



Working with Biomarker

What Every Programmer Should Know



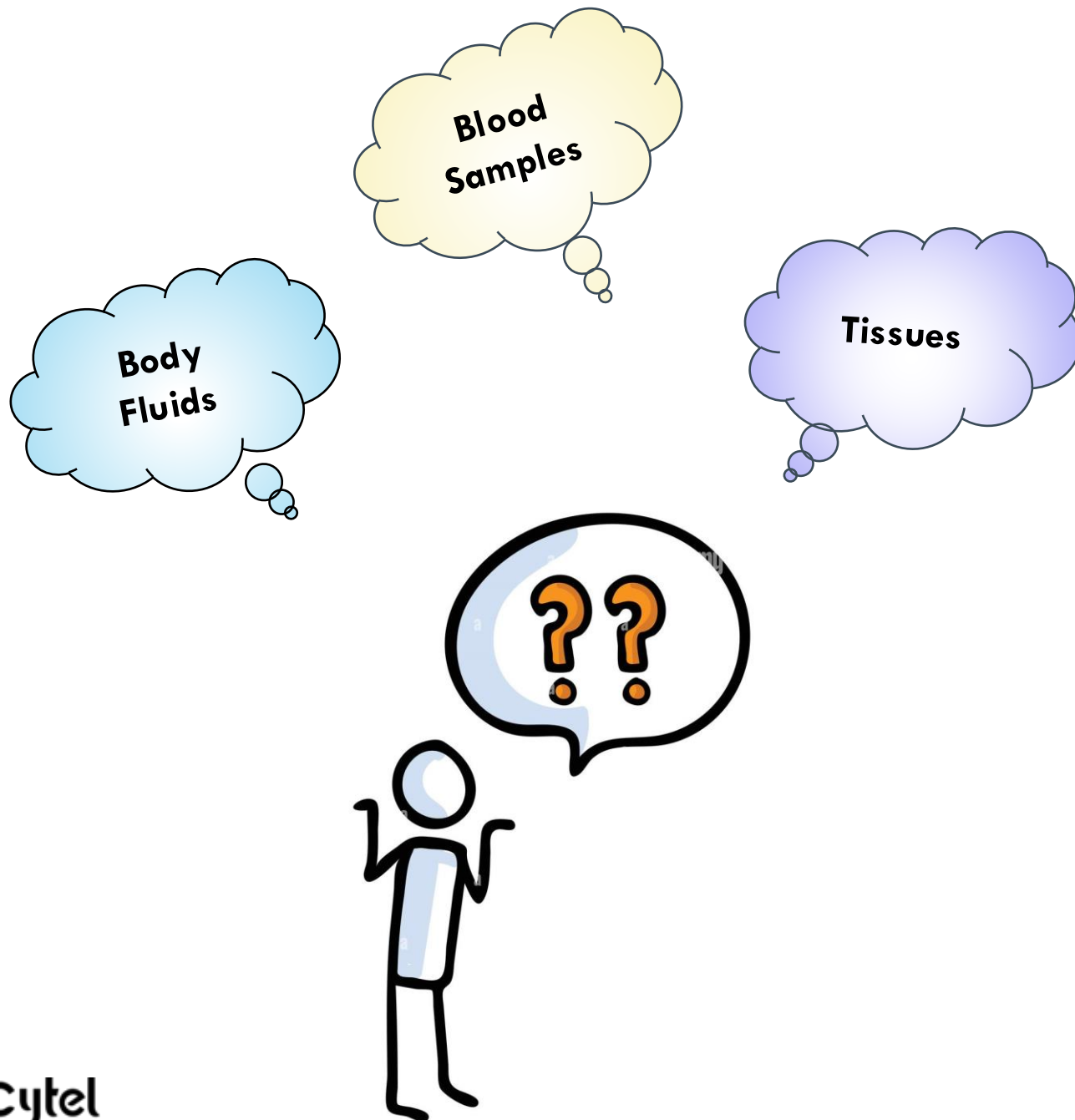
Key Topics

- **Science Behind Biomarkers**
- **Biomarker Data**
- **Statistical Analysis**
- **Summary**

01

Science Behind Biomarkers





What is a Biomarker??

**Measurable Characteristics
of the Body**

Biomarkers in Clinical Trials

Endocrine (Diabetes)

- HbA1c
- Insulin levels
- Fasting plasma glucose

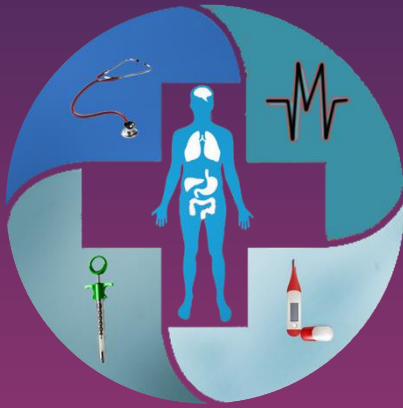
Cardiovascular

- Lipid profile
LDL, HDL,
triglycerides

Infectious

- CRP (C-Reactive Protein)

