19th International Ultmann Chicago Lymphoma Symposium

LIVE Symposium

APRIL 29-30
2022

19TH ULTMANN

THE UNIVERSITY OF CHICAGO
MEDICINE & BIOLOGICAL SCIENCES

Follicular Lymphoma in a Pandemic

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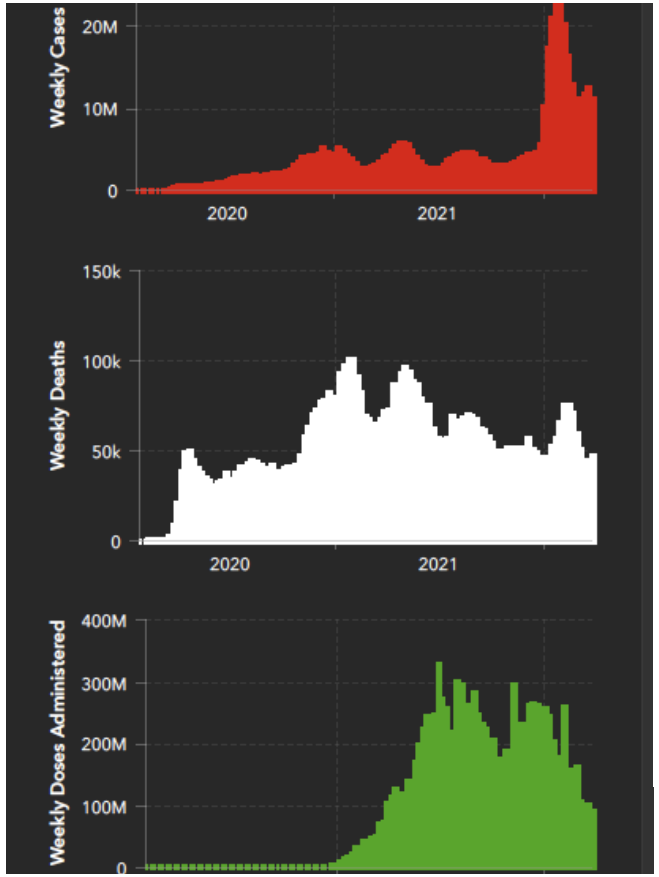
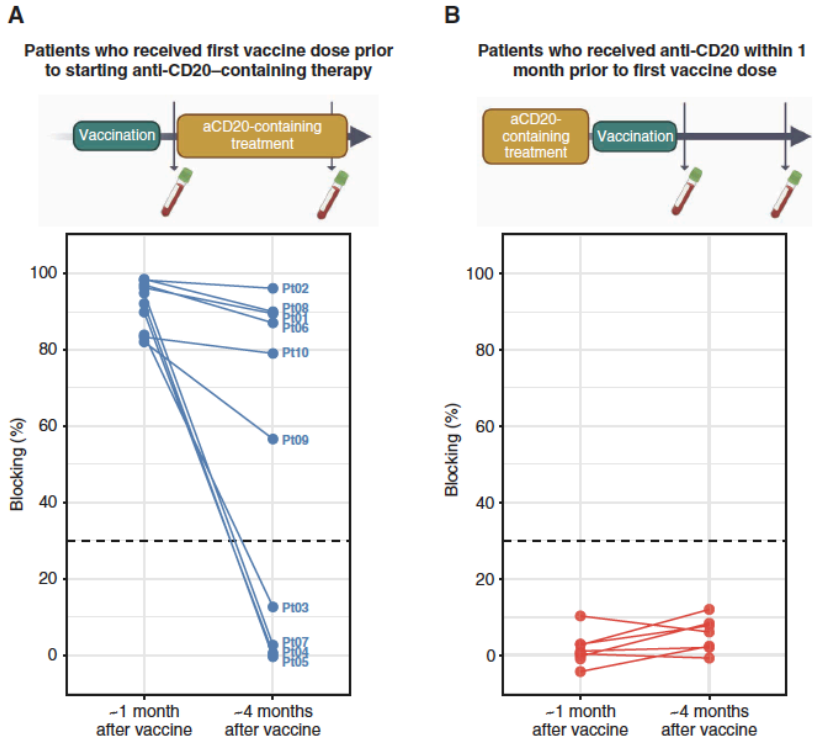
Disclosures

- Kite/Gilead advisory board
- BMS Advisory board
- Janssen DSMB
- Co-founder Zylem Therapeutics, Inc

Take Home Messages and Outline

- COVID-19: the global problem
- COVID-19: Mechanism of Infectivity
- COVID-19 in Immune Compromised hosts
- Follicular Lymphoma(FL) in 2022
- Treatment /Prevention of COVID
- How do we adjust practice based on what we know and where we are





The Global Pandemic

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COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)

Last Updated at (M/D/YYYY)
4/3/2022, 4:20 PM

Total Cases	Total Deaths	Total Vaccine Doses Administered
491,171,817	6,152,387	10,980,712,423

28-Day Cases	28-Day Deaths	28-Day Vaccine Doses Administered
45,379,895	159,839	427,072,954

Cases | Deaths by Country/Region/Sovereignty

Korea, South
28-Day: 9,417,952 | 8,278
Totals: 13,874,216 | 17,235

Germany
28-Day: 5,761,035 | 5,880
Totals: 21,665,200 | 130,029

Vietnam
28-Day: 5,483,762 | 1,837
Totals: 9,818,328 | 42,600

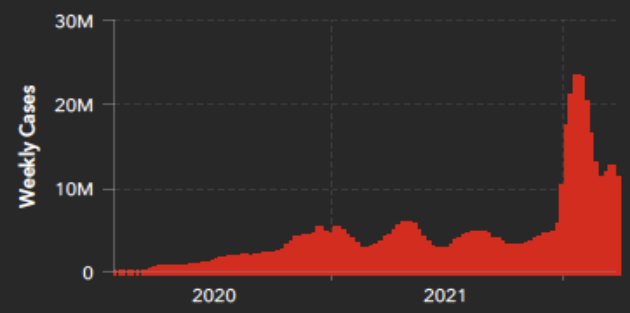
France
28-Day: 2,892,760 | 3,245
Totals: 26,186,606 | 143,540

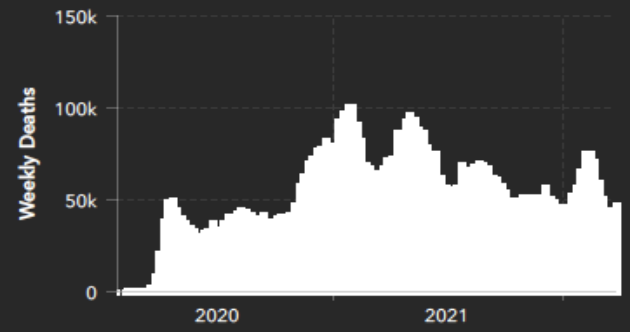
United Kingdom
28-Day: 2,122,710 | 3,586
Totals: 21,379,545 | 166,168

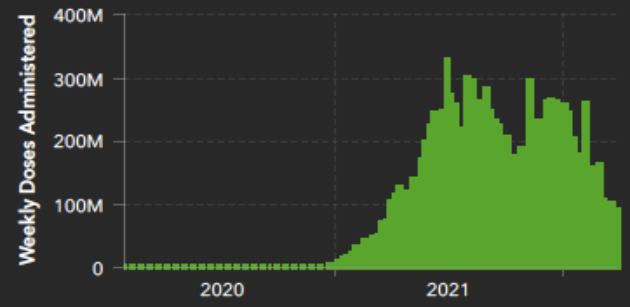
Italy
28-Day: 1,800,583 | 3,884
Totals: 14,845,815 | 159,784

