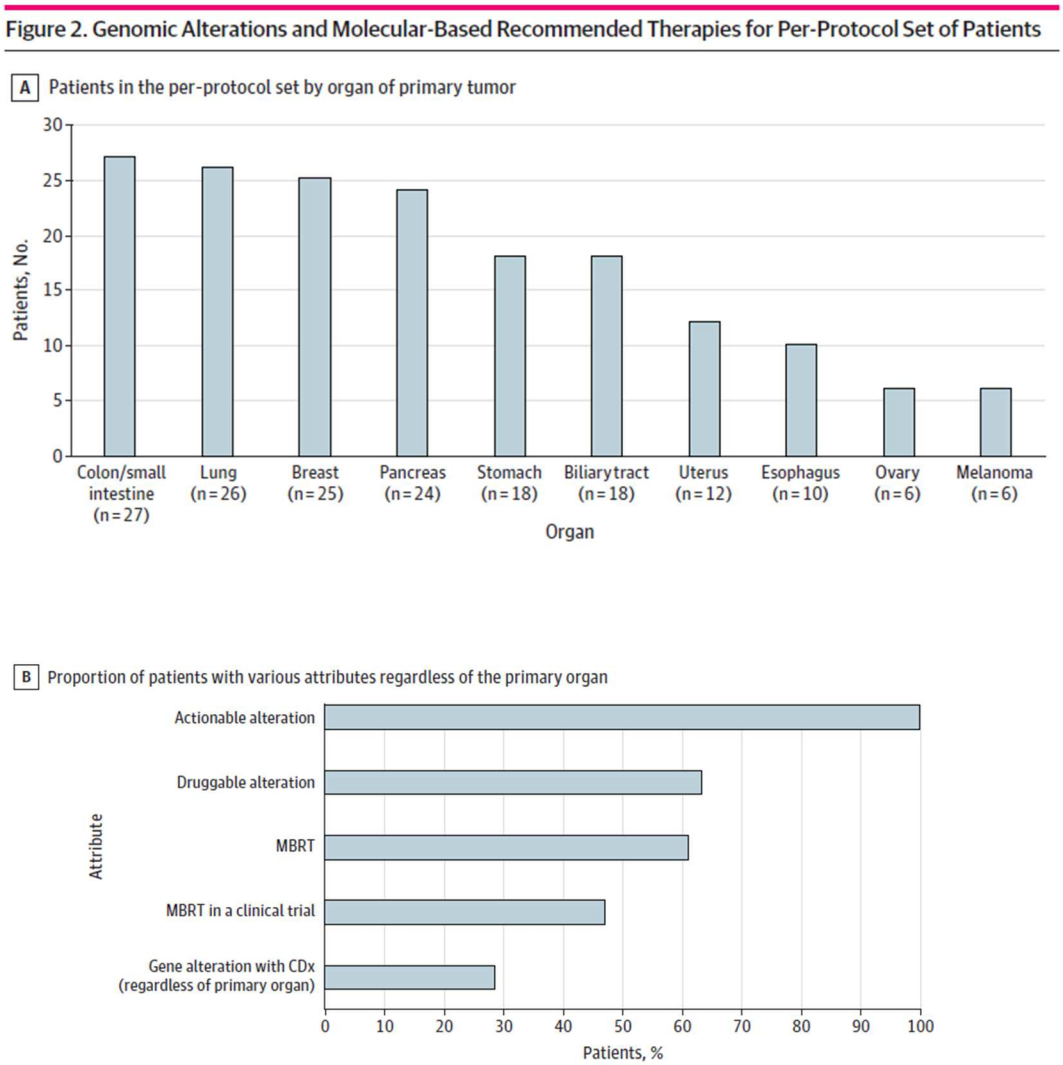
抄読会　Oct, 27, 2023

First-Line Genomic Profiling in Previously Untreated Advanced Solid Tumors for Identification of Targeted Therapy Opportunities. Matsubara, J. Mukai, K. Kondo, T. et al. JAMA Network Open 2023 Vol. 6 Issue 7 Pages e2323336

