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GIST and Soft Tissue Sarcoma
Focus on Personalized Medicine

The speaker will directly disclose the use of products for which they are not labeled (e.g., off label use) or if the product is still investigational.

18th Annual New Orleans Summer Cancer Meeting

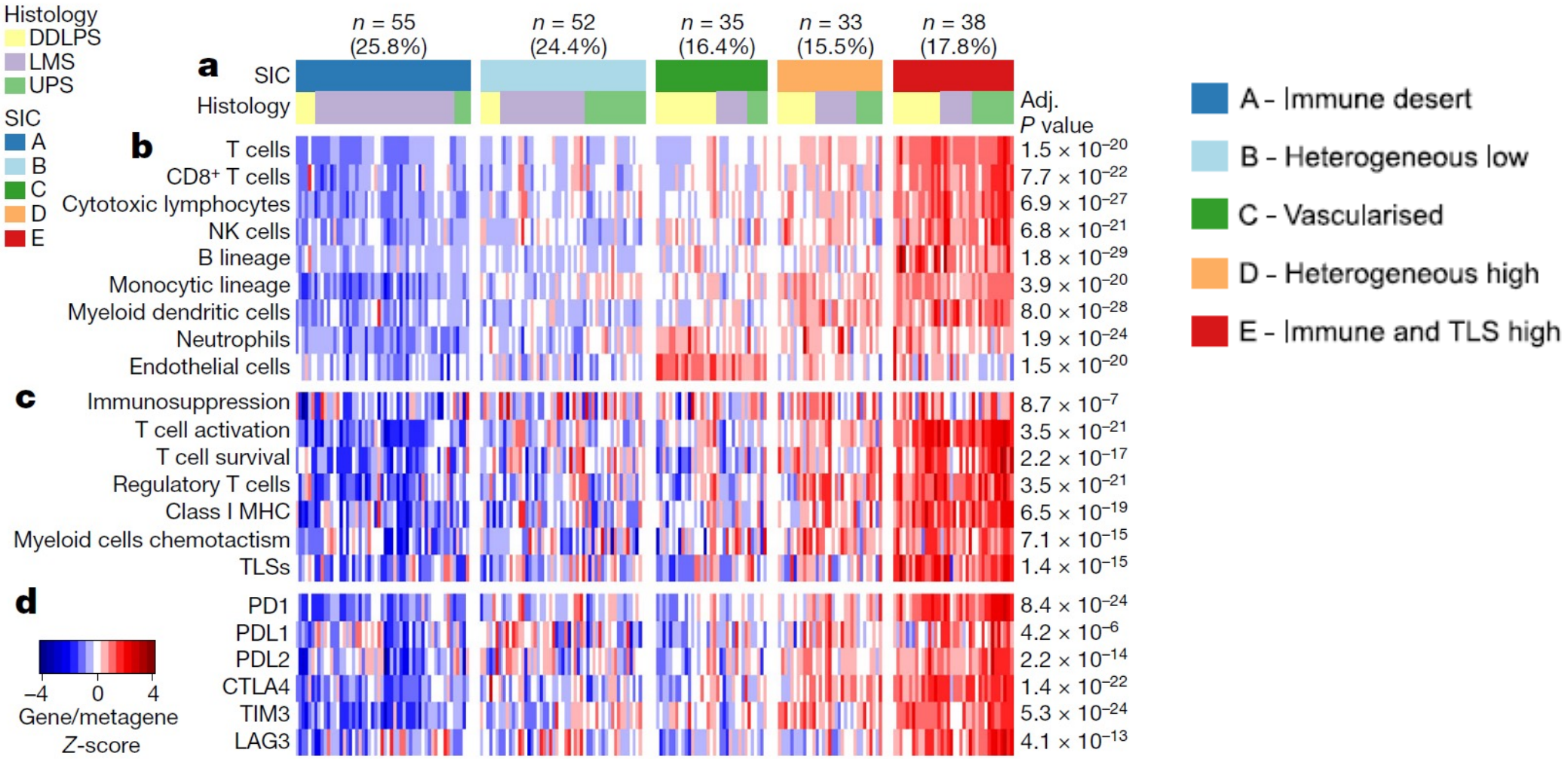
Outline

- Soft Tissue Sarcoma
  - Present landscape of immunotherapy for STS
  - Mechanisms to increase immunogenicity
  - Biomarkers: ctDNA, HMGB1
- GIST
  - mutations and therapy decisions

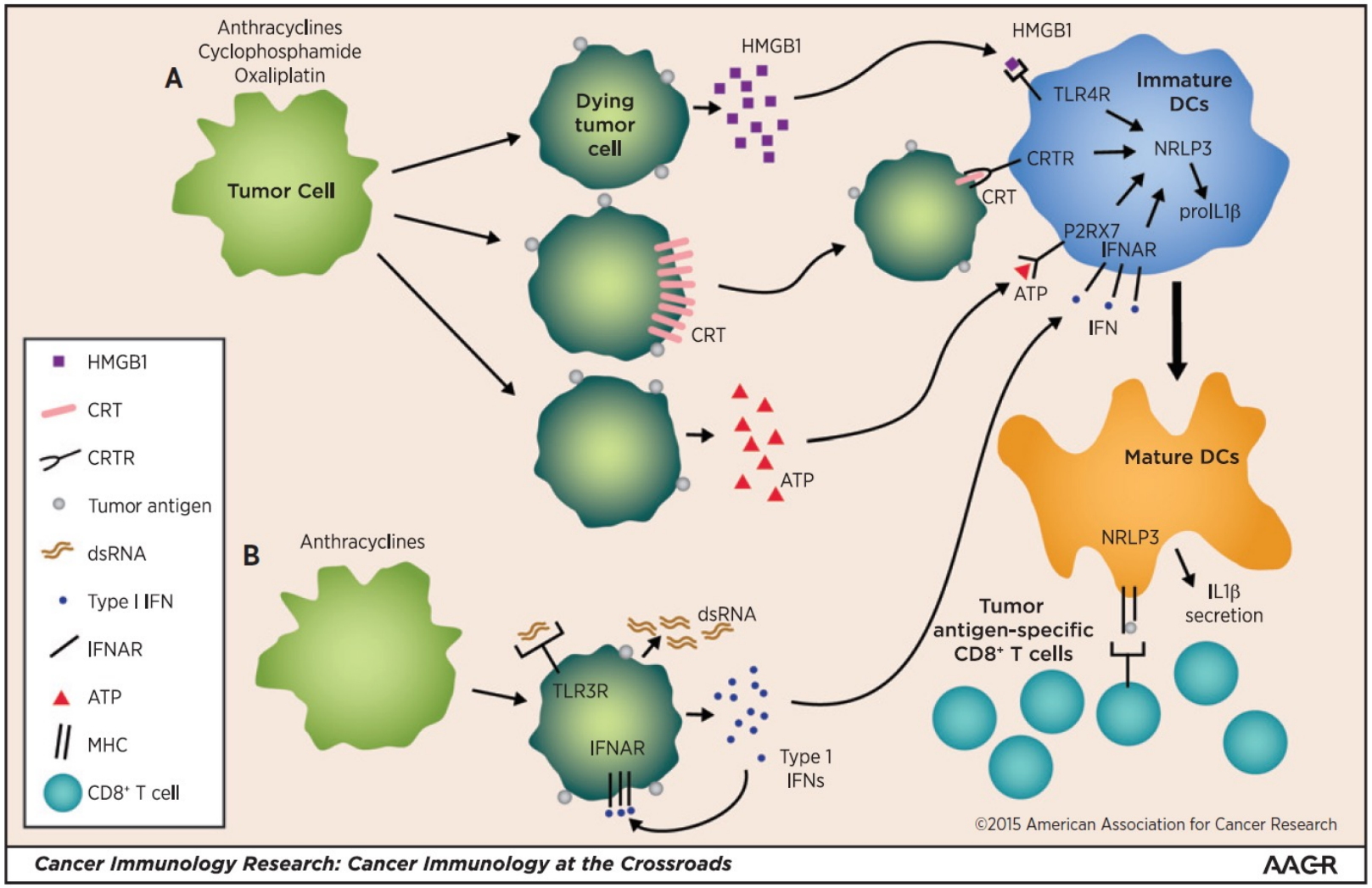
Single Agent Immunotherapy Soft Tissue Sarcoma

