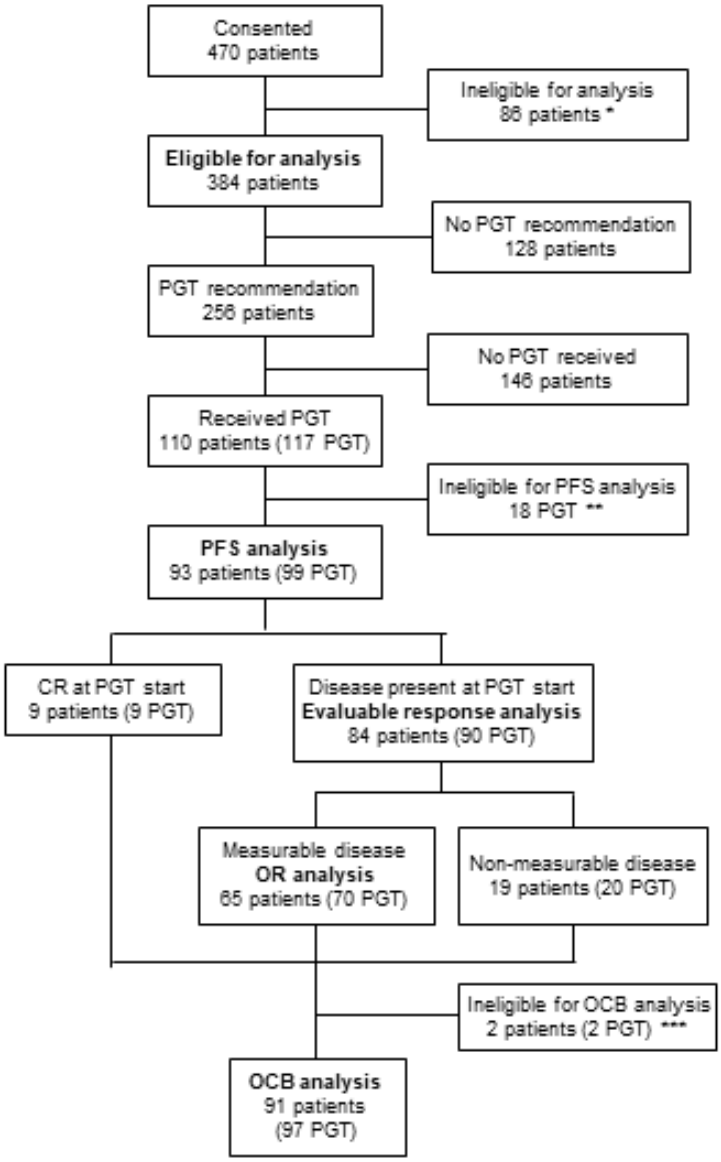
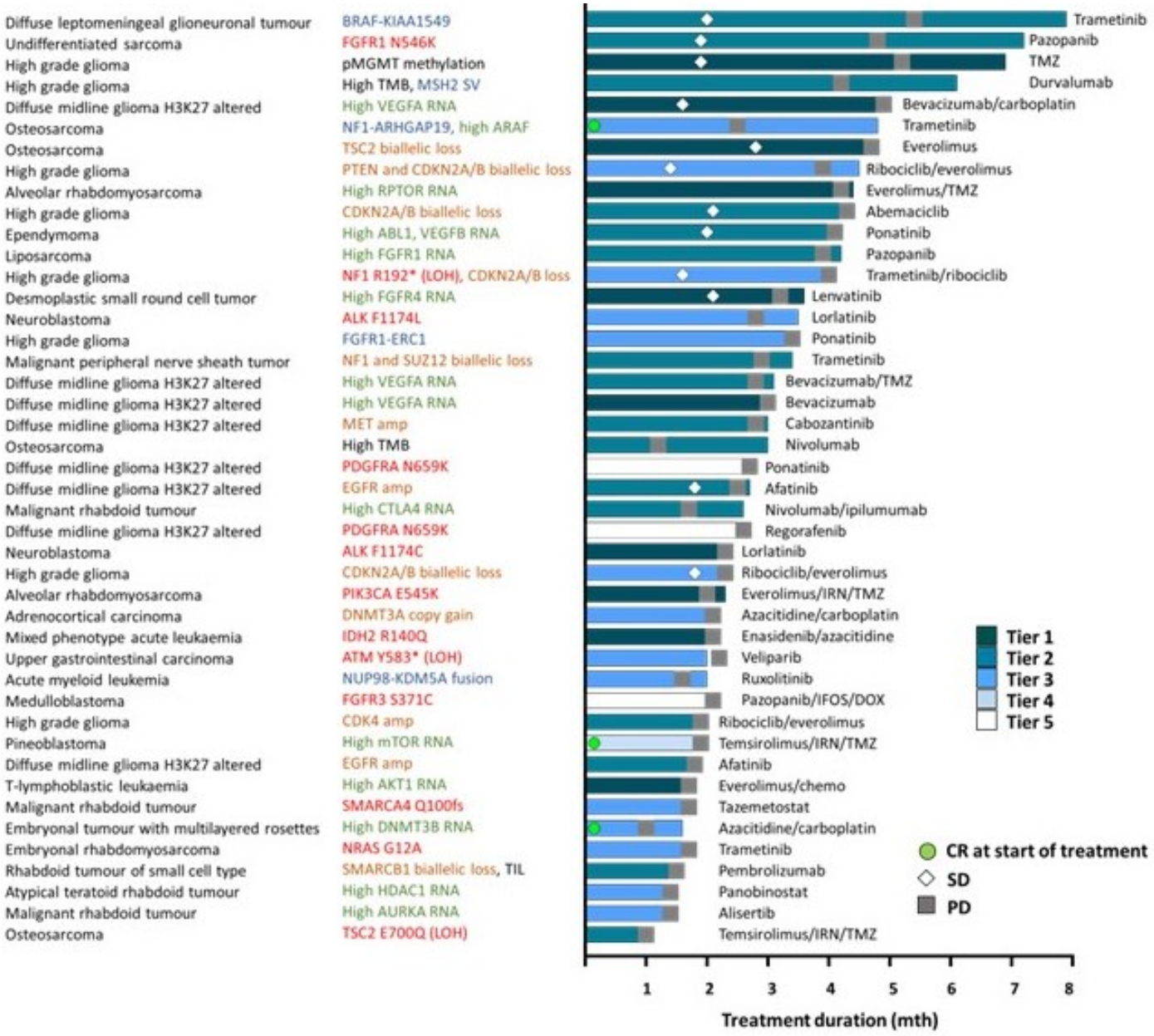
