基因檢測在臨床決策的應用

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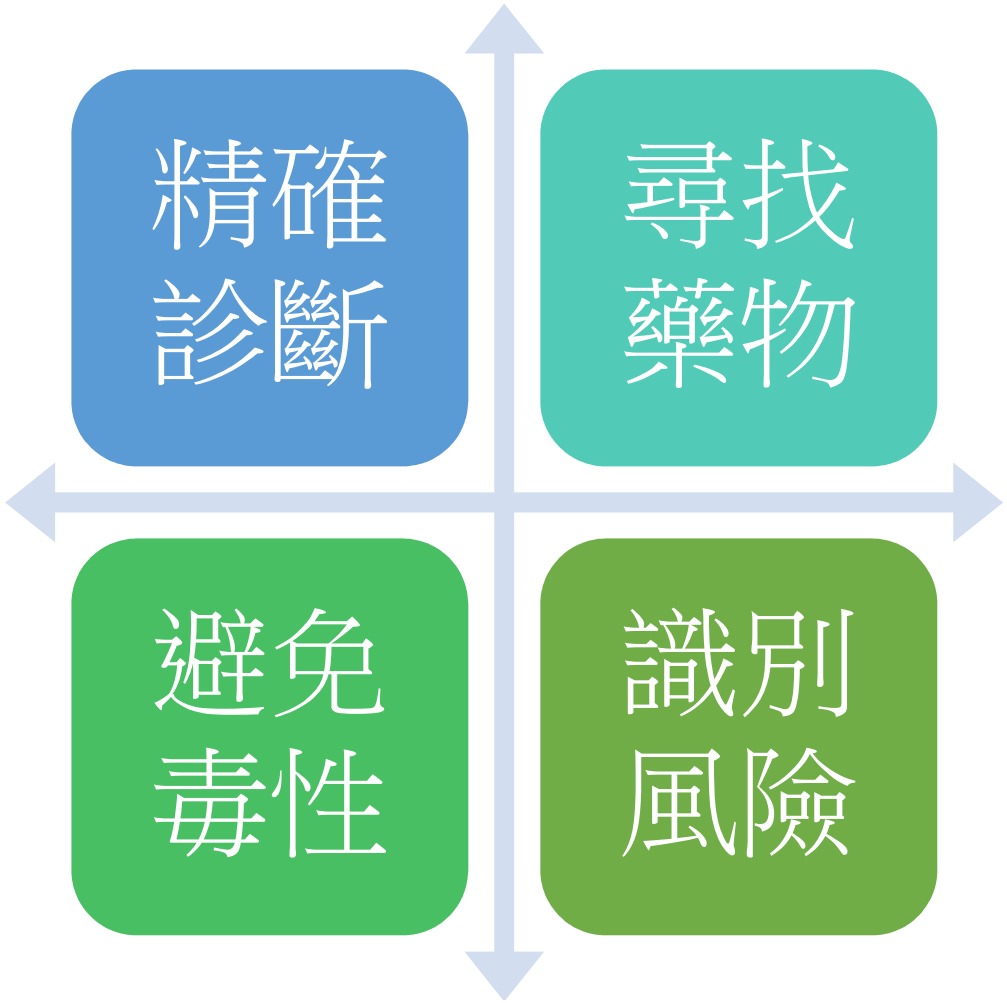
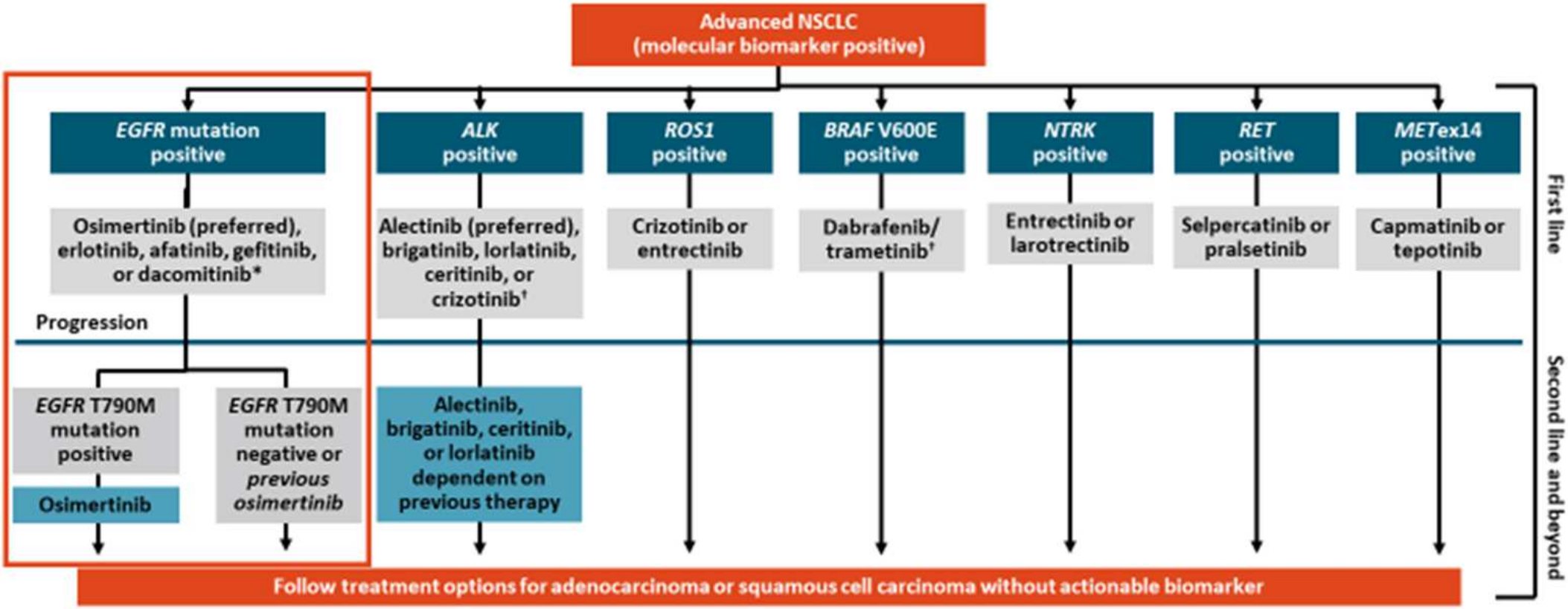
原發腫瘤位置
Ex. 乳癌
病理特徵
期別
藥物選擇
藥物選擇
藥物選擇
第一線
第二線
第三線
✓ 這真的是最好的治療模式嗎?
• 復發或治療失效?
• 少見腫瘤?
• 治療或預後效果不佳?
癌症患者
傳統治療
治療方案A
臨床有效率30%
癌症基因檢測
選擇適當的治療
治療方案A
臨床有效率75%
治療方案B
臨床有效率67%
治療方案C
臨床有效率67%

