New Advances for therapies in PCNSL

Sepideh Mokhtari, MD
Neuro-Oncology
Moffitt Cancer Center
March 25th, 2023

Introduction

- 4% of Intracranial tumors
- 4-6% of extra-nodal lymphoma
- Median age of 67 at diagnosis
- Spike in the early 1990s, due to the HIV epidemic
- Those who are 70–79 years of age have the highest incidence
  - 4.3 per 100 000/year
- 43% have nonspecific behavioral or neurocognitive changes
- Ocular involvement (20%)
  - Symptoms (4%)
    - Decreased acuity
    - Blurry vision
    - Floaters

Neurologic Deficits

- 70% have focal neurologic deficits
- Increased ICP (33%)
  - Headache
  - Confusion
  - Nausea/Vomiting
- Seizures (14%)
  - The cortex is less frequently involved
- Leptomeningeal disease (1/3)
- Spinal met
  - Intradural
  - Thoracic

Diagnostic work up

- MRI Brain
  - Isointense to hyperintense on T2-weighted MR image
  - Enhance homogeneously
  - Moderate amount of edema
  - Restricted on diffusion weighted images
- MRI whole spine
- Ophthalmologic evaluation (slit lamp)
  - To detect cellular vitreal or subretinal infiltrates.
- CSF evaluation
- CT TAP or fluorodeoxyglucose (FDG) PET
- Bone marrow biopsy
- Testicular ultrasound
- Definitive diagnosis requires pathologic confirmation
  - Stereotactic biopsy

MRI Pattern

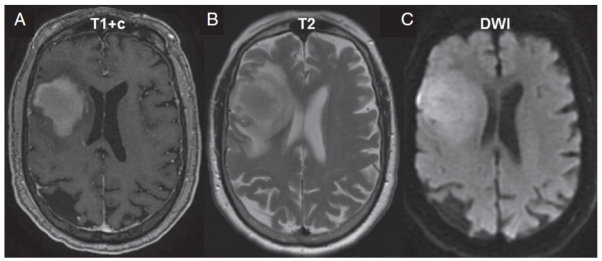


Fig. 1 PCNSL imaging pattern on MRI. (A) MRI T1 sequence with gadolinium contrast (T1+c) reveals homogeneously enhancing deep lesions. (B) Lesions are iso- to hyperintense on T2 imaging with a relatively small amount of edema. (C) Diffusion-weighted imaging (DWI) demonstrates restricted diffusion in the tumor.

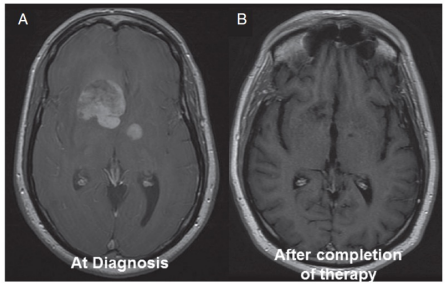
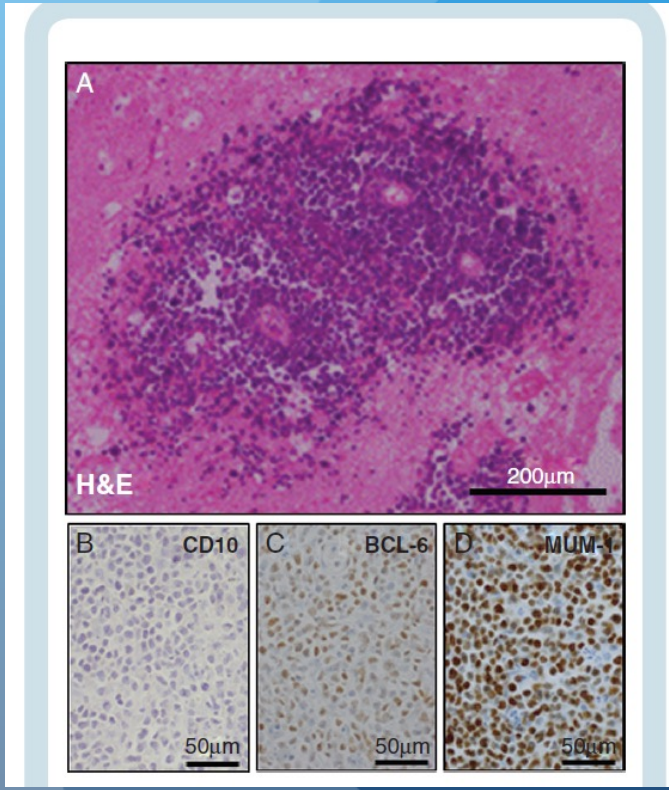


Fig. 2 PCNSL is highly chemosensitive. (A) PCNSL is highly chemosensitive with dramatic response on T1 with gadolinium (B) after initiation of methotrexate combination therapy.

