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Authors

Roberts, Holly
Ravi, Karthik
Marini, Bernard
et al.

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Retrospective Comparison of Targeted Anticancer Drugs Predicted by the CNS-TAP Tool Versus Those Selected by a Molecularly Driven Tumor Board in Children With DIPG

Holly J. Roberts, MD, Karthik Ravi, MPhil,† Bernard L. Marini, PharmD,‡ Allison Schepers, PharmD,‡ Cassie Kline, MD,§ Lindsay Kilburn, MD,‖ Michael Prados, MD,¶ Sara A. Byron, PhD,# Julie Sturza, MPH,** Sabine Mueller, MD, PhD,††‡‡ Carl Koschmann, MD,** and Andrea T. Franson, MD***

Abstract: The recent trial Pediatric Neuro-Oncology Consortium 003 (PNOC003) utilized a molecular tumor board to recommend personalized treatment regimens based on tumor sequencing results in children with DIPG. We separately developed the Central Nervous System Targeted Agent Prediction (CNS-TAP) tool, which numerically scores targeted anticancer agents using preclinical, clinical, and patient-specific data. We hypothesized that highly scored agents from CNS-TAP would overlap with the PNOC003 tumor board's recommendations. For each of the 28 participants, actionable genetic alterations were derived from PNOC003 genomic reports and input to CNS-TAP to identify the highest scoring agents. These agents were then compared with PNOC003 recommendations, with a resultant concordance percentage calculated. Overall, 38% of the total agents recommended by the tumor board were also selected by CNS-TAP, with higher concordance (63%) in a subanalysis including only targeted anticancer agents. Furthermore, nearly all patients (93%) had at least 1 drug chosen by both methods. We demonstrate overlap between agents recommended by CNS-TAP and PNOC003 tumor board, though this does not appear to improve survival. We do observe some discordance, highlighting strengths and limitations of each method. We propose that a combination of expert opinion and data-driven tools may improve targeted treatment recommendations for children with DIPG.

Key Words: diffuse intrinsic, diffuse midline glioma, next-generation sequencing, pontine glioma, precision oncology, targeted therapy

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Tumors of the central nervous system (CNS) are the leading cause of childhood cancer-related death.[1,2] There have been important advances in the treatment of pediatric cancer in the last 2 decades, with targeted therapies and immunotherapies most recently at the forefront of improving likelihood of cure. However, relatively little progress has been made in the treatment of pediatric high-grade glioma (HGG) during this time.[3]

Diffuse intrinsic pontine gliomas are an especially aggressive HGG subtype that primarily occur in children,[4] are unresectable, and have no known curative therapy, with a median survival of 9 to 11 months.[5–7] Although there are potentially promising therapies in development, the only therapy to date that has improved survival in these patients is focal radiation therapy, despite years of research in this arena.[8] Most recently, extensive sequencing of DIPG biopsy specimens has revealed genomic heterogeneity of these tumors, fueling an interest in individualized, targeted treatment approaches.[8–10]

The number of clinically available, targeted anticancer therapies is growing rapidly. In addition, the use of next-generation sequencing to identify tumor genetic alterations has become a mainstay of clinical practice.[11] There has been great interest in applying genomic data from an individual patient's tumor to the selection and evaluation of a personalized, targeted treatment regimen through clinical trials.[12] While this approach has not yielded a clear improvement in survival, it is still common in clinical practice, particularly for patients with limited treatment options. A recent feasibility study within the Pacific Pediatric Neuro-Oncology Consortium (PNOC) enrolled patients with newly diagnosed DIPG onto PNOC003:

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From the *Boston Children's Hospital, Boston, MA; †Stanford Medicine, Palo Alto; Departments of ¶Neurosurgery and Pediatrics; ††Neurology, Neurosurgery, and Pediatrics, San Francisco School of Medicine, University of California, San Francisco, CA; ‡Department of Clinical Pharmacy and Pharmacy Services, University of Michigan; **University of Michigan Medical School, Ann Arbor, MI; §Children's Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; ‖Children's National Health System, Washington, DC; #Translational Genomics Research Institute, Phoenix, AZ; and ‡‡Department of Pediatrics, University of Zurich, Switzerland.
A.T.F., C.K., and H.J.R. were responsible for conception and design. A.T.F. and H.J.R. were responsible for development of methodology and acquisition of data. A.T.F., H.J.R., K.R., and B.L.M. were responsible for analysis and interpretation of data. A.T.F., H.J.R., K.R., B.L.M., and A.S. were responsible for drafting the manuscript; all authors were involved with review and/or revision of the manuscript. A.T.F. was responsible for overall study.

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Reprints: Andrea T. Franson, MD, MS, Division of Hematology and Oncology, Department of Pediatrics, University of Michigan Medical School, 1500 East Medical Center Driver, Ann Arbor, MI 48109 (e-mail: atflynn@umich.edu).
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Molecular Profiling for Individualized Treatment Plan for DIPG (NCT02274987), in which a tumor board comprised of scientists and clinicians from academic medical centers reviewed genomic and molecular profiling of a patient's tumor to recommend targeted therapy with up to 4 FDA-approved agents.[13]

There are unique challenges inherent to using targeted anticancer agents in pediatric CNS tumors, including variable or unknown penetration of the blood-brain barrier (BBB), limited clinical response data for CNS tumors, and often minimal pediatric-specific safety data. Given the complexity and subjectivity of therapeutically targeting pediatric CNS tumors through expert tumor boards, our group developed the Central Nervous System Targeted Agent Prediction (CNS-TAP) tool that combines preclinical, clinical, and CNS-specific published data for targeted agents to allow for data-informed numeric scoring of the agents based on patient-specific tumor genomics.[14] This tool aims to assist clinicians in evaluating and selecting personalized targeted therapies for patients with brain tumors with increased efficiency and objectivity by incorporating objective measures of pharmacokinetic properties, efficacy, and safety.

