



CLL SOCIETY



CLL Society's Virtual Event  
October 26, 2022

## **Playing CLL/SLL Chess: Planning Your Therapy Moves**

**12 PM PT, 1 PM MT,  
2 PM CT, 3 PM ET**

# Agenda and Speakers



## Speaker and Moderator

**Terry Evans**

22-year CLL Patient and Advocate  
Director, CLL Society Support  
Network



## Speaker

**Susan O'Brien, MD**

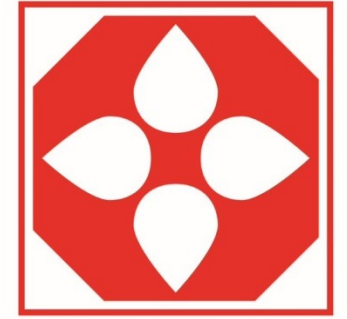
Professor of Medicine  
University of California, Irvine



## Welcome

**Brian Koffman, MDCM (retired) MS Ed**

Co-Founder, EVP, and Chief Medical  
Officer, CLL Society

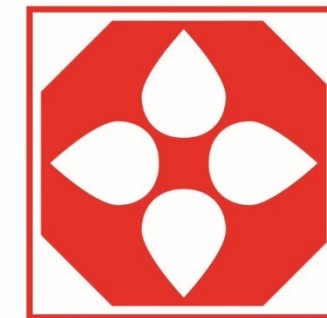


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## Agenda

12:00 PM PT	Program Welcome and Overview	Dr. Brian Koffman
12:10 PM	Patient Self-Advocacy and Education	Terry Evans
12:25 PM	Therapy Sequencing for CLL/SLL	Dr. Susan O'Brien
12:55 PM	Audience Q&A	Terry Evans and Dr. O'Brien
1:30 PM	Program Close	Terry Evans

This program was made possible by support from



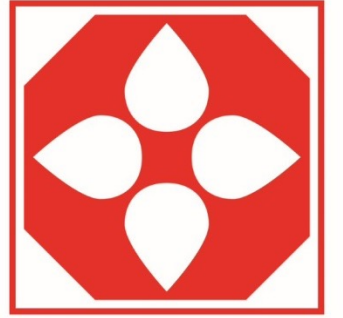
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Supported by an educational grant from Pharmacyclics LLC, an AbbVie Company and Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC

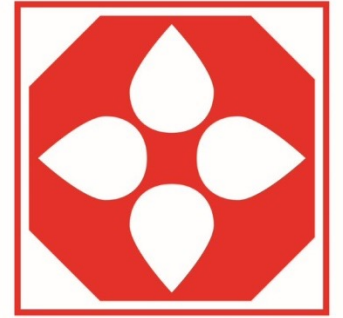
# Pre-Event Reminders

- The audience is muted
- Please direct your questions to speakers or CLL Society staff using the Q&A box (located at the bottom of your screen). Questions can only be seen by staff and speakers.
- Please complete the short post-event survey. Your response will help CLL Society plan future events.
- The event is being recorded and will be available along with the presentation slides on our website
- Please explore your screen to view resources, speaker bios, the post-event survey, and a link to donate to CLL Society



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# CLL Society Programs and Resources



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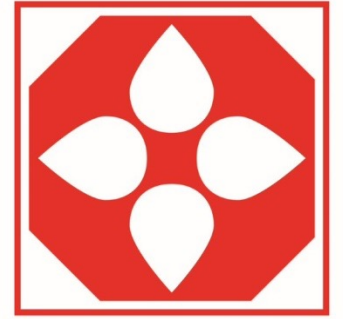
- CLL Society Patient & Caregiver Support Groups
- Expert Access™ Program – Free, online, 2nd opinion from a CLL expert physician
- Webinars / Virtual Community Meetings
- Weekly Email Newsletter
- COVID-19 & CLL-specific Updates, Expert Interviews & Conference News
- Ask the Expert
- Patient Centric Research
- Test Before Treat™ Campaign

Contact us at [Support@cllsociety.org](mailto:Support@cllsociety.org)



# Poll Question

A pop-up box will appear with the poll question below:



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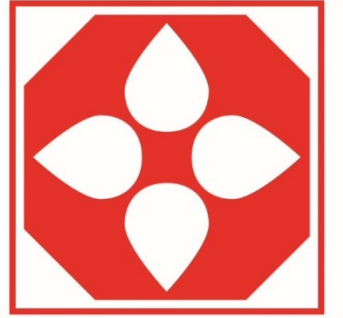
- 1. Please indicate your role in the shared decision making for your current or future treatment of CLL/SLL.**
  - a) My doctor does not provide me with treatment options. She or he tells me the plan
  - b) I listen to the options my doctor presents, but I primarily let the doctor make the decision
  - c) I listen to the options my doctor presents, but I primarily make the decision myself
  - d) I listen to the options my doctor presents but I also proactively research treatment options and I primarily make the decision myself
  - e) Not applicable



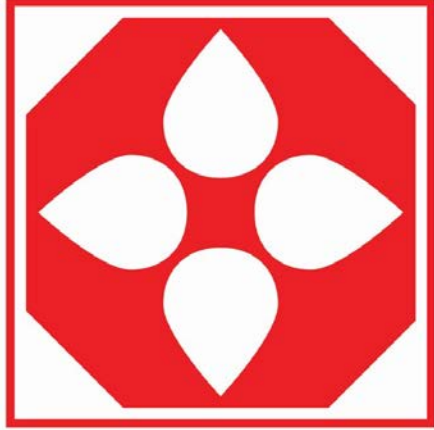
# Poll Question

A pop-up box will appear with the poll question below:

- 2. Have you identified a future treatment option, should you need to begin treatment or if your current treatment ceases to be effective?**
- a) Yes
  - b) No
  - c) Unsure
  - d) Not applicable



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*Smart Patients Get Smart Care™*

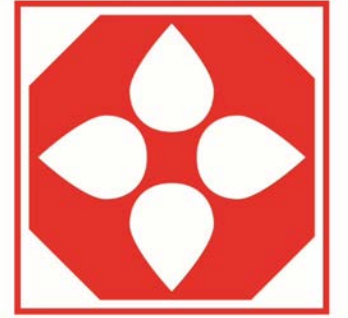
# Playing CLL/SLL Chess: Planning Your Therapy Moves

**Terry Evans**  
CLL Patient and Advocate

October 26, 2022



# Diagnosis

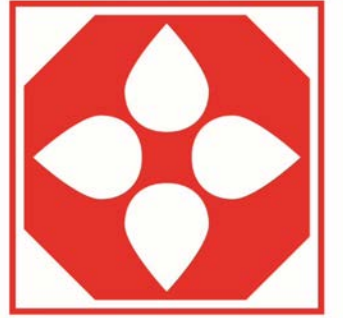


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- Diagnosed in 2000 by a routine blood test in an annual physical
- Flow Cytometry confirmed I had very early stage CLL
- I was told I had an uncurable leukemia, but we were just going to watch it??????????????
- Monitored by a local hematologist for the next 7 years
- No treatment during this time
- Then.....

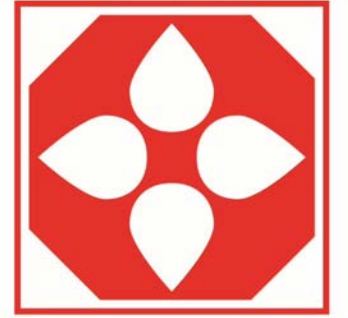
# Treatment Time

- In two months time WBC went from 280,000 - 540,000
- In October of 2007 I began treatment
- I was given no choice, although there were few options
- The treatment was not really explained
- FCR for only 3 days
- Developed Autoimmune Hemolytic Anemia



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# TIME TO MAKE A CHANGE!