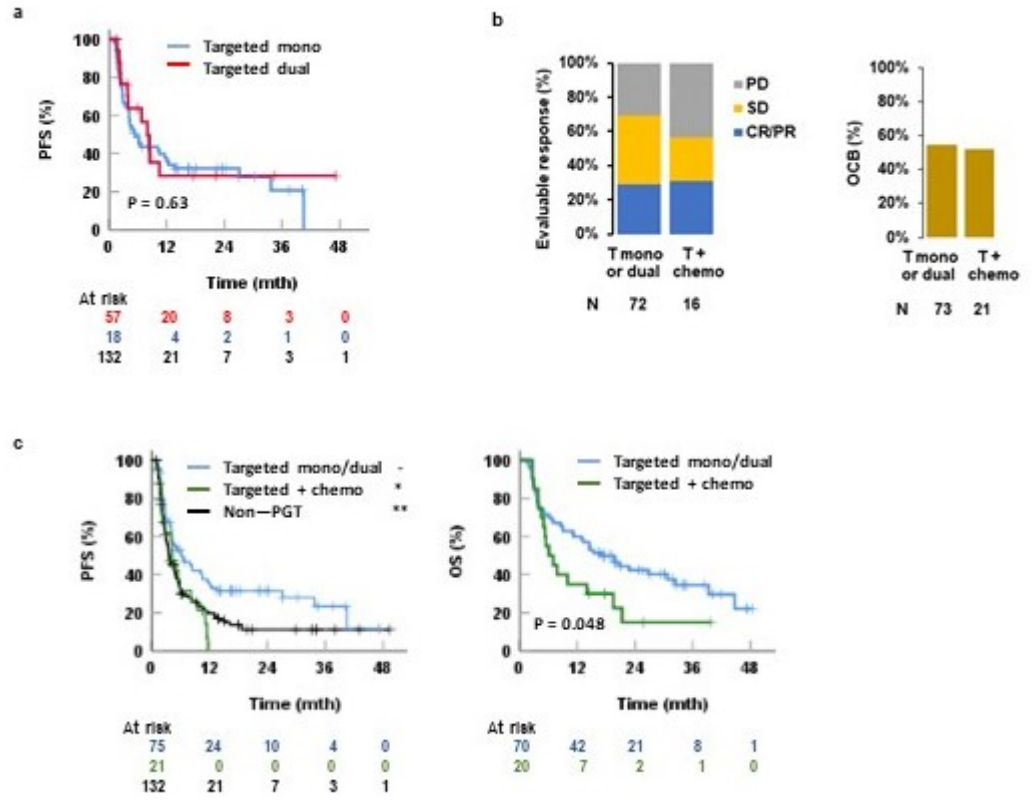
EXTENDED DATA



