Molecular Features of GISTs

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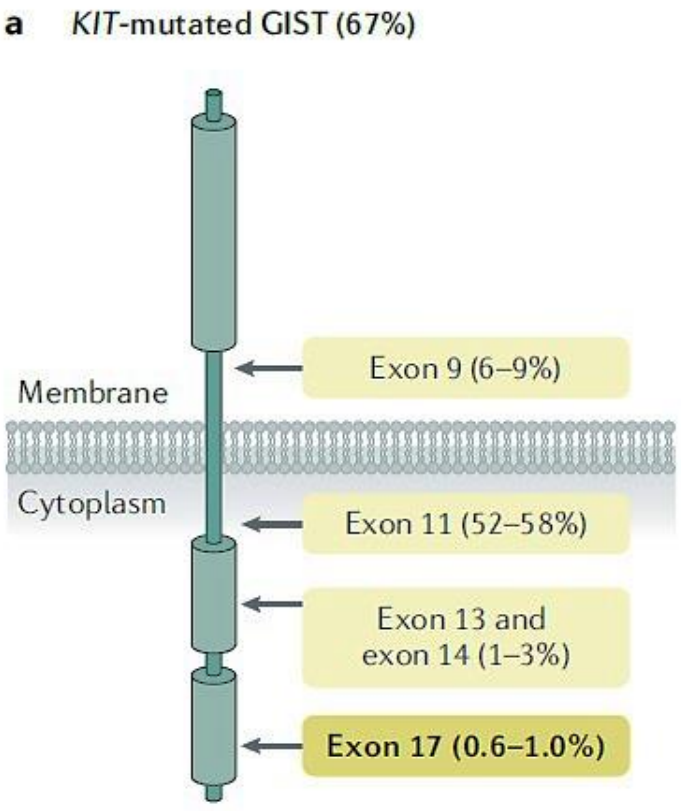
Outline

- KIT/PDGFRA mutated GISTs
- KIT/PDGFRA wt GISTs
- The role of CGP and ctDNA
- ESMO Recommendations 2024
- Current laboratory practice

KITm GISTs



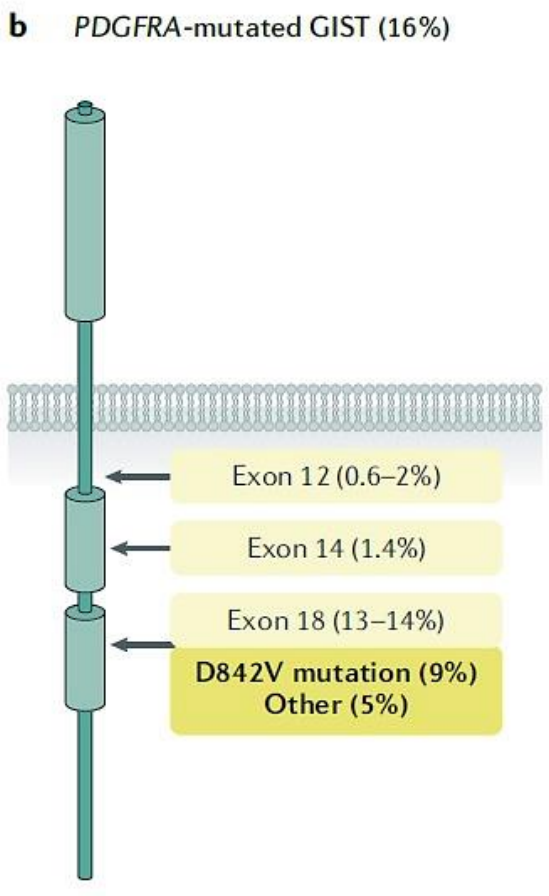
Blay JY - Nature reviews, 2021

EXON	FUNCTION	FREQUENCY	GIST SITE	IMATINIB SENSITIVITY	SUNITINIB SENSITIVITY	REGORAFENIB SENSITIVITY	AVAPRITINIB SENSITIVITY	RIPRETINIB SENSITIVITY
9	EXTRACELLULAR DOMAIN	5-10%	SMALL INTESTINE	Y (800mg)	Y	Y	Y	Y
11	JUXTAMEMBRANE DOMAIN	60-70%	ALL SITES	Y	Y	Y	Y	Y
13-14	ATP BINDING DOMAIN	<1%	ALL SITES	±	N	Y	Y	Y
17-18	ACTIVATION LOOP	1%	ALL SITES	N	±	±	Y	Y

