Rituximab 375 mg/m² IV cycles 1 through 6
Day 7-11 Temozolomide 150 mg/m² PO (odd cycles only)

Consolidation Therapy: EA
Day 1-4  Etoposide 40 mg/kg continuous IV over 96 hrs
Day 1-4  Cytarabine 2 gm/m² IV over 2 hrs every 12 hrs x 8 doses

James L. Rubenstein et al. JCO 2013;31:3061-3068
Clinical prognostic variables and their relationship to progression-free survival (PFS); median PFS survival was 2.4 years

James L. Rubenstein et al. JCO 2013;31:3061-3068
BCL6 expression is associated with short time to progression (TTP) and overall survival (OS) in patients with primary CNS lymphoma (PCNSL) treated in the 50202 study.

James L. Rubenstein et al. JCO 2013;31:3061-3068
**Table 3** Recent and active randomized controlled trials for PCNSL

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-PCNSL-SG1</td>
<td>HD-MTX-based induction +/- WBRT consolidation</td>
<td>Thiel et al. (81)</td>
</tr>
<tr>
<td>IELSG-20</td>
<td>HD-MTX +/- HD-Ara-C- &gt; WBRT consolidation</td>
<td>Ferreri et al. (80)</td>
</tr>
<tr>
<td>IELSG-32</td>
<td>Myeloablative vs. WBRT consolidation</td>
<td>Accrual complete</td>
</tr>
<tr>
<td><strong>Alliance 51101</strong></td>
<td><strong>Intensive vs. myeloablative consolidation</strong></td>
<td>Active</td>
</tr>
<tr>
<td>PRECIS</td>
<td>Myeloablative vs. WBRT consolidation</td>
<td>Active</td>
</tr>
<tr>
<td><strong>Matrix/IELSG43</strong></td>
<td><strong>Intensive vs. myeloablative consolidation</strong></td>
<td>Active</td>
</tr>
</tbody>
</table>

CALGB (Alliance) 51101 compares dose-intensive consolidation with infusional etoposide plus high-dose cytarabine (EA) with high-dose chemotherapy (BCNU plus thiotepa), supported by autologous stem cell transplant (7). The MATRIX/IELSG43 evaluates high-dose chemotherapy, BCNU plus thiotepa supported by autologous stem cell transplant in comparison to a dose-intensive consolidation regimen consisting of dexamethasone, etoposide, carboplatin and ifosfamide. HD-MTX, high-dose methotrexate; WBRT, whole brain radiotherapy; Ara-C, cytarabine.
Table 2. Randomized trials in PCNSL