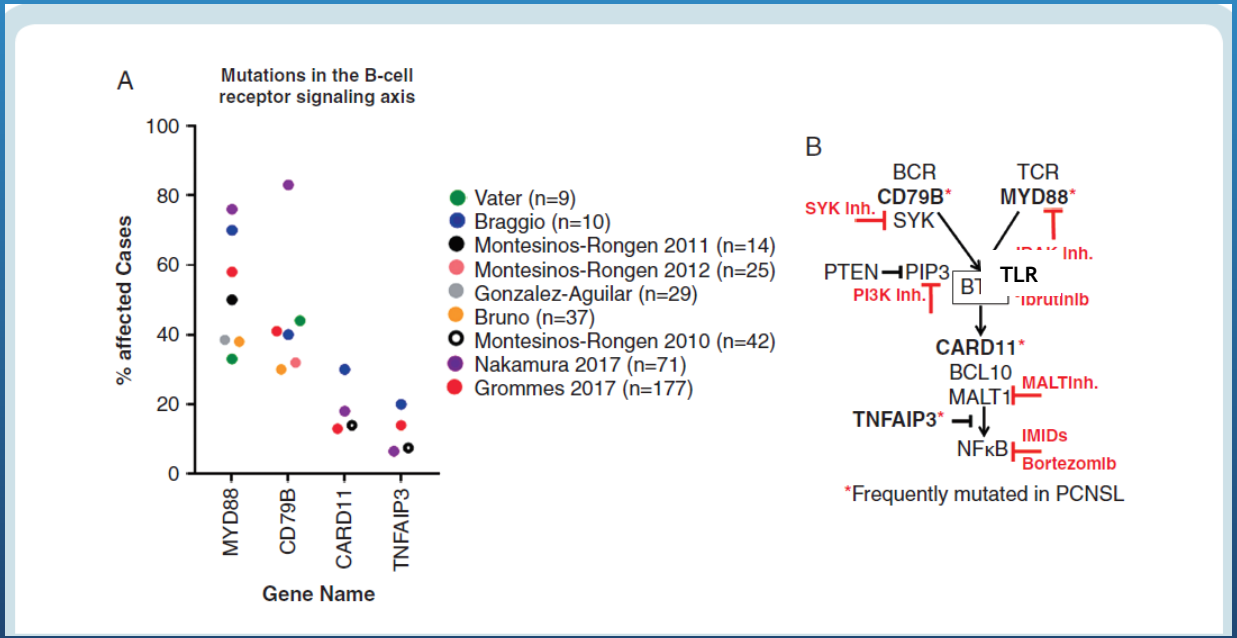
Pathology



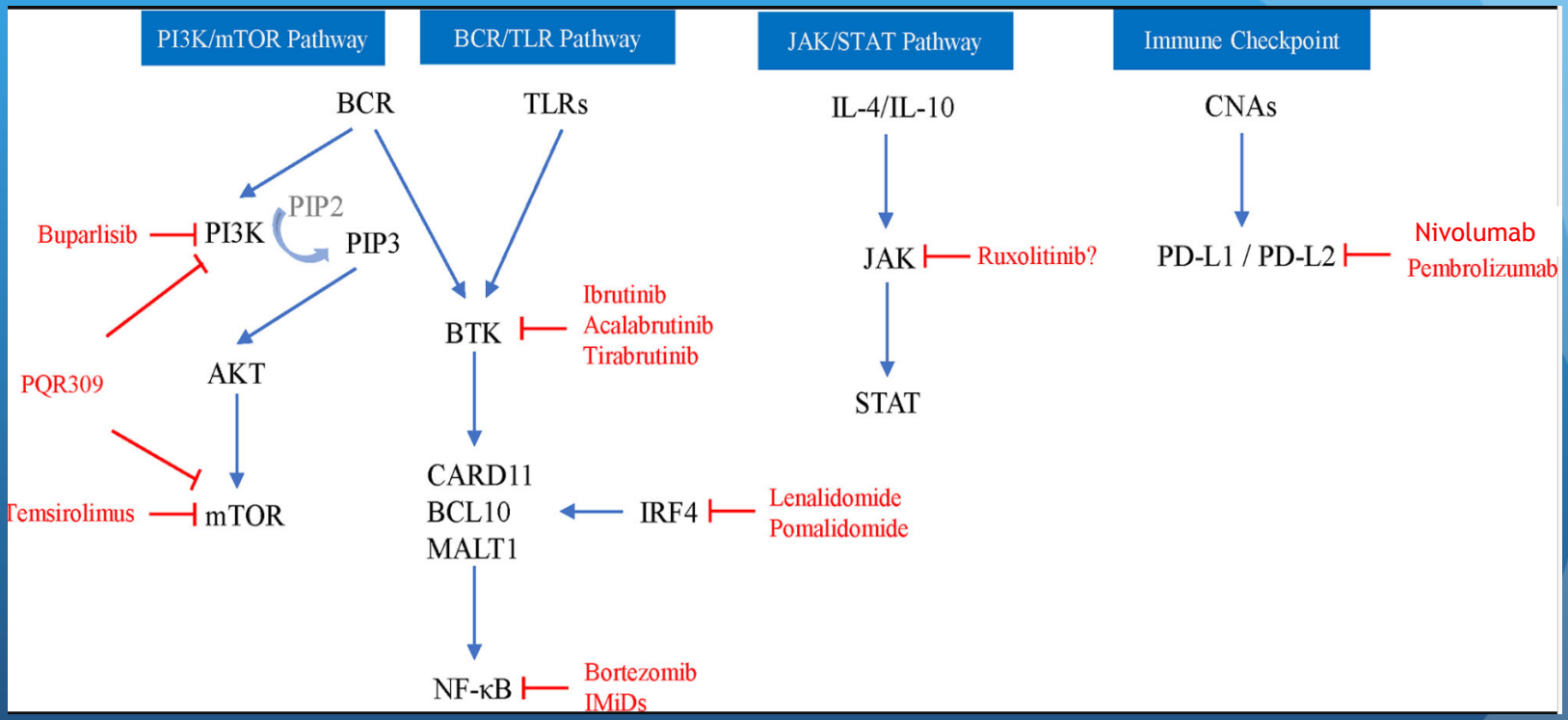
- DLBCLs (90%)
  - CD20, CD19, CD22, CD 79a
- Others:
  - Burkitt, T-cell, or low-grade lymphomas
- Perivascular growth
- Nongerminal center/activated B-cell subtype (>75%)
  - CD10
  - BCL-6
  - MUM-1

Genomic

- Most mutated genes: MYD88, CD79B, CARD11, and TNFAIP3
- NKκB promotes neoplastic proliferation and prevents apoptosis



Key Mechanisms of PCNSL and Related Targeted Agents



Tao *et al*. Front. Oncol., 29 April 2021

Pathogenesis

- Copy number alterations
  - Copy number Losses
    - 6p21.33 (HLA-B, HLA-C)
    - 6q21-23 (TNFAIP3)
    - 9p21.3 (CDKN2A)
  - Copy number gains
    - 12q (MDM2, CDK4) and 9p24.1
    - PD-L1, PD-L2)
- Somatic hypermutation (SHM)
- Genetic features of vitreoretinal lymphoma (VRL)
  - Activation of the TLR pathway by mutations in MYD88
  - SHM genes may be similarly mutated
- Tumor microenvironment
  - IL-10
    - STAT3 => ↑JAK2/STAT3
      - cell proliferation
      - Survival
      - Angiogenesis
  - Tumor associated Macrophages (TAM)
    - Overexpresses PDL1

Current Gold Standard

Surgery

- Biopsy only (stereotactic biopsy)
- To establish tissue diagnosis
- Avoid corticosteroid use prior to biopsy
- Surgical debulking is typically not pursued
  - Multiple retrospective studies have failed to demonstrate a survival benefit

Chemotherapy

- Methotrexate-based polychemotherapy
  - R-MPV
  - MT-R
  - MTX/cytarabine/thiotepa/rituximab (MATRix)
  - Rituximab/MTX/carmustine/teniposide/prednisolone (R-MBVP)
  - Rituximab/MTX (R-M)