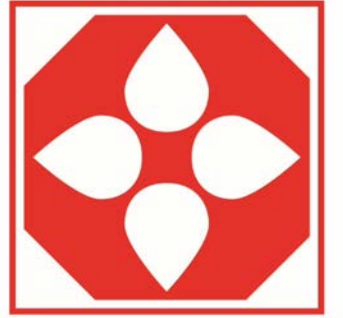


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- I had always 'intended' to see a CLL Specialist
- BUT I didn't....
- Now I was in a **critical situation** where my local hematologist refused to accept the fact that I had AIHA
- My wife contacted a doctor in England, Dr. Terry Hamlin, and he confirmed I probably had AIHA, and to get to a CLL Specialist
- She then contacted UCSD, faxed my blood tests, and had an appointment within 5 days with Dr. Tom Kipps at UCSD

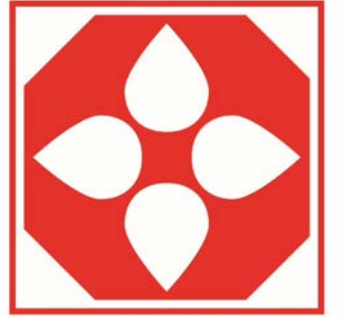
# I Had an Epiphany!

- I almost died
- I had not educated myself
- I had not seen a CLL specialist
- I needed to find other people with CLL



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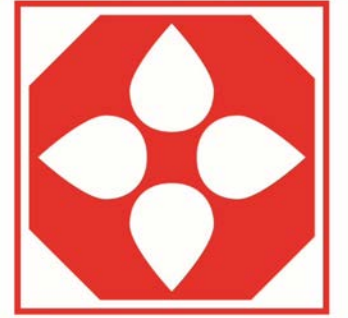
# Taking Control



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- I began educating myself on CLL, joining online forums, reading CLL papers online and going to conferences
- I became part of the decision-making team
- I got 2<sup>nd</sup> and 3<sup>rd</sup> opinions from respected CLL experts

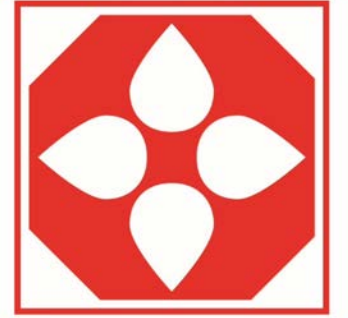
# How My Journey Has Changed



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- In 2008 I began participating in a group of CLL patients which would become the start of the CLL Society
- I am fortunate to now lead the original CLL Society Orange County, CA Support Group
- And have participated in starting the other 40+ CLL Society Support Groups across the U.S. and Canada

# Treatments

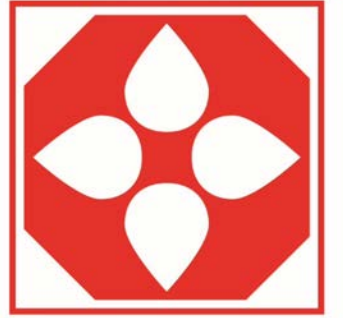


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- I have had 7 treatments in my 22 years with CLL
- During that time, I have had to do a lot of research to figure out what will happen next. Needed to plan for how next therapy might influence future therapy options or “sequencing”.
- This was real for me when I became resistant to BTK inhibitor
- I have used shared decision making with my medical team
- I have been on 3 Clinical Trials
- I have had to make some hard decisions based on the best information I could gather

# Takeaways

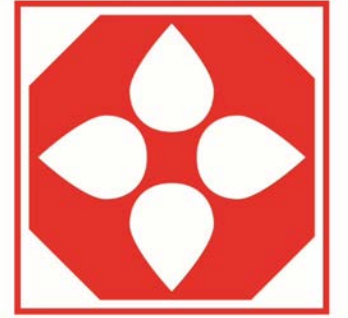
- Educate yourself
- Join a Support Group
- Get a CLL Expert on your team
- Be part of the decision-making process
  - Ask questions, have someone take notes or record your appointments
- If you don't 'click' with your doctor – **CHANGE DOCTORS**
- If your medical team doesn't offer a treatment you are interested in, search out where you can possibly receive it



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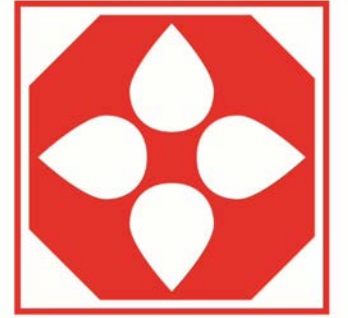
# Takeaways (Continued)



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- I have most ALL of the BAD markers
  - 17p, TP53, 11q, complex Karyotype, unmutated, Zap-70+
  - Don't be discouraged if you have any of these
- Here I am today, 22 years after diagnosis, all because of the advances made in the treatment of CLL and great doctors
- I want to publicly thank my wife, my medical teams, my friends and fellow patients, CLL Society, and the pharmaceutical companies for **SAVING MY LIFE**

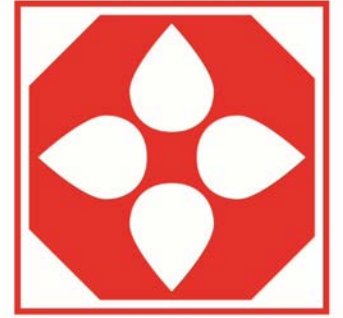
# Don't Be Complacent!



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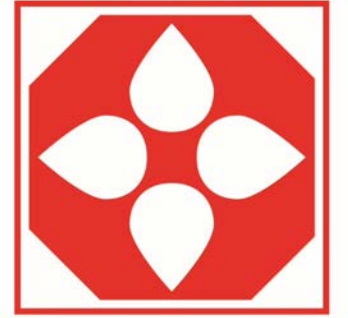
- Remember that CLL is still a largely an incurable disease
- Even though you may be doing well on a treatment, or you are having a lengthy remission, there is a chance you will relapse
- Be ready for that change by looking into treatments that you would qualify for **BEFORE** you relapse. Think about your next, next move when planning the present move.
- Don't be afraid to consider clinical trials in your options
- Don't be afraid to consult with other medical centers and other doctors for your NEXT treatment(s)

# Innovation and Intervention



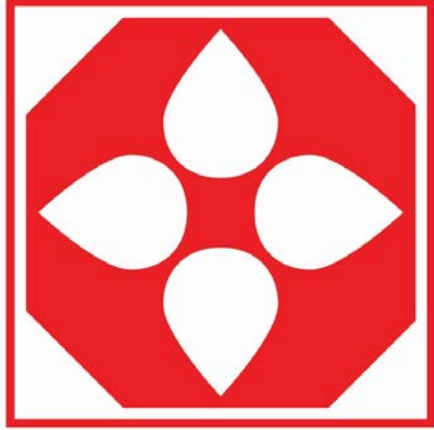
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- We are all aware of the tremendous strides that have happened in the last 10 years in the treatment of CLL
- But sometimes you need intervention
- I was in a Clinical Trial where there was no Crossover
- A group of dedicated CLL doctors lobbied for the change to be made
- Including this editorial by Dr. Susan O'Brien who said
  - **“Here’s the harsh reality: There are people on the control arm of RESONATE (the name of the trial) who will probably have disease progression and die.”**
- Soon after that, the trial was modified to include a crossover and that saved my life



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Thank you for your time



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*Smart Patients Get Smart Care™*

# Therapy Sequencing for CLL/SLL

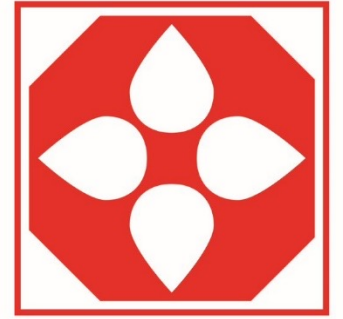
**Dr. Susan O'Brien, MD**

Professor of Medicine

Division of Hematology/Oncology

UC Irvine Health, University of California

# Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

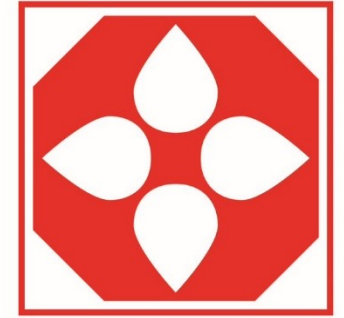


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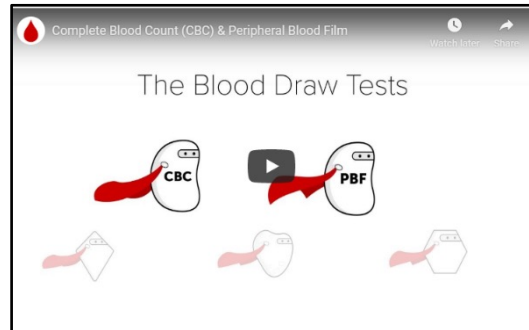
- Most common leukemia in Western world ~ 20,000 US cases annually
- Accounts for 30% of adult leukemias
- Median age at diagnosis 70 years

Most physicians in private practice will have some patients with CLL but are unlikely to have treated more than a handful.

