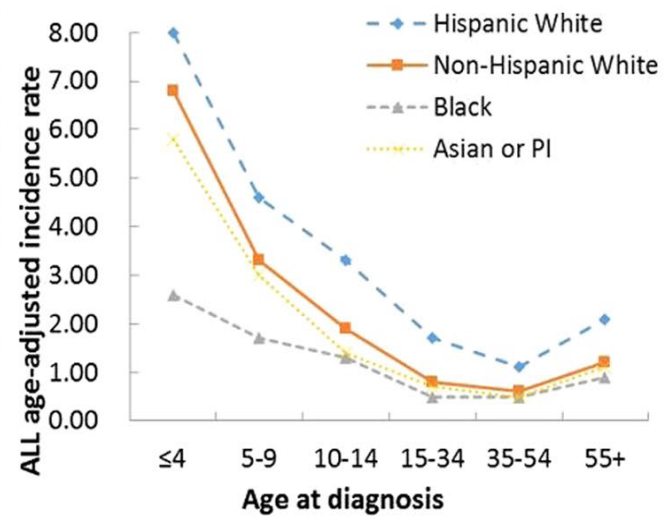
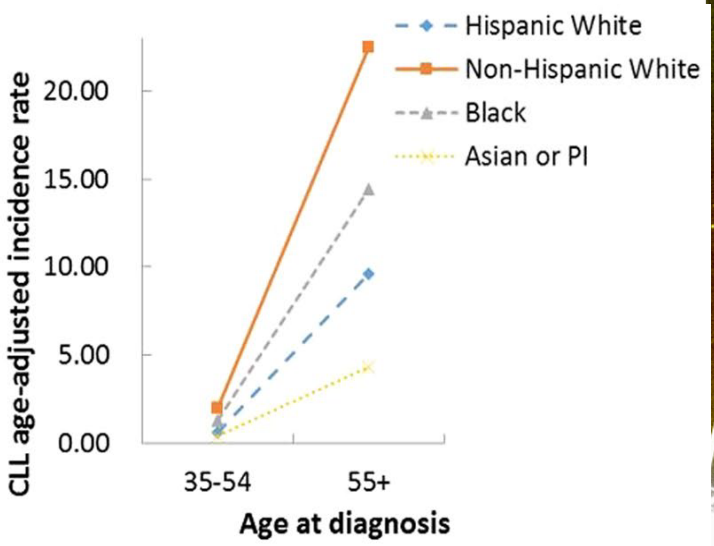
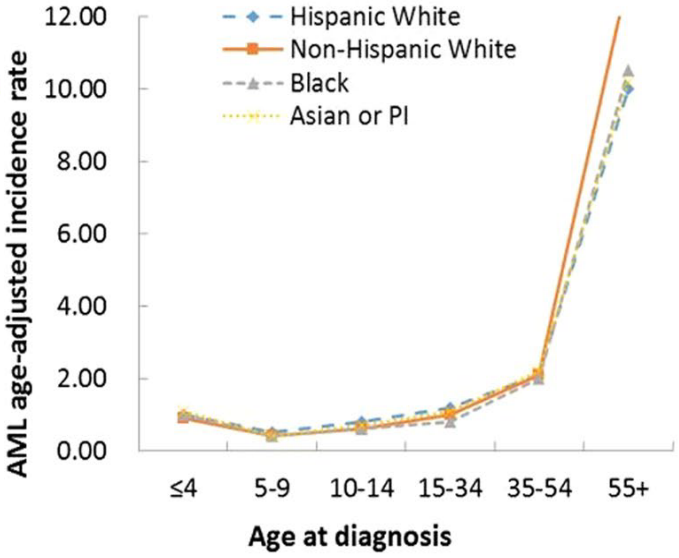
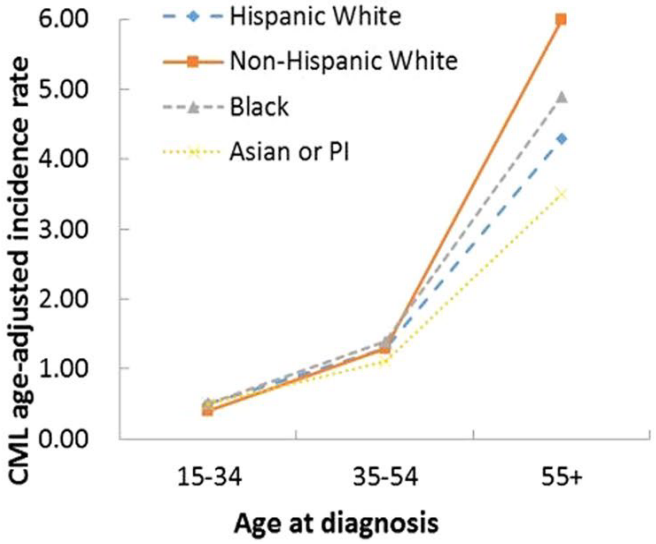

Hispanic White
Non-Hispanic White
Black
Asian or PI
ALL age-adjusted incidence rate
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
≤4
5-9
10-14
15-34
35-54
55+
Age at diagnosis


Hispanic White
Non-Hispanic White
Black
Asian or PI
CLL age-adjusted incidence rate
20.00
15.00
10.00
5.00
0.00
35-54
55+
Age at diagnosis

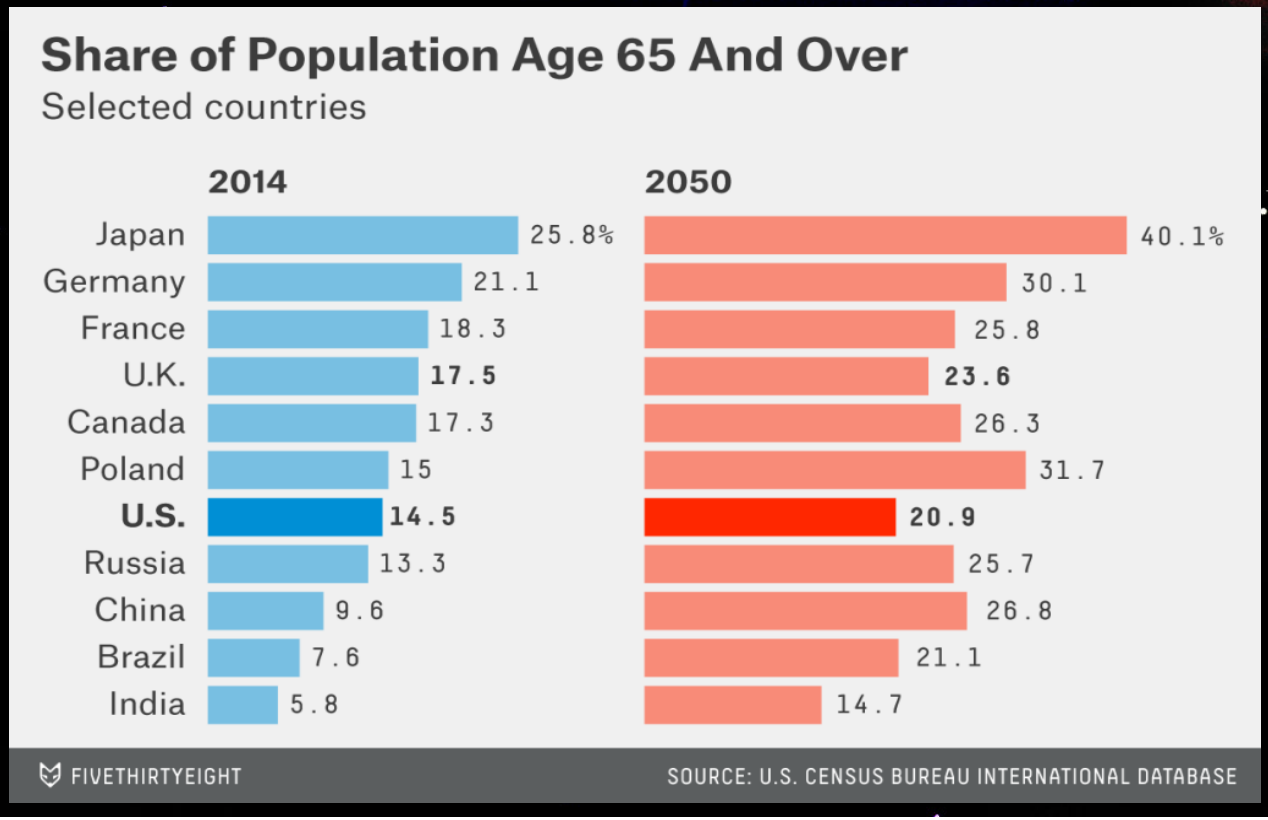

Hispanic White
Non-Hispanic White
Black
Asian or PI
AML age-adjusted incidence rate
12.00
10.00
8.00
6.00
4.00
2.00
0.00
≤4
5-9
10-14
15-34
35-54
55+
Age at diagnosis


Hispanic White
Non-Hispanic White
Black
Asian or PI
CML age-adjusted incidence rate
6.00
5.00
4.00
3.00
2.00
1.00
0.00
15-34
35-54
55+
Age at diagnosis

Ethnicity	Per 100.000/Y Male	Per 100.000/Y Female
White	6.0	2.9
Black	4.4	3.1
Pacific Islader	1.1	0.7
Hispanic	2.6	1.4
Indian/Alaska Native	2.1	n.a.
Chinese	0.4	0.2
Chinese Han	0.05	0.02
Japanese	0.4	0.2

CLL incidence increases with the age

Age	Per 100.000/Year
< 60 Years	2.2 – 3.7
60 - 79 years	14.3
> 80 Years	22.1



The aetiology of CLL is unknown

The exposure to ionizing radiation is associated with increased risk of cancer: primarily acute myeloid leukemia, thyroid, and breast cancer.

And for CLL?