Upfront Trials in PCNSL

MOFFITT CANCER CENTER

Author	Year	Agents	Patients	Median Age	ORR (PR+CR)	Median PFS, mo	Median OS, mo
DeAngelis et al[62]	1992	M(1)+RT(40 + 14 boost)+AraC(3)	31	58	27/31 (87%)	41	42.5
Glass et al[63]	1994	M(3.5)+RT(30–40)	25	56	23/25 (90%)	32	33
O'Brien et al[64]	2000	M(1)+RT (45 + 5.4 boost)	46	58	44/46 (96%)	NR	33
Abrey et al[65]	2000	M(3.5)+P(100)+V(1.4)+Ara-C(3)+IT M+IT A+RT(45)	52	65	49/52 (94%)	NR	60
Ferreri et al[66]	2001	M(3)+P(100)+V(1.4)+Ara-C(3)+RT(45)	13	54	12/13 (92%)	18	25+
DeAngelis et al[67]	2002	M(2.5)+V(1.4)+P(100)+AraC(3)+IT M+RT(45 or 36)	102 (98 treated)	56.5	47/50 (94%)	24	37
Herrlinger et al[72]	2002	M(8)	37	60	13/37 (35%)	10	25
Abrey et al[35]	2003	M(3.5)+AraC(3); BEAM	28 (14 transplanted)	53	Induction: 16/24 (57%), SCT 11/14 (77%)	5.6	Not reached
Batchelor et al[13]	2003	M(8)	25	60	17/23 (74%)	12.8	22.8+
Pels et al[74]	2003	M(5)+AraC(3)+V(2)+ifos(800)+dex(10)+cyclo(200)+IT M+IT A+IT P	65	62	43/61 (71%)	21	50
Poortmans et al[68]	2003	M(3)+Ten(100)+B(100)+MP(60)+IT M+IT A+RT(40)	52	51	42/52(81%)	NR	46
Colombat et al[87]	2006	M(3)+B(100)+eto(100)+pred (60); BEAM+RT(30)	25 (17 transplanted)	52	Induction: 21/25 (84%), SCT 16/16 (100%)	40	Not reached
Illerhaus et al[96]	2006	M(8)+AraC(3)+thio (40 mg/m^2); B(400)+thio(5 mg/kg)+RT(45)	30 (23 transplanted)	54	Induction: 21/30 (70%), SCT 21/21 (100%)	NR	Not reached
Ferreri et al[77]	2009	M(3.5)+/-AraC(2)+RT(45)	79	59/58	27/39 (69%) vs 16/40 (40%)	3 vs 18	Nr
Thiel et al[15]	2010	M(3;+ifos) +/- RT(45)	526 (all)/318 (TPP)	61	283/526 (53%)	18.3 vs 11.9	32.4 vs 37.1
Morris et al[72]	2013	R(500)+M(3.5)+V(1.4)+P(100)+RT(23.4)	52	60	41/52 (78%)	92.4	Not reached
Rubenstein et al[76]	2013	R(375)+M(8)+T(150)+AraC(2) vs eto(40)	44	61	34/47(72%)	48	Not reached
Omuro et al[79]	2015	R(500)+M(3.5)+V(1.4)+P(100); thio(250)+cyclo(60)+bus(3.2)	32 (26 transplanted)	57	Induction: 31/32 (97%), SCT 24/26 (92%)	Not reached	Not reached
Omuro et al[78]	2015	M(3.5)+V(1.4)+P(100)+AraC(3) vs M(3.5)+T(150)	95	72/73	37/45(82%) vs 34/42(74%)	9.5 vs 6.1	31 vs 14
Glass et al[80]	2016	R(375)+M(3.5)+T(100)+RT(36)	66	57	30/35 (86%)	63	90
Ferreri et al[75]	2016	M(3.5)+AraC(2)+/-R(375)+/-thio(30)	227	58/57/57	40/75(53%)/51/69(73%)/65/75 (86%)	6/20/not reached	12/30/not reached
Illerhaus et al[96]	2016	R(375)+M(8)+AraC(3)+thio(40); R(375)+B(400)+thio(5 mg/kg)	79 (73 transplanted)	56	Induction: 73/79 (92%), SCT: 72/79 (91%)	74	Not reached
Fritsch et al[90]	2017	R(375)+M(3)+P(60)+L(110)	107 (all)/(69 R-MPL)	73	53/107 (50%); 32/69 (46% r-mpl)	10.3/(9.6 r-mpl)	20.7/(15.4 r-mpl)

