WVU Cancer Institute

# 29th Annual Fall Cancer Conference

Myeloma and Lymphoma Tumor Board

October 18, 2019

# Panel Members

- Joseph Caveney, M.D.

  Fellow, Hematology & Oncology

- Abraham S. Kanate, M.D.

  Associate Professor, Hematology & Oncology

- Todd Tenenholz, M.D.

  Assistant Professor, Radiation Oncology

- Lauren Veltri, M.D.

  Assistant Professor, Hematology & Oncology

- David Howell, M.D., Ph.D.

  Assistant Professor, Pathology

# Case 1, S. H.

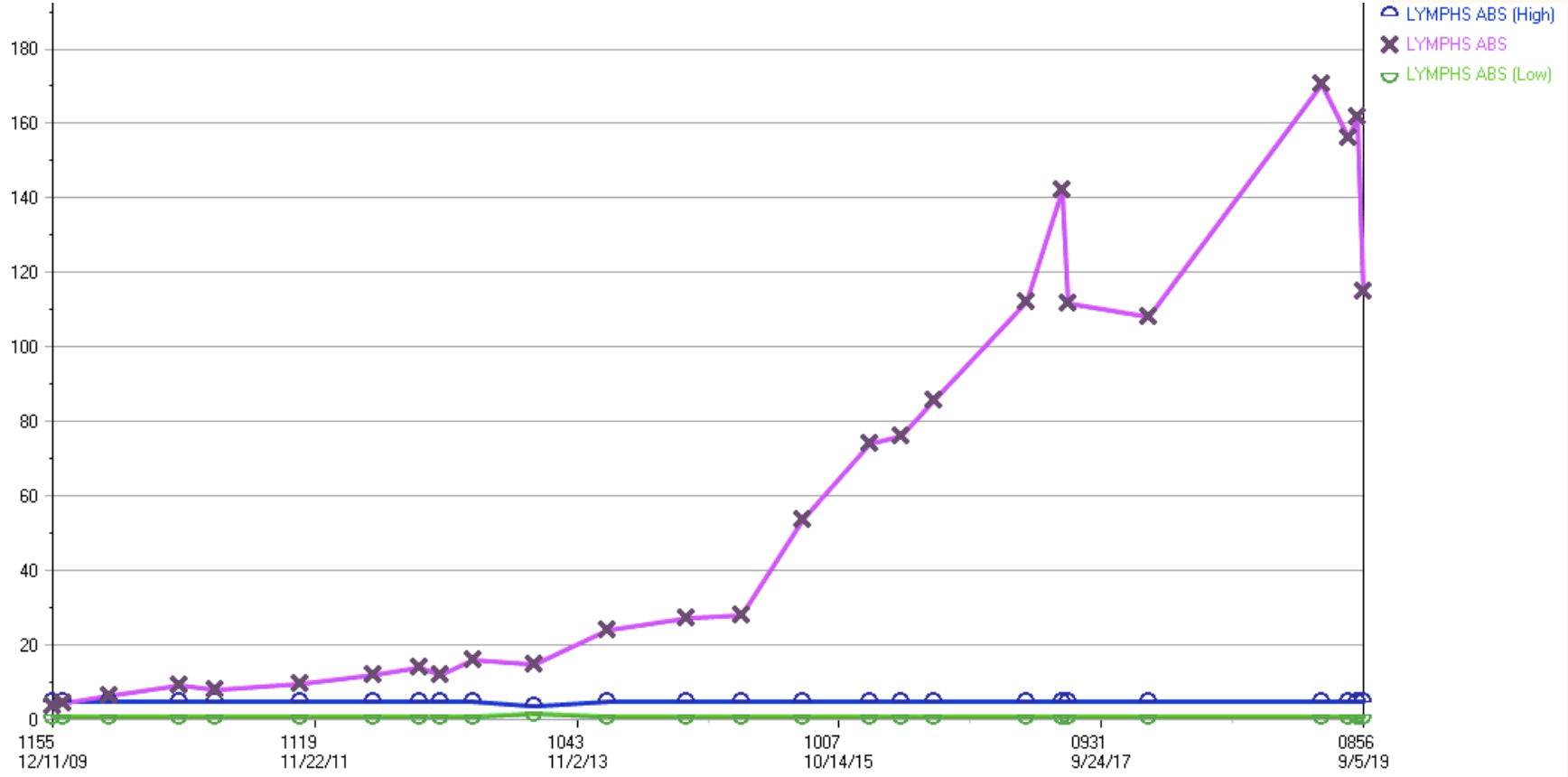
- **HPI:** 51 yo male presented with leukocytosis in 2009 consistent with CLL. CLL FISH panel with favorable 13q deletion and IgVH mutated by sequencing mutation analysis. October 2012 PET with mildly prominent axillary and mediastinal lymph nodes. Followed on observation up until 2019 when began to develop progressive fatigue and worsening renal insufficiency. No night sweats or weight changes.

- **PMH, PSH:** CLL, CKD, DM and HTN

- **SH:** Non smoker, occasional alcohol use.

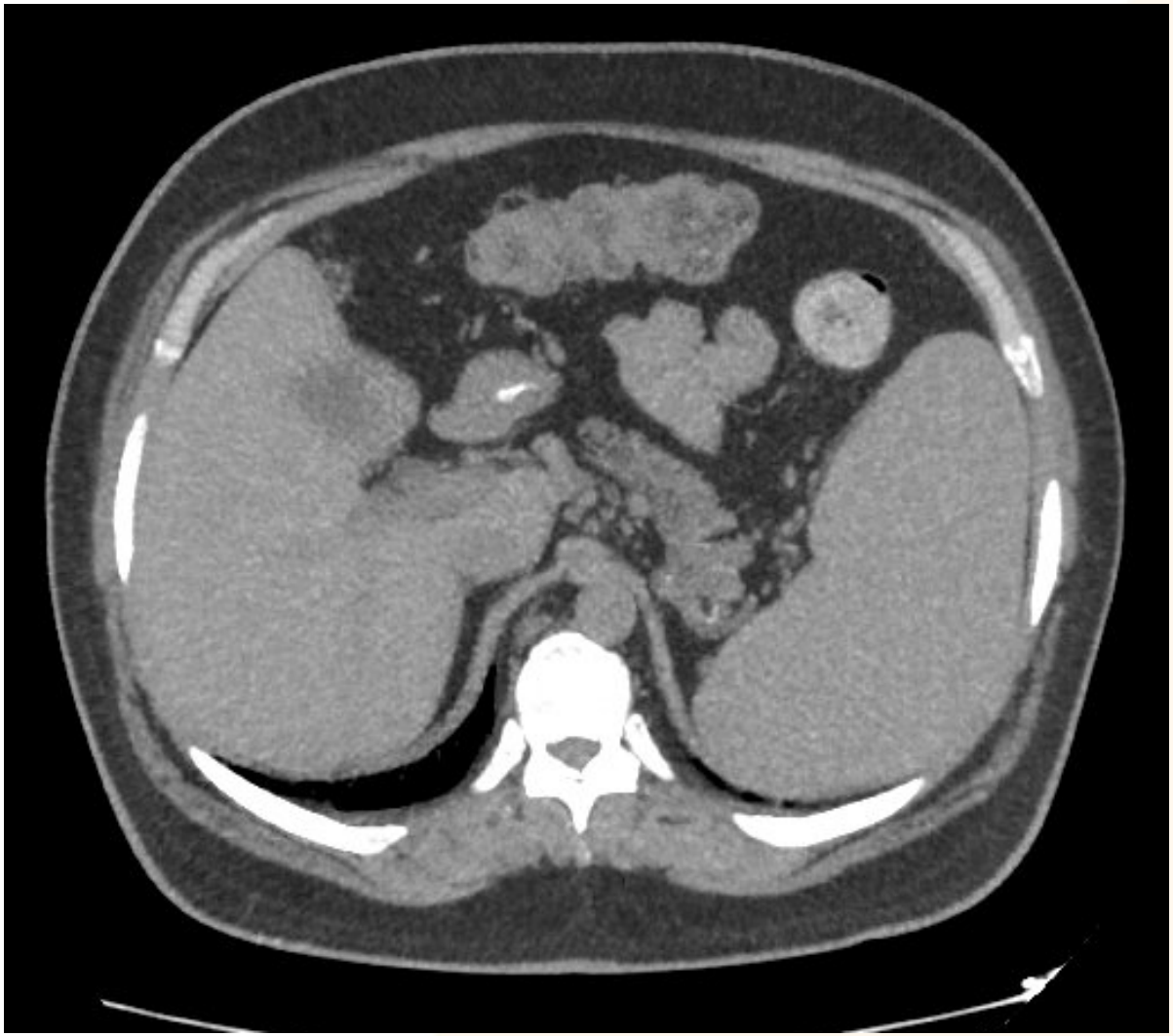
# Case 1, S. H.