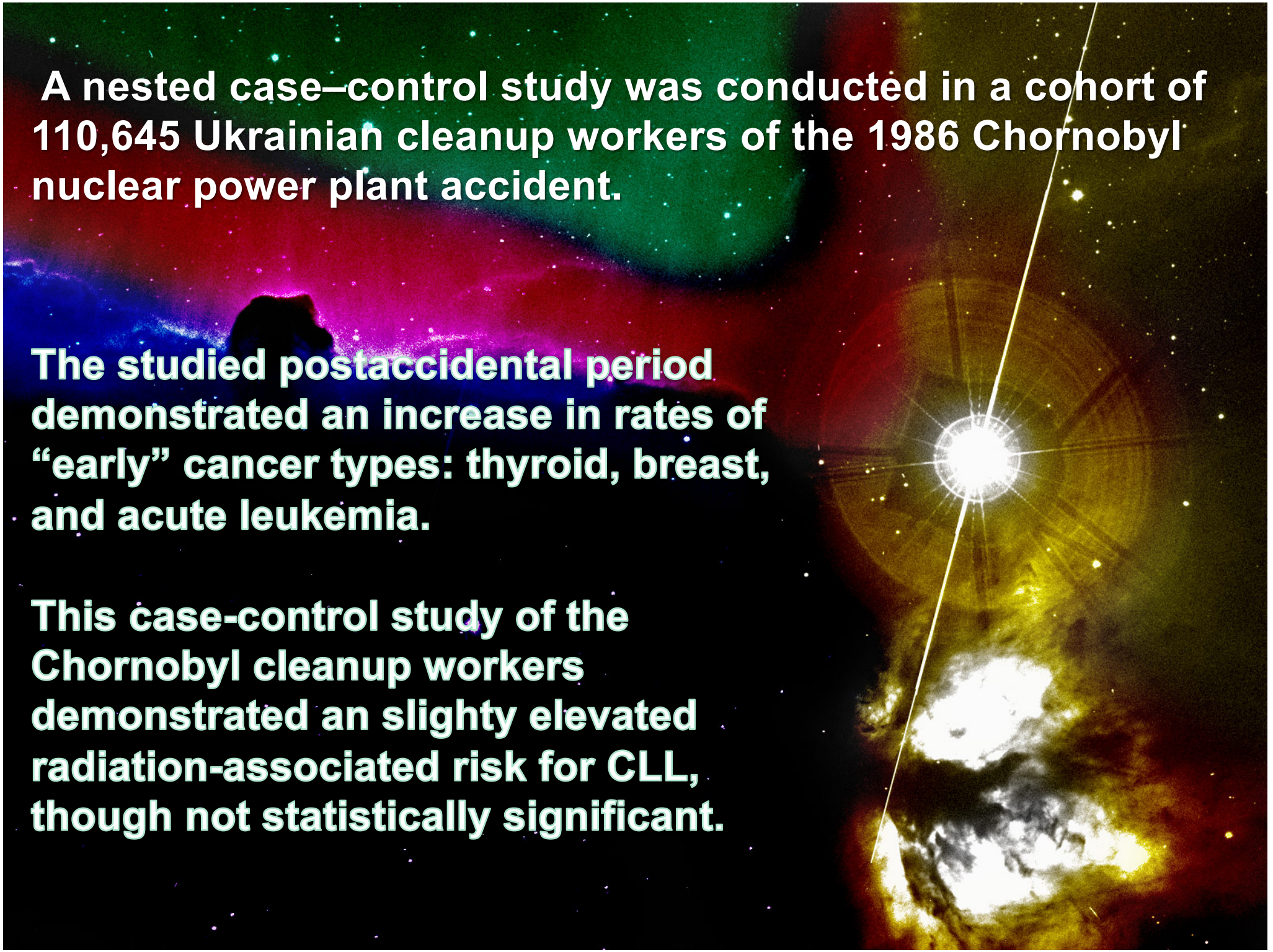
Note that the CLL risks were not analyzed in the atomic bomb survivors in Hiroshima and Nagasaki as such pathology is absent in Japan and it has not occurred among radiation-exposed.

We have two models:

- Patients exposed to thorium dioxide
- Groups of the population exposed after the Chernobyl accident

Thorotrast, a radioactive alfa-emitting solution of 232Th02w, as used as X-ray contrast medium in the 1930s and 1940s in Europe, North America and Japan

Disease	Observed	Expected
AML	16	< 1
MDS	8	< 1
ALL	1	< 0.5
CML	3	< 0.5
NHL	4	1.5
MM	2	1
CLL	2	1

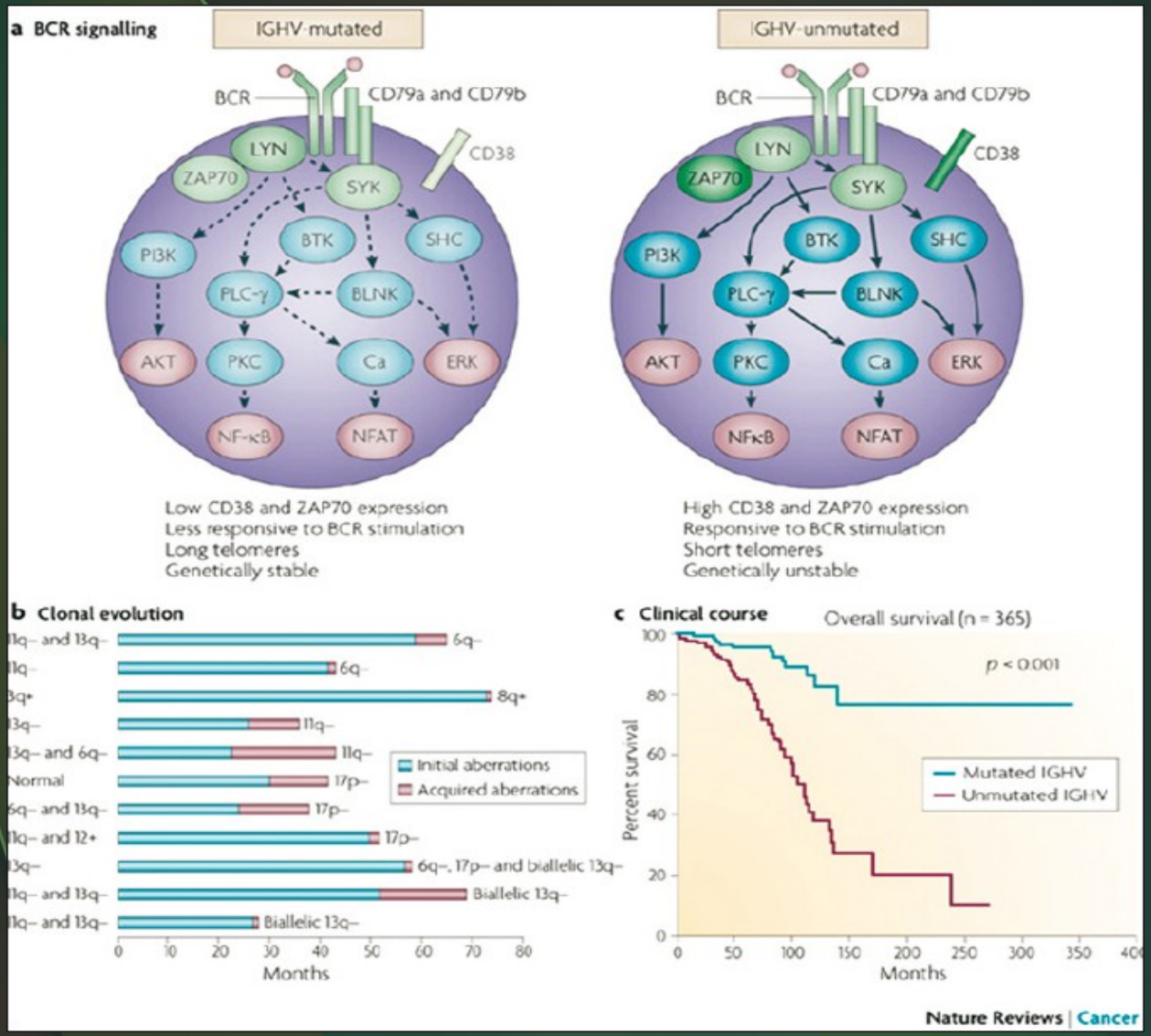

A nested case–control study was conducted in a cohort of 110,645 Ukrainian cleanup workers of the 1986 Chornobyl nuclear power plant accident.
The studied postaccidental period demonstrated an increase in rates of “early” cancer types: thyroid, breast, and acute leukemia.
This case-control study of the Chornobyl cleanup workers demonstrated an slighty elevated radiation-associated risk for CLL, though not statistically significant.

Abnormal karyotype in CLL

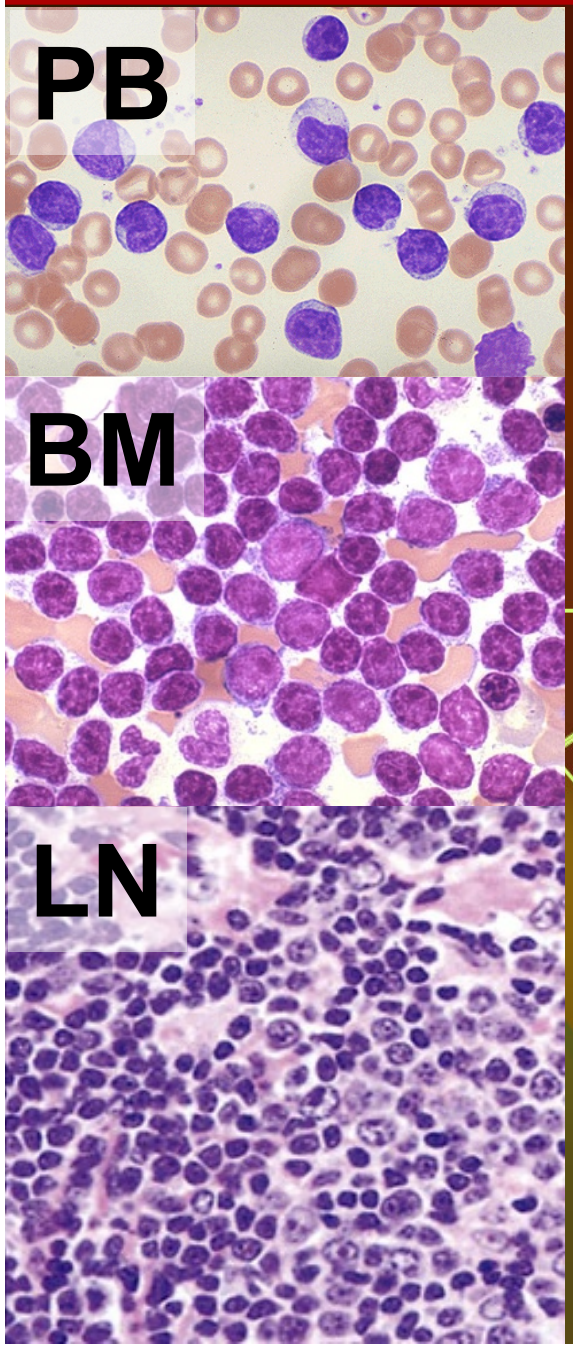
Common abnormalities			
13q-	40-50%	miRNA	Good
17p-	5-7%	p53	Very poor
11q-	15-20%	ATM	Intermediate
12 trisomy	15-20%	CD49	Intermediate
Normal	10-15%		Poor
Other abnormalities	5-8%		Poor