現在の日本ではcomprehensive genomic profiling (CGP)検査は標準治療がない症例または標準治療が行われた後にのみ保険適用となっている。そのため標準治療前のCGP検査の臨床的有用性はまだよく分かっていない。筆者らは転移または再発固形腫瘍未治療症例に対しFoundationOne CDx(F1CDx)検査を行い、その有用性について検討した。183例が登録され、180例について検査が行われ175例が検査成功(97.2%)、うち172例が暫定的な最終解析まで行われた。



Actionableな変異は172例全例で確認され、Druggableな変異は109例(63.4%)で確認された。

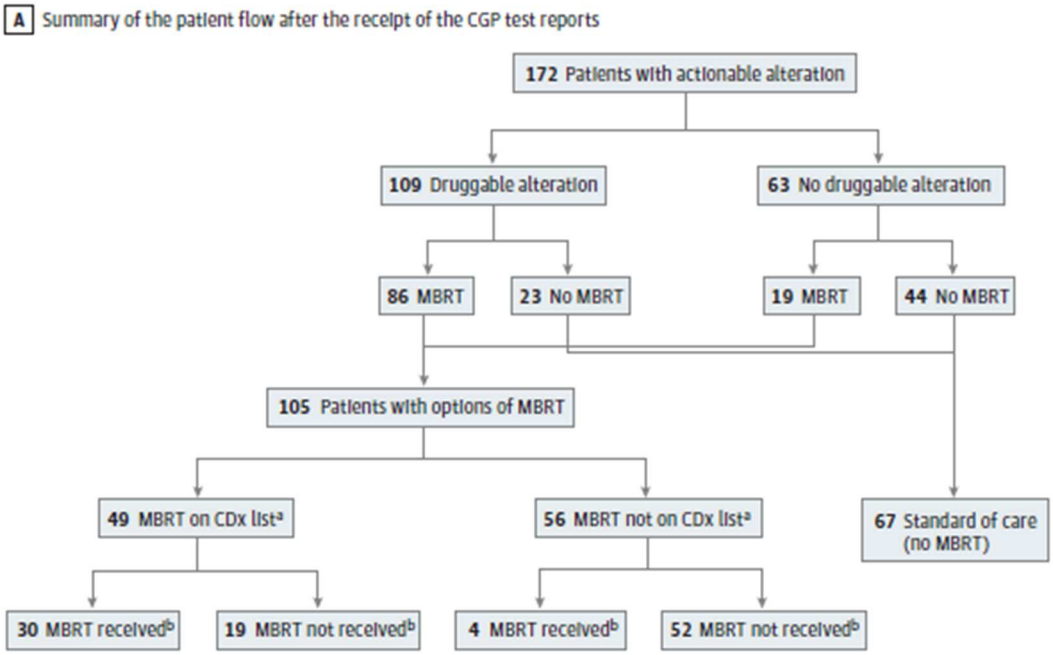
Figure 3. Frequency of Druggable Cancer Genomic Alterations