We hypothesized that high-scoring agents from the CNS-TAP tool for an individual patient would in part overlap with agents recommended by the molecular tumor board in the PNOC003 study. Here, we describe our findings of this retrospective study using deidentified genomic profiling from PNOC003 participants inputted into the CNS-TAP tool to test our hypothesis by quantifying the concordance of recommended therapies between these methods. In addition, we aimed to examine discordance between the 2 methods to explore how CNS-TAP may be best utilized when incorporated prospectively into clinical trials and clinical care to inform molecular tumor board recommendations.

MATERIALS AND METHODS

PNOC003 Molecular Profiling for Individualized Treatment Plan for DIPG (NCT02274987): Study Design

Before patient enrollment, each site received appropriate institutional approvals, including final approval from the institutional review board. All patients and legal guardians provided written consent and assent, where appropriate, at the time of enrollment, including future research on participants' deidentified health information.

PNOC003 included patients from 5 academic pediatric cancer centers in the United States from September 2014 through February 2018 with newly diagnosed diffuse intrinsic pontine gliomas who provided paired tumor and constitutional tissue samples, were age 3 to 25 years, and had no evidence of dissemination.[13] Tissue and peripheral blood samples underwent tumor-normal whole exome sequencing and tumor RNA sequencing, with results presented to a tumor board comprised of pediatric neuro-oncologists, genomics experts, and neuropharmacologists, who together recommended a treatment regimen of up to 4 agents for each patient. Only FDA-approved agents were recommended, including repurposed (FDA-approved with no cancer indication) agents with known or predicted BBB penetration, and reported activity against a cancer target.[13]

Patient Selection

PNOC003 included 28 patients who were eligible for enrollment. We retrospectively collected the following de-identified information: age at enrollment, clinical diagnosis, date of tumor board discussion, genomic reports, and agents recommended by the tumor board.

CNS-TAP Tool and Adaptation

CNS-TAP has been previously retrospectively validated as a targeted anticancer agent selection tool that is comparable to institutional expert opinion for pediatric patients with brain tumors.[14] The CNS-TAP version used in this study includes 51 agents targeting 17 molecular pathways commonly mutated in pediatric CNS tumors. Each agent in the tool is scored in 9 categories, with a higher numerical score suggesting the potential for greater clinical benefit.[14] The criteria within CNS-TAP are listed in Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/JPHO/A713 along with relevant clinical trial availability and FDA approval.[14] For this study we excluded clinical trial availability as a scored criterion given that cross-enrollment in another trial would not be permitted on PNOC003. We also excluded agents that were not FDA approved before the date of a patient's tumor board given FDA approval was a requirement for tumor board drug recommendation as part of PNOC003. Information regarding numeric score distribution and weight of each category in CNS-TAP as utilized in this study is available in Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/JPHO/A713 and has been published previously.[14]

Retrospective Agent Recommendation Utilizing CNS-TAP

For each patient, genomic reports identified actionable mutations relevant to the molecular pathways within the CNS-TAP tool. A list of evaluable pathways and included agents for each pathway within CNS-TAP is available in Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/JPHO/A714. For our purposes, we considered point mutations, insertions, deletions, copy number gains and losses, and fusions as potential therapeutic targets. We did not consider differential RNA expression as targets for therapy as was done by the PNOC003 tumor board, as CNS-TAP was designed for DNA-based events.

The scoring for patient-agnostic criteria except FDA approval were based on the CNS-TAP tool version dated April 17, 2019 and held constant for all patients regardless of tumor board date. Variant allele frequency was provided in the genomic reports, and points were assigned in CNS-TAP as outlined in Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/JPHO/A713. Variant tier score was determined using the 4-tiered system based on clinical significance of mutations proposed by Li et al.[15] Figure 1 provides a visual example of CNS-TAP scoring for a sample patient.

Once all agents from implicated pathways were scored in CNS-TAP, the highest scoring agent from each pathway was chosen to develop a recommended treatment regimen with up to 4 agents to align with PNOC003.

Evaluation and Comparison of CNS-TAP and Tumor Board Recommended Regimens

Once recommended agents were finalized, we compared CNS-TAP recommendations with those of the PNOC003 tumor board, calculating the percentage of

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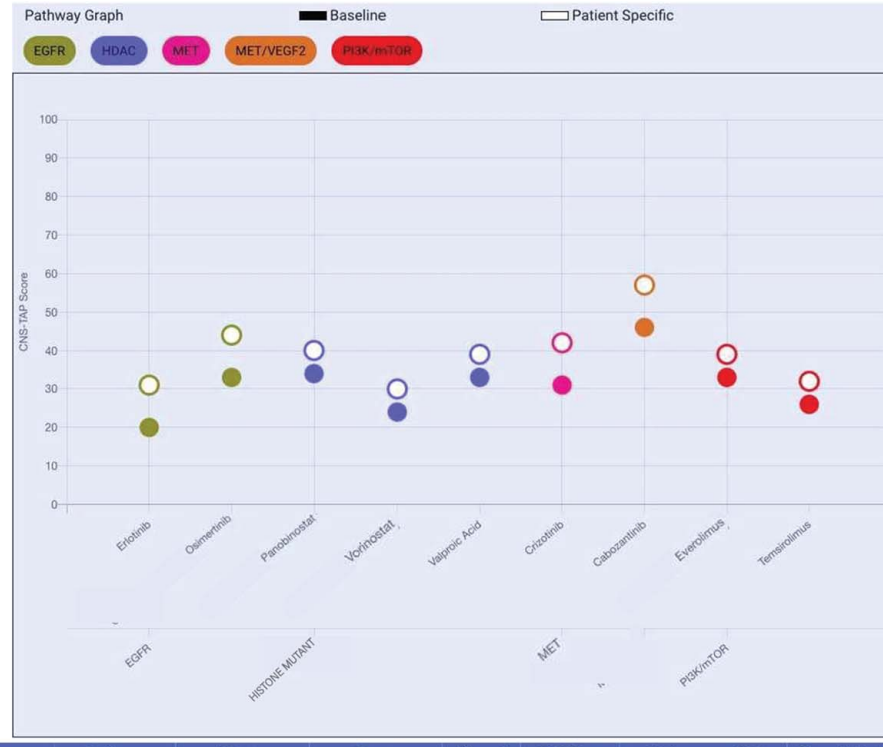

