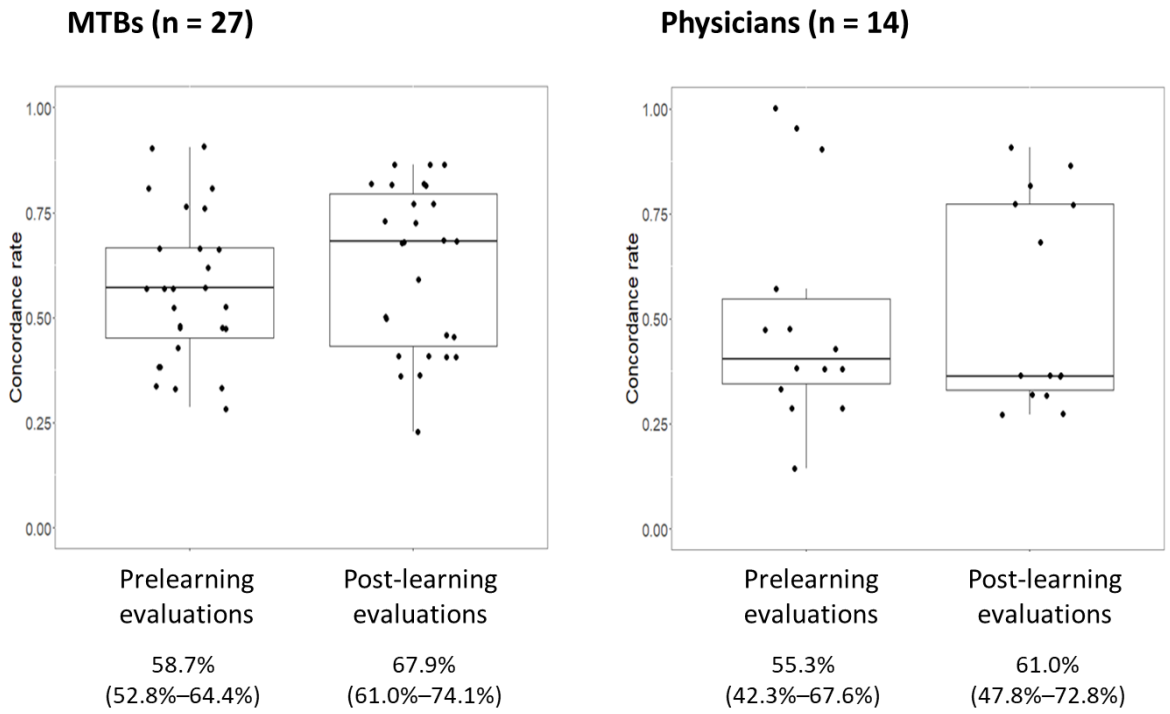
Supplementary Online Content

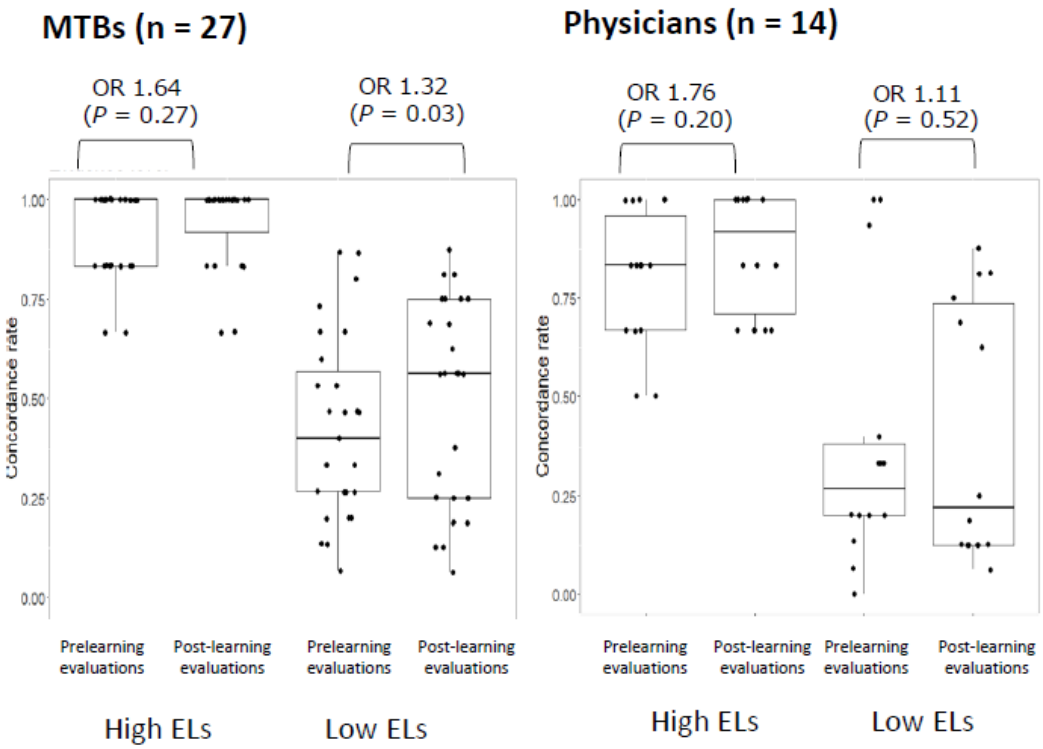
Sunami K, Naito Y, Saigusa Y, et al. A learning program on for treatment recommendations by molecular tumor boards and artificial intelligence. *JAMA Oncol*. Published online November 30, 2023. doi:10.1001/jamaoncol.2023.5120