# Tests For Diagnosing CLL

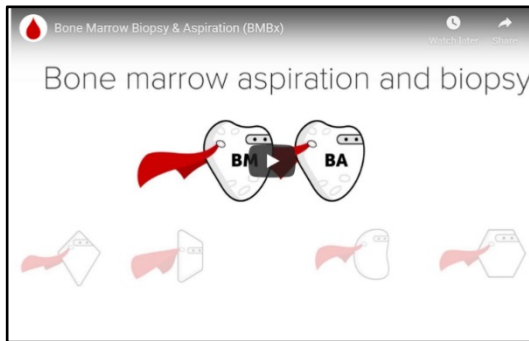


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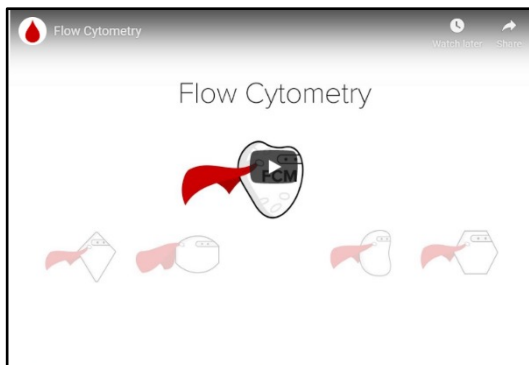
**Blood cell counts and examination**

**Bone marrow examination ?**

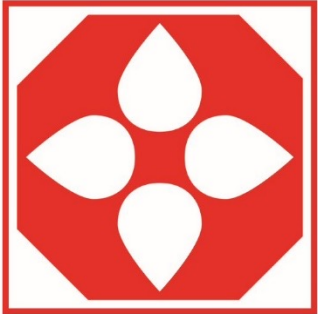


**Immunophenotyping (flow cytometry)**

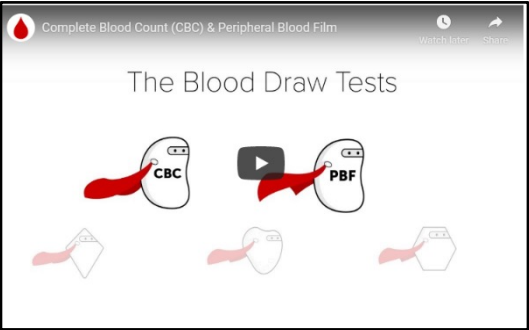
**Quantitative Immunoglobulin test is optional**



# Tests For Treatment Planning

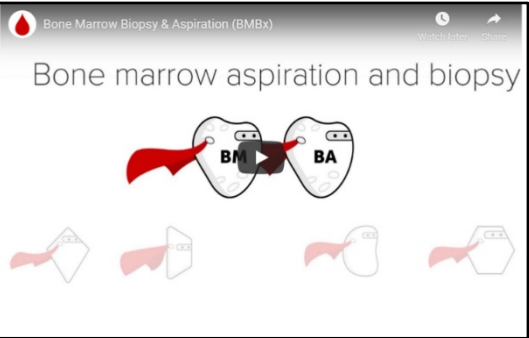


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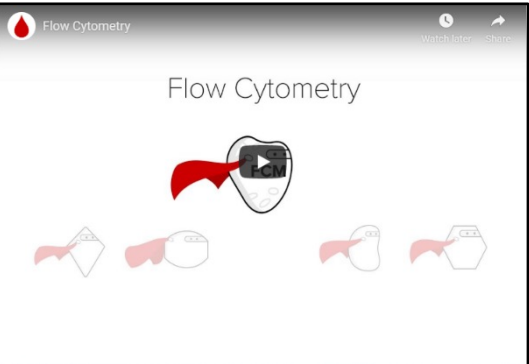
**Fluorescence In Situ hybridization (FISH)**

**Karyotyping**



**DNA Sequencing (TP53 mutation)**

**Beta-2 Microglobulin**

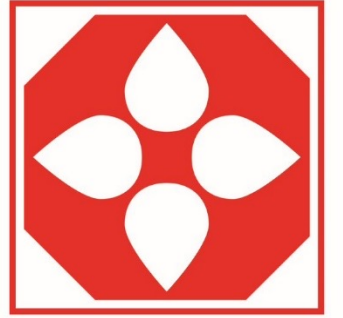


**Hepatitis B Testing**



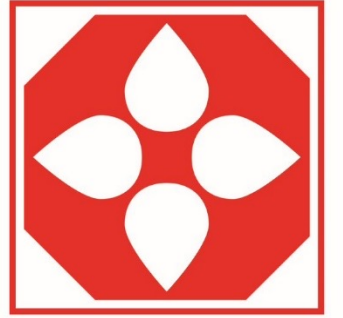
# Watch and Wait or Watch and Worry! Why Not Treat CLL at Diagnosis?

- Slowly progressing disease
- Often no symptoms
- Average age early 70's
- Most therapies are palliative or non-curative and many will need sequential therapies



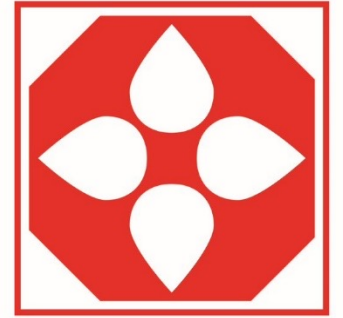
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# Is Watch and Wait Still Best?



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# SWOG CLL Study S1925



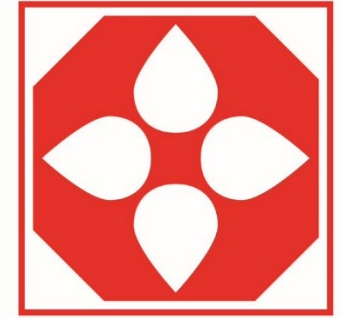
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Randomized, Phase III Study of Early Intervention with Venetoclax and Obinutuzumab versus DeLayed Therapy with Venetoclax and Obinutuzumab in Newly Diagnosed Asymptomatic High-Risk Patients with CLL:  
EVOLVE CLL Study