色の濃い所が高頻度部であるが、melanomaにおけるBRAF，乳癌におけるPIK3CA,胃癌における

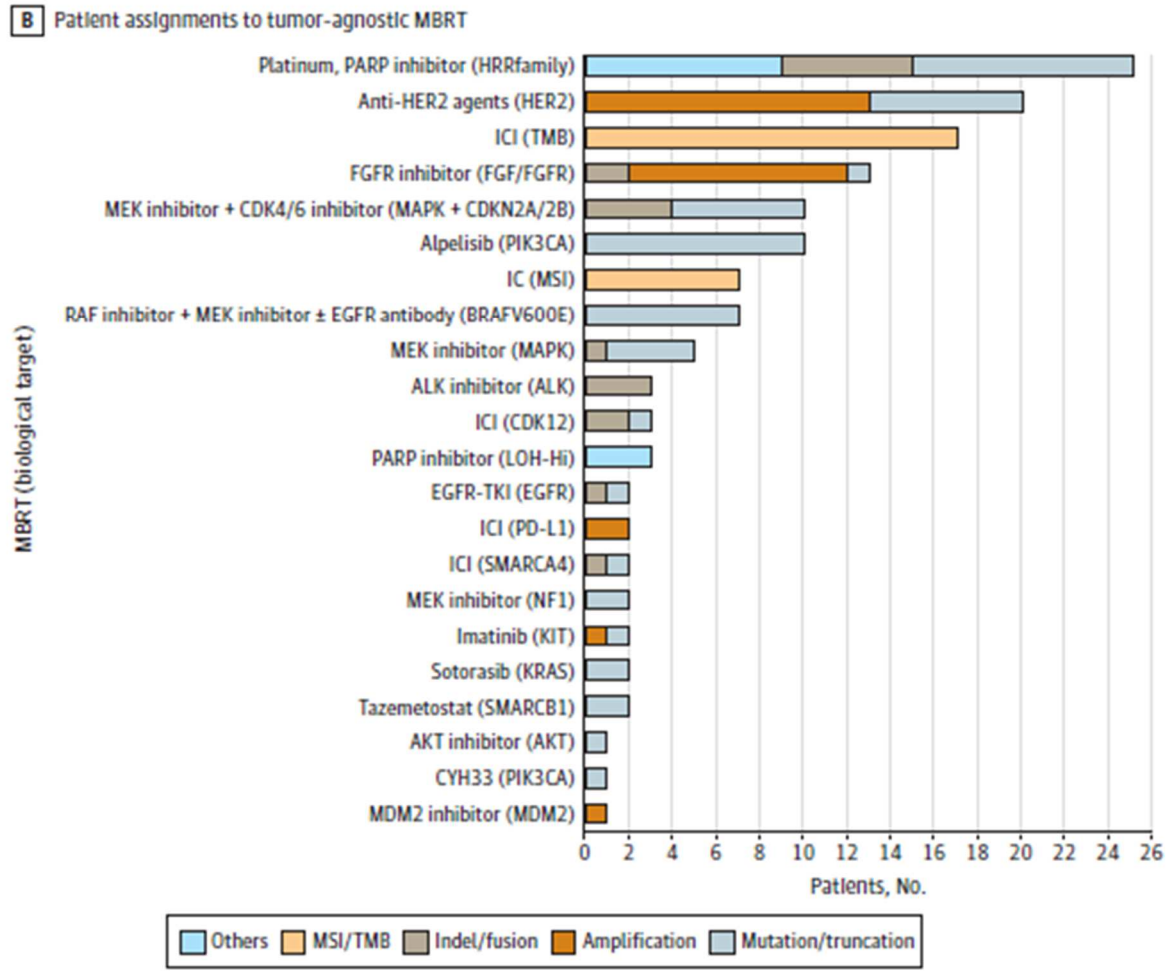
ERBB2、腸管癌におけるKRAS/NRASなどが高かった。

172例はCGP検査をもとに全例tumor boardにかけられた。

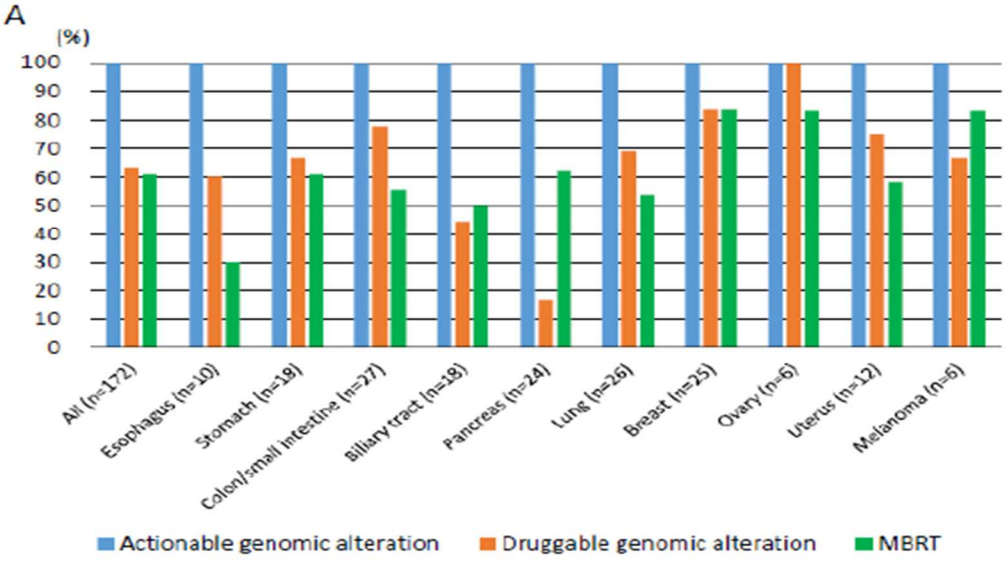
Figure 4. Summary of Patient Flow After Receipt of Comprehensive Genomic Profiling (CGP) Test Reports and Biological Targets of Molecular-Based Recommended Therapy (MBRT) in Tumor-Agnostic Setting



