POST-NEW ORLEANS 2022
Novità dal Meeting della Società Americana di Ematologia

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Milano
Teatro Dal Verme
2-3-4 Febbraio 2023

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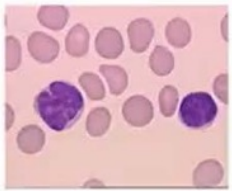
Topics

- TRIANGLE (Abstract N 1)
- Emerging therapies in BTK-refractory (Zilo+Ibr; Glofi)
- Car-T cells

LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN
MEDIZINISCHE KLINIK UND POLIKLINIK III
DIREKTOR: PROF. DR. H. VON BERGWELT

TRIANGLE:

AUTOLOGOUS TRANSPLANTATION AFTER A RITUXIMAB/IBRUTINIB/ARA-C CONTAINING INDUCTION IN GENERALIZED MANTLE CELL LYMPHOMA – A RANDOMIZED EUROPEAN MCL NETWORK TRIAL



M Dreyling, J Doorduijn, E Giné, M Jerkeman, J Walewski, M Hutchings, U Mey, J Riise, M Trneny, V Vergote, M Celli, O Shpilberg, M Gomes da Silva, S Leppa, L Jiang, C Pott, W Klapper, D Gözel, C Schmidt, M Unterhalt, M Ladetto*, E Hoster*

LMU University Hospital Munich, Germany; Erasmus MC Cancer Institute, University Medical Center Rotterdam, Netherlands; Hospital Clinic of Barcelona, Spain; Skane University Hospital and Lund University, Lund, Sweden; Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; Rigshospitalet, Copenhagen University Hospital, Denmark; Kantonsspital Graubuenden, Chur, Switzerland; Oslo University Hospital, Oslo, Norway; Charles University and General University Hospital, Prague, Czech Republic; University Hospitals Leuven, Belgium; Ospedale degli Infermi di Rimini, Italy; Assuta Ramat Hahayal Medical Center, Tel Aviv, Israel; Instituto Português de Oncologia, Lisboa, Portugal; Helsinki University Hospital Comprehensive Cancer Center, Finland; IBE, LMU University Munich, Germany; University of Schleswig-Holstein, Kiel, Germany; Az Ospedaliera Santi Antonio e Biagio e Cesare Arrigo, Alessandria, Italy

TRIANGLE: Trial Design

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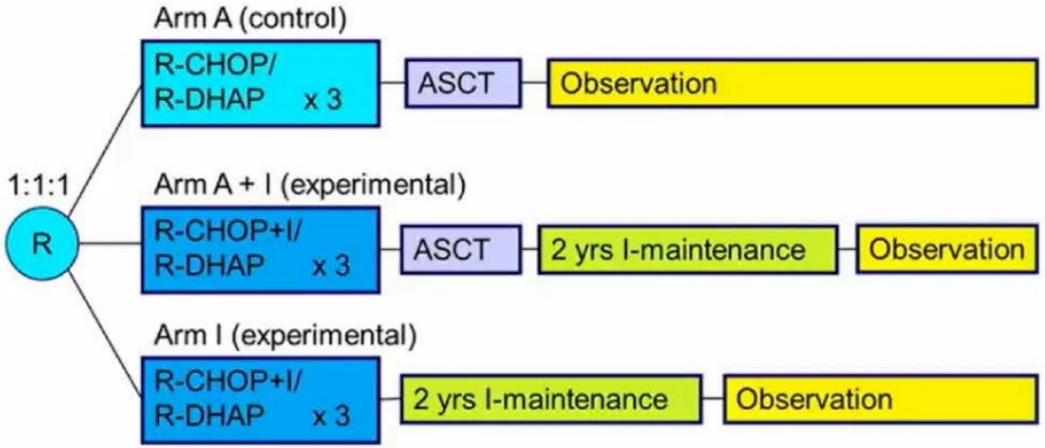
- MCL patients
- previously untreated
- stage II-IV
- younger than 66 years
- suitable for HA and ASCT
- ECOG 0-2

- Primary outcome: FFS

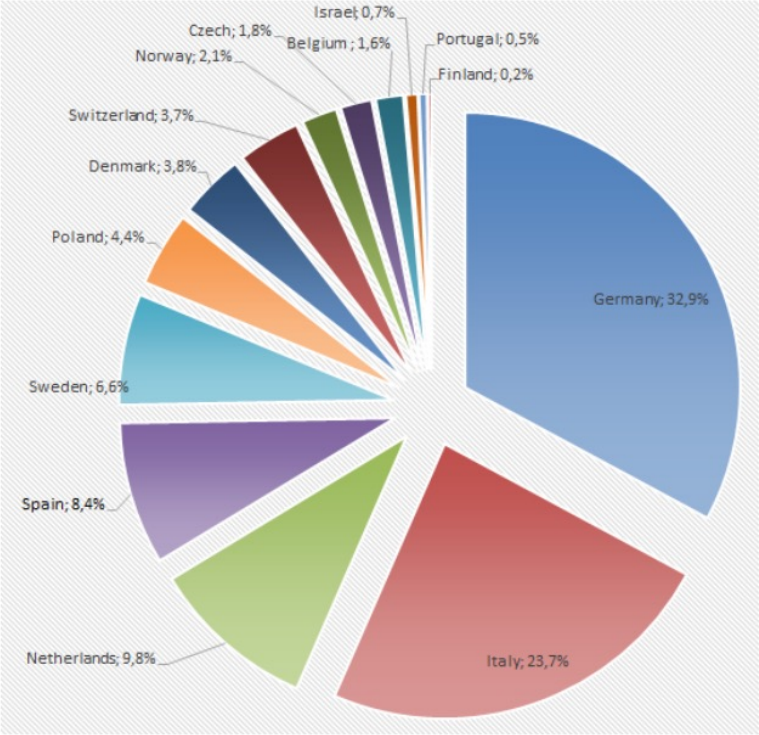
- Secondary outcomes:
  - Response rates
  - PFS, RD
  - OS
  - Safety



- R maintenance was added following national guidelines in all 3 trial arms
- Rituximab maintenance (without or with Ibrutinib) was started in 168 (58 %)/165 (57 %)/158 (54 %) of A/A+I/I randomized patients.