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Improvement in Concordance



eFigure 2. Improvement in Concordance of Treatment Recommendations for Cases With High ELs and Low ELs



eTable 1. Evidence Levels Based on Clinical Practice Guidance for Next-Generation Sequencing in Cancer Diagnosis and Treatment (Edition 2.1)

Level	Ctiterion
A	There is a drug approved in Japan for a specific tumor type There is a drug approved by the FDA for a specific tumor type A specific tumor type is included in the guidelines
B	There have been clinical studies and meta-analyses of high statistical reliability and is a consensus among experts for a specific tumor type
C	There is a drug approved in Japan or by the FDA for another tumor type There have been clinical studies and meta-analyses of high statistical reliability and is a consensus among experts for another tumor type Usefulness has been shown in a small clinical study in any tumor type
D	Usefulness has been shown in case reports in any tumor type
E	Usefulness has been reported in preclinical studies (in vitro or in vivo)
F	Known to be related to cancerous changes
R	Known to be related to drug resistance

eTable 2. List of Simulated Cases in Prelearning and Postlearning

	No.	Cancer type	genomic alterations	Central treatment recommendations as of April 2021	Central treatment recommendations as of August 2021
Pre-learning	1	Lung	KRAS G12C	AMG510 (sotorasib), JDQ443, BI3011441	AMG510 (sotorasib), JDQ443, BI3011441
	2	Lung	ERBB2 A775_G776insYVMA	Trastuzumab deruxtecan	Trastuzumab deruxtecan
	3	Lung	TP53 R248W, FGF amp, STK11 D53fs*11	Adavosertib, AMG650, TAS120	Adavosertib, AMG650
	4	Lung	CD74-ROS1 fusion	Entrectinib, crizotinib	Entrectinib, crizotinib
	5	Breast	AKT1 E17K, CDH1 c.832+2T>C, PTEN E201fs*41	TAS-117+TAS-120	TAS-117+TAS-120
	6	Breast	ERBB2 L755S	Trastuzumab deruxtecan	Trastuzumab deruxtecan
	7	Colorectal	KRAS G12D	R: cetuximab, panitumumab	R: cetuximab, panitumumab
	8	Prostate	CHEK2 E275*, PTEN loss, FGF19/3/4 amplification	Olaparib, TAS-117+TAS-120	Olaparib, TAS-117+TAS-120
	9	Gastric	PIK3CA H1047R, FGFR3 K650M	TAS-117+TAS-120	TAS-117+TAS-120
	10	Gastric	TP53 R175H	Adavosertib, AMG650	Adavosertib, AMG650
	11	Gastric	ERBB2 amp	Trastuzumab deruxtecan	Trastuzumab deruxtecan
	12	Liver	CTNNB1 S33C, TP53 R249S	E7386±lenvatinib, adavosertib, AMG650	E7386±lenvatinib, adavosertib, AMG650
	13	Cervix	PIK3CA E545K, KRAS G12V	SPYK04, BI3011441, TAS-117+TAS-120	SPYK04, BI3011441, TAS-117+TAS-120
	14	Cervix	KRAS G12D, TP53 R175H	SPYK04, BI3011441, AMG650, adavosertib	SPYK04, BI3011441, AMG650, adavosertib

