Little Flower Hospital & Research Centre

XVIII IWCLL
International Workshop on CLL
20-23 SEPTEMBER 2019 EDINBURGH

The Leeds Teaching Hospitals NHS
NHS Trust

Geographic Diversity and Management of CLL in Indian Patients

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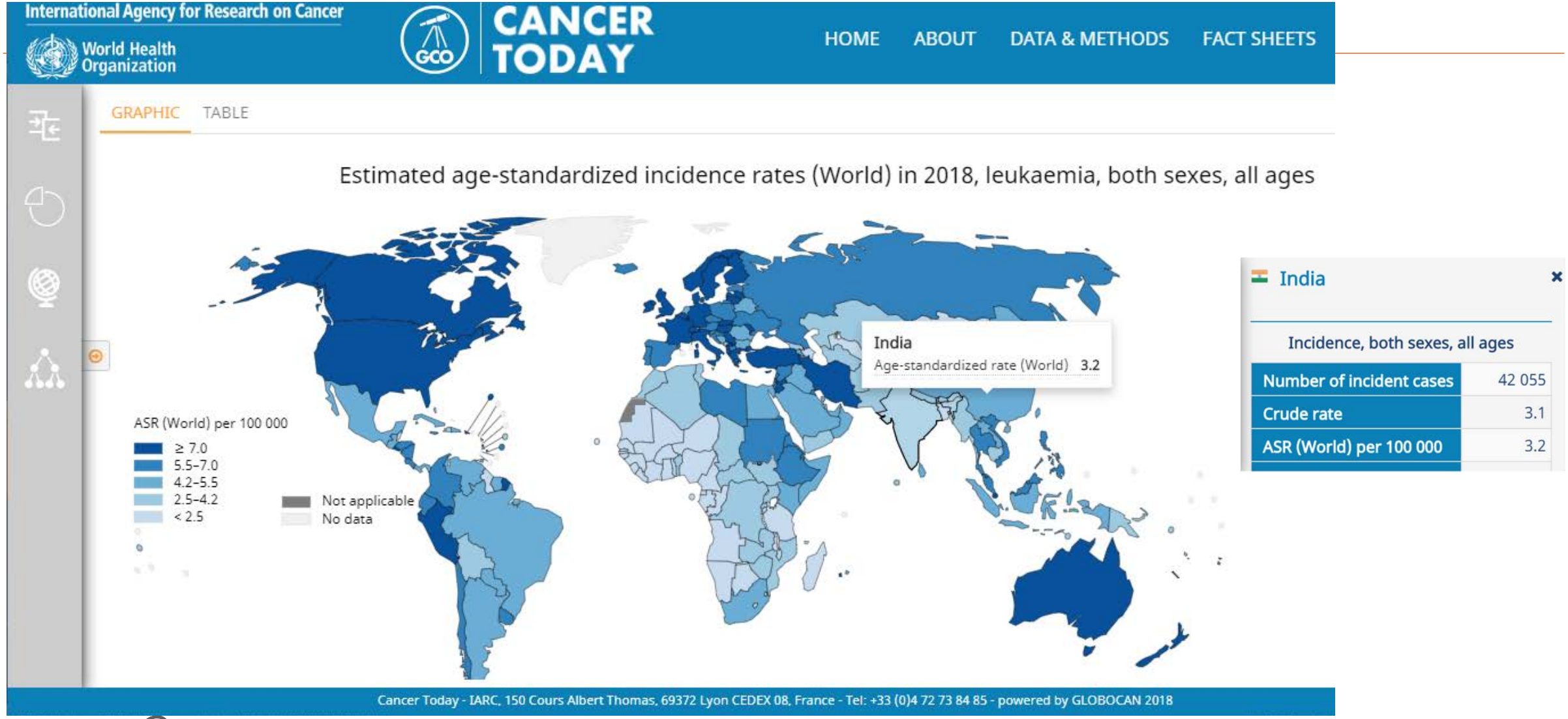
No conflict of interest to disclose

Overview....

- Epidemiology of CLL in India
- Health system of India
- Real life data on CLL
- Opinion of clinicians treating CLL
- Cultural aspects of treatment

GLOBOCAN 2018 - Registry Data on Leukaemia (ICD 10 C91-95)



Epidemiological studies from India.....

Study	Journal volume	Authors	Incidence of CLL
Incidence of Leukaemia. An analysis of 544 cases studied in Calcutta	*J Assoc Phy Ind*, 1962;10:673–76	*Chatterji JB, Ghose S, Ray RN et al*	
Leukaemia at Lucknow- a study of 200 cases	*Ind J Cancer* 1978;15:28-34	*Kushwaha MRS, Bagchi M, Mehrotra RML.*	
A study of 1126 leukaemia cases–epidemiologic and end result analysis.	*Ind J Cancer* 1979 Jun;16(2):8-17.	*Advani SH, Jussawalla DJ, Rao DN, et al*	
Leukaemia pattern in Delhi–a ten year study of 490 cases.	*Ind J Cancer* 1982 May-Jun;19(2):81-6.	*Rani S, Beohar PC, Mohanty TK, et al*	
Epidemiological observations on leukaemia in Kerala (A study of 1016 cases over three years),	*Ind J Haematol*, 1984;2:15-17.	*Varghese PR, Elayidom NB, Joseph CD et al*	
Leukaemia in north-west India..	*ActaHaematol* 1985;73 (4):244.	*Shome DK, Ghosh K, Mohanty D, Das KC*	*ALL 24%, AML29.3%, CML 36.7%, CLL 8%, others 2%*
Pattern of leukaemia: a ten-year incidence study of 242 cases.	*J Postgrad Med* 1989 Oct;35(4):191-5.	*D'Costa G, Siddiqui HM, Pradhan RM, Gupte SS.*	ALL 35.95% , AML 21.9%, CML 38.4% and CLL 2.89%
Incidence of acute and chronic leukaemia in rural area at tertiary care teaching hospital: a five years of study	*Indian Journal of Pathology and Oncology*, Oct-Dec 2016;3(4);710-713	*Baviskar J B.*	*AML 23.07%, ALL 26.28%, CML 33.97%, CLL 15.38%, others 1.28%*

Studies from major centres…

Chronic Lymphocytic Leukemia in India- A clinico-hematological profile

Agrawal N, Naithani R, Mahapatra M et al

Hematology, June 2007; 12(3): 229-233

- All India Institute of Medical Sciences (AIIMS) 2006- 11 year Retrospective study
- Managed around 4000 new patient and 17,500 follow up in haematology OPD per annum during that period
- 95 patients – median age 61years
- Eighteen (60%) young patients and 35 (54%) older patients required treatment with chlorambucil. (Age cut off 55years)
- Median survival of study group was 4 years (8 months-13 years).

Review article on epidemiology of NHL in India

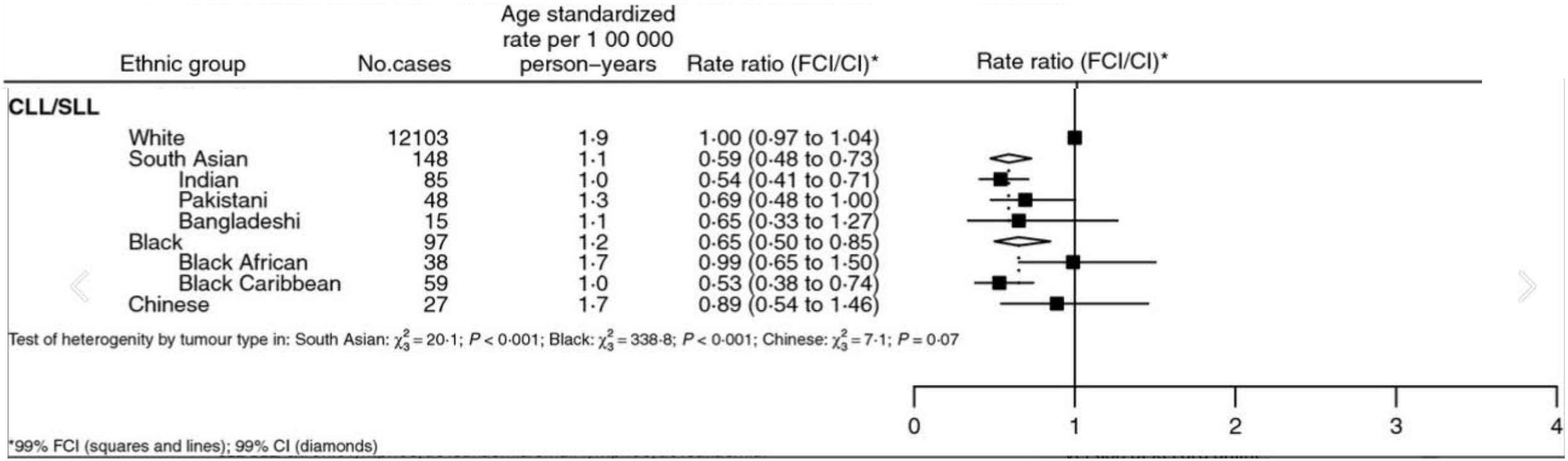
Table 3. Subtype distribution of lymphoma across the world and India

Subtype	India			China	USA	Korea	Japan	Thailand
	Arora et al. [14]	Naresh et al. [13]	Sahni and Desai [31]					
LBL-T	*0.42*	*6.06*	*6.9*		*1.09*	*4.79*	*0.7*	*4.11*
LBL-B	*2.21*	*0.6*	*0.2*		*3.75*	*13.88*	*0.2*	*0.88*
Total LBL	2.81	6.67	3.1	5.2	4.85	18.68	0.9	4.99
DLBCL	46.85	33.8	50.2	41.2	31.29	37.67	36.4	51.42
FL	10.51	12.6	13.1	5.8	13.81	2.10	20.1	8.38
BL	3.38	1.8	3.0	1.91	1.42			
MALT	2.17	6.1	2.7	6.31	4.19	15.24	4.6	4.16
CLL/SLL	3.95	5.6	5.4	4.61	21.91	2.24	1.6	2.58
MCL	1.59	3.4	2.1	3.15	2.18	2.26	3.0	1.04
HCL	0.77	0.01	0.1	–	1.44	0.12	–	–
LPL	2.42	0.6	0.1	0.79	2.65	0.32	0.2	0.82
SMZL	0.32	0.2	0.5	0.35	–	0.12	0.4	–
PMBCL	0.60	0.2	0.1	–	–	0.37	0.4	0.88
NMZBCL	0.65	1.9	0.2	0.09	–	1.25	1.5	–
ENKTCL	0.92	0.7	1.1	17.1	0	5.42	1.7	–
PTCL, NOS	5.91	1.9	4.6	3.99	3.27	4.87	5.0	13.14
ALCL	5.04	4.1	4.8	3.53	1.11	2.40	2.2	3.67
AILD	1.39	1.0	0.4	3.33	0.23	1.0	5.7	1.81
ATLL	0.08	–	–	–	–	0.02	11.0	–
SPTCL	1.02	0.1	–	0.97	–	0.39	–	0.49
PCCD30+LPD	0.05	0.1	0.2	0.67	–	0.18	–	0.27
MF/SS	2.17	0.9	0.6	0.25	2.29	0.48	0.5	1.26
HSL	0.55	0.01	–	0.25	–	0.07	–	–
EATCL	0.025	–	–	0.13	–	0.39	–	–
Others				–	9.34	1.87	3.0	1.04
Total, n	4,026	2,773	935	5,549	77,490	4,337	2,260	1,826

