THANZ 2019

Predicting thromboembolism (TE) in cancer Part 2 – an update on the BIOTEL model, biomarkers and global haemostatic testing

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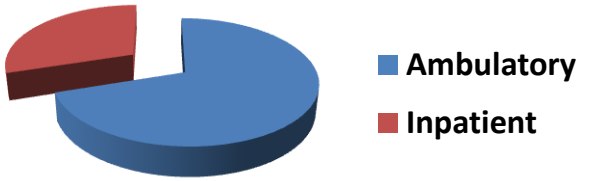
Victoria Australia

Thrombosis in cancer

Significant clinical (and economic) burden ~20% patient

mortality

TE occurrence



Largely preventable

SAVE-ONCO - semuloparin
PROTECHT – nadroparin
AVERT- apixaban
(CASSINI – rivaroxaban)

Selecting high risk patients

Khorana
CONKO
PROTECHT
CATS

Current risk models

Other methods for risk ax

?

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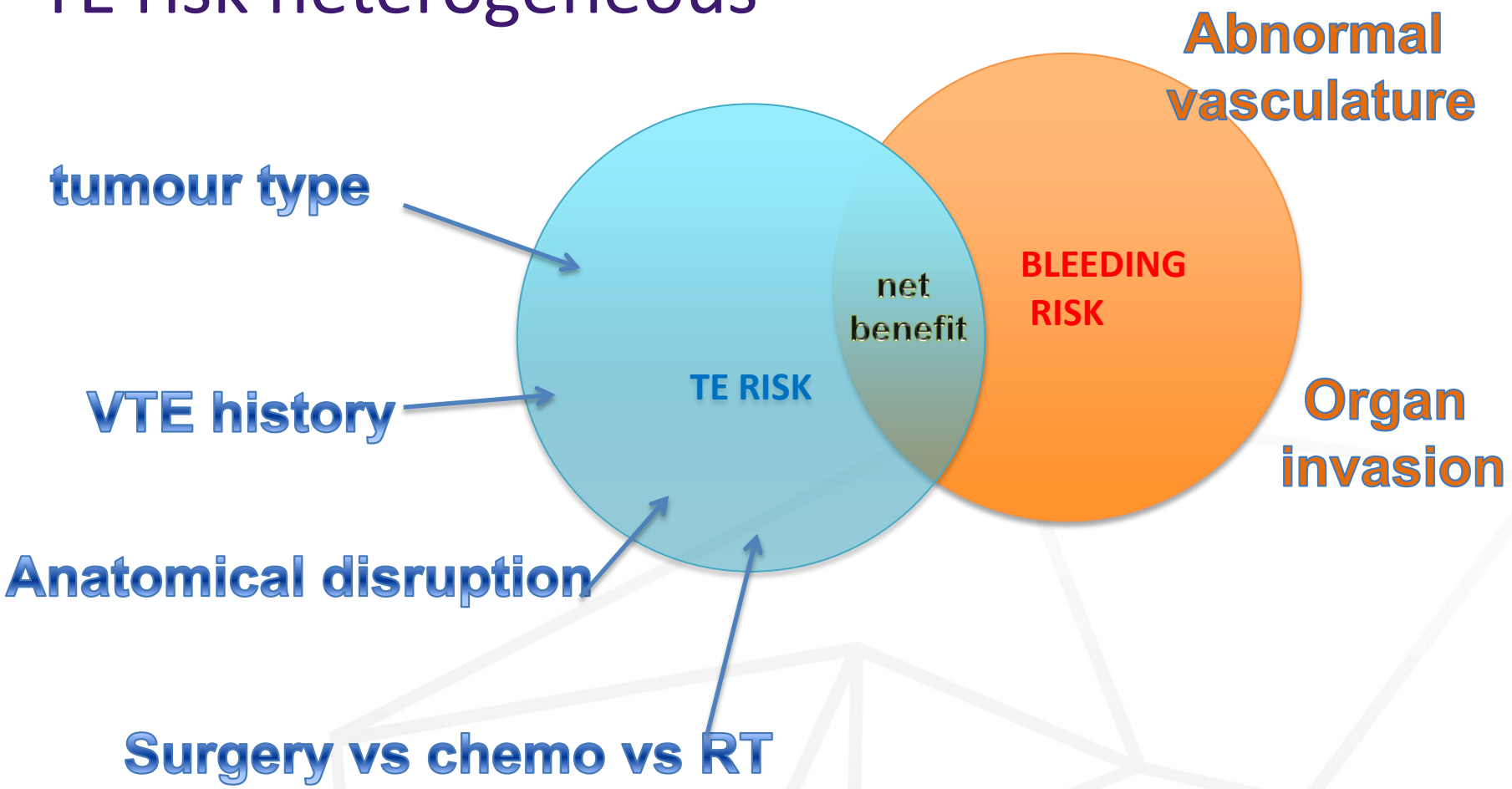
TE risk heterogeneous



ASCO Guideline update – August 2019

Clinical Question 2. Should ambulatory patients with cancer receive anticoagulation for VTE prophylaxis during systemic chemotherapy?

Recommendation 2.1. Routine pharmacologic thromboprophylaxis should not be offered to all outpatients with cancer (Type: evidence based; Evidence quality: intermediate to high; Strength of recommendation: strong).

Recommendation 2.2. High-risk outpatients with cancer (Khorana score of 2 or higher prior to starting a new systemic chemotherapy regimen) may be offered thromboprophylaxis with apixaban, rivaroxaban, or low-molecular-weight heparin (LMWH) provided there are no significant risk factors for bleeding and no drug interactions. Consideration of such therapy should be accompanied by a discussion with the patient about the relative benefits and harms, drug cost, and duration of prophylaxis in this setting (Type: evidence based; Evidence quality: intermediate to high for apixaban and rivaroxaban, intermediate for LMWH; Strength of recommendation: moderate).

Recommendation 2.3. Patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone should be offered pharmacologic thromboprophylaxis with either aspirin or LMWH for lower-risk patients and LMWH for higher-risk patients (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update

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TE in cancer

- The ideal risk stratification tool:
  - Identifies high risk patients and time periods
  - Maximises thromboprophylaxis benefit
  - Readily available in clinical setting
  - (Cost-effective)

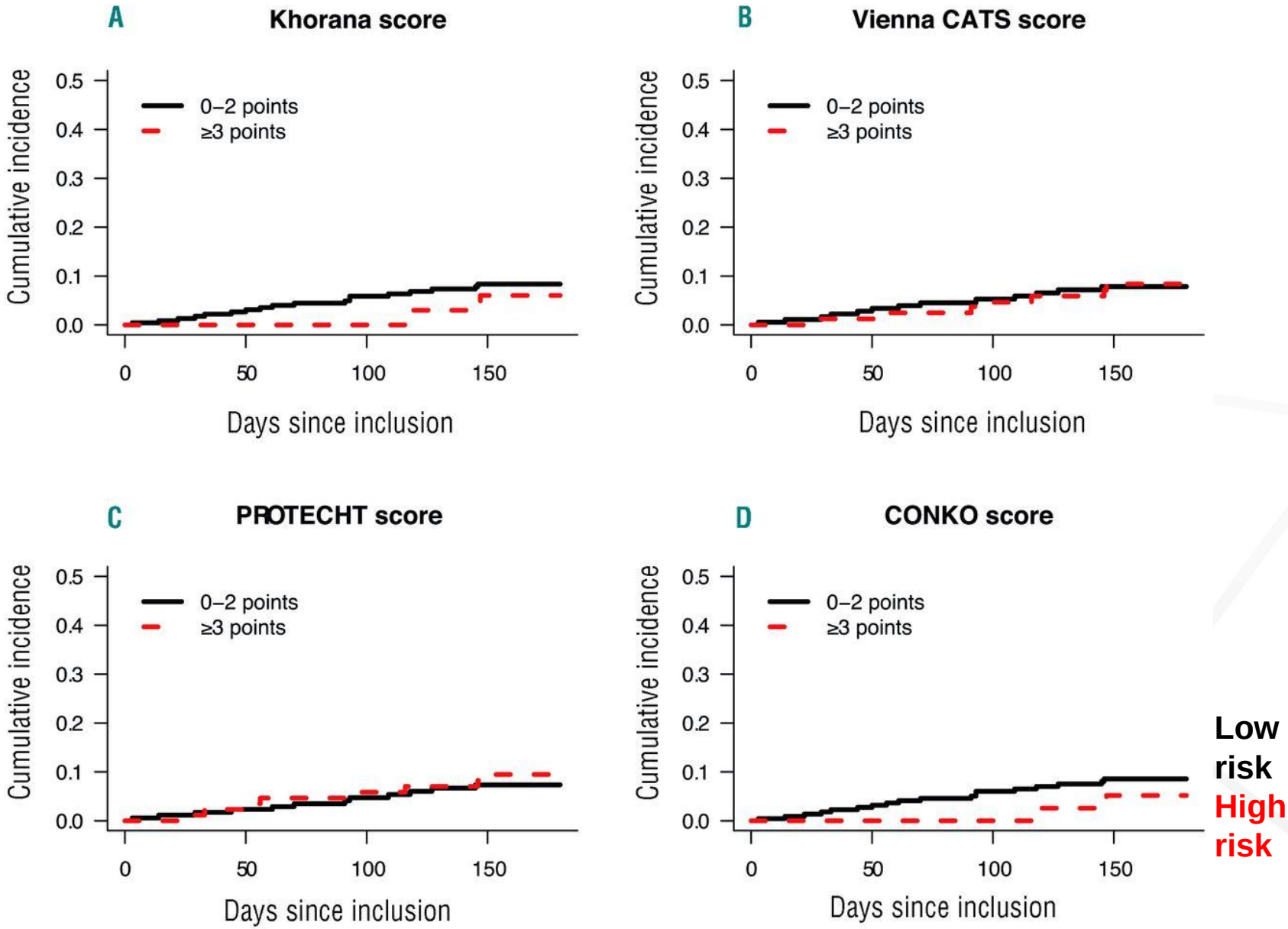
Functional

Practical

The trouble with ‘routine coags’

- APTT, PT (INR)
- These are relatively insensitive to predicting risk
  - Thrombosis
  - Bleeding
- Reflect only part of the in vivo coagulation/fibrinolytic process
- PPP (and platelets are a critical player)
- Sensitivity can can be reagent-dependent