- **Clinical course and w/u:**

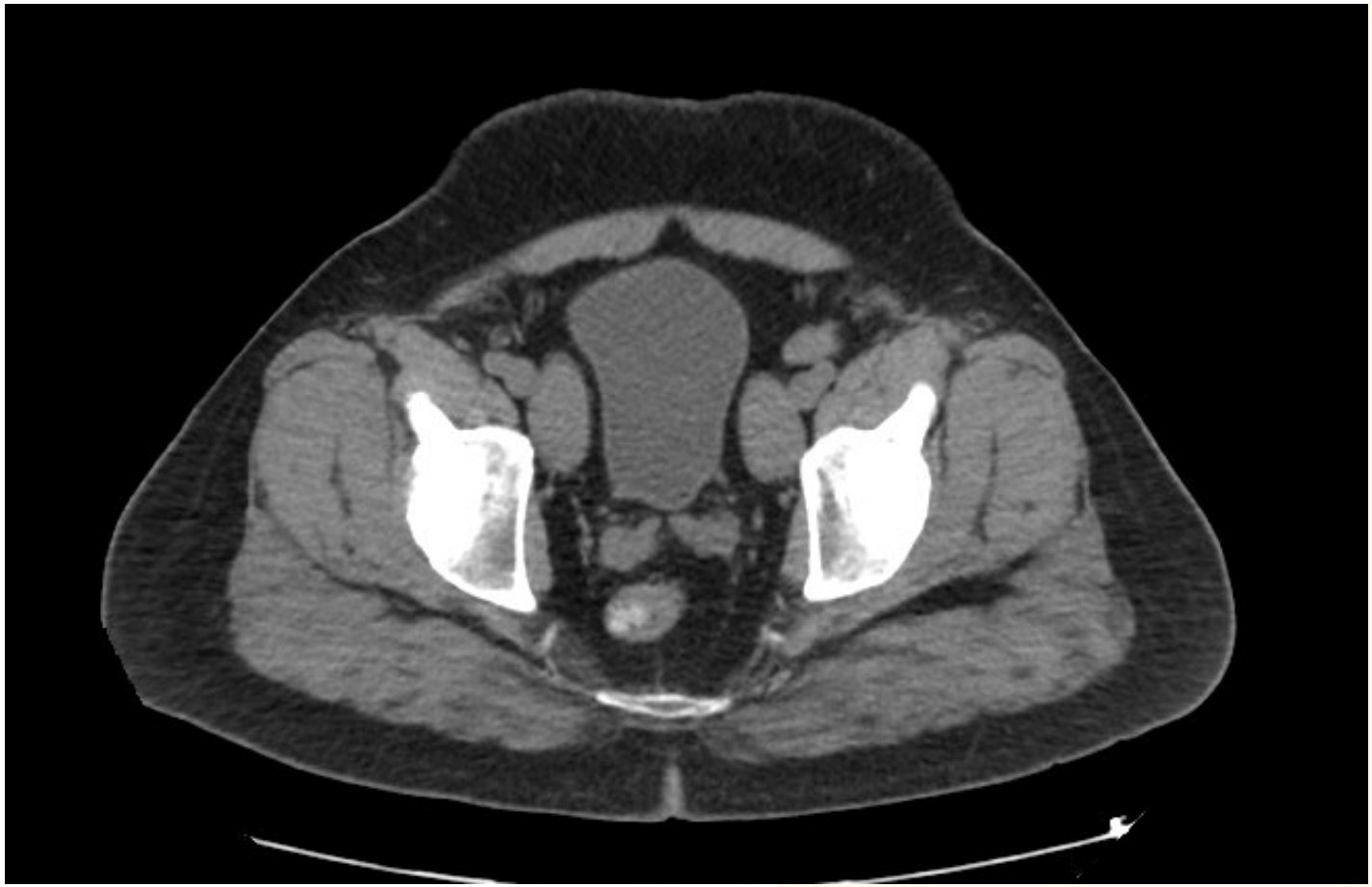


# Case 1, S. H.

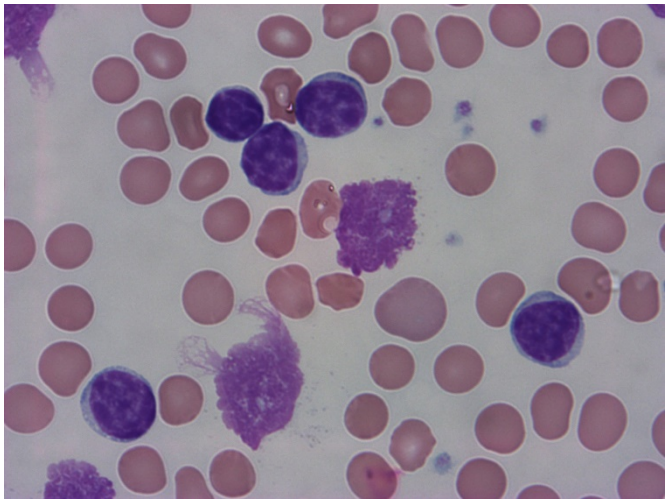
- **<u>Clinical course and w/u:</u>**
- **<u>CT C/A/P</u>**

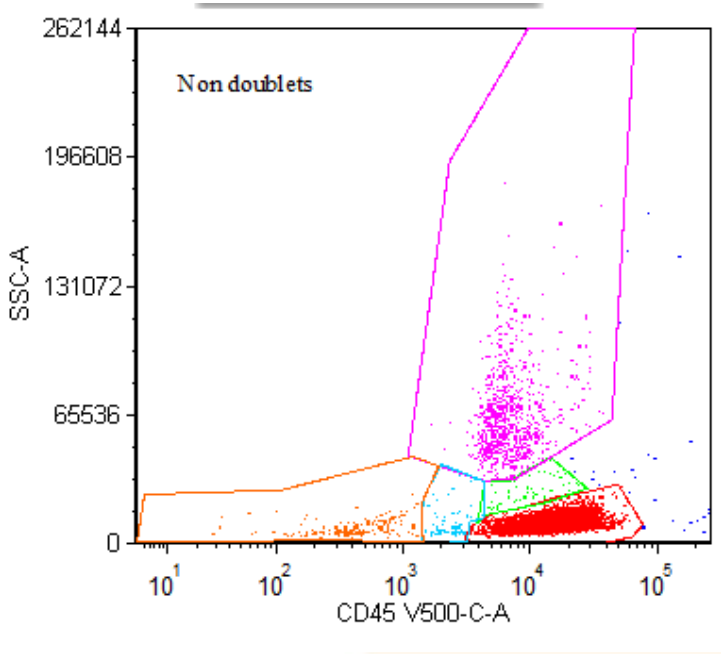


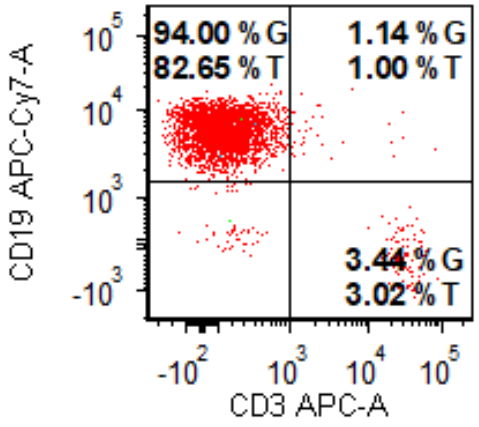
# Case 1, S. H.

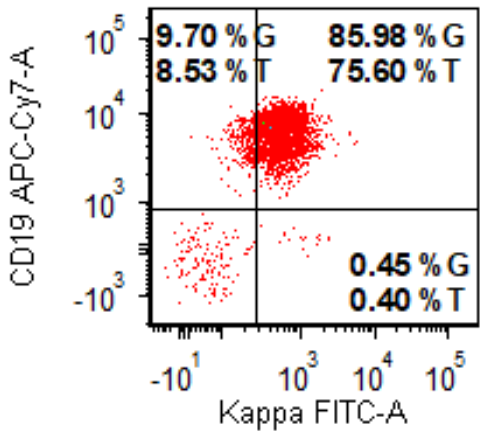


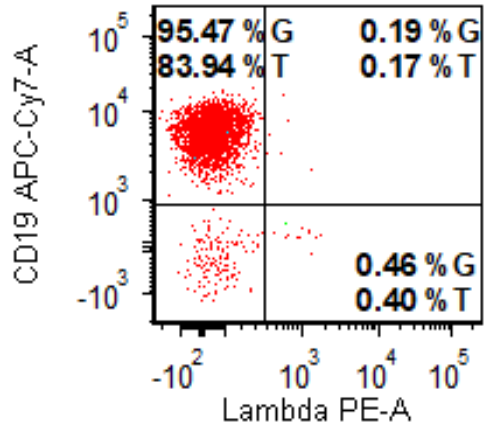
# Case 1, S. H.



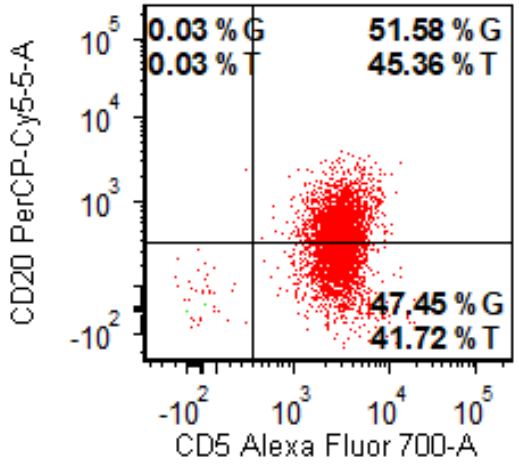

Non doublets
262144
196608
131072
65536
0
SSC-A
CD45 V500-C-A

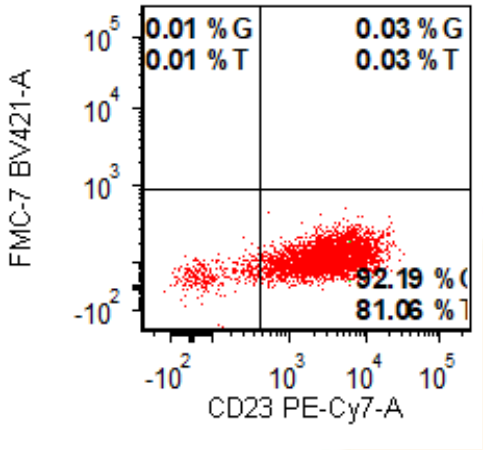

94.00 % G
82.65 % T
1.14 % G
1.00 % T
3.44 % G
3.02 % T
CD19 APC-Cy7-A
CD3 APC-A

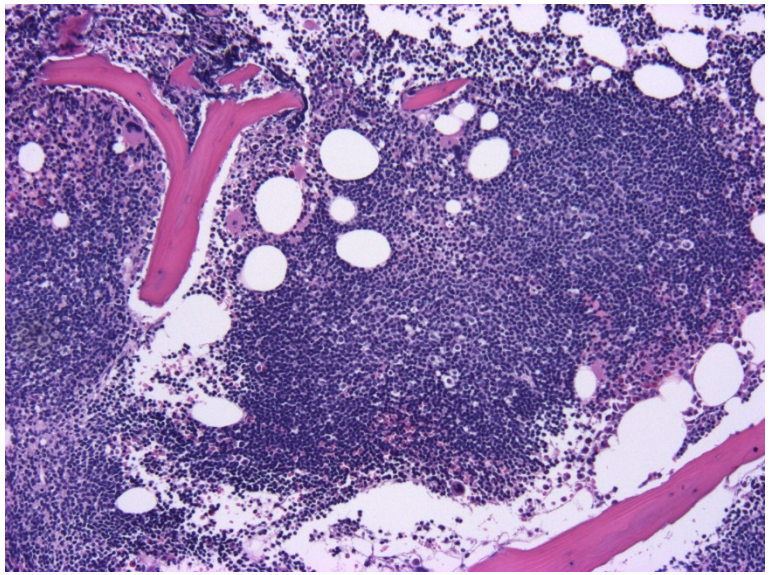

9.70 % G
8.53 % T
85.98 % G
75.60 % T
0.45 % G
0.40 % T
CD19 APC-Cy7-A
Kappa FITC-A


95.47 % G
83.94 % T
0.19 % G
0.17 % T
0.46 % G
0.40 % T
CD19 APC-Cy7-A
Lambda PE-A

# Case 1, S. H.


0.03 % G
0.03 % T
51.58 % G
45.36 % T
47.45 % G
41.72 % T
CD20 PerCP-Cy5-5-A
CD5 Alexa Fluor 700-A


0.01 % G
0.01 % T
0.03 % G
0.03 % T
92.19 %
81.06 %
FMC-7 BV421-A
CD23 PE-Cy7-A



# Case 1, S. H.

- **Clinical course and w/u:**

Final Pathologic Diagnosis

A. & B. BONE MARROW, RIGHT POSTERIOR ILIAC CREST, CLOT SECTION AND TREPHINE CORE BIOPSY:

- Chronic lymphocytic leukemia/Small lymphocytic lymphoma (see note).
- Hypercellular marrow (approximately 80% cellularity) with:
  - Diffuse lymphocytic infiltrate in a nodular and diffuse interstitial pattern.
  - Lymphocytes account for over 80% of marrow cellularity.
  - Scattered normal myeloid and erythroid elements.
  - Megakaryocytes reduced in number.
  - Incidental small histiocytic collection noted.
  - Stainable iron present.
  - Marrow reticulin fibers focally increased.
  - No metastatic tumor identified.
  - One clot section reviewed: mostly clotted blood with increased lymphocytes.