基因檢測在臨床決策的目的--(精準醫療)




Advanced NSCLC
(molecular biomarker positive)
EGFR mutation positive
ALK positive
ROS1 positive
BRAF V600E positive
NTRK positive
RET positive
METex14 positive
Osimertinib (preferred), erlotinib, afatinib, gefitinib, or dacomitinib*
Alectinib (preferred), brigatinib, lorlatinib, ceritinib, or crizotinib†
Crizotinib or entrectinib
Dabrafenib/ trametinib†
Entrectinib or larotrectinib
Selpercatinib or pralsetinib
Capmatinib or tepotinib
Progression
EGFR T790M mutation positive
Osimertinib
EGFR T790M mutation negative or previous osimertinib
Alectinib, brigatinib, ceritinib, or lorlatinib dependent on previous therapy
Follow treatment options for adenocarcinoma or squamous cell carcinoma without actionable biomarker
First line
Second line and beyond

The Landscape of Biomarkers

https://www.precisiononcologynews.com/companion-diagnostics/perspective-accessing-innovation-point-care-comprehensive-genomic-profiling

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

REVIEW

Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group

Others	Tumour multigene NGS can be used in ovarian cancers to determine somatic *BRCA1/2* mutations. In this latter case, larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy (drug included[a]) and if they report accurate ranking of alterations. Large panel NGS can be used in carcinoma of unknown primary. It is recommended to determine TMB in cervical cancer, salivary cancer, thyroid cancers, well-to-moderately differentiated neuroendocrine tumours, vulvar cancer, pending drug access (and in TMB-high endometrial and SCL cancers if anti-PD1 antibody is not available otherwise).