Performance of clinical scores



Van Es et al 2017, Haematologica

BIOTEL risk model development

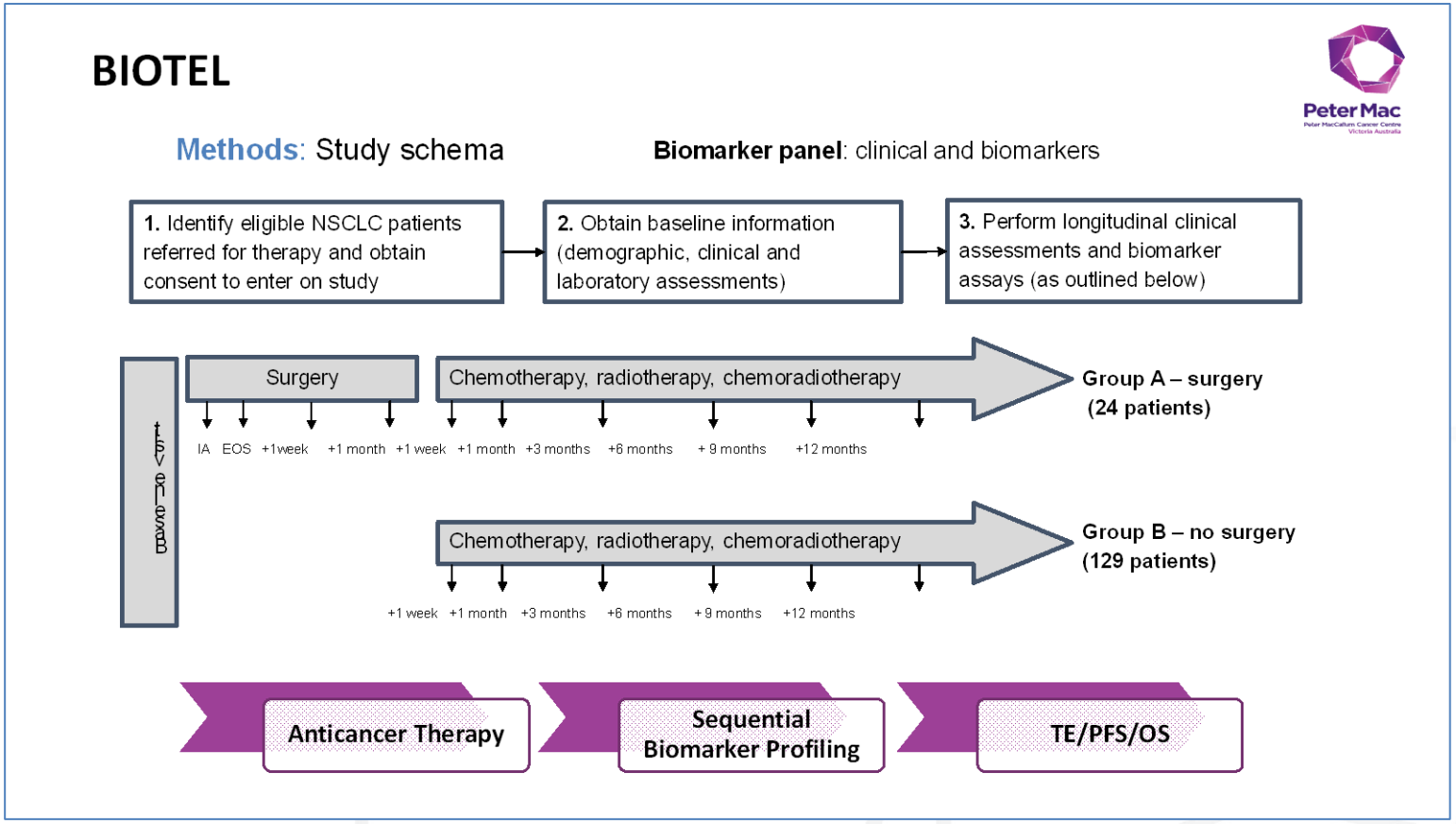
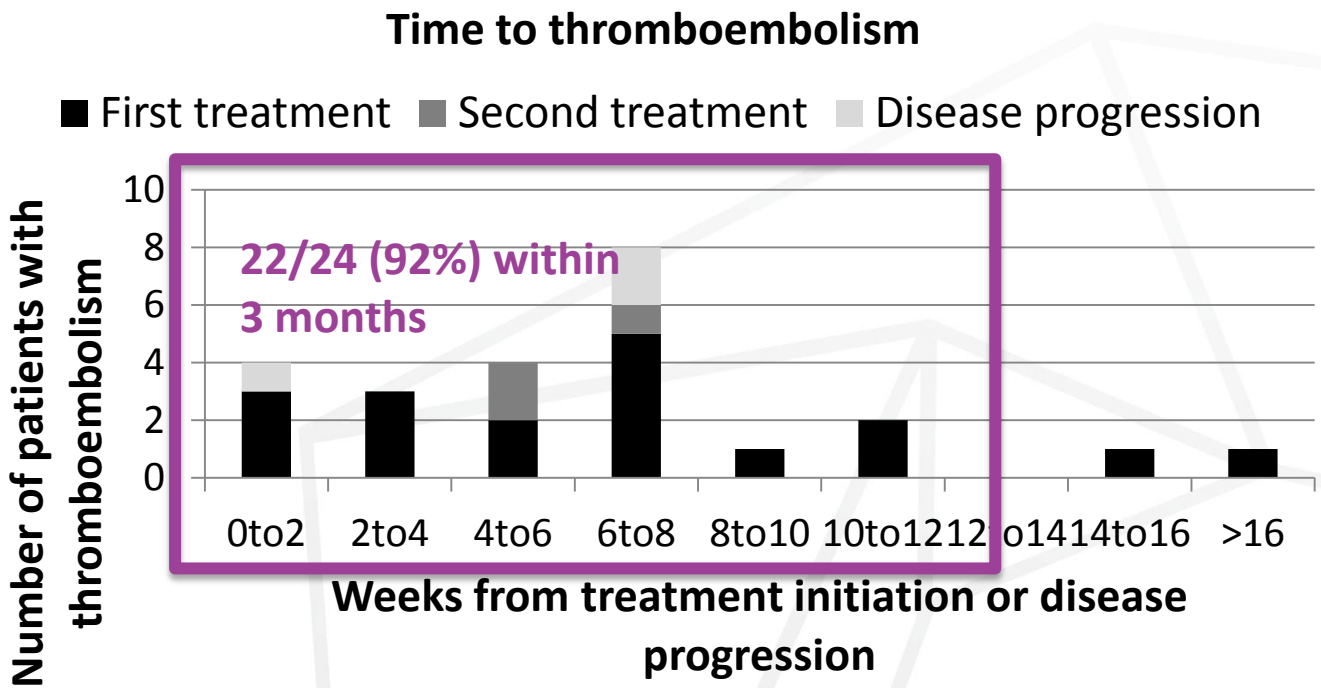


Image courtesy K Burbury

Cancer cohort risk profiling

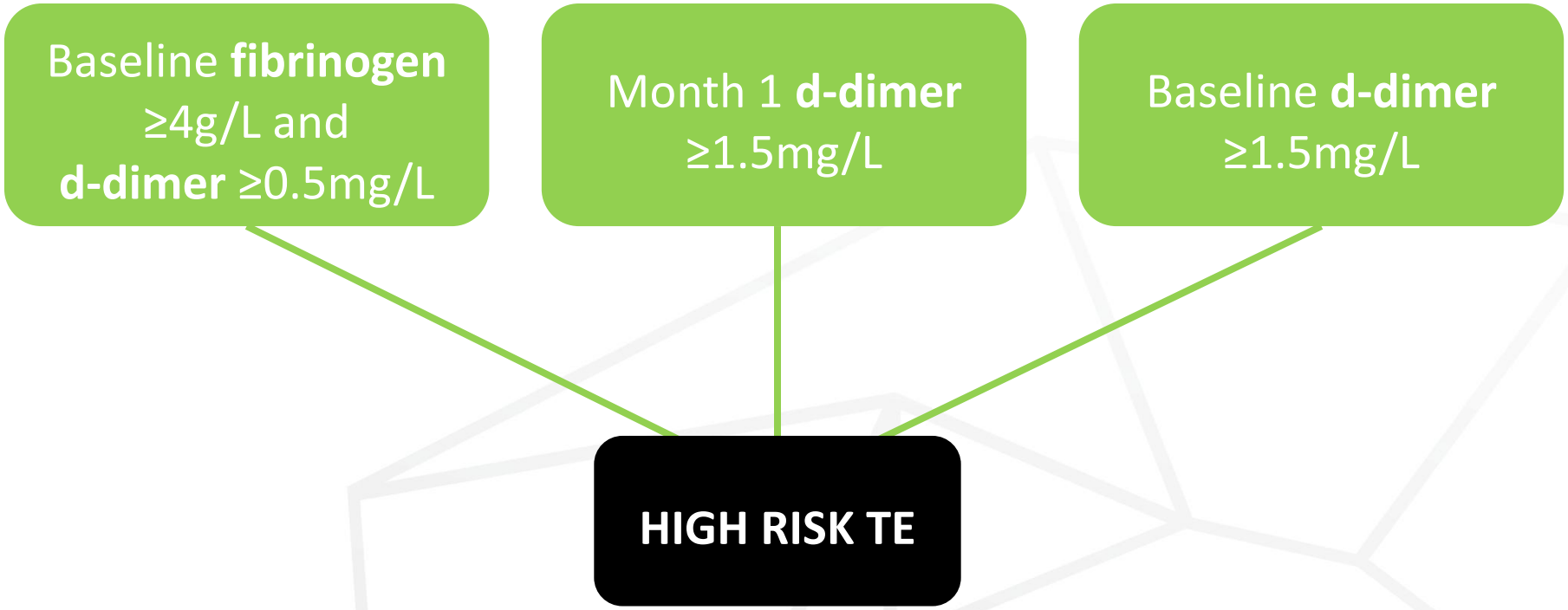
- **Key timeframe: first 3 months**
- TE rate **15%** (GI) - **19%** (lung)



Chemotherapy >70%

Key biomarkers:

BIOTEL model

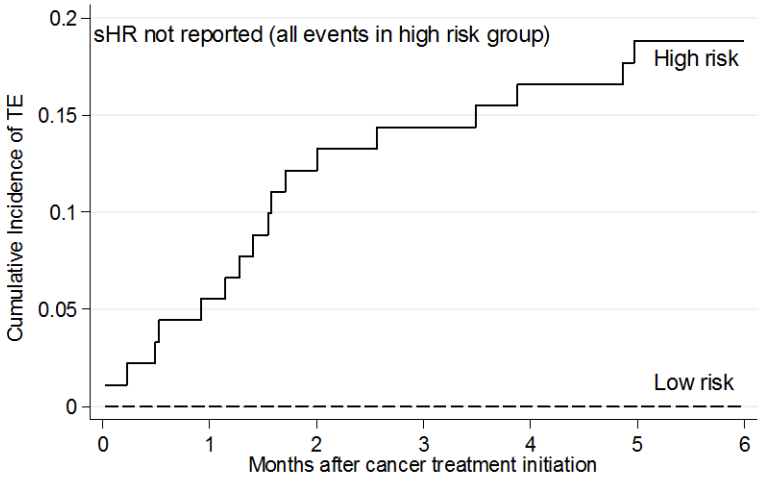


High sensitivity (100%) and potency

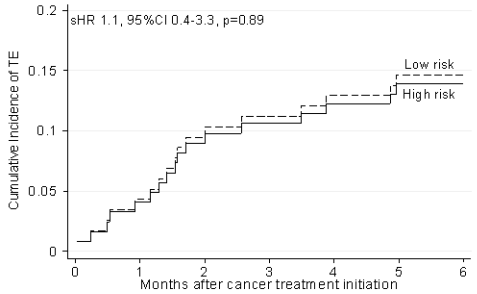
Validated in gastrointestinal cohort

Model Comparative Performance - TE

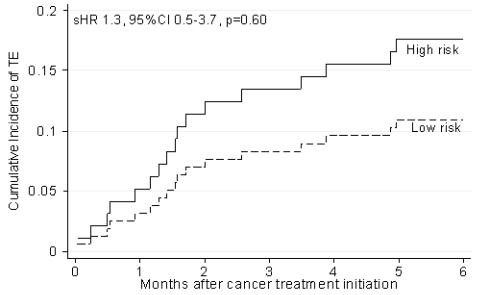
Khorana, CATS, PROTECHT, CONKO



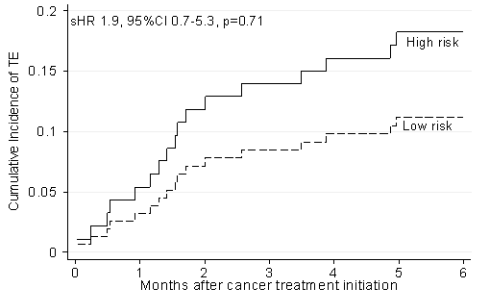
Study derived model



Khorana



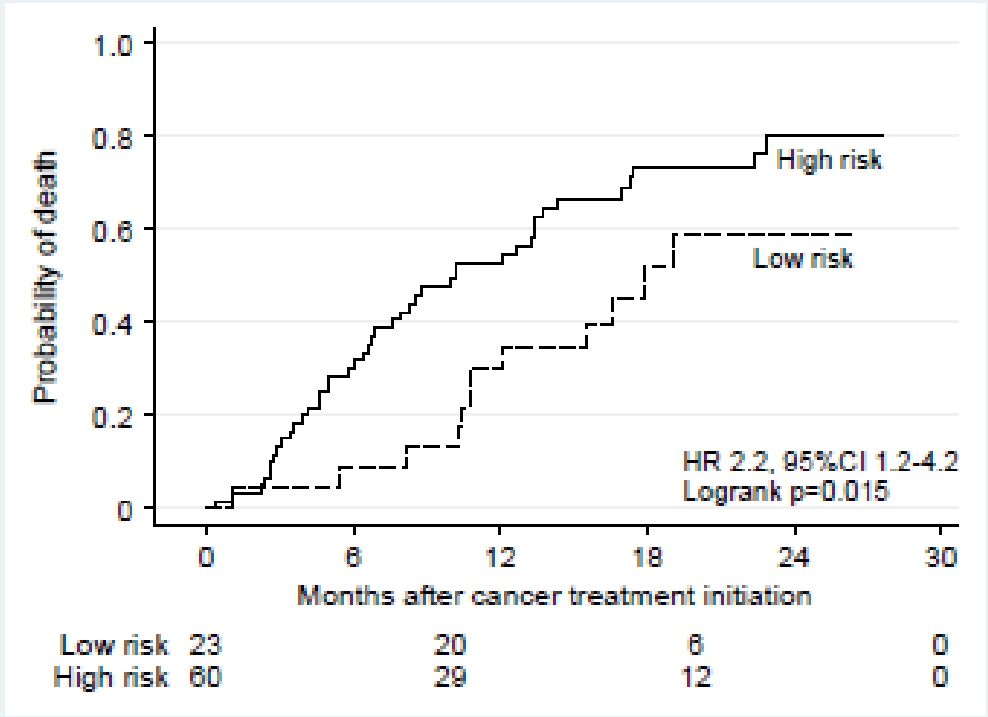
PROTECHT



CONKO

Image courtesy K Burbury

BIOTEL prediction of death



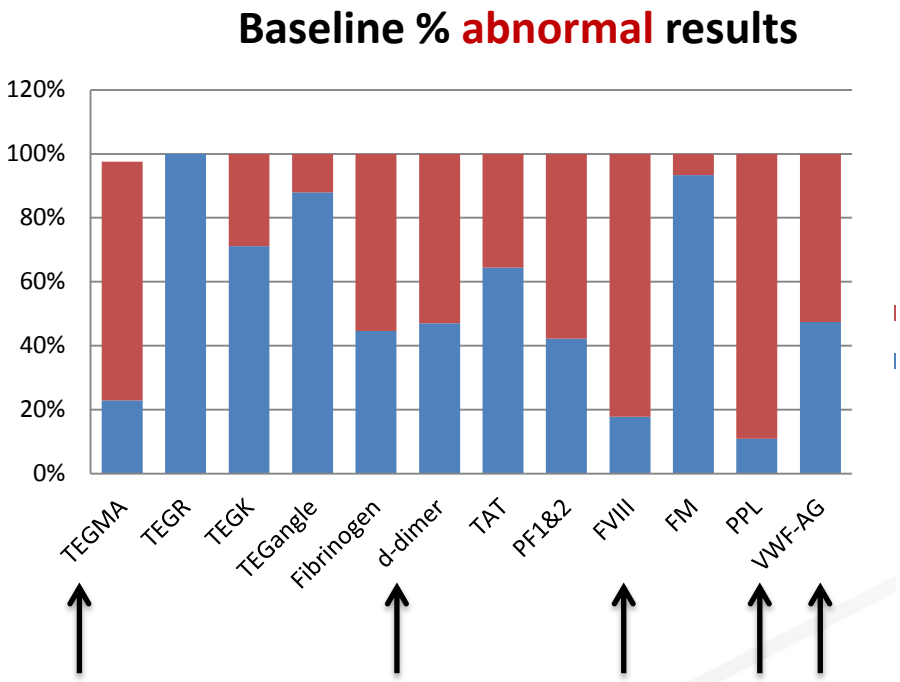
Predicting thromboembolism in cancer Part 2 – an update on the BIOTEL model, biomarkers and global haemostatic testing

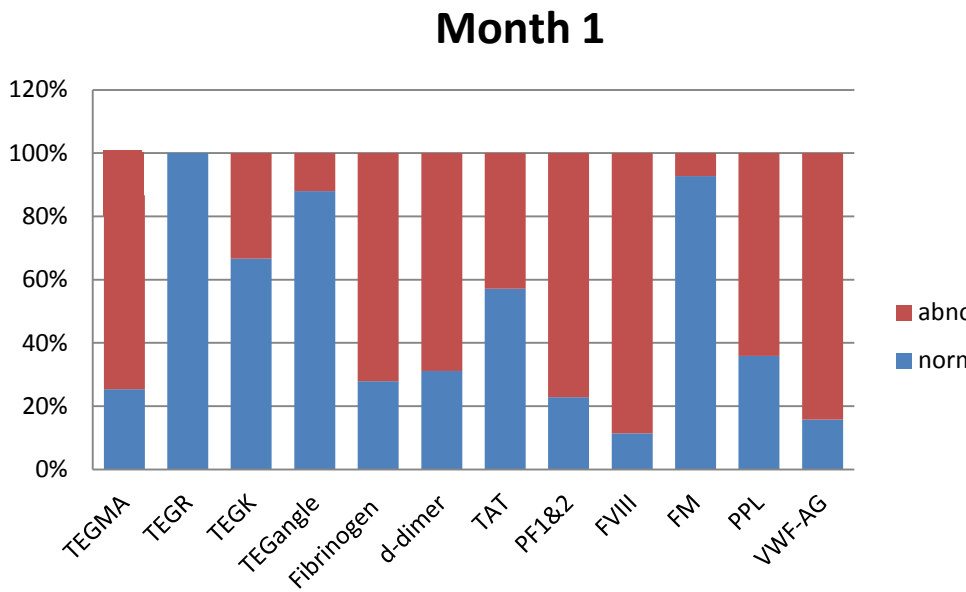
- Global haemostatic assays – more comprehensive assessment of coagulation process
- Thrombogenic biomarkers

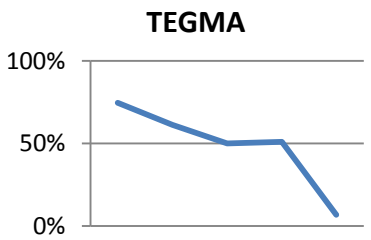
Cancer cohort risk profiling

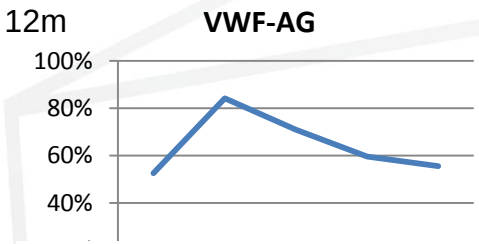
	BIOTEGIC (GI)	BIOTEL (lung)
Thrombogenic biomarkers 1	Fibrinogen ☑ D-dimer ☑ Platelet count WCC count + differential Haemoglobin NLR PLR	Fibrinogen ☑ D-dimer ☑ Platelet count WCC count + differential Haemoglobin NLR PLR
Global assays	**TEG**	**TEG** **ETP**
Thrombogenic biomarkers 2	**PPL** - procoagulant phospholipids **FM** – fibrin monomers **PF1+2** – prothrombin fragments **TAT** – thrombin antithrombin complex **FVIII** **VWF-Ag** n = 68	**PPL** **FM** **PF1+2** **TAT** **FVIII** **VWF-Ag** n = 83