Epidemiology of Non-Hodgkin's Lymphoma in India Oncology 2016;91(suppl 1):18–25. Nair R, Arora N, Mallath MK

Incidence of Hematological Malignancies by Ethnic Group in England, 2001–7

Cancer	Ethnicity	Male				Female			
		England		Globocan	CIV	England		Globocan	CIV
		Cases	ASR	ASR	ASR	Cases	ASR	ASR	ASR
Leukaemia	White	18 381	7·8			13 324	4·9		
	Indian	214	5·3	3·5	4·4	163	3·9	2·6	3·2



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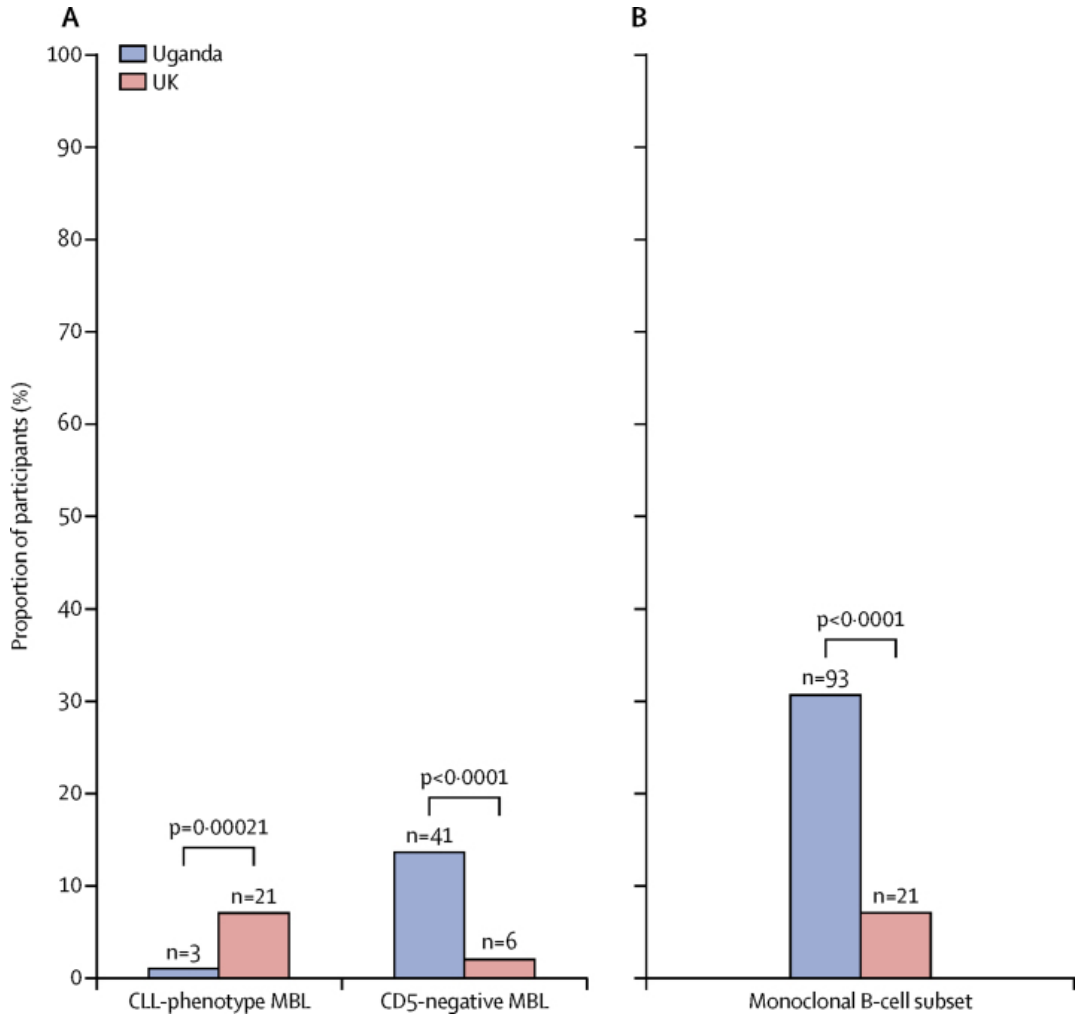
British Journal of Haematology, Volume: 163, Issue: 4, Pages: 465-477, First published: 14 September 2013, DOI: (10.1111/bjh.12562)

Comparison of MBL between Ugandan and the UK population

Study designed to find the prevalence of Monoclonal B-cell lymphocytosis (MBL) in healthy rural Ugandan population and comparing it with age-and-sex-matched populations from the UK.

This allowed comparison of prevalence across different populations independently of health-care provision.

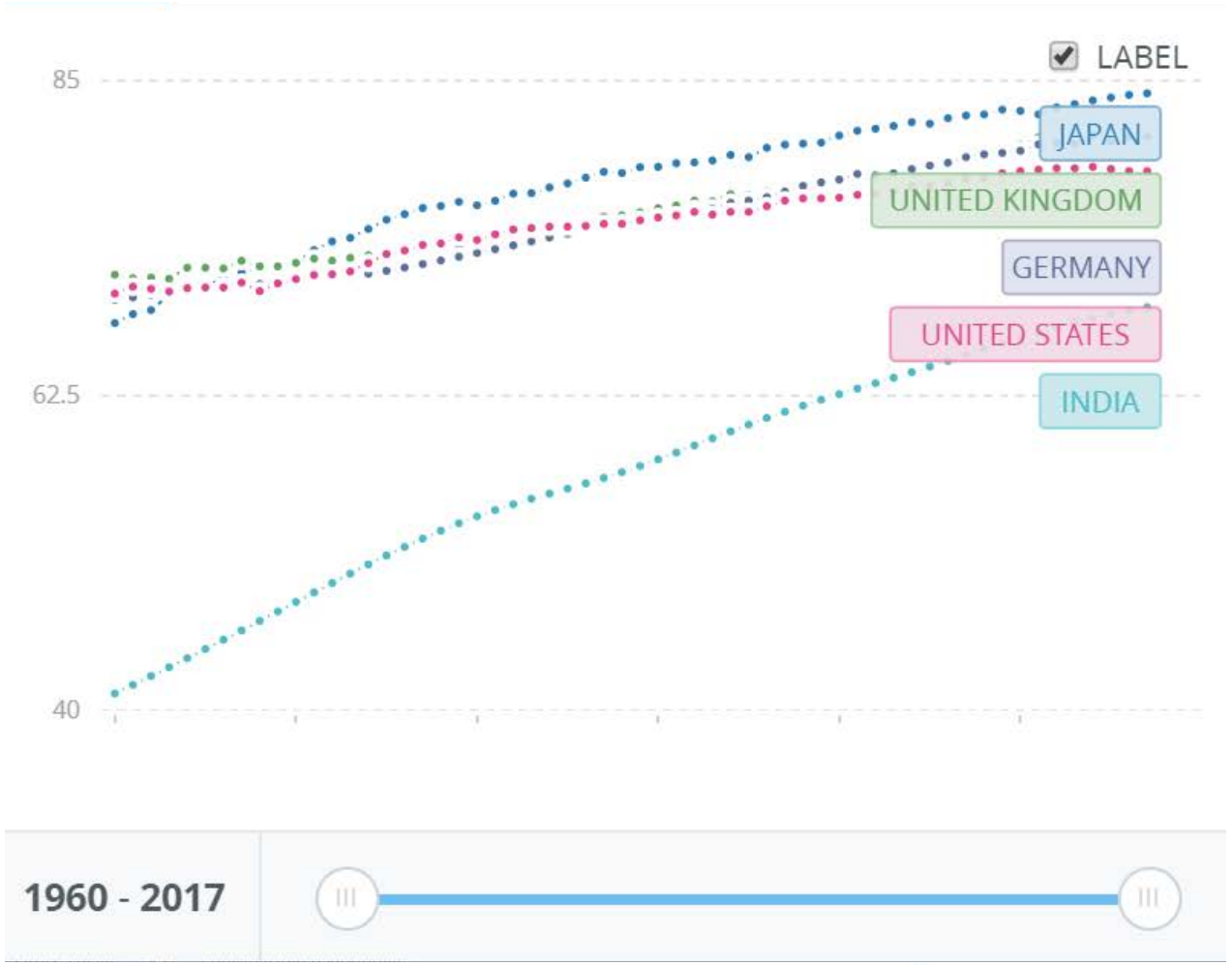
The prevalence of MBL is broadly similar in rural Uganda and the UK, but substantial qualitative differences exist, with a lower prevalence of CLL-phenotype MBL and higher prevalence of CD5-negative MBL in the Ugandan cohort than in the UK cohort.



Lancet Haematology. 2017 Jul; 4(7): e334–e340. Monoclonal B-cell lymphocytosis in a hospital-based UK population and a rural Ugandan population: a cross-sectional study Andy C Rawstron, Prof, PhD,[a]

Does this mean incidence is really low in Indian population?

- In India patients usually present to clinicians only if symptomatic
- Identifying asymptomatic patients from blood test for other reasons is very limited
- Average life span of an Indian is below the median age for CLL



India- A Land of Diversity

- 1.34 billion (Census, March 2017)
- 29 states and 7 Union territories
- 17 major languages and 900 dialects
- Birthplace of 4 major religions of world
- Some of the most beautiful monuments to the dirtiest slums
- Diversity in culture, race, language, religion, economic status etc
- >72% live in village

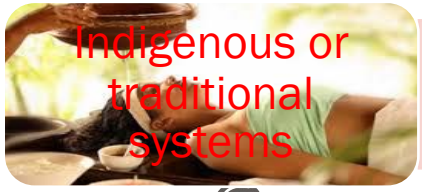
Health-care System in India

- Universal health-care system
- "Right to health" for all.
- National Health Policy-large **rural and poor population**
- Rural: **Three-tier** system: a sub-centre, a primary health centre, and a community health centre.
- Urban areas: **Two-tier** system with urban health centre followed by general hospital

- Only a fraction of patients can afford
- Mainly urban
- Health insurance: 10% of the population