Drug Names	Pathway	Tumor line/preclinical data(In vitro)	Tumor line/preclinical data(In vivo)	Phase I safety data	CNS Data with response	Brain penetration	FDA approval	Clonality/variant allele fraction(%)	Variant tier score	Total Points
Erlotinib	EGFR	4	0	6	-10	10	10	5	6	31
Osimertinib	EGFR	2	6	0	5	10	10	5	6	44
Panobinostat	HISTONE	2	6	6	10	0	10	0	6	40
Vorinostat	HISTONE	2	6	6	-10	10	10	0	6	30
Valproic Acid	HISTONE	4	3	6	0	10	10	0	6	39
Crizotinib	MET	4	6	6	5	0	10	5	6	42
Cabozantinib	MET	4	6	6	10	10	10	5	6	57
Everolimus	PI3K/mTOR	2	0	6	10	5	10	0	6	39
Temsirolimus	PI3K/mTOR	4	6	6	-5	5	10	0	6	32

FIGURE 1. Example of CNS-TAP application scoring and graphical output for patient 34. CNS-TAP indicates Central Nervous System Targeted Agent Prediction. full color online

agents selected by both modalities, both for each individual patient and cumulatively for all patients. The concordance percentage was calculated as the total number of matched agents divided by the total number of agents recommended by the PNOC003 tumor board.

As CNS-TAP was designed to recommend molecularly targeted anticancer agents, we performed a subanalysis in which generic cytotoxic (traditional chemotherapeutic) agents and repurposed, nonanticancer agents were excluded from CNS-TAP and tumor board recommendations, re-calculating the percentage of concordant agents. If zero agents remained from both the tumor board and CNS-TAP recommendations with these criteria, the concordance was considered 100%.

We performed another subanalysis to evaluate the impact of RNA-based drug recommendations by the PNOC003 tumor board on overall concordance since CNS-TAP only considered DNA-based alterations. Here, we again excluded cytotoxic chemotherapies and repurposed agents in addition to agents recommended by the tumor board based on RNA alterations.

To evaluate the repurposed agents selected by the PNOC003 tumor board that were not included in CNS-TAP (minocycline, mebendazole, propranolol, metformin, and sertraline), we performed a literature review to determine scores for these agents utilizing CNS-TAP criteria.

Survival Comparison Based on Concordance of CNS-TAP and PNOC003 Tumor Board

Overall survival (OS) and progression-free survival (PFS) were provided for each PNOC003 participant. For those patients who followed tumor board recommended

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regimens, OS and PFS were compared for statistical significance among those whose match percentages fell into the following tertiles: (1) 0% to 33.3% match, (2) > 33.3% to 66.7% match, and (3) > 66.7% match. We performed product-limit survival estimates with 95% CI between the tertile groups for both PFS and OS.

RESULTS

Concordance Among CNS-TAP and PNOC003 Tumor Board

Agents selected by the PNOC003 tumor board and the highest scoring agents within CNS-TAP for given pathways for each study participant are presented in Table 1 and Fig. 2A. Comparison of selected agents revealed that of the total 95 agents recommended by the tumor board across all participants, 36 were also selected by CNS-TAP (38%). These 36 instances were comprised of 7 distinct agents, most commonly panobinostat (n = 19), cabozantinib (n = 5), and everolimus (n = 5). In line with the targets of these frequently concordant drugs, the most frequently altered, targetable pathways in patient tumor samples included histone mutations (*H3F3A* and *HIST1H3B*) (n = 25), loss of *ATRX* (n = 7), *MET* mutations/amplifications (n = 5), and PI3K mutations (n = 5). Furthermore, 93% (26/28) of patients had at least 1 agent recommended by both the tumor board and CNS-TAP.

Independently, CNS-TAP recommended 10 distinct agents, most frequently panobinostat (n = 23), carboplatin (n = 8), and cabozantinib (n = 5). The tumor board recommended 18 unique agents, most frequently panobinostat (n = 19), mebendazole (n = 14), and everolimus (n = 11) (Fig. 2B). Compared with the 95 total agents recommended by the tumor board for all patients (median = 4/patient, range: 1 to 4), CNS-TAP recommended 53 total agents (median = 2/patient, range: 0 to 4).

We next evaluated the concordance between the 2 methods including only molecularly targeted anticancer drugs (Table 1). Higher concordance was seen in this subanalysis, with 34 of the 56 agents (63%) recommended by the tumor board also selected by CNS-TAP. Furthermore, 96% (27/28) of patients had at least 1 targeted agent selected by both methods or no agents recommended by either method. The percentage of concordant agents, both overall and limited to targeted anticancer agents, for each patient is displayed in Figure 2C. Of the 28 patients, the concordance increased in 25 patients and was unchanged in 3 patients compared with the original analysis (range: 0% to 100%).

Further analysis of targeted anticancer agents also excluding those recommended based on differential RNA expression by the tumor board (Table 1) further increased the concordance, with 34 of the 44 agents (77%) recommended by the tumor board also being selected by CNS-TAP.

Repurposed Drugs Utilized Exclusively by the Tumor Board

Among the 18 individual agents recommended by the tumor board, 5 were not included in the CNS-TAP tool and have no FDA-approved cancer-specific indications. These include mebendazole, metformin, propranolol, sertraline, and minocycline, with at least one of these agents selected by the tumor board for 22 of the 28 patients (79%) (Table 1). Seven participants received recommendations for these repurposed agents in place of targeted anticancer agents through 2 distinct mechanisms (Table 2). First, mebendazole was recommended as an inhibitor of PDGFR and was selected over dasatinib, an FDA-approved anticancer tyrosine kinase inhibitor, in 4 patients. Second, given the maximum of 4 agents per regimen, there were 3 instances in which repurposed agents directed at an alternative pathway were chosen over an agent targeting a histone mutation. The remaining 15 patients for whom one of these repurposed agents was recommended did not result in an altered pathway being unaddressed but was instead included as an additional agent.

