

Identifying High-Risk Patients in Follicular Lymphoma with a new prognostic score

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GALLIUM clinical trial improved outcomes

- med.PFS ≈8 years with SoC*!
- subpopulation relapse quite early (within 2 or 3 years)
- can a simple prognostic score identify those patients? (*±yes*)
- rationale: high-risk trial feasible?



*Standard of Care



Existing Scores not Enough





Model development focused on simplicity and clinical interpretability

- Initial list of 35 "flags" codifying 17 variables and one two-way interaction
- Variables dichotomised for simplicity (cutoffs not datadriven)
- Cross-validated pen. Cox (ElasticNet) for variable selection
- Equal weights* for selected factors: score range = 0 9



Missingness: ~16%

Complete case analyses: 198 patients (16%) and 65
 PFS events (18%), 26 (17%) POD24 events

PFS-INV events depending on FLEX missingness (column %).

BEP_FLEX	PFSCnsr	PFSEvnt
FALSE	133 (15.8)	65 (18.1)
TRUE	710 (84.2)	294 (81.9)

POD24 events depending on FLEX missingness (column %).

BEP_FLEX	POD24Cnsr	POD24Evnt
FALSE	172 (16.4)	26 (17)
TRUE	877 (83.6)	127 (83)

Missingness: seems OK



206 others



PFS overall, FLEX-BEP vs rest



Selected variables from Predefined List (PFS in GALLIUM*)

- Some "usual suspects"
 from other prognostic
 scores
- Tumor stage absent (but SPD present)
- Sex and NKCC "new"

	Variables selected	HR (95% CI)	p-value
	Sex: male	1.67 (1.32-2.11)	<0.0001
	SPD: >9320mm ² on CT scan (top quartile)*	1.64 (1.15-2.35)	0.0061
	Histology grade: 3a	1.49 (1.12-2)	0.0068
1	Extranodal sites: >2	1.16 (0.88-1.53)	0.0292
Ĵ	ECOG PS: >1	1.52 (0.89-2.61)	0.129
	Hemoglobin: <12g/L	1.39 (1.04-1.86)	0.028
1	β ₂ microglobulin: >ULN	1.30 (0.99-1.71)	0.056
	NK cell count: <100/µL	1.24 (0.87-1.76)	0.237
1	LDH: >ULN	1.25 (0.97-1.61)	0.085



Validation on external study

- Good generalization despite differences between studies*
- Cutoff of ≥3 for high-risk chosen with ROC on PFS status @36m
- ≥4 better for "early" progressions





Score equivalent to FLIPI in validation cohort ...



*FLEXW is weighted with log-HR estimates from Cox model on GALLIUM INV-PFS



... probably due to differences in FLIPI intermediate group

- ΔPFS between SABRINA and GALLIUM: 7% @2y and 10% @3y
- FLIPI unexpected results in SABRINA (should be worse than FLIPI-2)
- New score gives same results



SO WHAT? Clinical Utility?

- In new RCT:
 - include high-risk only
 - exclude low-risk
- ROC not enough: need to look at:
 - PPV/NPV
 - Predictiveness curves (need calibration)



Based on prevalence



Conclusions



- Prespecify objectives and missing data strategy as much as possible
- Define Reproducibility and Replicability Strategy (external validation)
- For clinical utility: PPV/NPV better than ROC





BACKUP

ROC Curves for POD24 event, SABRINA data





False positive rate

Non-zero coefficients CoxNet model







		Low			High					EV Llink	EL EX Law
Baseline Risk	Total	n	Events	Median	n	Events	Median	Hazard	95%	Retter	FLEX LOW Better
Factors	n			(month)			(month)	Ratio	Wald CI	Detter	Better
ALL	342	201	49	NA	141	67	NA	2.34	(1.62, 3.39)		— •—
Beta-2 Microglobulin: LOW vs HIGH (ref.: LOW)											
FALSE	150	128	29	NA	22	10	NA	2.49	(1.21, 5.12)		•
TRUE	192	73	20	NA	119	57	57	2.09	(1.25, 3.48)		•
ECOG at baseline >=2 (ref.: 0-1)											
FALSE	327	199	49	NA	128	59	NA	2.16	(1.48, 3.16)		_
TRUE	15	2	0	NA	13	8	11.96	NA	(NA, NA)		
Extranodal Sites >2 (ref.: <=2)											
FALSE	319	199	49	NA	120	55	NA	2.17	(1.48, 3.19)		_ _
TRUE	23	2	0	NA	21	12	37.67	NA	(NA, NA)		
Hemoglobin: >=120 vs <120 g/L (ref.: >=120)											
FALSE	260	177	46	NA	83	37	NA	2	(1.3, 3.09)		_
TRUE	82	24	3	NA	58	30	51.09	5.28	(1.61, 17.32)		\longrightarrow
Histological grade 3 or 3a											
FALSE	265	169	43	NA	96	43	NA	2.07	(1.36, 3.16)		_
TRUE	77	32	6	NA	45	24	48.85	3.69	(1.51, 9.03)		$ \longrightarrow $
LDH: Normal vs Elevated (ref.: Normal)											
FALSE	254	174	38	NA	80	31	NA	1.97	(1.22, 3.16)		_
TRUE	88	27	11	NA	61	36	37.9	1.85	(0.94, 3.64)	-	•
NKCC below normal Level (<0.1)											
FALSE	268	180	45	NA	88	46	50.89	2.57	(1.71, 3.88)		_
TRUE	74	21	4	NA	53	21	NA	2.38	(0.82, 6.94)		•
SPD in 4th quartile											
FALSE	264	180	44	NA	84	40	NA	2.3	(1.5, 3.53)		_
TRUE	78	21	5	NA	57	27	49.91	2.49	(0.96, 6.48)		•
Sex = male (ref. female)											
FALSE	183	129	32	NA	54	27	49.22	2.6	(1.56, 4.35)		
TRUE	159	72	17	NA	87	40	NA	2.19	(1.24, 3.86)		• • • • • • • • • • • • • • • • • • •
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