Australia
28-Day: 1,314,225 | 967
Totals: 4,680,972 | 6,384

Japan
28-Day: 1,312,175 | 3,437

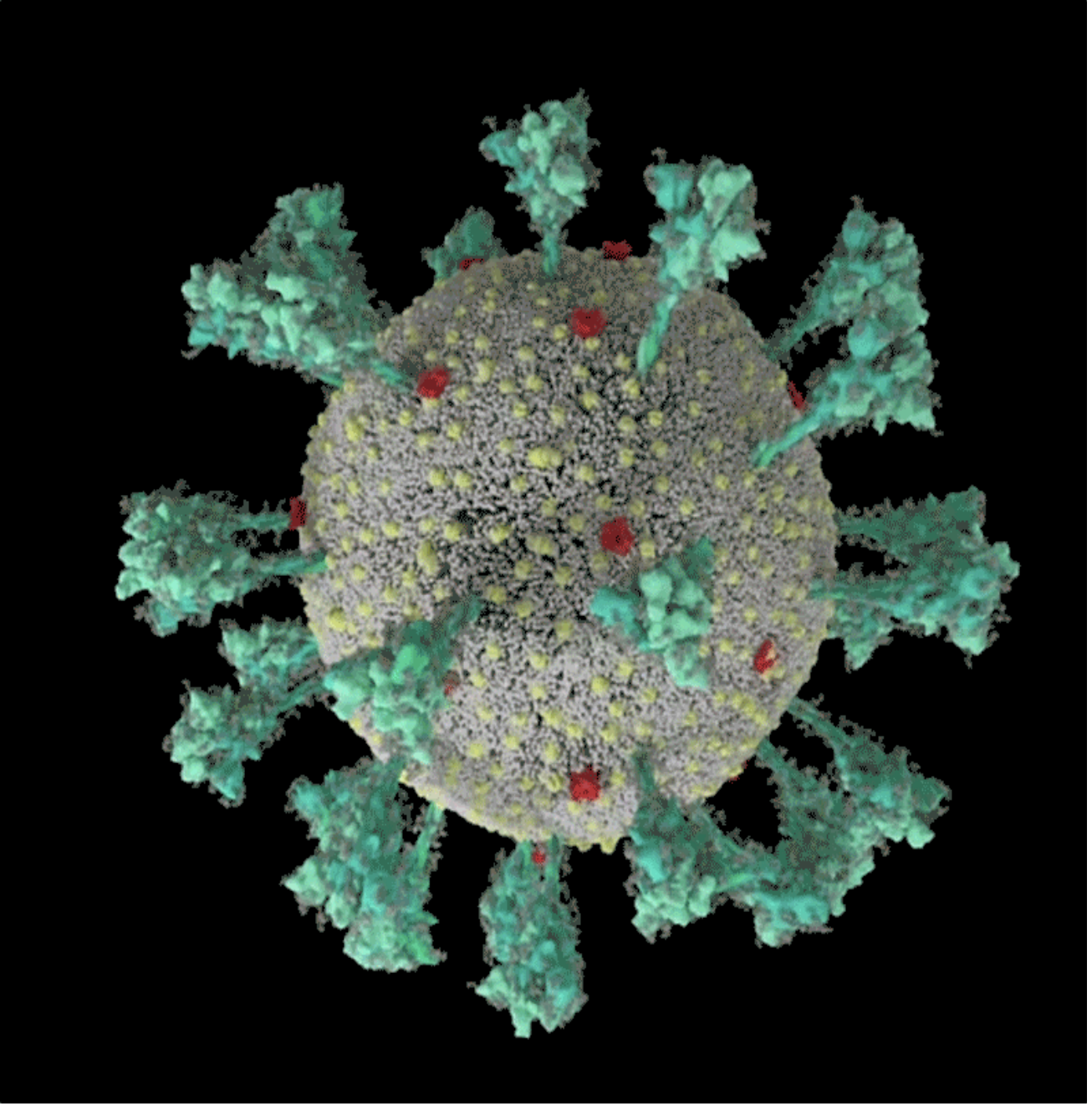






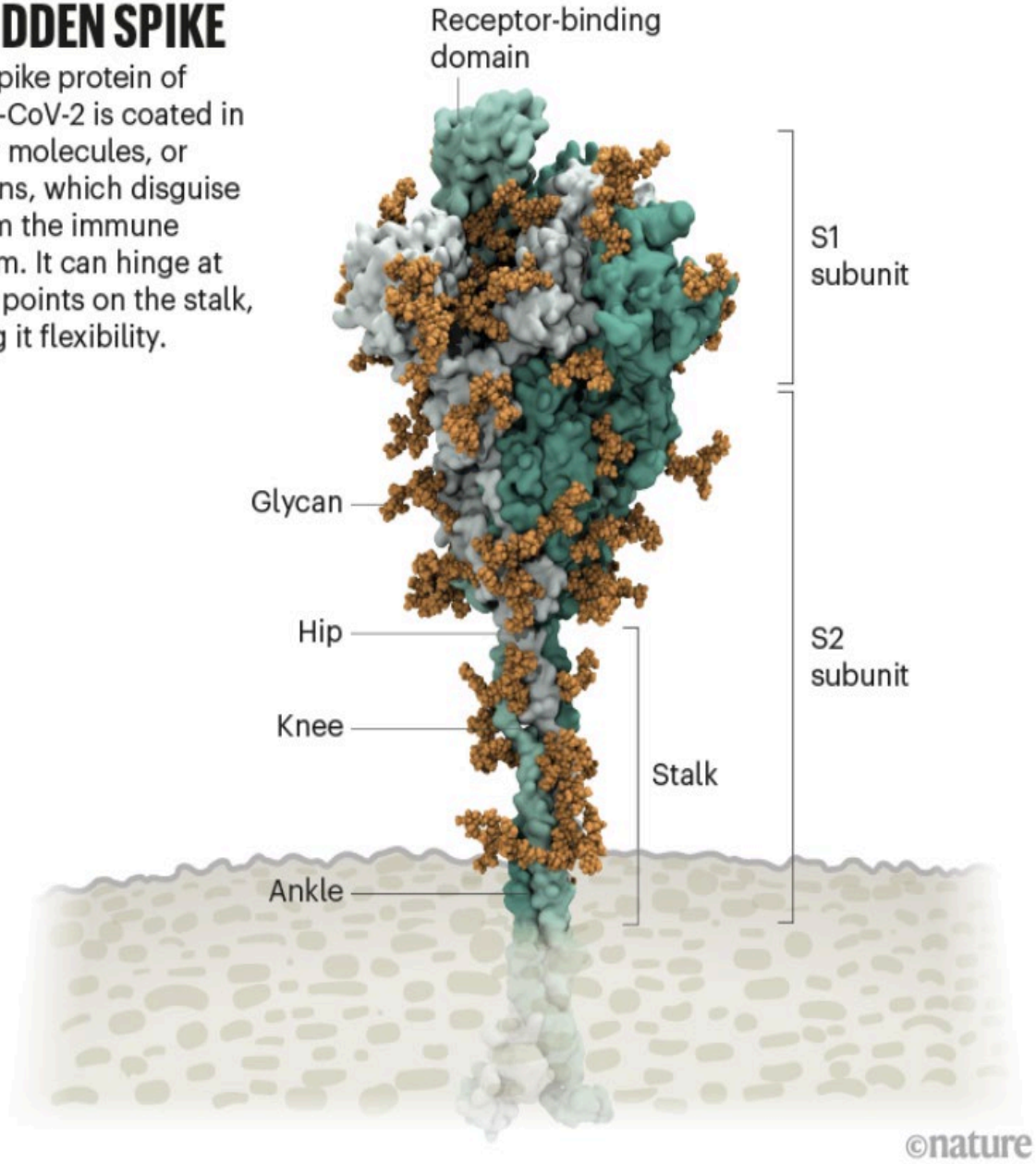
Admin0 | 28-Day | Weekly | 28-Day

Mechanism of Infectivity



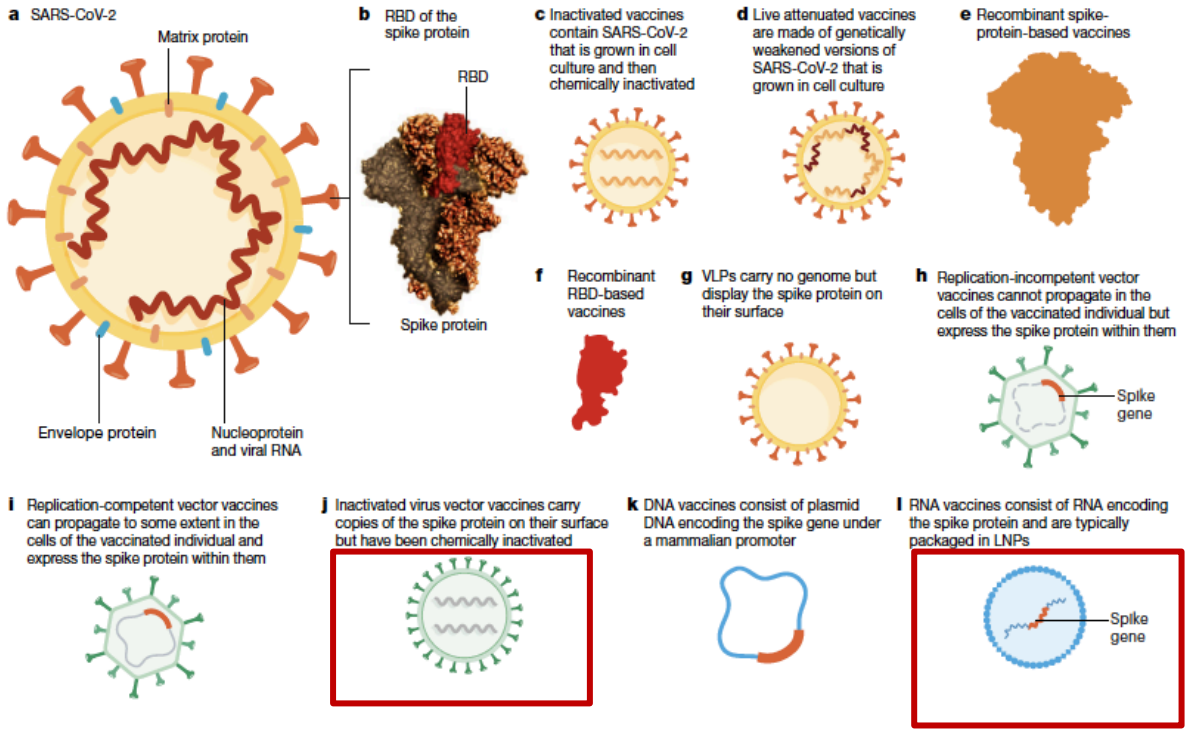
A HIDDEN SPIKE

The spike protein of SARS-CoV-2 is coated in sugar molecules, or glycans, which disguise it from the immune system. It can hinge at three points on the stalk, giving it flexibility.



Scudellari, M. Nature 2021; 595:640-644

Vaccine Strategies for COVID-19



Krammer, F. Nature 2020; 586:527