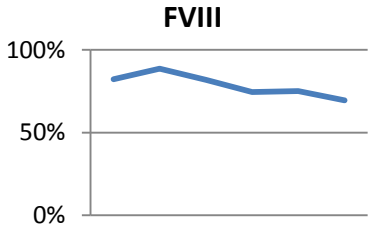
Biomarker profile – lung

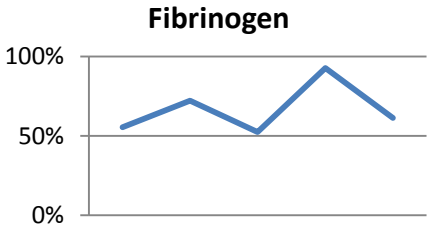


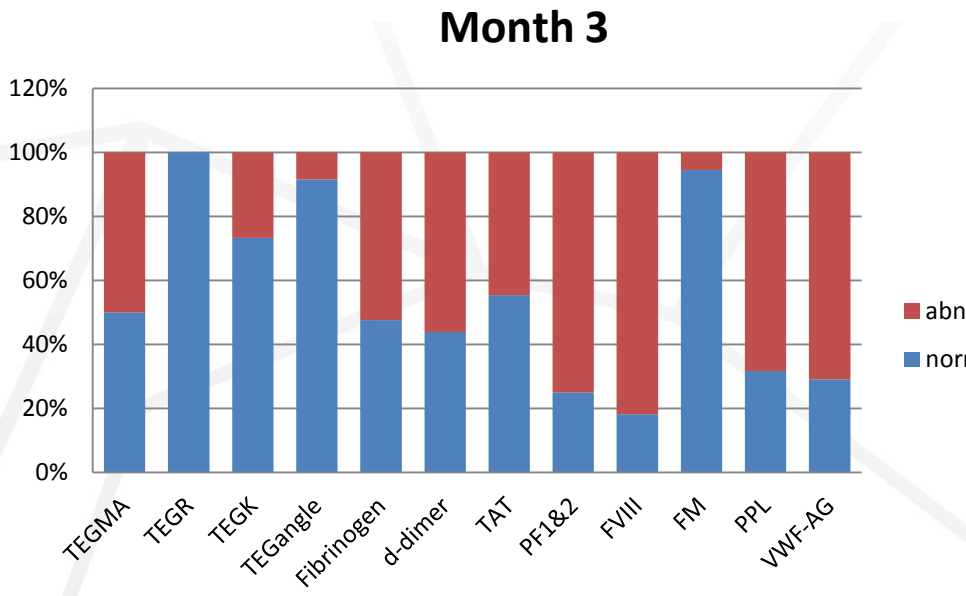




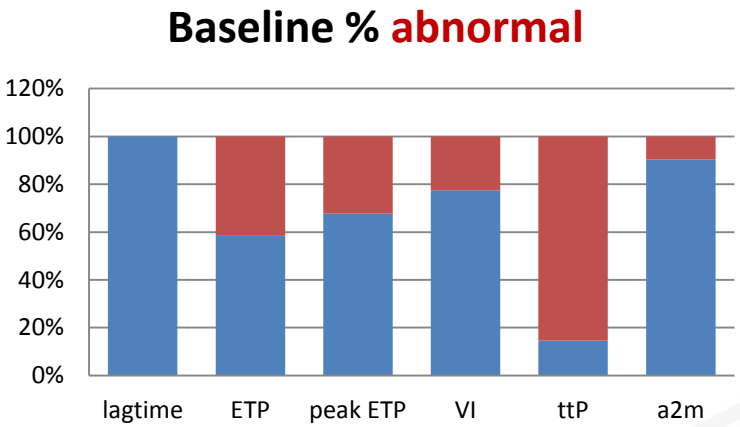


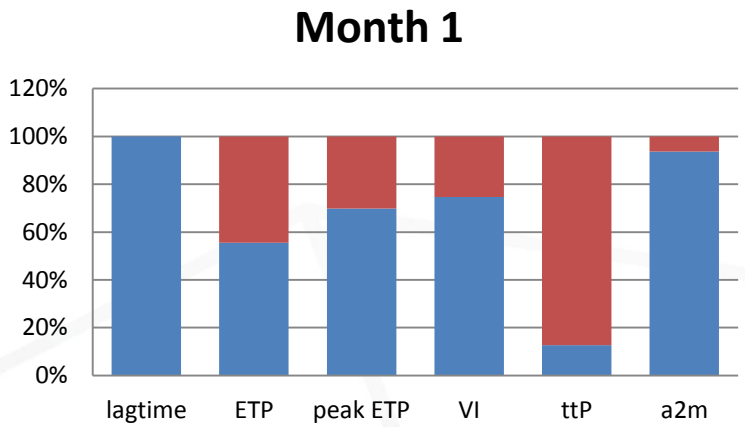


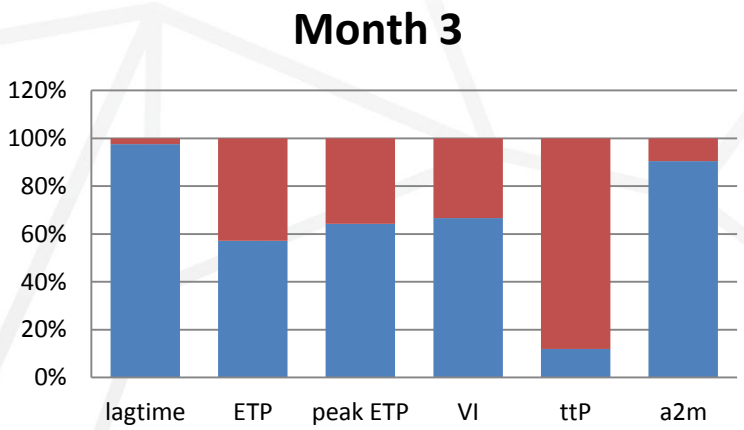




Biomarker profile – lung ETP

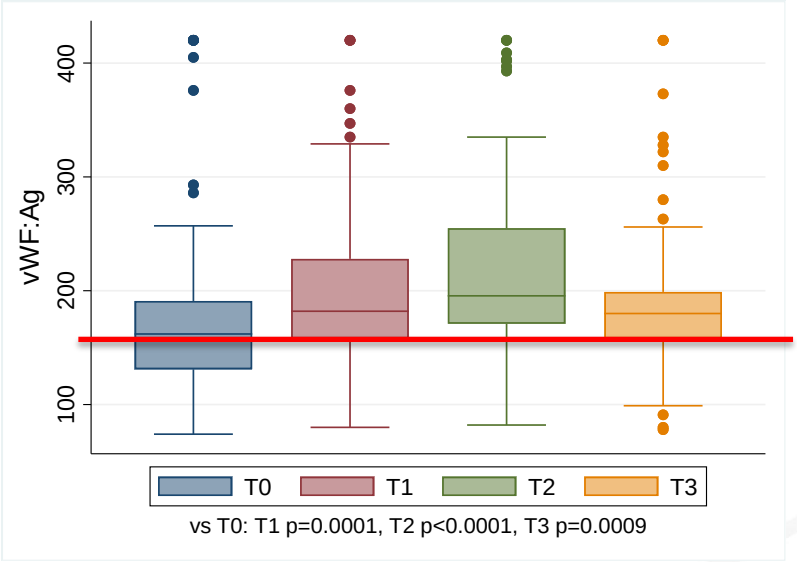


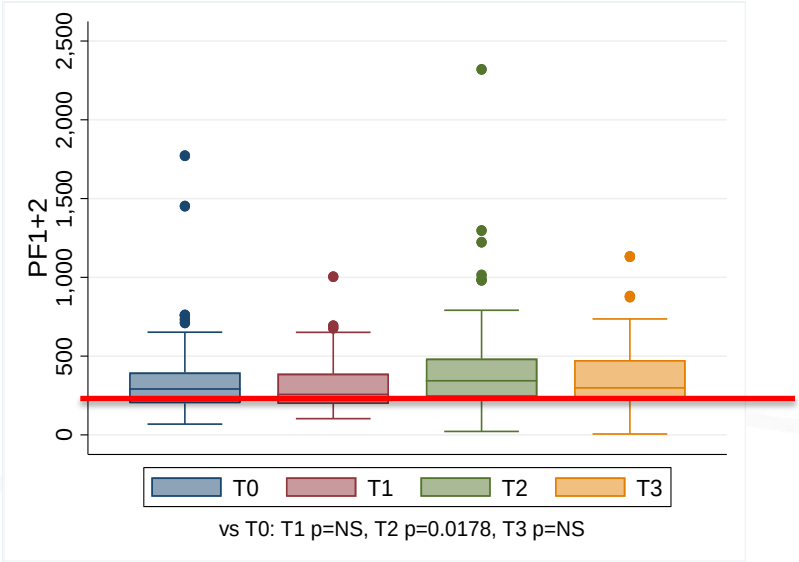


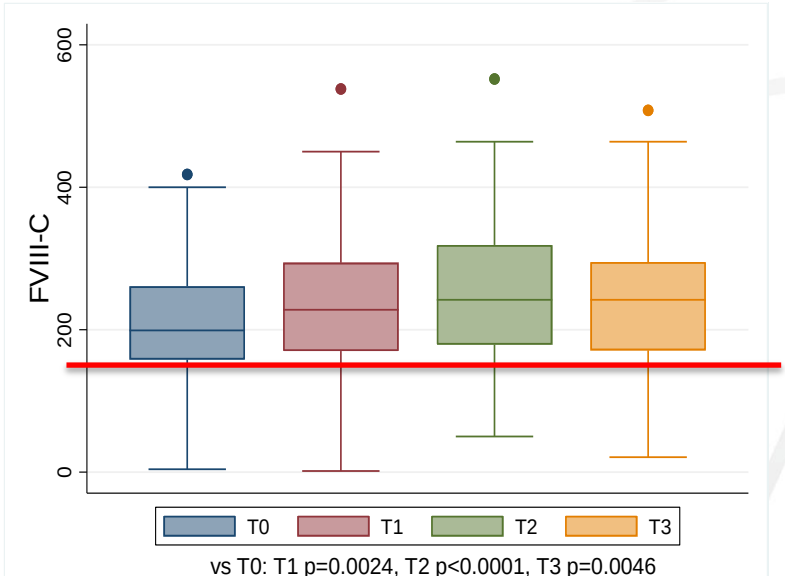


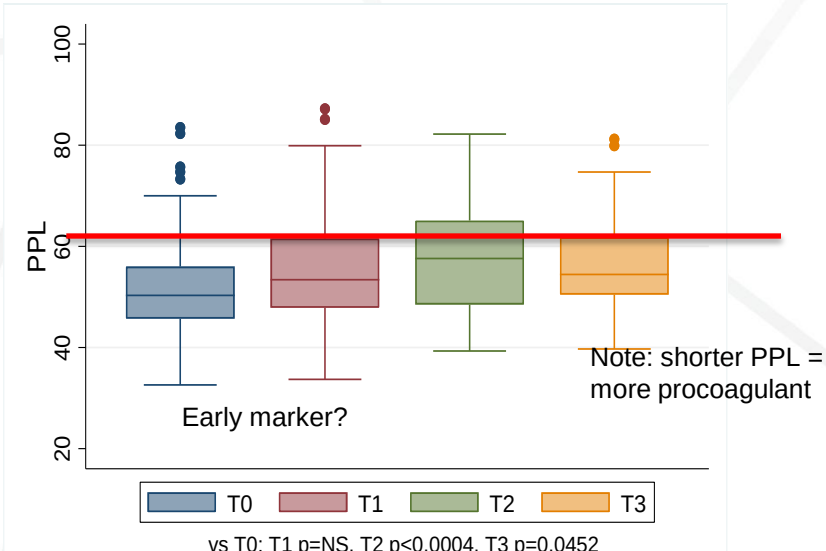
Changes in median levels of biomarkers over time- **lung – pre rx, w1, m1, m3**