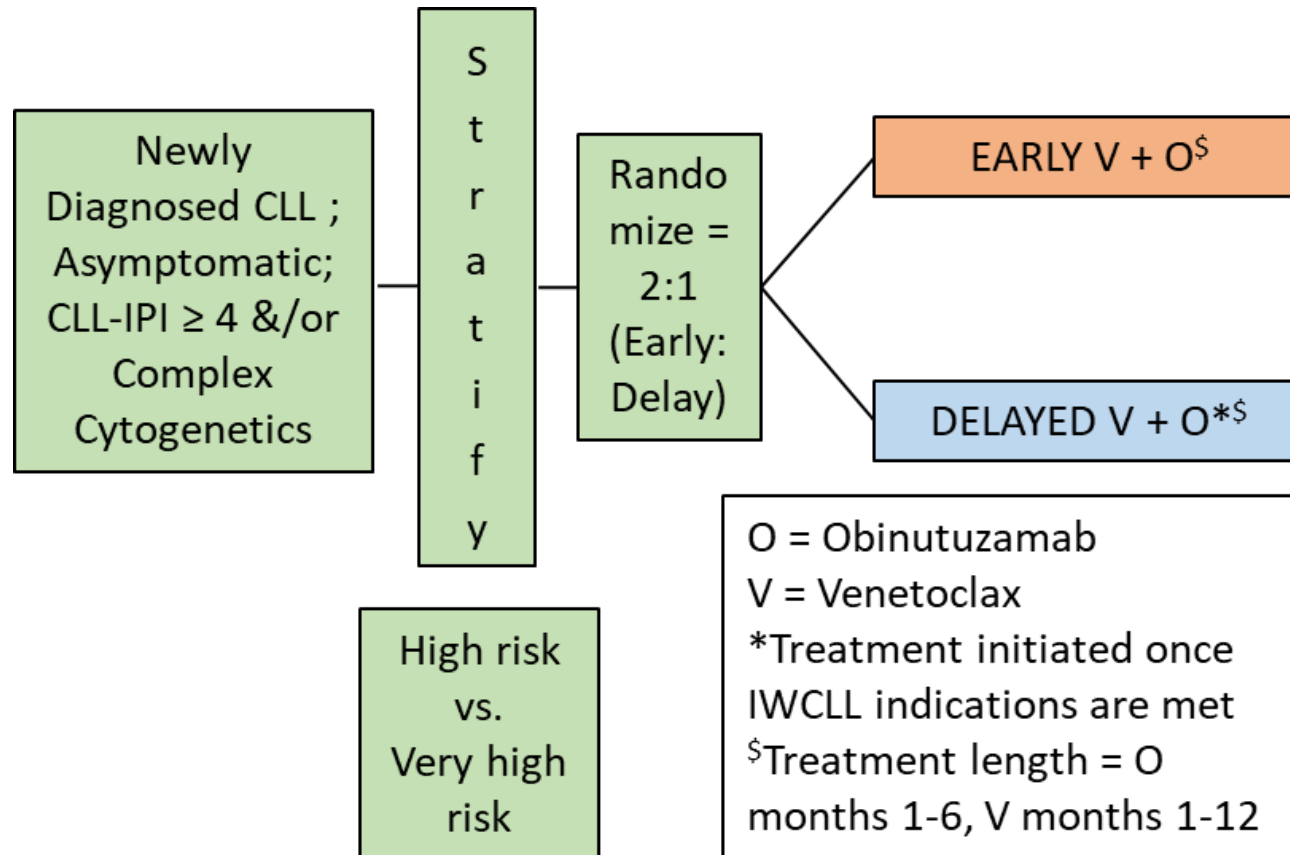
## SWOG CLL Study Group

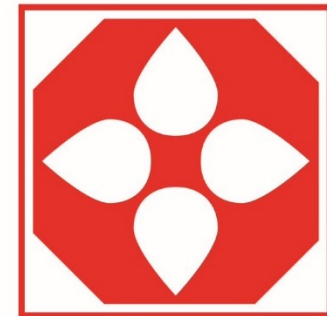
Debbie Stephens, Brian Hill, John Pagel, Alexey Danilov, Mazyar Shadman, Susan O'Brien, Steve Coutre  
ECOG Champion: Anthony Mato

# S1925: EVOLVE Study



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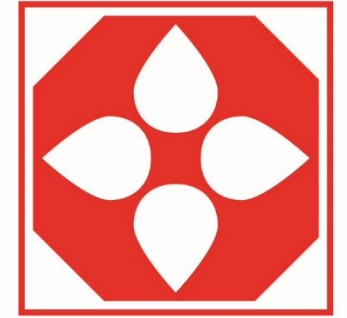




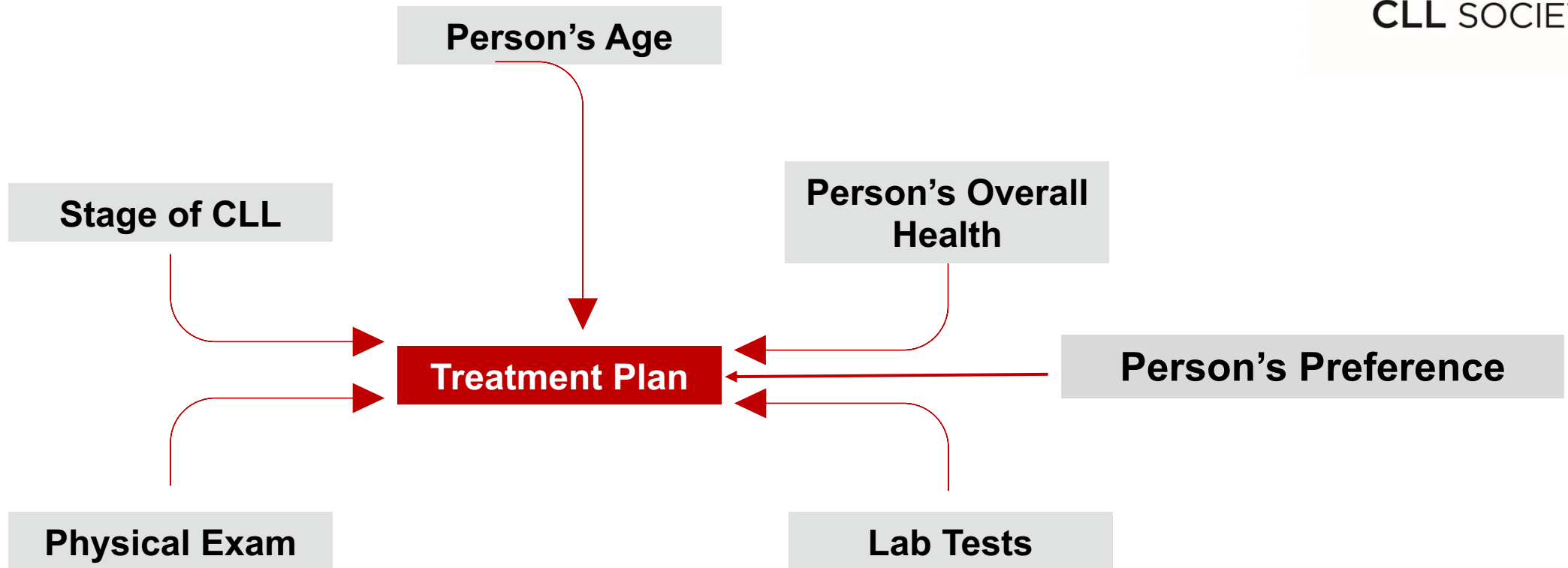
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# Frontline Therapy

# Treatment Planning: Frontline

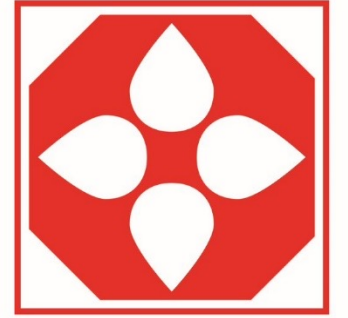


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**Frontline Therapy May Influence Choices Later**

# About Clinical Trials



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A CAREFULLY CONTROLLED **RESEARCH STUDY** CONDUCTED BY DOCTORS TO

- Improve treatment options
- Increase survival
- Improve quality of life

Designed to give patients the safest, potentially most effective therapies

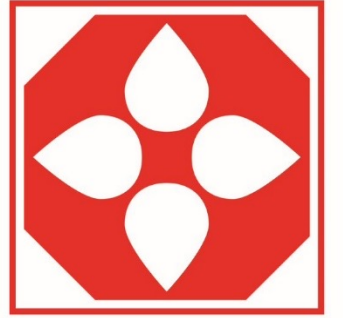
# More About Clinical Trials

## Who Should Participate?

**Patients should not wait for standard treatment to fail before asking about trials.**

**Trials are not only for people with the most advanced disease.**

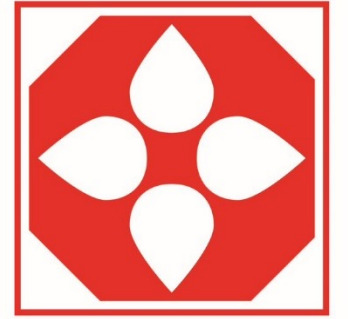
**Trials can be designed to test new treatments that improve response rates or improve quality of life of patients with newly diagnosed or very limited disease.**



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# Important Definitions Related to Clinical Trials

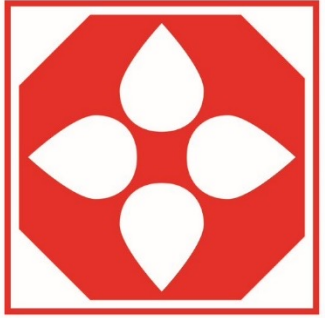


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**PFS: Progression Free Survival (after treatment)**  
Shows how many patients are in remission  
(disease has not recurred) and alive