AraC: cytarabine (g/m^2); B: BCNU (mg/m^2); BEAM: carmustine, etoposide, cytarabine, melphalan; bus: busulfan (mg/kg); CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; cyclo: cyclophosphamide (mg/m^2); eto: etoposide (mg/m^2); ifos: ifosfamide (mg/m^2); IT A: intrathecal cytarabine; IT M: intrathecal methotrexate; IT P: intrathecal prednisone; M: methotrexate (g/m^2); L: lomustine (mg/m^2) NR: not reported; P: procarbazine (mg/m^2/day), SCT: stem cell transplant; pred: methylprednisone (mg/m^2); R: rituximab (mg/m^2); RT: whole brain radiation (dose used in Gy); T: temozolomide (mg/m^2); Ten: teniposide (mg/m^2); thio: thiotepa (mg/m^2); V: vincristine (mg/m^2).

Dose of Methotrexate

- The optimal dose of MTX is not known,
- At least 3 g/m2 is required for adequate penetration of the CNS
- Some regimens utilize dosages up to 8 g/m2
  - Toxicity often necessitates dose reductions
  - There is no clear benefit to these higher doses
- Institutional and practitioner preference

Radiation for PCNSL History

- 1970s-1980s:
  - High dose WBRT 40-50 Gy + boost to 50-54 Gy
    - **RR 50-80%, 5-yr OS ~15-20% (at best)**
- 1980s-1990s:
  - High dose WBRT + boost + HD-MTX
- 2000s - present:
  - 5-8 x cycles R-MVP with optional treatment escalation
    - Autologous stem cell transplant
    - **Low-dose WBRT (23.4 Gy - RTOG 1114)**
    - IELSG32 (WBRT 36 Gy + 9 Gy boost)
    - PRECIS (WBRT 40 Gy)
      - Favored ASCT in young pts

Radiation for PCNSL

- As part of consolidation
  - Preferably low dose (23.4 Gy, in responsive patients)
  - Awaiting results of RTOG 1114
- Associated with increased neuro-cognitive deficits in elderly patients and at higher doses
- Some centers still use WBRT as part of consolidation delivered at a lower dose (23.4 Gy)
- Given to younger patients to avoid neurocognitive issues
  - (*J Clin Oncol*. 2013;31(31):3971–3979)

Recurrent/Relapsing PCNSL

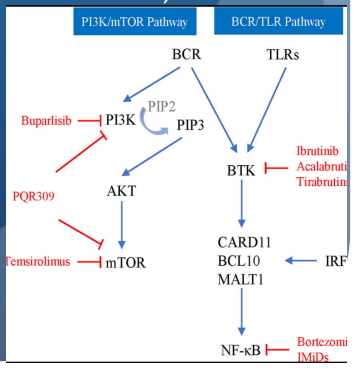
- Approximately 15%
- High in patents who are not candidates for HDC-ASCT
- Traditional strategies for salvage therapy:
  - MTX-rechallenge
  - Alternate cytotoxic chemotherapy regimens
  - WBRT
- Prognosis for relapsed disease is poor
  - PFS of only about a year with aggressive salvage therapy