Ann Oncol. 2020 Nov;31(11):1491-1505

Table 2. Summary recommendations

Tumour types	General recommendations for daily practice
Lung adenocarcinoma	Tumour multigene NGS to assess level I alterations. Larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy (drug included[a]) and if they report accurate ranking of alterations. NGS can either be done on RNA or DNA, if it includes level I fusions in the panel.
Squamous cell lung cancers	No current indication for tumour multigene NGS
Breast cancers	No current indication for tumour multigene NGS
Colon cancers	Multigene tumour NGS can be an alternative option to PCR if it does not result in additional cost.
Prostate cancers	Multigene tumour NGS to assess level I alterations. Larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy and if they report accurate ranking of alterations.
Gastric cancers	No current indication for tumour multigene NGS
Pancreatic cancers	No current indication for tumour multigene NGS
Hepatocellular carcinoma	No current indication for tumour multigene NGS
Cholangiocarcinoma	Multigene tumour NGS could be recommended to assess level I alterations. Larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy (drug included[a]) and if they report accurate ranking of alterations. RNA-based NGS can be used.

ESCAT

ESMO Scale for Clinical Actionability of Molecular Targets

Table 8. List of genomic alterations level I/II/III according to ESCAT in advanced pancreatic ductal adenocarcinoma (PDAC)

Gene	Alteration	Prevalence	ESCAT	References
BRCA1/2	Germline mutations	1%–4%	IA	The Cancer Genome Atlas Research Network. *Cancer Cell.* 2017[111] Golan T, et al. *N Engl J Med.* 2019[112]
	Somatic mutations	3%	IIIB	Shroff R, et al. *JCO Precis Oncol.* 2018[113]
	MSI-H	1%–3%	IC	Pihlak R, et al. *Cancers.* 2018[115] Marcus L, et al. *Clin Cancer Res.* 2019[97]
NTRK	Fusions	<1%	IC	Cocco E, et al. *Nat Rev Clin Oncol.* 2018[114] Doebele RC, et al. *Lancet Oncol.* 2020[60]
KRAS	Mutations	90%	IIIA	Zeitouni D, et al. *Cancers.* 2016[116]
PIK3CA	Hotspot mutations	3%	IIIA	Heestand G, et al. *Oncotarget.* 2015[117] Payne S, et al. *J Clin Oncol.* 2015[118]
BRAF^{V600E}	Mutations	3%	IIIA	Hyman D, et al. *N Engl J Med.* 2015[119]
MDM2	Amplifications	2%	IIIA	Azmi A, et al. *Eur J Cancer.* 2010[120]
ERBB2	Amplifications/ mutations	1%–2%	IIIA	Waddell N, et al. *Nature.* 2015[121] Harder J, et al. *Br J Cancer.* 2012[122] Hyman D, et al. *Nature.* 2018[55]
NRG1	Fusions	1%	IIIA	Jones M, et al. *Clin Cancer Res.* 2019[123]
ALK	Fusions	<1%	IIIA	Singhi A, et al. *J Natl Compr Canc Netw.* 2017[124]
RET	Fusions	<1%	IIIA	Drilon A, et al. *J Clin Oncol.* 2018[81]
ROS1	Fusions	<1%	IIIA	Pishvaian M, et al. *J Clin Oncol.* 2018[125]

Ann Oncol. 2020 Nov;31(11):1491-1505

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Recommendations for the use of next-generation sequencing (NGS) for patients with advanced cancer in 2024: a report from the ESMO Precision Medicine Working Group