HbA1c, Lipid Profile, CRP are called Biomarkers



“

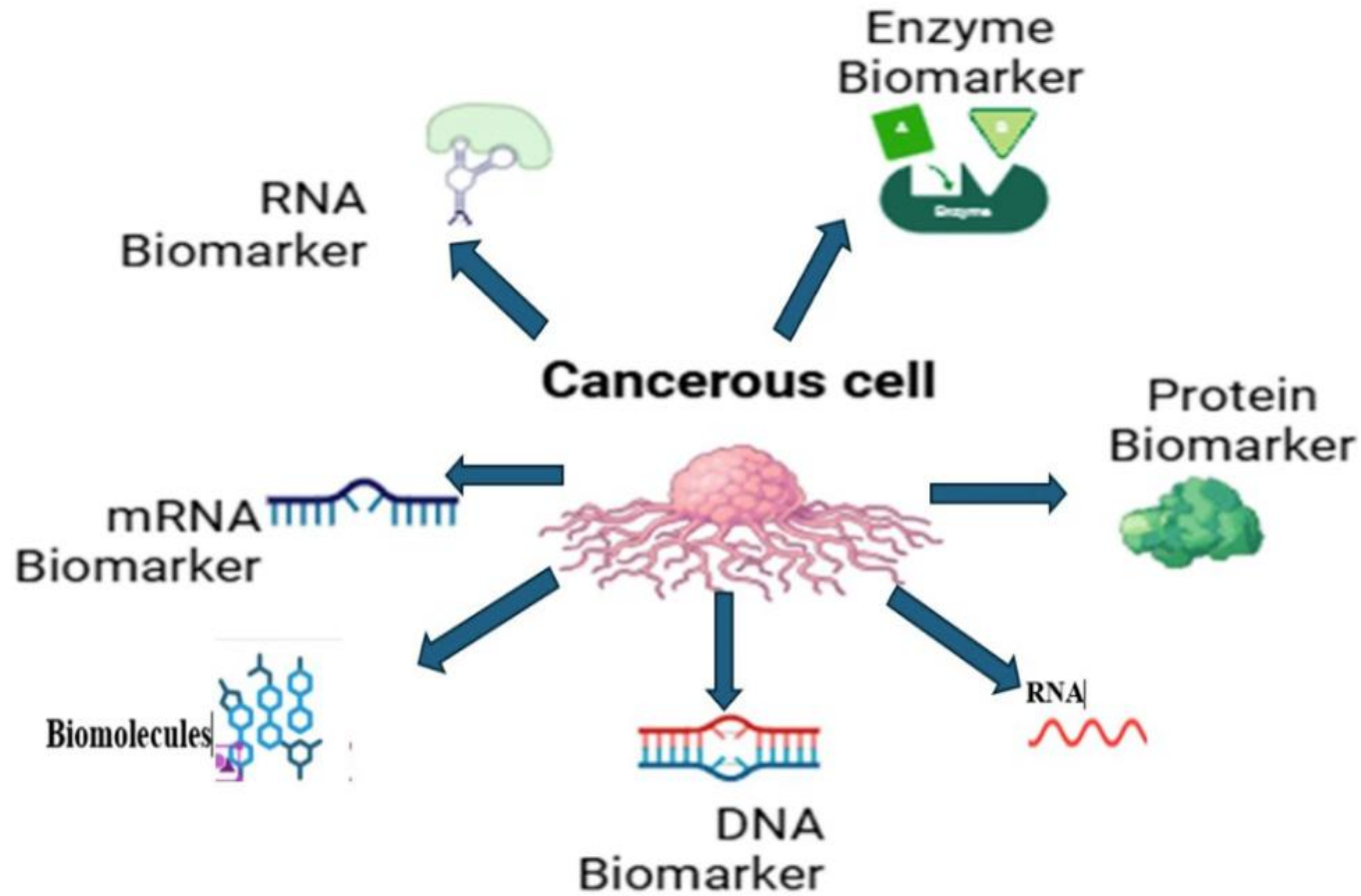
A biological molecule found in blood, other body fluids, or tissues that indicates a normal or abnormal process, condition, or disease.

A biomarker can be used to evaluate how well the body responds to treatment for a disease or condition.

It is also referred to as a molecular marker or signature molecule.”

National Cancer Institute (NIH)