<table>
<thead>
<tr>
<th>Induction</th>
<th>Consolidation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Completed trials</strong></td>
<td><strong>Completed trials</strong></td>
</tr>
<tr>
<td>Medical Research Council</td>
<td>G-PCNSL-SG-1 – NCT00153530</td>
</tr>
<tr>
<td>Phase 2, n = 53 (stopped early)</td>
<td>Phase 3, n = 551, ages ≥18 y</td>
</tr>
<tr>
<td>CHOP vs WBRT followed by CHOP³³</td>
<td>Arm 1: Methotrexate ± ifosfamide = &gt; WBRT</td>
</tr>
<tr>
<td>IELSG 20—NCT00210314</td>
<td>Arm 2: Methotrexate ± ifosfamide³¹</td>
</tr>
<tr>
<td>Phase 2; n = 79, ages 18-75 y</td>
<td><strong>Ongoing trials</strong></td>
</tr>
<tr>
<td>Induction arm 1: Methotrexate + Cytarabine = &gt; WBRT</td>
<td>IELSG 32—NCT01011920</td>
</tr>
<tr>
<td>Induction arm 2: Methotrexate = &gt; WBRT</td>
<td>Phase 2, n = 104, ages 18-70 y</td>
</tr>
<tr>
<td>ANOCEF-GOEALMS—NCT00503594</td>
<td>Consolidation arm 1: WBRT</td>
</tr>
<tr>
<td>Phase 2, n = 95, ages ≥60 y</td>
<td>Consolidation arm 1: HDT/ASCT</td>
</tr>
<tr>
<td>Arm 1: Methotrexate, procarbazine, vincristine, cytarabine</td>
<td>Consolidation arm 2: WBRT</td>
</tr>
<tr>
<td>Arm 2: Methotrexate, temozolomide</td>
<td><strong>ANOCIF-GOEALMS—NCT00863460</strong></td>
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<tr>
<td>IESLG 32—NCT01011920</td>
<td>Phase 2, n = 100, ages 18-60 y</td>
</tr>
<tr>
<td>Phase 2, n = 227, ages 18-70 y</td>
<td>(R-MBVP = &gt;</td>
</tr>
<tr>
<td>Induction arm 1: Methotrexate, cytarabine</td>
<td>Consolidation arm 1: HDT/ASCT</td>
</tr>
<tr>
<td>Induction arm 2: Methotrexate, cytarabine, rituximab</td>
<td>Consolidation arm 2: WBRT</td>
</tr>
<tr>
<td>Induction arm 3: Methotrexate, cytarabine, rituximab, thiotepa²⁵</td>
<td><strong>RTOG 1114—NCT01399372</strong></td>
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<tr>
<td><strong>Ongoing trials</strong></td>
<td>Phase 2, n = 84, ages ≥18 y</td>
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<tr>
<td>ALLG/HOVON—EuoraCT 2009-014722-42</td>
<td>Methotrexate, procarbazine, vincristine, rituximab = &gt;</td>
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<tr>
<td>Phase 3, n = 200, ages 18-70 y</td>
<td>Consolidation arm 1: WBRT (lower dose) = &gt;</td>
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<tr>
<td>Arm 1: Methotrexate, BCNU, teniposide, prednisone = &gt; Cytarabine, WBRT</td>
<td>cytarabine</td>
</tr>
<tr>
<td>Arm 2: Methotrexate, BCNU, teniposide, prednisone = &gt; Cytarabine, WBRT</td>
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<tr>
<td>Alliance 51101—NCT01511562</td>
<td><strong>MATRIX/IELSG43</strong></td>
</tr>
<tr>
<td>Phase 2, n = 160, ages 18-75 y</td>
<td>Phase 2, n = 220, ages 18-70 y</td>
</tr>
<tr>
<td>Methotrexate, temozolomide, rituximab, cytarabine = &gt;</td>
<td>Methotrexate, cytarabine, thiotepa, rituximab (MATRix) = &gt;</td>
</tr>
<tr>
<td>Consolidation arm 1: HDT/ASCT</td>
<td>Consolidation arm 1: HDT/ASCT</td>
</tr>
<tr>
<td>Consolidation arm 2: Etoposide, cytarabine</td>
<td>Consolidation arm 2: Dexamethasone, ifosfamide, VP-16, carboplatin (DEVC)</td>
</tr>
</tbody>
</table>