Agent	# Pts	ORR (%)	mPFS (m)	RR by subtype	
Ipilimumab	6	0	1.9	0 SS	Maki, 2013
Pembrolizumab (SARC028)	80	**18**	4.5	**23% UPS** (2 CR), 10% LPS	Burgess, 2019
Atezolizumab	32	**42**	NR	**42% ASPS**	Coyne, 2018
Nivolumab		0	1.8	0 Uterine LMS	Ben-Ami, 2017
Nivolumab Ipilimumab + Nivolumab (Alliance 091401)	43 42	5 **16**	1.7 4.1	**ASPS,** LMS **28.6% UPS**, 14.3% LPS	D'Angelo, 2018

Sarcoma Immune Classification (SIC)/Sarc028



Petitprez, et all Nature, 2020, 577:556



Dying Tumor cells release:

- "danger" associated molecules:
  - HMGB1
  - ATP
- CRT (calreticulin) –> phagocytosis signal
- type I IFN

Results in dendritic cell maturation and evolution of tumor specific CD8+ T cells

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Allavena P, Belgiovin

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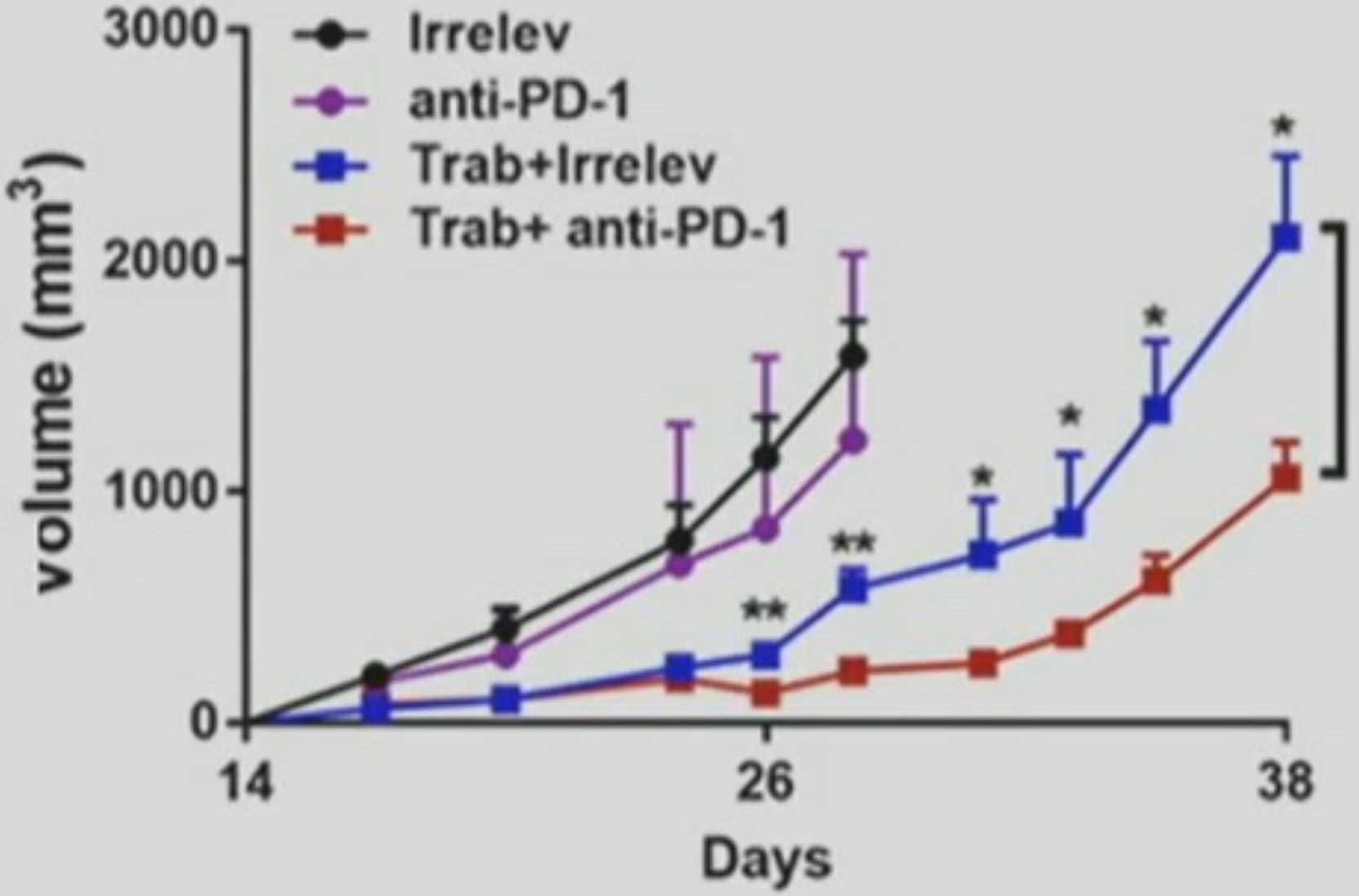
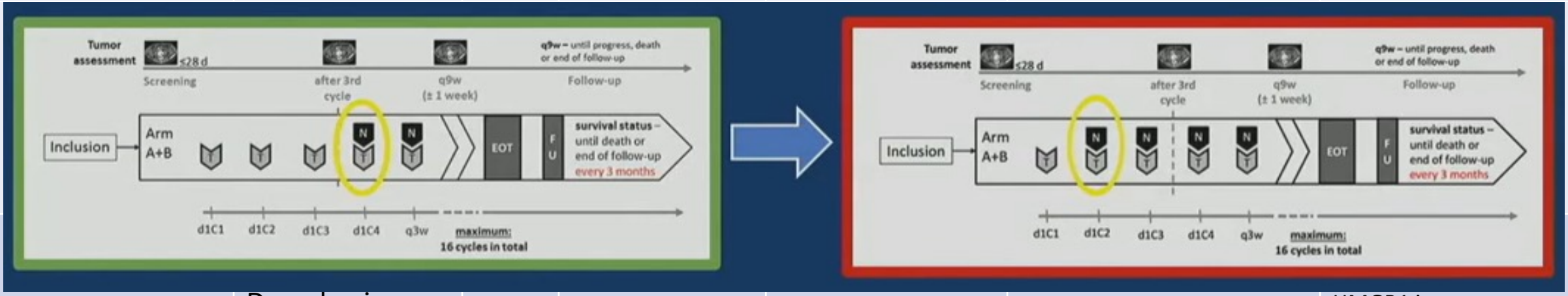
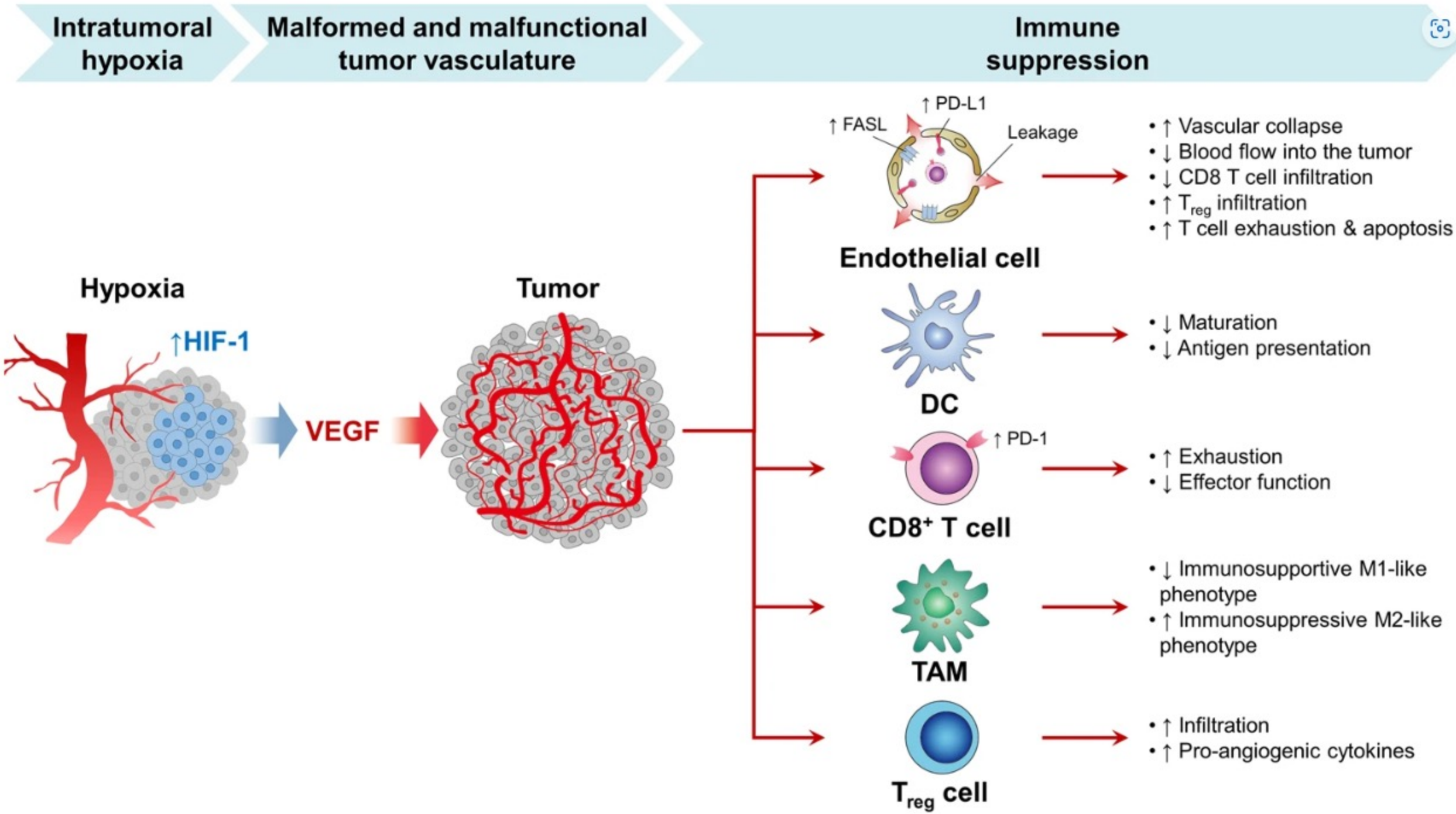