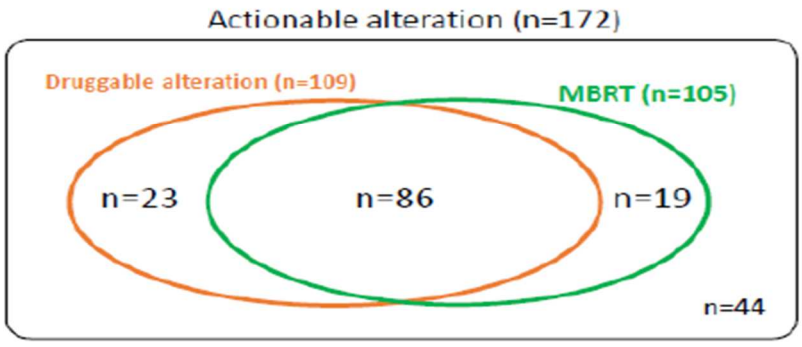
105例がmolecular-based recommended therapy (MBRT)のオプションがあると決定された。



A



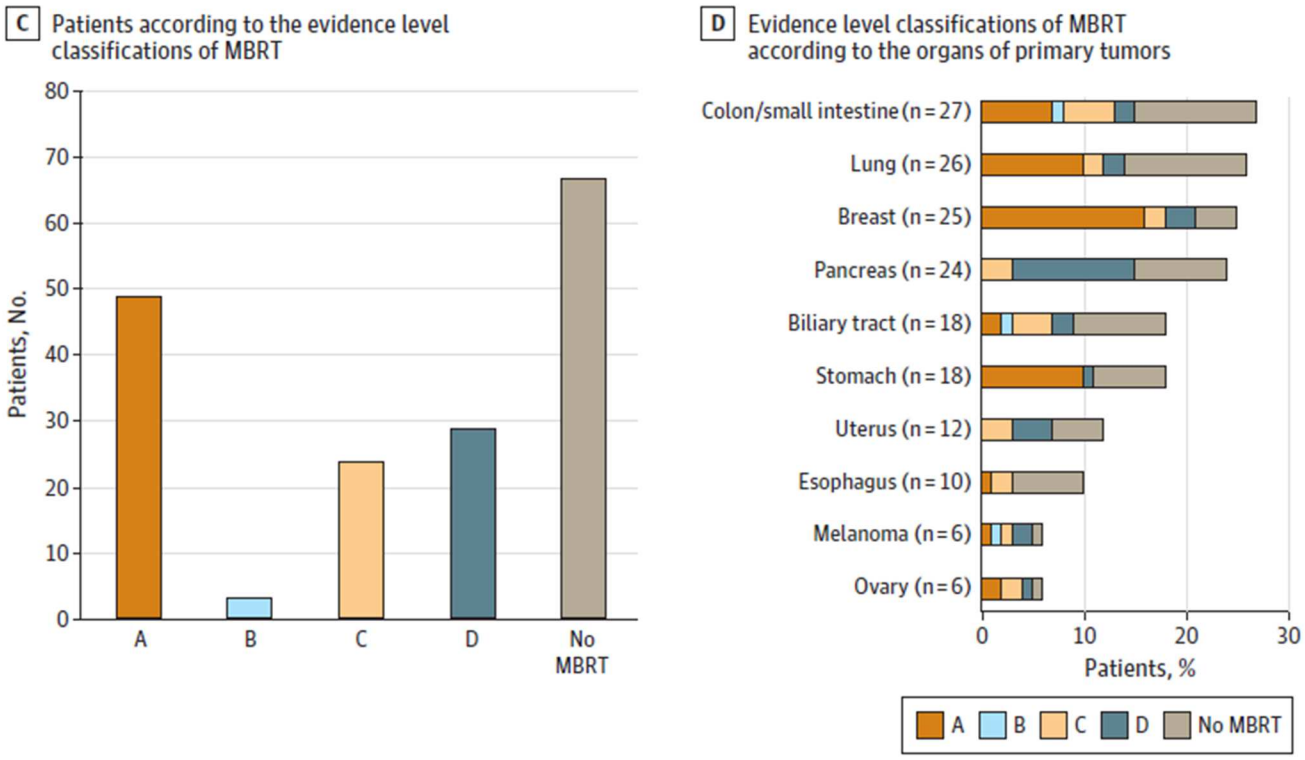
B