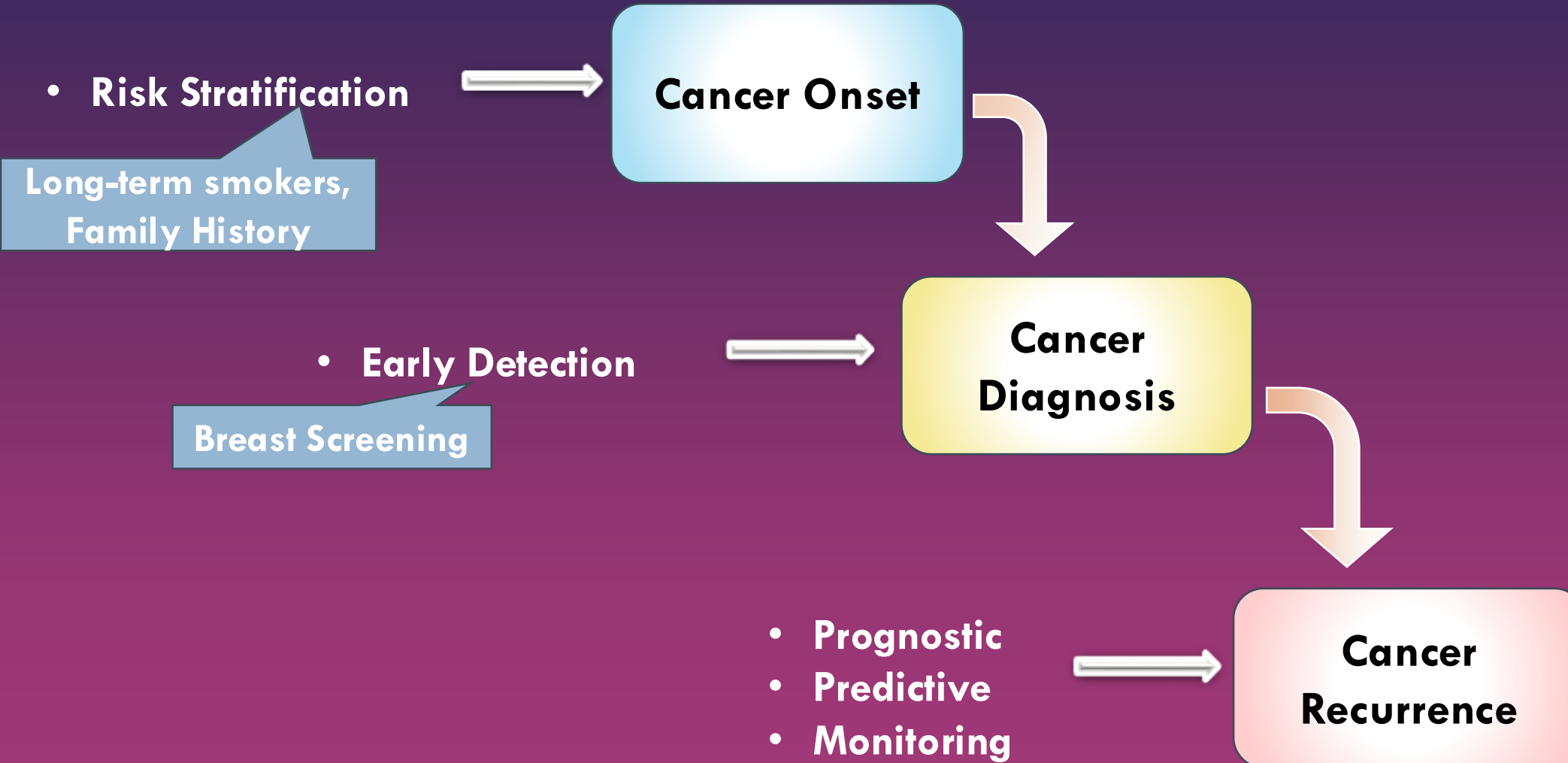
Biomarkers in Cancer



New Generation of Biomarkers

- Tumor Characteristics
- Disease Progression
- Treatment Responses

Biomarkers Across the Cancer Disease Process



Clinical Study Report and Exploratory Biomarker Analysis

- **Primary and Secondary Objectives, Influence Drug Approval**
- **Predefined and Structured**
- **Performed on all trial participants**
- **CDISC structure**

Clinical Study Report

Exploratory Biomarker Analysis

- **To Generate New Hypotheses, do not influence Drug Approval**
- **Separate Analysis Plan**
- **May not be performed on all trial participants**
- **External Vendor Data, no dedicated SDTM domains for all Biomarker types**

CP (Cell Phenotype), **BS** (Biospecimen Findings), **MB** (Microbiology Specimen),
GF (Genomics Findings), **MS** (Microbiology Susceptibility), **MI** (Microscopic Findings), **LB** (Laboratory),



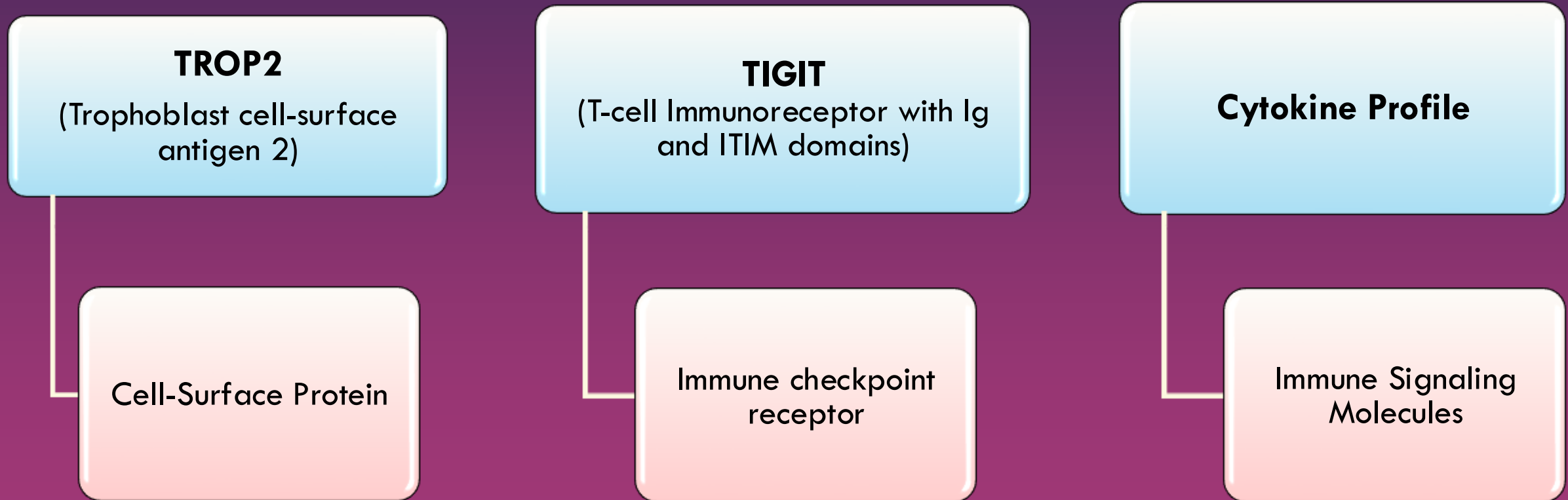
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Biomarker Data