Final Recruitment per Country

Countries active	Patients randomized total per country	Patients in percent
Germany	286	32,9%
Italy	206	23,7%
Netherlands	85	9,8%
Spain	73	8,4%
Sweden	57	6,6%
Poland	38	4,4%
Denmark	33	3,8%
Switzerland	32	3,7%
Norway	18	2,1%
Czech	16	1,8%
Belgium	14	1,6%
Israel	6	0,7%
Portugal	4	0,5%
Finland	2	0,2%
14 countries	**870**	100,00%



TRIANGLE: Baseline Characteristics

Characteristic	overall (n=870)	A (n=288)	A+I (n=292)	I (n=290)
Median age, years (range)	57 (27-68)	57 (31-65)	57 (36-68)*	58 (27-65)
Male sex	76%	76%	74%	79%
No MCL	8 (1%)	2 (CLL, FL)	4 (1 NHL NOS, 1 HD, 2 MZL)	2 (HCL, DLBCL)
Ann Arbor Stage (n=864)				
I	0%	0%	0%	0%
II	5%	4%	4%	6%
III	9%	8%	7%	10%
IV	87%	88%	89%	84%
ECOG > 1	1%	2%	1%	2%
MIPI Low	58%	58%	58%	58%
MIPI Intermediate	27%	27%	27%	27%
MIPI High	15%	14%	15%	16%

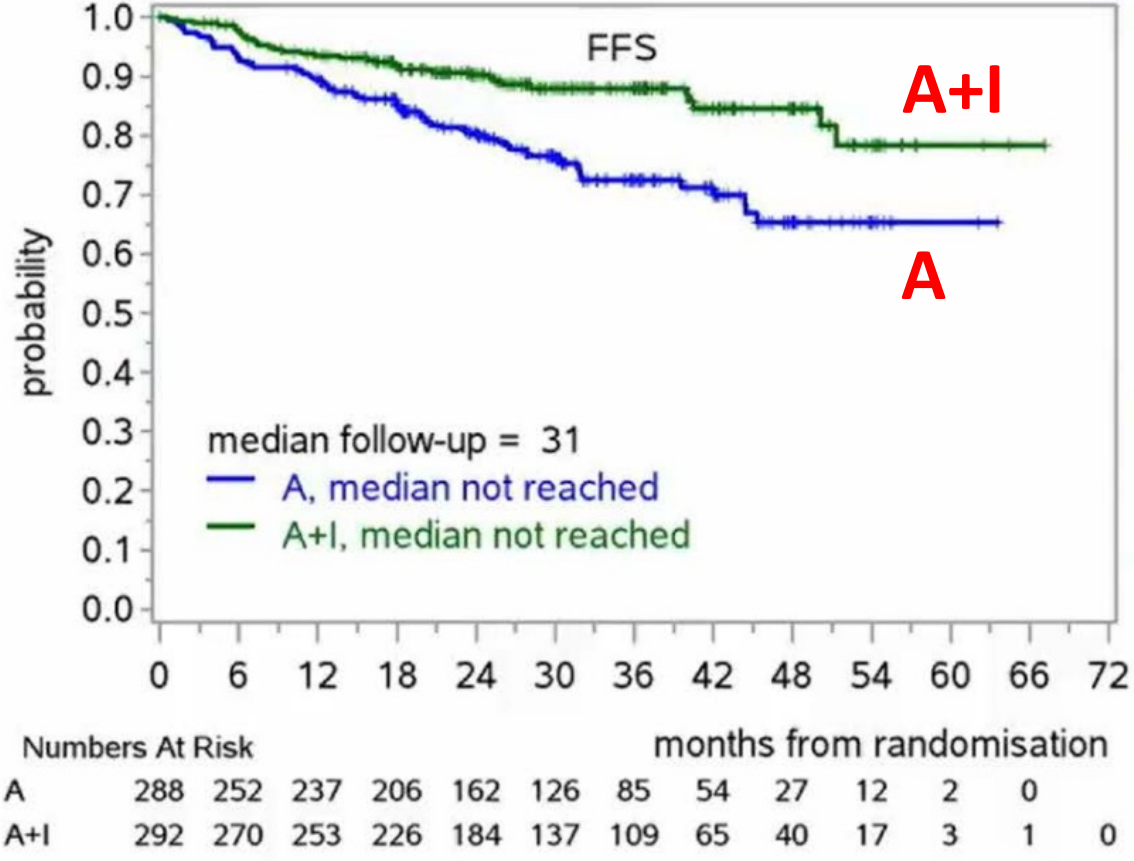
* 2 patients aged 66/68 randomized

TRIANGLE: Response at End of Induction

	Overall	A	A+I/I	A+I	I
ED	2 (0.2%)	1 (0.4%)	1 (0.2%)	1 (0.4%)	0 (0%)
PD	17 (2%)	11 (4%)	6 (1%)	3 (1%)	3 (1%)
SD	7 (1%)	4 (1%)	3 (0.5%)	1 (0.4%)	2 (0.7%)
PR	458 (55%)	158 (58%)	300 (54%)	152 (54%)	148 (53%)
CR	347 (42%)	98 (36%)	249 (45%)	124 (44%)	125 (45%)
CR+PR	805 (97%)	256 (94%)	549 (98%)	276 (98%)	273 (98%)
Total	831	272	559	281	278
NE	29	11	18	8	10
ND	10	5	5	3	2