BCR/TLR Pathway

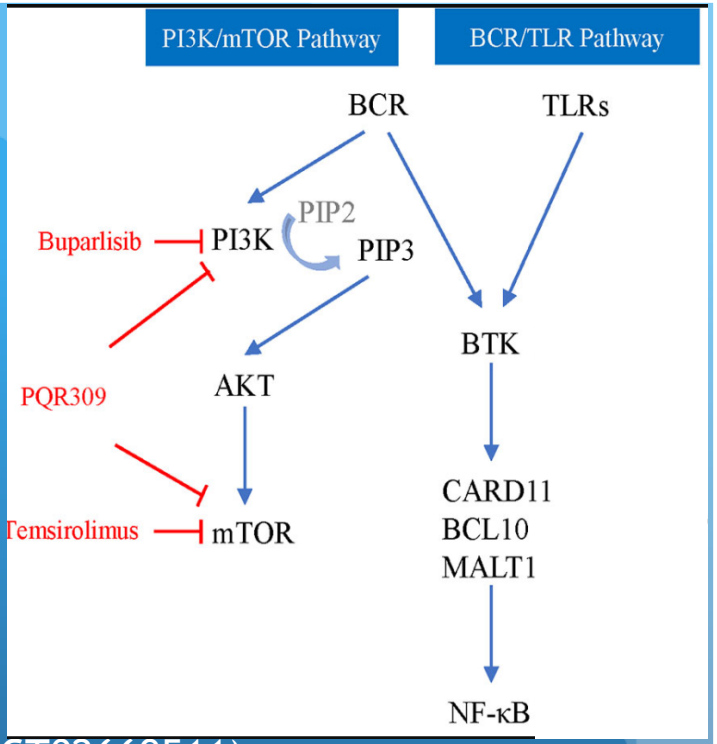
- PI3K Inhibitors
- Lenalidomide
  - IRF4 inhibition => NFκB
- Proteosome inhibitors
  - Prevent release of NKκB to the nucleus
  - Don't cross blood–brain barrier (BBB)
- Ibrutinib
  - Targets BTK pathway
  - Used for treatment of R/R PCNSL in NCCN guideline
  - RR ~ 52% vs 25% in systemic DLBCL
  - MYD88 & CD 79b appear to coincide in approximately 37% of cases of PCNSL
  - Potential resistance due to CARD11 & TNFAIP3 mutations
  - PFS < 5 months (Grommes *et al*. Cancer Discov. **2017**)

- Combination treatment PFS > 9 months (Grommes *et al*. Blood **2019**)
  - Lenalidomide (NCT03703167)
  - Copanlisib (NCT03581942)
  - checkpoint inhibition (NCT04421560, NCT03770416)
  - Traditional chemotherapy (NCT04066920, NCT02315326)
  - Studies underway for usage in upfront setting
  - DA-TEDDI-R (NCT02203526)
  - R-MVP (NCT02315326, NCT04446962)
- Maintenance therapy following response to induction therapy (NCT02623010)

- Acalabrutinib (NCT04548648, NCT04462328)
- Tirabrutinib (NCT04947319)



PI3K/mTOR Pathway



Temsirolimus

- mTOR inhibitor
- Phase II study
  - RR ~54%
  - PFS 2.1 months
  - CSF conc. subtherapeutic

Buparlisib

- RR 25%
- CSF conc. Subtherapeutic
- Incomplete blockade of the
- PI3K/AKT/mTOR pathway

PQR309 (NCT02669511)

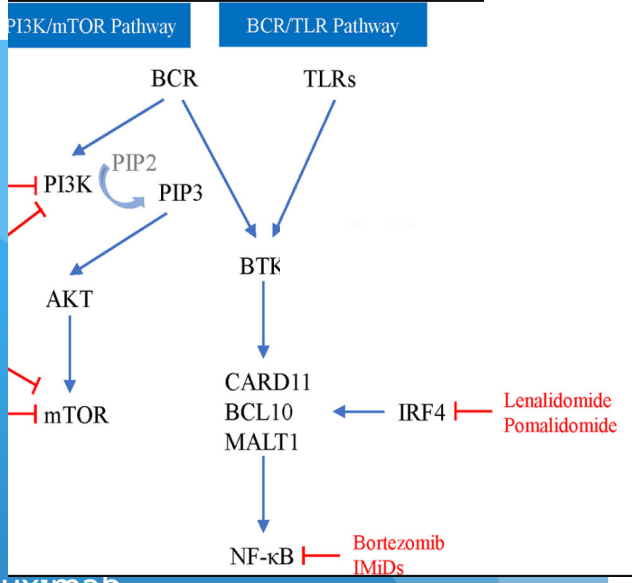
- dual PI3K/mTOR inhibitor

Paxalisib (NCT04906096)

- PI3K/mTOR inhibitor with CNS penetrance

Copanlisib (PI3K inhibitor) + Ibrutinib (NCT03581942)

Immunomodulatory



Lenalidomide and pomalidomide

- 3rd generation (IMiDs)
- Toxicity
  - Marrow suppression, infection, and fatigue
- ↓ IRF4
  - ↑ NKκB
  - ↑ MYC
- Block PI3K/AKT pathway
- Modulate TAM

Lenolidomide

- RR 64%

Lenolidomide + Rituximab

- ORR 35.6%
- PFS 17.7 mts
- OS 17.7 mts

Lenolidomide + Rituximab + Ibrutinib

- NCT03703167

Pomalidomide + Dexamethasone

- ORR was 48% with a PFS of 5.3 months

Pomalidomide + immunotherapy (NCT03798314)