STS:: IO + chemo

ICI	Chemo	# Pts	Histology	ORR (%)	mPFS (m)	Timing
Nivolumab[1]	Trabectedin	43 49	Lipo/LMS Non-L	NS	5.5 (C_2 4.4, C_4 **9.8**) 2.3 Did not meet statistical design endpoint	T → N C_2 v C_4
	Dacarbazine 400 mg/m2 d1,2					HMGB1 increase ass with ↑ mPFS
Pembrolizumab[4] 200 mg	Doxorubicin 45,75 mg/m2	37	Multiple	19	**8.1**	P → D



1 Peter Reichardt, MD, PhD NitroSarc HELIOS Klinikum Berlin-Buch, Klinik für Interdisziplinäre Onkologie,
2 Wilky, U Colo
3 Broto, Spain, Immunosarc
4 Pollack, U Wash


Intratumoral hypoxia
Malformed and malfunctional tumor vasculature
Immune suppression
Hypoxia
↑HIF-1
VEGF
Tumor
↑ PD-L1
↑ FASL
Leakage
Endothelial cell
• ↑ Vascular collapse
• ↓ Blood flow into the tumor
• ↓ CD8 T cell infiltration
• ↑ T_{reg} infiltration
• ↑ T cell exhaustion & apoptosis
DC
• ↓ Maturation
• ↓ Antigen presentation
↑ PD-1
$CD8^+$ T cell
• ↑ Exhaustion
• ↓ Effector function
TAM
• ↓ Immunosupportive M1-like phenotype
• ↑ Immunosuppressive M2-like phenotype
T_{reg} cell
• ↑ Infiltration
• ↑ Pro-angiogenic cytokines