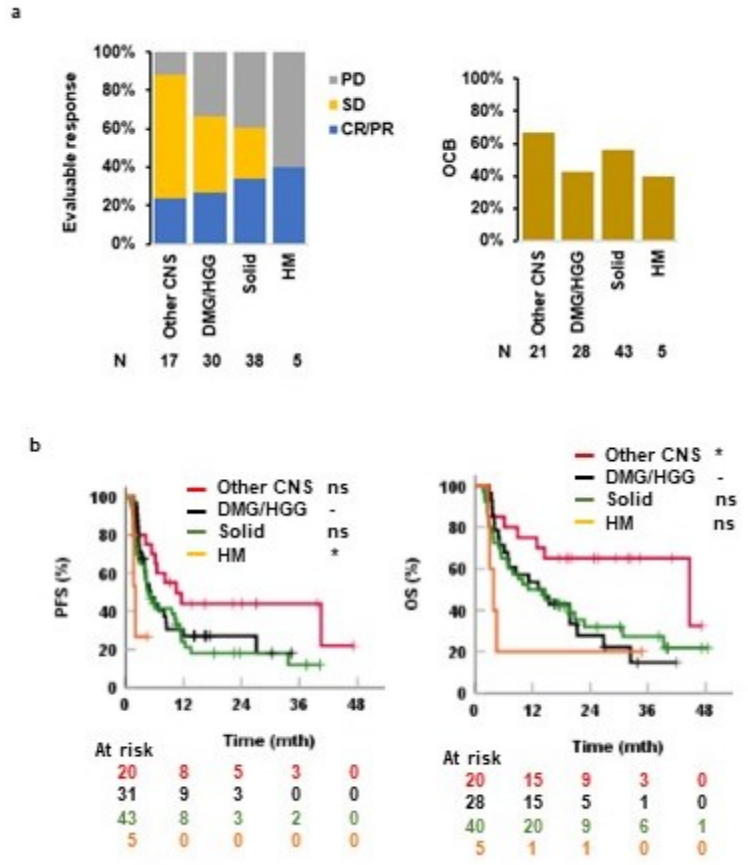
Extended Data Fig. 1. CONSORT diagram. Consort diagram of 470 patients consented in the PRISM study between Sep 2017 and Dec 2020. 384 patients were eligible for outcome analysis. * ineligible due to non-high-risk cancer diagnosis, lack of appropriate sample or death prior to presentation at the molecular tumour board. ** ineligible due to treatment duration <4 weeks, disease progression within the first 4 weeks of treatment or no response evaluation. *** not evaluable for OCB due to cessation of treatment before 24 weeks in the absence of disease progression where stable disease was best response. CR, complete remission; OCB, objective clinical benefit; OR, objective response of measurable disease; PGT, precision-guided treatment; PFS, progression-free survival.