Main marker of poor prognosis in CLL:

Mutated or Unmutated IgVH



IGHV mutation status impacts on all CLL clinical outcomes



- Survival
- Treatment need
- Progression after treatment
- Refractoriness
- Infection
- Autoimmune cytopenia
- Transformation

TP53 mutations

Clinical impact of clonal and subclonal TP53 mutations in CLL

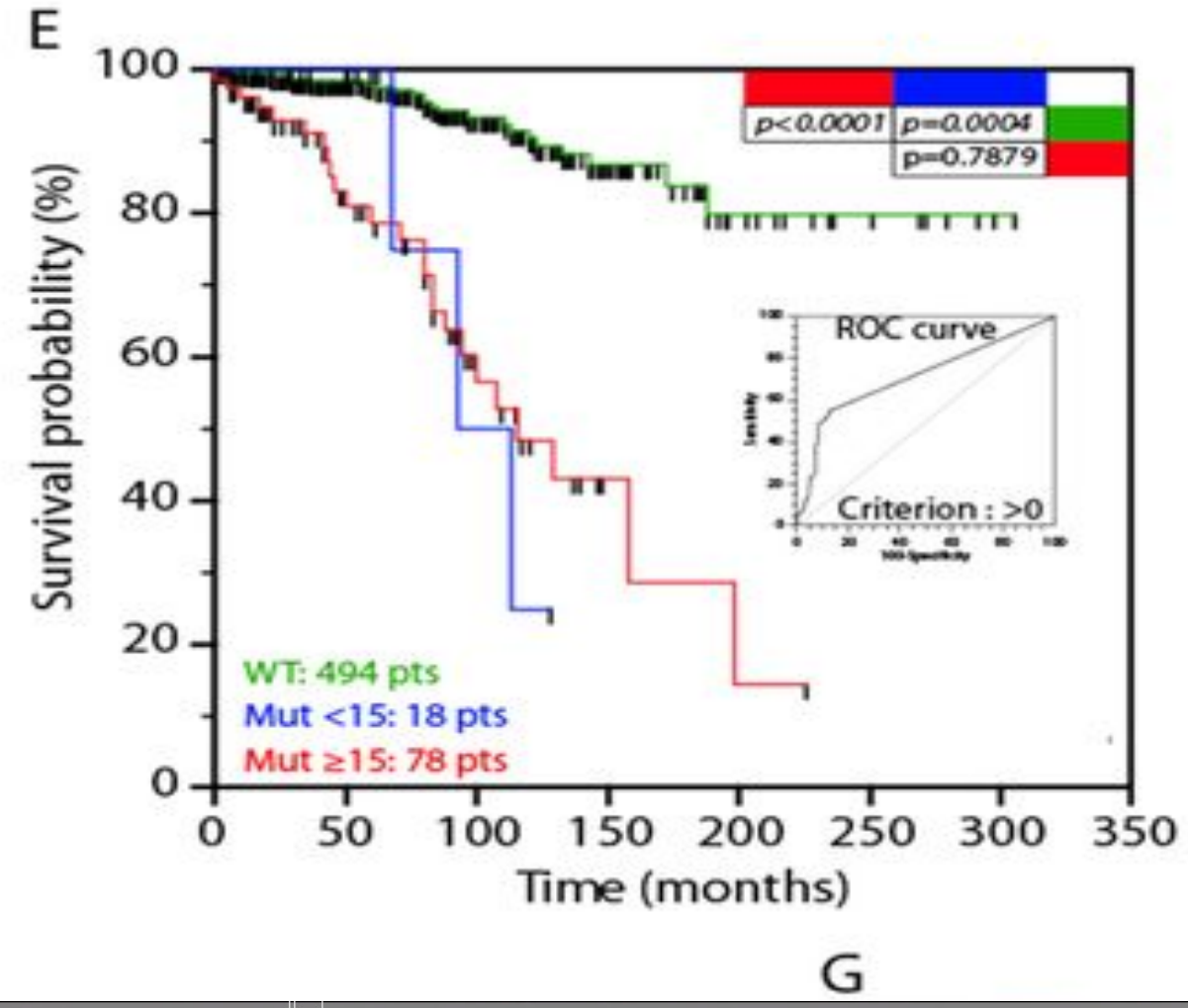
over 590 cases of CLL

Clonal (VAF >15%)	**13%**
Subclonal (VAF 1-15%)	**3%**

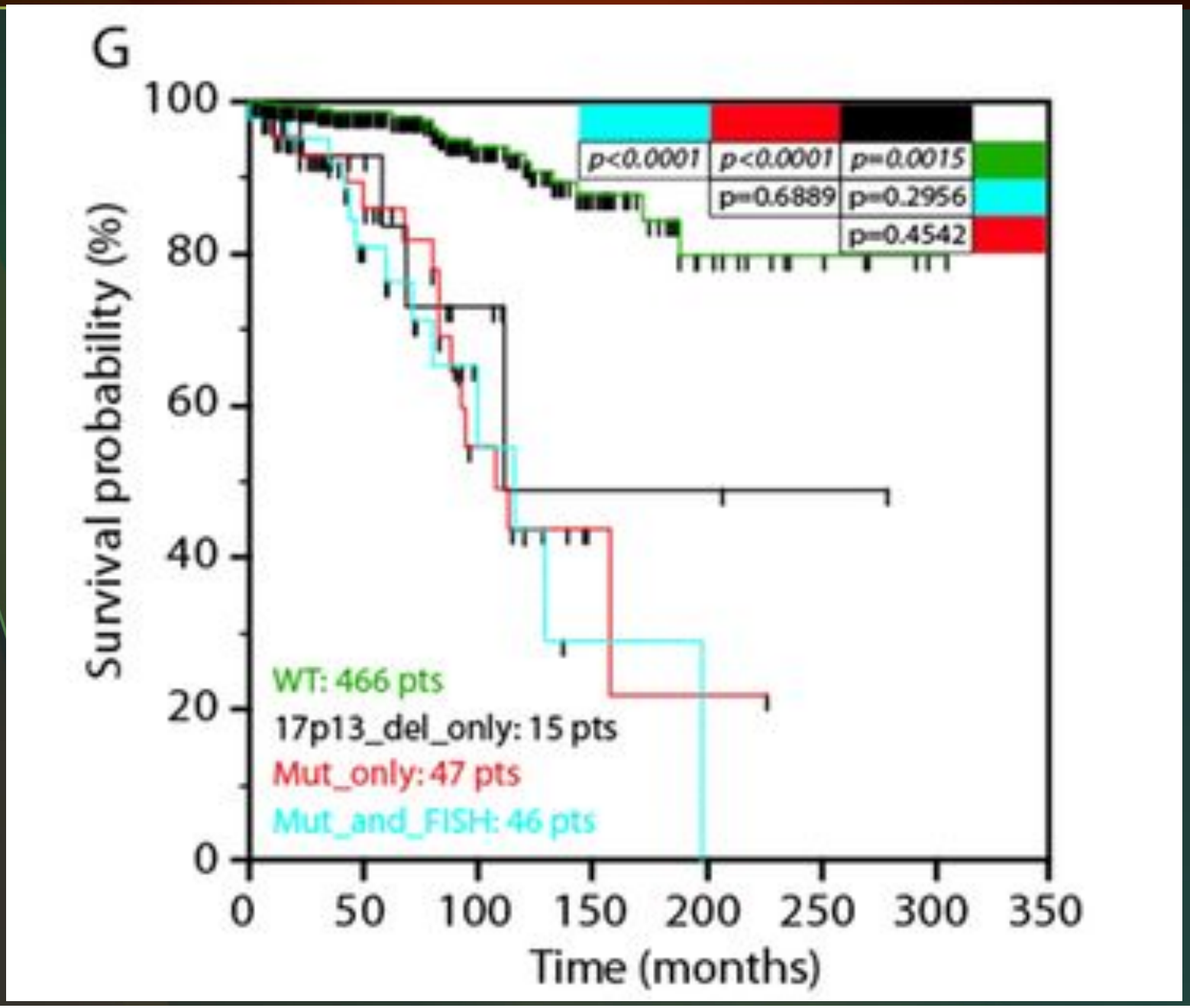
The clinical behavior was identical

VAF: variant allele frequency

Clonal and subclonal mutation of TP53 had the same impact on survival



Deletion or mutations of TP53 show the same negative impact on survival



The CLL patient

- Comorbid conditions assessment
- Geriatric assessment
- Patient Counseling and Supportive Care
- CLL complications management
- Selection of therapies for the cases with progressive CLL

CHARLSON COMORBIDITY INDEX

One Point

- Myocardial infarction (history, not ECG changes only)
- Congestive heart failure
- Peripheral disease (includes aortic aneurysm >= 6 cm
- Cerebrovascular disease: CVA with mild or no residua or TIA
- Dementia
- Chronic pulmonary disease
- Connective tissue disease
- Peptic ulcer disease
- Mild liver disease (without portal hypertension, includes chronic hepatitis)
- Diabetes without end-organ damage (excludes diet-controlled alone)

Two Points

- Hemiplegia
- Moderate or severe renal disease
- Diabetes with end-organ damage (retinopathy, neuropathy,nephropathy)
- Tumor without metastasis (exclude if > 5 y from diagnosis)
- Leukemia(acute or chronic)
- Lymphoma

Three Points

- Moderate or severe liver disease

Six Points

- Metastatic solid tumor
- AIDS (not just HIV positive)

Low indicates a score of ≤ 3;
Moderate indicates a score of a 4 or 5;
High indicates a score of a 6 or 7;
Very high indicates a score of ≥8.

Probability of survival in the basis of Charlson Index		
	At one year	At two years
Low	0.98	0,95
Mean	0.89	0.80
High	0.79	0.70
Very high	0.64	0.35

Table 3

Cumulative Illness Rating Score

ORGAN-SYSTEM	SEVERITY
1. Cardiac	0-1-2-3-4
2. Vascular	0-1-2-3-4
3. Hematological	0-1-2-3-4
4. Respiratory	0-1-2-3-4
5. Ophthalmological and ORL	0-1-2-3-4
6. Upper gastrointestinal	0-1-2-3-4
7. Lower gastrointestinal	0-1-2-3-4
8. Hepatic and pancreatic	0-1-2-3-4
9. Renal	0-1-2-3-4
10. Genito-urinary	0-1-2-3-4
11. Musculoskeletal and cutaneous	0-1-2-3-4
12. Neurological	0-1-2-3-4
13. Endocrine, metabolic, mammary	0-1-2-3-4
14. Psychiatric	0-1-2-3-4

Score, depending on the extent to which the organ/system is affected: 0 Absence of disease; 1 mild; 2 moderate; 3 severe; 4 very severe.