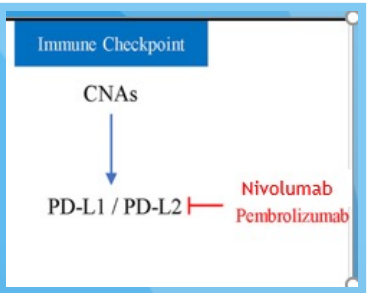
Recent Prospective Trials of Novel Agents

Author	Year	Agent(s)	Phase	Evaluable Patients	Disease Status	Median Age, y	ORR (PR + CR)	mPFS, mo	mOS, mo
Korfel [54]	2016	Temsirolimus	2	37	R/R	70	20/37 (54%)	2.1	3.7
Grommes [55]	2017	Ibrutinib	1	20 (13 PCNSL)	R/R	69	10/13 (77%)	4.6	15
Lionakis [40]	2017	TMZ, etoposide, liposomal doxorubicin, dexamethasone, rituximab, ibrutinib	1b	18	R/R, new	66	15/18 (83%)	15.3 in R/R	NR
Rubenstein [56]	2018	Lenalidomide + rituximab; lenalidomide maintenance	1	14 (7 PCNSL)	R/R	66	6/7 (86%)	6	NS
Tun [57]	2018	Pomalidomide + dexamethasone	1	25 (23 PCNSL)	R/R	NS, >60	11/23 (48%)	5.3	NS
Ghesquieres [58]	2019	Lenalidomide + rituximab	2	45 (34 PCNSL)	R/R	69	22/34 (65%)	3.9	NS
Grommes [59]	2019	Ibrutinib + M(3.5) + rituximab	1b	15 (9 PCNSL)	R/R	62	8/9 (89%)	NR	NR
Soussain [60]	2019	Ibrutinib	2	44	R/R	70	26/44 (59%)	4.8	19.2
Narita [61]	2021	Tirabrutinib	1/2	44	R/R	60	28/44 (64%)	2.9	NR

CR: complete response; M: methotrexate; mOS: median overall survival; mo: months mPFS: median progression-free survival; NR: not reached; NS: not specified; ORR: overall response rate; PCNSL: primary central nervous system lymphoma; PR: partial response; R/R: relapsed/refractory; TMZ: temozolomide; y: years.

Schaff and Grommes. Update on Novel Therapeutics for Primary CNS Lymphoma Cancers **2021**, 13, 5372.

Targeting the Immune System



PDL1

- Retrospective studies
  - Encouraging outcome
  - PFS > 13 months
  - Concurrent Rituximab or given after brain radiation
- Well tolerated
- Alternative treatment strategy
  - Elderly or frail
- Prospective studies
  - Monotherapy (NCT02857426)
  - + ibrutinib (NCT03770416, NCT04421560)
  - + lenalidomide (NCT04609046)
  - + pomalidomide (NCT03798314)
- Potential maintenance
  - (NCT04401774, NCT04022980)

CAR-T

- Initially patients with CNS disease were excluded from CART trials
  - Concern for ICANS
  - Potential for limited efficacy
- Preliminary data of trials enrolling pt w/ PCNSL
  - High rates of toxicity (CRS, ICANS)
- Ongoing trials
  - D19 CAR-T agents
    - tisagenlecleucel (NCT04134117)
    - axicabtagene ciloleucel (NCT04608487)

Other Targets

Abemaciclib (NCT03220646)