Table 1. List of tumour-agnostic genomic alterations

Gene/Signature[a]	Alteration	Estimated prevalence (illustration of tumours with high prevalence of the alteration)	ESCAT score	Drug class matched	References
NTRK1/2/3	Fusions	80%-90% secretory breast cancer 15%-20% Spitzoid melanoma	IC	TRK inhibitors	Hong et al., *Lancet Oncol* 2020[2] Demetri et al., *Clin Can Res* 2022[3]
MSI-H/dMMR[a]	MSI-H/dMMR	15%-20% endometrial cancer 15%-20% gastric adenocarcinoma	IC	PD-1 checkpoint inhibitors	Marcus et al., *Clin Can Res* 2019[4]
RET	Fusions	7% thyroid papillary cancer 2% salivary gland cancer	IC	RET inhibitors	Subbiah et al., *Lancet Oncol* 2022[5] Subbiah et al., *Nat Med* 2022[6]
BRAF	Mutations (p.V600E)	40%-45% melanoma 5%-6% small intestinal adenocarcinoma	IC	BRAF inhibitors + MEK inhibitors	Subbiah et al., *Cancer Discov* 2020[7] Salama et al., *J Clin Oncol* 2020[8]
FGFR1/2/3	Fusions Mutations	20%-40% bladder cancer 3% glioblastoma multiforme 10%-20% urothelial carcinoma 10% endometrial cancer	IC	Pan-FGFR TKIs	Pant et al., *Lancet Oncol* 2023[9]
TMB-H[a]	TMB-H	40% small-cell lung cancer	IC	PD-1/PD-L1 checkpoint inhibitors	Valero et al., *JAMA Oncol* 2021[10] Friedman et al., *Cancer Discov* 2022[11]

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Table 6. List of genomic alterations level I/II according to ESCAT in advanced pancreatic ductal adenocarcinoma

Gene	Alteration	Estimated prevalence	ESCAT score	Drug class matched	References
BRCA1/2	Germline pathogenic/likely pathogenic variants	4%-7%	IA	PARP inhibitors	Golan et al., *N Engl J Med* 2019[99] Kindler et al., *J Clin Oncol* 2022[100]
KRAS	Mutations (p.G12C)	1%-2%	IB	KRAS ^{G12C} TKIs	Strickler et al., *N Eng J Med* 2023[101] Bekaii-Saab et al., *J Clin Oncol* 2022[102]
PALB2	Germline pathogenic/likely pathogenic variants	3%-4%	IIB	PARP inhibitors	Reiss et al., *J Clin Oncol* 2021[103]
NRG1	Fusions	7%	IIB	Anti-HER2/HER3 bispecific antibody	Schram et al., *JCO* 2021[104]

Table 8. List of genomic alterations level I/II according to ESCAT in advanced cholangiocarcinoma

Gene	Alteration	Estimated prevalence	ESCAT score	Drug class matched	References
IDH1	Mutations	8%-18% iCCA	IA	IDH1 inhibitors	Abou-Alfa et al., *Lancet Oncol* 2020[124]
FGFR2	Fusions	5%-15% iCCA	IB	Pan-FGFR TKIs	Javle et al., *J Clin Oncol* 2018[125] Abou-Alfa et al., *Lancet Oncol* 2020[126] Pant et al., *J Clin Oncol* 2023[127] Goyal et al., *N Engl J Med* 2023[128]
ERBB2	Amplifications	10%-20% dCCA, pCCA, GBC	IB	Anti-HER2 monoclonal antibodies Anti-HER2 ADCs Anti-HER2 bispecific antibodies HER2 TKIs	Javle et al., *Lancet Oncol* 2021[129] Meric-Bernstam et al., *JCO* 2023[130] Harding et al., *Lancet Oncol* 2023[131] Nakamura et al., *J Clin Oncol* 2023[132]
	Mutations	3%-5%	IIB	Anti-HER2 monoclonal antibodies Pan-HER TKIs	Hyman et al., *Nature* 2018[51] Cannon et al., *J Clin Oncol* 2023[133] Harding et al., *Nat Comm* 2023[134]
BRAF	Mutations (p. V600E)	50%	IB	BRAF inhibitors + MEK inhibitors	Subbiah et al., *Lancet Oncol* 2020[135] Salama et al., *J Clin Oncol* 2020[8] Subbiah et al., *Nature Med* 2023[136]
KRAS	Mutations (p. G12C)	<1%	IC	KRAS ^{G12C} TKIs	Bekaii-Saab et al., *J Clin Oncol* 2022[102]