IMPRESSION: CLL FISH PANEL RESULT
13q DELETION [94.5%]

Interpretation
BONE MARROW, FLOW CYTOMETRY:

Monoclonal B-cell population identified (84% of total cells; 95% of lymphocytes), phenotypically consistent with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

Phenotype: CD19, CD20, CD5, CD22, CD23, surface kappa.
CD38 negative.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Ibrutinib–Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia

T.D. Shanafelt, X.V. Wang, N.E. Kay, C.A. Hanson, S. O'Brien, J. Barrientos, D.F. Jelinek, E. Braggio, J.F. Leis, C.C. Zhang, S.E. Coutre, P.M. Barr, A.F. Cashen, A.R. Mato, A.K. Singh, M.P. Mullane, R.F. Little, H. Erba, R.M. Stone, M. Litzow, and M. Tallman

# Case 1, S. H.

- Chronic lymphocytic Leukemia accounts for approximately 11% of hematologic neoplasms. Dramatic improvements in PFS and OS have been seen with addition of anti-CD20 monoclonal antibodies. Phase 3 trials established the chemoimmunotherapy regimen of fludarabine, cyclophosphamide and rituximab as the standard first-line treatment for suitable patients 65-70 years of age or younger.

- The interruption of leukemia proliferative signals mediated through the B-cell receptor is one of the most promising new therapeutic targets. Ibrutinib initially found to durable efficacy in patients with relapsed/refractory CLL. Subsequently was found to demonstrate superior PFS and OS as a first-line option in frail patients when compared to chlorambucil.

- This recent phase 3, multicenter, trial was conducted to evaluate the efficacy and safety of treatment with ibrutinib in combination with 6 cycles of rituximab, as compared with FCR in previously untreated patients with CLL 70 years of age or younger. Patients with 17p13 deletion were excluded because of known poor outcomes in these patients to FCR therapy. The primary end point was PFS and OS as secondary end point.



*Shanafelt, T.D. et al "Ibrutinib-Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia." N Engl J Med 2019; 381:432-43*

# Case 1, S. H.

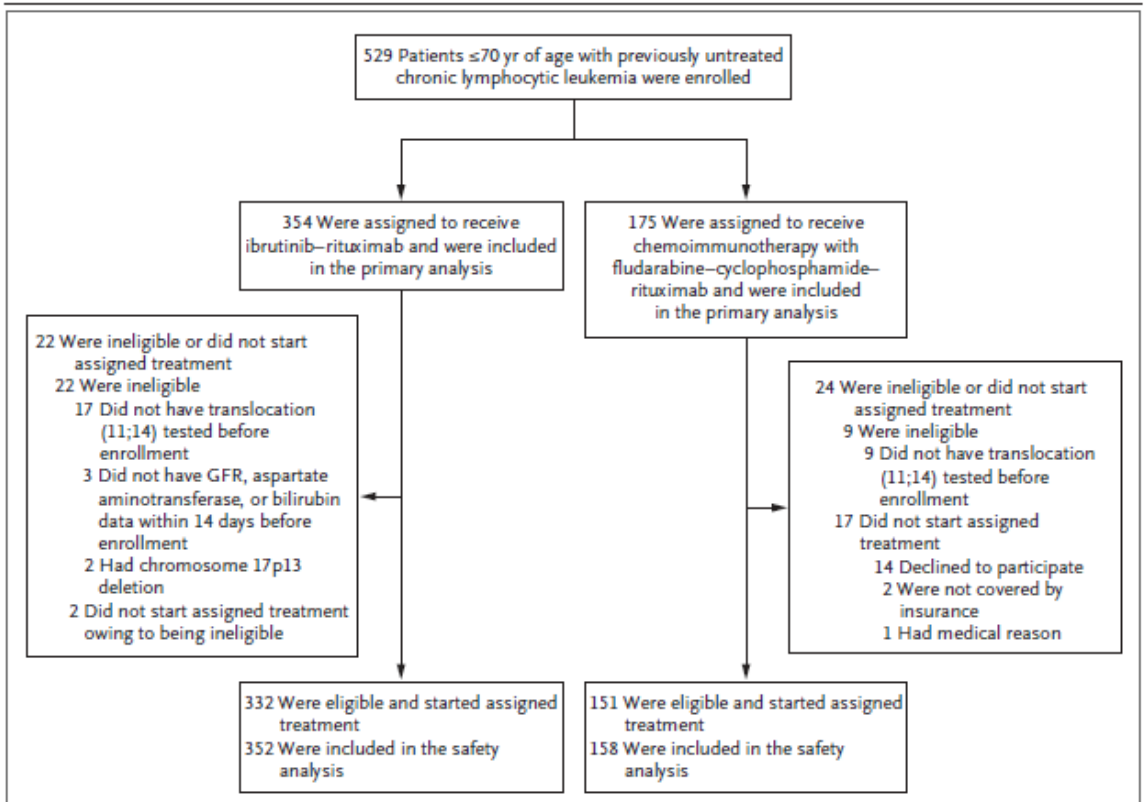



**Figure 1. Enrollment, Randomization, and Follow-up.**

All 529 patients who had been enrolled in the trial were included in the intention-to-treat analysis. Of the 529 patients who underwent randomization, 31 (5.9%) were determined to have not met the eligibility criteria and were excluded from the analysis of eligible patients who started assigned therapy (see the Supplementary Appendix). The safety analysis included 510 patients who started the assigned protocol therapy. GFR denotes glomerular filtration rate.



*Shanafelt, T.D. et al "Ibrutinib-Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia." N Engl J Med 2019; 381:432-43*

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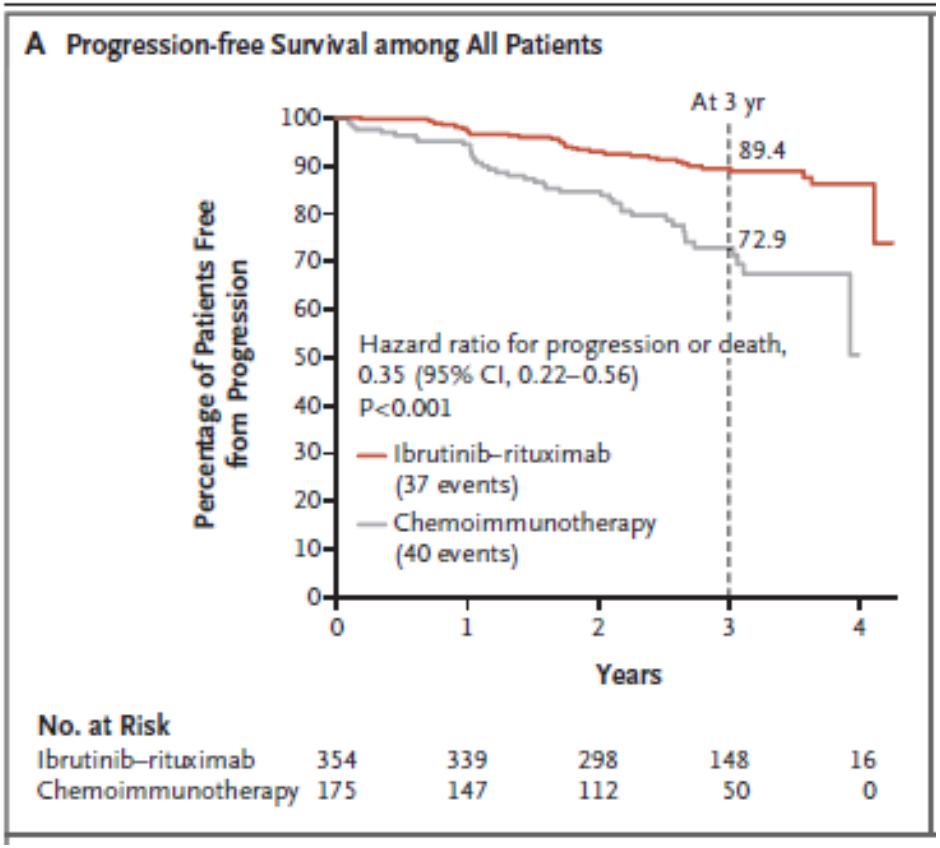


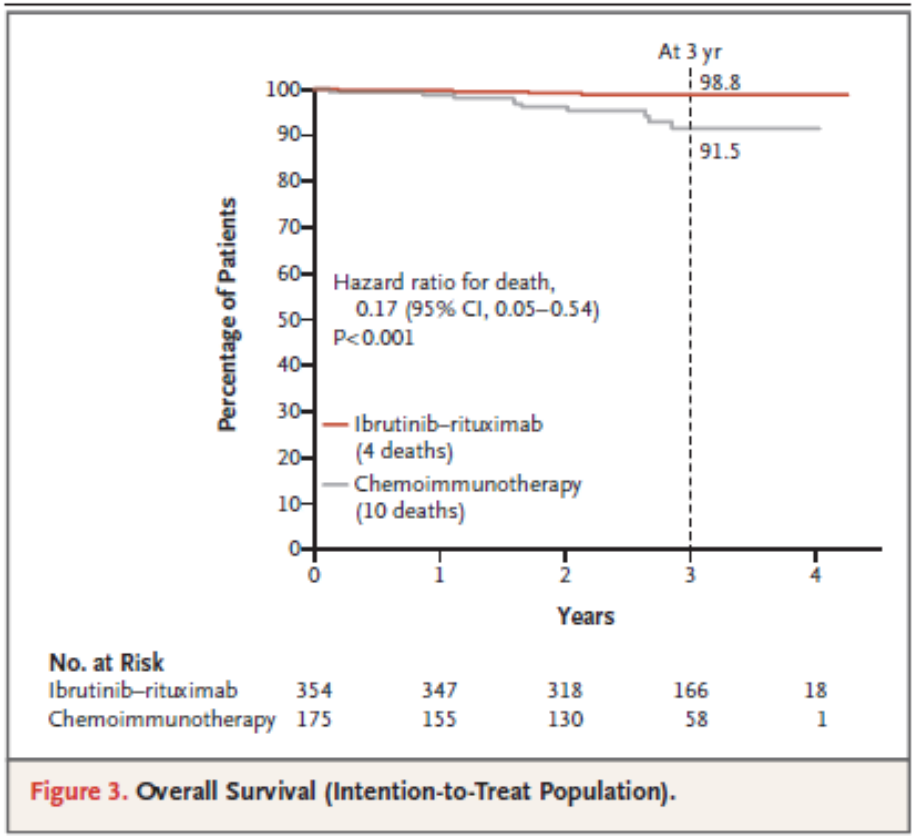
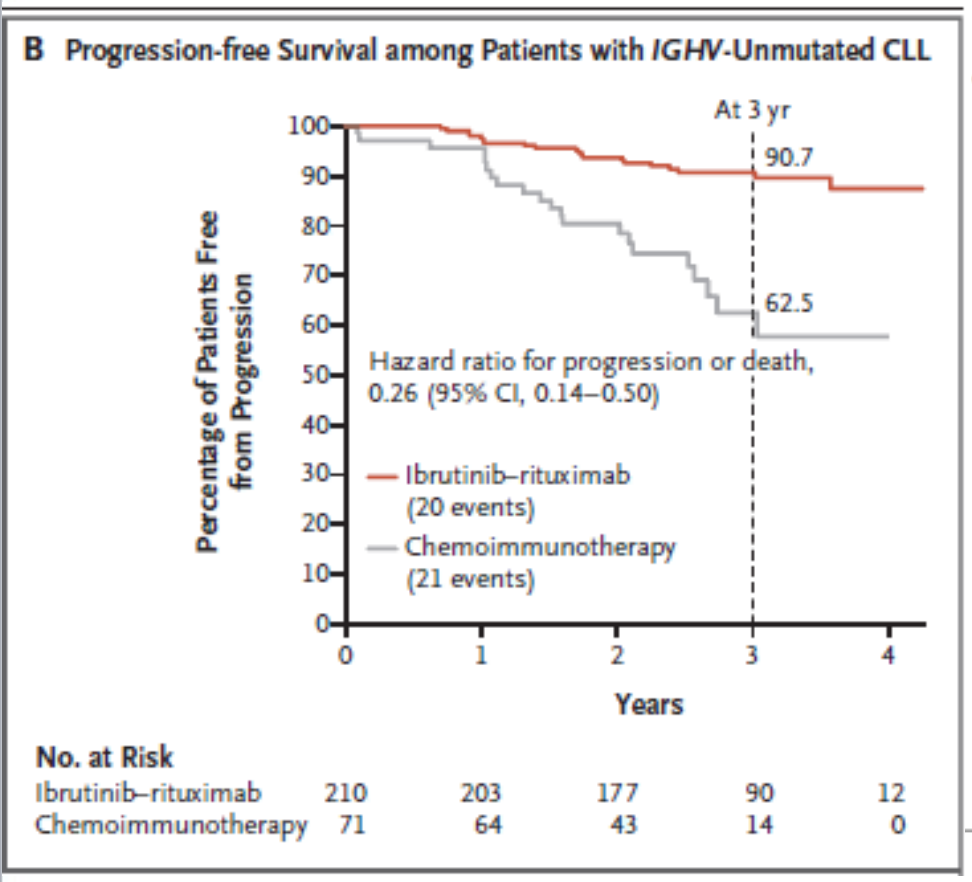