- CR- and OR-Rates significantly higher in the combined I induction (A+I/I) versus control (A) (CR: p=0.0203, OR: p=0.0025)
- MCL Younger R-CHOP/R-DHAP group: 38% (CR), 94% (OR)

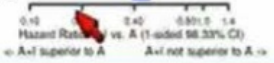
TRIANGLE: FFS Superiority of A+I vs. A



- Superiority of A+I vs. A (FFS) is confirmed
- Kaplan-Meier plots:
  - 3-year FFS A+I: 88%
  - 3-year FFS A: 72%
- p-value (corrected for sequential design) p=0.0008
- HR (A+I vs. A): HR=0.52

TRIANGLE: FFS Superiority of A+I vs. A

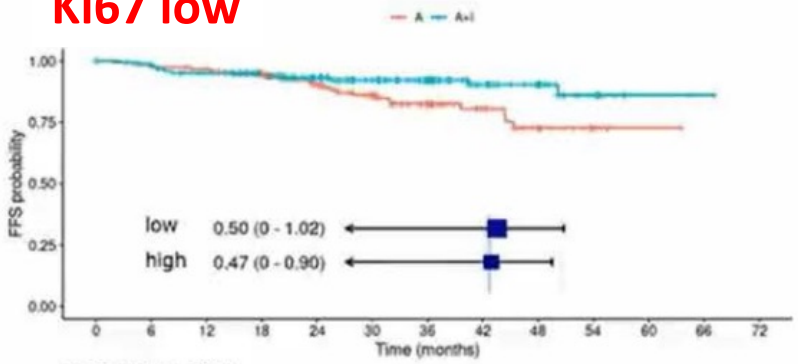
Subgroup (interaction p-value)	No. of patients	No. of events	Hazard ratio (1-sided 98.33% CI)
All	580	103	0.46 (0 - 0.72)
Sex (p=0.0016)			
Female	146	23	0.62 (0 - 1.51)
Male	434	80	0.43 (0 - 0.71)
MIPI			
Low	336	40	0.49 (0 - 0.99)
Intermediate (p=0.49)	159	35	0.35 (0 - 0.77)
High (p=0.69)	85	28	0.58 (0 - 1.32)
Cytology (p=0.48)			
Non-blastoid	426	68	0.36 (0 - 0.65)
Blastoid	60	18	0.57 (0 - 1.56)
Ki-67 (p=0.82)			
Low	234	39	0.50 (0 - 1.02)
High	150	38	0.47 (0 - 0.90)
P53 expression (p=0.039)			
Low	284	36	0.64 (0 - 1.32)
High	44	16	0.15 (0 - 0.60)
High risk biology (p=0.19)			
Low	270	31	0.63 (0 - 1.38)
High	64	25	0.32 (0 - 0.79)
R maintenance ITT (p=0.96)			
No	191	48	0.44 (0 - 0.84)
Yes	389	55	0.46 (0 - 0.85)
R maintenance mAT (p=0.94)			
No	217	55	0.45 (0 - 0.81)
Yes	363	48	0.44 (0 - 0.86)



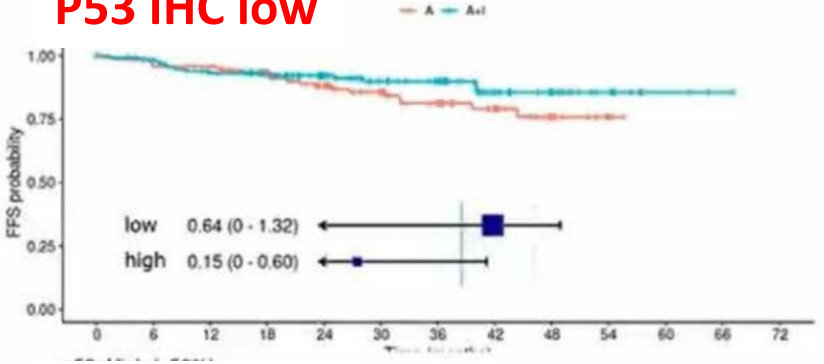
- similar in all MIPI groups
- No differential efficacy according to cytology and Ki-67
- More effective in high p53 expressors
- Trend toward higher efficacy in high risk biology
- No differential efficacy by rituximab maintenance