- A) the virion
- B) the RBD of the spike protein
- C) inactivated vaccines
- D) live attenuated
- E) recombinant protein vaccines
- F) RBD
- G) RBD on virus like particles
- H) replicon incompetent vector vaccines
- I) replicon competent vector vaccines
- J) inactivated virus vector vaccines with S protein
- K) DNA vaccines
- I) RNA vaccines

COVID-19 in Immune Compromised Hosts

Breakthrough infections, vaccine efficacy

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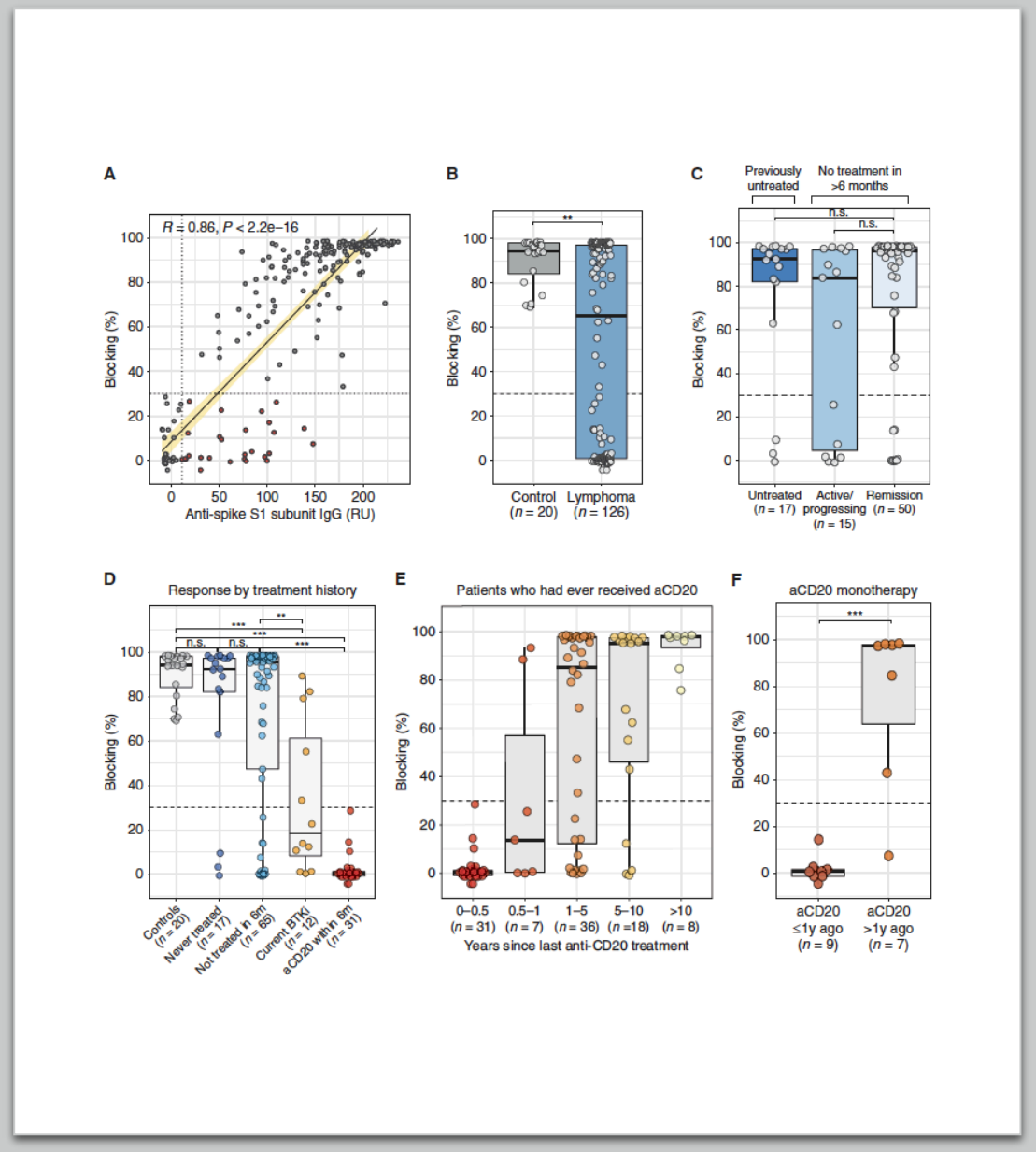
COVOD-19 in Hematologic Malignancies: National COVID Cohort Collaborative