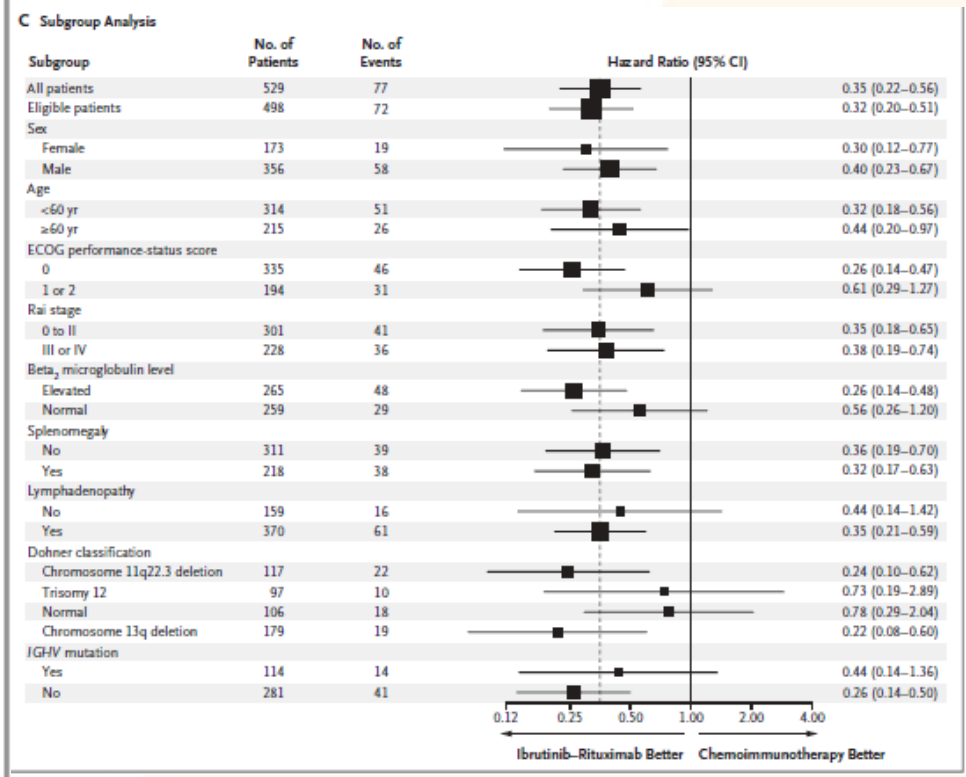

**Figure 3.** Overall Survival (Intention-to-Treat Population).



*Shanafelt, T.D. et al "Ibrutinib-Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia." N Engl J Med 2019; 381:432-43*

# Case 1, S. H.



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# Case 1, S. H.

**Table 2. Adverse Events of Grade 3 or Higher Reported in More Than 2% of Patients in Either Group.***

| Event | Ibrutinib–Rituximab Group (N=352) | | | Chemoimmunotherapy Group (N=158) | | |
|---|---|---|---|---|---|---|
| | Grade 3 | Grade 4 | Grade 5 | Grade 3 | Grade 4 | Grade 5 |
| | *number of patients (percent)* | | | | | |
| Hematologic event | | | | | | |
| Anemia | 17 (4.8) | 0 | 0 | 17 (10.8) | 6 (3.8) | 0 |
| Hemolysis | 2 (0.6) | 0 | 0 | 3 (1.9) | 1 (0.6) | 0 |
| Leukocytosis | 61 (17.3) | 1 (0.3) | 0 | 12 (7.6) | 0 | 0 |
| Lymphocyte count decreased | 10 (2.8) | 0 | 0 | 43 (27.2) | 32 (20.3) | 0 |
| Lymphocyte count increased | 77 (21.9) | 0 | 0 | 12 (7.6) | 0 | 0 |
| Neutropenia | 38 (10.8) | 52 (14.8) | 0 | 35 (22.2) | 36 (22.8) | 0 |
| Platelet count decreased | 9 (2.6) | 6 (1.7) | 0 | 16 (10.1) | 8 (5.1) | 0 |
| White-cell count decreased | 7 (2.0) | 1 (0.3) | 0 | 35 (22.2) | 23 (14.6) | 0 |
| Nonhematologic event | | | | | | |
| Infection† | 28 (8.0) | 4 (1.1) | 1 (0.3) | 9 (5.7) | 5 (3.2) | 1 (0.6) |
| Febrile neutropenia | 8 (2.3) | 0 | 0 | 21 (13.3) | 4 (2.5) | 0 |
| Alanine aminotransferase increased | 6 (1.7) | 2 (0.6) | 0 | 1 (0.6) | 0 | 0 |
| Aspartate aminotransferase increased | 9 (2.6) | 0 | 0 | 2 (1.3) | 0 | 0 |
| Hyperglycemia | 12 (3.4) | 2 (0.6) | 0 | 8 (5.1) | 0 | 0 |
| Hyponatremia | 11 (3.1) | 0 | 0 | 3 (1.9) | 0 | 0 |
| Atrial fibrillation | 9 (2.6) | 2 (0.6) | 0 | 1 (0.6) | 1 (0.6) | 0 |
| Arthralgia | 17 (4.8) | 0 | 0 | 2 (1.3) | 0 | 0 |
| Hypertension | 65 (18.5) | 1 (0.3) | 0 | 13 (8.2) | 0 | 0 |
| Fatigue | 7 (2.0) | 0 | 0 | 4 (2.5) | 0 | 0 |
| Maculopapular rash | 11 (3.1) | 0 | 0 | 8 (5.1) | 0 | 0 |
| Diarrhea | 15 (4.3) | 0 | 0 | 2 (1.3) | 0 | 0 |
| Any event, according to worst grade | 204 (58.0) | 75 (21.3) | 3 (0.9) | 57 (36.1) | 67 (42.4) | 2 (1.3) |



*Shanafelt, T.D. et al "Ibrutinib-Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia." N Engl J Med 2019; 381:432-43*

# Case 1, S. H.

**SUGGESTED TREATMENT REGIMENS[a,b,c,d]**
**CLL/SLL without del(17p)/*TP53* mutation**
**(alphabetical by category)**

| FIRST-LINE THERAPY | | |
|---|---|---|
| Frail patient with significant comorbidity (not able to tolerate purine analogs) OR Patients aged ≥65 y and younger patients with significant comorbidities (creatinine clearance [CrCl] <70 mL/min) | **Preferred regimens**<br>• Ibrutinib[e] (category 1)<br>• Venetoclax[e,f] + obinutuzumab | **Other recommended regimens**<br>• Bendamustine (70 mg/m² in cycle 1 with escalation to 90 mg/m² if tolerated) + anti-CD20 monoclonal antibody[d,g] (Not recommended for frail patients)<br>• Chlorambucil + obinutuzumab<br>• High-dose methylprednisolone (HDMP) + rituximab (category 2B)<br>• Ibrutinib[e] + obinutuzumab (category 2B)<br>• Obinutuzumab (category 2B)<br>• Chlorambucil (category 3)<br>• Rituximab (category 3) |
| Patients aged <65 y without significant comorbidities | **Preferred regimens**<br>• Ibrutinib[e] (category 1)<br>• Venetoclax[e,f] + obinutuzumab | **Other recommended regimens**<br>• Bendamustine + anti-CD20 monoclonal antibody[d,g,h]<br>• FCR (fludarabine,[i] cyclophosphamide, rituximab)[h,j,k] (preferred for patients with *IGHV*-mutated CLL)<br>• FR (fludarabine,[i] rituximab)[j,l]<br>• HDMP + rituximab (category 2B)<br>• Ibrutinib[e] + rituximab (category 2B)<br>• PCR (pentostatin, cyclophosphamide, rituximab) (category 3) |

| POST FIRST-LINE CHEMOIMMIUNOTHERAPY MAINTENANCE THERAPY |
|---|
| **Other recommended regimen** |
| • Consider lenalidomide for high-risk patients (blood MRD ≥$10^{-2}$ or ≥$10^{-4}$ and <$10^{-2}$ with unmutated *IGHV*)[m] after first-line therapy |

# Case 1, S. H.

**SUGGESTED TREATMENT REGIMENS[a,b,c,d]**
**CLL/SLL with del(17p)/*TP53* mutation**
**(alphabetical by category)**

## FIRST-LINE THERAPY

| Preferred regimens | Other recommended regimens |
|---|---|
| • Ibrutinib[e] | • Alemtuzumab[p] ± rituximab |
| • Venetoclax[e,f] + obinutuzumab | • HDMP + rituximab |
| | • Obinutuzumab |

## RELAPSED/REFRACTORY THERAPY

| Preferred regimens | Other recommended regimens |
|---|---|
| • Acalabrutinib[e,n] (category 1) | • Alemtuzumab[p] ± rituximab |
| • Ibrutinib[e] (category 1) | • HDMP + rituximab |
| • Venetoclax[e,f] + rituximab (category 1) | • Idelalisib[e] |
| • Duvelisib[e] | • Lenalidomide[q] ± rituximab |
| • Idelalisib[e] + rituximab[o] | • Ofatumumab[r] |
| • Venetoclax[e,f] | |

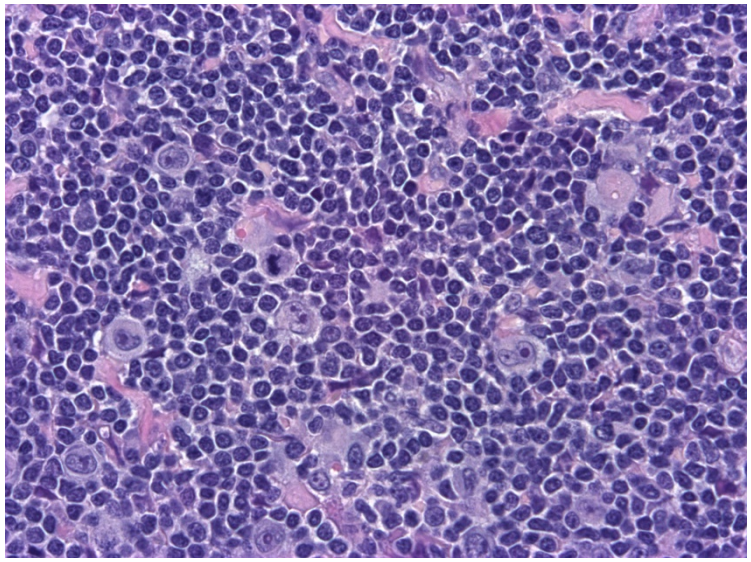
# Case 2, B.S.