TRIANGLE: FFS Superiority of A+I vs. A

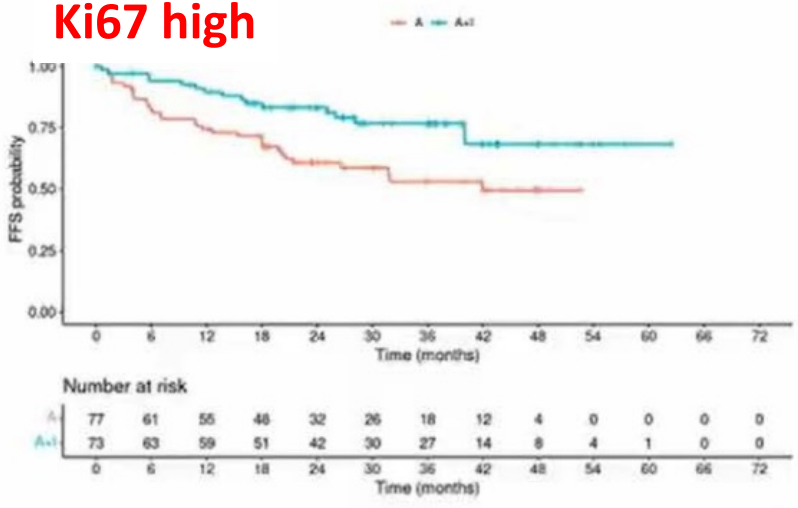
Ki67 low



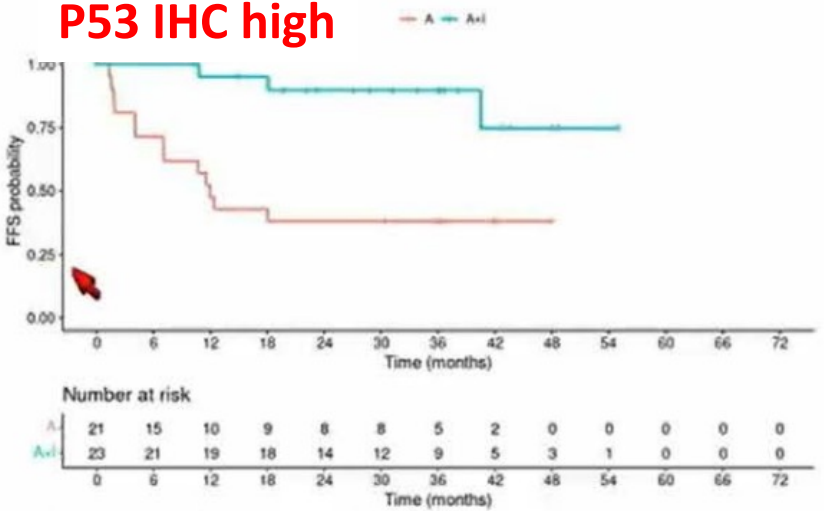
P53 IHC low



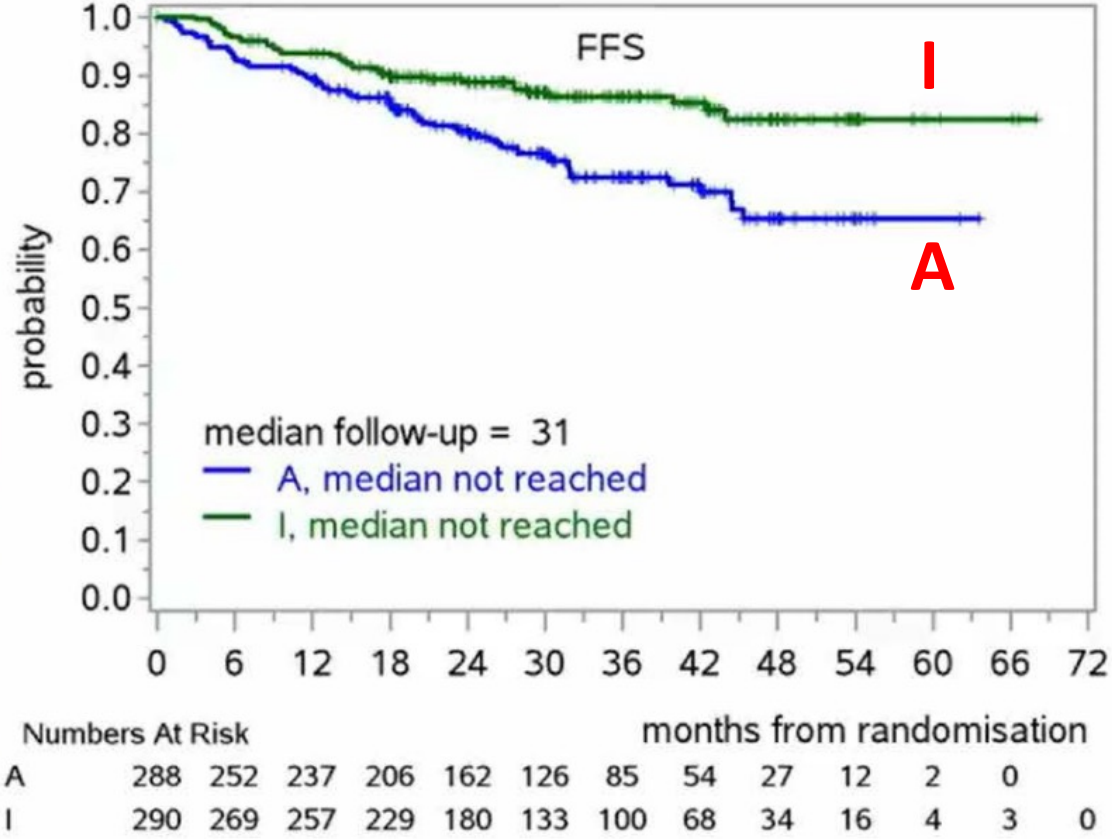
Ki67 high



P53 IHC high

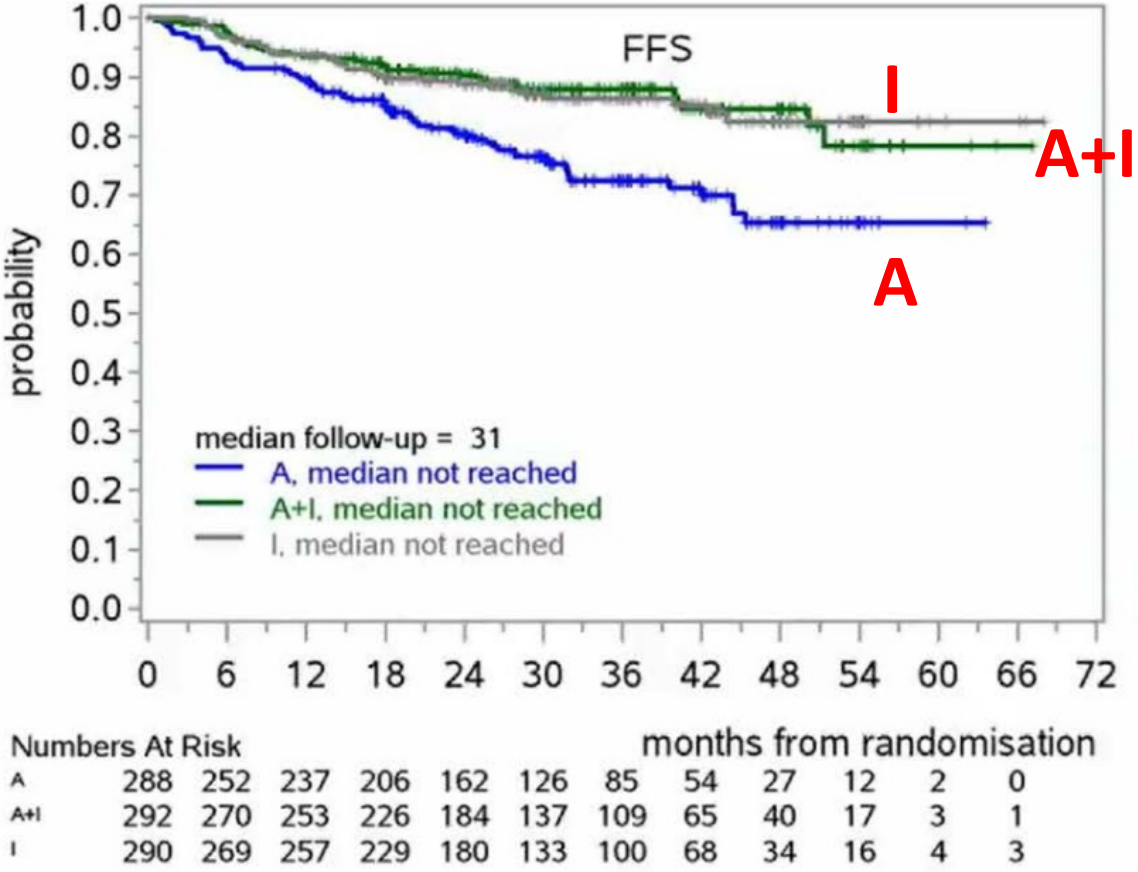


TRIANGLE: No FFS Superiority of A vs. I