MISSION HOSPITALS

- "No profit no loss basis"
- Fragmented service



- Ayurveda, Siddha, Homeopathy and Unani

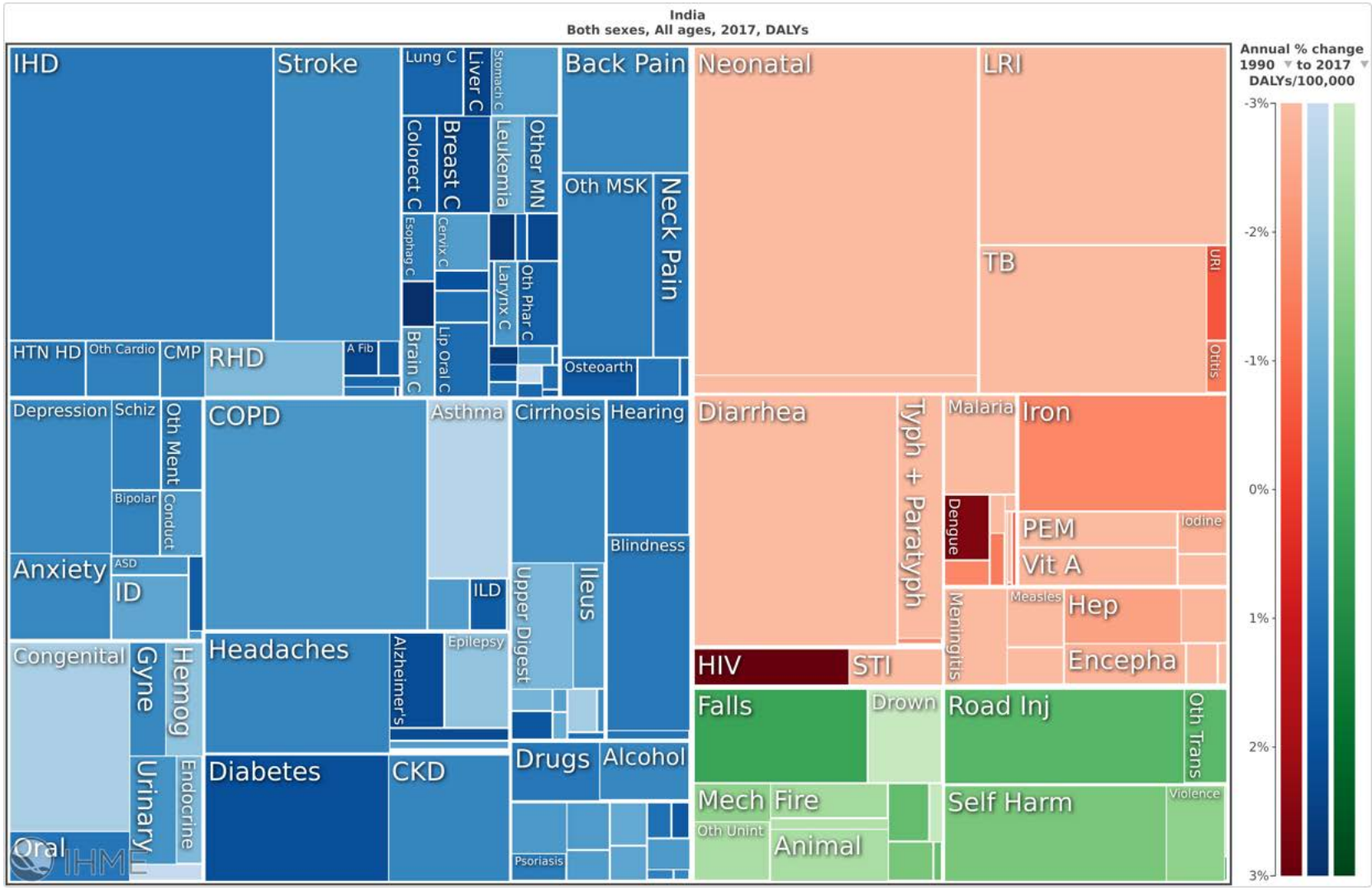
- GOVERNMENT ROLE- Central-Financing, legislation, and regulation

  State- financing, regulation, and direct provision of services
- PUBLIC SYSTEM FINANCING-General tax revenue
- PRIVATE INSURANCE ROLE- <4% of total expenditure
- PRIMARY CARE-Mainly public; some private, especially in urban areas
- HOSPITALS- Private nonprofit and for-profit (~63% of beds) and public
- PRIMARY CARE- Registration with GP is not required and there is no gatekeeping
- TOTAL HEALTH EXPENITURE-(2013–2014) 4.02 % of GDP. Government expenditures 1.5% (lower than the average for low-income countries.)
- **70% of total health expenditure is out-of-pocket payment**
- Despite various government health schemes,<20% is covered by any form of health coverage.
- **Health Care Spending per Capita, 2014 is $215**
- **Number of Practising Physicians per 1,000 Population, 2014- 0.7**
- More than 63 million Indians are faced with impoverishment every year because of catastrophic health care costs.

Disease Burden— Disability-Adjusted Life Years(DALY)

Heatmap (causes)- Annual % change 1990 to 2017 DALYs/100,000

- Growing burden of non-communicable diseases including cancer
- Reducing burden of communicable diseases



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GBD 2017 @ Indian Council of Medical Research, Public Health Foundation of India and Institute of Health Metrics and Evaluation

Biology of CLL in Indian Patients.....

	Indian study	Western study
17p-	13.3%	7% [a]
11q-	13.3%	18% [a]
ZAP70	37%	47% [b]
CD38	44%	29% [b]
ZAP70+C38	26%	23% [b]
Unmutated IGVH	36%	40% [c]
VH1-69; VH3-73; VH3-48; VH2-70; VH3-23; and VH1-03.	10%, 7%, 6%, 5%, 4%, 3%	[e]
TP53 mutation	18%	10%[d]
β2-microglobulin level	36%	33% [f]

- Limited number of articles
- 2016 ASH Abstract from All India Institute of Medical Science
- 100 patients evaluated

[a]Genomic aberration and survival in chronic lymphocytic leukemia N Engl J Med. 2000 Dec 28;343(26):1910-6.
[b]Combined analysis of ZAP-70 and CD38 expression as a predictor of disease progression in B-cell chronic lymphocytic leukemia , Leukemia (2005) 19, 750–758
[c]Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. Blood. 1999;94(6):1848–54.
[d]The Prognostic Value of *TP53* Mutations in Chronic Lymphocytic Leukemia Is Independent of Del17p13: Implications for Overall Survival and Chemorefractoriness Clin Cancer Res. 2009 Feb 1;15(3):995-1004.
[e]Chronic lymphocytic leukemia patients with a V1-69 gene rearrangement do not have inferior survival with respect to patients that express other unmutated VH genes," Leukemia Research, vol. 31, no. 2, pp. 245–248, 2007.
[f] Predictive value of β2-microglobulin (β2-m) levels in chronic lymphocytic leukemia since Binet A stages. Haematologica. 2009 Jun; 94(6): 887–888.

NATIONAL CANCER GRID

COLLABORATION FOR CANCER CARE

Management of CLL, Indian Guidelines....

NON HODGKIN LYMPHOMA - Low Grade (CLL/SLL, FL, MZL)

1. **Stage 1 & 2**
   Asymptomatic patients can be observed or treated with local RT
   Combined modality chemo-immunotherapy x 3 cycles→ local RT

2. **Stage 3 & 4- Asymptomatic**
   Observation alone or Single agent Rituximab weekly x 4 followed by Maintenance 2 to 3 monthly for 2 years.

3. **Stage 3 & 4- Symptomatic***
   Chemo-immunotherapy x 6 cycles followed by Maintenance Rituximab for 2 years

> ***Note:*** Symptomatic* disease is largely based on the BNLI Criteria which include the following: Subjective symptoms, threatened end organ dysfunction, Bulky disease, Cytopenias, disease progressing steadily (doubling time short).

Choice of regimen should be based on patient age (≤ 65yr or ≥65yrs), co-morbidities. It should be dictated by the local expertise. Common regimens include,

- **CVP +/-R**
- **CHOP+/-R**
- **Bendamustine+/- R**
- **In CLL, also consider FCR, Ofatumumab-Chl, Alemtuzumab-Rituximab (high risk CLL).**

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National Cancer Grid April 2017

Management of CLL, Indian Guidelines….

Management of Lymphomas: Consensus Document 2018 by an Indian Expert Group

Table 18 Management of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) [44–48]

Always

Fit for treatment

No mutation of del (17p): FCR × 6 (or, B-R × 6 is an option)

Mutation and/or del (17p): Ibrutinib OR High dose methylprednisolone-R

In the young, due consideration for Allogeneic HSCT must be given

Unfit for treatment with full dose FCR

No mutation or del(17p): B ± R × 6,

FC-R × 6 (dose reduced), CVP ± R × 6,

Chlorambucil ± R

Mutation del (17p): consider ibrutinib

[illegible] or constitutional B symptoms

Newer Therapy Options

Indolent B-Cell Lymphoma

Chronic Lymphatic Leukemia/Small Lymphocytic Leukemia

Consider participation in clinical trial with new agents.

1. Ibrutinib
2. Venetoclax (post-ibrutinib)
3. Idelalisib
4. Obinutuzumab or ofatumumab (especially in rituximab refractory)
5. Chemo-immunotherapy
    1. Rituximab (or obinutuzumab in rituximab refractory)
    2. Chemotherapy: fludarabine-cyclophosphamide v/s. CHOP v/s. ibrutinib-bendamustine, etc.
6. Non-chemo combination therapies
    1. Ibrutinib + Venetoclax
    2. Rituximab + Ibrutinib
    3. Rituximab + Venetoclax
7. Post-induction maintenance therapy must be considered in patients who have partial or complete response.
8. p53 mutated (or 17p deleted) disease is generally resistant to conventional therapies. In this subset of patients, allogeneic bone marrow transplant (BMT) must be considered in the young (especially those with a complex karyotype).

Indian J Hematol Blood Transfus. 2018 Jul; 34(3): 398–421.

Real-life data from a hospital in Delhi.

1250 bedded hospital
Private , for-profit hospital
Pay-out-of-pocket and private insurance

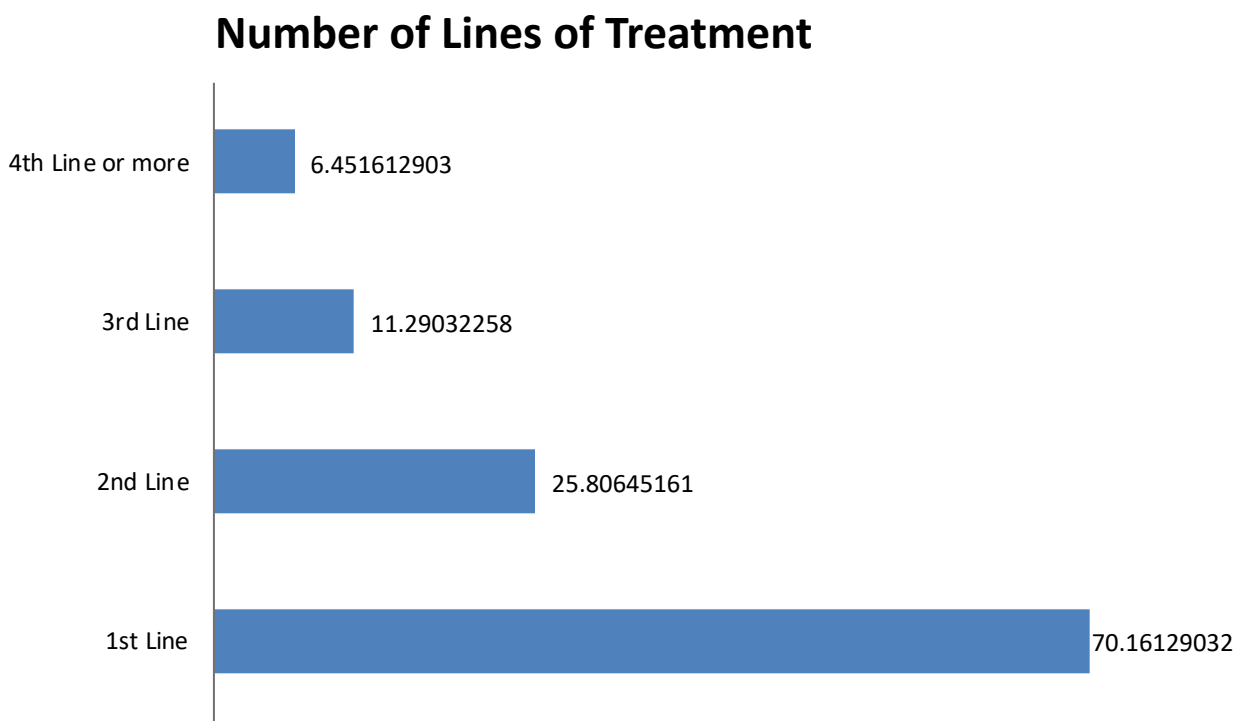
Acknowledgement to Dr. Nitin Sood for providing the data