Source: *Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc. 1968; 16(5):622-626.*

https://eforms.moffitt.org/cirsgScore.aspx
http://tools.farmacologiaclinica.info/index.php?sid=84143

Geriatric assessment

ADL (activity daily living) index (Katz S. 1963)

IADL (Instrumental Activity of Daily Living) index (Lawton MP 1969)

MMSE (Mini-Mental State Examination) (Folstein M. 1975)

Geriatric Depression Scale (Sheick JI. 1986)

Multidimensional Prognostic Index

Patient Counseling and Supportive Care

- **Patients should be educated about the nature of their illness, current management strategies and about the need of the follow-up**

- **Patients should be advised on the increased risk of second malignancy:**
  Smoking cessation
  Complete skin survey on an annual basis
  Fecal Occult Blood test on annual basis
  Appropriate screening for breast and prostate cancer

- **Patients should be advised on the increased risk of infections**
  Avoid adventure travels and countries endemic for malaria
  Influenza vaccination
  Avoid live attenuated vaccines (polio, typhoid, yellow fever, measles, mumps, rubella, BCG and Herpes zoster)

- **Impact of CLL on Quality of Life**
  The new diagnosis of CLL has a profound impact on QoF, even in patients without clinical symptoms. Deep concerns are: 1) shorter life 2) risk of complications 3)need of toxic terapies 4) social implications
  In addition, the "watch and wait" strategy leaves patients feeling that "nothing is being done" for their serious problem... "a leukemia !!!".

CLL complication menagement

Impaired Immunity

(B-T-NK-Monocytes disfunctions)

- Hypogammaglobulinemia
- Infectious complications
- Viral reactivation (CMV, HBV)

Auto-immunity

(Hematological autoimmune phenomena)

- Autoimmune hemolytic anemia
- Immune thrombocytopenia
- Pure red cell aplasia
- Autoimmune neutropenia

Criteria for initiating treatment : an active disease

IWCLL 2019

- **Progressive marrow failure : the development of anemia and/or thrombocytopenia**
- **Massive (ie, at least 6 cm below the left costal margin) or progressive or symptomatic splenomegaly**
- **Massive nodes (ie, at least 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy**
- **Progressive lymphocytosis with an increase of more than 50% over a 2-month period or LDT less than 6 months. .**
- **Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy**
- **Constitutional symptoms**
- **Symptomatic or functional extranodal involvement (eg, skin, kidney, lung, spine).**


Selection of therapies for the cases with progressive CLL

THE TREATMENTS ARE EVOLVING ....

More chemo-free therapies and less chemotherapies

- **R-Ibrutinib vs R-Benda first-line in elderly**
- **Ibrutinib ± different agents vs FCR first-line in young patients**
- **Ibrutinib + G vs Clorambucile + G first-line in elderly**
- **Venetoclax + G vs Clorambucile + G**
- **R-Venetoclax**
- **Ibrutinib + G + Venetoclax**

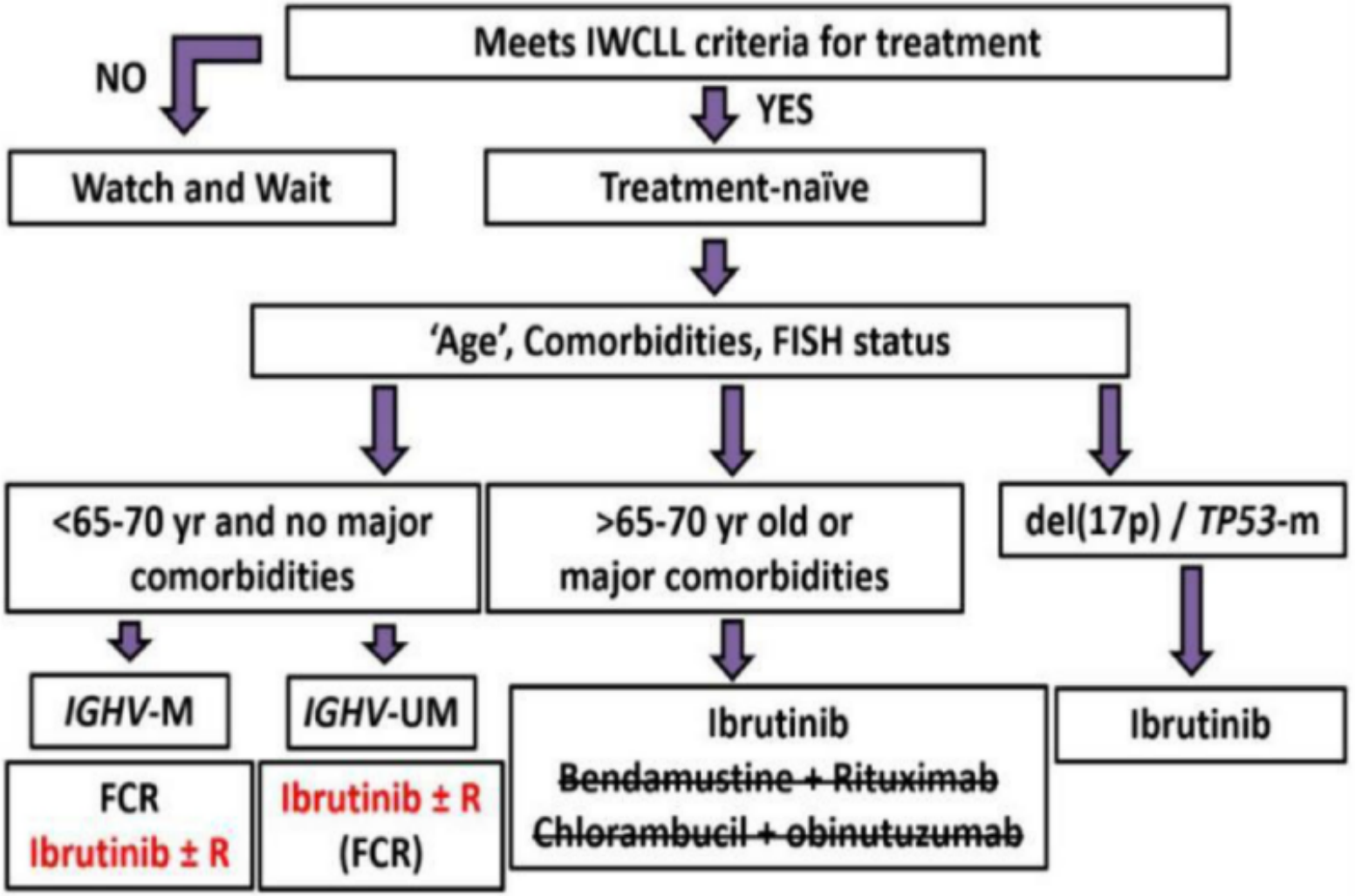
THE TREATMENTS ARE EVOLVING ....

BK-inhibitors (second wave)

Covalents : Acalabrutinib, Zanubrutinib

Non-covalents : Vecabrutinib, ARQ531

PI3K-inhibitors : Duvelisib, Umbralisib


Meets IWCLL criteria for treatment
NO
YES
Watch and Wait
Treatment-naïve
'Age', Comorbidities, FISH status
<65-70 yr and no major comorbidities
>65-70 yr old or major comorbidities
del(17p) / TP53-m
IGHV-M
IGHV-UM
Ibrutinib
Ibrutinib
FCR
Ibrutinib ± R
Ibrutinib ± R
(FCR)
Bendamustine + Rituximab
Chlorambucil + obinutuzumab

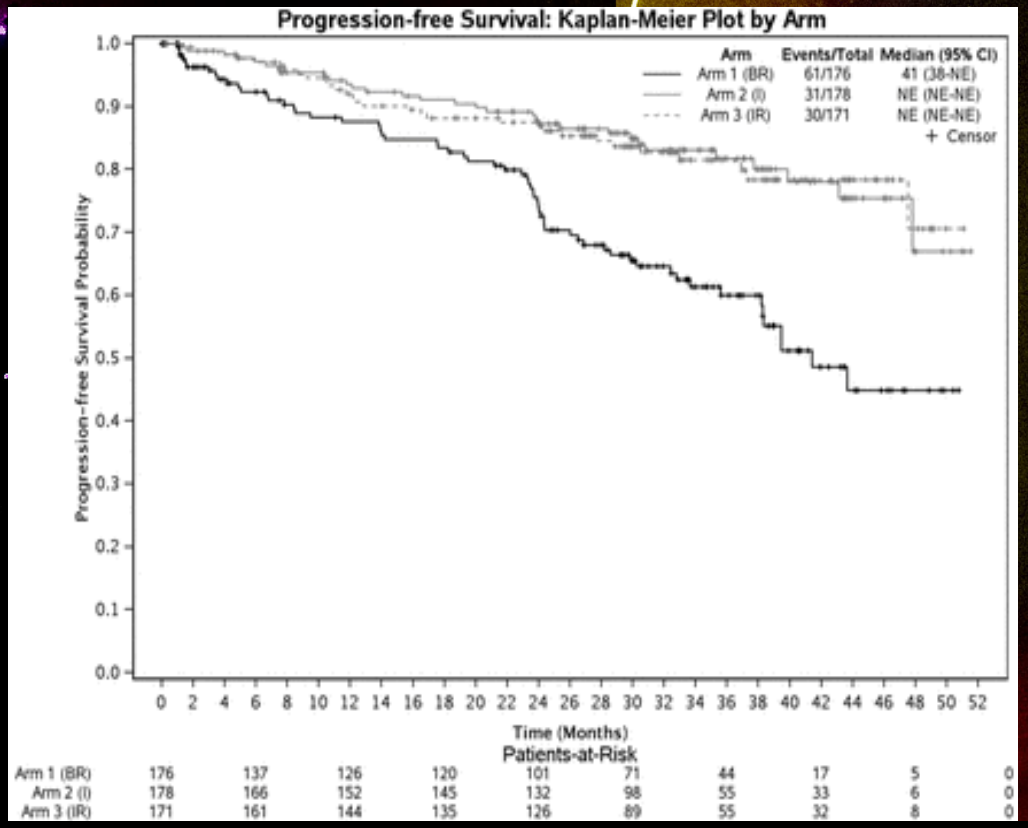
FIRST LINE (1)

TRIAL Alliance North American Intergroup Study

Patients >65 anni, ECOG 0-2 (any FISH, any molecular abnormalities)

547 casi arruolati

- **Bendamustina + Rituximab**
- **Ibrutinib**
- **Ibrutinib + Rituximab**



At the end of 2019 this trial continues to show the superiority of ibrutinib-based therapy over BR as frontline therapy.