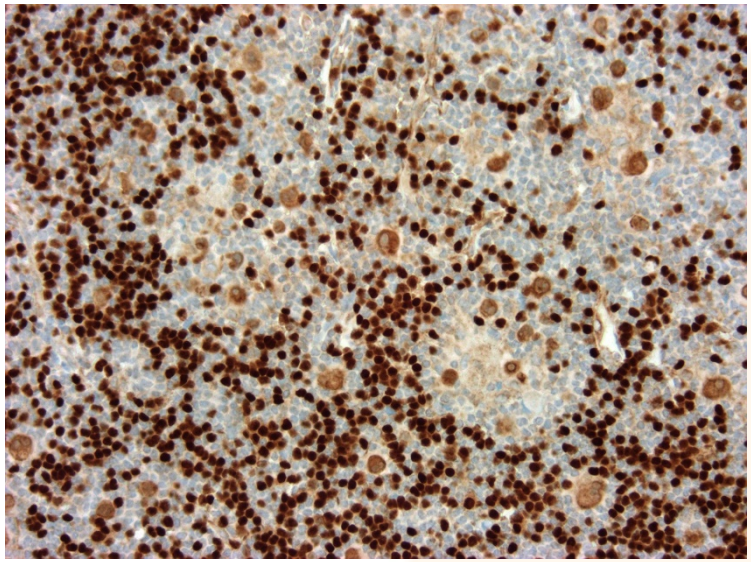
- **HPI:** 47 y.o. male with history of a slowly growing right neck mass for >1 year before seeking medical attention. Also having intermittent night sweats and unintentional weight loss (~20 pounds in the past year.)

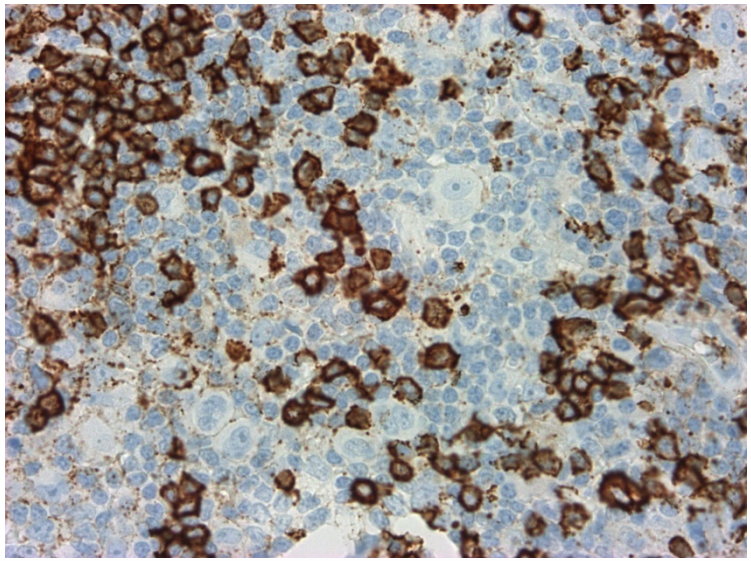
- **PMH, PSH:** migraine headaches

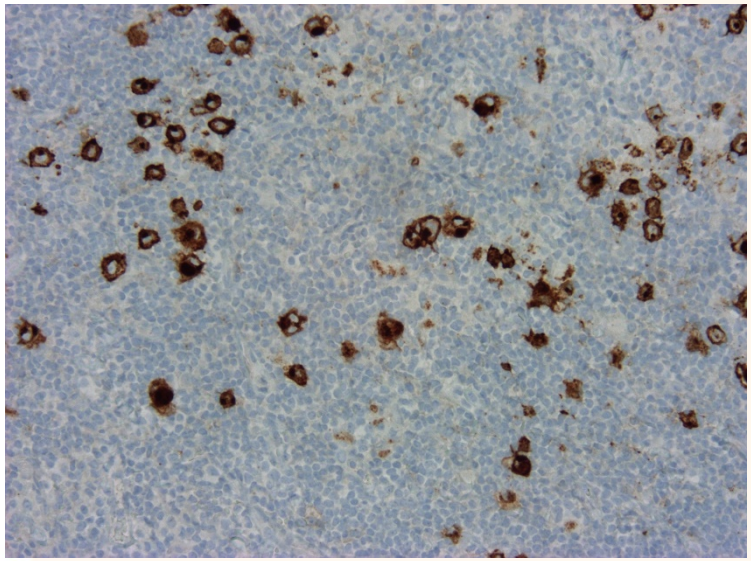
- **SH:** Former smoker, *12.5 pack year history.* Rare alcohol use.

# Case 2, B.S.

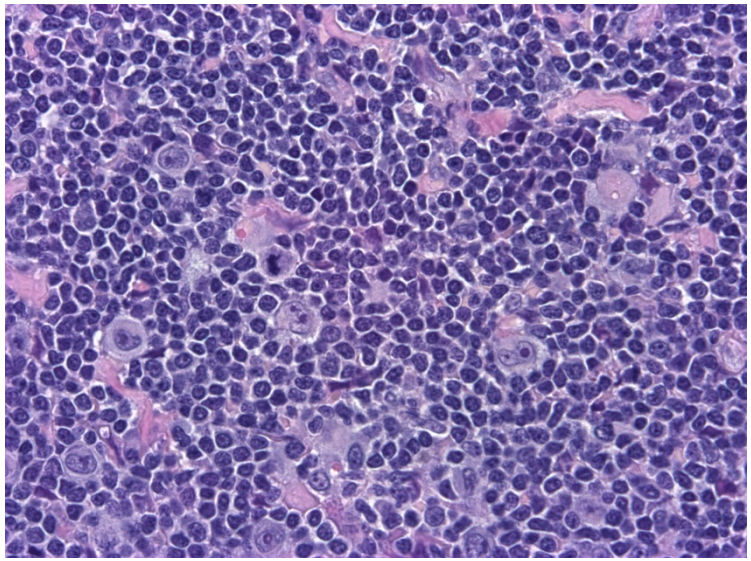


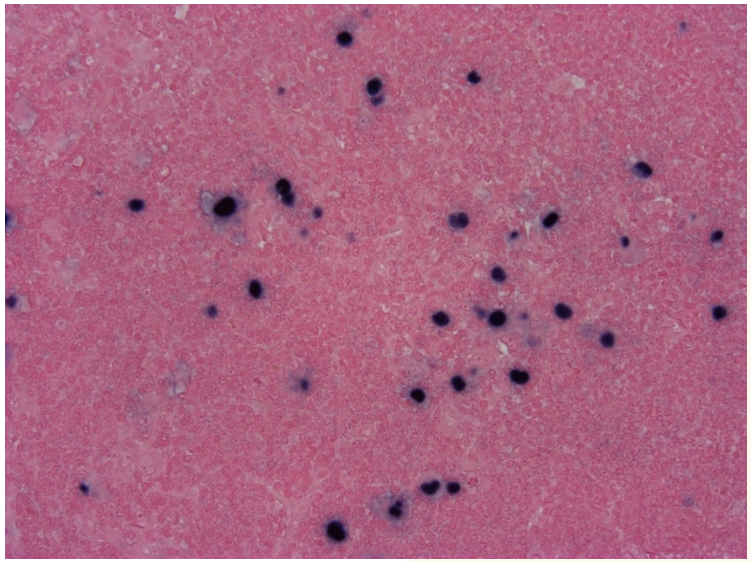






# Case 2, B.S.





# Case 2, B.S.

- **<u>Clinical course and w/u:</u>**

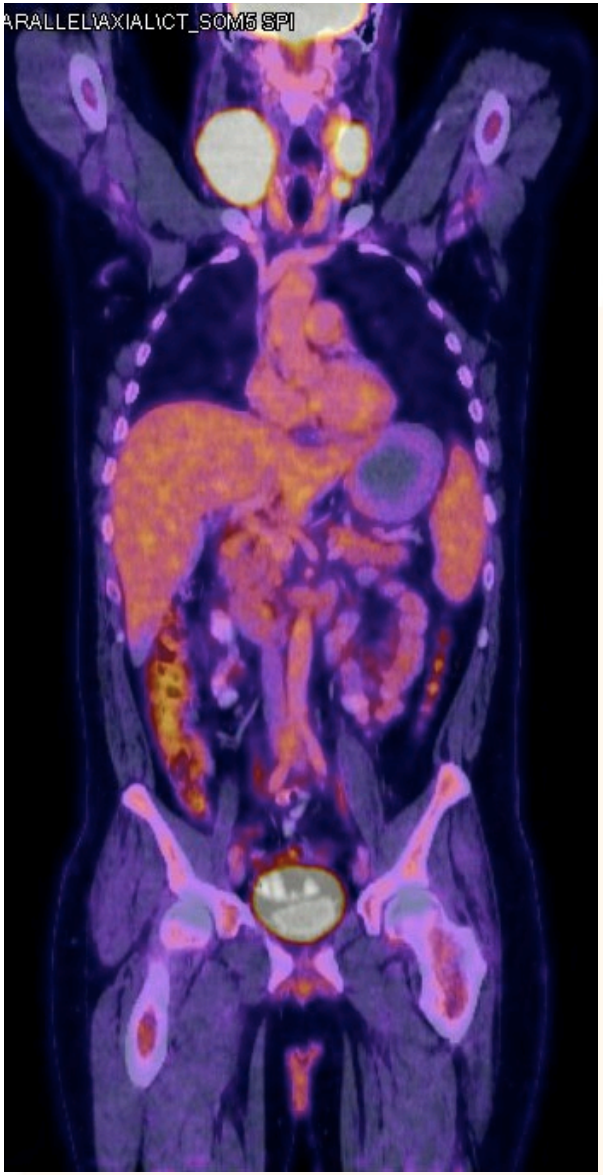
Open right cervical biopsy

Final Pathologic Diagnosis

A. RIGHT NECK MASS, BIOPSY:
- Classical Hodgkin lymphoma, mixed cellularity type. (See comment)

# Case 2, B.S.

| CBC | |
|---|---|
| SEDIMENTATION RATE | 136 ▲ |



# Case 2, B.S.

**UNFAVORABLE RISK FACTORS FOR STAGE I-II CLASSIC HODGKIN LYMPHOMA**

| Risk Factor | GHSG | EORTC | NCCN |
|---|---|---|---|
| Age | | ≥50 | |
| Histology | | | |
| ESR and B symptoms | >50 if A; >30 if B | >50 if A; >30 if B | ≥50 or any B symptoms |
| Mediastinal mass | MMR > .33 | MTR > .35 | MMR > .33 |
| # Nodal sites | >2* | >3* | >3 |
| E lesion | any | | |
| Bulky | | | >10 cm |

GHSG = German Hodgkin Study Group
EORTC = European Organization for the Research and Treatment of Cancer

MMR = Mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter
MTR = Mediastinal thoracic ratio, maximum width of mediastinal mass/intrathoracic diameter at T5-6

Final diagnosis: Unfavorable Stage IIB classical Hodgkin lymphoma, mixed cellularity variant

The NEW ENGLAND JOURNAL of MEDICINE

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# Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma

Peter Johnson, M.D., Massimo Federico, M.D., Amy Kirkwood, M.Sc., Alexander Fosså, M.D., Leanne Berkahn, M.D., Angelo Carella, M.D., Francesco d'Amore, M.D., Gunilla Enblad, M.D., Antonella Franceschetto, M.D., Michael Fulham, M.D., Stefano Luminari, M.D., Michael O'Doherty, M.D., Pip Patrick, Ph.D., Thomas Roberts, B.Sc., Gamal Sidra, M.D., Lindsey Stevens, Paul Smith, M.Sc., Judith Trotman, M.D., Zaid Viney, M.D., John Radford, M.D., and Sally Barrington, M.D.