- Retrospective case record audit
- Retrieved records from hospital electronic record with diagnosis of CLL
- Records from May 2009 to May 2019
- N=124

	N=124
Median Age (Range)	69 (40-91)
Female:Male	29:95
Cytogenetics done	40 (32%)
del17p positive (prior to 1st line)	4/28 (14.2%)
Other cytogenetic abnormalities	13/28 (46.4%)
del17p positive (previously treated patients)	2/12 (16.7%)
Other cytogenetic (previously treated patients) abnormalities	1/12(8.3%)

Indication for treatment

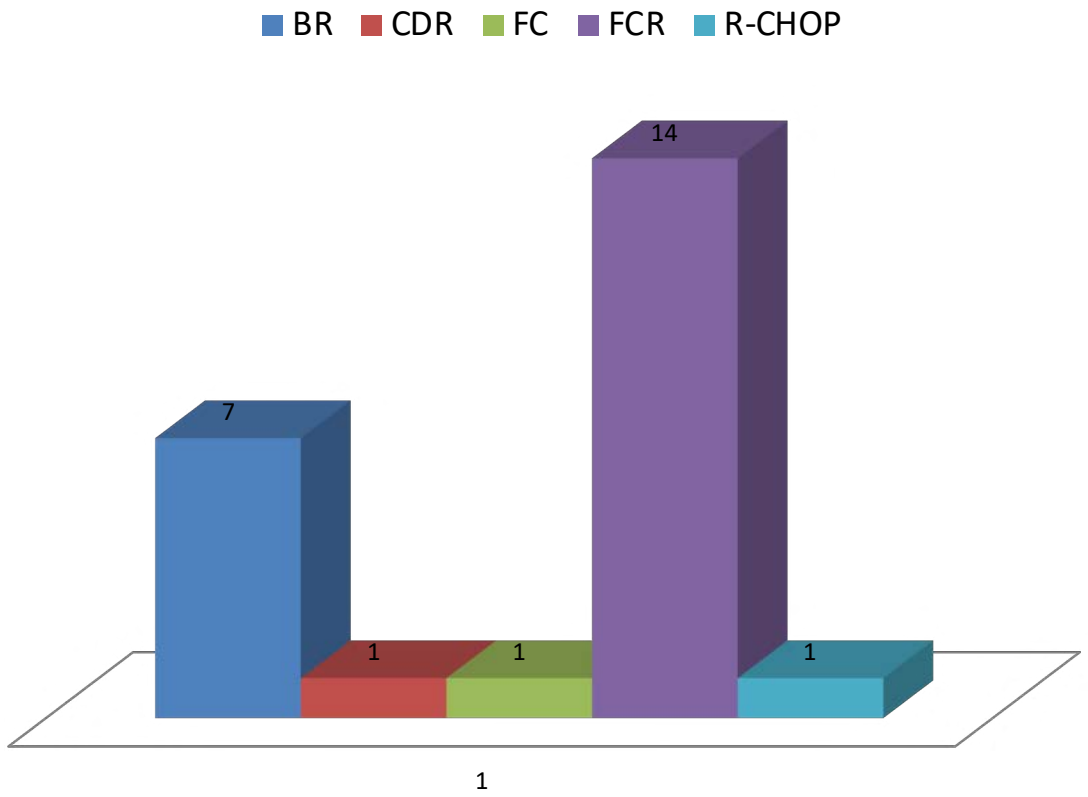
	N(%)
Patients requiring treatment	87 (70%)
Indication for treatment	N=87
Anaemia	35 (40%)
Thrombocytopenia	9 (10%)
B Symptoms	27 (31%)
Progressive lymph nodes	23 (26%)
Progressive lymphocytosis	41 (47%)
Symptomatic spleen	8 (9%)
others	5 (6%)



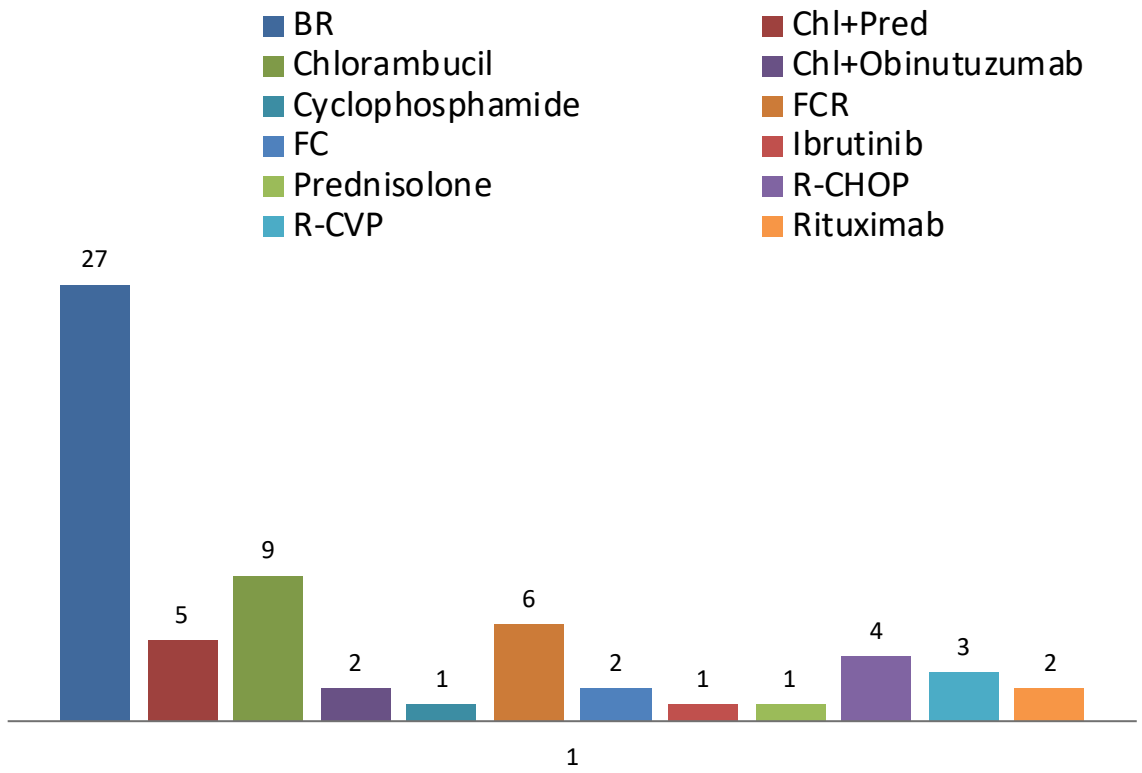
7 patients had major infection requiring hospital admission