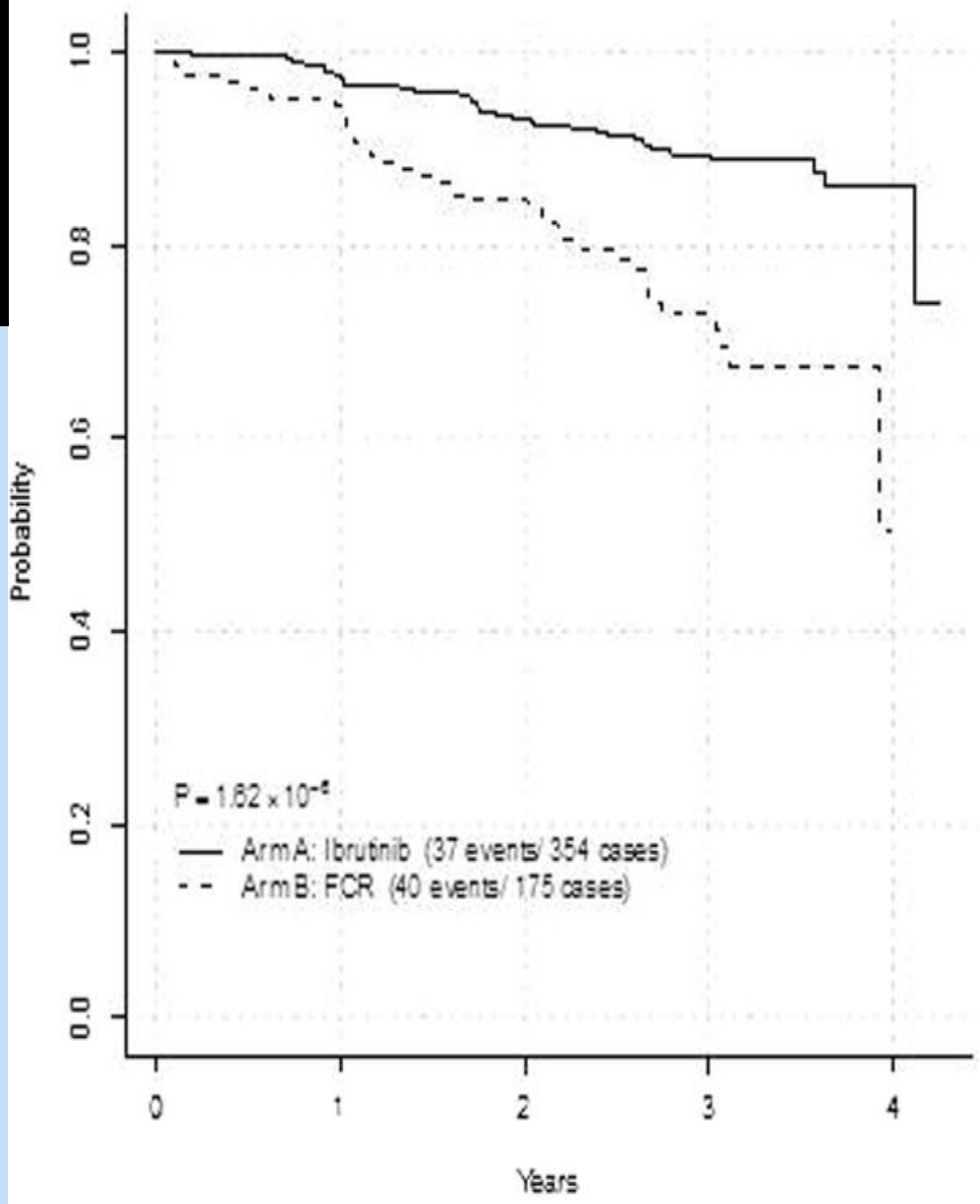
FIRST LINE (2)

Patients <70 years, p53WT, ECOG 0-2

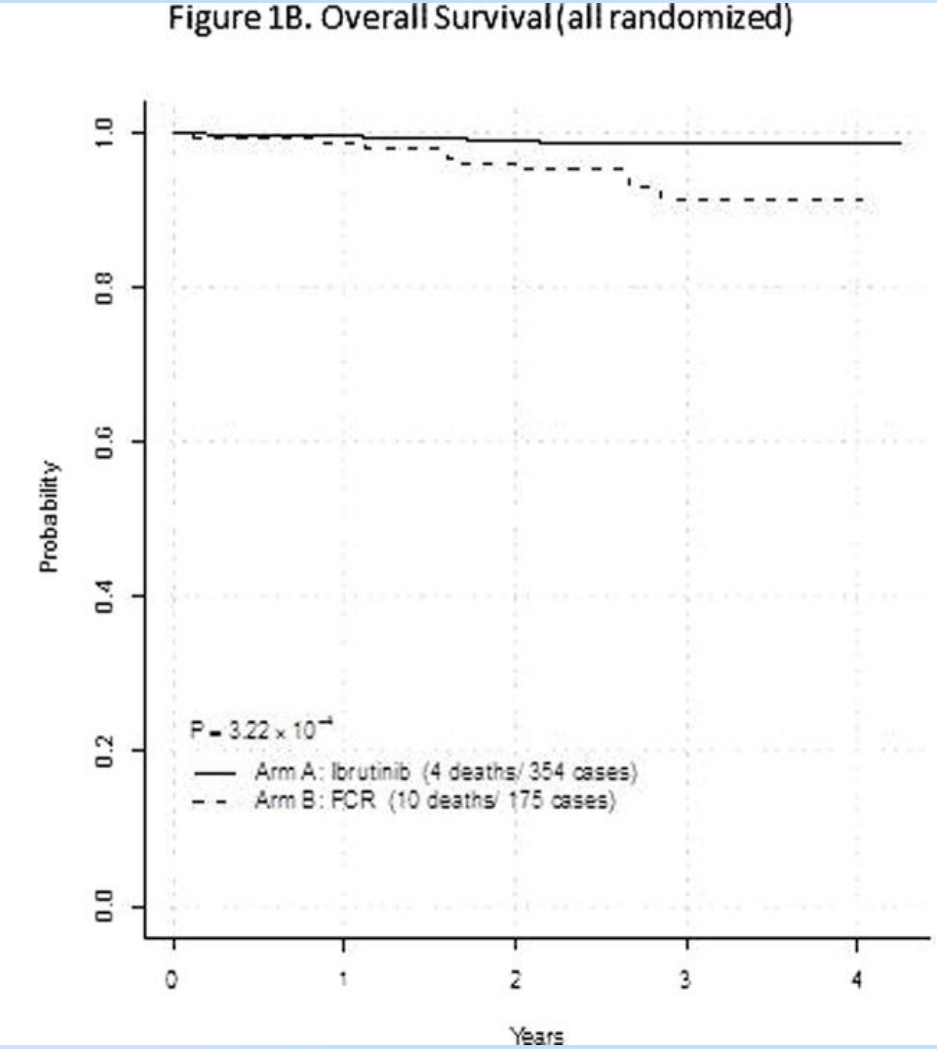
529 casi arruolati

- **Ibrunitib + Rituximab**
- **FCR (6 cycles)**

Figure 1. Progression-Free Survival (all randomized)



At the end of the 2019 the E1912 Trial continues to show the superiority of Ibrutinib based therapy over FCR



Death		
	I + R	FCR
CLL	1	6
Respiratory failure	2	0
Cancer	0	2
Irreversible pancytopenia	0	1
Not determined	1	1
	4 (1.1%)	10 (5.7%)

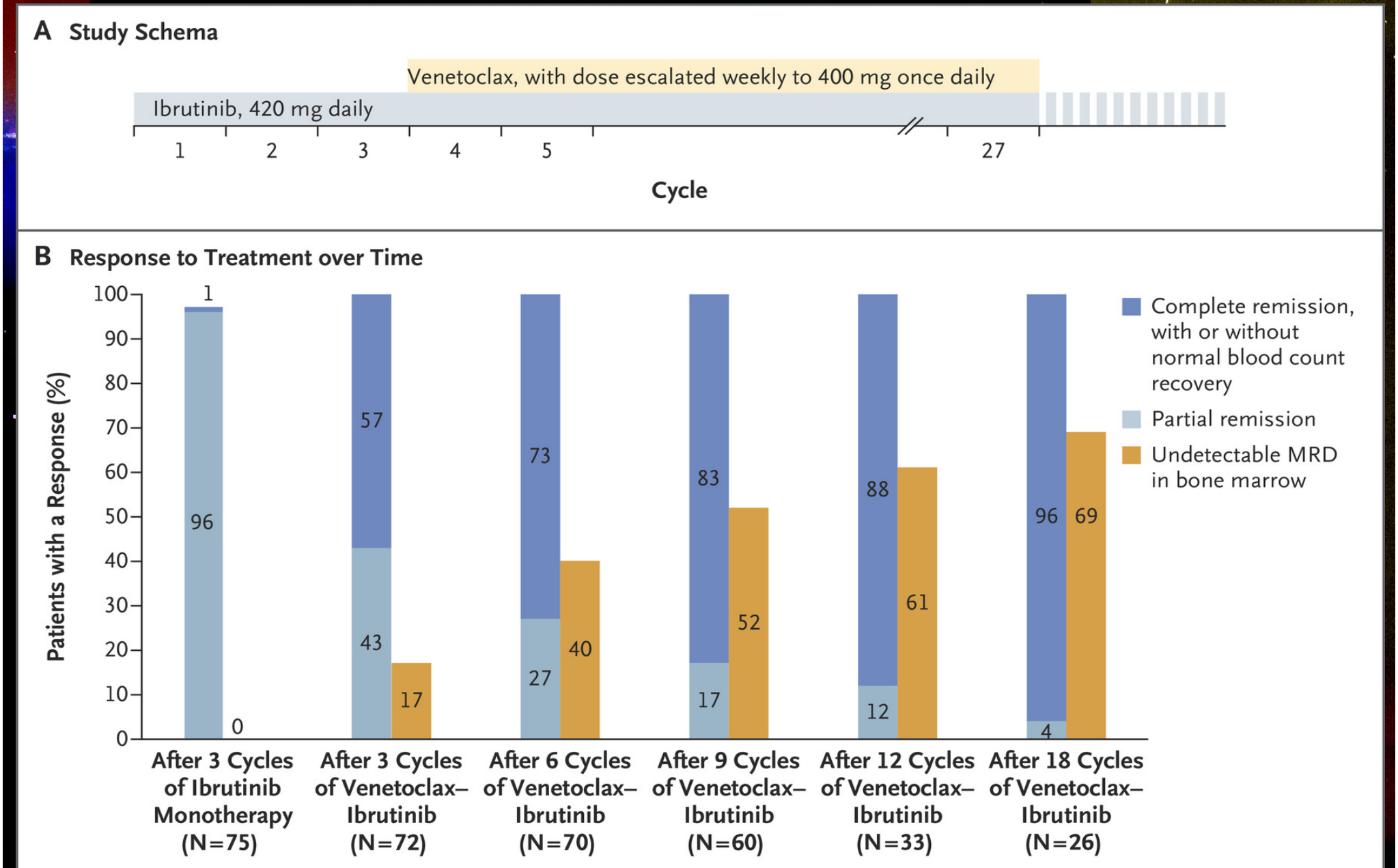
Ibrutinib and Venetoclax for First-Line Treatment of CLL