- Superiority of A vs. I (FFS) was rejected
- Kaplan-Meier plots:
  - 3-year FFS A: 72% (MCL Younger: 75%)
  - 3-year FFS I: 86%
- p-value corrected for sequential design: p=0.9979
- HR (A vs. I): HR=1.77

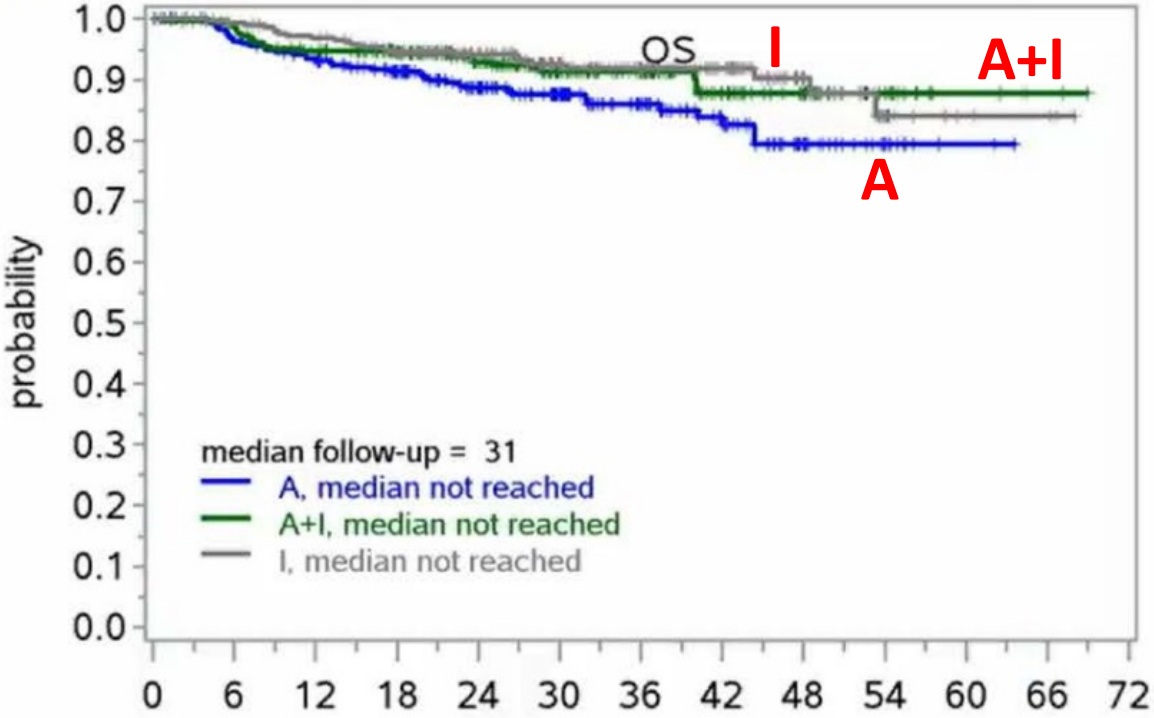
TRIANGLE: FFS Superiority of A+I vs. I ?