ALLG, Australasian Leukaemia and Lymphoma Group; ANOCIF, Association des Neuro-Oncologues d’Expression Française; GOEALMS, Groupe Ouest Est d’Etude des Leucémies et Autres Maladies du Sang; G-PCNSL-SG, German Primary CNS Lymphoma Study Group; HDT/ASCT, high-dose chemotherapy and autologous stem cell transplantation; HOVON, Stichting Hemato-Oncologie voor Volwassenen Nederland (Dutch-Belgian Cooperative Trial Group for Hematology Oncology); IELSG, International Extranodal Lymphoma Study Group; NCT, national clinical trial; RTOG, Radiation Therapy Oncology Group; WBRT, whole-brain radiation therapy.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Primary End Point</th>
<th>Response Criteria</th>
<th>Sample Size</th>
<th>Median Follow-Up</th>
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<tr>
<td>Mead et al</td>
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<td>OS</td>
<td>—</td>
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<tr>
<td>Bessell et al</td>
<td>Series</td>
<td>—</td>
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<tr>
<td>Bessell et al</td>
<td>Series/phase II</td>
<td>—</td>
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<td>Hoang-Xuan et al</td>
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<td>RR</td>
<td>Other</td>
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<td>59 months, 17 months</td>
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<td>Abrey et al</td>
<td>Series</td>
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<td>Other</td>
<td>NA</td>
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<tr>
<td>DeAngelis et al</td>
<td>Phase II</td>
<td>2-year OS</td>
<td>Other</td>
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<tr>
<td>O'Neil et al</td>
<td>Phase II</td>
<td>OS</td>
<td>Other</td>
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<td>Wu et al</td>
<td>Series</td>
<td>RR</td>
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<td>2-year OS</td>
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<td>30</td>
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<tr>
<td>DeAngelis et al</td>
<td>Series</td>
<td>—</td>
<td>M</td>
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<td>Nelson et al</td>
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<td>Sandor et al</td>
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<td>Herringer et al</td>
<td>Phase II</td>
<td>CRR</td>
<td>M</td>
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<td>Poortmans et al</td>
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<td>RR</td>
<td>Other</td>
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<td>Pels et al</td>
<td>Phase II</td>
<td>TTF</td>
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<td>IELSG 20</td>
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<td>39</td>
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<td>RTOG 0227</td>
<td>Phase I/II</td>
<td>MTD/2-year OS</td>
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<td>NA</td>
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<td>NABTT 2109</td>
<td>Phase II, 2 stage</td>
<td>CRR</td>
<td>Other</td>
<td>27-53</td>
<td>NA</td>
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Abbreviations: OS, overall survival; NA, not available; M, MacDonald criteria; RR, response rate; TTF, time to treatment failure; CRR, complete response rate; MTD, maximum tolerated dose; IELSG, International Extranodal Lymphoma Study Group; RTOG, Radiation Therapy Oncology Group; OHSU, Oregon Health Sciences University; MSKCC, Memorial Sloan-Kettering Cancer Center; NABTT, New Approach to Brain Tumor Therapy.
### Reported studies for PCNSL-AutoHSCT

<table>
<thead>
<tr>
<th>Ref.</th>
<th>#p/t</th>
<th>Tx line</th>
<th>Therapy (induction/intensification)</th>
<th>ASCT cond.</th>
<th>WBRT</th>
<th>Outcome</th>
<th>Neurotox</th>
<th>Medican Followup (mo)</th>
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<tr>
<td>Rubenstein</td>
<td>22</td>
<td>Salvage</td>
<td>EA</td>
<td>TT/Bu/Cy</td>
<td>N</td>
<td>3-y OS 64%</td>
<td>32</td>
<td>41</td>
<td>4</td>
</tr>
<tr>
<td>Illerhaus</td>
<td>43</td>
<td>Salvage</td>
<td>EA</td>
<td>TT/Bu/Cy</td>
<td>N</td>
<td>2-y OS 45%</td>
<td>5</td>
<td>36</td>
<td>7</td>
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<tr>
<td>Bromberg</td>
<td>6</td>
<td>First-line</td>
<td>MBVP</td>
<td>BEAM</td>
<td>Y</td>
<td>2-y OS 40%</td>
<td>33</td>
<td>41</td>
<td>0</td>
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<td>Korfel</td>
<td>25</td>
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<td>BEAM</td>
<td>Y</td>
<td>4-y OS 64%</td>
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<td>34</td>
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<tr>
<td>Wieduwilt</td>
<td>30</td>
<td>First-line</td>
<td>HD-MTX/AraC/TT</td>
<td>BCNU/TT</td>
<td>Y</td>
<td>5-y OS 69%</td>
<td>17</td>
<td>63</td>
<td>3</td>
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<td>Schabet</td>
<td>13</td>
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<td>HD-MTX/AraC/TT</td>
<td>BCNU/TT</td>
<td>Y</td>
<td>3-y OS 77%</td>
<td>0</td>
<td>23</td>
<td>0</td>
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<td>Cingolani</td>
<td>23</td>
<td>First-line</td>
<td>HD-MTX ! 7 Bu/Ty</td>
<td>Y</td>
<td>2-y OS 48%</td>
<td>39</td>
<td>15</td>
<td>13</td>
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<tr>
<td>Lai</td>
<td>28</td>
<td>First-line</td>
<td>HD-MTX ! araC</td>
<td>BEAM</td>
<td>N</td>
<td>2-y OS 55%</td>
<td>0</td>
<td>28</td>
<td>4</td>
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<tr>
<td>Shenkler</td>
<td>7</td>
<td>First-line</td>
<td>HD-MTX ! araC</td>
<td>TT/Bu/Cy</td>
<td>N</td>
<td>3-y OS 50%</td>
<td>0</td>
<td>28</td>
<td>14</td>
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</table>
Whole Brain Radiotherapy (WBRT) Versus Intensive Chemotherapy with Haematopoietic Stem Cell Rescue (IC + HCR) for Primary Central Nervous System Lymphoma (PCNSL) in Young Patients: An Intergroup Anocef-Goelams Randomized Phase II Trial (PRECIS)