ABSTRACT

# Case 2, B.S.

- Treatment of advanced stage Hodgkin's lymphoma with chemotherapy has produced high survival rates. ABVD, first described >40 years ago yields cure rates of 70 to 80%, similar to rates observed with more complex regimens.

- The possible exception is escalated BEACOPP which has demonstrated higher PFS rates and a possible small improvement in OS based on meta-analysis. However, these are achieved at significantly increased rates of short-term and long-term AE's.

- Long term toxic effects of treatment in Hodgkin's are important, because the majority of patient's have a left expectancy of many years. ABVD is generally well tolerated, but it does carry the risk of serious pulmonary toxicity due to bleomycin exposure.

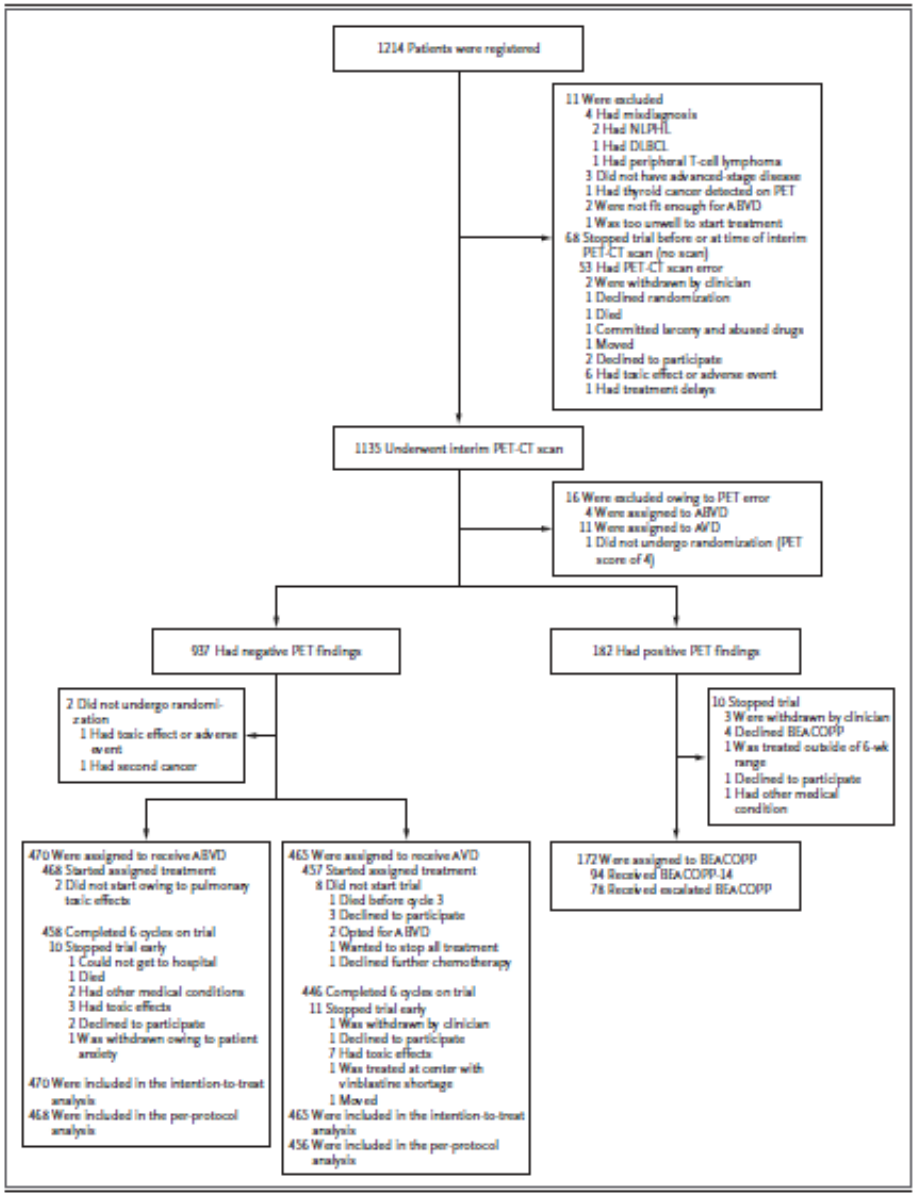
- The RATHL trial was performed to explore potential for adapting therapy by de-escalating treatment for patients with a good outlook and intensifying it for those at highest risk for failure.



*Johnson, P. et al "Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma." N Engl J Med 2016; 374*

# Case 2, B.S.

- This was a prospective, randomized controlled trial to determine whether the omission of bleomycin after negative findings on an interim PET/CT could yield a noninferior PFS rate at 3 years, compared to patients who continued on standard ABVD.



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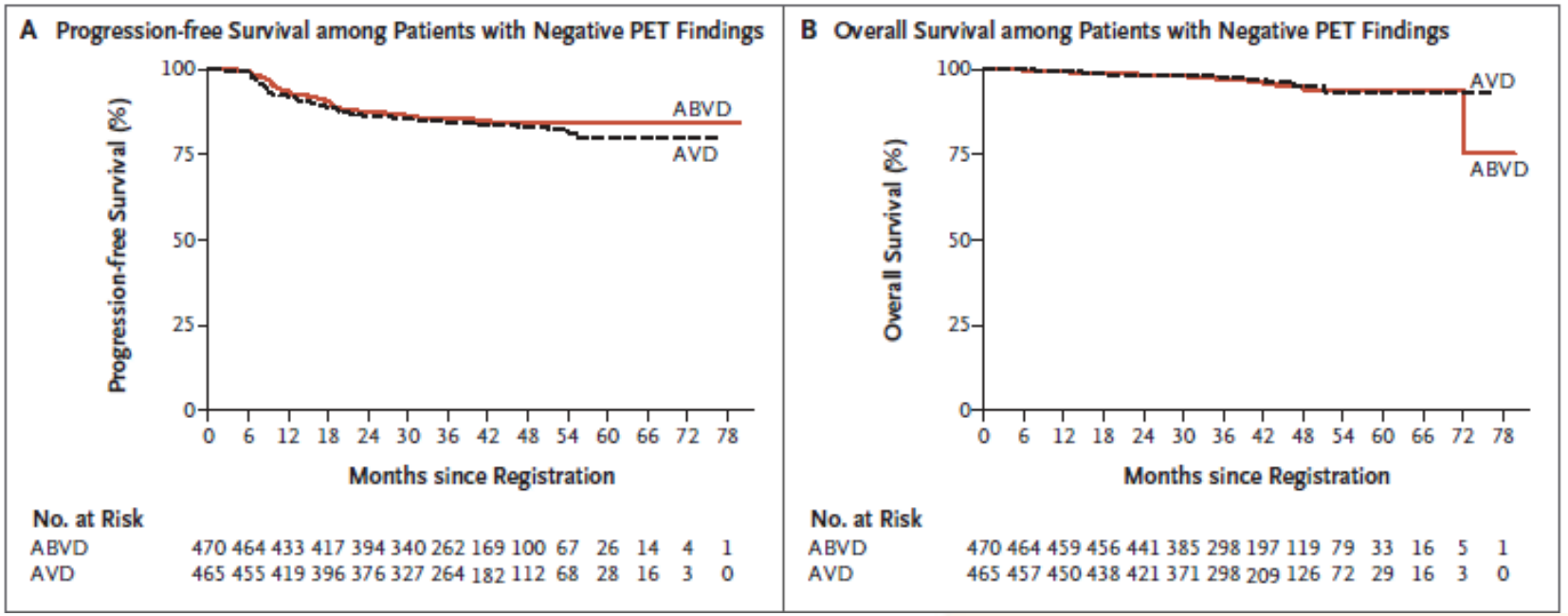





*Johnson, P. et al "Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma." N Engl J Med 2016; 374*

# Case 2, B.S.

**Table 3.** Grade 3 or 4 Adverse Events among Patients with Negative PET Findings Who Started Their Assigned Treatment.*

| Event | ABVD, Cycles 1 and 2 (N=1203) | ABVD, Cycles 3–6 (N=468) | AVD, Cycles 3–6 (N=457) | BEACOPP-14 (N=94) | Escalated BEACOPP (N=78) |
|---|---|---|---|---|---|
| | | | *number (percent)* | | |
| Any blood or bone marrow event | 711 (59) | 280 (60) | 273 (60) | 68 (72) | 58 (74) |
| Neutropenia | 694 (58) | 275 (59) | 269 (59) | 59 (63) | 52 (67) |
| Thrombocytopenia† | 16 (1) | 6 (1) | 15 (3) | 18 (19) | 33 (42) |
| Any cardiac event | 9 (1) | 6 (1) | 2 (<0.5) | 1 (1) | 0 |
| Any constitutional symptom | 36 (3) | 18 (4) | 13 (3) | 11 (12) | 11 (14) |
| Fatigue† | 14 (1) | 14 (3) | 5 (1) | 8 (9) | 3 (4) |
| Fever | 16 (1) | 4 (1) | 7 (2) | 2 (2) | 9 (12) |
| Any infection | 76 (6) | 68 (15) | 47 (10) | 35 (37) | 33 (42) |
| Febrile neutropenia† | 24 (2) | 22 (5) | 10 (2) | 10 (11) | 20 (26) |
| Any neurologic event | 20 (2) | 23 (5) | 14 (3) | 9 (10) | 3 (4) |
| Any pulmonary or upper respiratory event† | 8 (1) | 15 (3) | 3 (1) | 4 (4) | 4 (5) |
| Dyspnea† | 5 (<0.5) | 9 (2) | 1 (<0.5) | 2 (2) | 2 (3) |
| Pneumonitis | 0 | 5 (1) | 1 (<0.5) | 0 | 2 (3) |
| Any vascular event | 18 (1) | 23 (5) | 12 (3) | 8 (9) | 2 (3) |
| Thrombosis or embolism related to vascular access | 4 (<0.5) | 4 (1) | 1 (<0.5) | 0 | 0 |
| Thrombosis, thrombus, or embolism | 14 (1) | 20 (4) | 11 (2) | 8 (9) | 2 (3) |
| Any clinical adverse event‡§ | 188 (16) | 143 (31) | 96 (21) | 52 (55) | 47 (60) |
| Any grade 3 or 4 adverse event | 771 (64) | 322 (69) | 299 (65) | 75 (80) | 65 (83) |