Peak change at Month 1

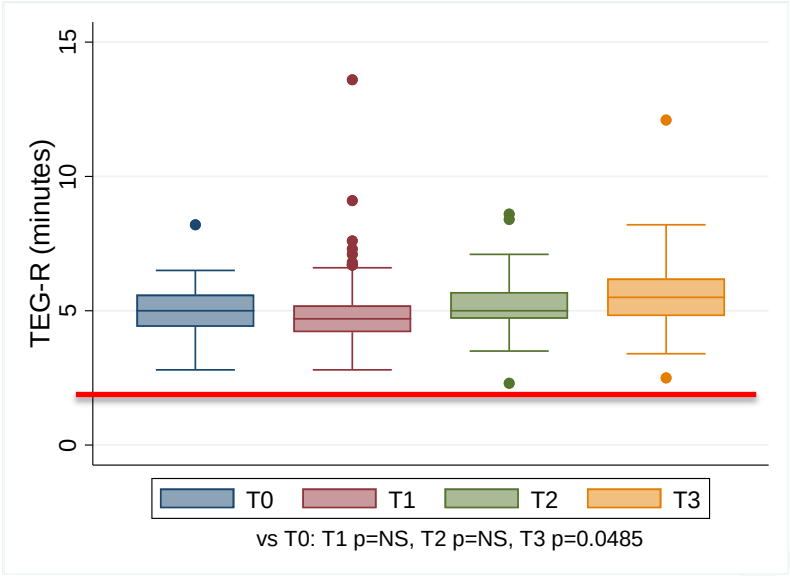


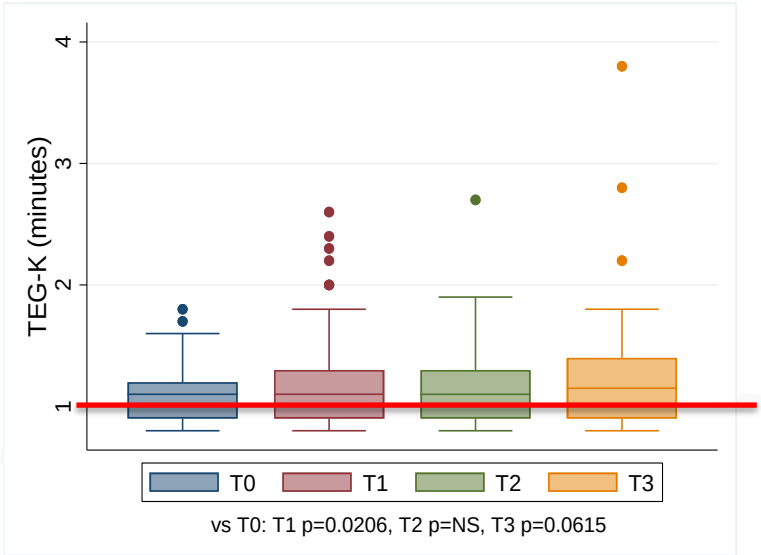


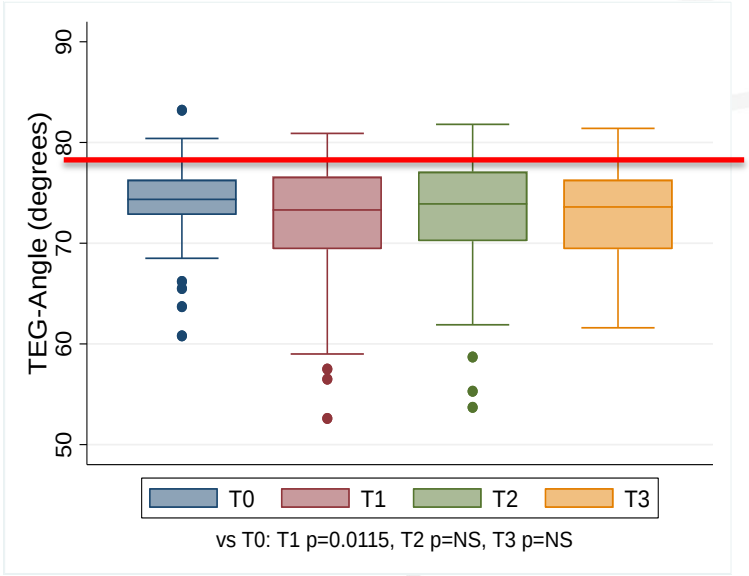


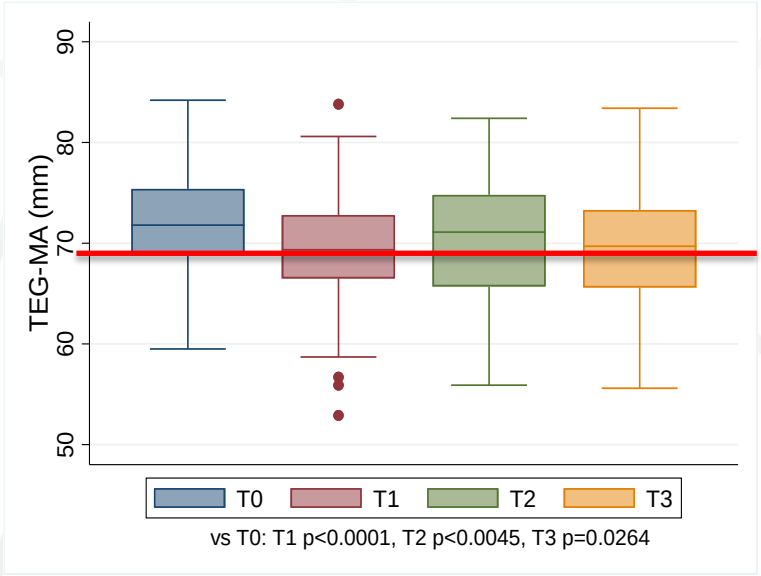


Changes in median levels of TEG over time- **lung**



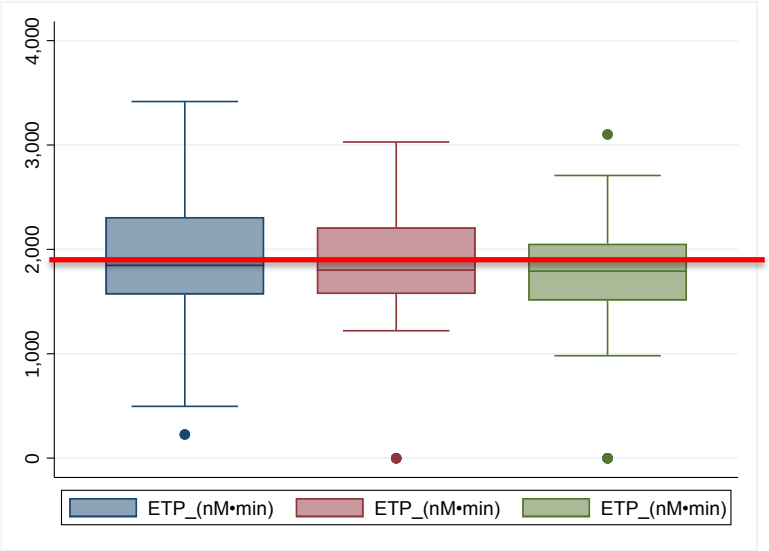


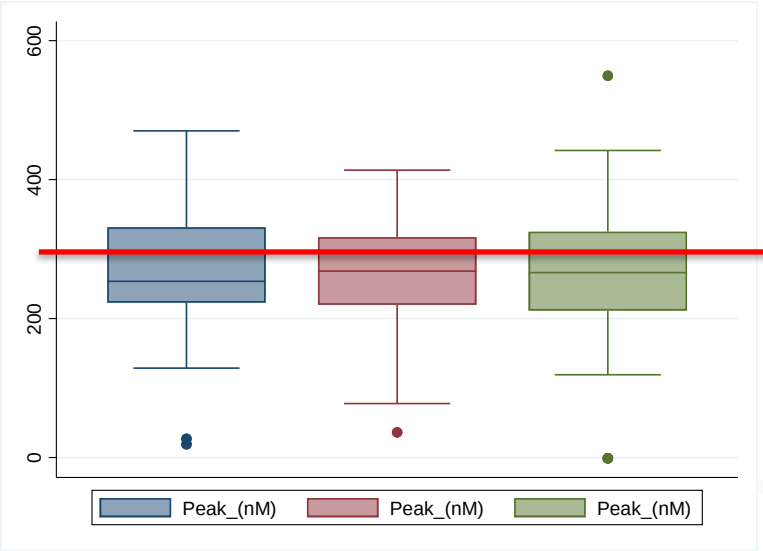


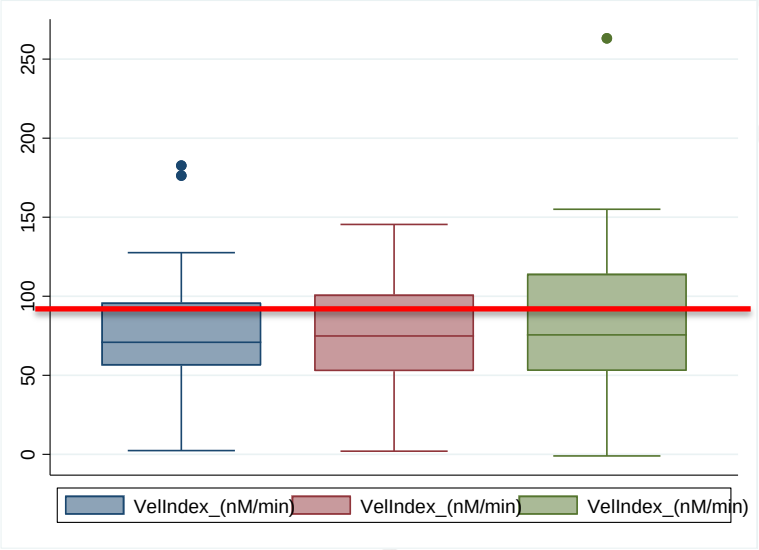


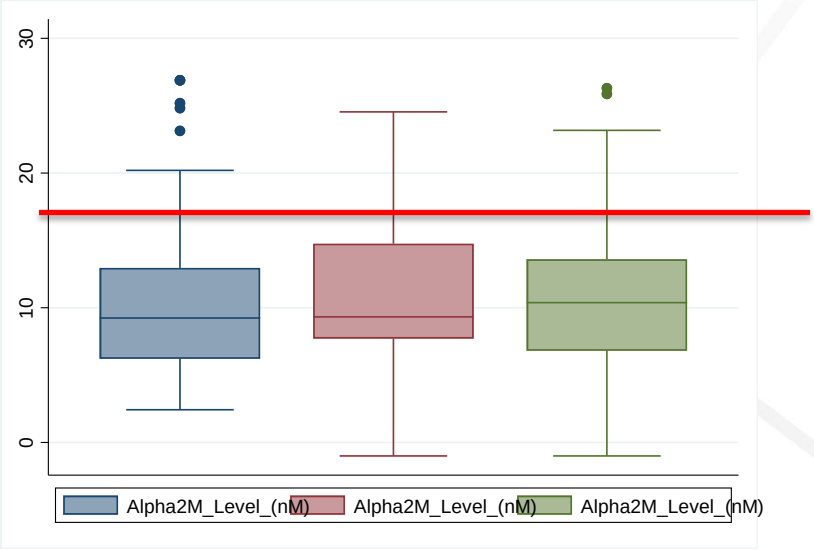
- medians
- procoag

Changes in median levels of ETP over time- **lung**



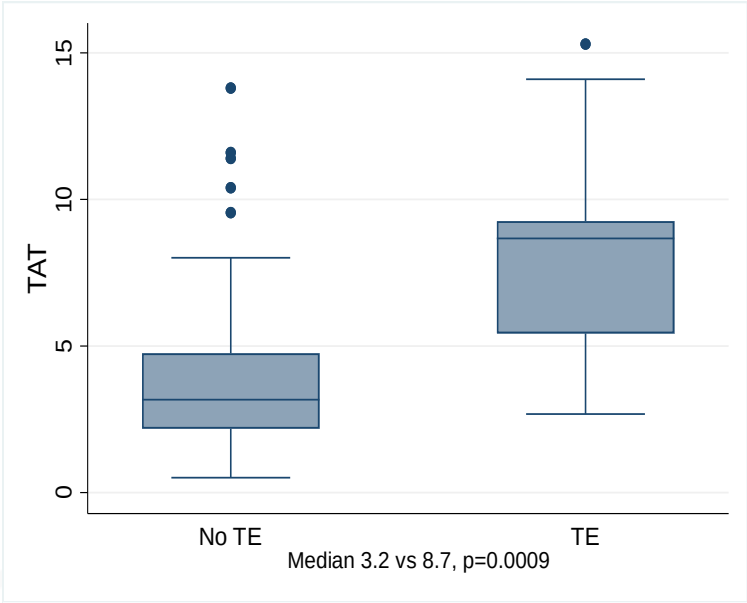


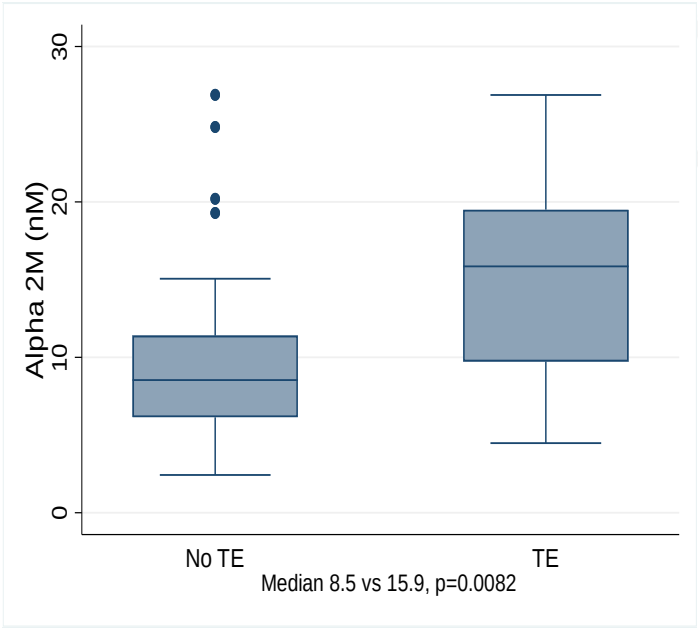


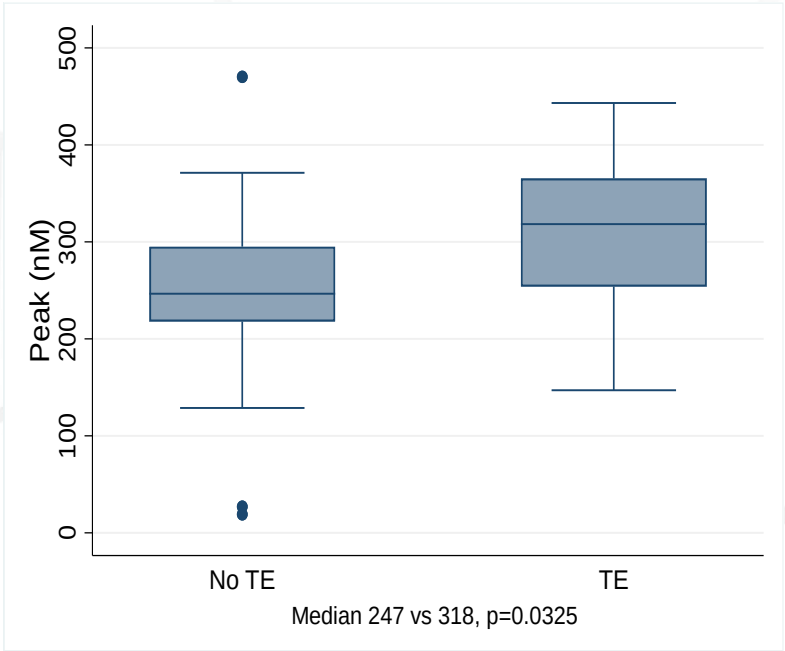


TE group vs no TE – **lung**

- Biomarker TAT month 1 higher
- ETP: BL peak ETP and α2m higher
- TEG: none







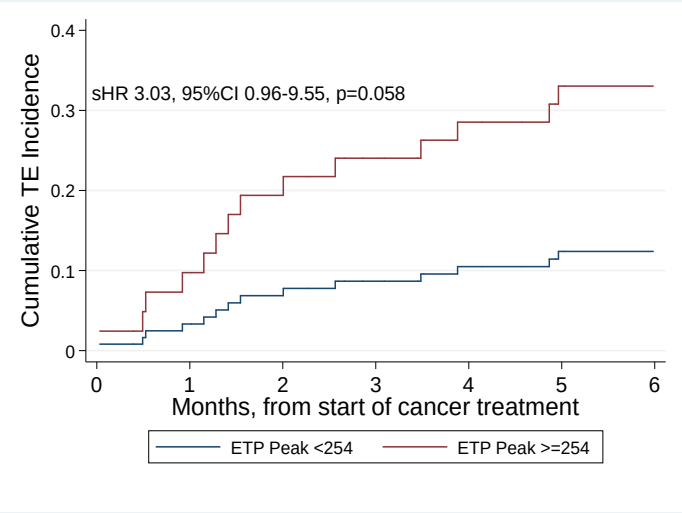
TE prediction - **lung**

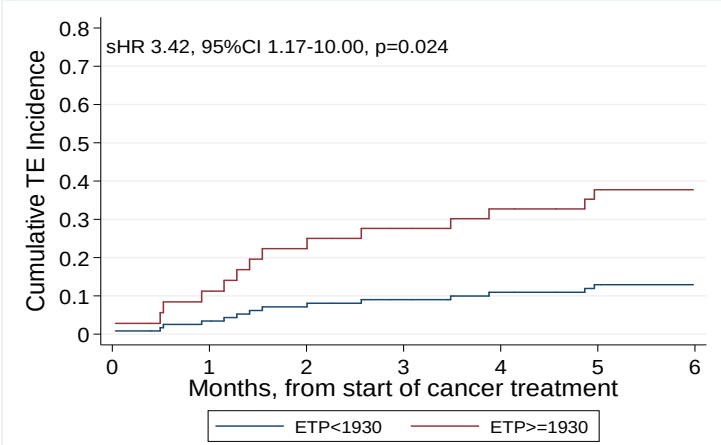
- Strongest predictors
- Biomarkers: Month 1 TAT >4.2ug/L
- ETP: multiple predictive thresholds (all baseline)
- TEG: none