SECONDARY RESISTANCE TO IMATINIB MUTATIONS

- EXON 13: codon V654
- EXON 14: codon T670
- EXON 17: codons D816, D820, N822, Y823
- KIT gene Amplification
- PDGFRA exon 18 D842V mutation
- Alternative Pathways/downstream kinases Activation

PDGFRAm GISTs



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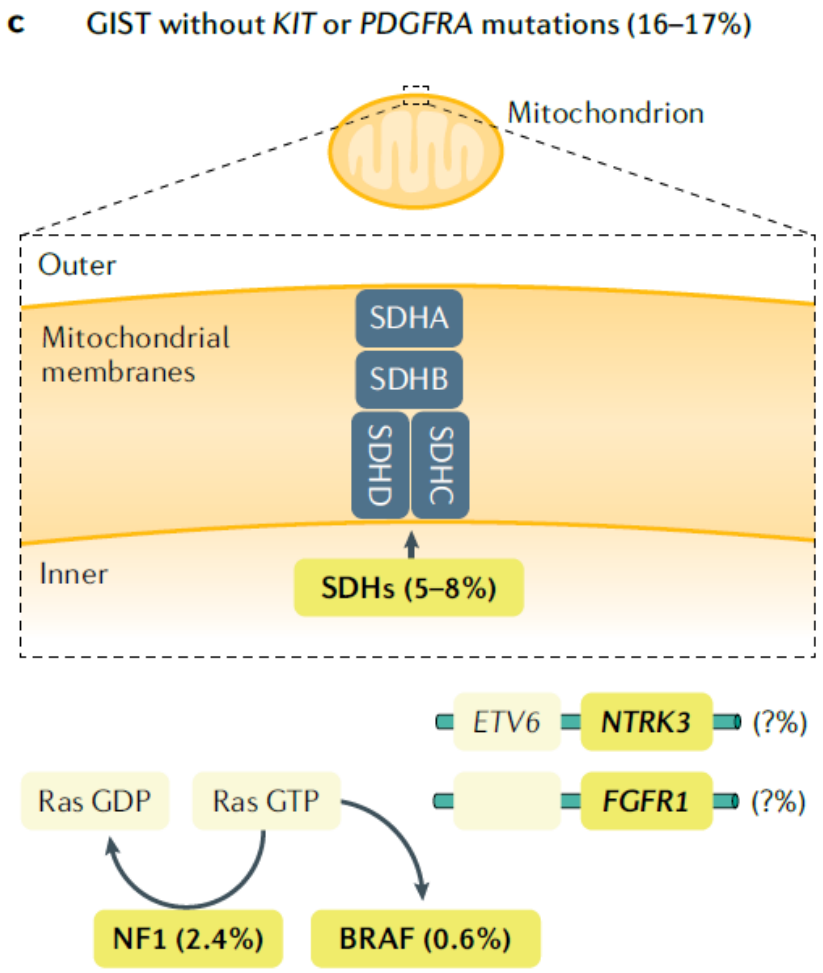
EXON	FUNCTION	FREQUENCY	GIST SITE	IMATINIB SENSITIVITY	SUNITINIB SENSITIVITY	REGORAFENIB SENSITIVITY	AVAPRITINIB SENSITIVITY	RIPRETINIB SENSITIVITY
12	JUXTAMEMBRANE DOMAIN	1-2%	STOMACH	±	±	±	±	±
14 (N659K)	TKD N-lobe	1%	STOMACH	±	±	±	N	±
18 (D842V)	TKD C-lobe	9-10%	STOMACH	N	N	N	Y++	Y
18	TKD C-lobe	5%	STOMACH	±	±	±	Y++	Y

SECONDARY RESISTANCE MUTATIONS

- EXON 18: D842V mutation
- EXON 13,14, 15: V658A, N659K, Y676C, G680R impairs Avapritinib binding
- Alternative Pathways/downstream kinases Activation