- from 12/1/20 through 5/31/21
- n=6860 breakthrough infections, n=1460 (21%) with cancer
- Cancer pts had higher risk than non-cancer patients adjusting for multiple factors
- hematologic malignancies at increased risk (adjusted odds ratio 2.07 for lymphoma to 7.25 for lymphoid leukemia
- 2nd vaccine reduced risk for all and for Moderna> Pfizer, especially for myeloma
- immune suppressive meds and stem cell transplant associated with breakthrough/severity among vaccinated population

Song et al J Clin Oncol 2022
htt[s://doi.org/10.1200/JCO.21.02419

CD-20 Targeted Therapy and Antibody Response to COVID Vaccination

- A) n=243 vaccination samples blocking Ab vs anti-spike IgG
- B) Blocking Ab control (n=26) vs lymphoma (n=126)
- C) by disease activity not on treatment
- D) by treatment history
- E) blocking Ab based in interval from anti-CD20 Rx
- F) blocking Ab after vaccination only anti-CD20 Ab Rx < 1 year or > 1 year

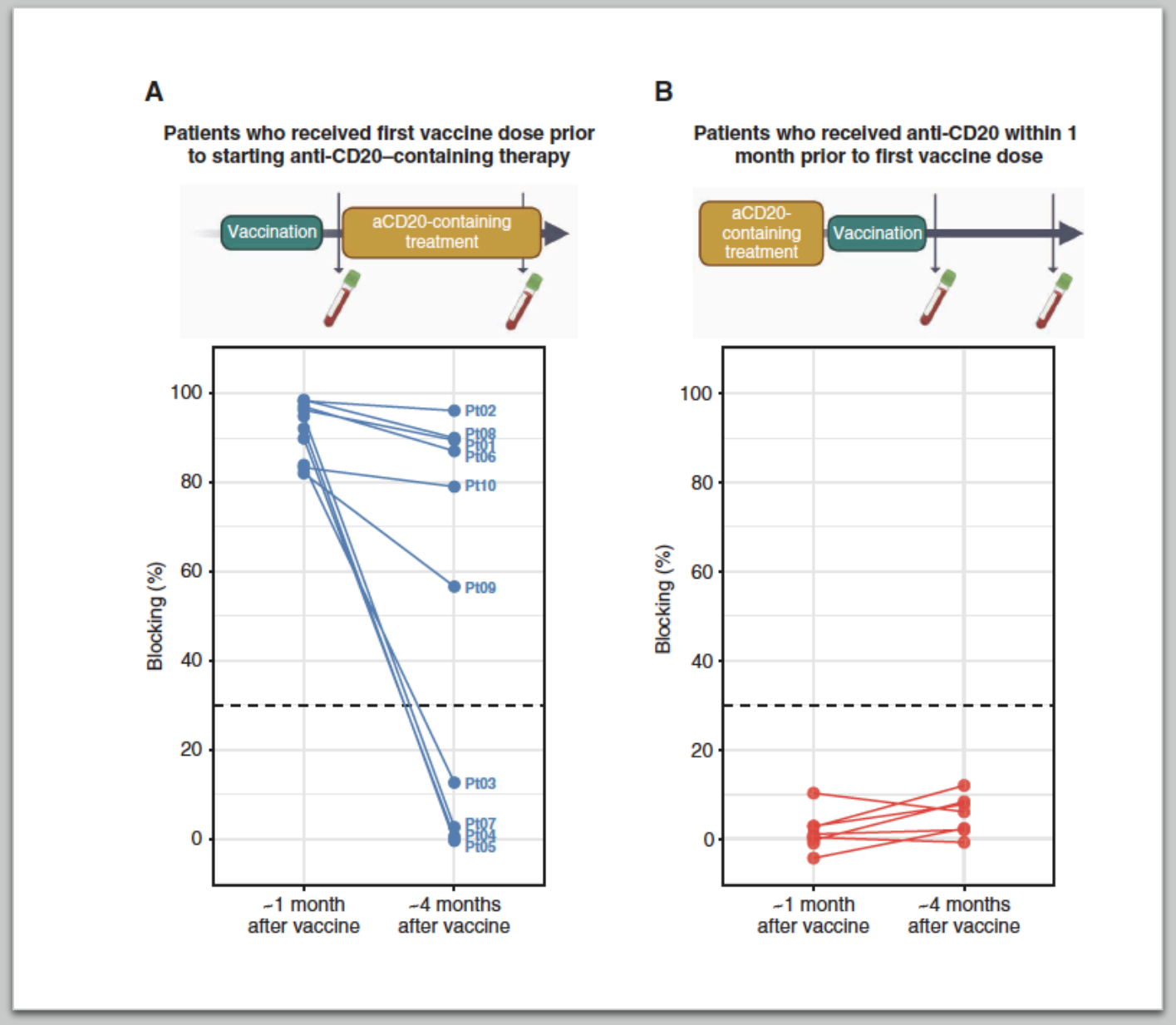


Shree et al Blood Cancer Discovery 2022; 3:95-102

CD-20 Targeted Therapy and Antibody Response to COVID Vaccination

- **Left Panel:** 1st dose of vaccine prior to starting anti-CD20 therapy

- **Right Panel:** 1st dose of vaccine within 1 month prior to 1st vaccine dose



Shree et al Blood Cancer Discovery 2022; 3:95-102

Follicular Lymphoma in 2022

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Follicular Lymphoma

- Heterogeneous
- Protracted course, remission and relapses
- Molecular and clinical risk factors identified
- When to treat and with what

Ardeshna KM Lancet Oncology 2014; 15: 424 ,

Soumerai, JD BLOOD 2016;128:1777,

Casulo, C JCO 2015;33:2516

Current Prognostic Models Have Limitations

- Current **risk stratification models** do not have sufficient sensitivity/specificity to guide decision making and remain primarily research tools:

Model	Criteria	Risk stratification	Prognosis
FLIPI[1,2]	1. Age: >60 y 2. Ann Arbor Stage: III–IV 3. Hb concentration: <12 g/dL 4. Number of nodal sites: >4 5. Serum LDH concentration: > normal	Low: 0–1 risk factors	2-y OS: 98%; 2-y PFS: 84%
		Intermediate: 2 risk factors	2-y OS: 94%; 2-y PFS: 72%
		High: 3–5 risk factors	2-y OS: 87%; 2-y PFS: 65%
FLIPI-2[3]	1. Age: >60 y 2. Bone marrow involvement: yes 3. Hb concentration: <12 g/dL 4. Greatest diameter of largest involved node: >6 cm 5. Serum β2 microglobulin concentration: >ULN	Low: 0–1 risk factors	3-y PFS: 91%
		Intermediate: 2 risk factors	3-y PFS: 69%
		High: 3–5 risk factors	3-y PFS: 51%
GELF[4]	1. Tumor size: any site >7 cm or ≥3 sites >3 cm 2. B symptoms: yes 3. Spleen: below umbilical line 4. Compressive symptoms: yes 5. Pleural or peritoneal effusion: yes 6. Leukemic phase >5 × 10^9/L 7. Neutropenia (<1 × 10^9/L) or thrombocytopenia (<100 × 1^{09}/L) due to disease	High tumor burden: ≥1 risk factors	

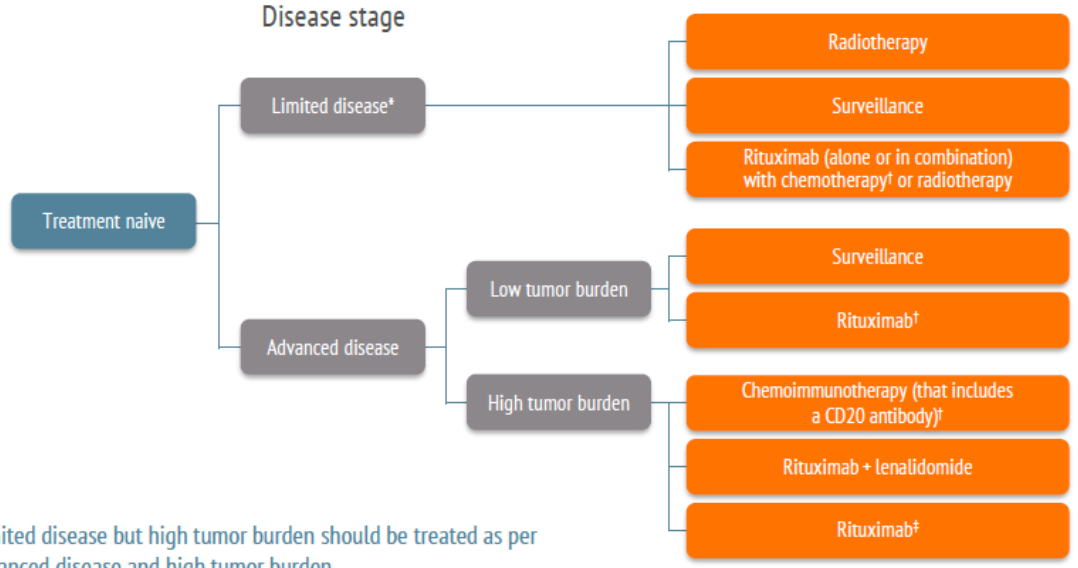
FLIPI, Follicular Lymphoma International Prognostic Index; Groupe d'Etude des Lymphomes Folliculaires; Hb, haemoglobin; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; ULN, upper limit of normal; y, year

1. Solal-Celigny P, et al. Blood 2004;104:1258-1265, 2. Nooka AK, et al. Ann Oncol 2013;24:441-448, 3. Federico M, et al. J Clin Oncol 2009;27:4555-4562, 4. Brice P, et al. J Clin Oncol 1997;15:1110-1117.

Solal-Celigny P et al BLOOD 2004;104:1258, Federico, M . et al. J Clin Oncol 2009;27:4555, Brice P. et al J Clin Oncol 1997; 15:1110

Treatment Options in Newly Diagnosed FL

- **Newly-diagnosed FL** can be broadly classified as limited- or advanced-stage disease, which can further be classified based on the **degree of tumor burden**, with the choice of management varying accordingly



*Patients with limited disease but high tumor burden should be treated as per patients with advanced disease and high tumor burden.

†With or without anti-CD20 maintenance therapy.
‡For frail patients; FL, follicular lymphoma.

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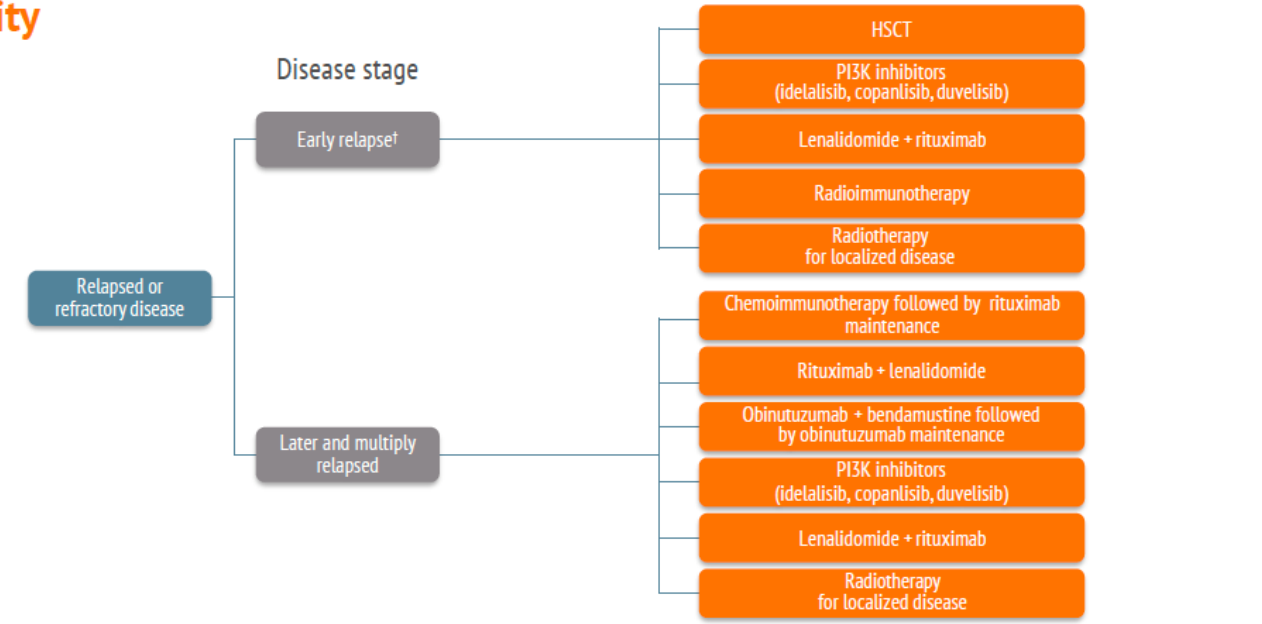
Treatment Options in R/R FL

- In patients with R/R FL, **successive lines of therapy** will often be required in the disease course, and the choice of each treatment should **aim to achieve disease control, promote QoL**, and minimize **treatment-related toxicity**



†Relapse within 2 years of initial therapy (POD 24, progression of disease within 24 months).
FL, follicular lymphoma; HSCT, haemopoietic stem cell transplantation; R/R, relapsed/ refractory; QoL, quality of life.