To evaluate the potential safety and efficacy of these repurposed agents and to compare them with the targeted agents CNS-TAP recommended for the patients in Table 2, we separately scored them using the CNS-TAP tool criteria, with baseline scores listed in Supplemental Table 3, Supplemental Digital Content 3, http://links.lww.com/JPHO/A715 and patient-specific scores in Table 2.

Impact of CNS-TAP and Tumor Board Concordance on Patient Survival

67.9% (n = 19/28) of patients followed PNOC003 tumor board therapy recommendations. There was no statistically significant difference in OS ($P = 0.42$) or PFS ($P = 0.51$) among patients who had 0% to 33.3% match (n = 2 patients), > 33.3% to 66.7% match (n = 10), and > 66.7% match (n = 7 as seen in Fig. 3).

DISCUSSION

Many pediatric HGGs harbor genetic aberrations that may be amenable to targeted therapies. Several recent clinical trials aim to determine the role of a "precision medicine" approach to recommend patient-specific targeted therapy through a multidisciplinary tumor board. However, there is inherent subjectivity in such an approach. Our group previously described an approach to score targeted agents using published data about pharmacokinetic properties, preclinical efficacy, and clinical safety and efficacy combined with patient sequencing results for potential use in pediatric patients with brain tumors, with the resultant creation of the CNS-TAP tool. Here, we aimed to compare purely human decision-making and data-driven algorithms as related to targeted anticancer drug selection by determining the overlap of agent recommendations made by a tumor board and highest-scoring agents within the CNS-TAP tool. Importantly, we acknowledge that targeting unique genomic alterations in individual patients' tumors has not demonstrated universally improved outcomes, particularly in pediatric HGGs given their molecular complexity. In contrast, pediatric low-grade gliomas often harbor single driver mutations and as such have demonstrated response to molecularly targeted therapies. However, use of molecularly targeted therapy is still a frequent practice, both clinically and within the context of clinical trials, in patients with aggressive malignancies with limited treatment options, such as DIPG. In this study, we demonstrate concordance between agents recommended by an expert tumor board and CNS-TAP for children with DIPG, with nearly all patients having at least 1 agent recommended by both methods. Importantly, the percentage of concordant agents between CNS-TAP and PNOC003 tumor board increases when only targeted anticancer agents are considered, highlighting the utility of CNS-TAP specifically for selecting

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TABLE 1. Patient Demographic, Diagnostic, and Tumor Genomic Information

PNOC-003 patient ID	Age at enrollment (y)	Diagnosis	Date of tumor board (month-year)	Followed therapy (yes/no)	Actionable mutations from CNS-TAP	Highest scoring drug (s) from implicated pathway	CNS-TAP score	All drugs		Targeted anticancer drugs only	
								CNS-TAP regimen predicted	Tumor board drugs recommended	CNS-TAP regimen predicted	Tumor board drugs recommended
01	4	DMG, H3K27M-mutant, WHO gr IV	October-2014	No	H3F3A K27M	Valproic Acid	39	Valproic Acid	Etoposide* Dasatinib*	Valproic Acid	Dasatinib*
02	5	DMG, H3K27M-mutant, WHO gr IV	February-2015	Yes	H3F3A K27M	Valproic Acid	39	Valproic Acid Cabozantinib Dasatinib	Etoposide* Cabozantinib Mebendazole	Valproic Acid Cabozantinib Dasatinib	Cabozantinib
					MET Copy Number Gain	Cabozantinib	49				
					PDGFRA Copy Number Gain	Dasatinib	47				
04	9	Diffuse astrocytoma, IDH- and H3-wildtype, WHO gr II	May-2015	No	N/A	N/A	N/A		Sertraline		
05	7	DMG, H3K27M-mutant, WHO gr IV	May-2015	No	H3F3A K27M	Panobinostat	40	Panobinostat Dasatinib	Panobinostat Cabozantinib Mebendazole	Panobinostat Dasatinib	Panobinostat Cabozantinib
					PDGFRA Copy Number Gain	Dasatinib	52				
06	13	DMG, H3K27M-mutant, WHO gr IV	August-2015	Yes	H3F3A K27M	Panobinostat	40	Panobinostat Carboplatin	Panobinostat Mebendazole*	Panobinostat	Panobinostat
					ATRX W2001Stop	Carboplatin	47				
07	7	DMG, H3K27M-mutant, WHO gr IV	August-2015	No	H3F3A K27M	Panobinostat	45	Panobinostat Everolimus	Panobinostat Everolimus Sertraline Mebendazole*	Panobinostat Everolimus	Panobinostat Everolimus
					PIK3R1 K567E	Everolimus	39				
08	14	DMG, H3K27M-mutant, WHO gr IV	August-2015	Yes	H3F3A K27M	Panobinostat	40	Panobinostat Carboplatin	Panobinostat	Panobinostat	Panobinostat
					ATRX Copy Number Loss	Carboplatin	47				
09	7	DMG, H3K27M-mutant, WHO gr IV	August-2015	No	H3F3A K27M	Panobinostat	45	Panobinostat Carboplatin	Panobinostat	Panobinostat	Panobinostat
					ATRX A1812P	Carboplatin	42				

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TABLE 1. (*continued*)