Chemotherapy given

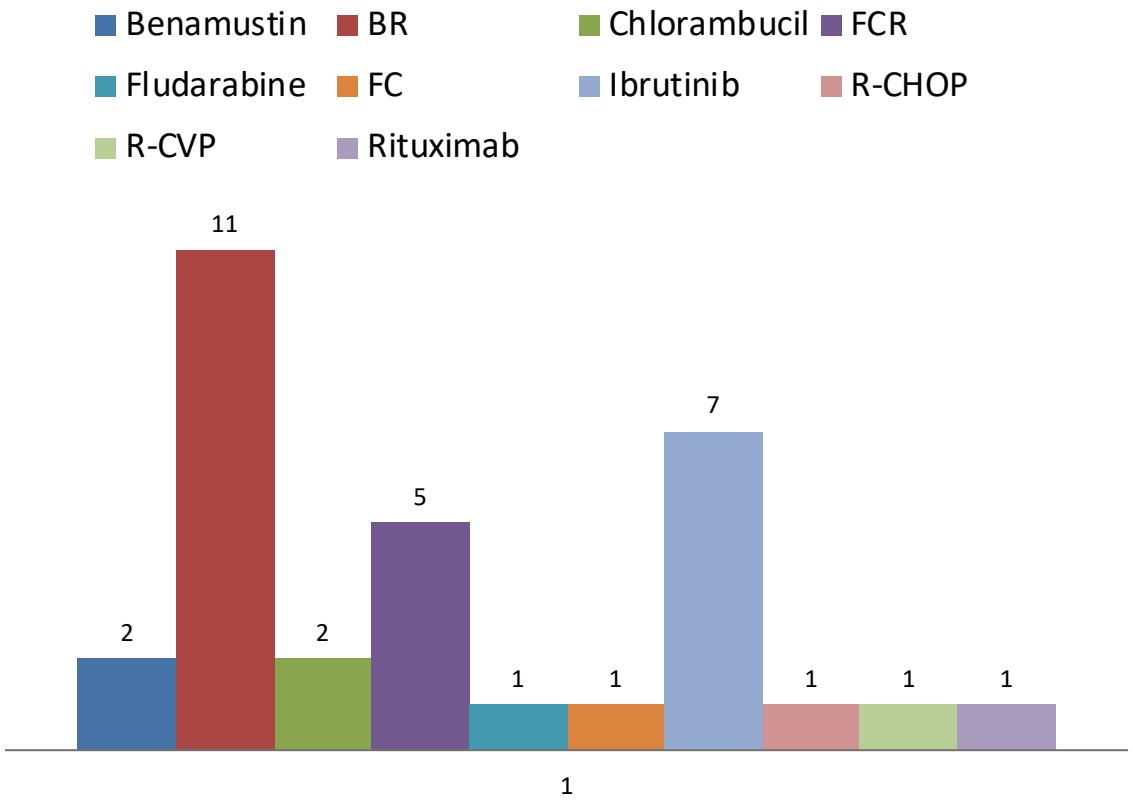
<60 , n=24



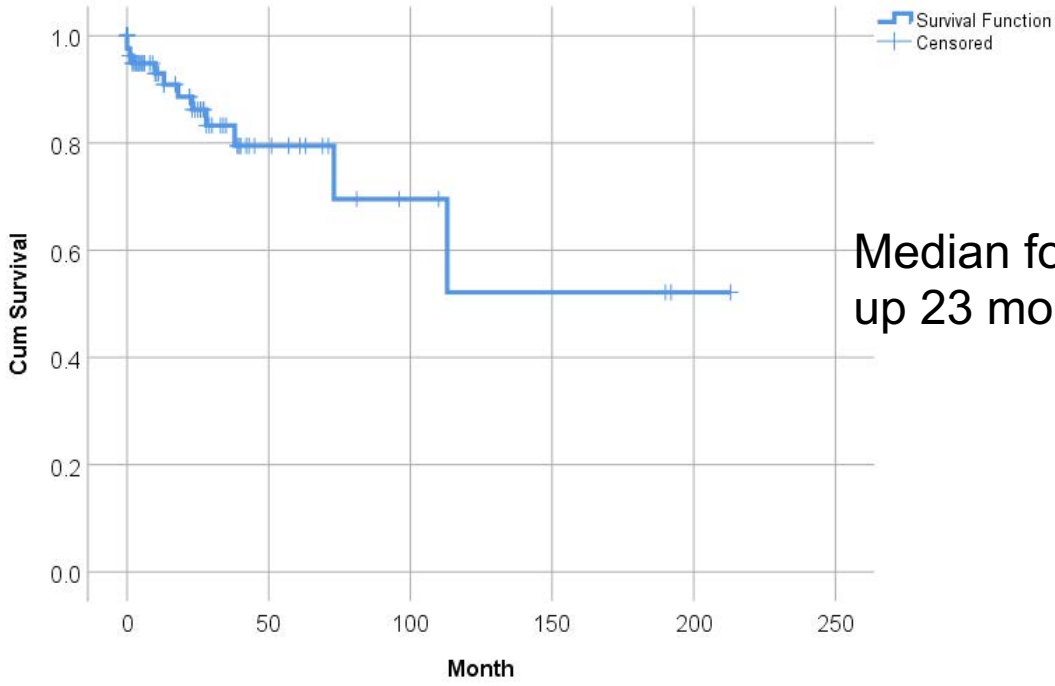
>60, n=63



2nd line treatment, n=32

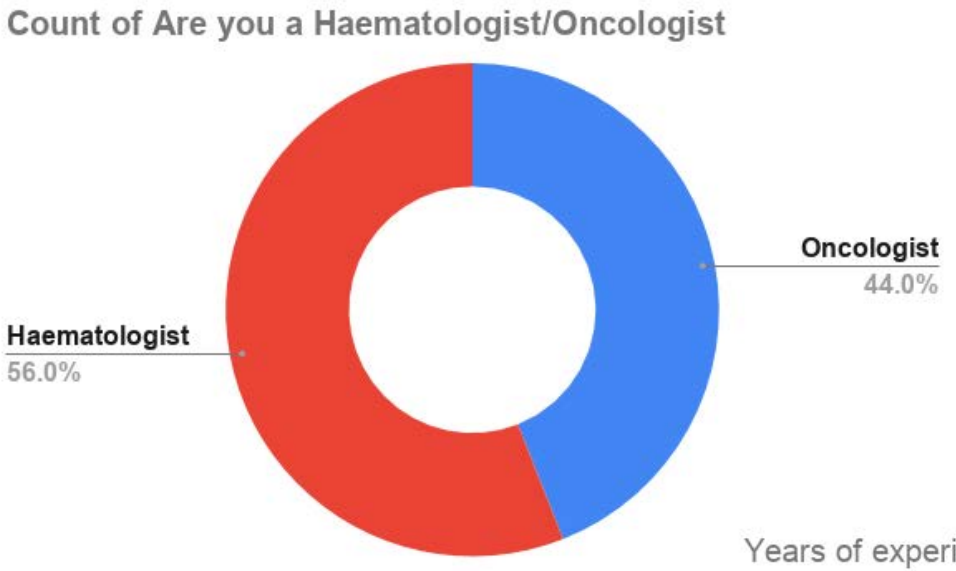


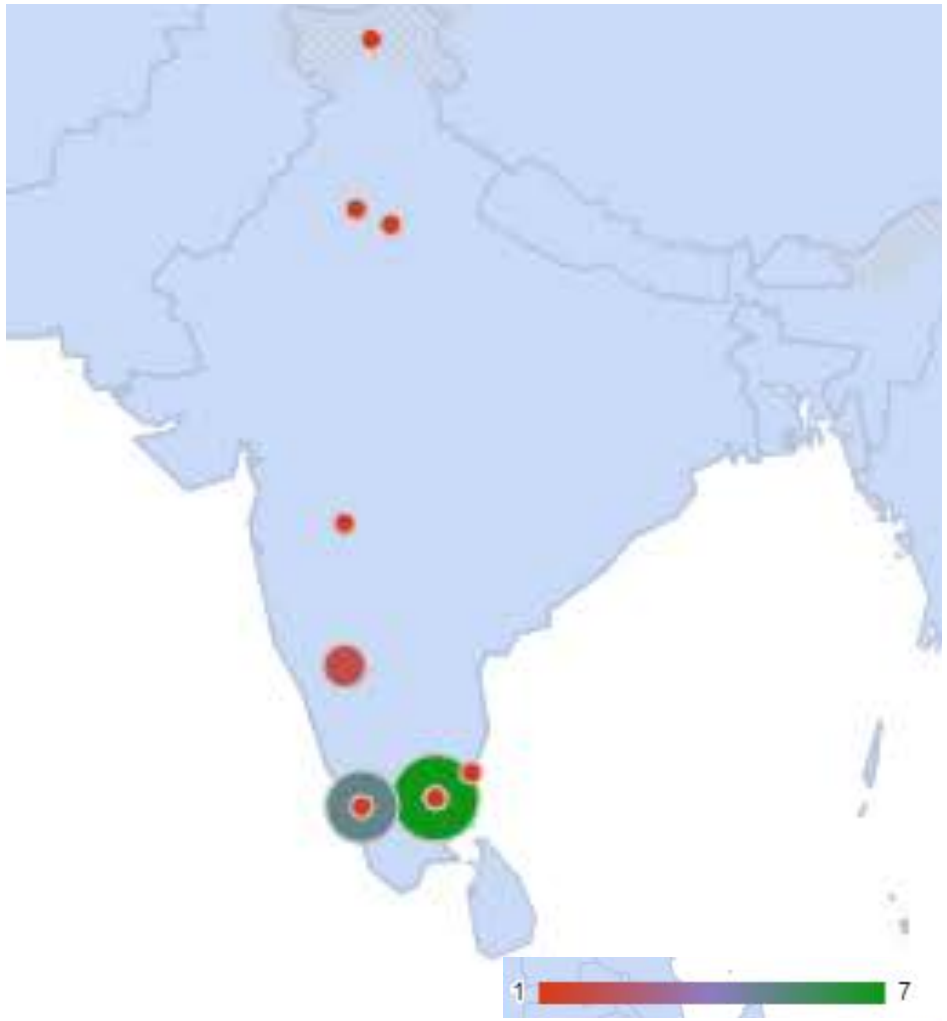
Overall Survival



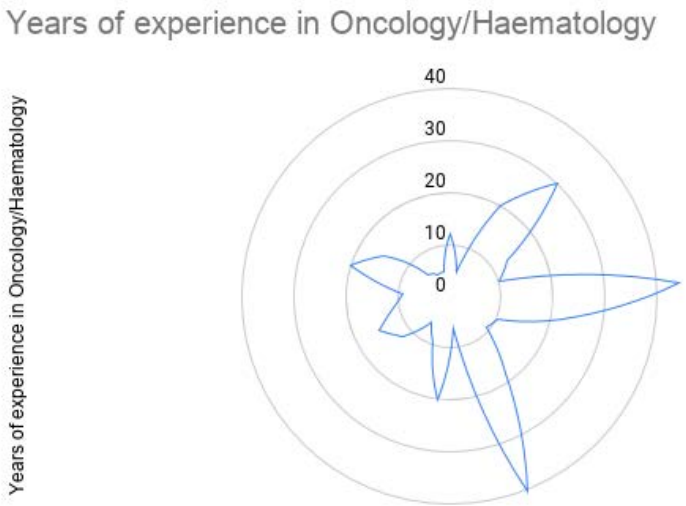
Median follow up 23 months

Survey on Management of CLL from Clinicians

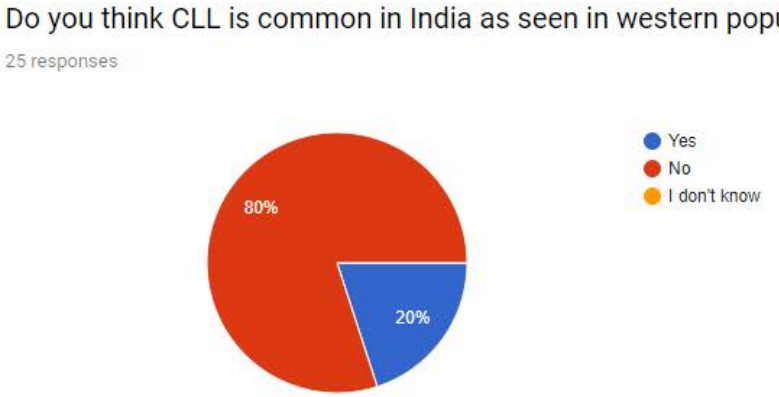


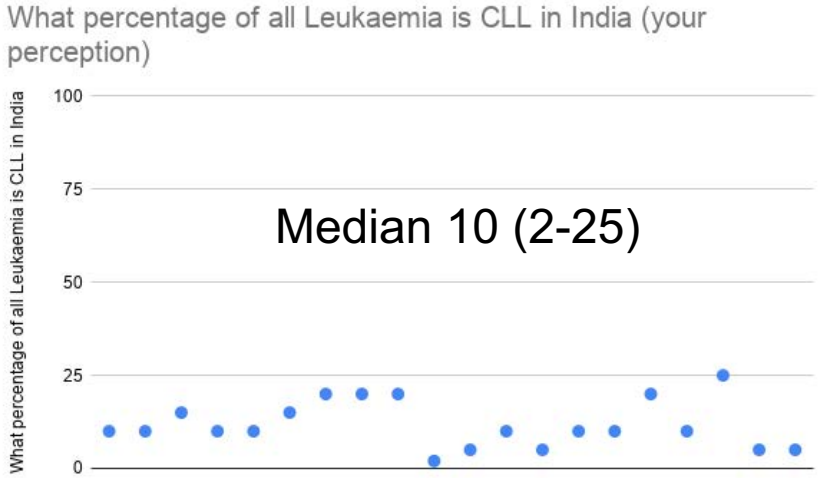


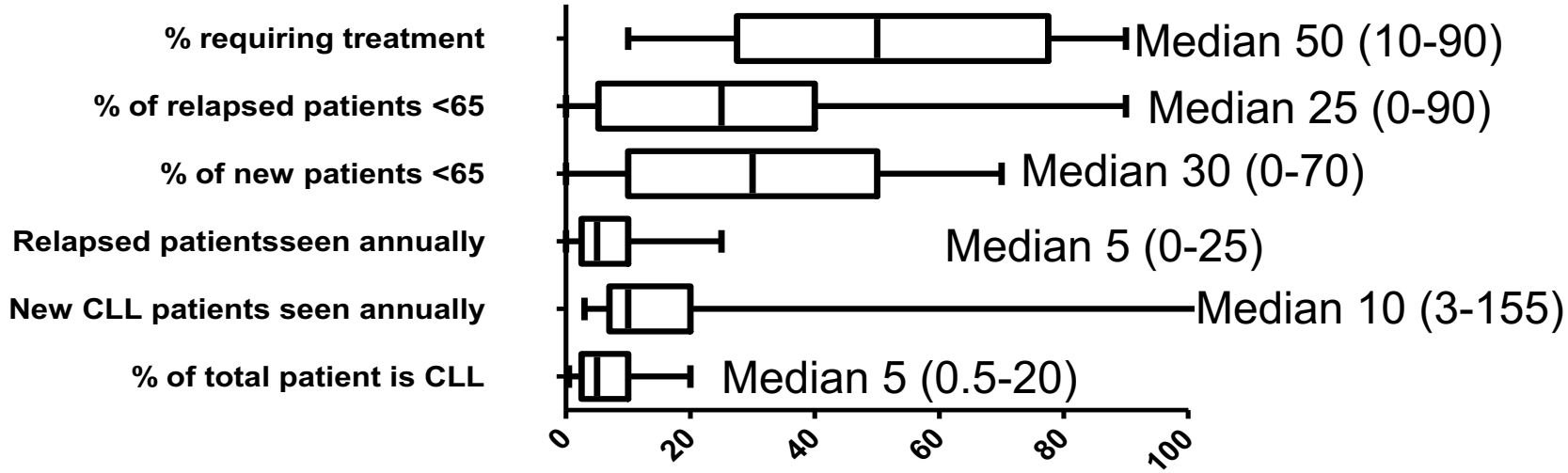
Google survey form was used.
23 questions
10-15mts survey
Send to 188 clinicians.
25 responded!!