A:BreastとovaryではMBRTが高率であるのに対し、esophagusではMBRTは低率であった。

B:Druggable alterationとMBRTとの関係。N=23は日本では使用許可がおりていない治療薬に対するDruggable alterationをもつ症例, n=19はF1CDxではひっかからないが、症例報告などで効果が認められている症例である。

MBRTのエビデンスレベル



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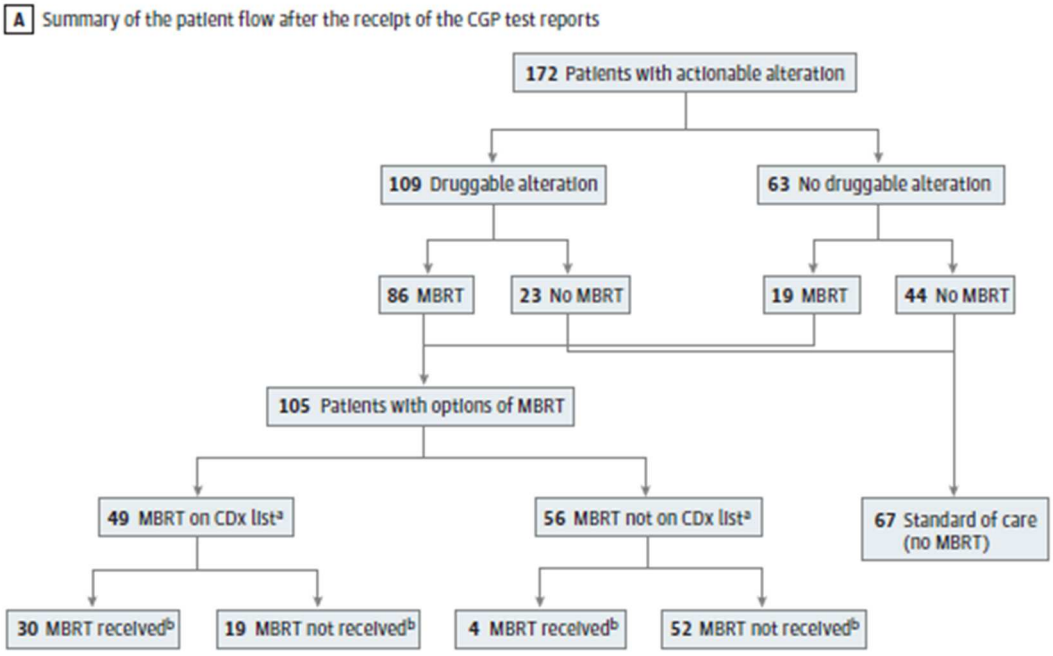
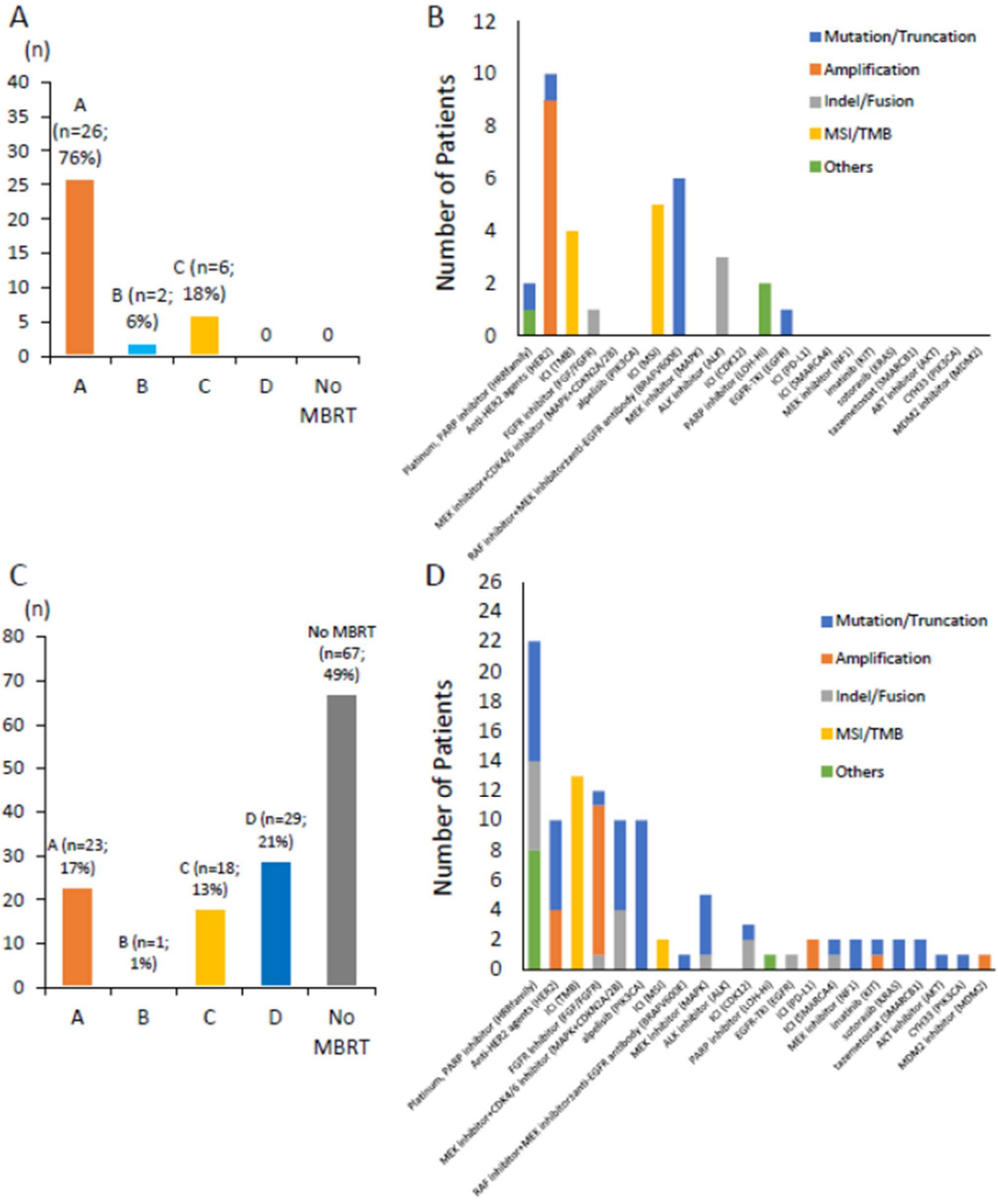