PNOC-003 patient ID	Age at enrollment (y)	Diagnosis	Date of tumor board (month-year)	Followed therapy (yes/no)	Actionable mutations from CNS-TAP	Highest scoring drug (s) from implicated pathway	CNS-TAP score	All drugs		Targeted anticancer drugs only	
								CNS-TAP regimen predicted	Tumor board drugs recommended	CNS-TAP regimen predicted	Tumor board drugs recommended
10	9	DMG, H3K27M-mutant, WHO gr IV	September-2015	Yes	H3F3A K27M	Panobinostat	45	Panobinostat Dabrafenib	Panobinostat Dabrafenib Trametinib Minocycline	Panobinostat Dabrafenib	Panobinostat Dabrafenib Trametinib
					BRAF V600E	Dabrafenib	47				
11	25	Anaplastic astrocytoma, gr II	September-2015	Yes	ATRX E2279*	Carboplatin	36	Carboplatin	Carboplatin Etoposide* Metformin Mebendazole*		
12	10	DMG, H3K27M-mutant, WHO gr IV	September-2015	Yes	H3F3A K27M	Panobinostat	40	Panobinostat Carboplatin Dasatinib	Panobinostat Mebendazole Everolimus Valproic acid*	Panobinostat Dasatinib	Panobinostat Everolimus Valproic acid*
					ATRX A1812P	Carboplatin	42				
					PDGFRA Copy Number Gain	Dasatinib	52				
13	5	DMG, H3K27M-mutant, WHO gr IV	September-2015	Yes	H3F3A K27M	Panobinostat	40	Panobinostat Cabozantinib Dasatinib	Panobinostat Cabozantinib Mebendazole Valproic acid*	Panobinostat Cabozantinib Dasatinib	Panobinostat Cabozantinib Valproic acid*
					MET Copy Number Gain	Cabozantinib	57				
					PDGFRA Copy Number Gain	Dasatinib	52				
14	6	DMG, H3K27M-mutant, WHO gr IV	October-2015	No	H3F3A K27M	Panobinostat	40	Panobinostat Cabozantinib	Panobinostat Cabozantinib Mebendazole* Valproic acid*	Panobinostat Cabozantinib	Panobinostat Cabozantinib Valproic acid*
					MET Copy Number Gain	Cabozantinib	57				
16	4	DMG, H3K27M-mutant, WHO gr IV	February-2016	Yes	HIST1H3B K27M	Panobinostat	40	Panobinostat	Panobinostat Mebendazole* Valproic acid* Propranolol*	Panobinostat	Panobinostat Valproic acid*

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17	5	Diffuse astrocytoma, gr II	February-2016	No	H3F3A K27M	Panobinostat	40	Panobinostat	Panobinostat Olaparib Irinotecan	Panobinostat	Panobinostat Olaparib
19	12	Diffuse astrocytoma, gr UNK	July-2016	Yes	CDKN2A Copy Number Loss	Palbociclib	24	Palbociclib Trametinib	Palbociclib Trametinib Everolimus Mebendazole*	Palbociclib Trametinib	Palbociclib Trametinib Everolimus
					NF1 G629R & Del	Trametinib	44				
21	12	Anaplastic astrocytoma, gr III	August-2016	No	H3F3A K27M	Panobinostat	40	Panobinostat	Panobinostat Trametinib Everolimus Metformin	Panobinostat	Panobinostat Trametinib Everolimus
23	4	DMG, H3K27M-mutant, WHO gr IV	October-2016	Yes	H3F3A K27M	Panobinostat	40	Panobinostat	Panobinostat Mebendazole* Etoposide*	Panobinostat	Panobinostat
26	5	DMG, H3K27M-mutant, WHO gr IV	December-2016	Yes	H3F3A K27M	Panobinostat	40	Panobinostat Palbociclib	Panobinostat Palbociclib Mebendazole* Dasatinib*	Panobinostat Palbociclib	Panobinostat Palbociclib Dasatinib*
					CCND2 Copy Number Gain	Palbociclib	29				
27	6	DMG, H3K27M-mutant, WHO gr IV	February-2017	Yes	H3F3A K27M	Panobinostat	40	Panobinostat	Panobinostat Everolimus Propranolol* Mebendazole	Panobinostat	Panobinostat Everolimus
30	6	High grade pontine glioma, gr III-IV	April-2017	Yes	H3F3A K27M	Panobinostat	40	Panobinostat	Panobinostat Everolimus Mebendazole* Etoposide*	Panobinostat	Panobinostat Everolimus
31	6	DMG, H3K27M-mutant, WHO gr IV	May-2017	No	H3F3A K27M	Panobinostat	40	Panobinostat	Panobinostat Everolimus* Propranolol* Dasatinib*	Panobinostat	Panobinostat Everolimus* Dasatinib*
33	8	DMG, H3K27M-mutant, WHO gr IV	August-2017	Yes	H3F3A K27M	Panobinostat	45	Panobinostat Everolimus Carboplatin	Everolimus Etoposide* Metformin Dasatinib*	Panobinostat Everolimus	Everolimus Dasatinib*
					ATRX R2111L	Carboplatin	42				
					PIK3CA E545K MTOR E1799K	Everolimus	39				
34	6	DMG, H3K27M-mutant, WHO gr IV	October-2017	Yes	H3F3A K27M	Panobinostat	40	Panobinostat Osimertinib Cabozantinib Everolimus	Cabozantinib Everolimus Erlotinib Propranolol	Panobinostat Osimertinib Cabozantinib Everolimus	Cabozantinib Everolimus Erlotinib

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TABLE 1. (*continued*)