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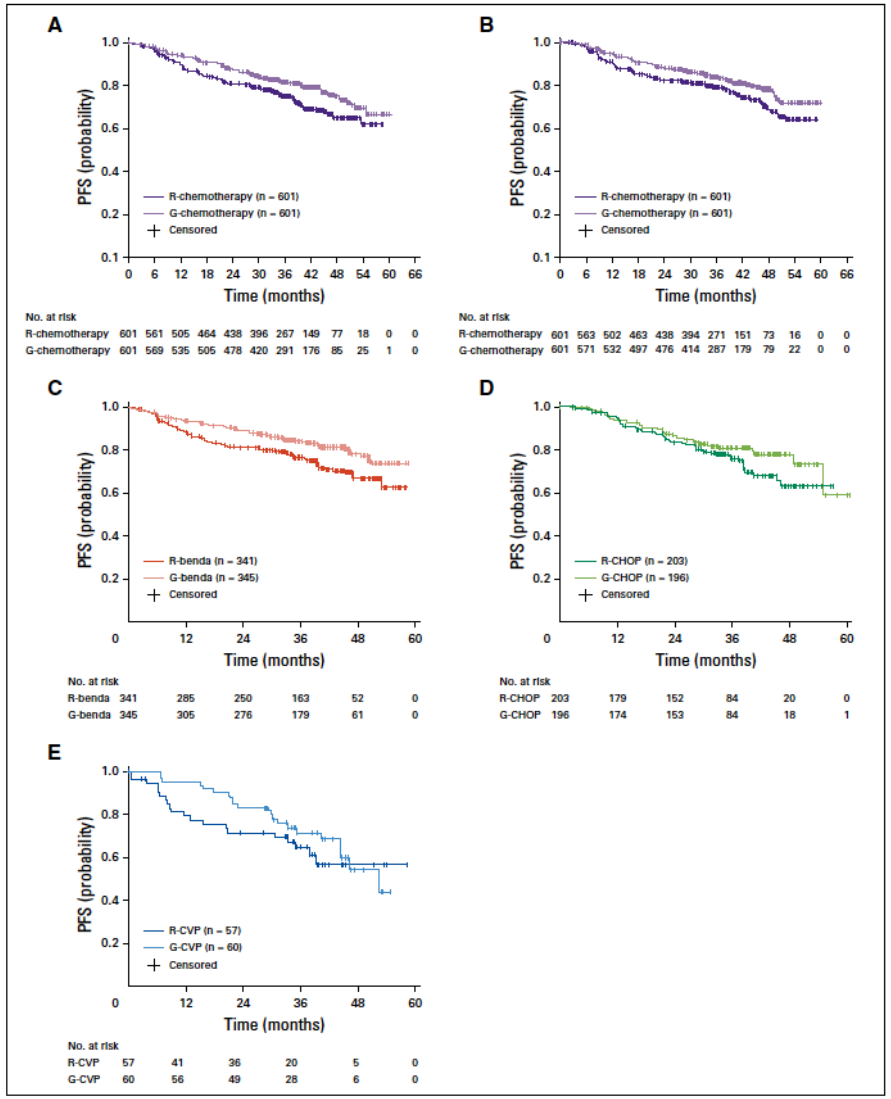
Gallium Study: PFS by Chemotherapy Regimen

- PFS advantage favors Obinutuzumab with bendamustine, CHOP and CVP
- Maintenance x 2 years in all



Hiddeman et al 2018; JCO 36: 1-10

Adverse Events in Gallium: Higher Mortality with Bendamustine

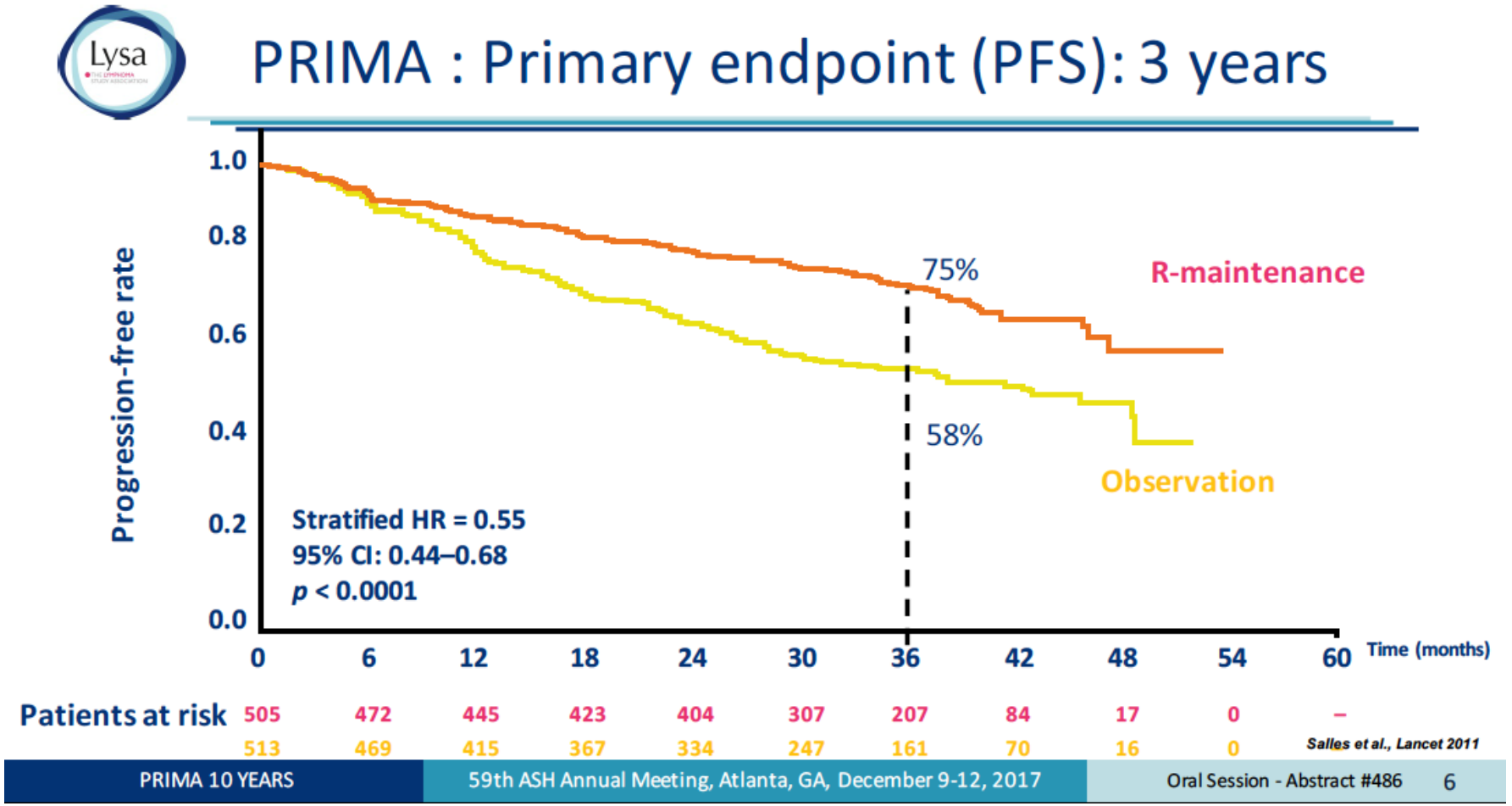
- In patients >70 y.o., fatal events in chemotherapy regimen containing Bendamustine was 13% vs 2% with CHOP
- Second malignancies and infections in pts on Bendamustine and Obinutuzumab and nervous system disorders in BR
- This had not been observed in prior BR studies
- Post hoc analysis
- Bendamustine patients were older and CHOP patients had bulkier disease