All patients had at least one high-risk genetic feature: del(17p), mutated TP53, chromosome 11q deletion [del(11q)] or unmutated IGHV; patients 65 years of age or older were eligible, independent of high-risk genetic features

Characteristics

Age Median (range)	yr 65 (26–83)
≥65 yr N° (%)	43 (54)
≥70 yrN° (%)	24 (30)

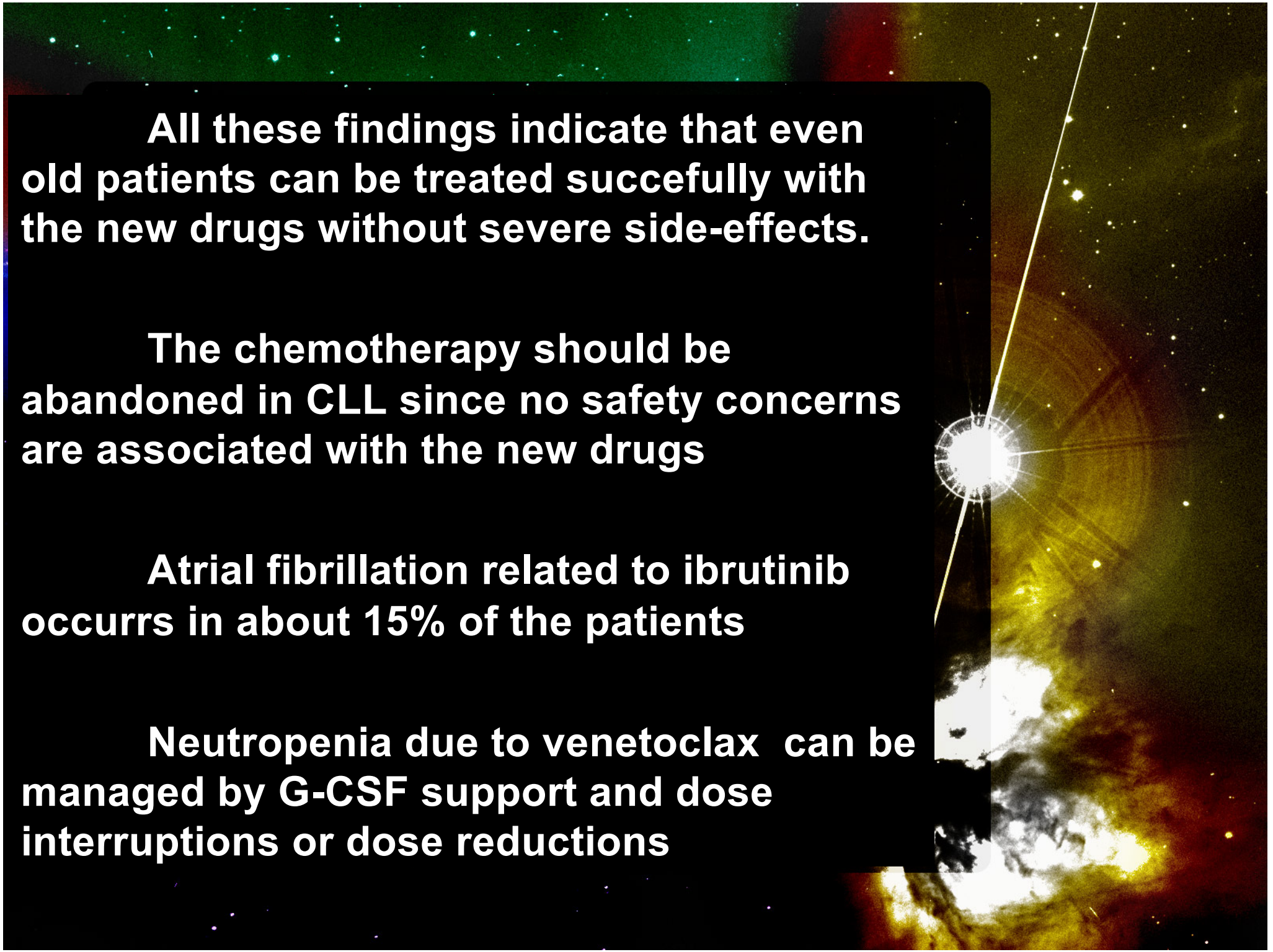
Ibrutinib and Venetoclax for First-Line Treatment of CLL



Ibrutinib and Venetoclax for First-Line Treatment of CLL

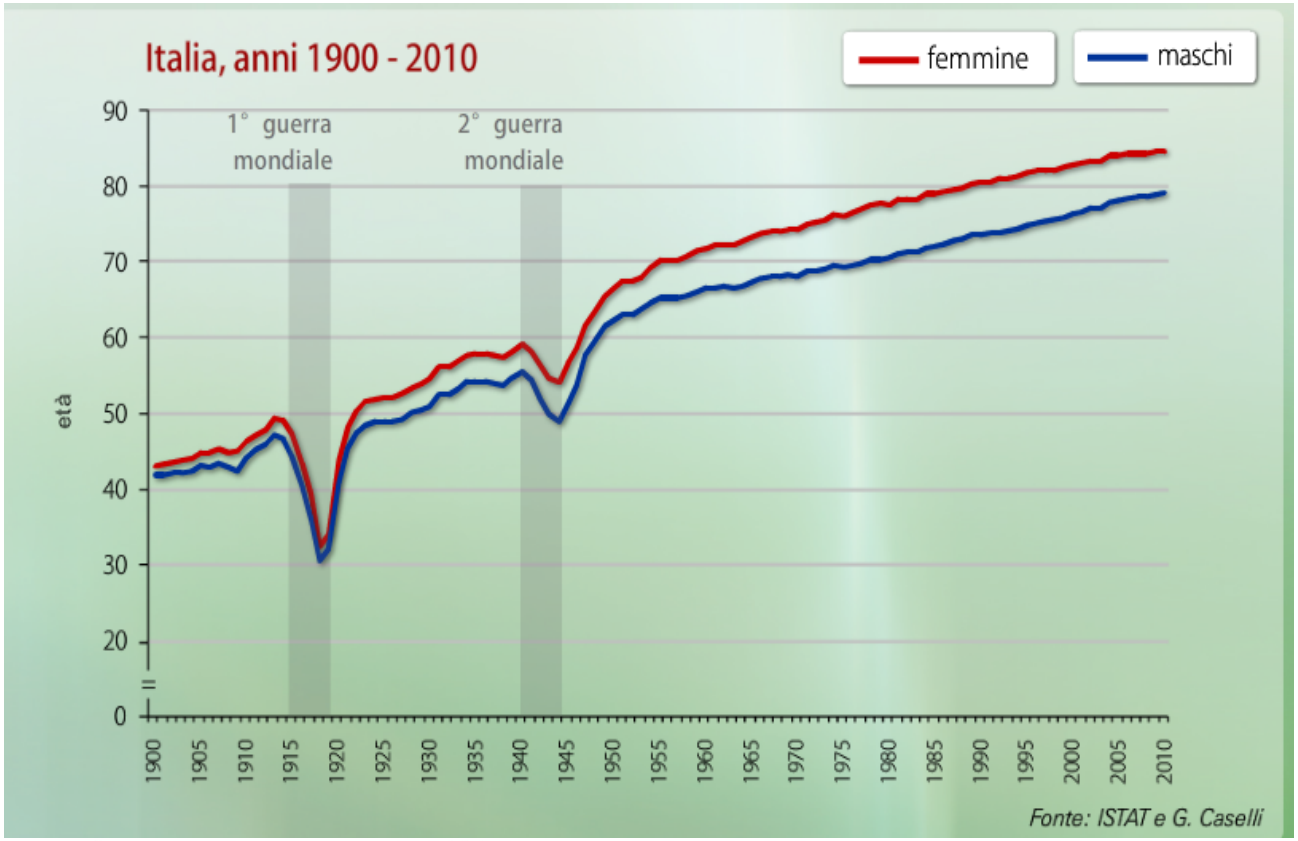
Patients 65 years of age or older had a high rate of response.
A total of 74% had complete remission or complete remission with incomplete count recovery.
44% had undetectable minimal residual disease in bone marrow after 6 cycles of the combination; these rates increased to 94% and 76%, respectively, after 12 cycles

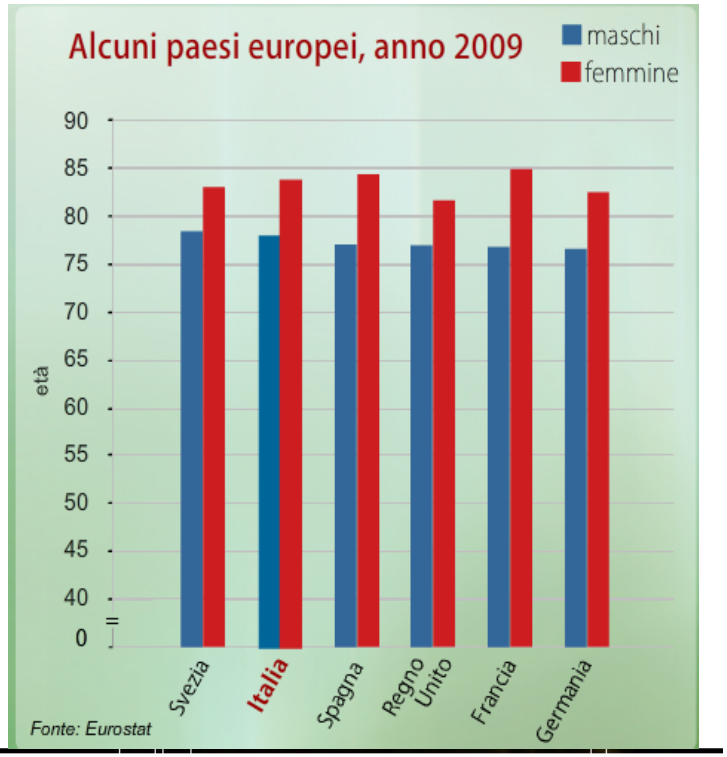
Responses were seen across all high-risk subgroups, independent of IGHV mutation status, FISH category, TP53 mutation, NOTCH1 mutation, and SF3B1 mutation