KIT/PDGFRA WT GISTs



Blay JY - Nature reviews, 2021

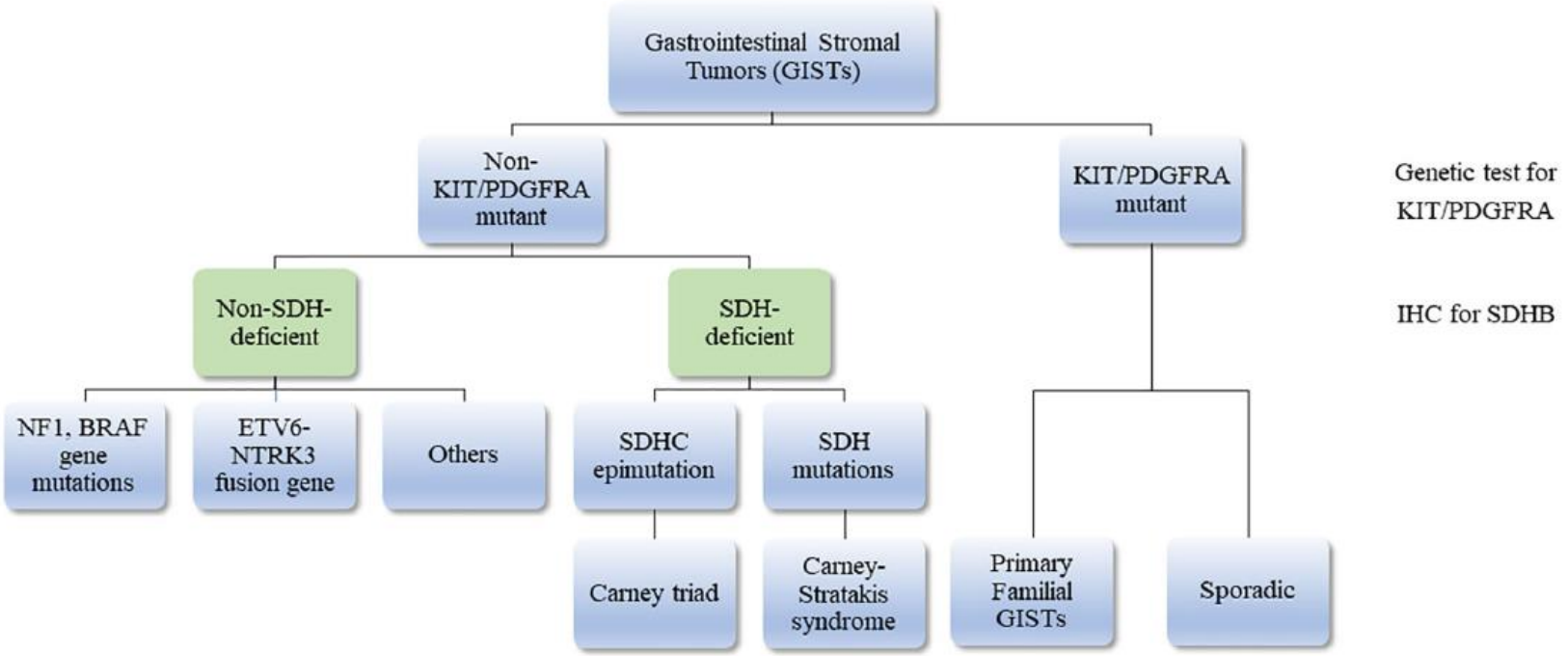
SDH-Deficient GISTs

- 60% - inactivating mutation SDH cpx
- 40% - SDHC promoter methylation
- Stomach, early onset (<40), female prevalence, indolent clinical course
- TKIs Resistance!