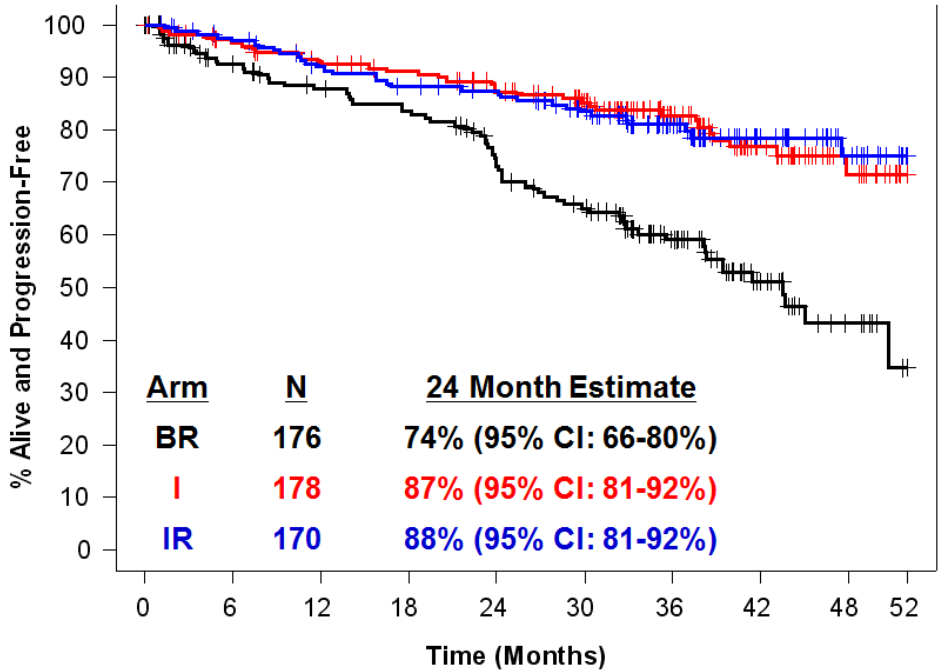
**OS: Overall Survival shows how many patients are  
alive (whether they are in remission or not)**  
OS is measured from the start of the therapy

# How Does Ibrutinib Square Up against Chemoimmunotherapy (BR, FCR)?



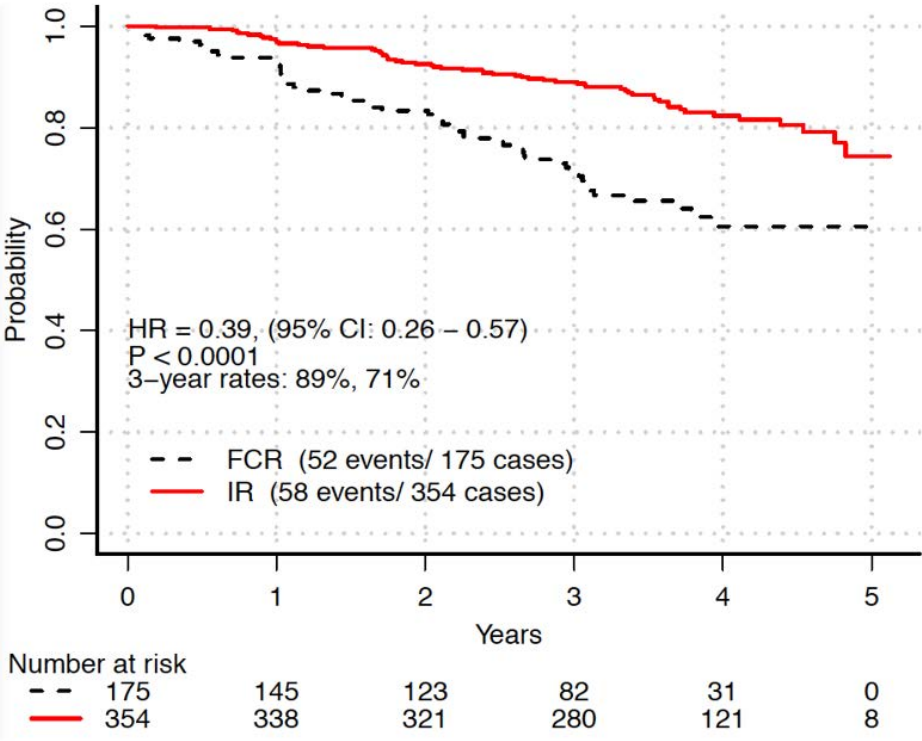
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## IR vs BR Progression Free Survival

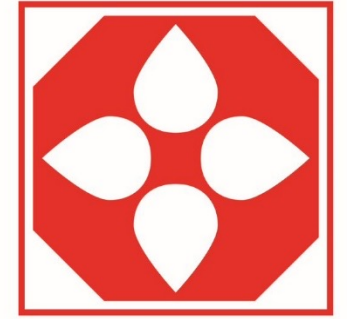


	Patients-at-Risk									
	0	6	12	18	24	30	36	42	48	52
Arm A (BR)	176	140	129	122	103	88	57	26	11	0
Arm B (I)	178	165	154	147	136	120	78	45	22	0
Arm C (IR)	170	159	145	138	132	115	74	40	20	0