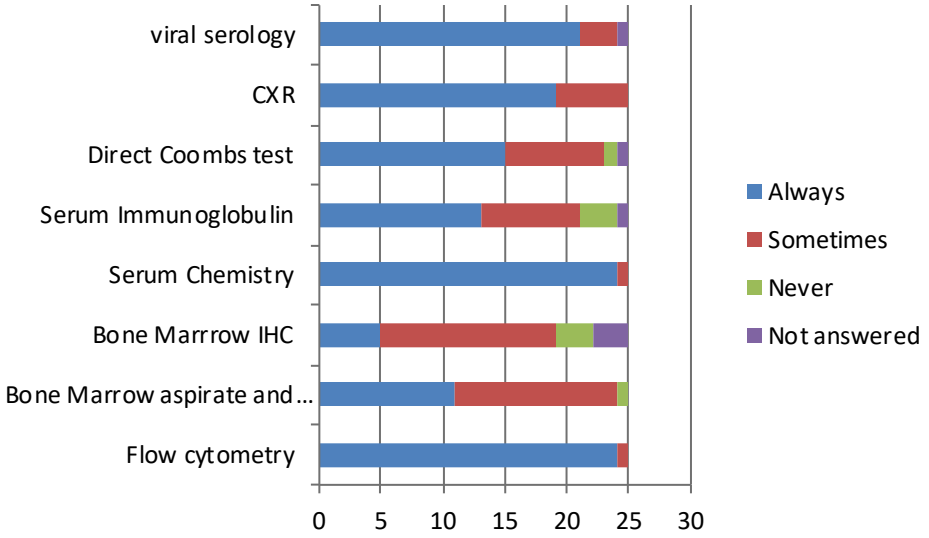
Demographics

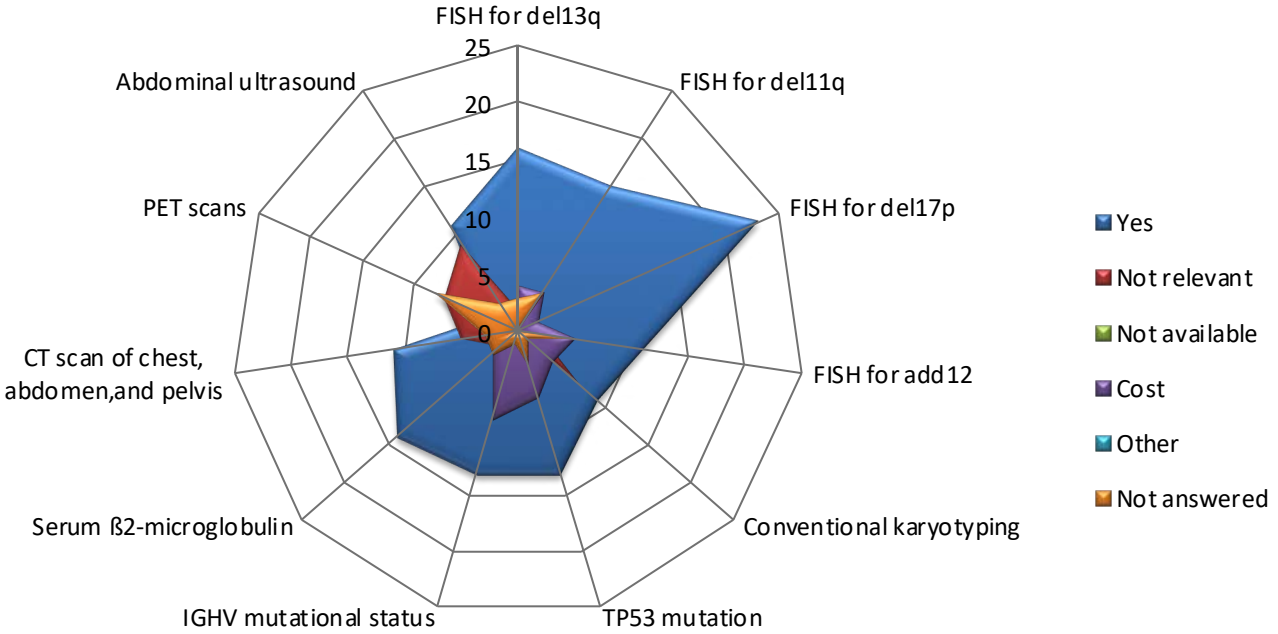




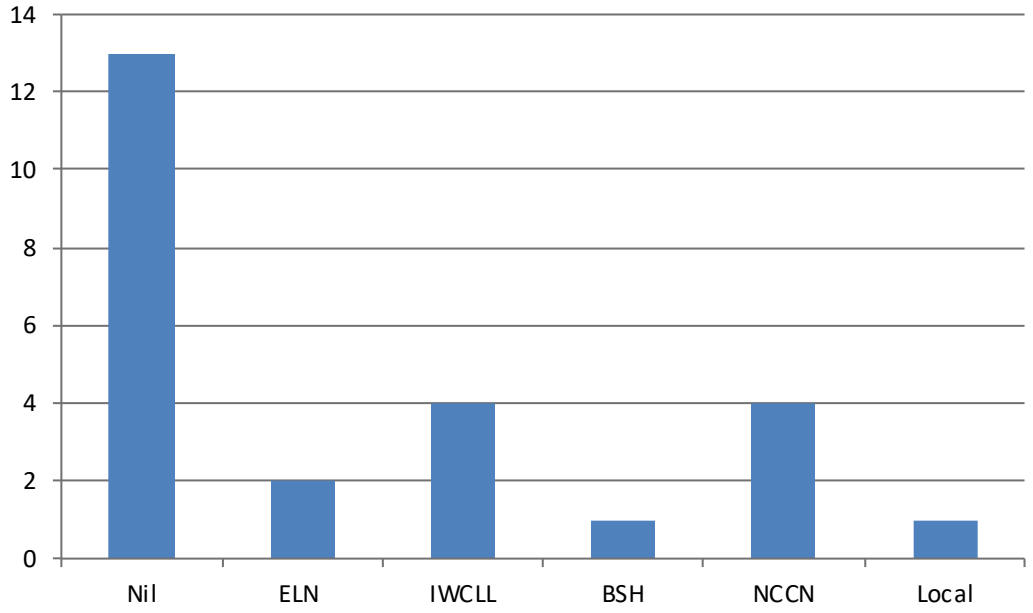


Investigations done…

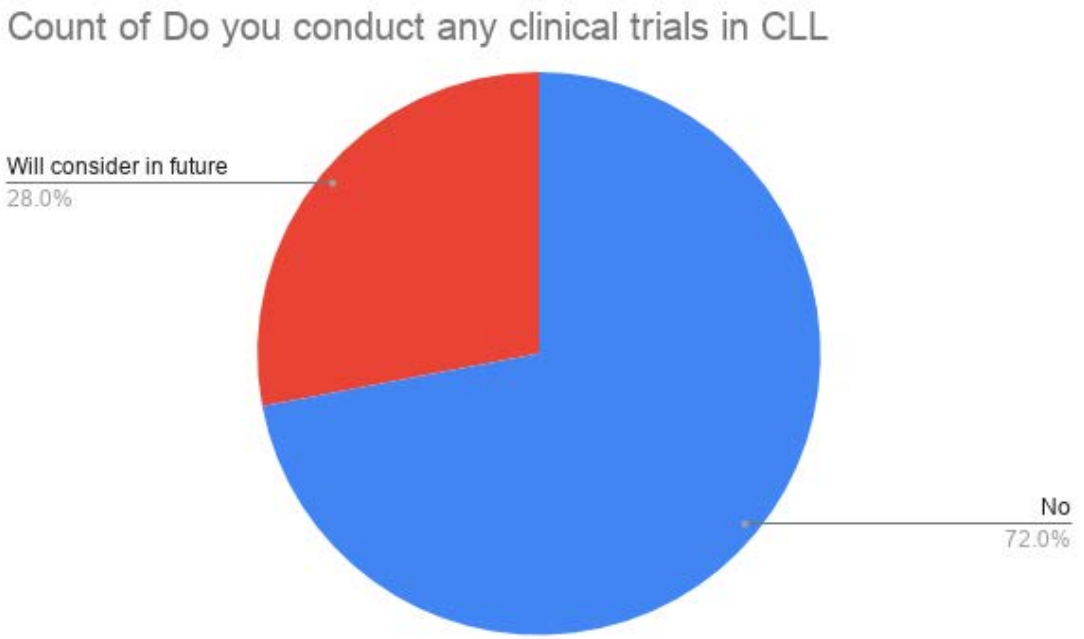




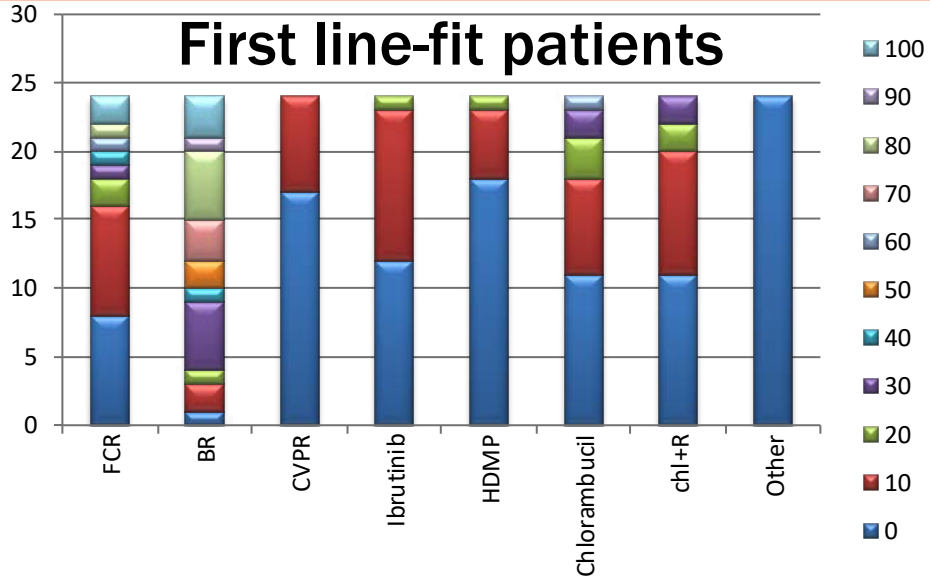
Guidelines followed and Clinical trials...