- Test A+I vs. I ongoing, no decision yet

Next lymphoma treatment (among patients with first treatment failure)	A (n=68)		A+I (n=35)		I (n=37)	
Treatment with Ibrutinib	34	79%	4	24%	3	11%
Treatment without Ibrutinib	9	21%	13	76%	24	89%
No treatment	25		18		10	

TRIANGLE: Overall survival

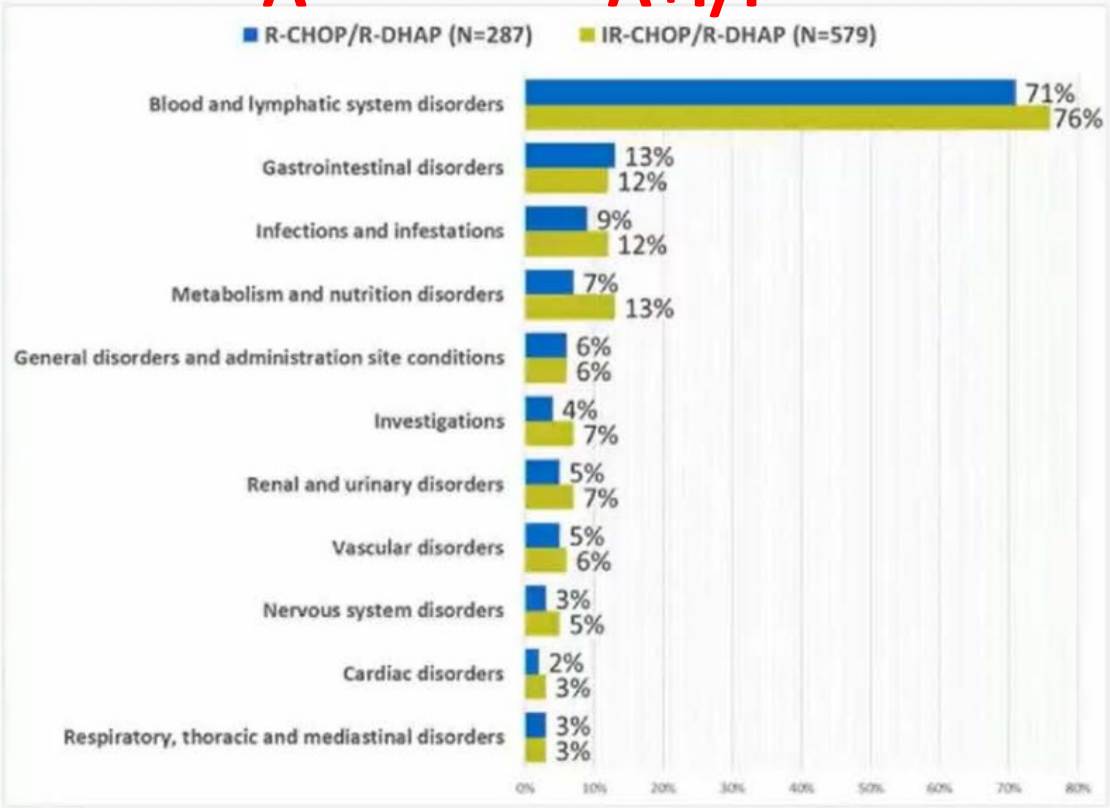


Numbers At Risk												
A	288	270	256	230	181	145	97	63	32	15	2	0
A+I	292	280	262	238	195	142	113	67	42	19	4	2
I	290	281	272	248	197	145	109	77	38	16	4	3

- 3-year OS:
  - A: 86% (MCL Younger exp.: 84%)
  - A+I: 91%
  - I: 92%
- Too early to evaluate statistical significance

TRIANGLE: Grade 3-5 AEs (induction period; >2%)

A A+I/I



Grade 3-5

Adverse Events by Preferred Term	R-CHOP/R-DHAP (N=287)		IR-CHOP/R-DHAP (N=579)	
Thrombocytopenia	169	59%	351	61%
Neutropenia	134	47%	283	49%
Anaemia	62	22%	140	24%
Leukopenia	44	15%	88	15%
Febrile neutropenia	25	9%	70	12%
Lymphopenia	15	5%	38	7%

Grade 5

Adverse Events by System Organ Class	R-CHOP/R-DHAP (N=287)		IR-CHOP/R-DHAP (N=579)	
Gastrointestinal disorders	2	1%	0	0%
Infections and infestations	1	0%	1	0%
Psychiatric disorders	0	0%	1	0%

TRIANGLE: Causes of death

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	A		A+I		I	
Cause of death	**A n=39/288 (13,5%)**		**A+I n=25/292 (8,6%)**		**I n=23/290 (7,9%)**	
Lymphoma	16	5,6%	4	1,4%	11	3,8%
Concomitant disease	11	3,8%	7	2,4%	5	1,7%
Lymphoma and concomitant disease	0	0%	1	0,3%	1	0,3%
Secondary malignancy	1	0,3%	2	0,7%	0	0%
Therapy	4	1,4%	3	1,0%	0	0%
Therapy and concomitant disease	1	0,3%	0	0%	0	0%
Unknown	6	2,1%	8	2,7%	6	2,1%

Conclusions: current Triangle results

Based on FFS (primary endpoint):