Blood
Volume 128(22):782-782
December 2, 2016

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Whole Brain Radiotherapy (WBRT) Versus Intensive Chemotherapy with Haematopoietic Stem Cell Rescue (IC + HCR) for Primary Central Nervous System Lymphoma (PCNSL) in Young Patients: An Intergroup Anocef-Goelams Randomized Phase II Trial (PRECIS)


Blood
Volume 128(22):782-782
December 2, 2016
Abstract 137

Lenalidomide is highly active in recurrent CNS lymphoma

- Lenalidomide active in aggressive NHL esp ABC subtype
- Case report in 2011- efficacy of lenalidomide in ocular lymphoma
- Phase 1 trial of Lenalidomide in CNS NHL

Rubenstein et al
Temsorilimus for R/R PCNSL
Methods

- Determine safety and efficacy of 3 dose levels of Lenalidomide in refractory CD20+ CNS lymphoma
- Determine CSF penetration of Lenalidomide
- Feasibility of combined IT and IV rituximab
- Effect of lenalidomide on tumor microenvironment
Results

- 9 patients on phase 1 (7 PCNSL, 2 SCNSL)
- 8 evaluable
- 6/8 had response at 1 month of therapy, 2 CRs, 1 PR in brain NHL, 1 CR of CSF NHL and 1 CR and 2 PR of intraocular lymphoma
- 3 maintain response to mono therapy at > 6 months and 2 beyond 1 year.
Results

• Independent cohort of 10 patients received lenalidomide maintenance after initial salvage therapy
• Median fu is 18 months
• 5 pts have durable response after 2 years
• Lenalidomide levels detected in ventricular CSF in 4 patients, 12-15 hours after a 20 mg dose
• Metabolic profiling suggested CSF lactate correlated with response
Lugano 2015
Phase I/II study of TEDDI-R in PCNSL

- Temozolomide, etoposide, doxil, dex, ibrutinib and rituximab with IT cytarabine
- MTX excluded due to interaction with ibrutinib in vivo
Additional abstracts of interest: TEDDI-R for CNS lymphoma

Dunleavy, Lai, Roschewski, Brudno, Widemann, Pittaluga, Jaffe, Lucas, Stevenson, Yuan, Harris, Cole, Butman, Little, Staudt, and Wilson

Dose Adjusted-TEDDI-R

- Temozolomide 100 mg/m²/day IV days 2 to 5
- Etoposide 50 mg/m²/day IV days 2 to 5
- Doxil 50 mg/m² IV day 2
- Dexamethasone 10 mg/m² BID PO days 1 to 5
- Ibrutinib (560-TBD mg) PO days 1-10 (days -14 to 5 on cycle 1)
- Rituximab 375 mg/m² IV on days 1 and 2
- Pegfilgrastim 6mgs on day 6
- Cytarabine 70 mg IT or ICV on days 1 and 5 of cycles 2 to 6

No MTX

Repeat cycle q21 days x 6
Methods

- Untreated or R/R PCNSL
- Ibrutinib 560 mg PO daily for 14 days
- followed by brain MRI/PET
- Followed by DA-TEDDI-R every 21 days x 6 cycles
- Plasma and CSF PKs of Ibrutinib and its metabolite PCI-45227
Results