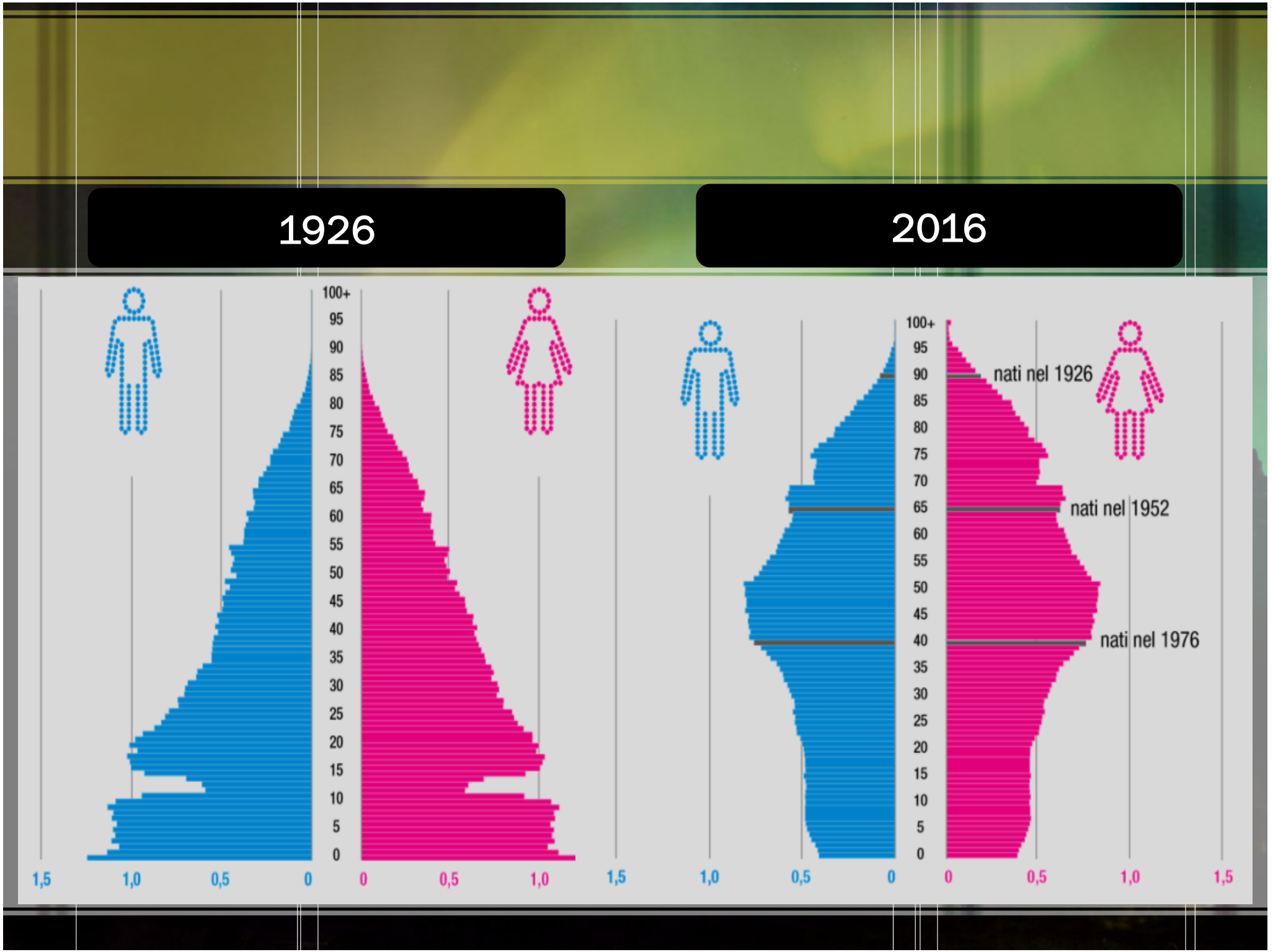

All these findings indicate that even old patients can be treated succefully with the new drugs without severe side-effects.
The chemotherapy should be abandoned in CLL since no safety concerns are associated with the new drugs
Atrial fibrillation related to ibrutinib occurrs in about 15% of the patients
Neutropenia due to venetoclax can be managed by G-CSF support and dose interruptions or dose reductions

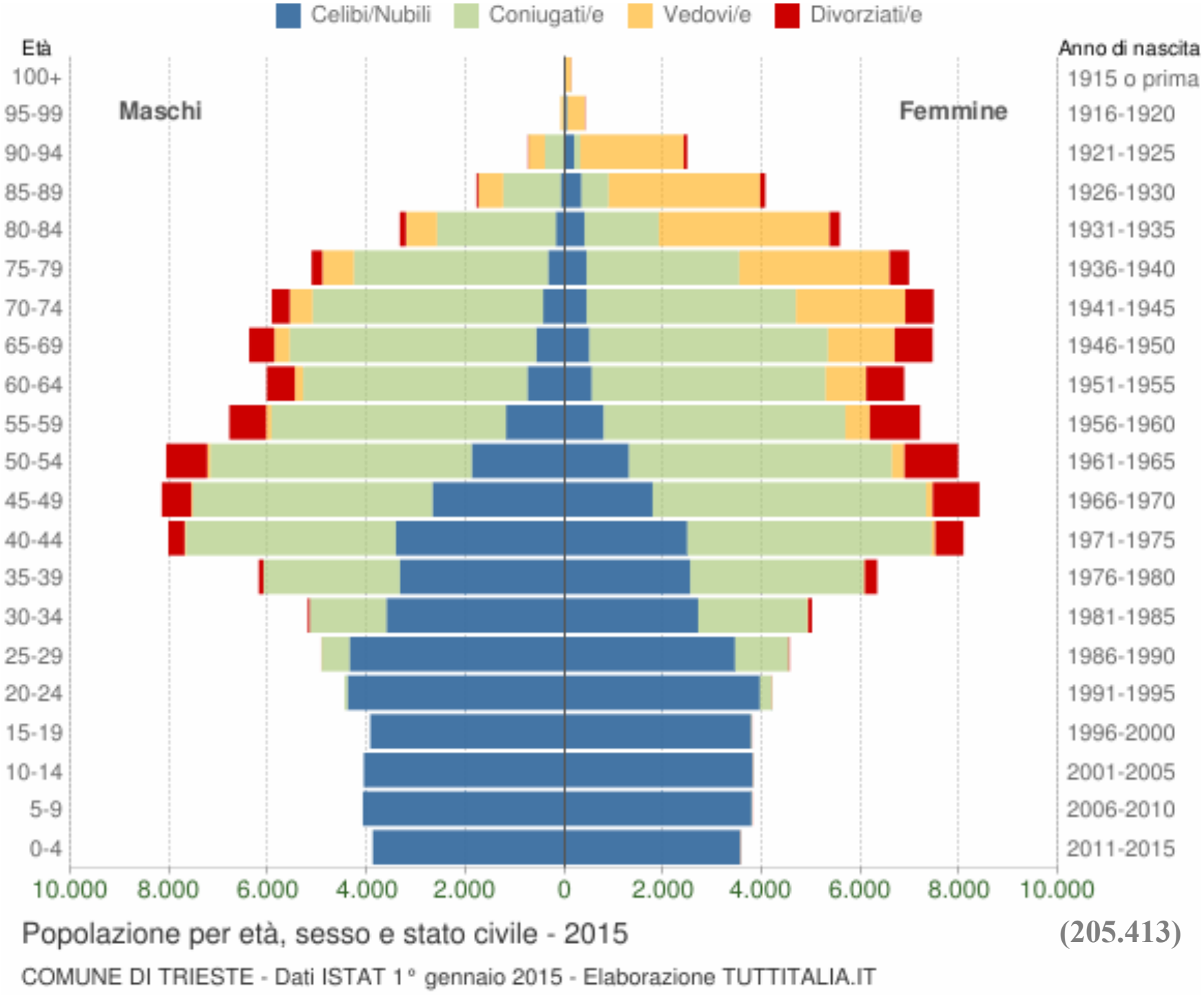
e a Trieste ????

LIFE EXPECTANCY AT BIRTH BY SEX IN ITALY (ISTAT)