SDH-Competent GISTs

- NF1 mutations (2%)
- HRAS, NRAS, KRAS mutations (<1%)
- BRAF V600E mutation (1%)
- NTRK fusions (Rare)
- FGFR 1-2-3 alterations (Rare)

Hereditary GISTs



Pitsava G. – Frontiers in Endocrinology, 2021

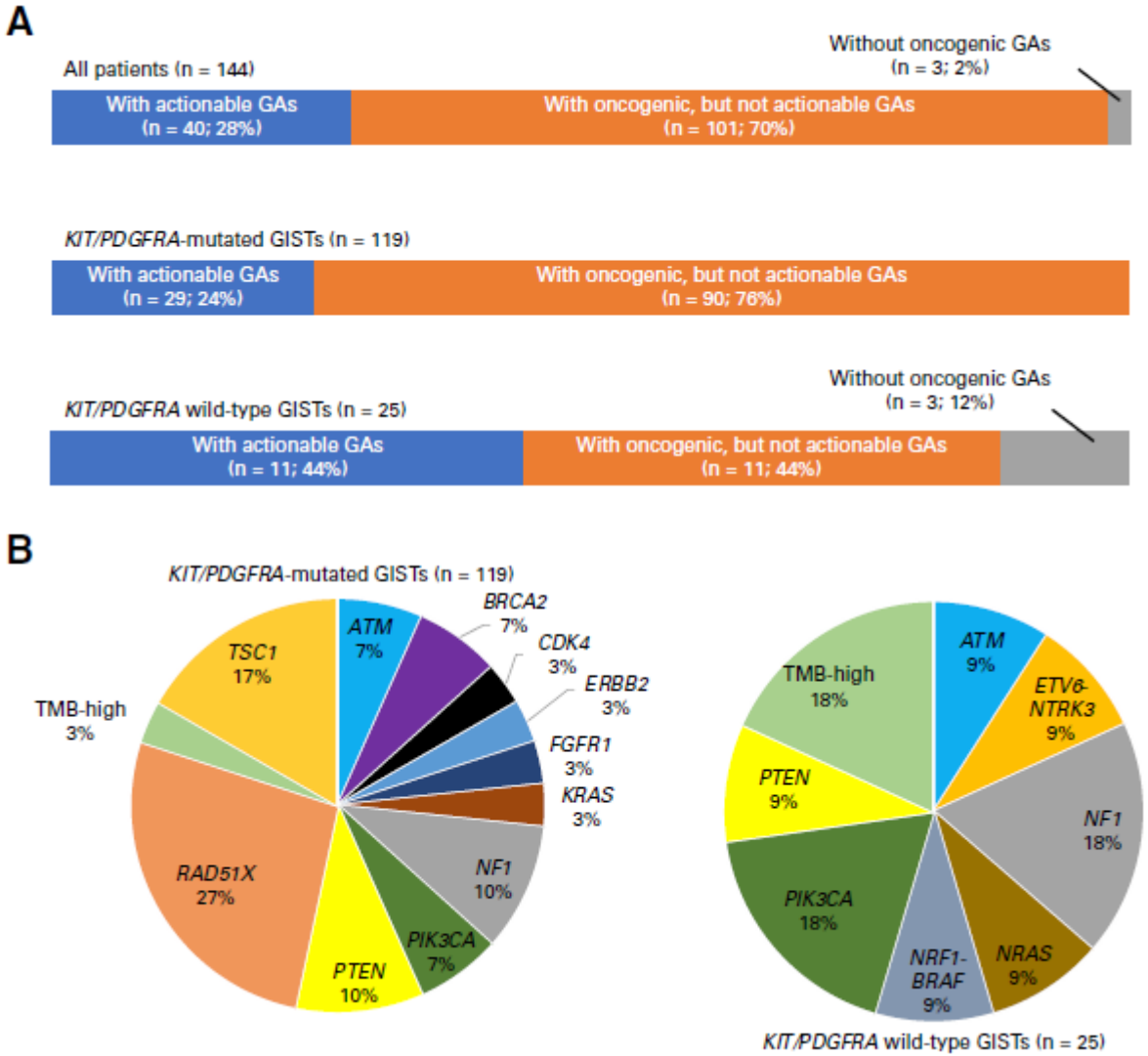
About 10% GISTs are Familial GISTs (85% in children and young adults)