- 6 enrolled so far
- 6 completed ibrutinib
- 4 completed at least 2 cycles of chemo
- Pk in 4 patients have shown CSF penetration of Ibrutinib and its metabolite
- Tumor improvement seen in 5/6 patients with Ibrutinib alone
Results and conclusions

- 51 (4%) developed CNS relapse at a median time of 9 months
- CI of CNS relapse at 2 years was
  - Low risk - 0.5%
  - Intermediate risk - 2.5%
  - High risk – 12.3% - (85/235 of high risk received CNS prophylaxis, IT alone 22%, systemic 31%, both 47%). Number of CNS events was the same with or without prophylaxis i.e 12%
Plasma/CSF Concentration x Time Profile
(Mean±SD)

Patients 1-6: 560mg dose

Ibrutinib and its active metabolite achieve meaningful CSF concentrations
RESULTS: Case Example Patient 4 (52 yo) – DA-TEDDI-R

Ibrutinib  DA-TEDDI-R
Nivolumab (anti-PD1) therapy for recurrent/refractory primary central nervous system lymphoma and primary testicular lymphoma

Lakshmi Nayak, Fabio M. Iwamoto, Ann LaCasce, Srinivasan Mukundan, Margaretha G. M. Roemer, Bjoern Chapuy, Philippe Armand, Scott J. Rodig, Margaret A. Shipp
Background

- Primary central nervous system lymphoma (PCNSL) and primary testicular lymphoma (PTL):
  - rare & aggressive extranodal non-Hodgkin lymphomas
  - shared molecular features
  - poor prognosis
Background: PCNSL

- Treatment of PCNSL:
  - Induction chemotherapy: HD-MTX based
  - Consolidation with whole brain radiation (WBRT) or high-dose chemotherapy with autologous stem-cell transplant (ASCT) in young & healthy pts.

- Relapse rates:
  - 50-60% in the 1st 2 yrs
  - 1/3rd pts are primary refractory

Korfel et al. Nat Rev Neurol 2013; 9:317
Treatment of PTL:
- Induction treatment: R-CHOP
- CNS prophylaxis & RT to the contralateral testis

Relapse:
- Relapse site: CNS or contralateral testis
- 5 yr RR 42-66%
- Majority of the relapses in the 1st 2 yrs

Background

- Optimal salvage treatment for recurrent/refractory (R/R) PCNSL & PTL is not established

- Responses are often poor & not durable

- The majority of pts. ultimately die of their disease
Preclinical & clinical studies have shown that lymphoid malignancies with 9p24.1/PD-L1/PD-L2 alterations are genetically predisposed to rely on PD-1 mediated immune evasion.
9p24.1 Amplicon Block

**PD–L1 and PD-L2 copy gain and further induction via JAK2/STAT signaling**

Green et al, Blood 2010; 116:3268
Hao et al, Clin Cancer Res 2014; 20:2674
Roemer et al. J Clin Oncol 2016; 34:2690
Clinical Evaluation of PD-1 Blockade in R/R classical Hodgkin’s Lymphoma (cHL)

- cHL is genetically designed to rely on PD1 mediated immune evasion prompting the assessment of the efficacy of PD1 blockade in cHL

- 65-87% ORR in R/R cHL with anti-PD1 antibody (Nivolumab, Pembrolizumab)

Engert et al EHA Annual Meeting Abstract 2016
Moskowitz et al EHA Annual Meeting Abstract 2016
Comparison of DLBCL vs. PCNSL/PTL

Copy Number Alterations

Monti and Chapuy et al, Cancer Cell, 2012; 22:359-72
Chapuy and Roemer et al Blood 2016; 127:869-881
To evaluate this hypothesis, we treated 5 pts with R/R PCNSL & PTL with Nivolumab
Patients & Methods

• N = 5 pts (2 women, 3 men)
  ▪ Recurrent PCNSL 3
  ▪ Refractory PCNSL 1
  ▪ Recurrent PTL (SCNSL) 1

➤ Median Age = 64 yrs (range, 54-85 yrs)
➤ Median KPS = 70% (range, 40-80 %)
Prior Treatments