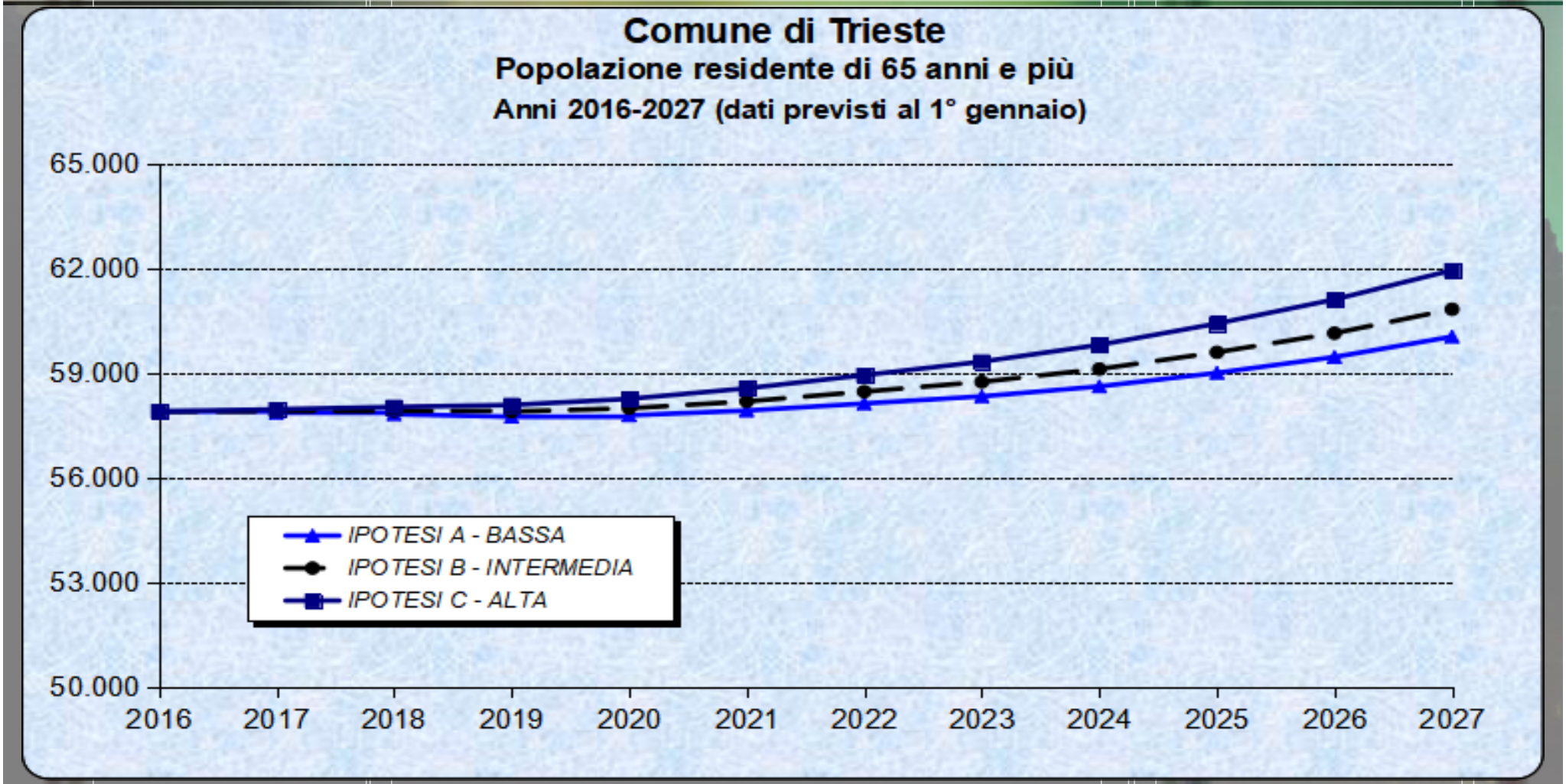

1926
2016
100+
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
1,5
1,0
0,5
0
nati nel 1926
nati nel 1952
nati nel 1976



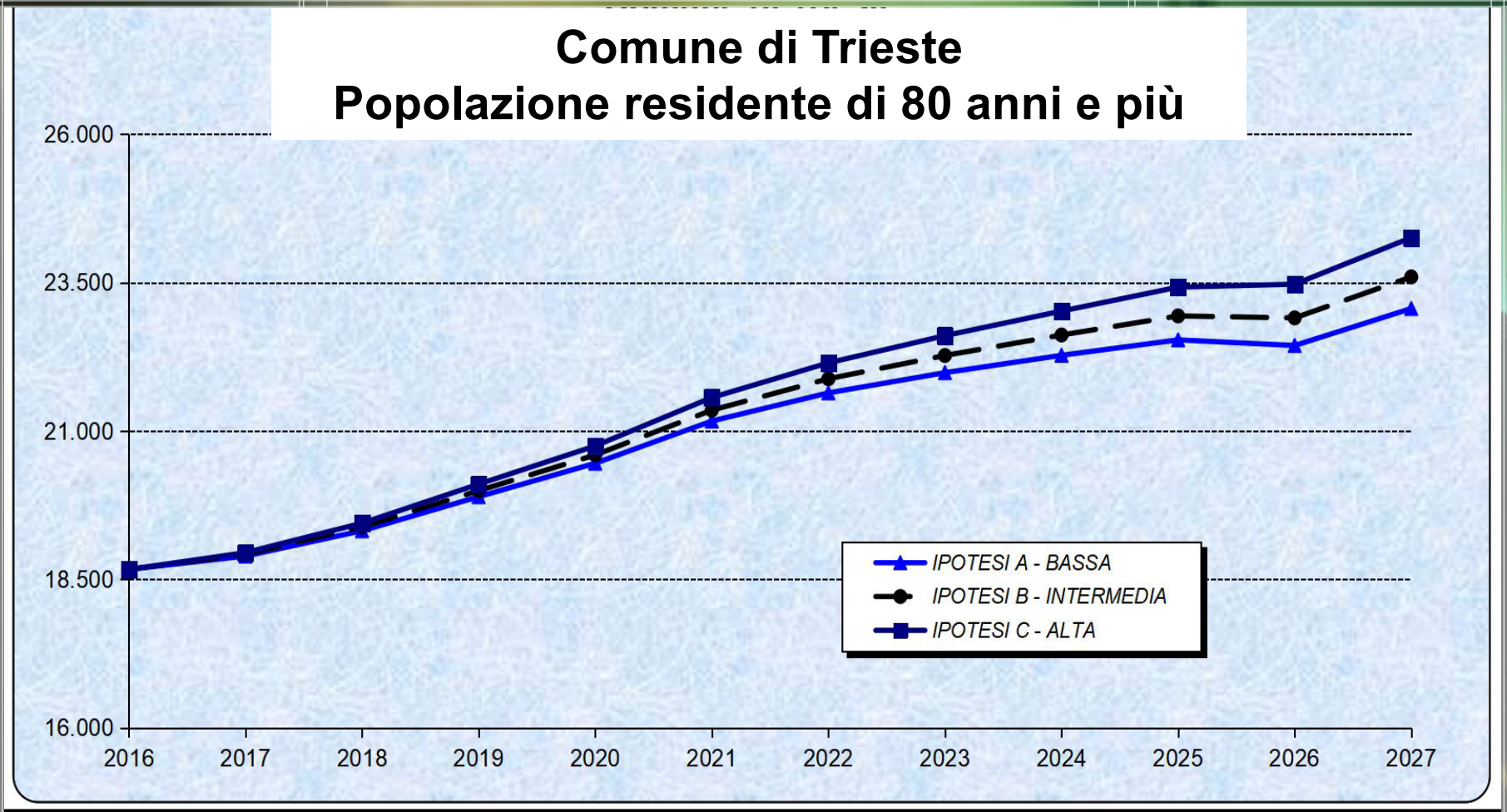
Popolazione per età, sesso e stato civile - 2015 **(205.413)**

COMUNE DI TRIESTE - Dati ISTAT 1° gennaio 2015 - Elaborazione TUTTITALIA.IT

PROIEZIONI SULLA POPOLAZIONE DELL'UFFICIO STATISTICO DEL COMUNE DI TRIESTE



PROIEZIONI SULLA POPOLAZIONE DELL'UFFICIO STATISTICO DEL COMUNE DI TRIESTE



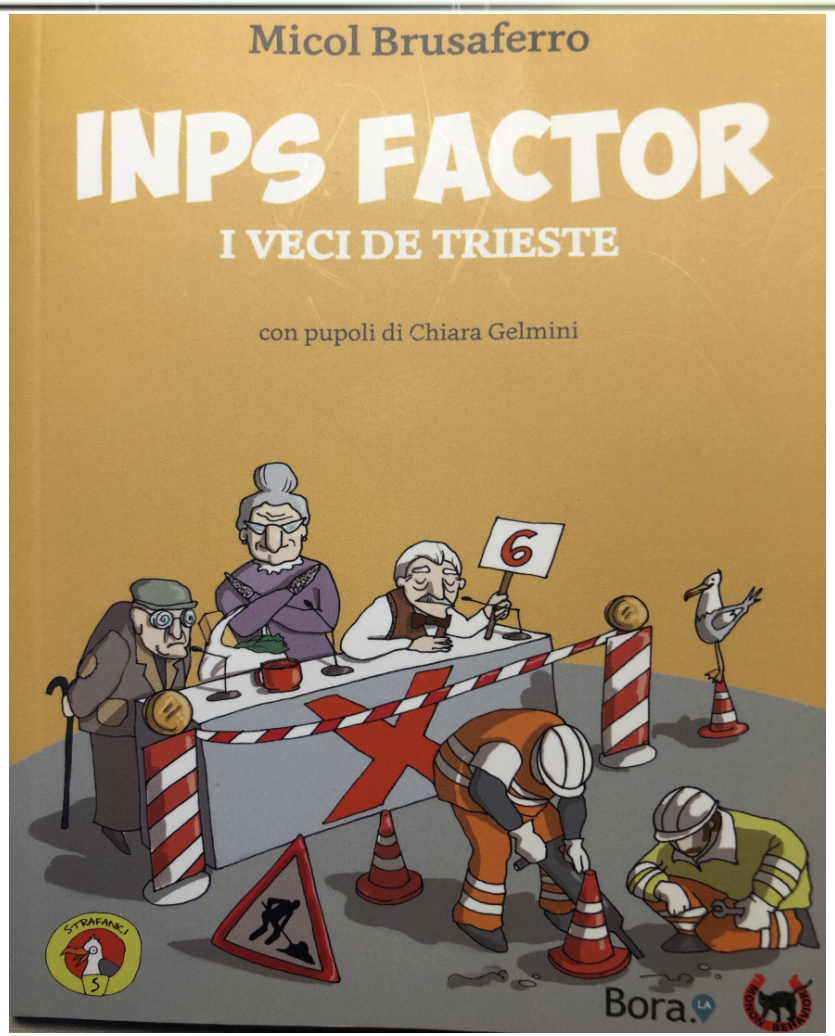
La carica della quarta età e la crescita inarrestabile dell’esercito di over 80 (Il Piccolo 2019)

Anziani a scuola di tablet e smartphone: Presentata all’ITIS la app “iNonni” già sperimentata con successo da molti ultra-ottantenni (Il Plccolo 2019)

Malore dopo il tuffo Due ottantenni rischiano di affogare (Il Piccolo 2018)

Cadono dalla ferrata: due alpinisti muoiono in Val Rosandra Si tratta dell'84enne RN del 78enne GP. I corpi dei due anziani sono stati ritrovati in tarda serata dagli uomini del soccorso alpino (Il Piccolo 2018)

Un salto con il parapendio sopra San Dorligo. Così il super nonno Tullio festeggia i 90 anni (Il Piccolo 2019)



Trieste - Nuove diagnosi di LLC

	2016	2017	2018	totali
LLC casi nuovi)	29	40	42	294
LLC < 70 aa	14	7	13	72 (24%)
LLC > 70 aa	15	33	29	222 (75%)
IGH MUTATE	18	28	29	197 (72%)
IGH NON -MUTATE	11	12	13	75 (27%)
17p/p53 WT	23	35	38	248 (91%)
17p/p53 M /D	6	5	4	24 (8%)
			Media	75 ± 9
			Mediana	76
			Moda	79
			Range	48 - 101

Trieste – Terapie in LLC

Terapia	2017	2018	2019
Pts in osservazione mai trattati	102	130	170
Pts Terapia 1 L	7	6	14
Pts Terapia salvataggio	10	11	21
FCR	3	1	1
BR	7	7	2
Ibrutinib	5	6	22
Idelalisib	1	3	5
Venetoclax	1	1	5
Allo SCT	0	0	0

GRAZIE

DELL'ATTENZIONE !