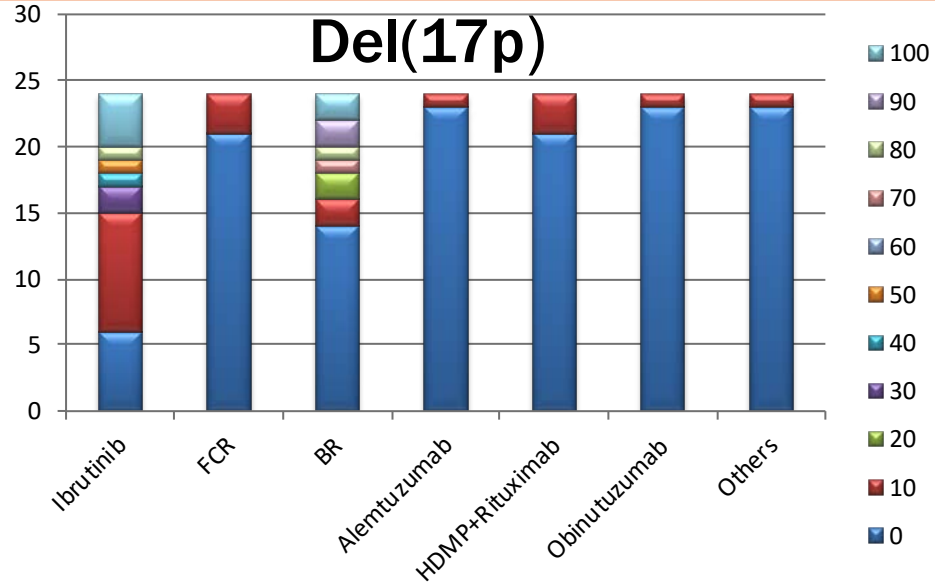


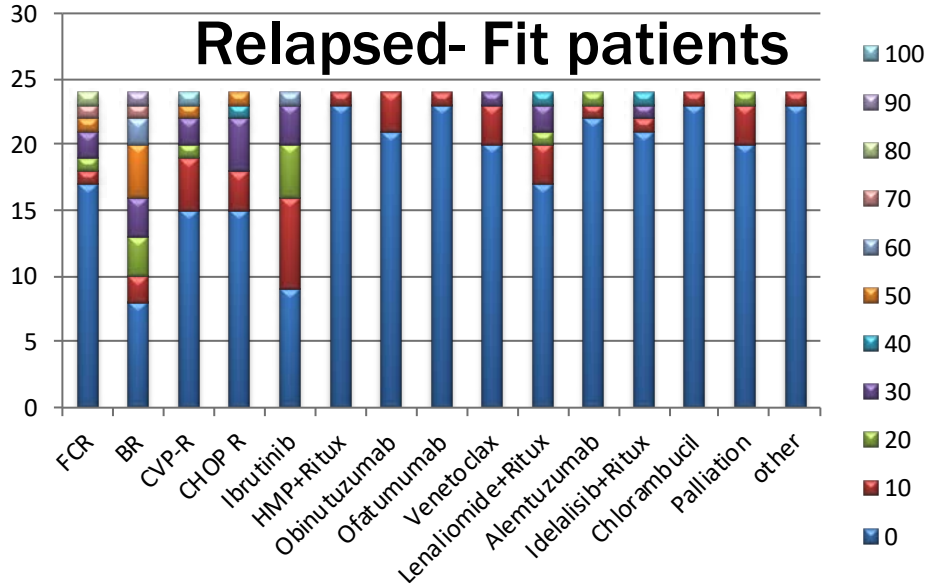
ELN- European leukaemia network
IWCLL- International working committee for CLL
BSH- British society of haematology
NCCN- National Comprehensive Cancer Network

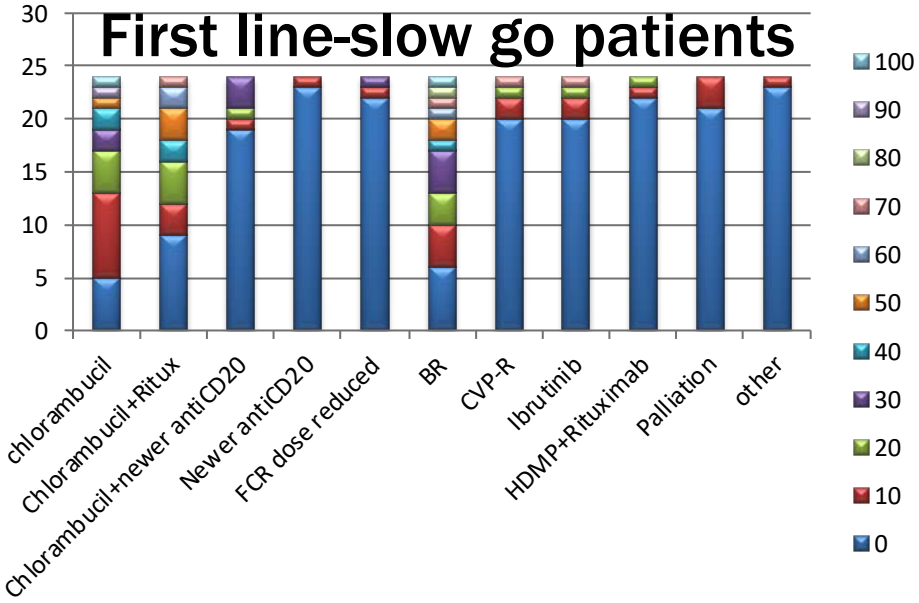


Treatments used.....





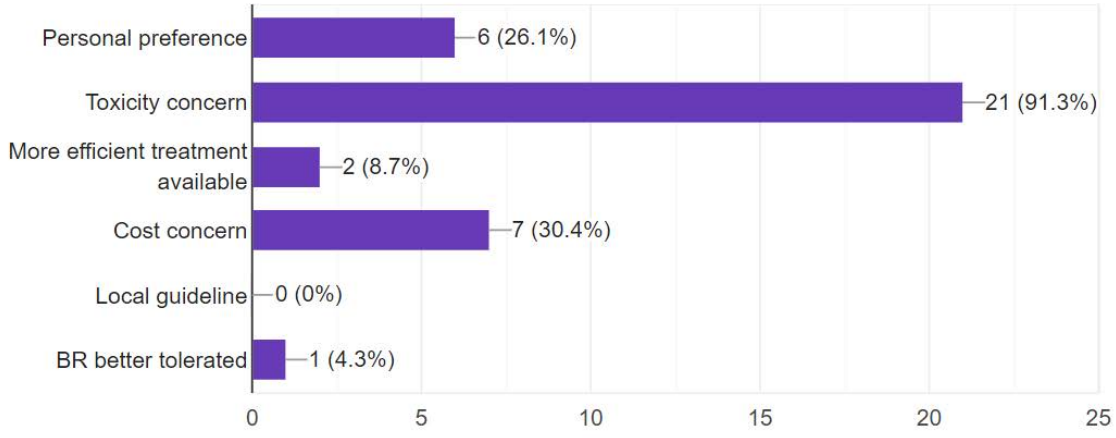




Reason for not using FCR.....

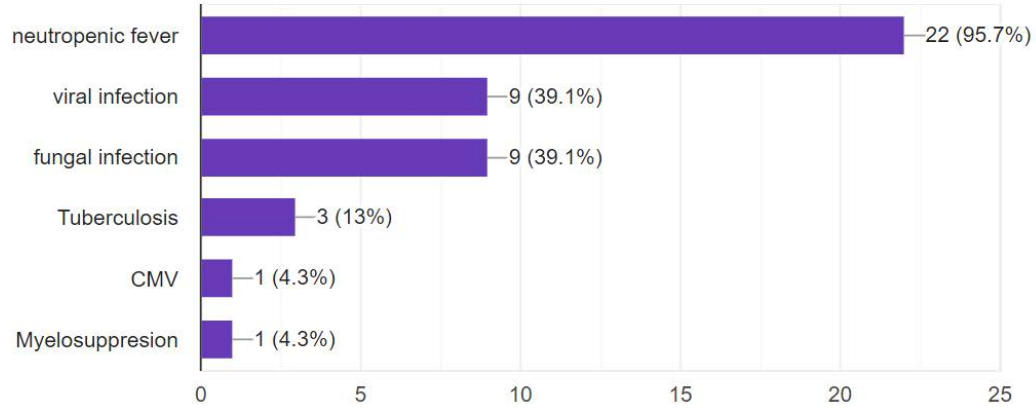
If FCR is not preferred as first choice the reason for not choosing