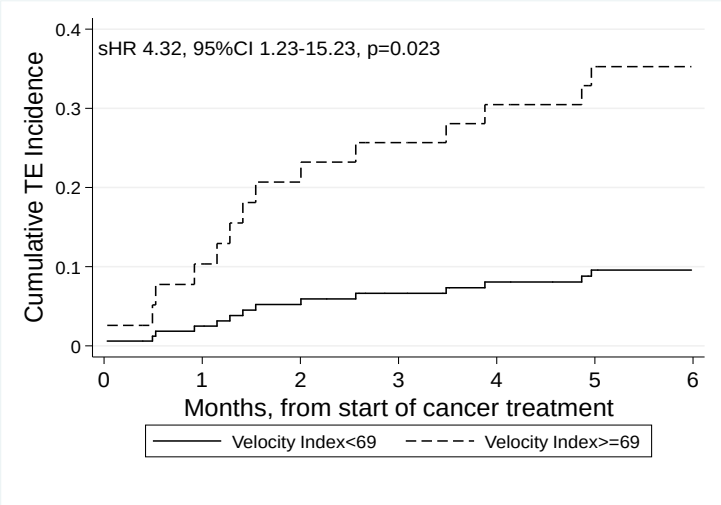
	sHR	95% CI	p
Month 1 TAT ≥4.2ug/L	***7.23***	1.64-31.79	0.009
α2m ≥15	***7.44***	*2.6-21.29*	*<0.001*
ETP peak ≥254 nM	***7.42***	2.37-23.27	p = 0.001
ETP total >2308 nM*min	***4.83***	1.7-13.71	0.003
Vel Index ≥69	***4.35***	1.23-15.37	0.022

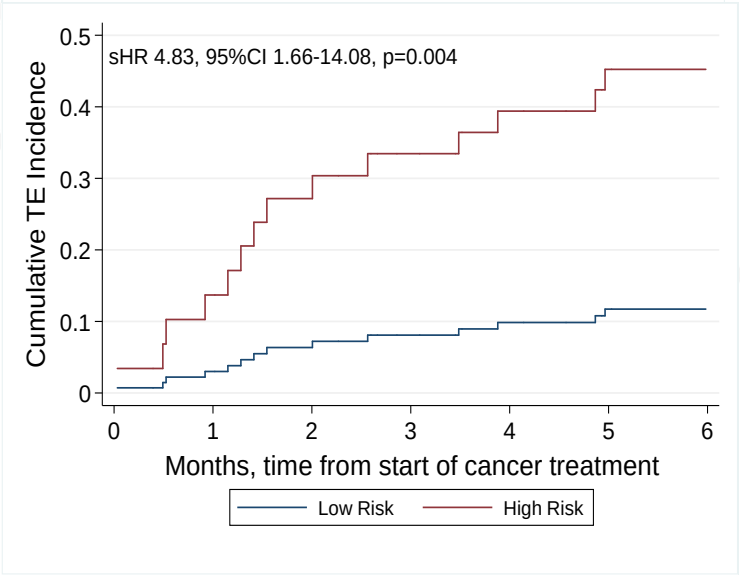
Cumulative incidence TE – **lung**

(Significant) stratification thresholds







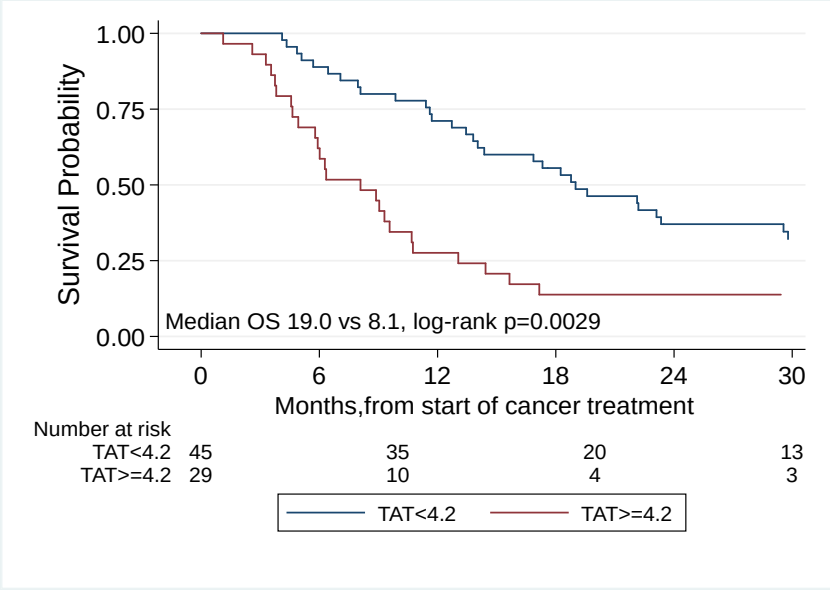


Death and overall survival – lung

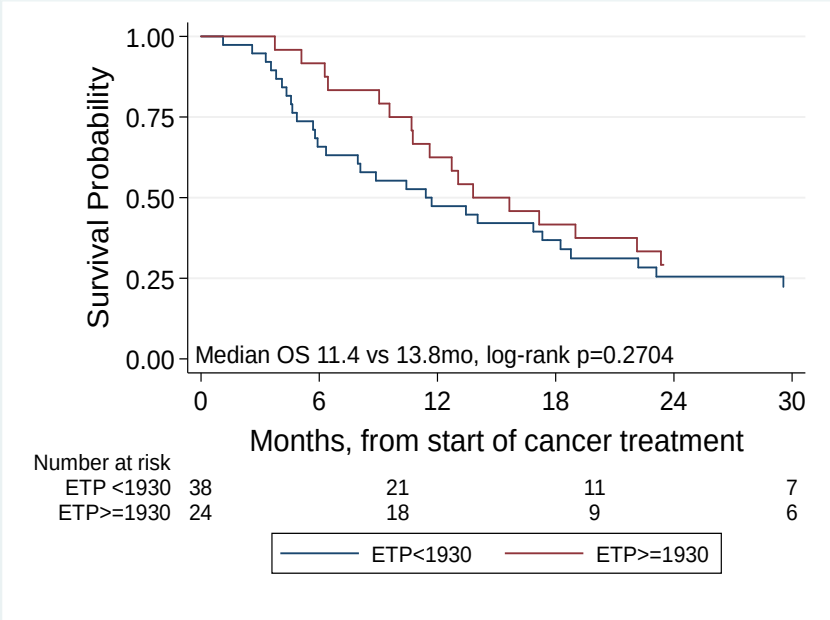
- Strongest predictors for higher risk of death
- Biomarkers: **baseline TAT >4.2ug/L**
- ETP: none
- TEG: none

Risk factor	HR	95% CI	p
ETP ≥1930	0.73	0.42-1.28	0.272
ETP ≥2308	0.64	0.34-1.21	0.172
ETP ≥2650	1.32	0.62-2.80	0.478
Peak≥254	0.53	0.31-0.92	0.024
Peak≥300	0.84	0.47-1.49	0.549
Vel index ≥69	0.61	0.36-1.05	0.076
Vel index ≥71	0.61	0.36-1.05	0.076
α2m≥13	1.03	0.54-1.97	0.923
α2m ≥16	0.79	0.37-1.68	0.54
TAT ≥ 4.2 baseline	**2.13**	**1.28-3.54**	**0.004**
ETP Peak ≥254 and α2m≥9	0.57	0.31-1.07	0.082
ETP Peak ≥254 + α2m≥9 + VI≥71	0.6	0.32-1.16	0.128