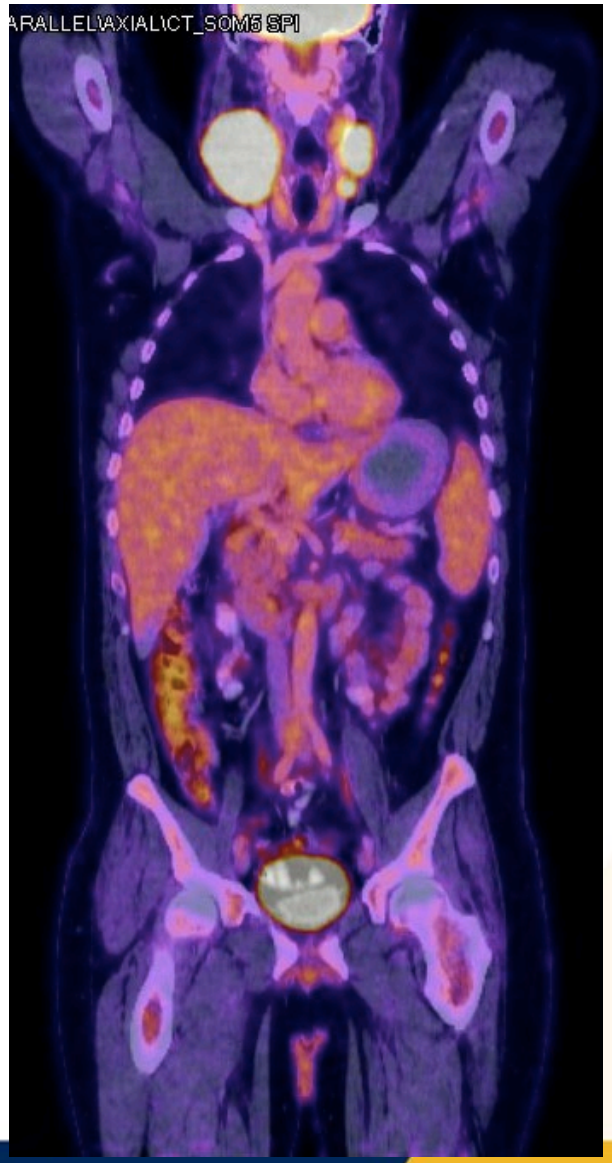
* Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3. BEACOPP-14 is an accelerated version of BEACOPP that involves growth-factor support. Escalated BEACOPP involves higher-than-standard doses of etoposide, doxorubicin, and cyclophosphamide.
† $P<0.05$ for the comparison of ABVD with AVD during cycles 3 through 6.
‡ Blood or bone marrow events and laboratory events were excluded.
§ $P<0.005$ for the comparison of ABVD with AVD during cycles 3 through 6.

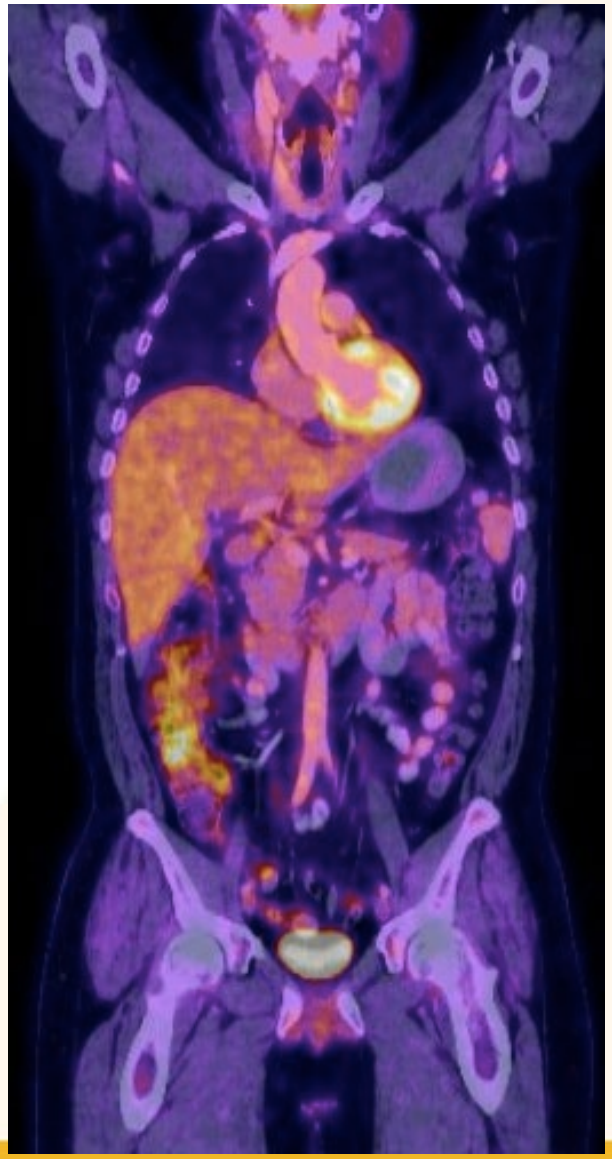


*Johnson, P. et al "Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma." N Engl J Med 2016; 374*

# Case 2, B.S.

- Overall, bleomycin's omission after a negative interim PET carries a estimated 1.6% increased risk of treatment failure but significantly lowers the incidence of fatigue, respiratory events and better preservation of DLco. Overall clinical events of any grade were also improved in the AVD group with the number of overall higher grade events relatively similar between the two groups.

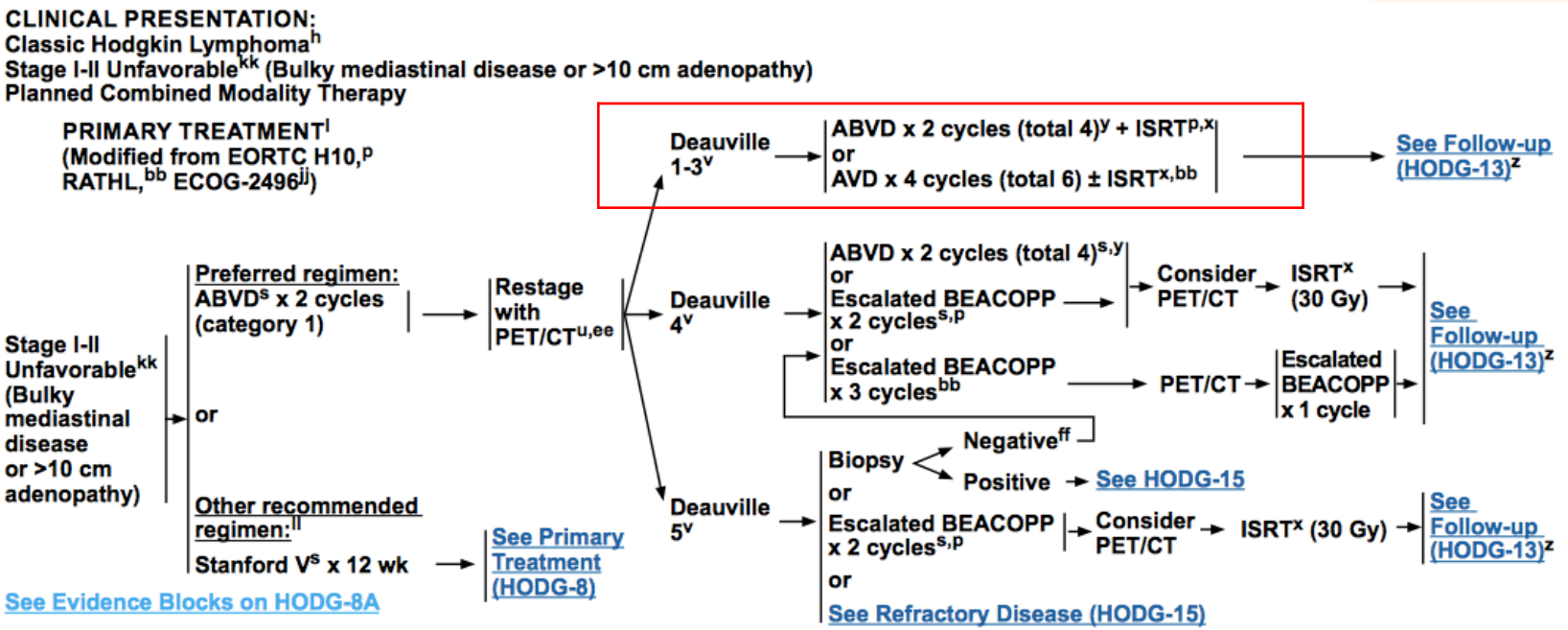




*Johnson, P. et al "Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma." N Engl J Med 2016; 374*

# Case 2, B.S.


CLINICAL PRESENTATION:
Classic Hodgkin Lymphoma[h]
Stage I-II Unfavorable[kk] (Bulky mediastinal disease or >10 cm adenopathy)
Planned Combined Modality Therapy
PRIMARY TREATMENT[l]
(Modified from EORTC H10,[p] RATHL,[bb] ECOG-2496[jj])
Stage I-II Unfavorable[kk] (Bulky mediastinal disease or >10 cm adenopathy)
Preferred regimen:
ABVD[s] x 2 cycles (category 1)
or
Other recommended regimen:[ll]
Stanford V[s] x 12 wk
See Evidence Blocks on HODG-8A
Restage with PET/CT[u,ee]
See Primary Treatment (HODG-8)
Deauville 1-3[v]
ABVD x 2 cycles (total 4)[y] + ISRT[p,x]
or
AVD x 4 cycles (total 6) ± ISRT[x,bb]
See Follow-up (HODG-13)[z]
Deauville 4[v]
ABVD x 2 cycles (total 4)[s,y]
or
Escalated BEACOPP x 2 cycles[s,p]
Consider PET/CT
ISRT[x] (30 Gy)
or
Escalated BEACOPP x 3 cycles[bb]
PET/CT
Escalated BEACOPP x 1 cycle
See Follow-up (HODG-13)[z]
Deauville 5[v]
Biopsy
Negative[ff]
Positive
See HODG-15
or
Escalated BEACOPP x 2 cycles[s,p]
Consider PET/CT
ISRT[x] (30 Gy)
See Follow-up (HODG-13)[z]
or
See Refractory Disease (HODG-15)

# Case 3a, A.A.

- **HPI:** 44 y.o. female with recent neck pain/stiffness and mild cervical adenopathy. Otherwise largely feeling well, denied night sweats and unintentional weight loss. Denies dyspnea, fatigue and neurological symptoms as well.

- **PMH, PSH:** No significant medical history. No chronic medications. Surgical history positive for 3 caesarian sections.

- **SH:** Homemaker. Social alcohol use. No tobacco use.

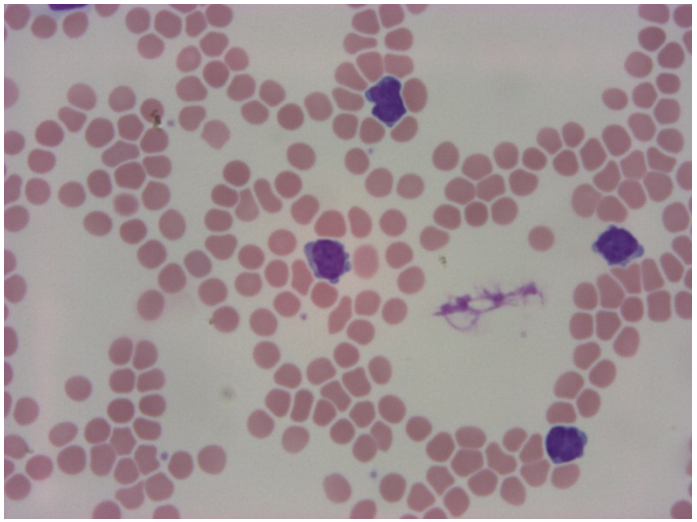
# Case 3a, A.A.