	15	Pancreas	KRAS G12D, TP53 R196*	Adavosertib, AMG650	Adavosertib, AMG650
	16	Pancreas	BRCA2 S2835* (germline)	Olaparib maintenance, niraparib	Olaparib maintenance, niraparib
	17	CNS	EGFR amp, EGFR A289V	No recommendation	No recommendation
	18	CNS	ATM splice site 6573-1G>A	No recommendation	AMG650, adavosertib
	19	Melanoma	RAF1 rearrangement	Trametinib	Trametinib
	20	Ovary	BRCA2 L63* (germline), TP53 R248Q	Adavosertib, AMG650	Adavosertib, AMG650
	21	Ovary	KRAS G12R, TP53 R175H	SPYK04, BI3011441, Adavosertib, AMG650	Adavosertib, AMG650
	22	Soft tissue	TP53 R248W, RB1 loss	Adavosertib, AMG650	Adavosertib, AMG650
	23	Cholangiocarcinoma	FGFR2-BICC1 fusion	Pemigatinib	Pemigatinib,TAS117+TAS120, E7090
	24	bladder cancer	No significant genetic abnormalities are detected	No recommendation	No recommendation
	25	Soft tissue	No significant genetic abnormalities are detected	No recommendation	No recommendation
Post-learning	1	Lung	EGFR L858R	No recommendation	patritumab deruxtecan
	2	Lung	BRAF G466A, KEAP1 G477D	SPYK04	SPYK04, BI3011441
	3	Lung	EML4-ALK fusion	Ceritinib, lorlatinib	Ceritinib, lorlatinib, brigatinib
	4	Lung	MET c.3028+2T>C	Capmatinib, tepotinib	Capmatinib, tepotinib
	5	Breast	PIK3CA H1047R, TP53 E339K	TAS-117+TAS-120, alpelisib+fulvestrant	TAS-117+TAS-120
	6	Breast	CDK12 R117fs*9, TP53 C275Y	Olaparib, Adavosertib, AMG650	Olaparib, Adavosertib, AMG650

7	Colorectal	BRAF V600E	Encorafenib+Binimetinib+Cetuximab	Encorafenib+Cetuximab+/-Binimetinib
8	Colorectal	KRAS G12A, TP53	SPYK04, BI3011441 R: cetuximab, panitumumab	SPYK04, BI3011441, BI3011441+BI1701963, TNO155+Spartalizumab/ribociclib R: cetuximab, panitumumab
9	Colorectal	APC R1450*, RNF43 G659fs*41, KRAS G12S	E7386, E7386+Lenvatinib, SPKY04, BI3011441 R: cetuximab, panitumumab	E7386, E7386+Lenvatinib, SPKY04, BI3011441, BI3011441+BI1701963, TNO155+Spartalizumab/ribociclib, TAS117+TAS120, R: cetuximab, panitumumab
10	Colorectal	MSI-high, MSH2 E580*	Pembrolizumab, nivolumab, nivo+ipilimumab	Pembrolizumab, nivolumab, nivo+ipilimumab
11	Prostate	ATM E2444*	No recommendation	No recommendation
12	Gastric	TP53 Y234C	Adavosertib, AMG650	Adavosertib, AMG650
13	Cervix	ERBB2 S310F, TP53 Q331*	Adavosertib, AMG650	Adavosertib, AMG650, T-Dxd, BI1810631, tucatinib
14	Esophagus	TP53 R175H, PIK3CA, FGF	Adavosertib, AMG650	Adavosertib, AMG650, TAS120
15	Esophagus	CDKN2A loss, CDKN2B loss, MTAP loss	No recommendation	No recommendation
16	Esophagus	TP53 R196*	AMG650, adavosertib	AMG650, adavosertib
17	CNS	BRAF V600E	Dabrafenib＋Trametinib, Encorafenib+Binimetinib	Dabrafenib＋Trametinib, Encorafenib+Binimetinib
18	CNS	IDH1 R132H, TP53 R273C	LY3410738, AMG650, adavosertib	LY3410738, AMG650, adavosertib

19	Melanoma	BRAF V600E, BRCA1 L63*	Dabra+trame, encora+binime, olaparib	Dabrafenib＋Trametinib, Encorafenib+Binimetinib, olaparib
20	Melanoma	NRAS Q61R, TP53 A189V	SPYK04, BI3011441, AMG650, adavosertib	SPYK04, BI3011441, AMG650, adavosertib
21	Ovary	NF1 1333fs*7	SPYK04	SPYK04
22	Soft tissue	MDM2 amp, CDK4 amp	BI907828＋BI754091＋BI754111, BI907828	BI907828+BI754091+BI754111, BI907828
23	Thyroid	CCDC6-RET fusion	Serpercatinib	Serpercatinib, Prasetinib
24	adrenal cortex	No significant genetic abnormalities are detected	No recommendation	No recommendation
25	Pancreas	TP53 R273P, KRAS G12V	Adavosertib, AMG650	Adavosertib, AMG650, BI3011441, BI3011441+BI1701963

R: non-recommended treatment due to resistance

eTable 3. List of Central Treatment Recommedations of High Frequent Genomic Alterations