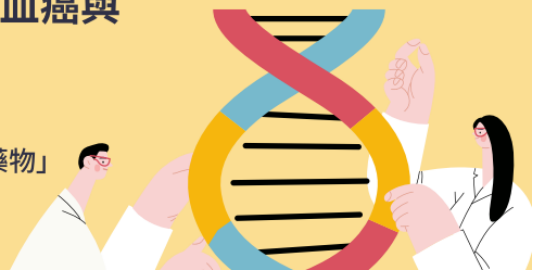
癌症精準治療利器

健保給付次世代基因定序檢測(NGS)

113年5月1日上路

健保給付 NGS 檢測適用癌別

- **14大類實體腫瘤** 非小細胞肺癌、三陰性乳癌、卵巢癌/輸卵管癌/原發性腹膜癌、攝護腺癌、胰臟癌、NTRK基因融合實體腫瘤、肝內膽管癌、甲狀腺癌、甲狀腺髓質癌、大腸直腸癌★、泌尿道上皮癌★、黑色素瘤★、腸胃道間質瘤★、胃癌★
- **5大類血液腫瘤** 急性骨髓性白血病(AML)、高風險的骨髓分化不良症狀群(MDS)、急性淋巴芽細胞白血病(B-ALL 及 T-ALL)、B細胞淋巴癌(BCL)★及T或NK細胞血癌與淋巴癌(NKTL)★



註 ①NGS 檢測給付以檢測結果有對應「具藥證的標靶藥物」且「效果明確之癌別及檢測基因」為優先

②7大類癌症★專家共識建議採單基因檢測

癌別	適應症 (符合下列任一條件)	應先執行之檢測項目	必須包含之檢測基因及變異別	NGS檢測 (符合左列條件者，得申報下列任一NGS檢測)
肝內膽管癌 Intrahepatic cholangiocarcinoma	經多專科團隊評估無法手術切除或已有轉移者。	無。	FGFR1 (fusion)、FGFR2(fusion)、FGFR3 (fusion)、BRAF(mutation)、IDH1 (mutation)、IDH2(mutation)、RET(fusion)	• 小套組(≦100個基因) • 大套組(＞100個基因)
胰臟癌 Pancreatic cancer	經多專科團隊評估無法接受根除手術者。	無。	Germline BRCA1、BRCA2 (全外顯子分析)	• BRCA1/2基因檢測(限使用血液檢體)