- Germline PV KIT-PDGFRA: 50 known families, mostly KIT ex11 point mut. (NO INDELS), multiple GISTs, cutaneous hyperpigmentation, mastocytosis, germinal cells tumors.
- Carney-Stratakis Syn.: germ. PV SDHx, 80% young women, AD with incomplete penetrance, PGLs/PHEOs and GISTs
- NF1-related condition: av. Lifetime risk of 10% of developing GISTs in Neurofibromatosis-I patients

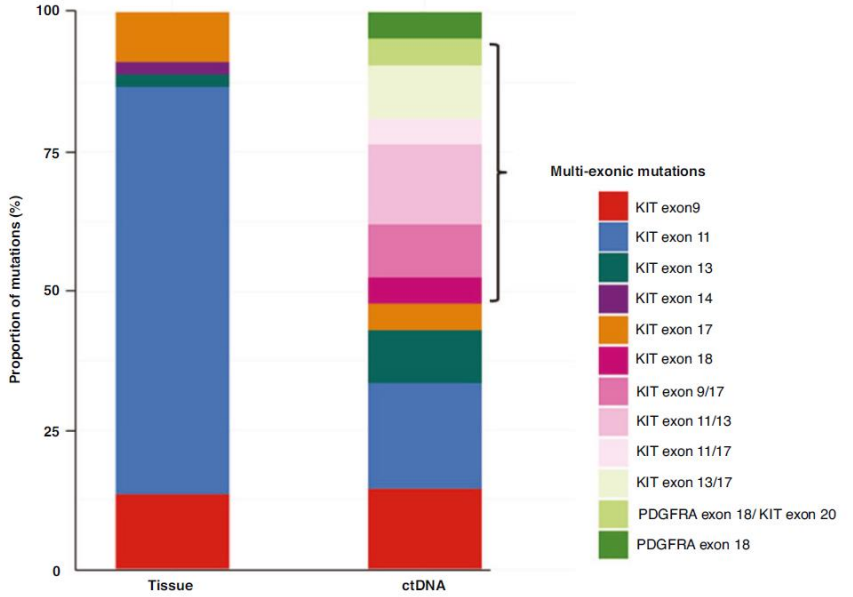
Cancer Type and Specific Population	More Strongly Recommended (higher relative risk of cancer or highly actionable)	Less Strongly Recommended (moderate relative risk of cancer or potential impact for therapy/change in medical management)
Gastrointestinal stromal tumors	*KIT*, *PDGFRA* If SDH-deficient or *SDH*-mutant tumor: *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD* If *NF1*-mutated tumor: *NF1*	If tumor is not SDH-deficient, *SDH*-mutated, or *NF1*-mutated: *NF1*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*

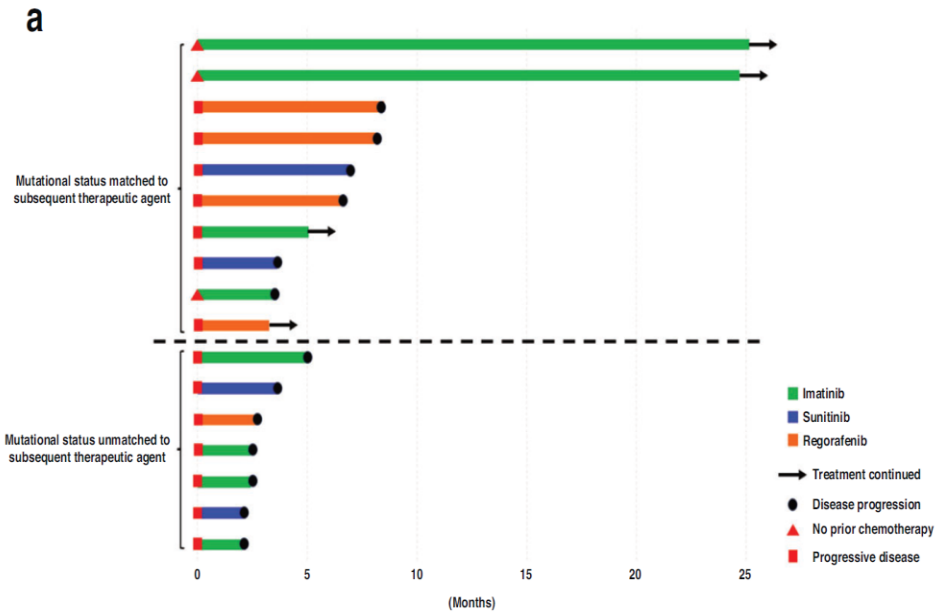
Tung N - JCO, 2024

Role of CGP and ctDNA



Fujii H. - JCO, 2024





Hashimoto T. - BJC, 2024

ESMO ESCAT-I Alterations

Table 9. List of genomic alterations level I/II according to ESCAT in advanced gastrointestinal stromal tumour