Hiddeman et al JCO 36:2018

Adverse Events in Gallium: Higher Mortality with Bendamustine

- CD4 counts were lower in patients on Bendamustine
- < 200 through most of treatment and < 100 in some
- Began to recover month 18-30 and by month 36 were not quite back to baseline
- Caveats: older, small actual numbers of deaths, post hoc analysis

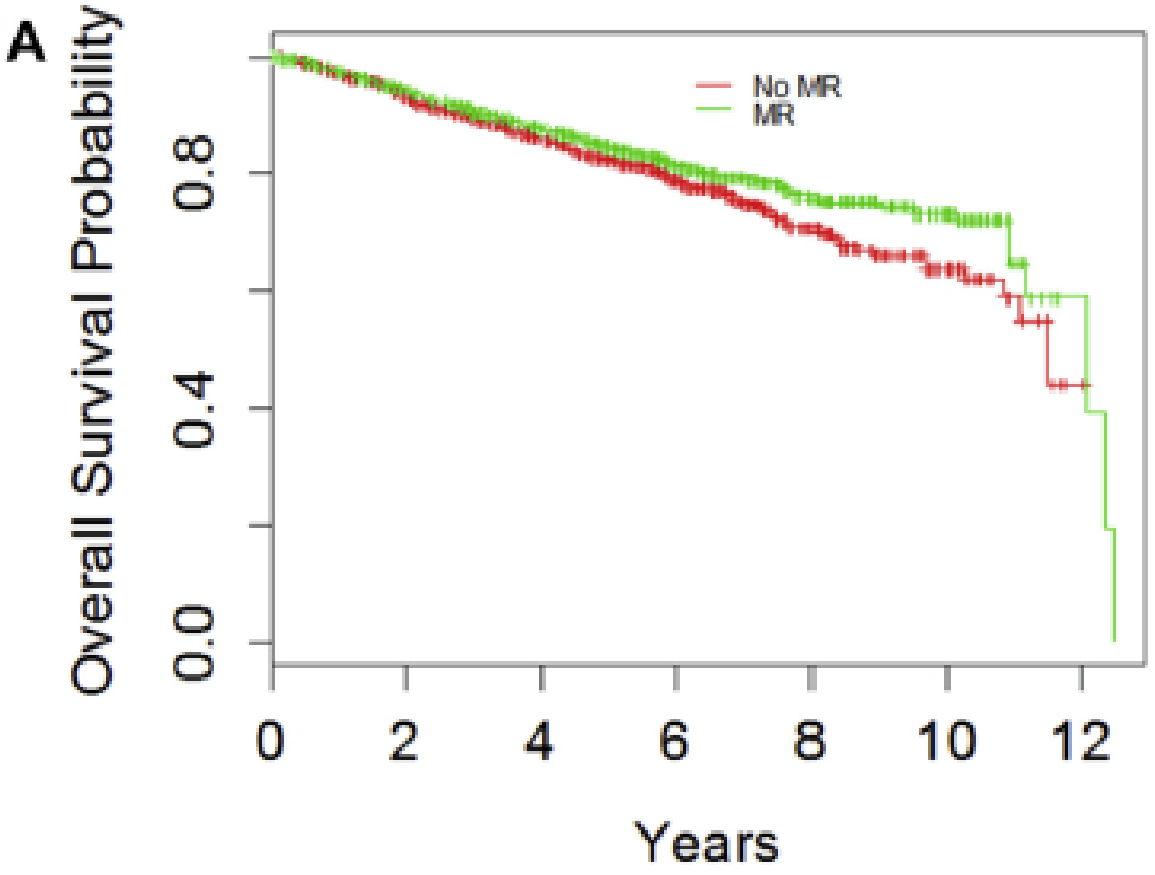
Maintenance or not in FL



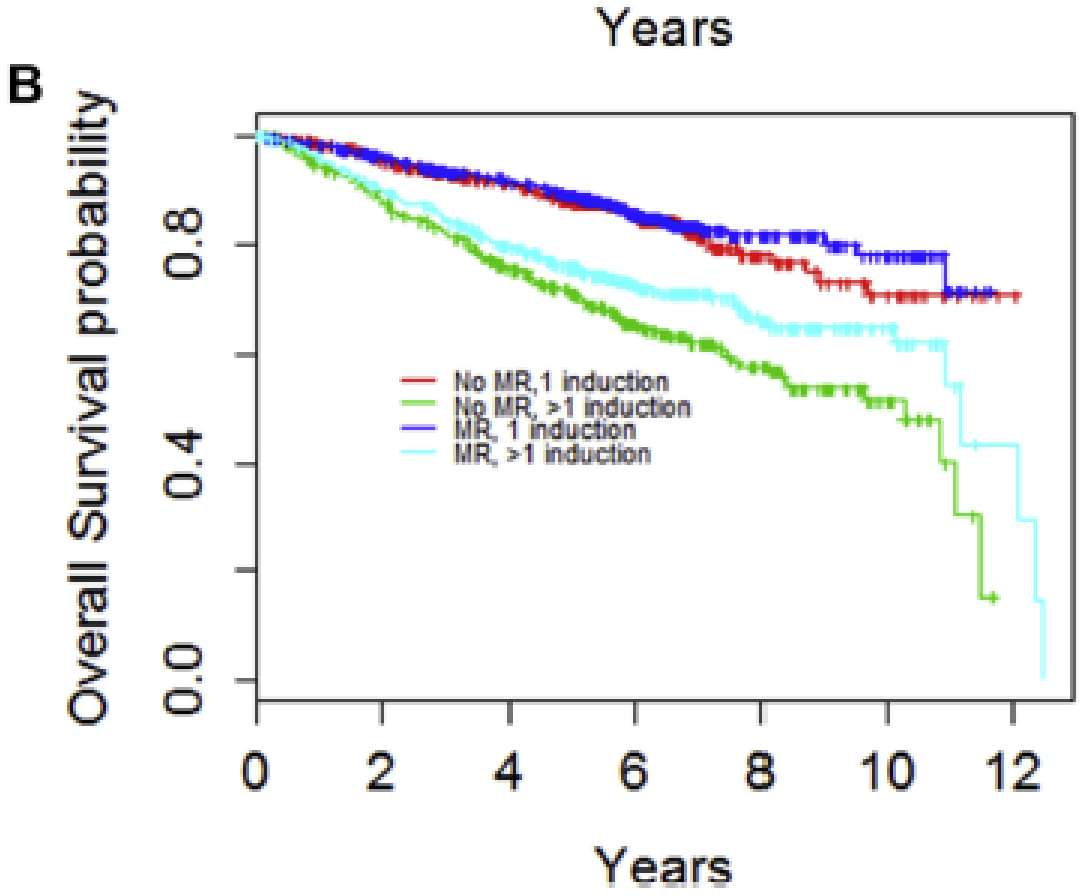
Bachy et al J Clin Oncol 2019; 37(31): 2815-2824