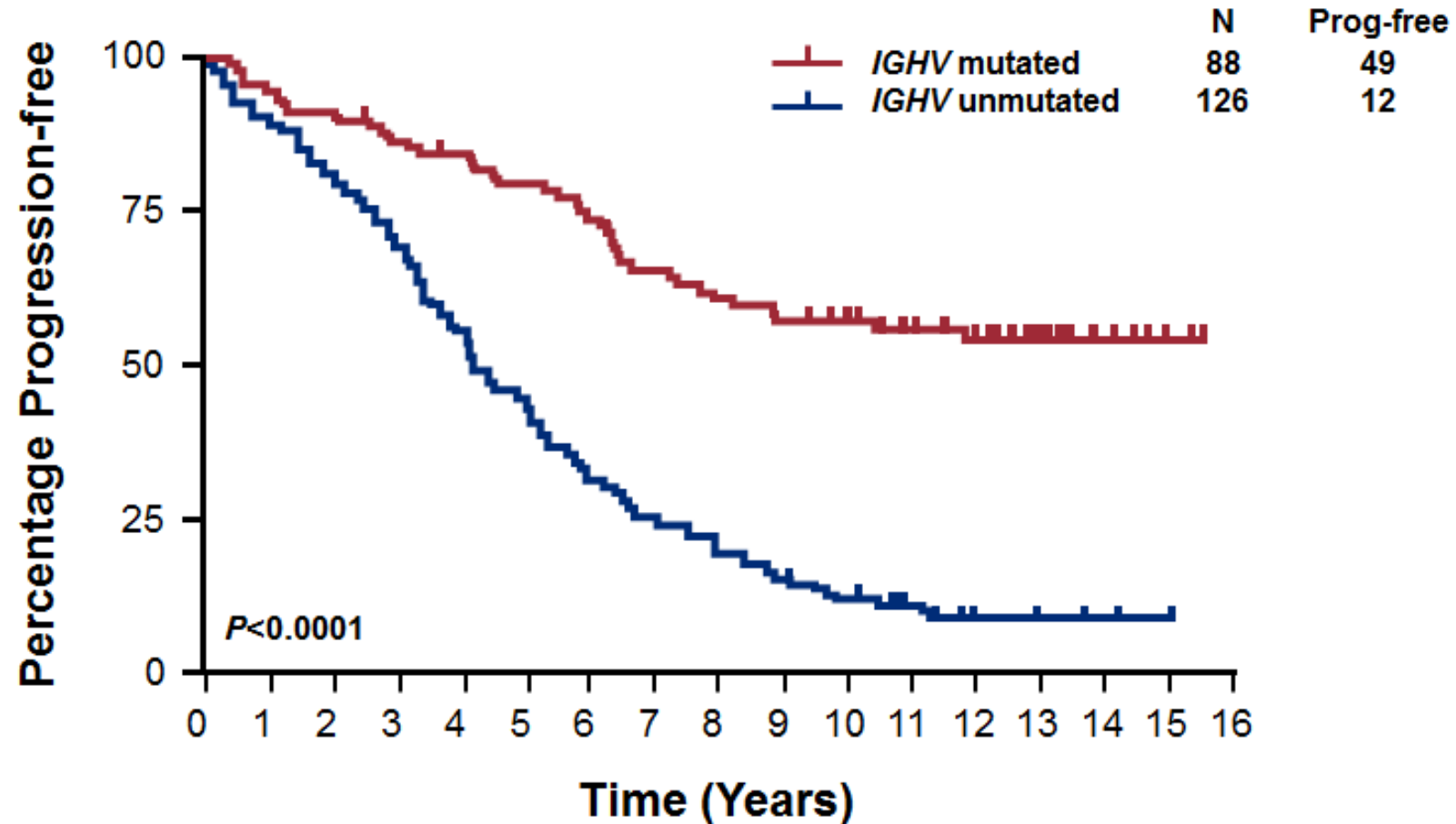
## IR vs FCR Progression Free Survival



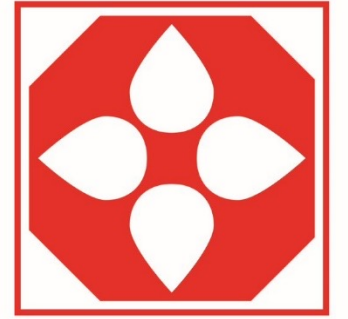
# Favorable Long-term PFS with Firstline FCR in *IGHV*-M Subgroup



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# This Data Suggests That Some People Treated With FCR Are Cured

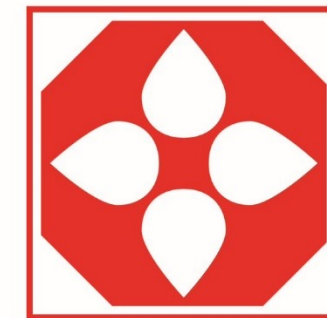


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- **However, this population is limited to younger patients (who can tolerate FCR) and who have a mutated IGHV gene (so the minority of all patients)**

# Acalabrutinib +/- Obinutuzumab vs. Chlorambucil + Obinutuzumab PFS

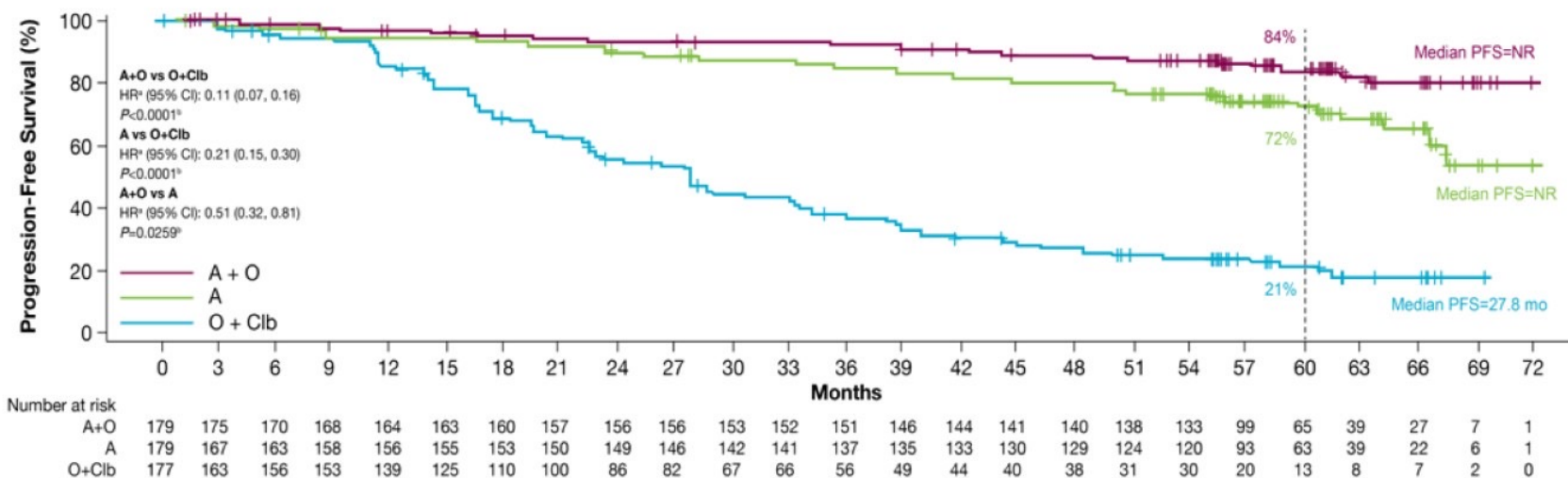
## Investigator-assessed PFS



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- Median PFS was significantly longer for acalabrutinib containing arms than obinutuzumab and chlorambucil
- At 60 months, estimated PFS rates were in favor of A+O (84%) and A (72%)

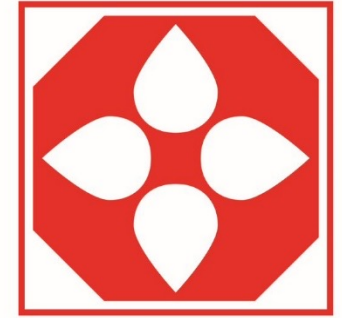
### A. Investigator-assessed PFS



<sup>a</sup>Hazard ratio based on Cox proportional-hazard model stratified by 17p deletion status (yes vs no based on interactive voice/web response system). <sup>b</sup>P-value based on log-rank test stratified by 17p deletion status (yes vs no based on interactive voice/web response system).

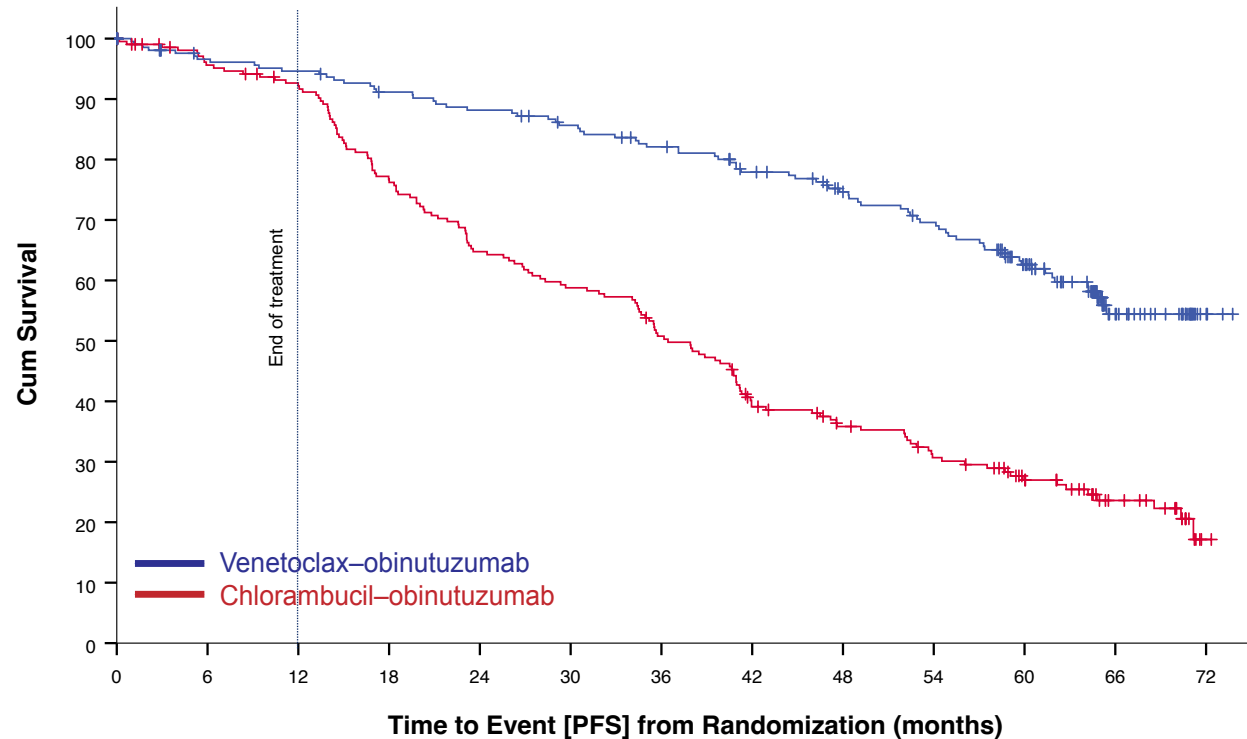
A = acalabrutinib; CI = confidence interval; Clb = chlorambucil; NR = not reached; O = Obinutuzumab; PFS = progression free survival; vs = versus.