23 responses

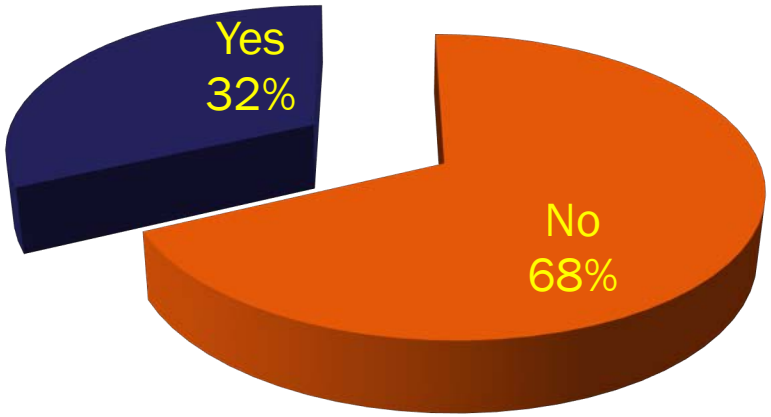


If toxicity is the concern what type of toxicity

23 responses



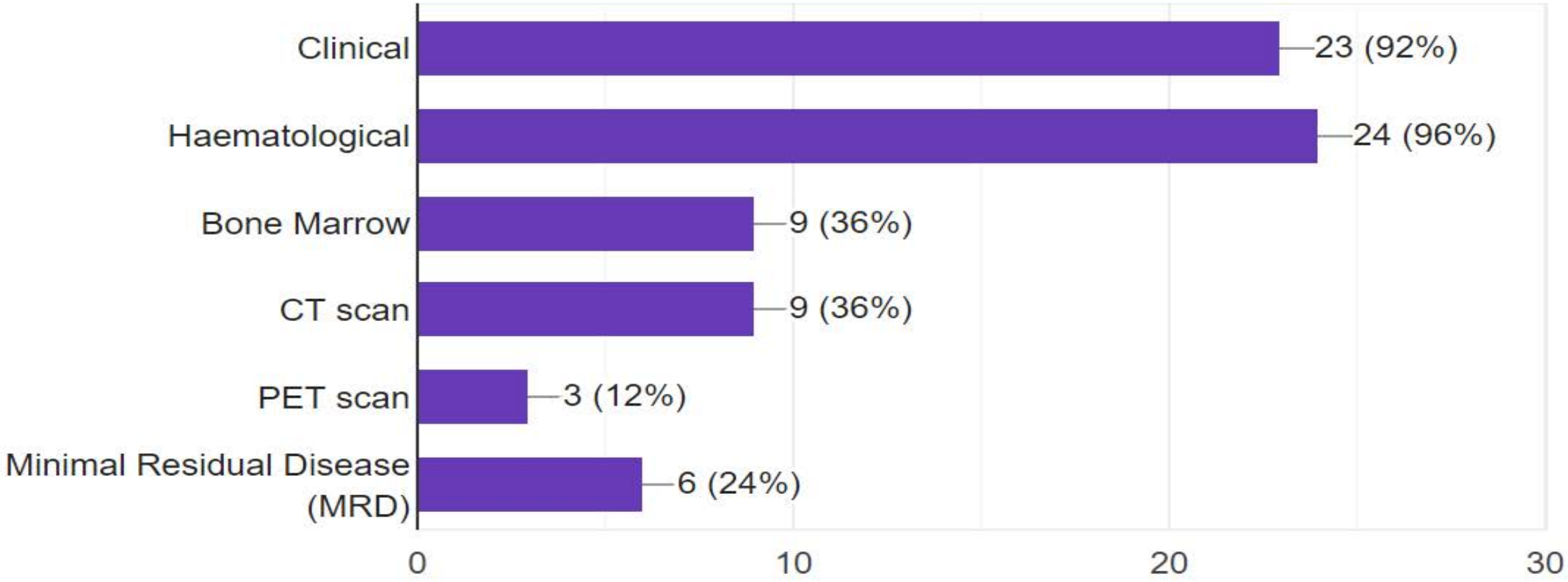
Allogeneic Transplant



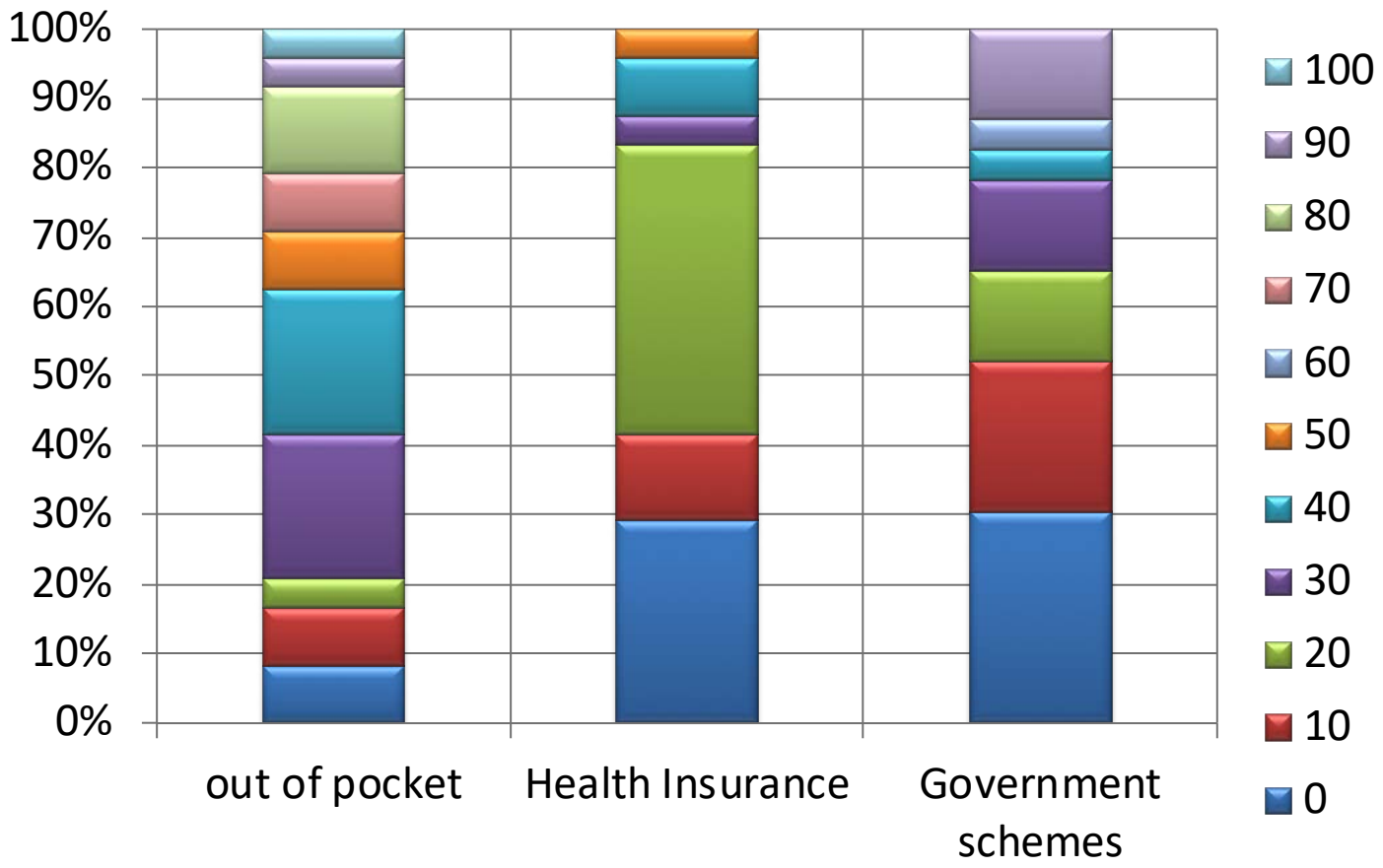
	Yes	No		
		If no reason for not using		
			Not available	Cost of treatment
Ibrutinib	72%	28%	16%	86%
Venetoclax	16%	84%	62%	38%
Other newer agents		100%	100%	

Response assessment

25 responses



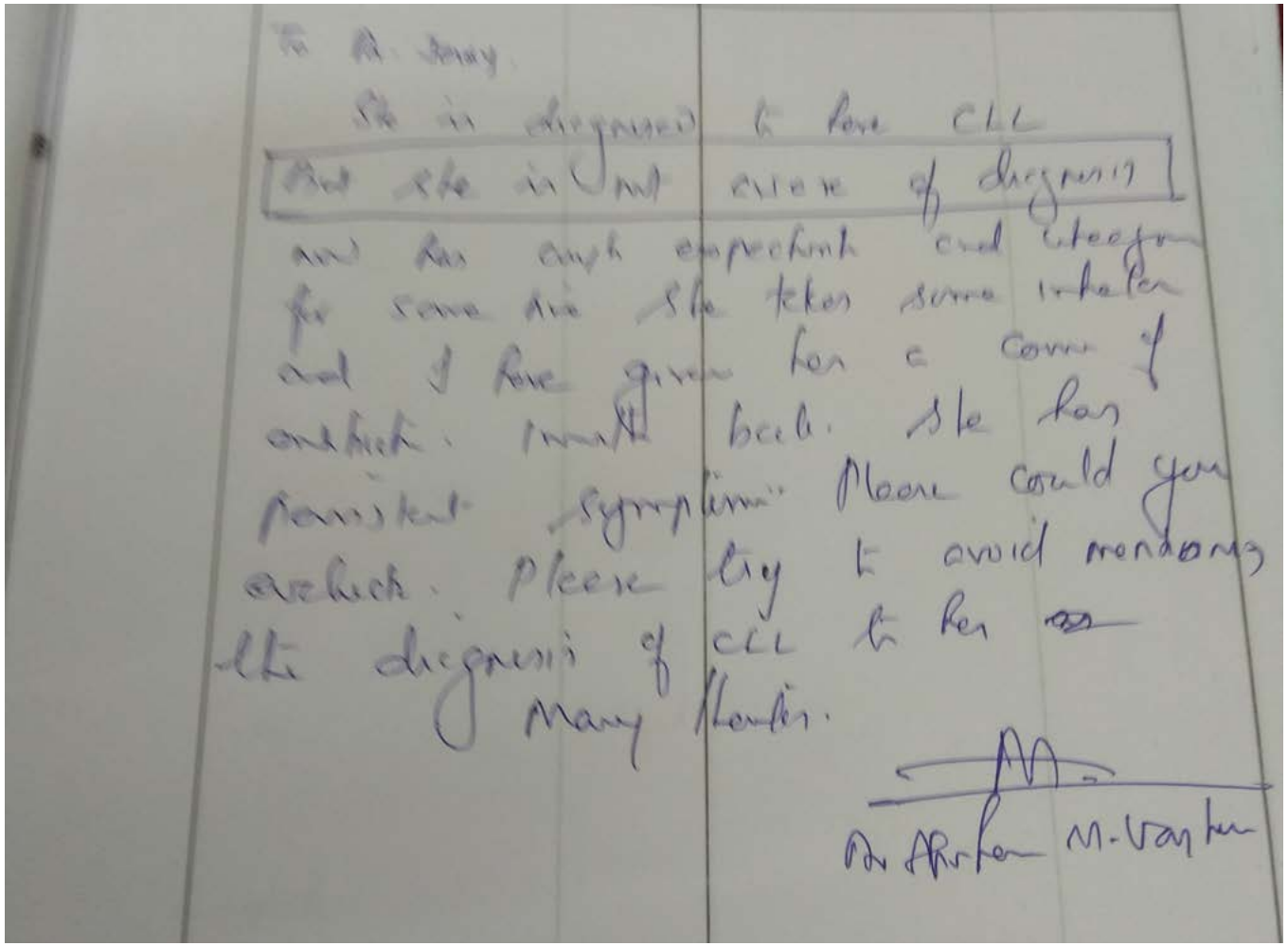
Treatment funding source.....



Comments....

- It is unfortunate that we can only juggle between BR, R-COP and Chlorambucil.
- We sometimes use oral metronomic chemotherapy, combination of oral etoposide, cyclophosphamide and prednisolone.
- The cost of Ibrutinib and venetocloax are extremely prohibitive. It is truly frustrating to treat CLL in this regard.
- We have the means to do MRD at the end of first-line treatment but do not see any purpose to wasting money on it.
- FCR is extremely toxic and costly. With the limited hospital bed availability it would be difficult to sustain such length hospital admissions. Moreover, our patients are biologically older and more frail. Sometimes, BR and R-COP tolerance is also a major concern.
- Many of the drugs are costly to be used in India. Medical insurance and govt help is not usual
- I believe it is underdiagnosed as well as under reported.

Cultural aspects.....



Conclusions

- More epidemiological studies are needed before concluding that CLL has low incidence in Indian population
- Over the next few years establishment of real world data registry for CLL in India.. Advise and support from established registries will be very helpful
- Geographical difference in the incidence and biology will help us to understand the pathophysiology of disease better. Collaborative research like Ugandan MBL study in Indian population.
- Treatment of CLL has to go a long way to catch up with rest of the world.
- Cost of the new drugs are much beyond the scope of majority of Indian patients.
- We need to think about different costing model for countries like India.
- India needs to have its own trial portfolio to guide the treatment of CLL for regional population.
- Collaborative research with established groups in IWCLL will be very helpful.

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Medanta THE MEDICITY dedicated to life

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Medicine and Haematology

Little Flower Hospital and Research Centre, Kerala, India

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