PNOC-003 patient ID	Age at enrollment (y)	Diagnosis	Date of tumor board (month-year)	Followed therapy (yes/no)	Actionable mutations from CNS-TAP	Highest scoring drug (s) from implicated pathway	CNS-TAP score	All drugs: CNS-TAP regimen predicted	All drugs: Tumor board drugs recommended	Targeted anticancer drugs only: CNS-TAP regimen predicted	Targeted anticancer drugs only: Tumor board drugs recommended
					EGFR Copy Number Gain	Osimertinib	44				
					MET Copy Number Gain	Cabozantinib	57				
					PIK3CA H1047R	Everolimus	39				
35	10	DIPG, H3K27M-mutant, WHO gr IV	November-2017	Yes	H3F3A K27M	Panobinostat	40	Panobinostat Cabozantinib	Cabozantinib Dasatinib* Etoposide* Metformin	Panobinostat Cabozantinib	Cabozantinib Dasatinib*
					MET Copy Number Gain	Cabozantinib	57				
36	4	Diffuse infiltrating astrocytoma	November-2017	Yes	H3F3A K27M	Panobinostat	40	Panobinostat	Panobinostat Etoposide* Dasatinib* Cabozantinib*	Panobinostat	Panobinostat Dasatinib* Cabozantinib*
37	5	DMG, H3K27M-mutant, WHO gr IV	January-2018	Yes	HIST1H3B K27M	Panobinostat	45	Panobinostat Carboplatin Trametinib Everolimus	Carboplatin Trametinib Everolimus Etoposide*	Panobinostat Trametinib Everolimus	Trametinib Everolimus
					TUBB3 Copy Number Loss	Carboplatin	36				
					NRAS Q61K	Trametinib	39				
					PIK3CA E545Q	Everolimus	39				
38	6	DMG, H3K27M-mutant, WHO gr IV	February-2018	Yes	H3F3A K27M	Panobinostat	45	Panobinostat Carboplatin Everolimus	Panobinostat Everolimus Etoposide* Metformin	Panobinostat Everolimus	Panobinostat Everolimus
					ATRX R81T	Carboplatin	42				
					PIK3CA E545K	Everolimus	39				

*Therapy recommended based on RNA sequencing data.

Includes agents selected by the tumor board and recommended by CNS-TAP for each patient, (1) inclusive of all agents, (2) excluding generic cytotoxic and repurposed nonanticancer agents, and (3) excluding generic cytotoxic and repurposed agents as well as those recommended on the basis of RNA alterations.

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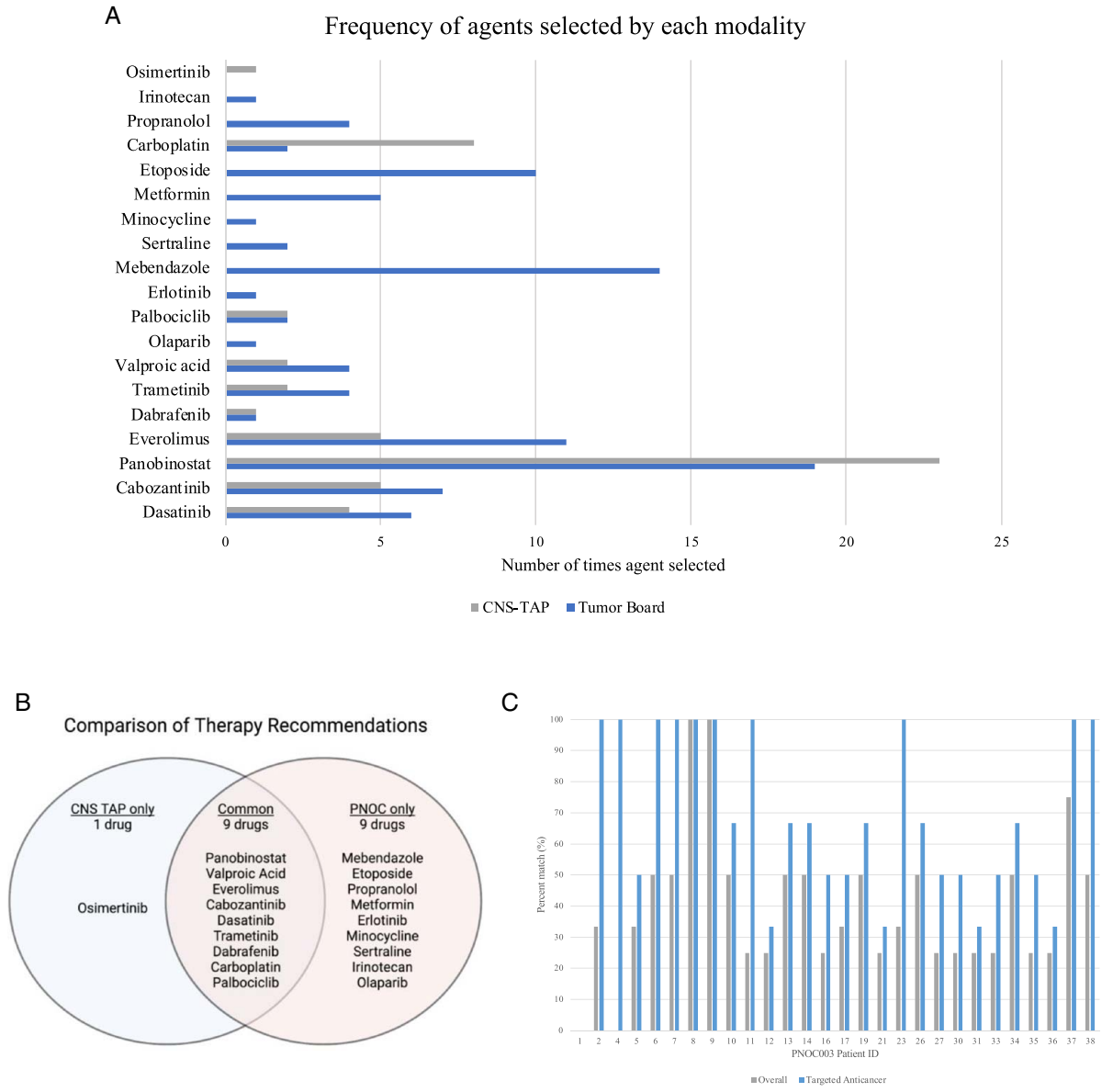

FIGURE 2. Comparison of CNS-TAP and PNOC003 tumor board recommendations. A, Comparison of frequency of agents selected by each modality. B, Comparison of agents selected independently by CNS-TAP and PNOC, as well as overlapping agents. C, Percentage of matched agents recommended by both CNS-TAP and PNOC tumor board compared with total number of agents recommended by tumor board for each participant. CNS-TAP indicates Central Nervous System Targeted Agent Prediction; PNOC, pediatric neuro-oncology consortium. full color online

targeted agents with the most compelling data for use in pediatric patients with brain tumors.[13]