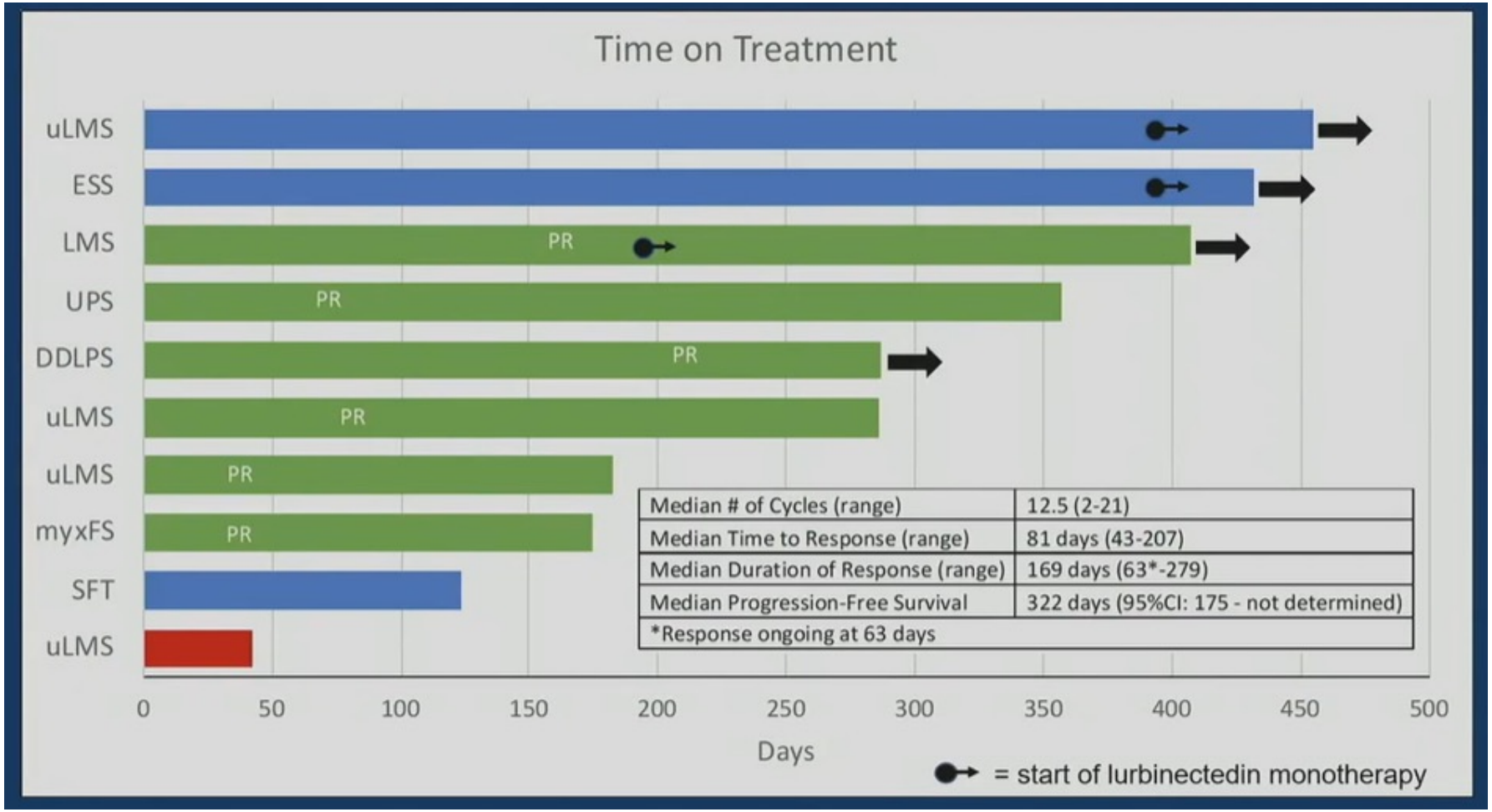
STS: ICI + VEGFRi

ICI	Chemo	# Pts	Histology	ORR	mPFS (mos)	
Nivolumab[3]	Cabozantinib (60)	22	Angiosarc	59% CR 9	9.6 3.8-6.6 Taxane 4.9 Doxo 2-4 VEGF TKI OS NR	Prior taxane required, Response in both cutaneous and non-cutaneous sites
Ipilimumab/ Nivolumab[2]	Cabozantinib (40)	105	Multiple LMS (54) DDLPS (3) UPS (5)	11% v 6% 5PR 2CR	**5.36 v 3.7 C** **(p= 0.016)**	RCT 2:1 triplet v C ; ≥ 2L DCR triplet 80% Cabo 42 p=0004
Temozolomide[1]	Cabozantinib (40)	42 30	LMS Non LMS	14% (22uLMS) 7% (angio)	6.3 4.1	**PFS 12 week 74%**
Pembrolizumab[4]	Lenvatinib 20	10 6/3	5 cohorts: LMS SS/MPNST	SD 33% (2/6 SS)	32 wks	L → P

[1] Agrulnik, City of Hope, [2] Van Tine, Wash Univ. [3] Grilley-Olson, Duke, [4] Muvva, MSKCC, ASCO 2023

Doxo/Lurbinectedin Phase Ib

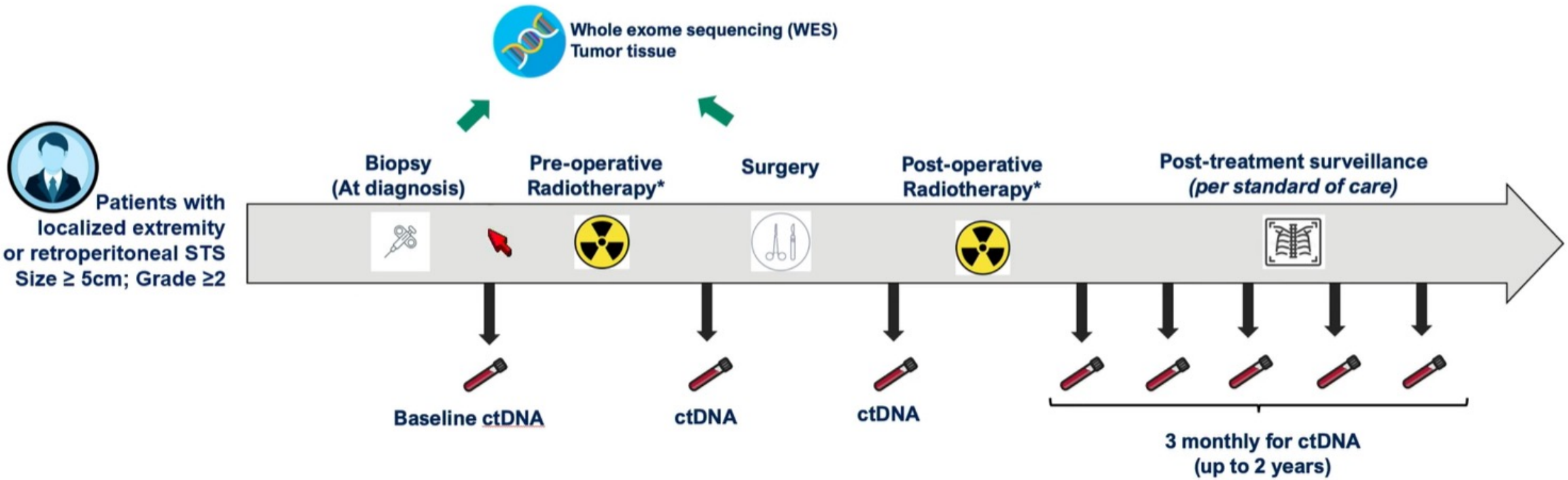
Doxorubicin	Lurbinectedin	#Pts	Histology	ORR	mPFS
Level 1: 25	3.2 mg/m2 q3w	6	LMS (5)	60 (3 LMS)	322 d
Level 2: 25 d1, d8	3.2 mg/m2 q3w	4			
Single agent Doxo				35	4.2 m



Biomarkers in STS – ctDNA

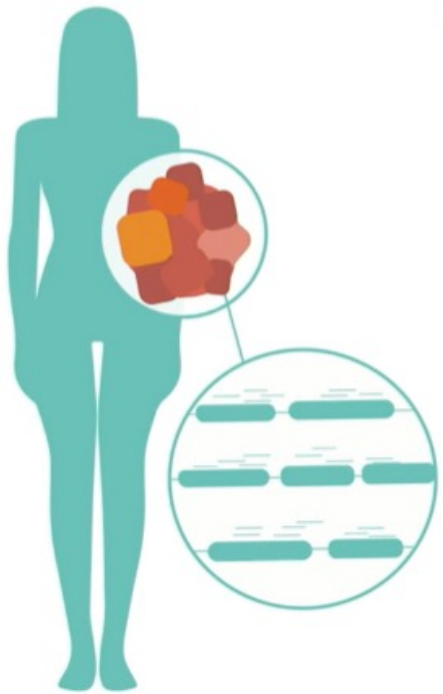
Circulating tumor DNA detection in Soft Tissue Sarcoma (DNA-TSAR)

- Prospective, longitudinal study **[NCT03818412]**
- Single center - Princess Margaret Cancer Center, Toronto

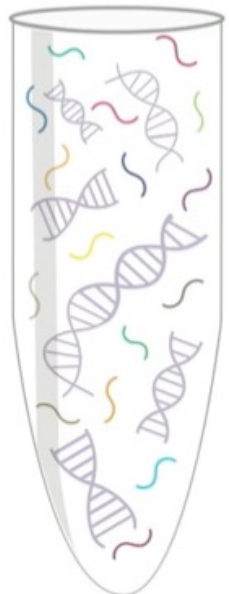


The Signatera tumor informed ctDNA assay is a highly sensitive test that is personalized to the patient's unique tumor profile

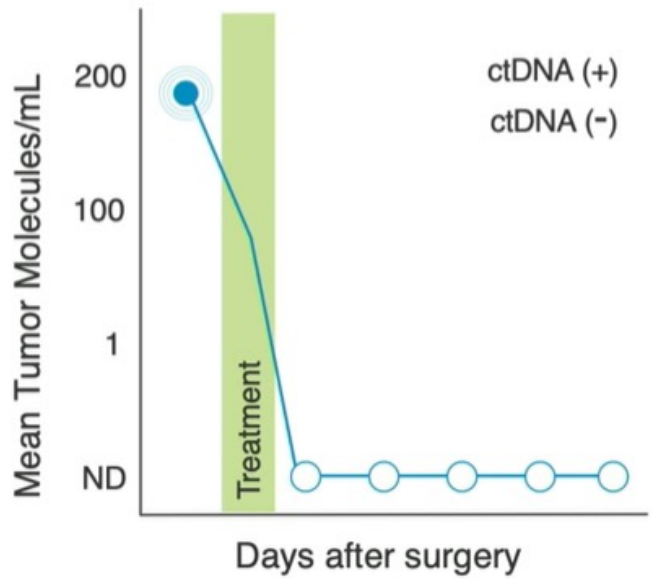
Sequence tumor tissue to identify unique signature of tumor mutations



Custom-design mPCR assay for each patient, targeting the top 16 clonal mutations found in tumor



Use personalized assay to test patient's blood for presence of circulating tumor DNA (ctDNA)



Statistical analysis of variant genes in patients with sarcoma based on previous data

✓45.57% of variant genes occur independently in a single patient: Highly heterogeneous;

✓ Personalized panel may be more suitable for sarcoma MRD detection.