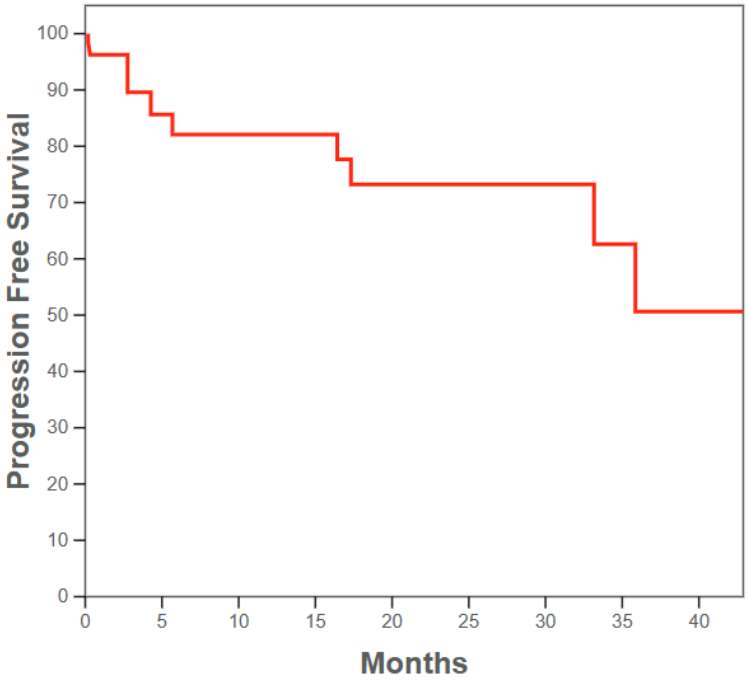
- **A+I (auto SCT + ibrutinib) is superior to A (auto SCT only)**
- **A (auto SCT) is not superior to I (ibrutinib without auto SCT)**
- **currently, no decision whether autologous SCT adds to I (ibrutinib) but toxicity favors Ibrutinib only**

numerical overall survival benefit in the ibrutinib arms (I, A+I)

Conclusions: current Triangle results

1) E’ chiaro che l’attuale standard non è migliore di nessuno dei due bracci di confronto.
2) Aggiunta di ibrutinib con o senza ASCT: efficace e buon profilo di tossicità.
3) Ci vorrà tempo per capire se ASCT serve o no nel braccio con ibrutinib, ma tossicità a favore.
4) Questo studio stabilisce un nuovo standard!

Phase 1/2 Study of Zilovertamab and Ibrutinib in Mantle Cell Lymphoma (MCL), Chronic Lymphocytic Leukemia (CLL), or Marginal Zone Lymphoma (MZL). Lee HJ et al.



Curves	N	Median (95% CI)
Zilovertamab + Ibrutinib	28	35.9 (17.3-0)

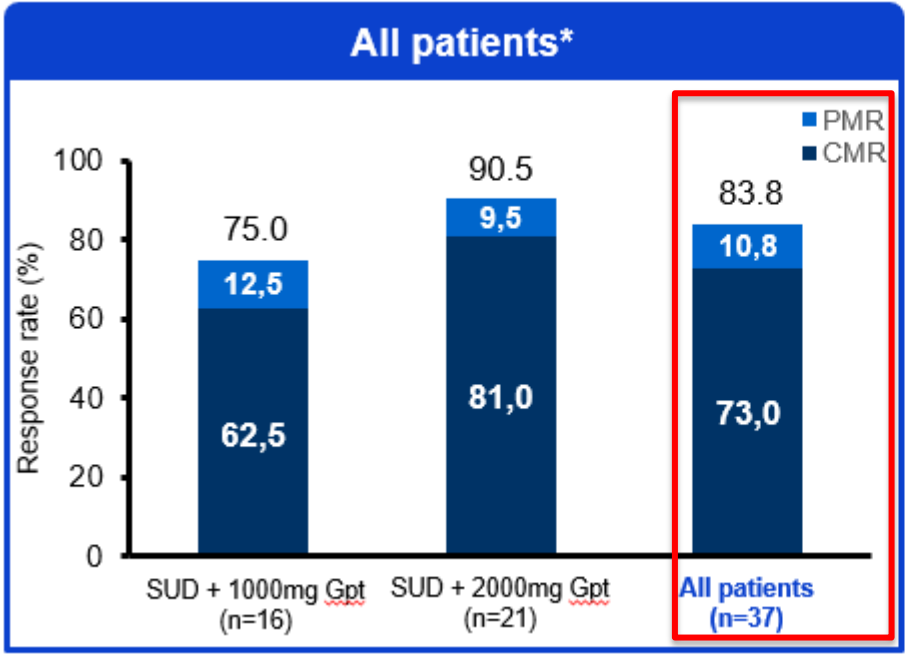
Zilo+Ibr is well-tolerated with a safety profile that is very similar compared with Ibr alone

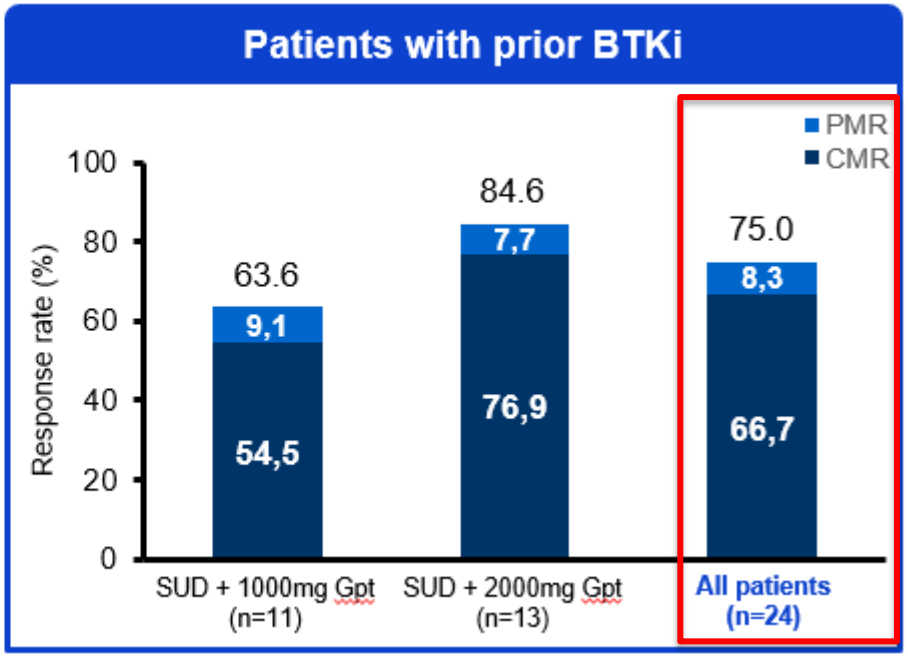
ORR 85.2%, CR 40.7%

Promising activity in TP53 mutated (n=6)

Glofitamab Monotherapy Induces High Complete Response Rates in Patients with Heavily Pretreated Relapsed or Refractory Mantle Cell Lymphoma. Phillips TJ et al.