In Meta Analysis Rituximab Improves OS in FL

A= by Intervention Group



B= By treatment line and intervention Group



Vidal et al European Journal of Cancer 76 (2017) 216-225

Treatment and Prevention of COVID-19

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What we can do to prevent and treat COVID in Immune Compromised patients

Monoclonals

- Tixagevimab+Cilgavimab PreP
- Sotrovimab (treatment)
- Bamlanivimab + Etesivimab (treatment) (better for Omicron)

Anti-Virals

- nirmatrelvir tablets; ritonavir tablets 300 mg BID x 5 (within 5 days onset)
- Molnupiravir 800 mg BID x 5 (within 5 days onset
- Remdesivir IV x 3 days 200-100-100 (within 7 days onset)

COVID-19 Vaccine Update

- Third dose in primary series for ages 5-11 years (Pfizer only)
- Booster dose approved for ages 12-15 years (Pfizer only)
- Shorter interval from last dose to booster for Pfizer and Moderna, from 6 months→ 5 months
- EUA for 4th dose for >50 and for immune compromised

How do we adjust practice based on what we know and where we are

https://www.hematology.org/covid-19/covid-19-and-indolent-lymphomas

https://www.hematology.org/covid-19/covid-19-and-hodgkin-lymphoma

https://www.hematology.org/covid-19/covid-19-and-aggressive-lymphoma

So, how does this all affect management of FL and other indolent lymphomas

- Threshold for starting treatment should be carefully re-thought
- High GELF and FLIPI scores do not equal need for treatment
- Monitor with exams and possible imaging
- Treatment arm (asymptomatic low volume) of RESORT not indicated

https://www.hematology.org/covid-19/covid-19-and-indolent-lymphomas

If treatment required, then what?

- Consider RT for locally symptomatic sites
- Consider single agent Rituxan x 4, as significant responses can be seen but may take 2-4 months or longer for maximum response
- Common regimens for immunotherapy/chemotherapy (e.g., Gallium)
  - R-Bendamustine
  - R-CHOP
  - R-CVP
- Common regimens for small molecule inhibitors and IMIDS
  - R^2
  - BTKi
  - Pi3Ki

https://www.hematology.org/covid-19/covid-19-and-indolent-lymphomas

If treatment required, then what?

- R-Bendamustine is an excellent way to deplete B-cells and T-cells
- CD-4 counts <200 for >36 months and counting and < 100 for the 6-month duration of therapy on the Gallium study
- R^2 may have limited effect on innate immune system but duration of therapy usually up to 2 years
- I would favor R-CVP or R-CHOP as alternative first line regimen in FL to limit immune suppression
- Growth factor controversial. Only when clearly needed. The problem is not the ANC
- Maintenance in selected cases only and probably not after R-Bendamustine

https://www.hematology.org/covid-19/covid-19-and-indolent-lymphomas

If treatment required, then what?

- Encourage vaccine x 4 in patients and yourself
- Evusheld (though the trials were done during Delta)
- Have a plan for when patients become COVID+
  - Sotrovomab (not so great with Omicron)
  - Bamlanivimab+Etesevimab (preferred with Omicron)
  - Nirmatrelvir tablets; ritonavir tablets (drug interactions)

https://www.hematology.org/covid-19/covid-19-and-indolent-lymphomas

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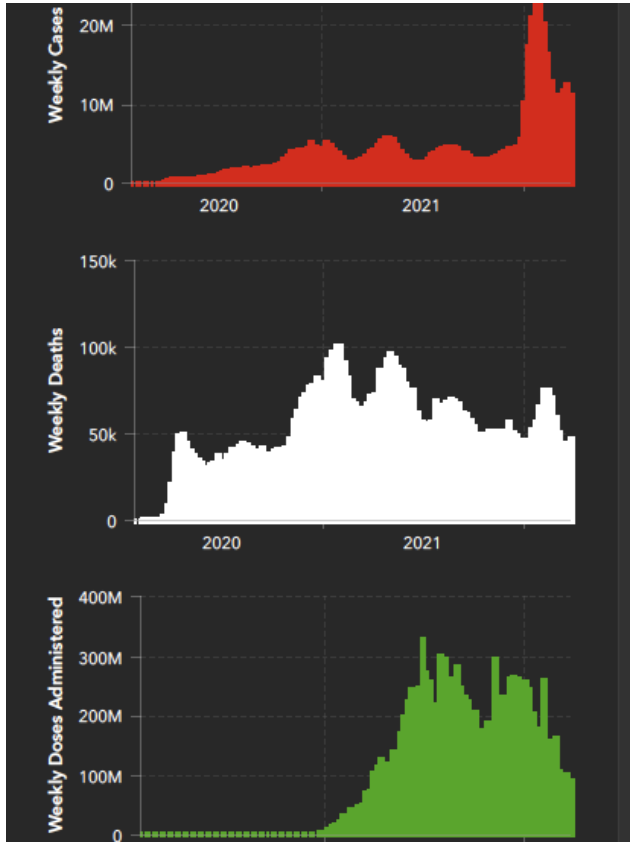

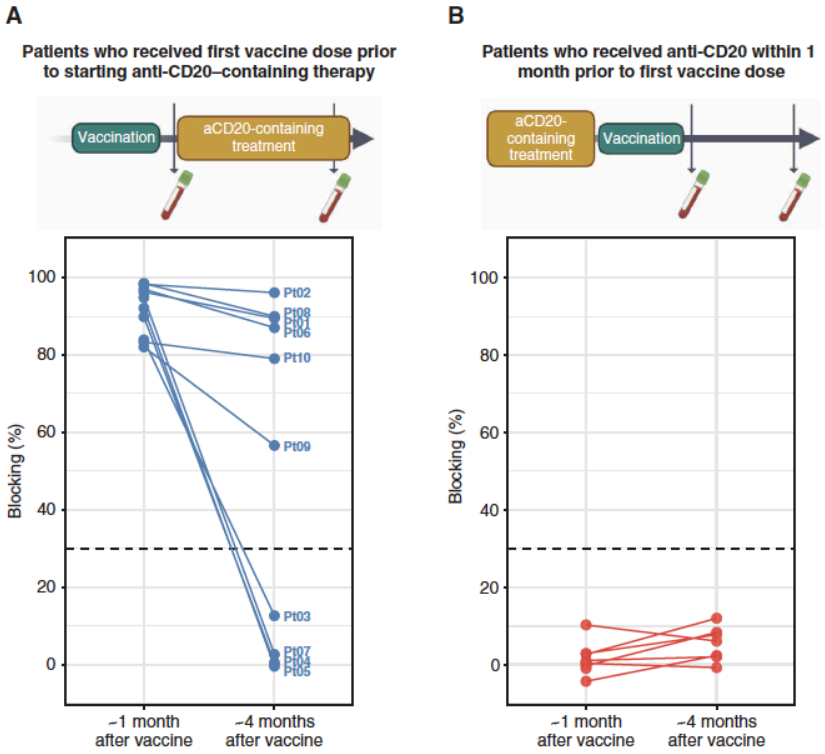

Audience Response Question

55-year-old male with new diagnosis of FL. Has a 4 cm mesenteric mass incidentally discovered on imaging for kidney stone. Has normal counts and mild epigastric discomfort. He is healthy and says that he does not need a COVID vaccine. How would you treat?

1) Observation
2) R-Bendamustine
3) Single agent Rituximab
4) R-CHOP
5) R-CVP