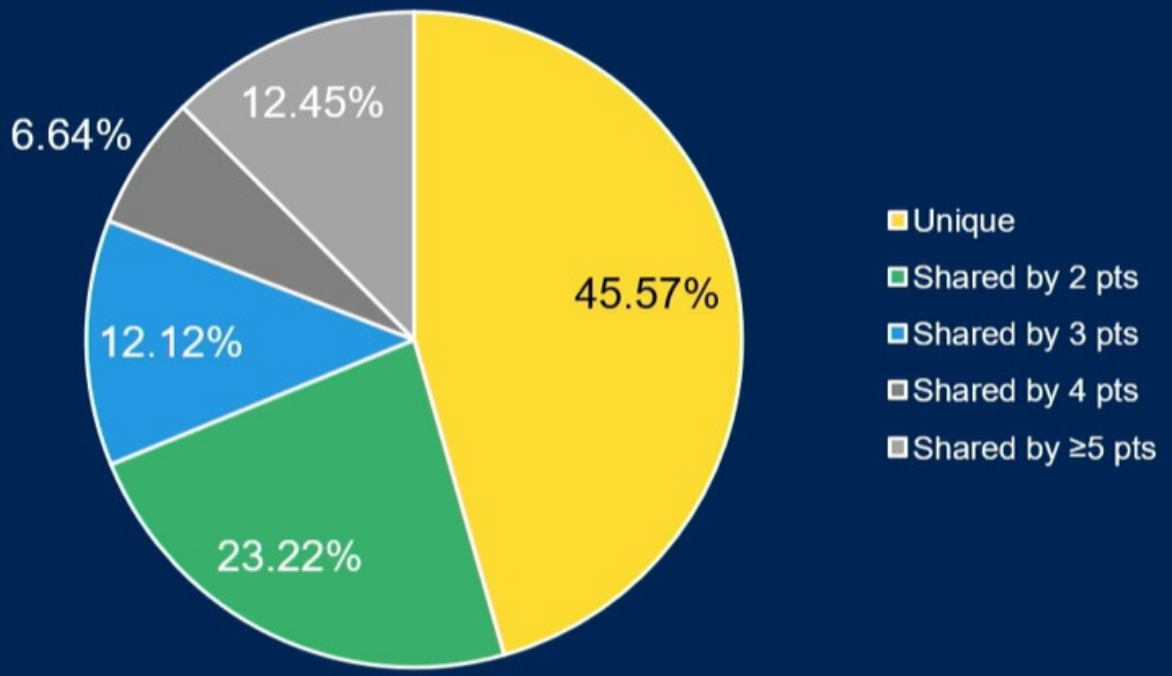
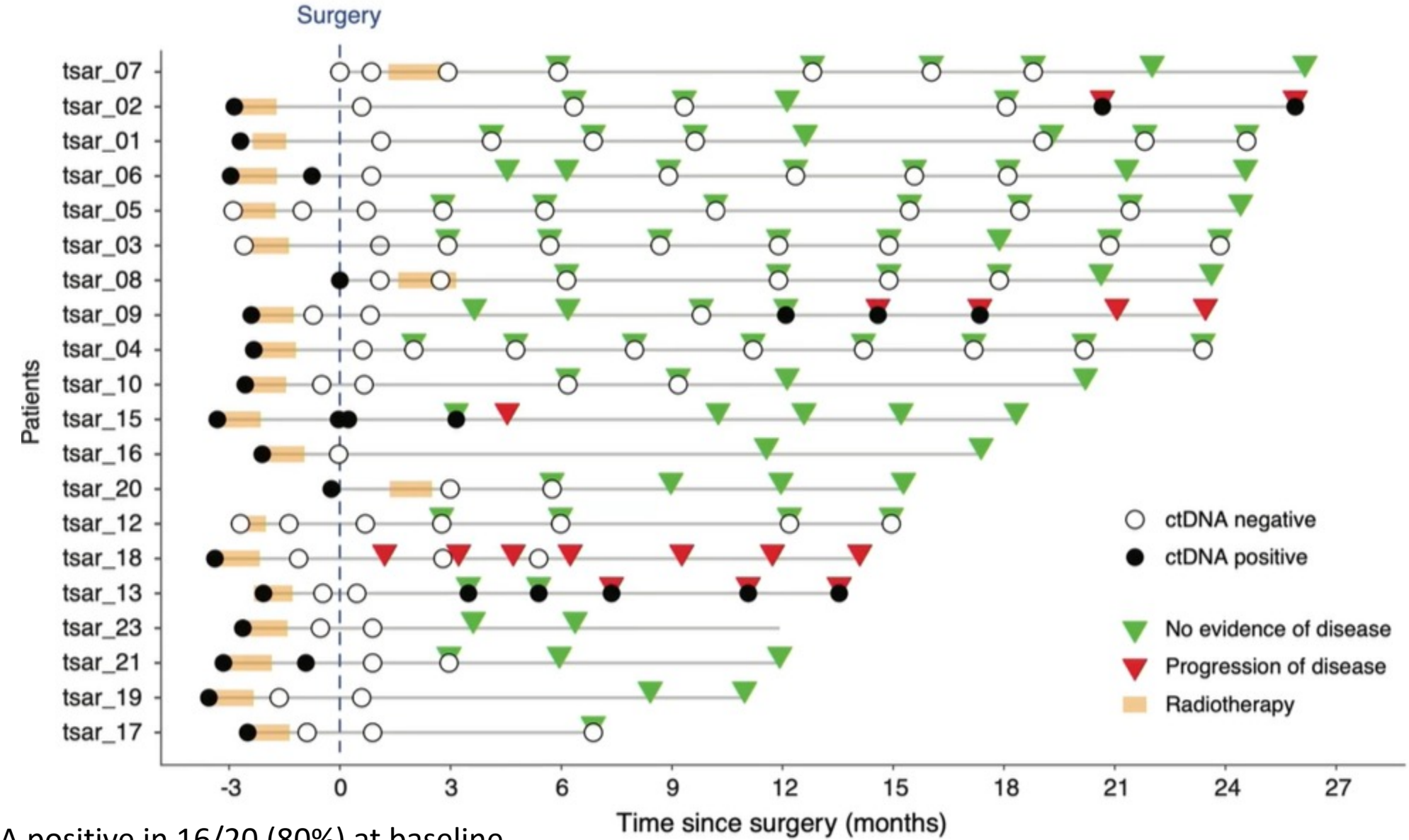


Figure 1. Distribution of shared variant genes in patients according to previous data including 474 sarcoma patients with 11139 genes