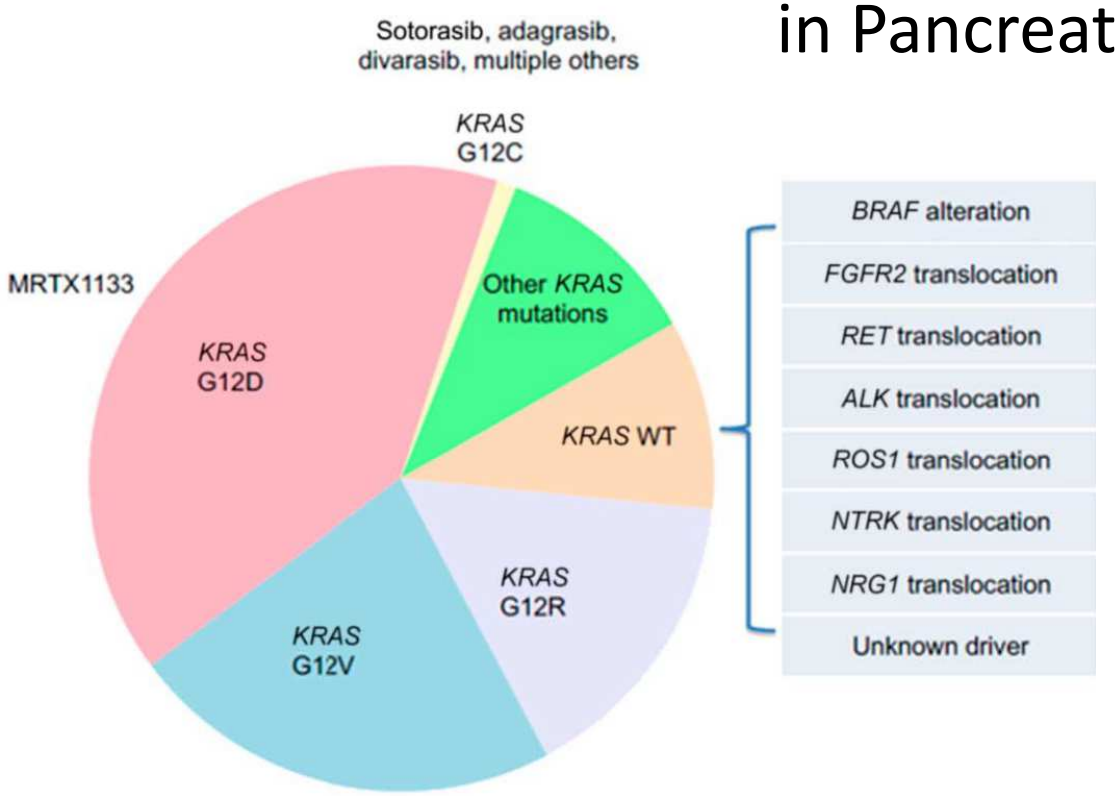
1 BRCA基因檢測 給付 1 萬點

2 小套組(≦100 基因) 給付 2 萬點

3 大套組(>100 基因) 給付 3 萬點

Molecularly Targeted Therapies in Pancreatic Cancer

KRAS multiple mutations	RMC6236, BI-2865



MSI-H	Pembrolizumab
TMB ≥10	Pembrolizumab
BRCA1/2, PALB2, other HR pathway deficiency	Platinum chemotherapy, PARP inhibitor
MTAP deletion	PRMT5 inhibitor: AMG193, MRTX1719

Am Soc Clin Oncol Educ Book. 2024 Jun;44(3):e438598.

Biomarkers in Gastric Cancer

Biomarker	Prevalence in metastatic gastric cancer
ERBB2/HER2	**20%**
MSI-high	**5%** in Stage IV **20%** in Stage I-III
EBV-positive	**3%**
PD-L1 CPSBio	**80%** CPS ≥ 1 **60%** CPS ≥ 5
FGFR2b overexpression	**30%**
CLDN18.2	**35%**
TCAG Tumor sequencing	NTRACK, EGFR, MET, RAS amplification
Plasma DNA	Monitoring for response and resistance

Table 7. List of genomic alterations level I/II/III according to ESCAT in metastatic gastric cancer (mGC)

Gene	Alteration	Prevalence	ESCAT	References
ERBB2	Amplifications	16%	IA	The Cancer Genome Atlas Research Network. *Nature.* 2014[102] Bang Y-J, et al. *Lancet.* 2010[103]
	Hotspot mutations	3%	IIIA	Hyman D, et al. *Nature.* 2018[55]
	MSI-H	8%	IC	The Cancer Genome Atlas Research Network. *Nature.* 2014[102] Marcus L, et al. *Clin Cancer Res.* 2019[97]
NTRK	Fusions	2%	IC	Drilon A, et al. *N Engl J Med.* 2018[48]
EGFR	Amplifications	6%	IIB	Maron S, et al. *Cancer Discov.* 2018[104]
MET	Amplifications	3%	IIB	Lennerz J, et al. *J Clin Oncol.* 2011[105]
	Mutations	1.3%	IIIA	Lee J, et al. *Oncotarget.* 2015[107]

Summary of recommendations. There is no current need to perform tumour multigene NGS in patients with mGC in daily practice. Detection of MSI and NTRK fusions should be done using cheap standard methods.