Extended Data Fig. 2. Swimmer plot of 44 precision-guided treatments (PGTs) which did not lead to objective clinical benefit (OCB). Lack of OCB includes patients with disease at the start of treatment who had stable disease (SD) for <24 weeks duration or progressive disease (PD) and patients in complete remission (CR) at the start of treatment with relapse-free duration <24 weeks. The color of the bars indicates tier of a PGT recommendation. Symbols indicate responses and treatment status. The diagnosis and molecular targets for each patient are shown. The types of molecular aberration are denoted by different color text. Fusion or structural variant (SV) is shown in blue, single nucleotide variants in red, high RNA expression in green, copy number variant in brown and other alterations in black.



Extended Data Fig. 3. Clinical outcome of different types of precision-guided targeted therapy. a, Progression-free survival (PFS) for targeted monotherapy (mono) and targeted dual therapy. **b,** Evaluable response and objective clinical benefit (OCB) rate by type of targeted therapy. **c,** PFS and OS by types of treatment. Log rank test is used to compare the Kaplan Meier survival curves of 2 groups. P value is denoted by * ≤ 0.05, ** ≤ 0.01, *** ≤ 0.001, ns > 0.05 and the reference subgroup is indicated by a dash. Chi-square test is used to compare evaluable response and OCB rate between 2 groups (panel c) and the actual P values are presented in Table 1.



Extended Data Fig 4. Clinical outcome of precision-guided therapy by cancer type. a, Evaluable response and objective clinical benefit (OCB) rate by cancer type. **b,** Progression-free survival (PFS) and overall survival (OS) stratified by cancer type. Chi-square test is used to compare evaluable response and OCB rate between 2 groups, and the actual P values are presented in Table 1. Log rank test is used to compare the Kaplan Meier survival curves of 2 groups. P value is denoted by * ≤ 0.05, ** ≤ 0.01, *** ≤ 0.001, ns > 0.05 and the reference subgroup is indicated by a dash. CR, complete response; DMG, diffuse midline glioma H3K27M-altered; HGG, high grade glioma; HM, hematologic malignancy; PR, partial response; PD, progressive disease; SD, stable disease.

Extended Data Table 1. Baseline characteristics and sequencing method

Variable	
No. of patients	384 *
Median age (y) (range)	10.9 (0.1 – 46)
Sex, n (%)	
Female	173 (45)
Male	211 (55)
Disease status, n (%)	
Diagnosis	160 (42)
Relapse 1	184 (48)
Relapse ≥2	40 (10)
Cancer type, n (%)	
No. of samples analysed	385
CNS tumor	**146 (38)**
DMG, H3 K27 altered	38 (9.9)
High grade glioma	36 (9.4)
Ependymoma	22 (5.5)
Medulloblastoma	10 (2.6)
Other glioma	14 (3.6)
Other	28 (7.3)
Solid tumor	**183 (47)**
Neuroblastoma	30 (7.8)
Ewing sarcoma	31 (8.1)
Rhabdomyosarcoma	29 (7.5)
Osteosarcoma	23 (6.0)
Wilms tumor	10 (2.6)
Other sarcoma	37 (9.6)
Other solid	23 (6.0)
Hematologic malignancy	**56 (15)**
Acute myeloid leukemia	22 (5.7)
Acute lymphoblastic leukemia	18 (4.7)
Lymphoma	13 (3.4)
Other	3 (0.8)
Sequencing method, n (%)	
WGS + WTS	319 (82.9)
WGS	54 (14.0)
Targeted panel	10 (2.6)
Targeted panel + WTS	2 (0.5)

DMG, diffuse midline glioma; WGS, whole genome sequencing; WTS, whole transcriptomic sequencing. * One patient had two tumors analysed (synchronous medulloblastoma and osteosarcoma)

Extended Data Table 2. Tier of PGT recommendations

Tier	Evidence
1	Evidence from clinical studies of the same cancer type [a]
2	Evidence from clinical studies of different cancer type [a]
3	Evidence from preclinical studies of the same cancer type [b]
4	Evidence from preclinical studies of different cancer type [b]
5	Consensus opinion of the molecular tumor board

[a] Patients from these clinical studies can be molecularly selected or unselected
[b] Preclinical models in these studies can be molecularly selected or unselected

Extended Data Table 3. Multivariate cox regression analysis of factors influencing progression-free survival

Variables	Hazard ratio	95% CI	P
Tier 1 evidence	0.43	0.24 – 0.77	0.005
Fusion/SV	0.42	0.18 – 0.98	0.045
No PD since enrolment	0.50	0.31 – 0.82	0.006
Non-hematologic malignancy	0.21	0.06 – 0.79	0.02
Targeted mono/dual therapy	0.62	0.34 - 1.11	0.11