# CLL14: Venetoclax + Obinutuzumab vs Chlorambucil + Obinutuzumab PFS



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Median observation time 65.4 months



## Median PFS

Ven-Obi: not reached

Clb-Obi: 36.4 months

## 5-year PFS rate

Ven-Obi: 62.6%

Clb-Obi: 27.0%

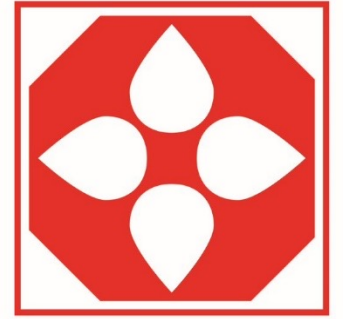
HR 0.35, 95% CI [0.26-0.46]

P<0.0001

Ven-Obi	216	196	192	183	177	169	160	147	134	123	97	35	4
Clb-Obi	216	195	185	154	130	118	101	75	64	53	39	21	1

# Frontline Therapy Options

Therapy	PFS at 5 years
Ibrutinib	70%
Acalabrutinib	72%
Acalabrutinib and Obinutuzumab	84%
Venetoclax and Obinutuzumab	63%, 60% unmutated,
Zanubrutinib	No 5-year data yet
FCR	80% mutated IGHV gene

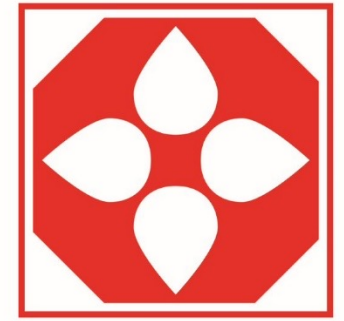


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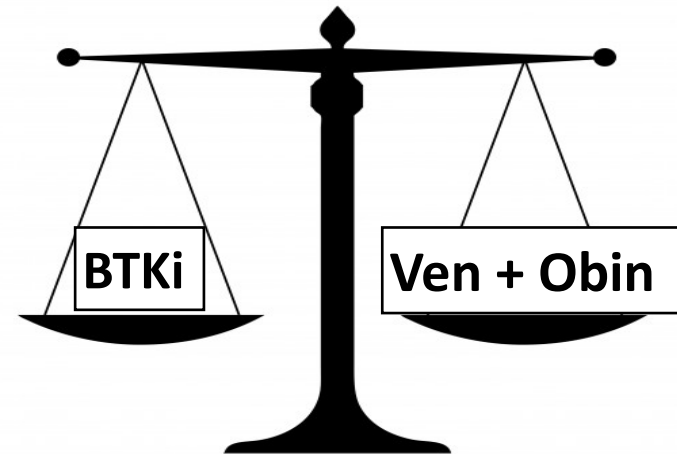
## Important Points

- Ibrutinib, acalabrutinib and zanubrutinib are continuous therapy
- Venetoclax is time-limited therapy (1 year total)
- Side effect profiles vary between all of the small molecules
- FCR is the only chemo-based regimen that may have a cure fraction but limited to younger, fit patients who can tolerate it and have a mutated IGHV gene

# Frontline BTK Inhibitor vs. Venetoclax + Obinutuzumab: Factors to Consider



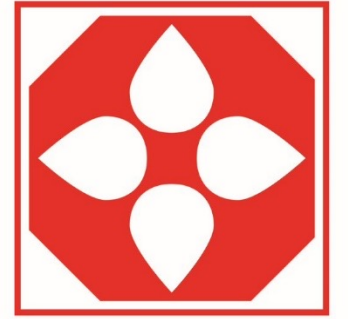
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- **Convenience (no infusions, tumor lysis monitoring)**
- **Longer term data**
- **Ibrutinib shown to be better than both FCR and BR**
- **More data for response to venetoclax at time of ibrutinib progression**

- **Potential for 1-year time-limited therapy**
- **No known cardiac or bleeding risks**
- **Less concern for long term adherence**
- **Potential for cost-saving if 1-year of therapy is durable**

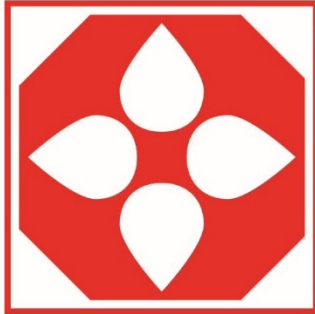




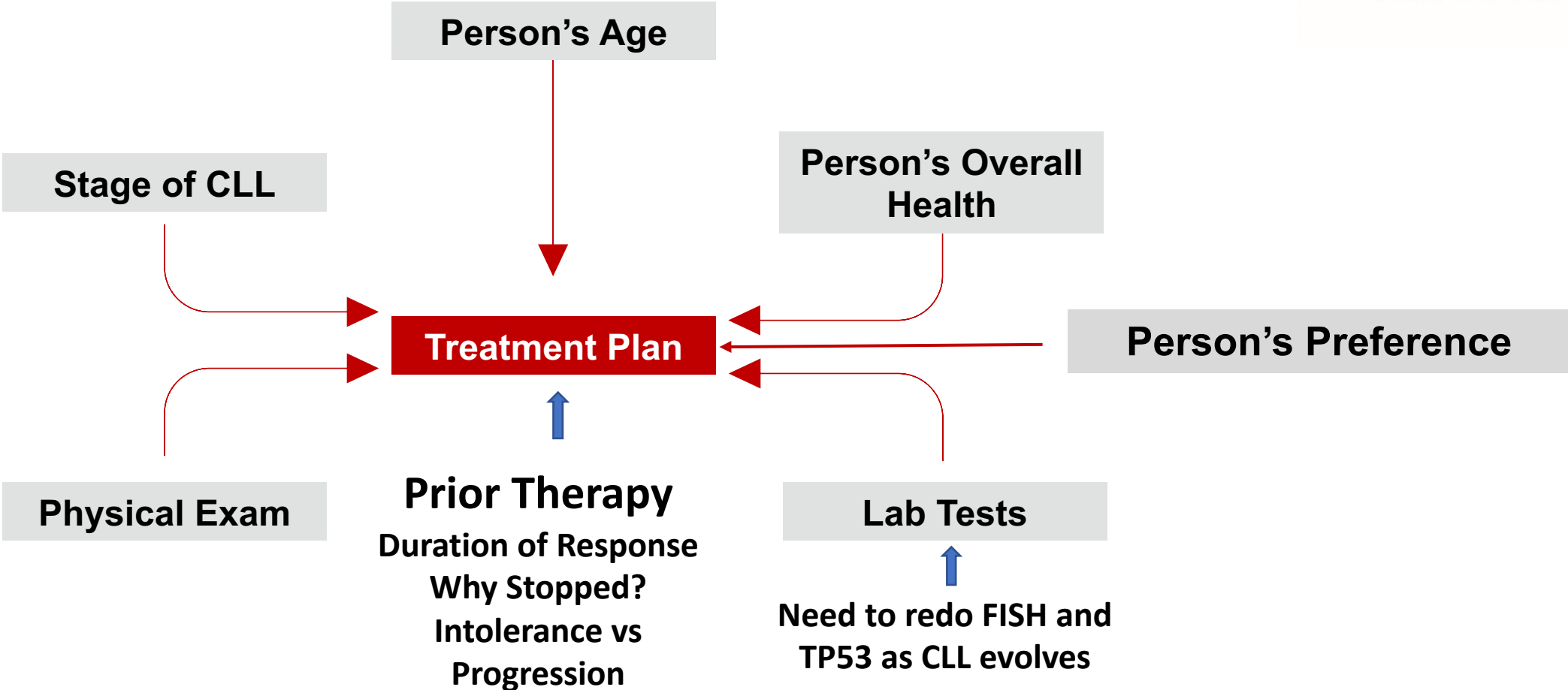
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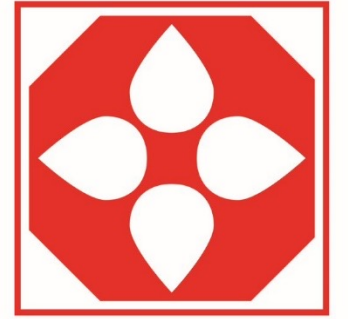
# Second Line Therapy