- Loss of CDKN2A

Venetoclax

- BCL-2
- Penetrate the BBB

Selinexor

- Exportin 1
  - Blocks nuclear export

  => accumulation of tumor suppressor proteins in the nucleus

  => cell death

Ongoing Trials of Novel Agents

Agents	Clinicaltrails.Gov ID	Trial Start	Phase	Target Accrual	Eligible Age	Country
Upfront Induction						
Rituximab, MTX, lenalidomide, nivolumab	NCT04609046	2020	1	27	18+	USA
Rituximab, MTX, procarbazine, vincristine; and lenalidomide or ibrutinib	NCT04446962	2020	1b/2	128	18 to 60	France
Rituximab, MTX ± lenalidomide	NCT04481815	2020	2	240	18 to 75	China
Rituximab, lenalidomide, MTX, and TMZ	NCT04737889	2021	2	30	18 to 70	China
Rituximab, MTX, procarbazine, vincristine, and ibrutinib	NCT02315326	2021	2	30	18+	USA
Upfront Maintenance						
Nivolumab maintenance	NCT04022980	2019	1b	20	65+	USA
MTX, rituximab, lenalidomide, with lenalidomide maintenance	NCT04120350	2019	1b/2	47	18 to 75	China
Rituximab, MTX, with ibrutinib maintenance	NCT02623010	2016	2	30	60 to 85	Israel
MTX or TMZ-based therapy with procarbazine or lenalidomide maintenance	NCT03495960	2019	2	208	70+	Italy
Lenalidomide/rituximab maintenance	NCT04627753	2020	2	30	19+	Korea
Nivolumab maintenance	NCT04401774	2020	2	25	18+	USA
Relapsed/Refractory Disease						
TMZ, etoposide, liposomal doxorubicin, dexamethasone, ibrutinib, rituximab, IT-cytarabine	NCT02203526	2014	1	93	18+	USA

Schaff and Grommes. Update on Novel Therapeutics for Primary CNS Lymphoma Cancers **2021**, 13, 5372.

Ongoing Trials of Novel Agents (Cont.)

Agents	Clinicaltrails.Gov ID	Trial Start	Phase	Target Accrual	Eligible Age	Country
Tisagenlecleucel	NCT04134117	2019	1	6	18+	USA
Acalabrutinib and durvalumab	NCT04462328	2020	1	21	18+	USA
Fludarabine, cyclophosphamide, axicabtagene ciloleucel	NCT04608487	2020	1	18	18+	USA
Ibrutinib with rituximab and lenalidomide	NCT03703167	2019	1b	40	18+	USA
Copanlisib with ibrutinib	NCT03581942	2018	1b/2	45	18+	USA
Pembrolizumab, ibrutinib, and rituximab	NCT04421560	2020	1b/2	37	18+	USA
PQR309	NCT02669511	2015	2	21	18+	Germany
Nivolumab	NCT02857426	2016	2	47	18+	USA
Abemaciclib	NCT03220646	2017	2	10	18+	USA
Ibrutinib, rituximab, ifosfamide and etoposide, with ibrutinib maintenance	NCT04066920	2019	2	30	20 to 79	Korea
Nivolumab and ibrutinib	NCT03770416	2019	2	40	18+	USA
Nivolumab and pomalidomide	NCT03798314	2019	1	3	18+	USA
Acalabrutinib	NCT04548648	2020	2	32	18+	USA
Ibrutinib versus lenalidomide, with MTX, rituximab, etoposide	NCT04129710	2020	2	120	18 to 75	China
Orelabrutinib	NCT04438044	2020	2	39	18 to 75	China
Paxalisib	NCT04906096	2021	2	25	18+	USA
Tirabrutinib	NCT04947319	2021	2	44	18+	USA

IT: intrathecal; MTX: methotrexate; TMZ: temozolomide.

Schaff and Grommes. Update on Novel Therapeutics for Primary CNS Lymphoma Cancers **2021**, 13, 5372.

Challenges to Development and Delivery

- PCNSL is a rare disease, limiting the ability to perform statistically significant head-to-head comparisons of treatment strategies
- Achieve adequate understanding of drug pharmacokinetics in the CNS
  - Proteasome inhibitors have poor penetration in CNS
- Penetration of the BBB
  - Multi-center study of BBB disruption (BBBD)
    - Mannitol + intra-arterial (IA) MTX
      - ORR of 81.9% (CRR 57.8%)
      - OS of 3.1 years
- Development of drug resistance as monotherapy

Future Directions

- Will these agents obviate the need for MTX?
- Novel treatments are given in combination to MTX based treatment in the upfront setting
- Many of the novel therapies are oral and most can be administered in the outpatient setting
- Would be great to find agents that can be as effective as MTX
- Usage of biomarkers such as IL-10 may help monitor treatment response and allow for early detection of relapse
- ctDNA for detection and confirmation of genetic arrangements in CSF to monitor treatment response (NCT04401774)

Conclusion

- Understanding of Molecular drivers of PCNSL have led to the development of novel drug strategies.
- Important feature for PCNSL
  - Penetrate the CNS
  - Create responses
  - Responses are durable
- Consideration of combination therapy to avoid early resistance
- Harnessing of the immune system
- Genetic characterization and monitoring to further our understanding and predicting response