Gene symbol	Central TRs	Clinical trial information
TP53	AMG650	jRCT2031200176
KRAS (except G12C)	SPYK04 BI3011441 BI1701963	JapicCTI-205361/NCT04511845 NCT04742556 jRCT2031200385/NCT04835714
PIK3CA	TAS-117+TAS-120	JapicCTI-194864
CDKN2A	—	—
CDKN2B	—	—
APC	E7386 E7386+E7080	JapicCTI-194659 JapicCTI-194859/NCT04008797
ARID1A	—	—
PTEN	TAS-117+TAS-120	JapicCTI-194864
ERBB2	DS-8201a Tucatinib	JapicCTI-194707 jRCT2031210113/NCT04579380
MTAP	—	—
NF1	—	—
MYC	—	—
RB1	—	—
TERT	—	—
CCND1	—	—
EGFR	—	—
FGF19	TAS117+TAS120	JapicCTI-194864
ATM	BAY 1895344	JapicCTI-183998
SMAD4	—	—
FGF4	TAS117+TAS120	JapicCTI-194864
BRCA2	—	—
FGF3	TAS117+TAS120	JapicCTI-194864
FBXW7	−	−
BRAF class3	SPYK04	JapicCTI-205361
CTNNB1	E7386 E7386+E7080	JapicCTI-194659 JapicCTI-194859/NCT04008797
MDM2	BI907828＋BI754091＋BI754111 BI907282	JapicCTI-194836 NCT03449381
GNAS	−	−
BRCA1	−	−

FGFR1	TAS117+TAS120 TAS120+Pembrolizumab Erdafitinib	JapicCTI-194864 JapicCTI-195063 JapicCTI-205204
STK11	–	–
AKT1	TAS117+TAS120	JapicCTI-194864
PIK3R1	TAS117+TAS120	JapicCTI-194864
NOTCH1	–	–
CDK4	–	–
SMARCA4	–	–
RET	TAS0953/HM06 LOXO-292	NCT04683250 NCT03157128
HRAS	SPYK04	JapicCTI-205361
KMT2D (MLL2)	–	–
KDM6A	–	–
NRAS	SPYK04 BI3011441	JapicCTI-205361/NCT04511845 NCT04742556
PTCH1	–	–
FGFR3	TAS117+TAS120 Erdrafinitnib	JapicCTI-194864 JapicCTI-205204
BAP1	–	–
PBRM1	–	–
KIT	-	–
EP300	–	–
MUTYH	–	–
FLT3	–	–
CREBBP	–	–
CCNE1	–	–
IDH1	LY3410738	jRCT2031200178/NCT04521686
PDGFRA	–	–
PRKCI	–	–

- : genomically matched trials not available

eTable 4. Concordance Rate in Postlearning

	Concordance rate (%)	95% CI
MTBs (n = 27)	67.9	61.0–74.1
Physicians (n = 14)	57.5	51.7–63.1
Al (n = 1)	88	68.7–96.1

MTB: molecular tumor board, AI: artificial intelligence, CI: confidence interval

eTable 5. Univariable Analysis for Factors Associated With Concordance Rate

	Factors	OR	95% CI	P-value
Group (n = 27)	Post-learning v.s. Prelearning	1.27	0.99–1.62	0.06
	ELs low v.s. high	0.046	0.029–0.076	<0.001
Individuals (n = 14)	Post-learning v.s. Prelearning	1.17	0.82–1.66	0.38
	ELs low v.s. high	0.08	0.048–0.13	<0.001

OR: odds ratio, CI: confidence interval, ELs: evidence level

eTable 6. Concordance of Treatment Recommendations for AMG 650

	Concordance rate (%)		
	Mean	Median	SD
MTBs (n = 27)	31.3	22.2	0.34
Physicians (n = 14)	36.5	5.6	0.43
AI (n = 1)	88.9	-	-

eMethods. Details of Multivariable Mixed-Effects Model

The logistic mixed effects model consisted of the fixed-effect term for two variables and the random intercept term. The random intercept was used to deal with the heterogeneity of participants in the models. The fixed-effect variables were pre- and post- learning evaluations and the level of evidence.

In terms of interaction terms, since an interaction between learning evaluations and evidence levels was not considered during the planning stage, we adopted a no-interaction model in the analysis, the results of which are presented in Table 1. As a post hoc analysis, we compared the goodness-of-fit of the no-interaction model with the model that included the interaction using Akaike information criterion (AIC). The AIC values for the no-interaction and interaction models were 1234.2 and 1236.1 for MTBs and 639.4 and 640.6 for physicians, respectively. As both models exhibited similar goodness-of-fit, we reported the results based on the no-interaction model, as originally planned.

The model's predictive performance was evaluated using the mean area under the receiver operating characteristic curve (AUROC) obtained from 200 iterations of 5-fold cross-validation. The mean AUROCs were 0.811 and 0.828 for MTBs and physicians, respectively.