Despite the overlap in recommended agents, there is discordance among CNS-TAP and the PNOC003 tumor board recommendations, for which we propose 3 main causative factors. First, the tumor board recommended agents based on differential RNA expression in the absence of genetic alterations, where RNA expression data were not considered within CNS-TAP. Therefore, the exclusion of therapies recommended based on RNA expression led to higher treatment recommendation concordance. Data supporting the use of differential RNA expression to recommend targeted therapy in pediatric HGG are lacking currently. However, investigation into the use of CNS-TAP to recommend targeted therapies based on RNA expression may be warranted, particularly given recent insight into the utility of RNA sequencing to identify targetable alterations in low-grade gliomas.[15] However, increasing reports of pediatric HGG patient responses to targeted therapies with specific DNA alterations continue to support that DNA changes likely are more successfully "targeted" by small molecule inhibitors than RNA expression changes.[16,17] Second, the use of nonanticancer and generic cytotoxic agents by the tumor board contributed to the discordance in treatment recommendations. For example, mebendazole has evidence of anticancer activity in CNS tumor models in vivo, including glioma.[18,19] However, human clinical trial data are lacking with only small, single institution phase 1 clinical studies in

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TABLE 2. Evaluation of Repurposed Drugs

			CNS-TAP			Tumor board		
Study ID	**TB date (month/year)**	**Dx**	**Pathway**	**Targeted anticancer agent**	**Score**	**Pathway**	**Agent**	**Score**
2	2/2015	DMG, H3K27M-mutant, WHO grIV	PDGFR	Dasatinib	47	PDGFR	Mebendazole	42
5	5/2015	DMG, H3K27M-mutant, WHO grIV	PDGFR	Dasatinib	52	PDGFR	Mebendazole	47
12	9/2015	DMG, H3K27M-mutant, WHO grIV	PDGFR	Dasatinib	52	PDGFR	Mebendazole	47
13	9/2015	DMG, H3K27M-mutant, WHO grIV	PDGFR	Dasatinib	52	PDGFR	Mebendazole	47
33	8/2017	DMG, H2K27M-mutant, WHO GrIV	Histone mutant	Panobinostat	45	PIK3CA	Metformin	39
34	10/2017	DMG, H3K27M-mutant, WHO GrIV	Histone mutant	Panobinostat	40	EGFR	Propanolol	44
35	11/2017	DIPG, H3K27M-mutant, WHO GrIV	Histone mutant	Panobinostat	40	IGF1R	Metformin	44

The highest scoring drug from CNS-TAP is compared with the CNS-TAP score of the repurposed agent recommended by the tumor board for applicable patients. CNS-TAP indicates Central Nervous System Targeted Agent Prediction.

patients with CNS tumors.[20] While repurposed agents may have preliminary data suggesting efficacy in CNS malignancies, it may be premature to recommend their clinical use, as demonstrated by the relatively low CNS-TAP scores for most of these agents, largely due to lack of clinical data (Table 2). Lastly, there may be instances in which the tumor board considers drug-drug interactions, patient-specific comorbidities, or other variables in treatment recommendations, which are not considered within CNS-TAP scoring. Therefore, CNS-TAP requires clinician input for combination therapy recommendations, adding subjectivity.

Our study reveals limitations of both CNS-TAP and molecular tumor boards, which both remain reliant on expert opinion for selection of targeted treatment regimens. In addition to CNS-TAP limitations noted previously, data within the tool cannot realistically be updated in real-time, so clinicians may be aware of new data before its incorporation into CNS-TAP. Similarly, there may be repurposed nonanticancer agents with strong evidence of potential efficacy in patients with brain tumors not included in CNS-TAP. In addition, both CNS-TAP and a tumor board require clinical expertise among users given the nuances in targeting genetic alterations. For example, NF1-deficient glioma cell lines have demonstrated sensitivity to MEK inhibition,[21] so MEK is frequently targeted in such tumors, as for patient 19 (Table 1). When a genetic alteration is not a direct target of an agent but is implicated within the molecular pathway, knowledge of applicable cancer biology is critical. In addition, CNS-TAP was developed using the clinical judgment of its creators regarding the weight of various categories and agents to include, though all scoring is based entirely on published data. Conversely, tumor boards are inherently subjective as they rely on input from experts whose recommendations are likely influenced by personal experiences and biases as well as personal knowledge and recollection of published data. Given the strengths and limitations of each method, we anticipate that a combination of data-driven scoring tools and expert opinion through incorporation of such technology within molecular tumor boards will optimize therapy recommendations for patients. In line with this hypothesis, an international panel of neuro-oncology experts identified precision medicine and incorporation of technology as 2 important factors in advancing treatment of primary brain tumors.[22]

Our study has several limitations. First, publication of these data was delayed compared with PNOC003 study completion due to the publication of full data analysis, specifically with regards to survival outcomes. In addition, the retrospective nature of our investigation results in inconsistent availability of data at the time of original tumor board and subsequent CNS-TAP scoring. We partly rectify this by using a version of CNS-TAP dated April 17, 2019 and ensuring that recommended agents from CNS-TAP were FDA-approved as of each individual patient's tumor board date. Another confounding factor is that, while we aim to evaluate the concordance between a tumor board and a data-based method for agent selection, some clinical judgment is required to properly utilize CNS-TAP. We performed comprehensive literature searches to support such decisions in pursuit of objectivity. The inability to include non-FDA approved agents is a limitation of our study as well, given that targeted investigational drugs are used in DIPG in the context of clinical trials or, less frequently, compassionate access. Importantly, CNS-TAP