Scenario 1

Cancer that develops in the inner lining of the Bladder or Urinary Tract

Phase II Study Drug vs Chemotherapy in Advanced Urothelial Carcinoma



TIGIT and TROP2 Raw Data

SUBJID	MITESTCD	MITSTDTL	MIORRES	MIORRESU	MISPEC	MIMETHOD	VISIT
201	TROP2	STAINING INTENSITY 0	35	%	TUMOR TISSUE	IHC	Screening
201	TROP2	STAINING INTENSITY 1+	25	%	TUMOR TISSUE	IHC	Screening
201	TROP2	STAINING INTENSITY 2+	25	%	TUMOR TISSUE	IHC	Screening
201	TROP2	STAINING INTENSITY 3+	15	%	TUMOR TISSUE	IHC	Screening
201	TROP2	H SCORE TOTAL SCORE	120		TUMOR TISSUE	IHC	Screening
201	TROP2	TUMOR PROPORTION SCORE	65	%	TUMOR TISSUE	IHC	Screening
201	TROP2	STAINING INTENSITY 0			TUMOR TISSUE	IHC	Screening
201	TROP2	STAINING INTENSITY 1+			TUMOR TISSUE	IHC	Screening
201	TROP2	STAINING INTENSITY 2+			TUMOR TISSUE	IHC	Screening
201	TROP2	STAINING INTENSITY 3+			TUMOR TISSUE	IHC	Screening
201	TROP2	H SCORE TOTAL SCORE			TUMOR TISSUE	IHC	Screening
201	TROP2	TUMOR PROPORTION SCORE			TUMOR TISSUE	IHC	Screening
201	TIGIT	VISUALLY-ESTIMATED COMBINED POSITIVE	25	%/tumor area	TUMOR TISSUE	IHC	Screening
201	TIGIT	VISUALLY-ESTIMATED COMBINED POSITIVE	10	%/tumor area	TUMOR TISSUE	IHC	Screening
202	TIGIT	VISUALLY-ESTIMATED COMBINED POSITIVE	5	%/tumor area	TUMOR TISSUE	IHC	Screening
202	TIGIT	VISUALLY-ESTIMATED COMBINED POSITIVE	<1	%/tumor area	TUMOR TISSUE	IHC	Screening

Composite Score
 $(0*35 + 1*25 + 2*25 + 3*15)$
 $= 0 + 25 + 50 + 45$

TIGIT and TROP2 Raw Data



SUBJID	MITESTCD	MITSTDTL	MIORRES	MIORRESU	MIDT	EVALDTC
201	TROP2	STAINING INTENSITY 0	35	%	2024-03-18	2024-04-02
201	TROP2	STAINING INTENSITY 1+	25	%	2024-03-18	2024-04-02
201	TROP2	STAINING INTENSITY 2+	25	%	2024-03-18	2024-04-02
201	TROP2	STAINING INTENSITY 3+	15	%	2024-03-18	2024-04-02
201	TROP2	H SCORE TOTAL SCORE	120		2024-03-18	2024-04-02
201	TROP2	TUMOR PROPORTION SCORE	65	%	2024-03-18	2024-04-02
201	TROP2	STAINING INTENSITY 0			2024-03-18	2024-06-10
201	TROP2	STAINING INTENSITY 1+			2024-03-18	2024-06-10
201	TROP2	STAINING INTENSITY 2+			2024-03-18	2024-06-10
201	TROP2	STAINING INTENSITY 3+			2024-03-18	2024-06-10
201	TROP2	H SCORE TOTAL SCORE			2024-03-18	2024-06-10
201	TROP2	TUMOR PROPORTION SCORE			2024-03-18	2024-06-10
201	TIGIT	VISUALLY-ESTIMATED COMBINED POSITIVE	25	%/tumor area	2023-03-06	2024-12-18
201	TIGIT	VISUALLY-ESTIMATED COMBINED POSITIVE	10	%/tumor area	2023-03-06	2025-01-27
202	TIGIT	VISUALLY-ESTIMATED COMBINED POSITIVE	5	%/tumor area	2022-09-23	2024-12-14
202	TIGIT	VISUALLY-ESTIMATED COMBINED POSITIVE	<1	%/tumor area	2022-09-23	2025-01-27

Clinically
meaningful

Below
detection
limit

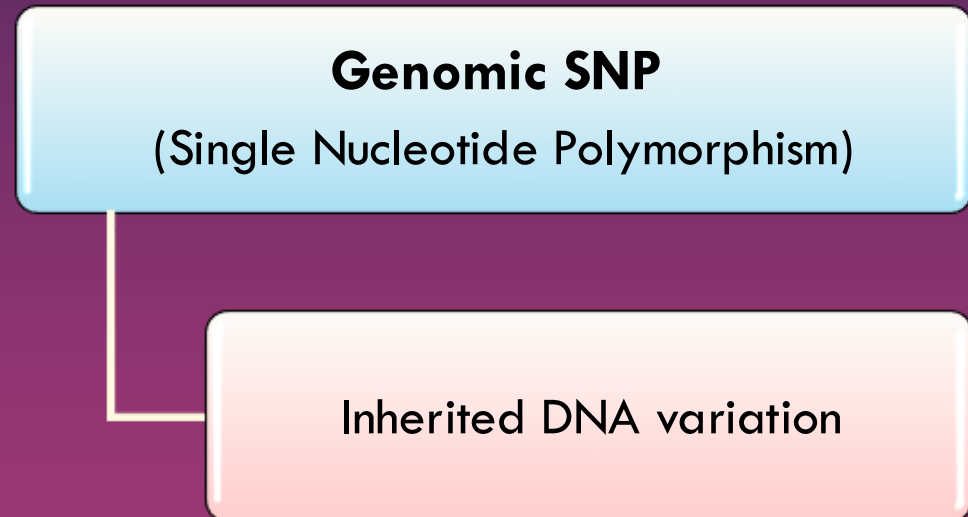
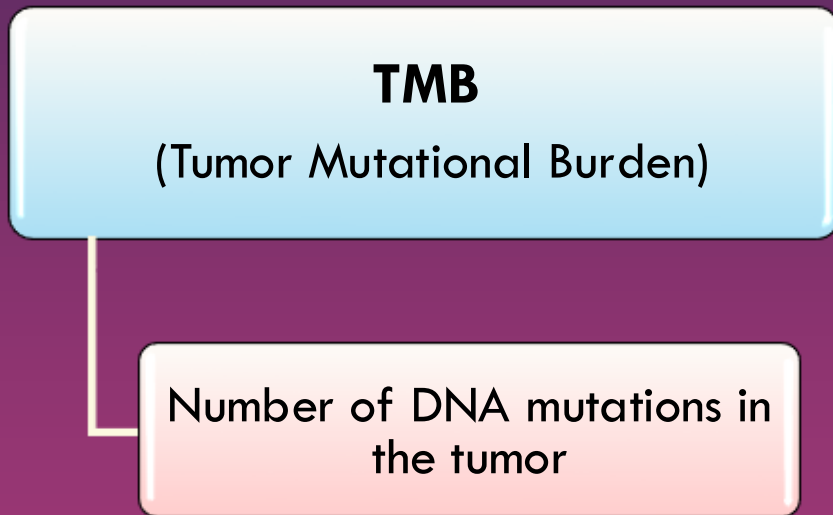
Cytokine Profile Raw Data