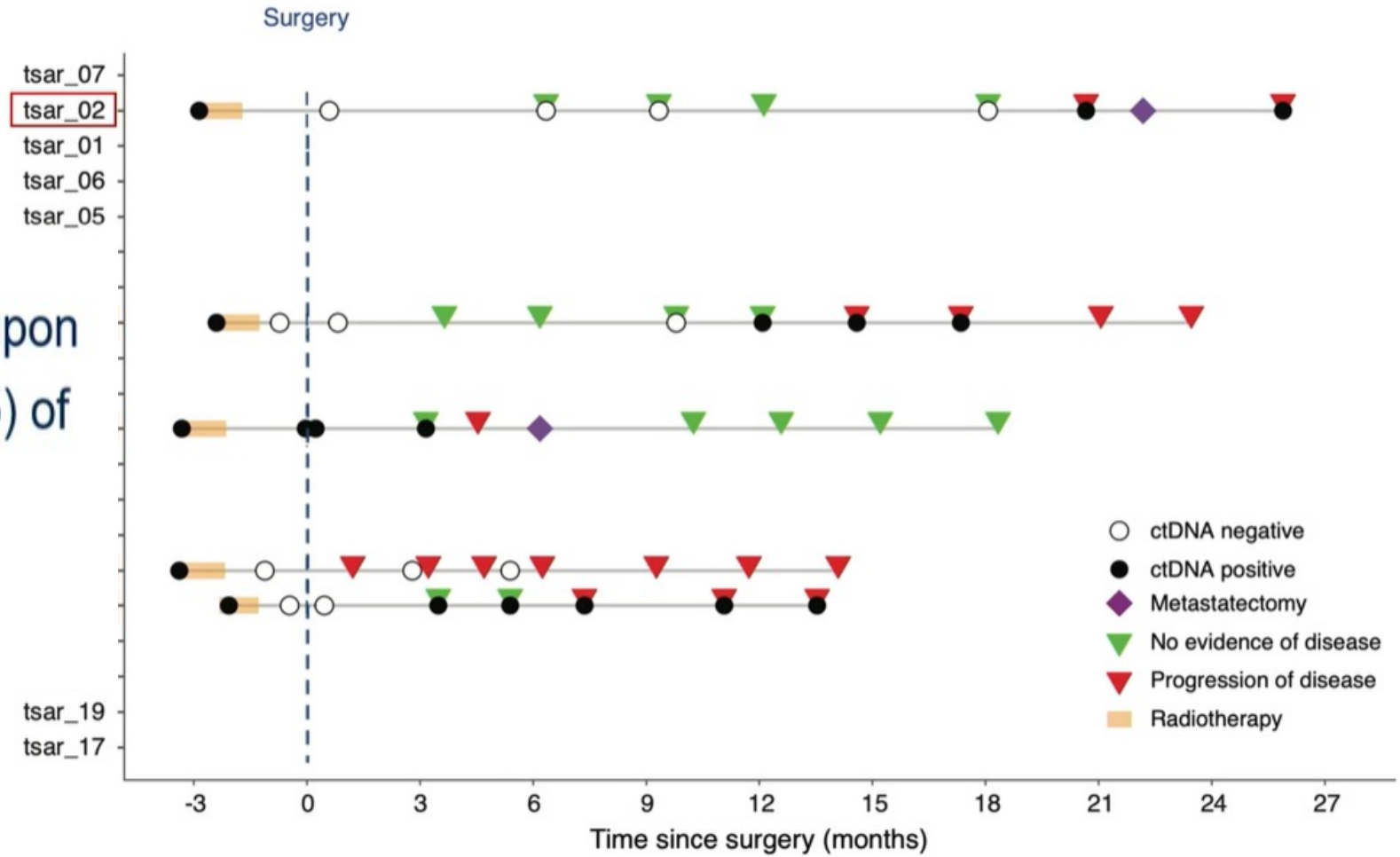


- ctDNA positive in 16/20 (80%) at baseline
- 8/11 + at baseline → negative after neoadj RT
- 5 relapses
- Median F/U 22.5 m

Circulating tumor DNA detection in Soft Tissue Sarcoma (DNA-TSAR)

In follow up – patients with radiologic relapse

- 5 out of 20 patients (25%) had radiologic recurrence with distant
  - ctDNA was detected prior to, or upon radiologic recurrence in 80% (4/5) of cases
    - **Median lead time: 97 days**



GIST

GIST

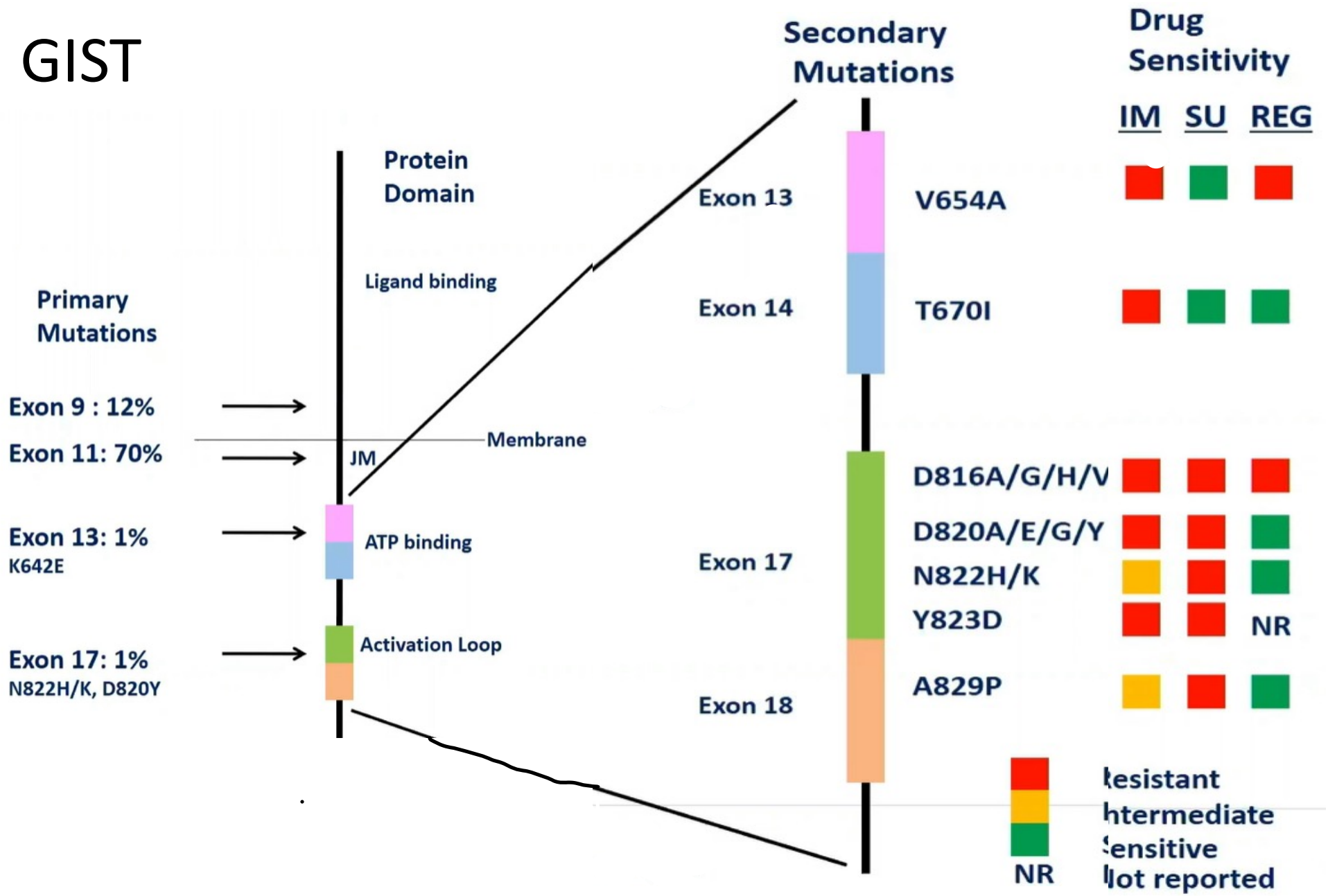
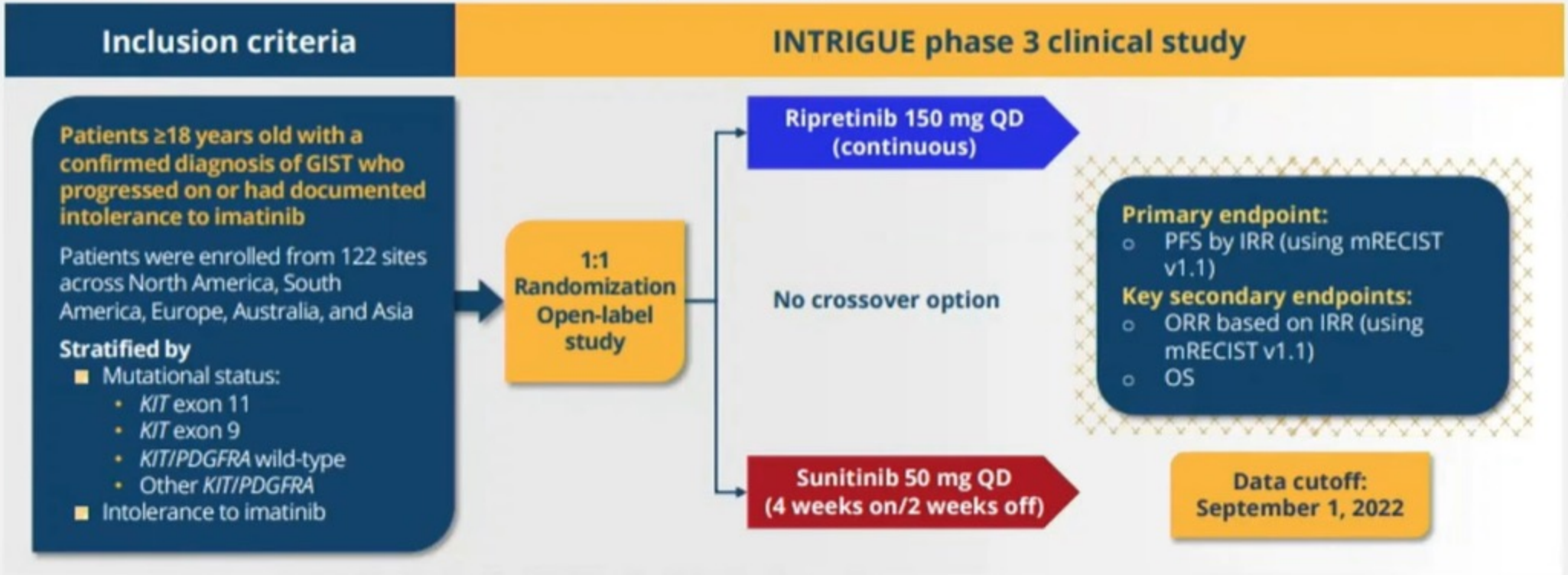