# Treatment Planning – Second Line



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# Second Line Therapy

Must Retest Prognostic Tests\* Before Starting Second Line Therapy as CLL/SLL Evolves

\* IGVH does not change over time and does not need to be retested

# Second Line Therapy Options

## Therapy

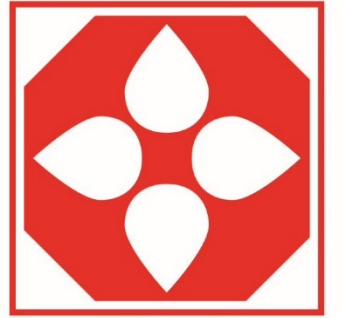
BTK inhibitor alone

BTK inhibitor with Obinutuzumab

Venetoclax and Obinutuzumab (or Rituximab)

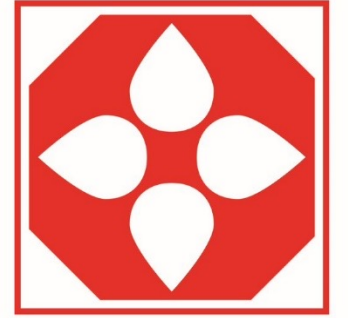
Off Label Medications or Combinations (i.e. I+V)

Clinical Trial



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# Second Line Therapy Options

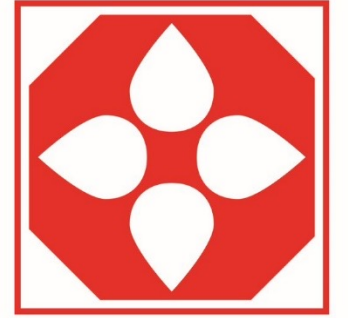


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## Important Points: BTKi Based Therapy First

- If progress on any of the licensed BTK inhibitors (ibrutinib, acalabrutinib, and zanubrutinib), switching to a different member of the class won't work
- If intolerant to one of the BTK inhibitors, switching to another may help
- There are new BTK inhibitors in trials that do work after progression on the licenced BTK inhibitors as the new drugs bind differently
- Good data that venetoclax based therapy works well after BTK inhibitor
- Essentially no role for chemo-immunotherapy second line
- Clinical trial may be best choice

# Second Line Therapy Options



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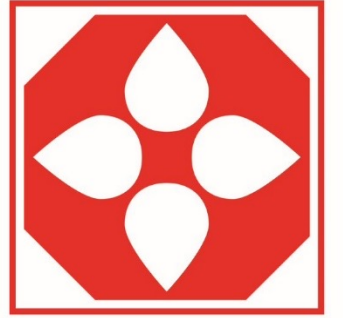
## Important Points: Venetoclax Based Therapy First

- Venetoclax based therapy is 2-year time limited when used second line
- It is approved with rituximab, but can be and often is used off label with obinutuzumab
- Can repeat venetoclax based time limited therapy if well tolerated and first response was durable
- Less but encouraging data that BTKi works well post venetoclax
- Again, no role for chemo-immunotherapy second line
- Clinical trial may be best choice

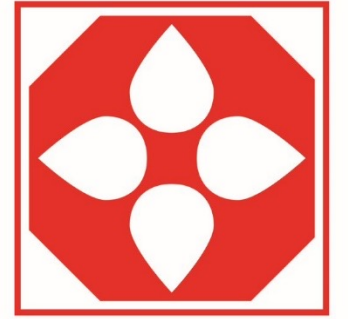
# Second Line Therapy Options

## **Important Points: Chemotherapy Based Therapy First**

- Especially important to recheck prognostic markers
- Again, no role for chemo-immunotherapy second line
- Both venetoclax and BTK inhibitor therapies will work
- Clinical trial may be best choice



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# Third and Later Line Therapy



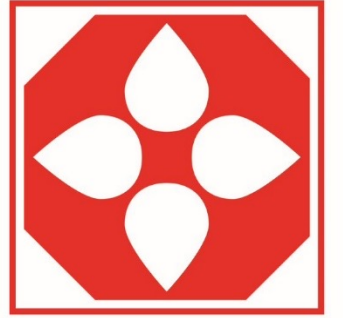
# Third and Later Line Therapy Options

## Therapy

PI3K Inhibitor

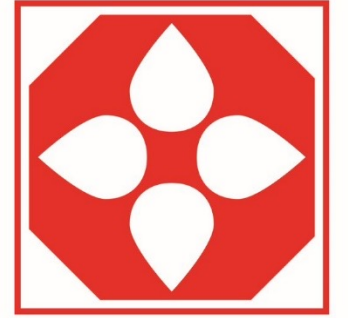
Off Label Medications or Combinations (i.e. I+V)

Clinical Trial



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# Third and Later Line Therapy



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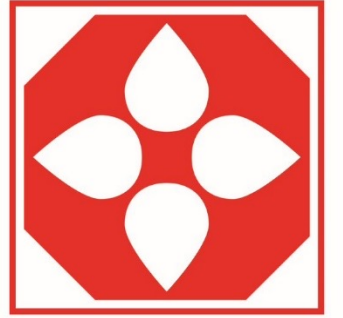
## Important Points

**“Double Exposed or “Double Refractory” (there is a difference)  
Patients who have been exposed or progress after both a BTK inhibitor  
and Venetoclax**

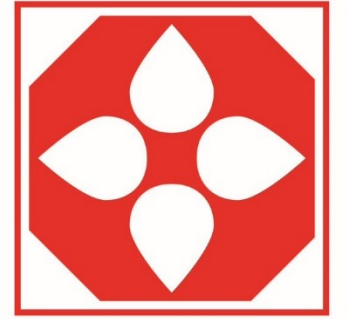
- Again, must retest prognostic markers
- One of the biggest and growing unmet needs in CLL/SLL as patients are living longer
- All the prior points related to second line therapy apply, especially that a clinical trial might be the best choice
- PI3K inhibitors are still an option as of now, but have significant toxicities
- Still a role for hematopoietic stem cell (bone marrow) transplant in some patients

# Therapy Sequencing for CLL/SLL

- What therapy you choose first influences what you do later
- Progressing after a particular medication doesn't mean it won't work again, especially if:
  - You have a long progression free response after stopping
  - You plan to use it in combination with another medication
- Clinical trials are often the best choice, even in the frontline setting

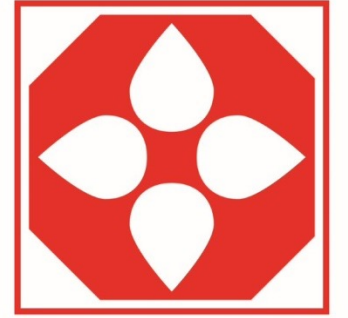


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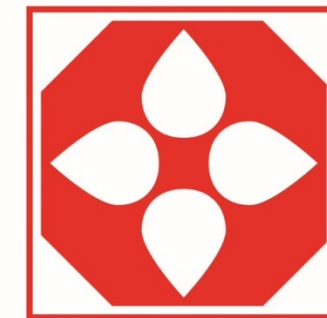
Thank You



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# Audience Questions & Answers

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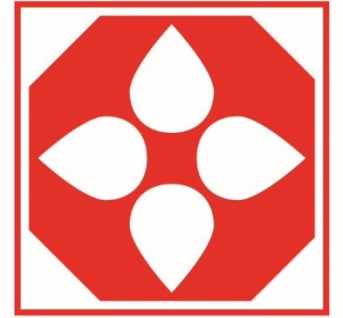
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# Thank You for Attending!

Please take a moment to complete our **post-event survey**, your feedback is important to us



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Join us on November 16<sup>th</sup> for our **Annual Patient and Caregiver Ed Forum** and watch out for the **Deep Dive into Five Podcast** expanding on this event

If your question was not answered, please feel free to email [asktheexpert@cllsociety.org](mailto:asktheexpert@cllsociety.org)

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