- All pts treated with standard regimens
  - HD-MTX based chemotherapy
  - AraC
  - Pemetrexed
  - WBRT
  - Thiopotepa based autologous transplant
  - No other available options
**Treatment**

- Nivolumab 3mg/kg IV Q2wks
  - Rituximab x3 doses in 1 pt
  - RT in 2 pts (prior to starting Nivolumab)
    - WBRT in 1
    - Focused RT in 1

- 1 pt received corticosteroids
  - Dexamethasone 2mg daily, tapered over 1 month
Toxicities

- Related G1 pruritus in 1

- Worsening of baseline renal insufficiency (Grade 4) requiring HD in 1
  - Nivolumab was discontinued
  - Renal biopsy:
    - Chronic renal failure
    - No evidence of interstitial nephritis
Response

- Objective Radiographic Response (ORR)
  - Complete response in 4
  - Partial response in 1
  - Median no. of treatments to ORR = 3 (range, 2-4)

- Clinical Response in 4
  - 1 was asymptomatic at presentation

- Persistent ocular disease in 1
Patient with Primary Refractory PCNSL treated with PD-1 Blockade

Pre Nivolumab

Post Nivolumab
Response

- Objective Radiographic Response (ORR)
  - Complete response in 4
  - Partial response in 1
  - Median no. of treatments to ORR = 3 (range, 2-4)

- Clinical Response in 4
  - 1 was asymptomatic at presentation

- Persistent ocular disease in 1
Response

- Objective Radiographic Response (ORR)
  - Complete response in 4
  - Partial response in 1
  - Median no. of treatments to ORR= 3 (range, 2-4)

- Clinical Response in 4
  - 1 was asymptomatic at presentation

- Persistent ocular disease in 1
## PD-1 Blockade in Patients with Recurrent/Refractory PCNSL or PTL/SCNSL

<table>
<thead>
<tr>
<th>Patients</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tr>
<td>Disease</td>
<td>Refractory PCNSL</td>
<td>Relapsed PCNSL</td>
<td>Relapsed PCNSL</td>
<td>Relapsed PCNSL</td>
<td>Relapsed PTL in brain</td>
</tr>
<tr>
<td>Presenting symptoms, KPS %</td>
<td>Visual field defect, cognitive change; 70</td>
<td>Mild cognitive change; 80</td>
<td>Nausea, vomiting, ataxia; 40</td>
<td>Asymptomatic; 80</td>
<td>Aphasia, impaired LOC; 40</td>
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<tr>
<td>Radiographic response</td>
<td>CR</td>
<td>CR</td>
<td>PR</td>
<td>CR</td>
<td>CR</td>
</tr>
<tr>
<td>Neurologic response, KPS %</td>
<td>Complete resolution; 90</td>
<td>Complete resolution; 80</td>
<td>Resolution; 70</td>
<td>Stable (asym); 80</td>
<td>Resolution; 80</td>
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<tr>
<td>Progression-free survival (mo)</td>
<td>11+</td>
<td>14+</td>
<td>15+</td>
<td>14</td>
<td>11+</td>
</tr>
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</table>
Survival

- All pts are alive at a median f/u of 14 months

- 4 pts remain progression-free (radiographic & clinical)

- 1 pt with PCNSL developed systemic recurrence without recurrent CNS disease at 14 months
## PD-1 Blockade in Patients with Recurrent/Refractory PCNSL or PTL/SCNSL

<table>
<thead>
<tr>
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<td>Resolution; 70</td>
<td>Stable (asym); 80</td>
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<tr>
<td>Progression-free survival (mo)</td>
<td>11+</td>
<td>14+</td>
<td>15+</td>
<td>14</td>
<td>11+</td>
</tr>
</tbody>
</table>
Conclusions