Overall survival – **lung**

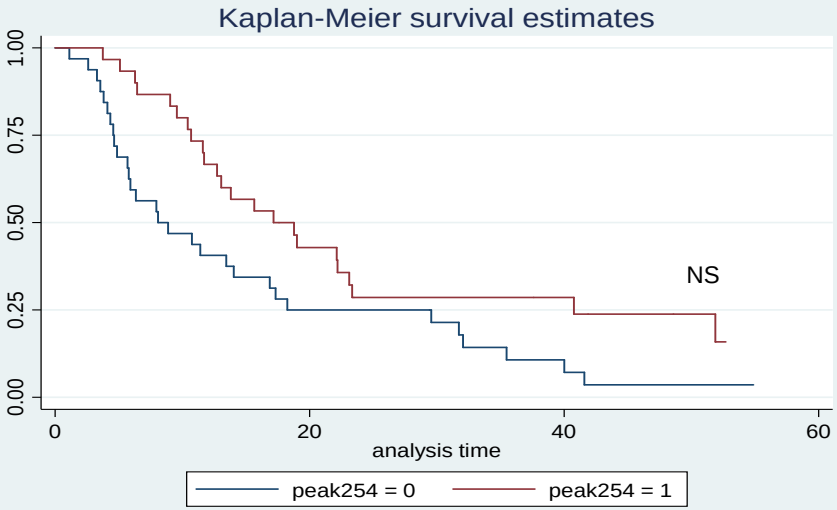


Baseline TAT
p = 0.0029

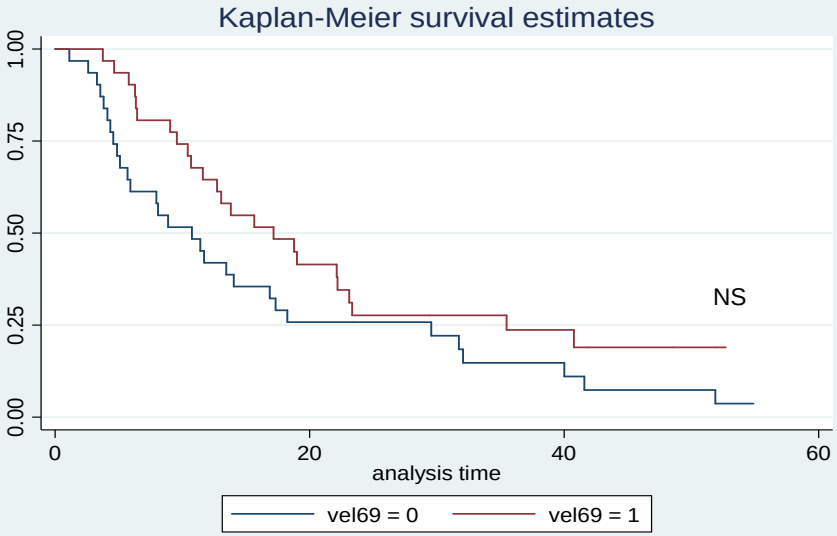


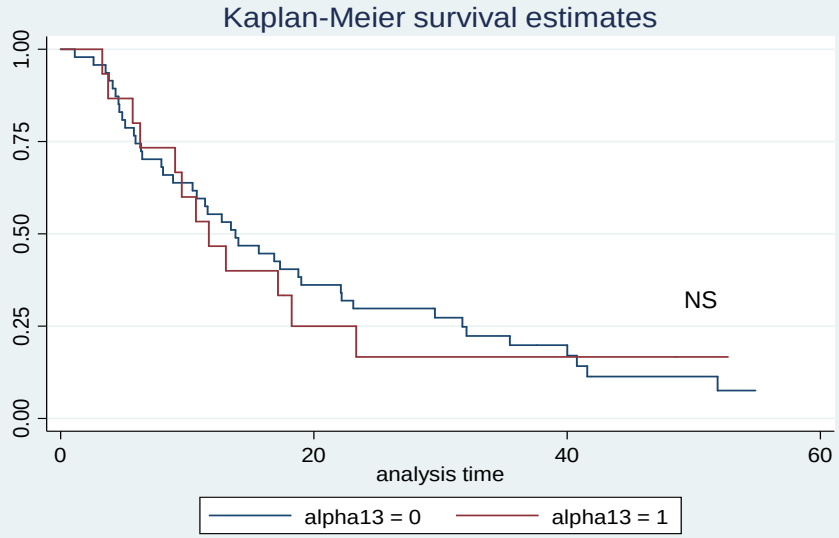
Baseline ETP
NS

Overall survival – **lung**

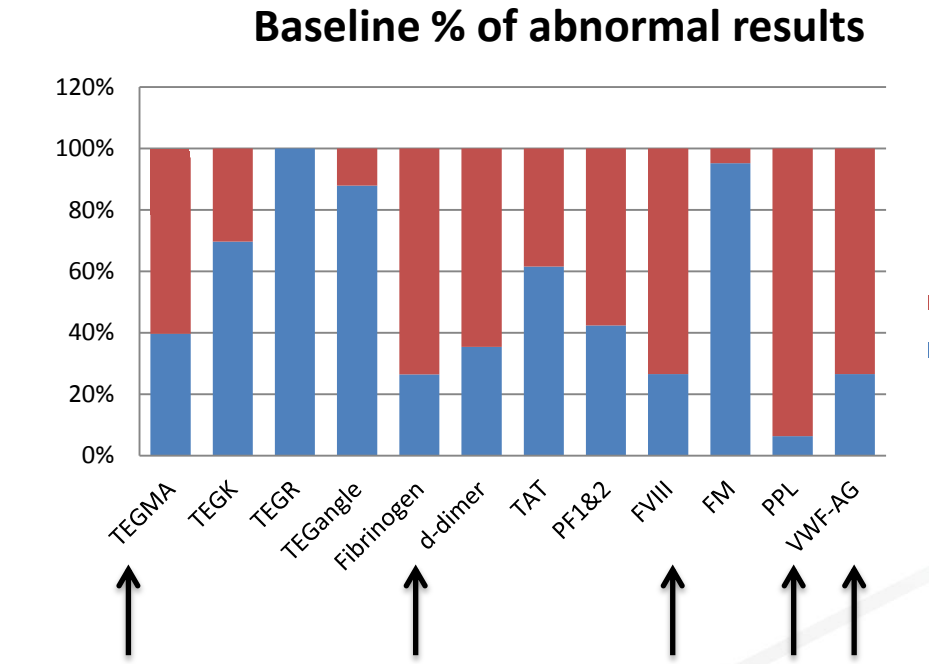


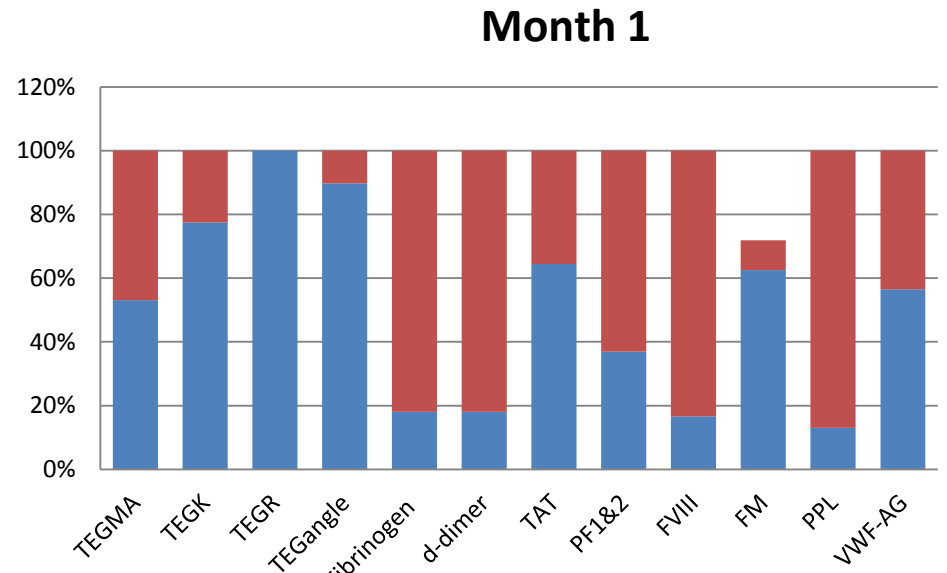
ETP peak, Vel Index, a2m NS

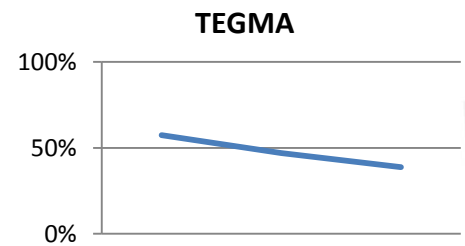


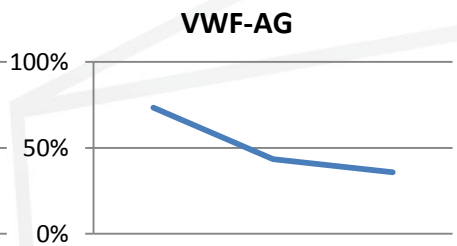


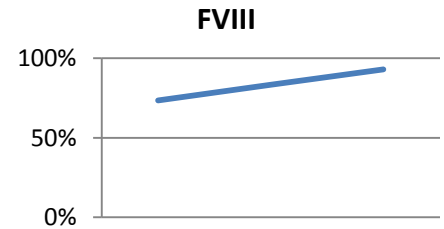
Hypercoagulable profile– GI

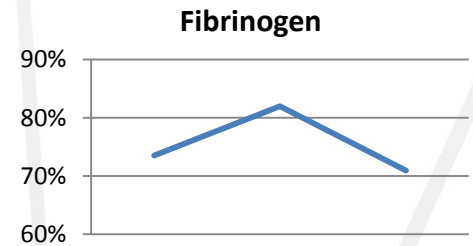


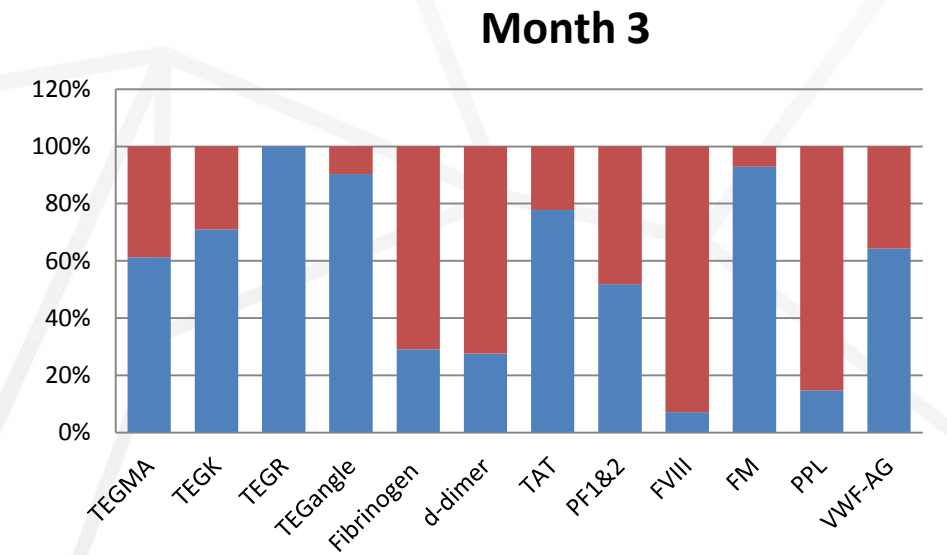




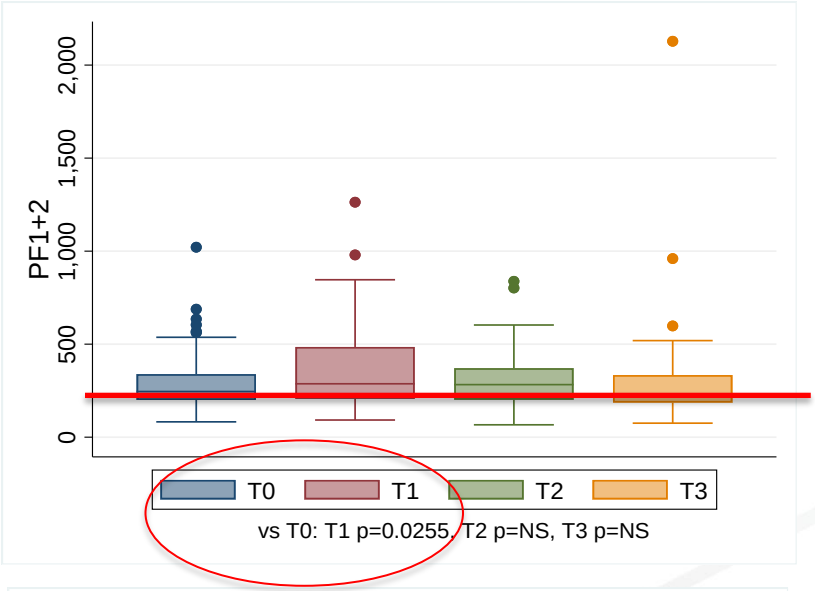


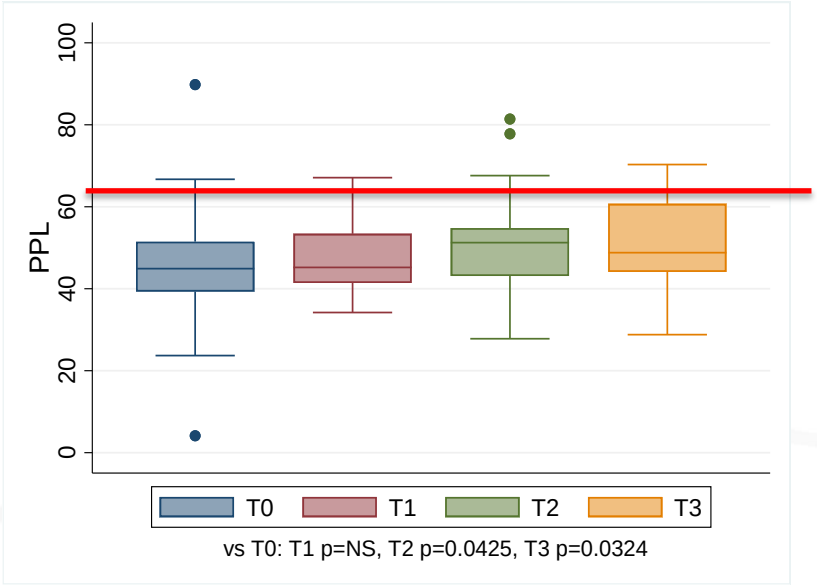


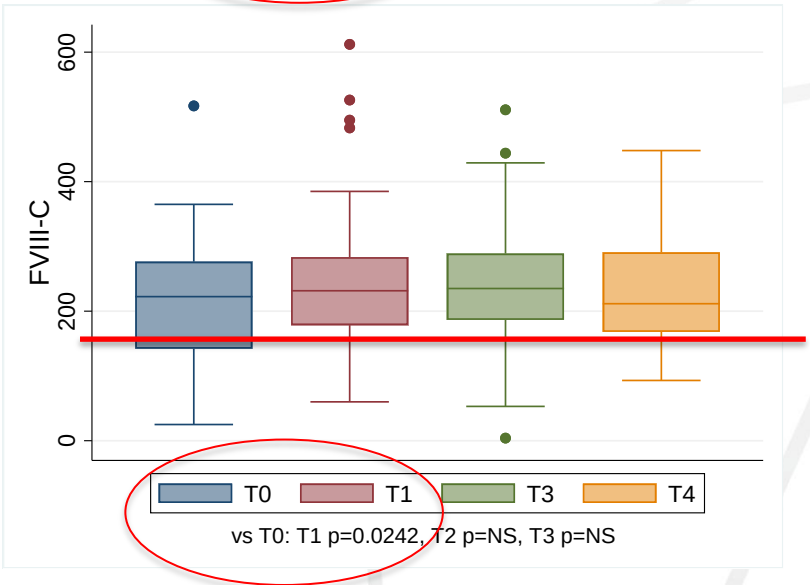




Changes in median levels of biomarkers over time- **GI**

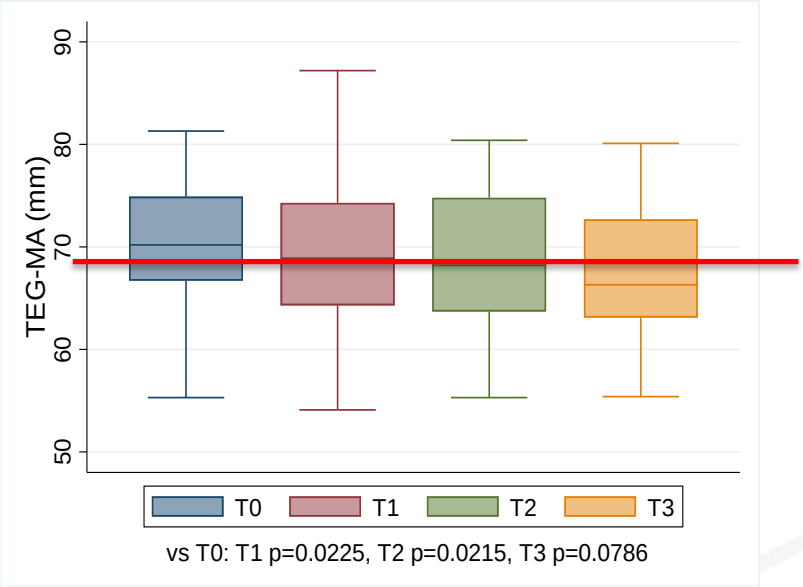


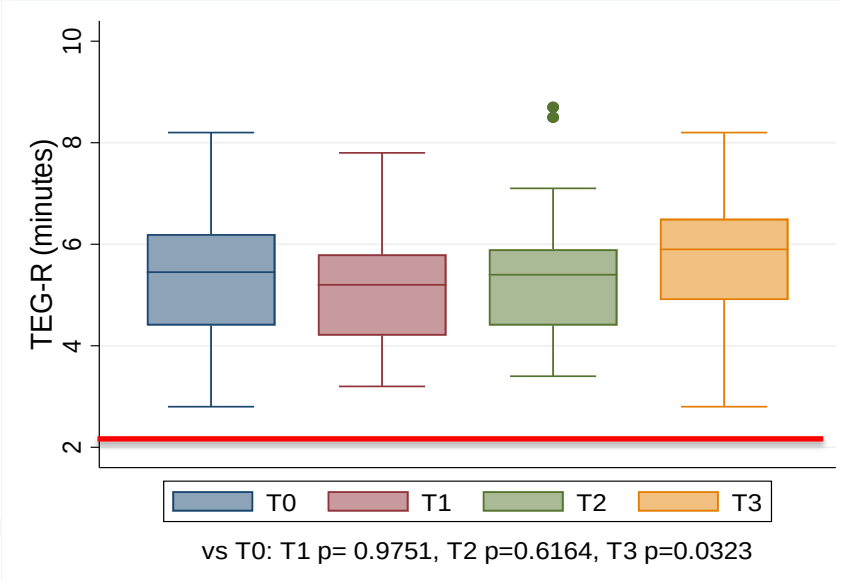


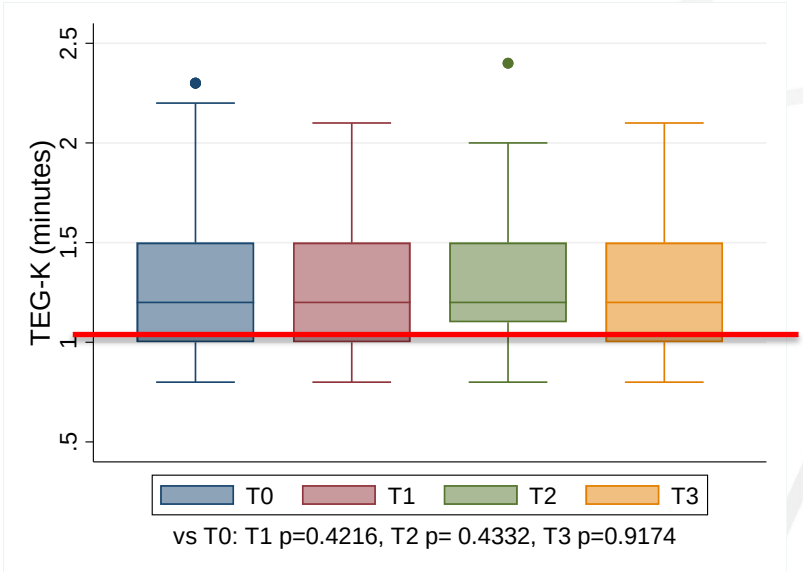


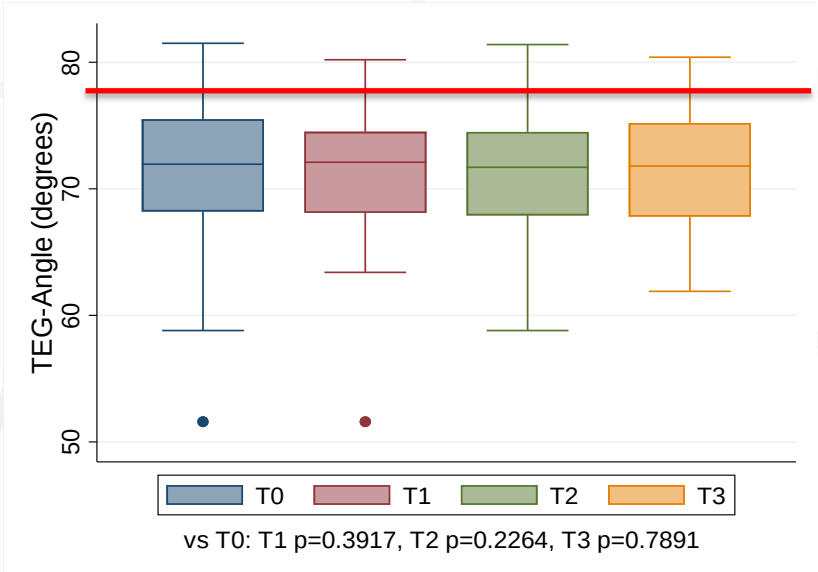
Early procoagulant changes

Changes in median levels of TEG over time - **GI**









TE group vs no TE – **GI**

- Biomarkers: Month 1 FM higher
- TEG: baseline TEG K shorter

	Baseline				**Month 1**		
	TE	*no TE*	*p*		*TE*	*no TE*	*p*
VWF	163	152	0.324		159	156	0.815
FVIII	276.5	202	0.065		278	226	0.136
PPL	42.6	44.9	0.789		55	49.55	0.067
FM	4.21	3.035	0.490		41.26	2.765	0.003
PF1+2	329.5	242	0.200		302.5	282.5	0.560
TAT	3.505	3.21	0.880		6.225	3	0.140
FM	4.21	3.04	0.492		41.26	2.765	**0.003**
TEG-R	4.75	5.55	0.1745		5.8	5.4	0.621
TEG-K	0.85	1.25	**0.022**		1.2	1.2	0.568
TEG-angle	76.75	71.6	0.066		72.65	71.7	0.571
TEG-MA	75.25	70.2	0.147		72.1	68.2	0.361

TE prediction - **GI**

Risk factor	sHR	95% CI	P
PF1+2 >229	All TE events		
FVIII >150	All TE events		
PPL<61	All TE events		
TEG-K <1.3	All TE events		
TEG MA >69	All TE events		
VWF-Ag >160	4.00	0.43-37.58	0.225
TEG-angle >78 degrees	**7.47**	**1.13-49.25**	**0.037**
Month 1 FM >25.71	**13.71**	**2.13-88.19**	**0.006**

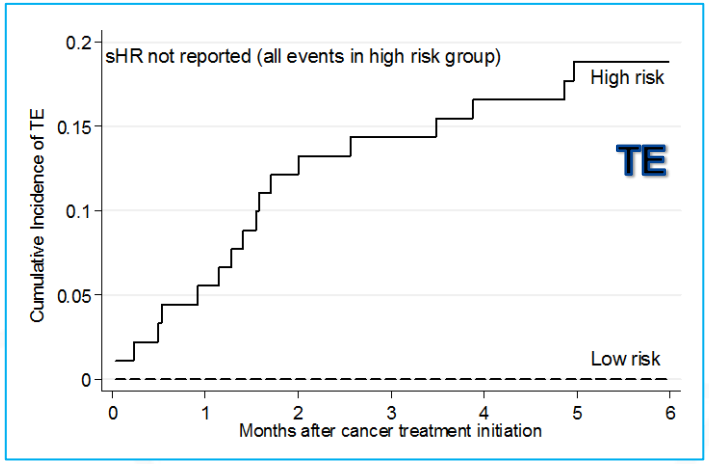
NB: only 5 TE events for analysis

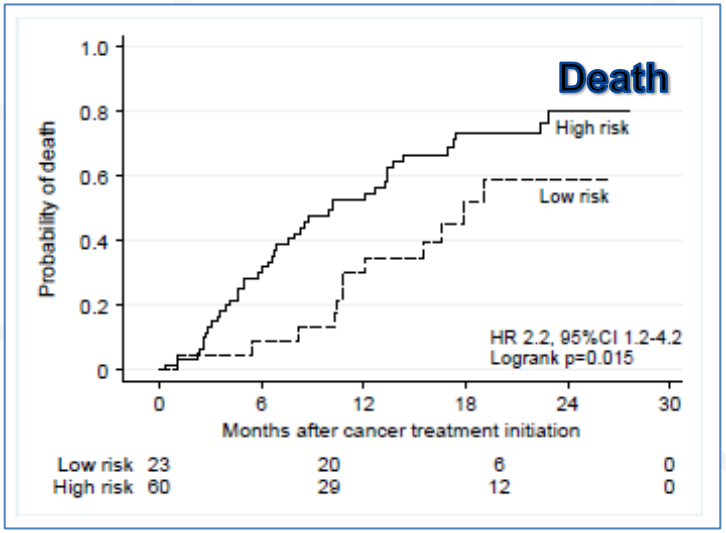
Death and OS – GI

	HR for death	95%CI	p
TAT>4.2mcg/L	1.36	0.56-3.28	0.499
PF1&2 >229	1.34	0.55-3.24	0.52
FVIII >150	0.75	0.09-5.58	0.78
FM >25.71	2.20	0.65-7.48	0.21
PPL<61	0.55	0.13-2.38	0.42
VWF-AG >160	1.84	0.76-4.48	0.177
TEG R<5.0	0.70	0.28-1.72	0.439
TEG K<1.0	0.82	0.27-2.48	0.731
TEG K<1.3	0.39	0.15-0.99	0.047
TEG MA>69.0	1.93	0.73-5.05	0.183
TEG MA>72	1.21	0.50-2.99	0.664
TEG MA>75	1.78	0.71-4.47	0.220