USUBJID	DOMAIN	LBTESTCD	LBCAT	LBSTRESC	LBSTRESU	LBSPEC	VISIT	LBDC
201	LB	IFNG	SOLUBLE FACTOR	3.68	ng/L	SERUM	WEEK 1 DAY 1	2023-08-16
201	LB	INTLK10	SOLUBLE FACTOR	1.01	ng/L	SERUM	WEEK 1 DAY 1	2023-08-16
201	LB	INTLK12	SOLUBLE FACTOR	<2.44	ng/L	SERUM	WEEK 1 DAY 1	2023-08-16
201	LB	INTLK13	SOLUBLE FACTOR	<8.42	ng/L	SERUM	WEEK 1 DAY 1	2023-08-16
201	LB	INTLK1B	SOLUBLE FACTOR	<1.29	ng/L	SERUM	WEEK 1 DAY 1	2023-08-16
201	LB	INTLK2	SOLUBLE FACTOR	<1.78	ng/L	SERUM	WEEK 1 DAY 1	2023-08-16
201	LB	INTLK4	SOLUBLE FACTOR	<0.44	ng/L	SERUM	WEEK 1 DAY 1	2023-08-16
201	LB	INTLK6	SOLUBLE FACTOR	<1.27	ng/L	SERUM	WEEK 1 DAY 1	2023-08-16
201	LB	INTLK8	SOLUBLE FACTOR	19.00	ng/L	SERUM	WEEK 1 DAY 1	2023-08-16
201	LB	TNF	SOLUBLE FACTOR	2.37	ng/L	SERUM	WEEK 1 DAY 1	2023-08-16

Scenario 2

Phase III Study Drug vs Chemotherapy in PD-L1+ Advanced Non-Small Cell Lung Cancer



TMB Raw Data



USUBJID	PFSCAT	PFRUNID	VISIT	PFSTRESC	PFSTDTL	PFDTC
201	TUMOR MUTATIONAL BURDEN	tumor-only	SCREENING	4.88	Somatic_variants_per_Mb	2016-12-20
201	TUMOR MUTATIONAL BURDEN	tumor-only	SCREENING	589	Non_synonymous_Somatic_Variants	2016-12-20
201	TUMOR MUTATIONAL BURDEN	tumor-only	SCREENING	8.66	Non_synonymous_Somatic_Variants_per_Mb	2016-12-20
201	TUMOR MUTATIONAL BURDEN	tumor-only	SCREENING	4785	Variant which Change Protein Structure	16-12-20
201	TUMOR MUTATIONAL BURDEN	tumor-only	SCREENING	70.37	Somatic_variants_per_Mb	2016-12-20
201	TUMOR MUTATIONAL BURDEN	tumor-only	SCREENING	5117	Somatic_variants	2016-12-20
201	TUMOR MUTATIONAL BURDEN	tumor-only	SCREENING	75.25	Somatic_variants_per_Mb	2016-12-20

Genomic SNP Raw Data

SUBJECT_ID	TREATMENT_ARM	SPEC_TYPE	VARIANT_TYPE	GENE_SYMBOL	MEASUREMENT	RESULT	UNIT	reference_id
201	CHEMO	DNA	SNP	IL6	Allele_Zygosity	Homozygous		rd1345
201	CHEMO	DNA	SNP	IL6	Base_Call	G/G		rd1345
201	CHEMO	DNA	SNP	FCGR2A	Allele_Zygosity	Homozygous		rd7738
201	CHEMO	DNA	SNP	FCGR2A	Base_Call	A/A		rd7738
201	CHEMO	DNA	SNP	FCGR3A	Allele_Zygosity	Heterozygous		rd3837
201	CHEMO	DNA	SNP	FCGR3A	Base_Call	C/A		rd3837
202	INVEST	DNA	SNP	IL6	Allele_Zygosity	Homozygous		rd1345
202	INVEST	DNA	SNP	IL6	Base_Call	G/G		rd1345
202	INVEST	DNA	SNP	FCGR2A	Allele_Zygosity	Heterozygous		rd7738
202	INVEST	DNA	SNP	FCGR2A	Base_Call	G/A		rd7738
202	INVEST	DNA	SNP	FCGR3A	Allele_Zygosity	Homozygous		rd3837
202	INVEST	DNA	SNP	FCGR3A	Base_Call	C/C		rd3837

Biologically relevant to Drug Mechanism

Data Transfer Specification (DTS)

Column Name	Label (" ") / Description	Data Type (max. length)	Examples / Options	Mandatory
STUDY_ID	“Study ID” / As specified in Shipping Manifest	Char (20)	e.g. FSP_ZZZ	Yes
SUBJECT_ID	“Subject ID” / As specified in Shipping Manifest	Char (10)	e.g. 201	Yes
VISIT	“Visit Name” / As specified in Shipping Manifest	Char (50)	e.g. W1D1	Yes
SPEC_TYPE	“Specimen Type” / This field captures the type of specimen assayed.	Char (50)	DNA	Yes
VENDOR	“Vendor Name”	Char (100)	XX	Yes
METHOD	“Test Method”	Char (200)	REAL-TIME POLYMERASE CHAIN REACTION ASSAY	Yes
VARIANT_TYPE	“Variant Type”	Char (8)	SNP	Yes
GENE_SYMBOL	“Official Gene Symbol”	Char (25)	e.g. FCGR3A	No