- Nivolumab is active in R/R PCNSL and PTL with CNS relapse

- A multi-institutional phase 2 open-label, single-arm trial of nivolumab in R/R PCNSL and PTL pts (CA209-647) has been initiated
  - Currently accruing pts.
Figure 1  Intracerebroventricular administration of T_{N/MEM}-derived CD19CAR T cells induces complete remission of CNSL
Figure 2  Intracerebroventricular administration of $T_{N/MEM}$-derived CD19CAR T cells is able to completely eradicate both CNSL and systemic lymphoma
New Therapeutic Approach for Central Nervous System Lymphoma By Intracerebroventricular Delivery of CD19CAR T Cells

Figure 1. Intraventricularly delivered CD19CAR T cells eradicated central nervous system lymphoma in immunodeficient mice. Isolated naïve and central memory T cells (Tn/Tmem) were genetically modified with a CD19CAR lentivirus and expanded in vitro for 14 days. 0.1x10^6 human B cell lymphoma Daudi cells were intracranially injected into NSG mice, and tumor was allowed to engraft for 5 days. We administered CD19CAR T cells by three different delivery routes: 1x10^6 cells for intracranial local infusion (i.c.), 1x10^6 cells for intracerebroventricular (i.c.v.) administration, and 3x10^6 cells for intravenous injection (i.v.). Non-transduced mock T cells were used as controls. Tumor signals were monitored with Xenogen imaging once a week. The bioluminescence signal was measured as total photon flux normalized for exposure time and surface area and expressed in units of photons (p) per second per cm² per steradian (sr). Means ± SEM from 5 mice per group are presented.
Newly diagnosed primary CNS lymphoma

Adequate renal function? (GFR > 30)

Yes

Combination chemotherapy with HD-MTX

CR / CRu / significant partial response

Consolidation therapy
• WBRT
• Non-myeloablative chemotherapy
• ASCT with thiotepa-based regimen (preferred)

Stable or progressive disease

Salvage therapy with CNS-penetrative agents

CR / CRu / significant partial response

Surveillance

Stable or progressive disease

Palliative WBRT

No

Combination therapy without HD-MTX

CR / CRu / significant partial response

Consolidation therapy
• WBRT
• Non-myeloablative chemotherapy

Stable or progressive disease

Palliative WBRT if not previously done or best supportive care

Relapse or disease progression

Salvage therapy (including HD-MTX if previous response and adequate GFR) vs. WBRT.

CR / CRu / significant partial response

ASCT with thiotepa-based regimen (if not previously received) and clinically eligible or WBRT (if not previously received)

Stable or progressive disease
Targetable genetic features of primary testicular and primary central nervous system lymphomas

by Bjoern Chapuy, Margaretha G. M. Roemer, Chip Stewart, Yuxiang Tan, Ryan P. Abo, Liye Zhang, Andrew J. Dunford, David M. Meredith, Aaron R. Thorner, Ekaterina S. Jordanova, Gang Liu, Friedrich Feuerhake, Matthew D. Ducar, Gerald Illerhaus, Daniel Gusenleitner, Erica A. Linden, Heather H. Sun, Heather Homer, Miyuki Aono, Geraldine S. Pinkus, Azra H. Ligon, Keith L. Ligon, Judith A. Ferry, Gordon J. Freeman, Paul van Hummelen, Todd R. Golub, Gad Getz, Scott J. Rodig, Daphne de Jong, Stefano Monti, and Margaret A. Shipp

Blood
Volume 127(7):869-881
February 18, 2016
GISTIC-defined CNAs in LBCL subtypes.

PCNSLs, PTLs, and PMBLs clustered by recurrent CNAs. (A) Unsupervised bihierarchical clustering of all 47 GISTIC-defined CNAs (y-axis) in 39 primary LBCLs (21 PCNSLs [dark green], 7 PTLs [light green], 11 PMBLs [orange]; y-axis).

Chromosomal rearrangements in PCNSL and PTL. (A,C) Detected chromosomal rearrangements in 24 PCNSL (A) and 7 PTL (C) are summarized as circos plots.

Somatic mutations and patterns of genetic alterations in PCNSL and PTL. (A) Frequency of mutations in PCNSLs (mutations initially identified by WES in 5 tumor/normal pairs and subsequently assessed in 9 additional tumors without paired normals by RNA-Seq).


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Functional consequences of 3q12.3/NFKBIZ copy gain and IκB-ζ overexpression.