TEG Angle>78 deg Month 1	All deaths occurred with TEG angle >78 (no deaths in TEG angle <78 group)		
FM >25.71 – Month 1	All deaths occurred with FM<25.71 (No deaths with FM >25.71)		

Relationship with BIOTEL model

- Procoagulant profile
  - Assessed with a variety of biomarkers showing peak trends within 3 months
  - Similar risk period identified in BIOTEL
- Risk prediction
  - TE: Best correlation with lung baseline TAT
  - Death: Best correlation with lung Month 1 TAT





Relationship to BIOTEL model

	Predictive for TE	Predictive for death	Corresponding BIOTEL model stratification values		
			High	Low	p
BIOTEL model	**Yes**	**Yes**			
Lung cohort Month 1 FM	Y	N	3.31 (Median)	1.88	0.241
Lung Baseline TAT ≥4.2	**N**	**Y**	**4.17**	**2.65**	**0.003**
Lung Month 1 TAT ≥4.2	**Y**	**N**	**4.26**	**2.89**	**0.046**
ETP total (nM*min)	Y	N	1903	1644	0.069
a2m (nM)	Y	N	8.9	10.8	0.145
ETP peak (nM)	Y	N	255	244	0.094
Velocity index (nM/min)	Y	N	82	66.3	0.368
TT peak (min)	**N**	**N**	**8.67**	**7.67**	**0.043**
Lag time (s)	**N**	**N**	**5.09**	**3.97**	**0.003**

Summary of findings

	BIOTEGIC (gastrointestinal)		BIOTEL (lung)	
Strongest TE predictors and associations (TE within 6 months)	**Baseline** PF1+2 ≥229pmol/L FVIII ≥150% PPL ≤61s TEG K ≤1.3min TEG MA ≥69mm *TEG-Angle ≥78	**Month 1** FM >25.71ug/mL	**Baseline** α2m≥ 15nM ETP peak ≥254 nM+ a2m≥9 ETP total ≥2308 nM*min	**Month 1** *TAT ≥4.2ug/L
Predictors for death		*TEG Angle ≥78	*TAT ≥4.2ug/L	
TE vs no TE	Shorter TEG-K	Higher FM values	Higher ETP peak Higher α2m levels	Higher TAT

Discussion

- Highest TE risk period first 3 months
  - Clinical outcomes & serial coagulation profiles
  - Earlier ? Week 1?
- Some predictive biomarkers did not necessarily show longitudinal changes/trends (eg ETP, TAT, FM)
- Performance of global assays
  - TEG a 'true global assay' yet inconsistent across cancer types and within TEG parameters (GI vs lung, MA vs angle)
  - ETP reflects only TE pathway and not death
- Performance of thrombogenic markers
  - Different predictors between cancer types
  - Biological vs statistical
- Applicability to other cancers
- Real life application
  - Cost and availability; selective use ?
- Opportunity to explore further

Targeted thromboprophylaxis

Ambulatory patients with lung or GI cancers, receiving anticancer therapies: open-label, multicentre, PIII randomised trial

(TARGET-TP)

Teletrial

CPI – A/Prof Kate Burbury, kate.burbury@petermac.org

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End