Processed Biomarker Data



USUBJID	SNPFL	FASFL	PDL1ST1C	TMBGR1	FCGR3A	FCGR2A	OS	PFSIE	CENOS	CENPFSIE
201	Y	Y	High (80–100%)	>8.95-<=10.80	Homozygous A/A	Homozygous A/A	23	12.6	0	0
202	Y	Y	Low (1–<50%)	>7.05-<=8.95	Heterozygous C/A	Homozygous A/A	12	2.8	0	0
203	High, Low, Moderate		Low (1–<50%)	<=7.05	Homozygous C/C	Homozygous A/A	15	1.2	0	0
204		Y	Low (1–<50%)	>10.80	Find quantiles for TMB and assign <= {TMBQ1} > {TMBQ1} - <= {TMBMED} > {TMBMED} - <= {TMBQ3} > {TMBQ3}			14.1	0	0
205		Y	Low (1–<50%)	>8.95-<=10.80				5.6	1	1
206		Y	Low (1–<50%)	<=7.05				3.8	1	1
207	Y	Y	Moderate (50–<80%)	>7.05-<=8.95	Homozygous A/A	Homozygous G/G	24	1.5	0	0
208	Y	Y	High (80–100%)	>10.80	Heterozygous C/A	Homozygous A/A	9.7	4.6	0	0
209	Y	Y	Low (1–<50%)	>7.05-<=8.95	Homozygous A/A	Homozygous A/A	15	1.2	1	1

03

Statistical Analysis

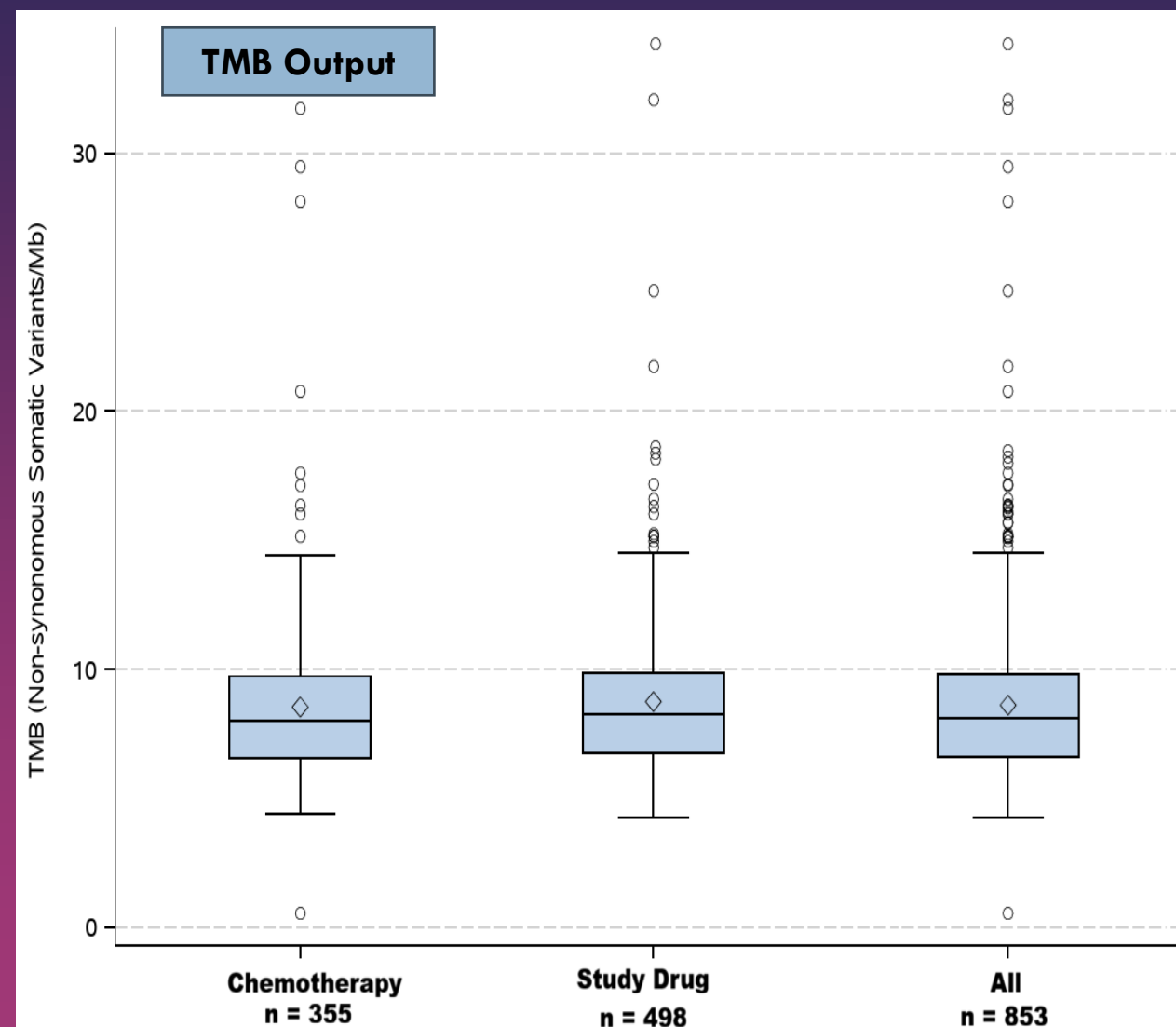
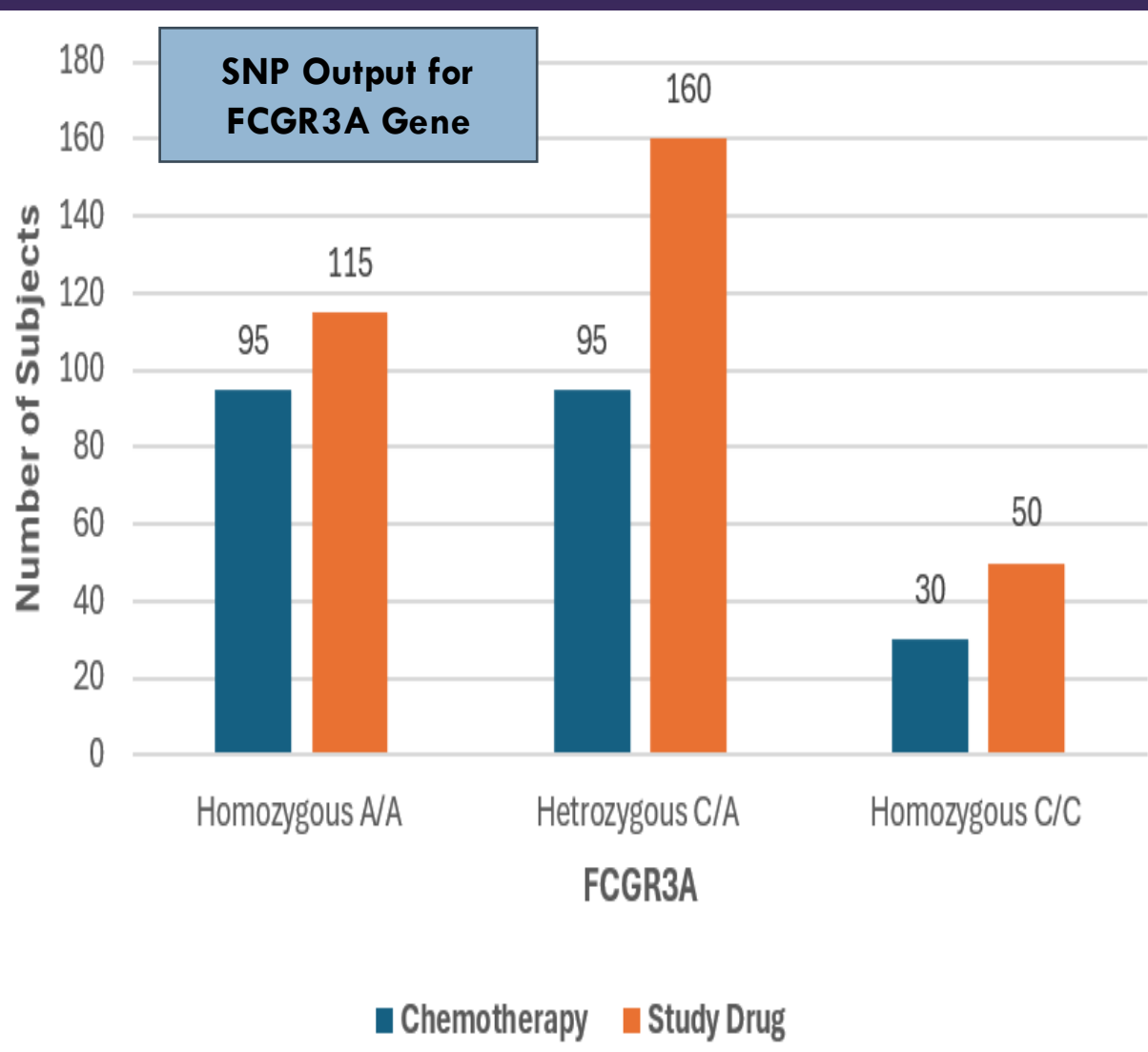