Genetic alterations of PD-L1 and PD-L2 in PTL and PCNSL. (A) CNs of PD-L1 in 43 PTL cases from the extension cohort.

Unique combinations of structural alterations in discrete LBCL subtypes.

<table>
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<tr>
<th>Genomic instability</th>
<th>DLBCL</th>
<th>PTL</th>
<th>EBV&lt;sup&gt;−&lt;/sup&gt; PCNSL</th>
<th>PMBL</th>
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<td><em>CDKN2A&lt;sup&gt;loss&lt;/sup&gt; bi-allelic</em></td>
<td>All: 24% (43/180)&lt;sup&gt;a&lt;/sup&gt; 19% (8/43)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ABC-type: 35% (19/55)&lt;sup&gt;a&lt;/sup&gt; 26% (5/19)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>88% (44/50)&lt;sup&gt;c&lt;/sup&gt; 77% (34/44)</td>
<td>0% (0/11) 0% (0/11)</td>
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<tr>
<td>CNAs of additional p53/cell cycle components</td>
<td>multiple&lt;sup&gt;a,b&lt;/sup&gt; high</td>
<td>multiple&lt;sup&gt;a,b&lt;/sup&gt; high</td>
<td>rare&lt;sup&gt;d&lt;/sup&gt; high</td>
<td>no low</td>
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**Oncogenic TLR and BCR Signaling**

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<th>DLBCL</th>
<th>PTL</th>
<th>EBV&lt;sup&gt;−&lt;/sup&gt; PCNSL</th>
<th>PMBL</th>
</tr>
</thead>
</table>
| *MYD88<sup>L265P</sup>* | 12% (6/49)<sup>e</sup> 29% (45/155)<sup>f</sup> | 78% (38/49)<sup>g</sup> 42% (21/50)<sup>h</sup> | 60% (33/55)<sup>i</sup> 45% (28/62)<sup>m</sup> | NA
| *NFKBIZ<sup>gain</sup>* | 9% (16/180)<sup>a</sup> 20% (11/55)<sup>a</sup> | 92% (45/49) | 83% (44/53)<sup>n</sup> | NA
| *NFKBIZ<sup>gain</sup> and/or MYD88<sup>L265P</sup>* | NA | NA | NA | NA |
| *CD79B<sup>Y196mut</sup>* | Total: 16% (8/49)<sup>e</sup> 38% (3/8)<sup>e</sup> | 49% (22/45)<sup>i</sup> 91% (20/22) | 38% (19/50)<sup>o</sup> 89% (17/19) | NA
| | Concurrent with *MYD88<sup>L265P</sup>*: 23% (35/155)<sup>f</sup> 43% (15/35)<sup>f</sup> | 42% (21/50)<sup>h</sup> 91% (20/22) | 38% (19/50)<sup>o</sup> 89% (17/19) | NA

**PD-1 Ligand Deregulation**

<table>
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<tr>
<th></th>
<th>DLBCL</th>
<th>PTL</th>
<th>EBV&lt;sup&gt;−&lt;/sup&gt; PCNSL</th>
<th>PMBL</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>9p24.1/PD-L&lt;sup&gt;1&lt;/sup&gt;&lt;sup&gt;gain&lt;/sup&gt; and/or PD-L&lt;sup&gt;2&lt;/sup&gt;&lt;sup&gt;gain&lt;/sup&gt;</em></td>
<td>6% (11/180)&lt;sup&gt;a&lt;/sup&gt; 7% (4/55)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>54% (26/50)&lt;sup&gt;h&lt;/sup&gt; 52% (33/63)&lt;sup&gt;p&lt;/sup&gt;</td>
<td>55% (6/11) 20% (25/125)&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><em>PD-L&lt;sup&gt;1&lt;/sup&gt; or PDL-2 translocation</em></td>
<td>NA</td>
<td>NA</td>
<td>4% (2/50)&lt;sup&gt;j&lt;/sup&gt; 6% (4/66)&lt;sup&gt;q&lt;/sup&gt;</td>
<td></td>
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</table>