105例がmolecular-based recommended therapy (MBRT)のオプションがあると決定され、うち49例がF1CDxにおけるコンパニオン診断に当てはまったが、日本での決まりでは26例に減少した。暫定的にMBRTに基づいた治療を受けたのは34例（19．8%）であった。71例はMBRTに基づい

た治療は受けなかった。



Take Home Message

・標準治療前のCGP検査により、有効な薬剤の投与を早期に行うことができるかもしれない。

Table. Summary of Patients Who Received MBRT

Patient	Cancer type	Histologic details	Biomarker		MBRT	Evidence level	Genomic alterations*	Access
			Type	Annotation				
012	Stomach	Adenocarcinoma	MSI-high	Others	Immune checkpoint inhibitor	A	Yes	Clinical trial
017	Uterus	Adenocarcinoma	ERBB2	Amplification	Trastuzumab	C	Yes	Clinical trial
025	Stomach	Adenocarcinoma	ERBB2	Amplification	Anti-HER2 agents	A	Yes	Approved
026	Lung	Small cell carcinoma	TMB-high (21 mutations/Mb)	Others	Immune checkpoint inhibitor	A	Yes	Approved
028	Breast	Adenocarcinoma	BRCA1	Others	PARP inhibitor	A	Yes	Clinical trial
030	Stomach	Adenocarcinoma	ERBB2	Amplification	Trastuzumab, T-DXd	A	Yes	Approved
031	Stomach	Adenocarcinoma	ERBB2	Amplification	Anti-HER2 agents	A	Yes	Approved
032	Ovary	Adenocarcinoma	ERBB2	Amplification	Anti-HER2 agents	C	Yes	Clinical trial
038	Lung	Adenocarcinoma	ALK fusion	Fusion	ALK inhibitor	A	Yes	Approved
045	Lung	Adenocarcinoma	EGFR L858R	Missense mutation	EGFR-TKI	A	Yes	Approved
047	Pancreas	Adenocarcinoma	ERBB2	Amplification	Anti-HER2 agents	C	Yes	Clinical trial
059	Colon	Adenocarcinoma	BRAF V600E	Missense mutation	Cetuximab + encorafenib ± binimetinib	A	Yes	Approved
062	Ovary	Adenocarcinoma	LOH score-high	Others	PARP inhibitor	A	No	Approved
067	Colon	Others	RANBP2-ALK fusion	Fusion	ALK inhibitor	B	Yes	Clinical trial
074	Skin melanoma	Others	BRAF V600E	Missense mutation	Dabrafenib + trametinib, encorafenib + binimetinib	A	Yes	Approved
075	Colon	Others	BRAF V600E	Missense mutation	Cetuximab + encorafenib ± binimetinib	A	Yes	Approved
087	Lung	Adenocarcinoma	TMB-high (35 mutations/Mb)	Adenocarcinoma	Immune checkpoint inhibitor	A	Yes	Approved
093	Breast	Adenocarcinoma	BRCA1	Truncation	PARP inhibitor	A	Yes	Approved
096	Biliary tract	Adenocarcinoma	ERBB2	Amplification	Anti-HER2 agents	C	Yes	Clinical trial
108	Colon	Adenocarcinoma	BRAF V600E	Missense mutation	Cetuximab + encorafenib ± binimetinib	A	Yes	Approved
112	Stomach	Adenocarcinoma	ERBB2	Amplification	Anti-HER2 agents	A	Yes	Approved
118	Colon	Adenocarcinoma	BRAF V600E	Missense mutation	Cetuximab + encorafenib ± binimetinib	A	Yes	Approved
			CDK12 E659*	Truncation	Platinum, PARP inhibitor	C	No	Approved
122	Colon	Small cell carcinoma	ERBB2 S310Y	Missense mutation	pan-HER TKI, T-DXd	C	No	Clinical trial
125	Ovary	Adenocarcinoma	LOH Score-high	Others	PARP inhibitor	C	No	Approved
134	Lung	Adenocarcinoma	EML4-ALK fusion	Fusion	ALK inhibitor	A	Yes	Approved
135	Stomach	Adenocarcinoma	MSI-high	Others	Immune checkpoint inhibitor	A	Yes	Clinical trial
145	Biliary tract	Adenocarcinoma	TMB-high (20 mutations/Mb)	Others	Immune checkpoint inhibitor	A	Yes	Approved
155	Skin melanoma	Others	BRAF V600R	Missense mutation	Dabrafenib + trametinib, encorafenib + binimetinib	B	No	Clinical trial
165	Biliary tract	Adenocarcinoma	FGFR2-KIAA1598 fusion	Fusion	FGFR inhibitor	A	Yes	Approved
166	Stomach	Adenocarcinoma	MSI-high	Others	Immune checkpoint inhibitor	A	Yes	Approved
167	Breast	Adenocarcinoma	ERBB2	Amplification	Anti-HER2 agents	A	Yes	Approved
179	Lung	Adenocarcinoma	TMB-high (10 mutations/Mb)	Others	Immune checkpoint inhibitor	A	Yes	Approved
181	Stomach	Adenocarcinoma	MSI-high	Others	Immune checkpoint inhibitor	A	Yes	Approved
183	Stomach	Adenocarcinoma	MSI-high	Others	Immune checkpoint inhibitor	A	Yes	Clinical trial

Abbreviations: MBRT, molecular-based recommended therapy; MSI, microsatellite instability; PARP, poly(adenosine diphosphate-ribose) polymerase; TMB, tumor mutational burden.

* Alterations included in the companion diagnostics list in the tumor-agnostic setting.