N=37; Median age 72 (41-84)





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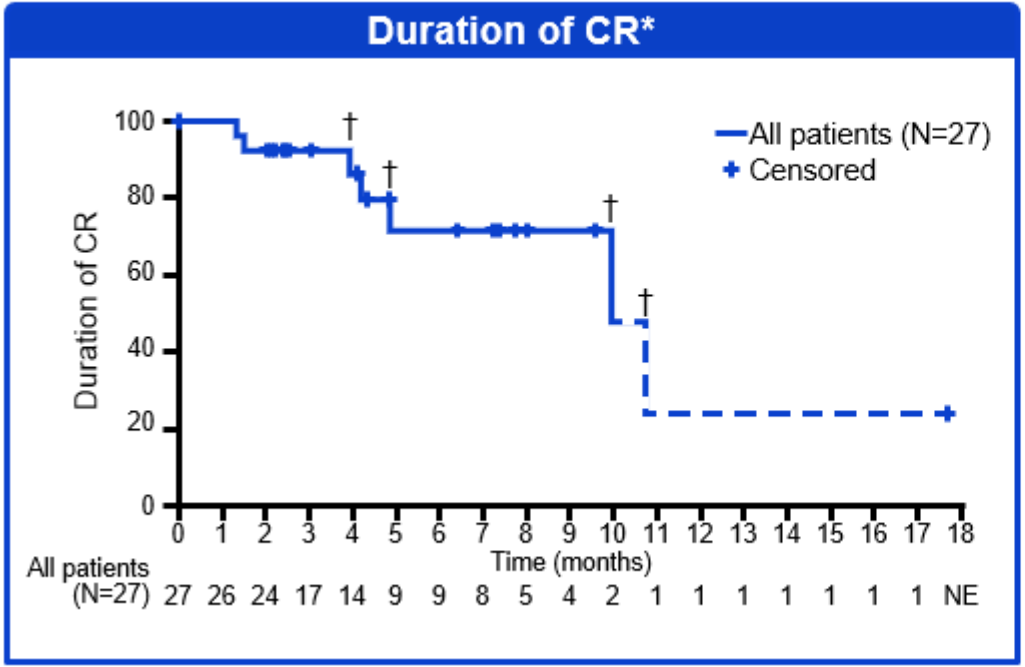
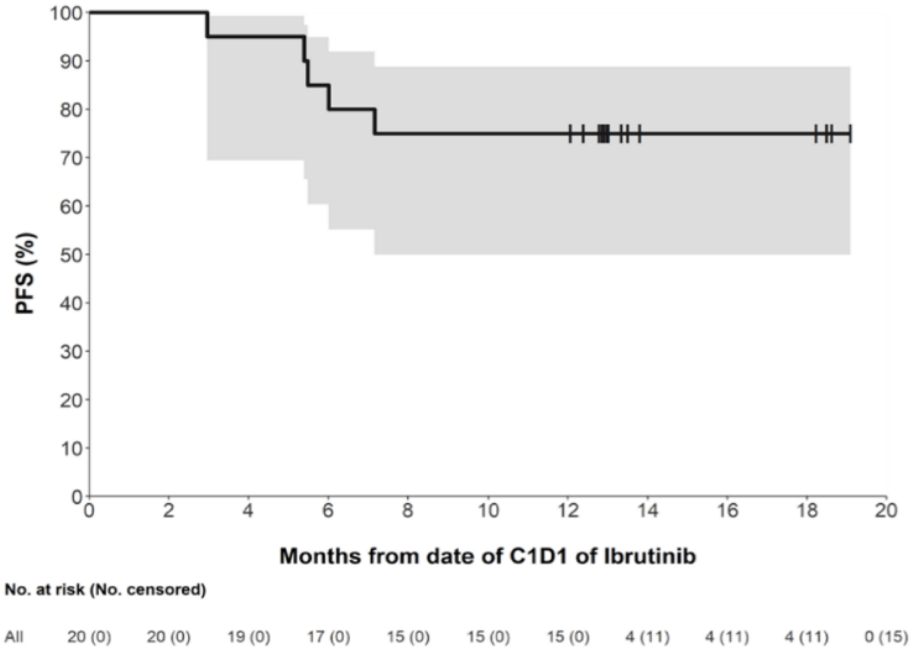


- Median DOCR follow-up: 5.1 months (range, 0.0–18.0)
- Median DOCR: 10.0 months (95% CI: 4.9–NE)
- At data cut-off, **74.1%** (20/27) of patients with a CR remained in remission
- Durable CRs were maintained after cessation of therapy
- Four events due to COVID-19 deaths; when excluded, median not reached and 87% (20/23) CRs were ongoing

- Fixed-duration treatment: maximum 12 cycles (21-day cycles)

Time-Limited Ibrutinib and Tisagenlecleucel Is Highly Effective in the Treatment of Patients with R/R MCL: First Report of the Tarmac Study. Minson et al.



Ibrutinib lowers CRS and increases Car-T cells expansion

N=21.
Prior Tx 2 (1-5); 44% TP53 mut
Ibru 7 days prior to leukapheresis, then 6 months after reinfusion

CR 80%. No difference by risk factors
High CarT cells expansion and peak

Grazie
per l’attenzione