Gene	Alteration	Estimated prevalence	ESCAT score	Drug class matched	References
KIT	Mutations/insertions/deletions/indels	85%	IA	KIT/PDGFR TKIs	Demetri et al., *N Engl J Med* 2002[138] Demetri et al., *Lancet* 2006[139] Demetri et al., *Lancet* 2013[140] Blay et al., *Lancet Oncol* 2020[141]
PDGFRA	Mutations/insertions/deletions/indels	10%-15%	IA	KIT/PDGFR TKIs	Demetri et al., *N Engl J Med* 2002[138] Demetri et al., *Lancet* 2006[139] Demetri et al., *Lancet* 2013[140] Blay et al., *Lancet Oncol* 2020[141]
	Exon 18 D842V mutations	5%	IB	KIT/PDGFR TKIs	Heinrich et al., *Lancet Oncol* 2020[142]

ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; PDGFR, platelet-derived growth factor receptor A; TKIs, tyrosine kinase inhibitors.

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

M. F. Mosele[1,2], C. B. Westphalen[3], A. Stenzinger[4], F. Barlesi[1,2,5], A. Bayle[5,6,7,8], I. Bièche[9], J. Bonastre[7,8], E. Castro[10], R. Dienstmann[11,12,13], A. Krämer[14,15], A. M. Czarnecka[16,17], F. Meric-Bernstam[18], S. Michiels[7,8], R. Miller[19,20], N. Normanno[21], J. Reis-Filho[22], J. Remon[2], M. Robson[23], E. Rouleau[24], A. Scarpa[25], C. Serrano[11], J. Mateo[11] & F. André[1,7,*]

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]

Current Laboratory Practice

- Actionable molecular targets
- Parallele Analysis of SNPs, InDels, Fusions, CNVs
- Low Input DNA/RNA
- Pan-solid cancer solution
- High Multiplexing capacity
- FFPE/ctDNA as starting material

DNA							RNA	
Deletions, insertions, and substitutions					Copy number alternations		Fusions and splicing variants	
AKT1	*CTNNB1*	*FGFR4*	*MAP2K1*	*PTEN*	***AR***	***FGFR2***	*ALK*	***NRG1***
AKT2	*EGFR*	*FLT3*	*MAP2K2*	*RAF1*	***EGFR***	***FGFR3***	***AR***	*NTRK1*
AKT3	*ERBB2*	*GNAS*	*MET*	*RET*	***ERBB2***	***KRAS***	***BRAF***	*NTRK2* ✓
ALK	*ERBB3*	*HRAS*	*NRAS*	*ROS1*	***ERBB3***	***MET***	***EGFR***	*NTRK3*
AR	*ERBB4*	*IDH1*	*NTRK1*	*STK11*	***FGFR1***	***PIK3CA***	***ESR1***	***NUTM1***
ARAF	*ESR1*	*IDH2*	*NTRK2*	*TP53*			***FGFR1***	*RET*
BRAF ✓	*FGFR1*	*KEAP1*	*NTRK3*				***FGFR2*** ✓	*ROS1*
CDK4	*FGFR2*	*KIT* ✓	*PDGFRA* ✓				***FGFR3***	***RSPO2***
CHEK2	*FGFR3*	*KRAS* ✓	*PIK3CA*				*MET*	***RSPO3***

Oncomine Express Test IVDR

Take Home Message

- Different KIT/PDGFRA somatic mutations leads to different responce to TKIs
- Broader biomarker testing enables the detection of actionable mutations in KIT/PDGFRA wt cases
- Mid size NGS panels for GIST molecular testing represents a useful tool
- Germline PV should be assessed in selected cases

Thank You!

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I R C C S

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