Biomarker-Evaluable Population and Full Analysis Set

	SNP Biomarker Population (N = 545)	FAS Set (N = 1190)
Analysis Age		
n	545	1190
Missing	0	0
Mean (SD)	61.8(9.42)	62.4(9.67)
Min;Max	29.0;87.0	24.0;88.0
Q1;Q3	55.0;69.0	56.0;70.0
Median	62.0	63.0
Pooled Analysis Age Group 1 (N)		
<65	296 (54.3%)	618 (51.9%)
>=65	249 (45.7%)	572 (48.1%)
Sex		
Male	401 (73.6%)	876 (73.6%)
Female	144 (26.4%)	314 (26.4%)

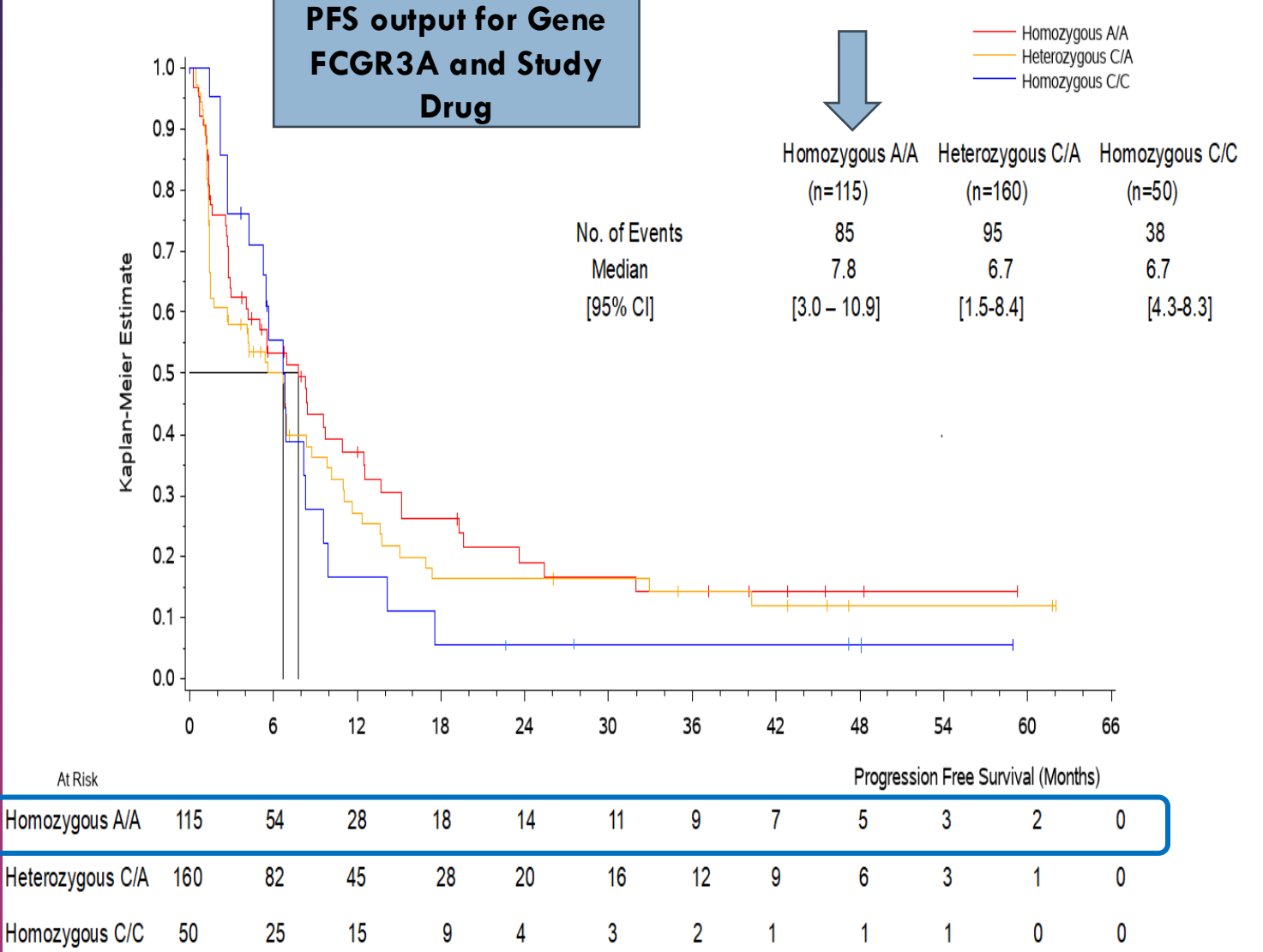
	TMB Biomarker Population (N = 853)	FAS Set (N = 1190)
Analysis Age		
n	853	1190
Missing	0	0
Mean (SD)	63.4 (9.11)	63.9 (9.48)
Min; Max	27.0; 87.0	24.0; 88.0
Q1; Q3	57.0;70.0	57.0;71.0
Median	63.0	64.0
Pooled Analysis Age Group 1, n (%)		
<65	468 (54.9)	631 (53.0)
>=65	385 (45.1)	559 (47.0)
Sex, n (%)		
Male	636 (74.6)	896 (75.3)
Female	217 (25.4)	294 (24.7)

Summaries of the Biomarker-Evaluable Population



Efficacy Endpoints Analysis

PFS output for Homozygous A/A		Chemotherapy N=95	Study Drug N=115
Number of events (PD or Deaths), n (%)		62 (65.3)	85 (73.9)
PFS (IERC)			
Median (months)		6.5	7.8
Min, Max		0.2, 38.9	0.3, 55.6
95% CI		[5.4, 7.8]	[3.0, 10.9]
Number of subjects			
at risk/failed/PFS (IERC) rates (%)			
up to [95% confidence interval]			
6 months		42 / 36 / 56.2 [45.7,65.4]	54 / 45 / 60.8 [51.3,69.2]
12 months		18 / 54 / 30.4 [21.7,40.0]	28 / 63 / 38.7 [30.1,47.1]
18 months		11 / 60 / 22.1 [14.5,31.0]	18 / 74 / 28.9 [21.2,36.9]
24 months		9 / 62 / 18.9 [11.8,27.4]	14 / 80 / 24.6 [17.7, 32.1]
30 months		7 / 62 / 16.0 [9.5, 24.3]	11 / 82 / 21.7 [15.1, 29.2]



Statistical Modeling Approach

Cox Proportional
Hazard Ratio by
Proc Phreg

Model1:
Treatment +
FCGR3A

Effect		Hazard Ratio		
Factor	p-value	Comparison	(HR) [95% CI]	
FCGR3A	0.184	C/A vs A/A	1.22	[0.91–1.63]
		C/C vs A/A	1.15	[0.74–1.77]
Treatment Group	0.231	Investi vs Chemo	0.88	[0.71–1.11]

Model2:
Treatment +
FCGR3A +
Treatment *
FCGR3A

FCGR3A	0.612	—	—	—
Treatment Group	0.744	—	—	—
Treatment Group by FCGR3A	0.802	Investi vs Chemo (A/A)	0.93	[0.67–1.30]
		Investi vs Chemo (C/A)	0.81	[0.56–1.16]
		Investi vs Chemo (C/C)	1.09	[0.59–2.00]

How a Patient will do in
the future

Prognostic

Which patients benefit
from the drug, and which
do not

Predictive



04

Summary

Key Takeaway

Research study Biomarkers

**Understand Analysis Objectives, Data Sources,
Vendor Differences, and the Expectations of
Expert Team**

**Always Consult an SME or
Statistician; Don't assume**

**Knowing one Biomarker doesn't mean We
can Manage Any Biomarker Study**



Cytel

Thank You

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