Secondary Mutations
Drug Sensitivity
IM SU REG
Protein Domain
Ligand binding
Primary Mutations
Exon 9 : 12%
Exon 11: 70%
Membrane
JM
Exon 13: 1%
K642E
ATP binding
Activation Loop
Exon 17: 1%
N822H/K, D820Y
Exon 13
V654A
Exon 14
T670I
Exon 17
D816A/G/H/V
D820A/E/G/Y
N822H/K
Y823D
Exon 18
A829P
NR
Resistant
Intermediate
Sensitive
Not reported
NR

Figure 1. INTRIGUE study design



Mutational status used for randomization was based on local pathology reports at the time of randomization.
GIST, gastrointestinal stromal tumor; IRR, independent radiologic review; mRECIST v1.1, modified response evaluation criteria in solid tumors version 1.1; ORR, objective response rate; OS, overall survival; PDGFRA, platelet-derived growth factor receptor α; PFS, progression-free survival; QD, once daily.

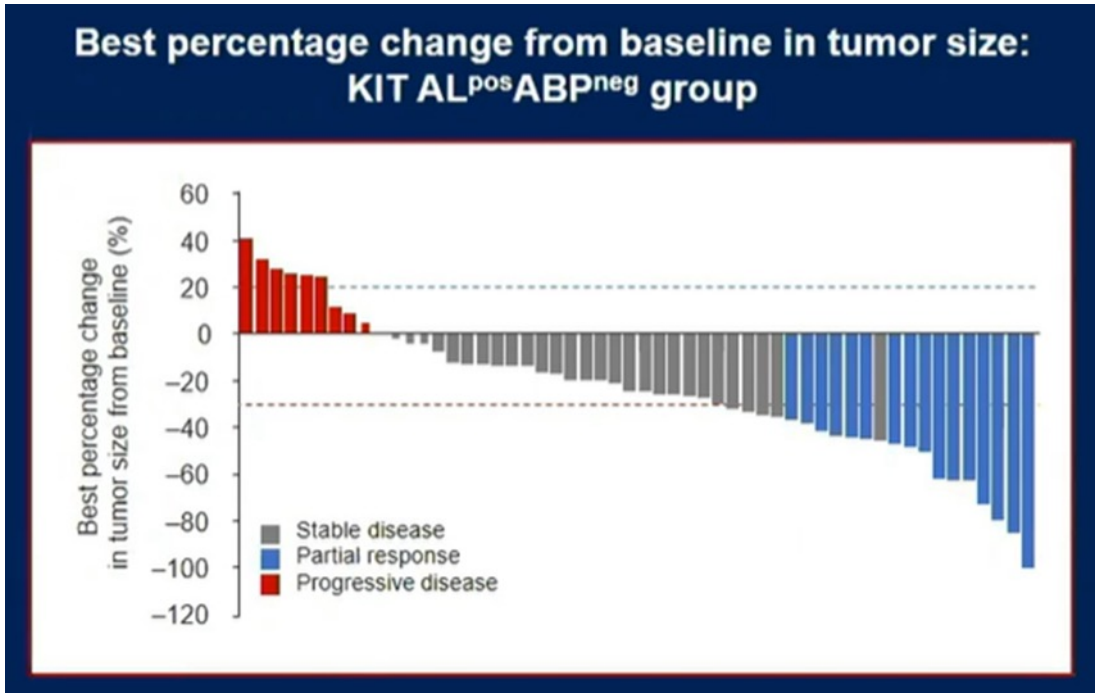
INTRIGUE TRIAL

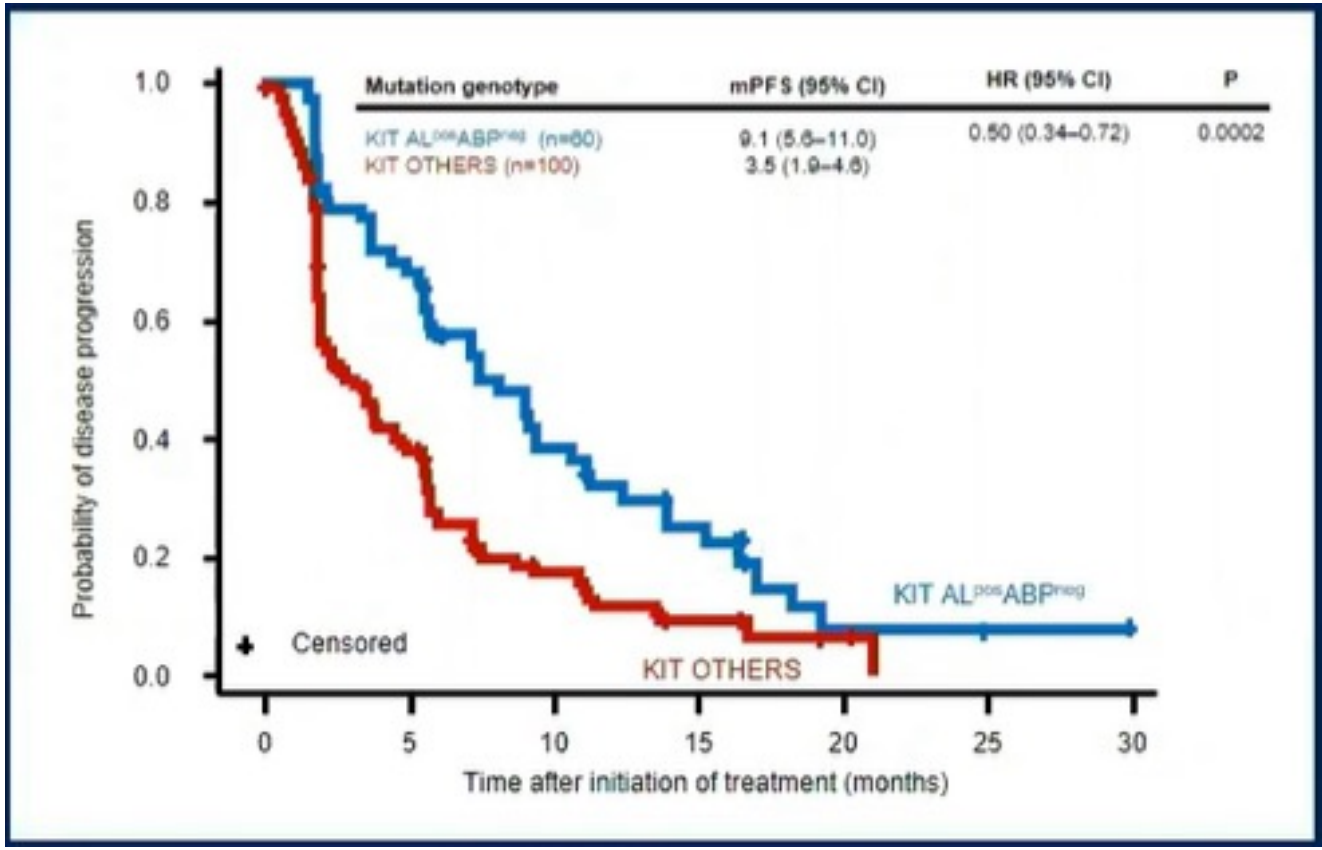
Outcomes by ctDNA analysis in *KIT* exon 11 + secondary mutation subpopulations