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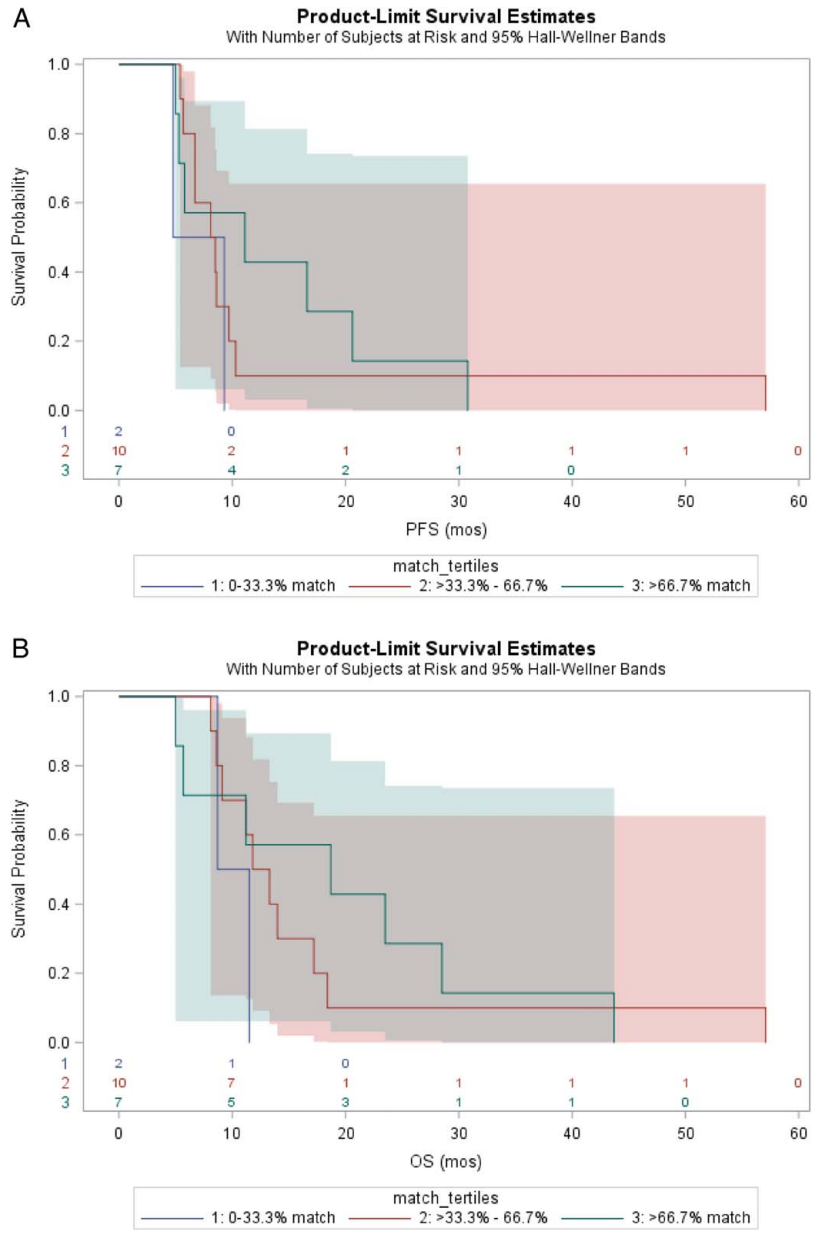

FIGURE 3. Survival analysis. A, PFS is not statistically different between groups of patients based on percent match tertiles of agents selected by tumor board and predicted by CNS-TAP ($P=0.51$). B, OS is not statistically different between groups of patients based on percent match tertiles of agents selected by tumor board and predicted by CNS-TAP ($P=0.42$). CNS-TAP indicates Central Nervous System Targeted Agent Prediction; OS, overall survival; PFS, progression-free survival. full color online

does include investigational drugs within the tool, but we were unable to evaluate these given the PNOC003 protocol requirement that agents recommended be FDA approved. Lastly, we were limited by a lack of additional clinical information about patients that may have influenced the tumor board's recommendations.

While our study demonstrates concordance among recommended agents by a tumor board and the CNS-TAP tool, we did not observe any difference in OS or PFS based on the degree of concordance between the 2 methods in patients who followed tumor board therapy recommendations. In addition, the PNOC003 study concluded that there was no survival difference among patients who followed tumor board recommendations compared with those who did not follow recommendations.[21] As such, we do not intend to claim that either CNS-TAP or a molecular tumor board is more likely to recommend clinically beneficial therapies. We instead assert that since the use of individualized molecularly targeted therapies is common in clinical practice and research for patients with DIPG, data-driven adjuncts like CNS-TAP to molecular tumors boards can better inform the use of targeted therapies in these patients. Future investigation will prospectively evaluate the utility of CNS-TAP as an adjunct to a tumor board in children with CNS tumors, as it has been prospectively incorporated into a precision medicine trial, PNOC008: Clinical Benefit of

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Using Molecular Profiling to Determine an Individualized Treatment Plan for Patients With High Grade Glioma (NCT03739372), which was recently completed and survival data were recently presented and are encouraging.[23] Manuscript preparation is underway, which will include comparison of the concurrent use of CNS-TAP with the expert tumor board. However, this initial retrospective investigation importantly demonstrates the feasibility of utilizing CNS-TAP to obtain similar results to those of a molecular tumor board and highlights the likely synergy of combined data-driven algorithms and expert tumor boards. As an independent tool, CNS-TAP continues to be expanded to increase the number of agents and objectivity of the tool through integration of data from large databases and functional drug screens. This expanded scope of the CNS-TAP tool will ultimately assist clinicians in selecting agents with the most compelling evidence from the ever-growing number of targeted therapies available to children with brain tumors. Furthermore, this may represent a first step toward artificial intelligence (AI)-based approaches to drug selection in oncology.

Overall, our study demonstrates similarity in agents selected by an expert tumor board and the CNS-TAP tool for patients with DIPG, particularly when focused on targeted anticancer agents. Despite the overlap, there is discordance between the 2 methods, which we hope to further investigate and ameliorate through the prospective PNOC008 clinical trial. In conclusion, CNS-TAP is a data-driven drug scoring tool with utility in the clinical research setting for efficient and minimally biased targeted anticancer therapy recommendation and will likely serve as a useful adjunct to commonplace expert tumor boards for patients with CNS tumors.

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