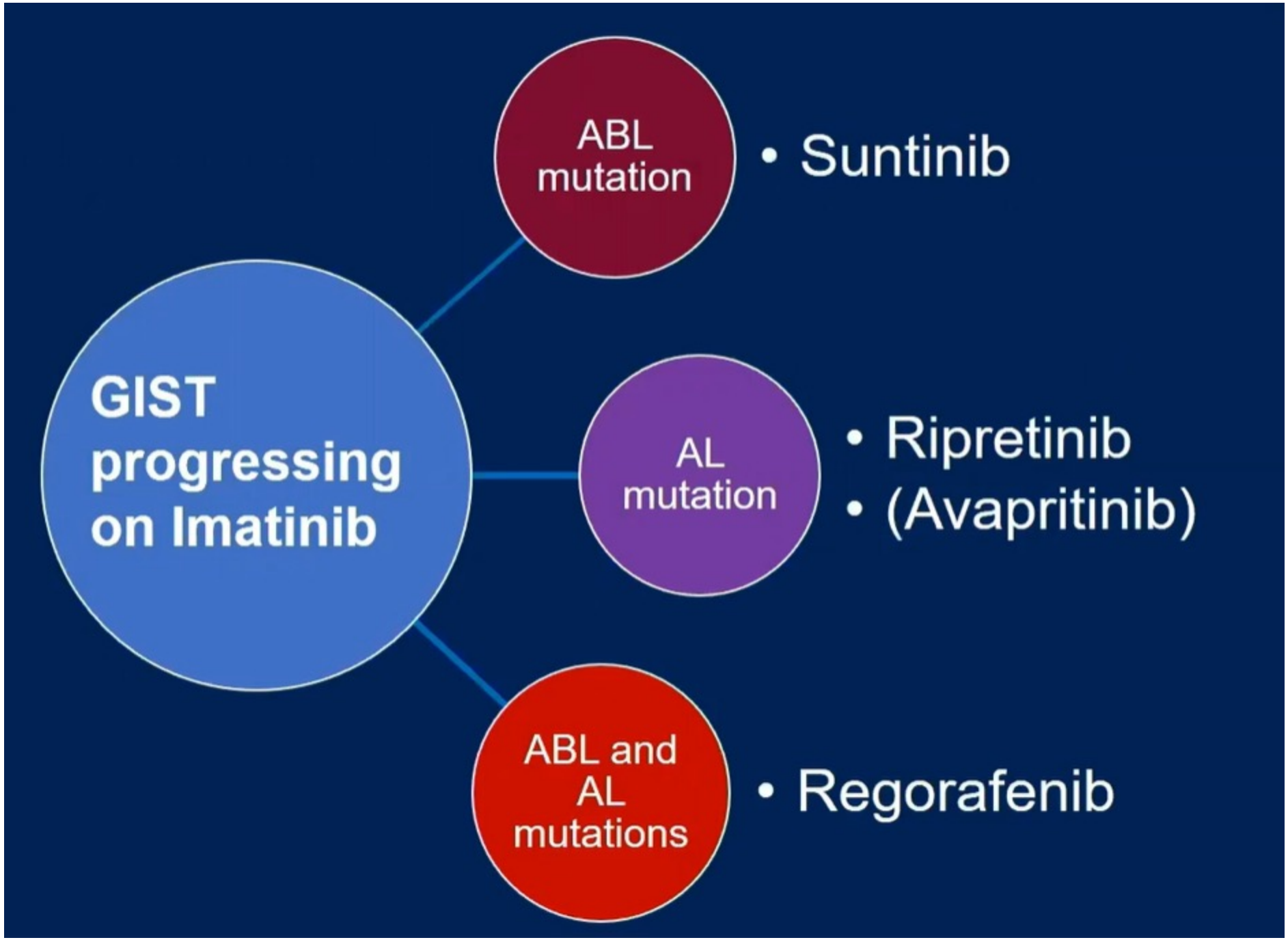
	Activation loop (*KIT* exon 11 + 17/18 only)[a]		ATP-binding pocket (*KIT* exon 11 + 13/14 only)[b]	
	Ripretinib n = 27	Sunitinib n = 25	Ripretinib n = 21	Sunitinib n = 20
mPFS, months	14.2	1.5	4.0	15.0
HR (95% CI)	0.22 (0.11, 0.44)		3.94 (1.71, 9.11)	
ORR, %	44.4	0	9.5	15.0
mOS, months	Not estimable	17.5	24.5	Not estimable
HR (95% CI)	0.34 (0.15, 0.76)		1.75 (0.72, 4.24)	

Phase I Navigator + Phase I/II CS3007-101 (Pooled data)

- Avapritinib 300 mg daily; ≥ 2 L
- kit mutation or D842V PDGFRA
- AL+/ABP- secondary mutation; 60 pts






GIST progressing on Imatinib
ABL mutation
• Suntinib
AL mutation
• Ripretinib
• (Avapritinib)
ABL and AL mutations
• Regorafenib

Future Directions

- PEAK Trial:
  - Phase III randomized trial of bezuclastinib (AL+) + sunitinib (ABP+) versus sunitinib in second line GIST
- INSIGHT Trial:
  - Repretinib v sunitinib in 2L for exon 11 kit with secondary mutations in AL
- Possible Trial of Immunotherapy for PDGFRA mutations (outside of D842V)

STS Conclusions

- Chemo/ICI combinations are well tolerated at full doses of each agent without signals of new or enhanced toxicity
- Timing of administration may be important to treatment outcome in chemo/ICI combinations. Priming with cytotoxic therapy prior to ICI may improve expected response rates and tumor control (Reichert)
- Level of HMGB1 may be biomarker of response
- Synergy or additive effect unclear with TKI/ICI combinations; may be consequence of patient selection
- Unclear if we can convert immune COLD tumors to immune HOT
- Lower doses of standard agents may “synergize” to produce longer disease control (lurbinectedin trial)

Conclusions

- Biomarkers
  - ctDNA can be detected and quantified in plasma at diagnosis in the majority of patients with high grade, large sarcomas using a patient specific assay
  - ctDNA promising technology which appears predictive for relapse with approx. 3+ month lead time
  - Elevated levels of HMGB1 may predict treatment response

GIST Conclusions

- Kit mutation analysis is appropriate in choosing first line therapy for GIST
  - WT kit and PDGFRA D842V mutation not responsive to imatinib
  - Demonstration of TME immune hot phenotype for PDGFRA tumors suggest possible role for immunotherapy
- Repeat mutational testing at time of progression appears important in choice of next line of therapy
  - D842V mutation in PDGFRA highly responsive to avapritinib
  - Drug sensitivity of secondary mutations in activation loop (AL) versus ATP binding site differ.
  - AL mutations appear more responsive to ripretinib, avapritinib
  - ABP mutations appear more responsive to sunitinib

Thank You !!