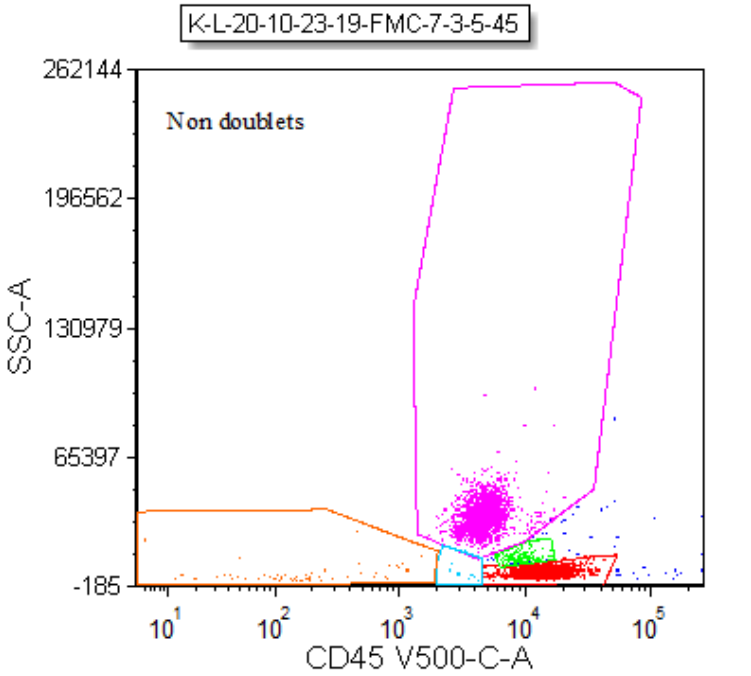
| CBC | |
|---|---|
| WBC | 15.9 ▲ |
| HGB | 14.2 |
| HCT | 42.7 |
| PLATELET COUNT (AUTO) | 214 |
| PLATELET COUNT | 214 |
| RBC | 4.66 |
| MCV | 91.6 |
| MCHC | 33.3 |
| MCH | 30.5 |
| RDW-CV | 13.4 |
| MPV | 9.5 |
| GIEMSA STAIN (CBC ... | ! |

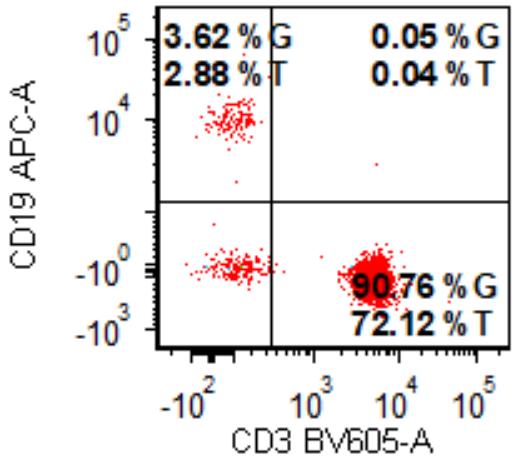
| CHEM 1 | |
|---|---|
| SODIUM | 139 |
| POTASSIUM | 4.1 |
| CHLORIDE | 104 |
| CARBON DIOXIDE | 27 |
| BUN | 11 |
| CREATININE | 0.75 |
| ESTIMATED GLOMERUL... | >59 |
| CALCIUM | 9.4 |
| PHOSPHORUS | 4.0 * |
| URIC ACID | 3.2 |
| **LIVER/PANCREAS FUN...** | |
| ALBUMIN | 4.5 |
| BILIRUBIN, TOTAL | 0.5 * |
| AST (SGOT) | 13 |
| ALT (SGPT) | 14 |
| ALKALINE PHOSPHATASE | 44 |
| LDH | 148 |

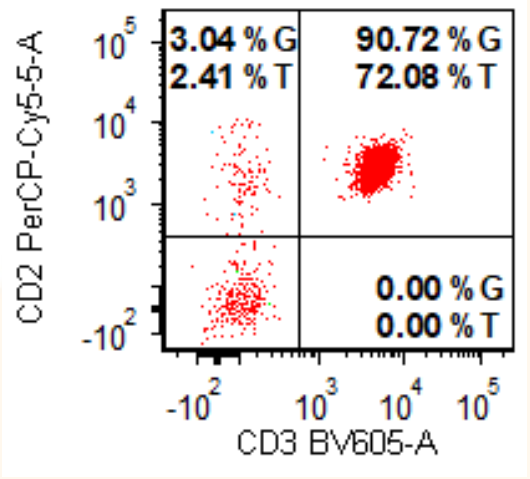
| ABS COUNT | |
|---|---|
| PMN ABS (AUTO) | |
| PMN ABS | 3.34 |
| LYMPHS ABS | 11.61 ▲ |
| EOS ABS | 0.32 |
| MONOS ABS | 0.64 |
| BASOS ABS | <0.10 |

# Case 3a, A.A.

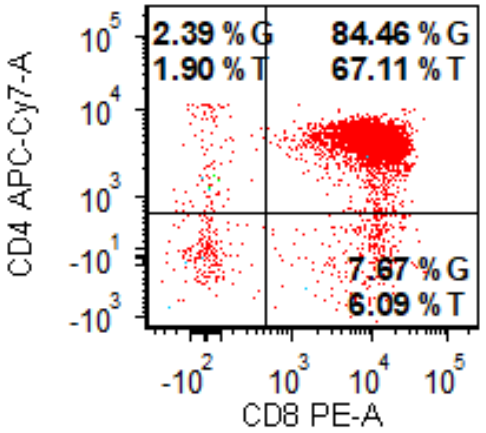


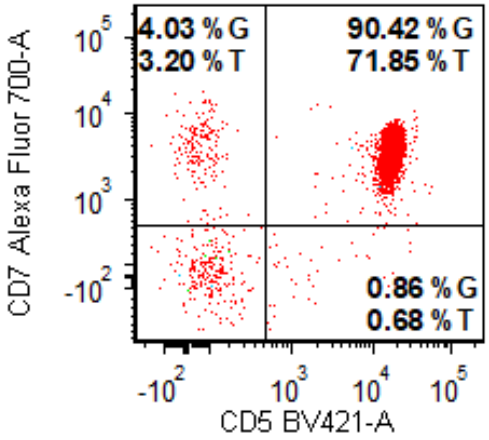

K-L-20-10-23-19-FMC-7-3-5-45
Non doublets
SSC-A
CD45 V500-C-A

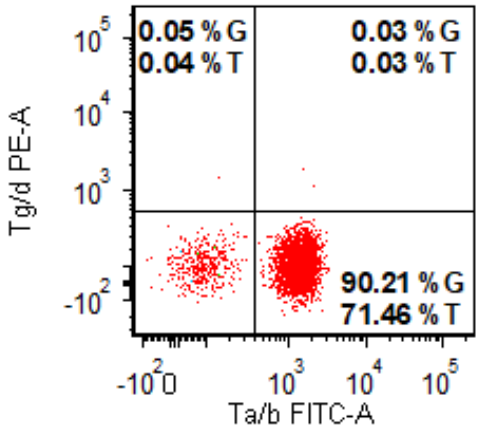

3.62 % G
2.88 % T
0.05 % G
0.04 % T
90.76 % G
72.12 % T
CD19 APC-A
CD3 BV605-A


3.04 % G
2.41 % T
90.72 % G
72.08 % T
0.00 % G
0.00 % T
CD2 PerCP-Cy5-5-A
CD3 BV605-A

# Case 3a, A.A.


2.39 % G
1.90 % T
84.46 % G
67.11 % T
7.67 % G
6.09 % T
CD4 APC-Cy7-A
CD8 PE-A


4.03 % G
3.20 % T
90.42 % G
71.85 % T
0.86 % G
0.68 % T
CD7 Alexa Fluor 700-A
CD5 BV421-A


0.05 % G
0.04 % T
0.03 % G
0.03 % T
90.21 % G
71.46 % T
Tg/d PE-A
Ta/b FITC-A

# Case 3a, A.A.

**Clinical course and w/u**

T-cell Lymphoma, FISH, B/BM

Result Summary: Abnormal

Interpretation: SEE COMMENTS

The result is abnormal and indicates that 56.5% of nuclei have trisomy/tetrasomy 8, most of which have an additional copy of the MYC gene region. In addition, 45% of nuclei had a rearrangement involving TCL1A. This observation likely indicates an inv(14) or t(14;14), which are common rearrangements in T-cell Prolymphocytic Leukemia (PLL).

Additional cytogenetic studies are reported separately.

Clinical and pathologic correlation is recommended.

Result Table: SEE COMMENTS

| Abnormality Name | Result | Abn% | Cutoff% |
|---|---|---|---|
| -7q31(D7Z1x2,D7S486x1) | Normal | | <4.5 |
| -7(D7Z1,D7S486)x1 | Normal | | <3.5 |
| +8/+8q24.1(D8Z2x2-4,MYCx3-4) | Abnormal | 56.5 | <3.5 |
| 14q32(TCL1A sep) | Abnormal | 45 | <6.5 |

Final Pathologic Diagnosis

PERIPHERAL BLOOD, FLOW CYTOMETRY:

- Consistent with T-cell lymphoproliferative disorder, favor T-cell prolymphocytic leukemia (see comment).

Phenotype: CD3, CD2, CD5, CD7, dual CD4/CD8 coexpression, T alpha/beta

# Case 3b, C.P.

- **HPI:** 73 yo female who presented at outside facility with worsening fatigue, sore throat, itching and left upper abdominal pain. Initially felt to have strep throat. Subsequently developed jaundice and transferred to WVUH.

- **PMH, PSH:** Asthma, HTN, prediabetes, knee replacement

- **SH:** Retired. Non smoker and denies alcohol use.

# Case 3b, C.P.

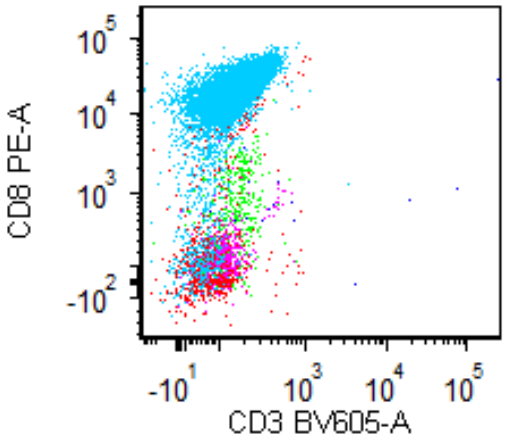
| CBC | |
|---|---|
| WBC | >400.0 |
| HGB | 11.6 |
| HCT | 33.5 |
| PLATELET COUNT (AUTO) | |
| PLATELET COUNT | 130 * |
| RBC | 4.07 |
| MCV | 82.2 |
| MCHC | 34.5 |
| MCH | 28.4 |
| RDW | 15.5 |
| RETICULOCYTE COUNT % | 1.82 |
| RETICULOCYTE COUNT... | 72.6 |
| IMMATURE RETIC FRA... | 0.62 |
| MPV | SEE COMMENT * |
| GIEMSA STAIN (CBC ... | |

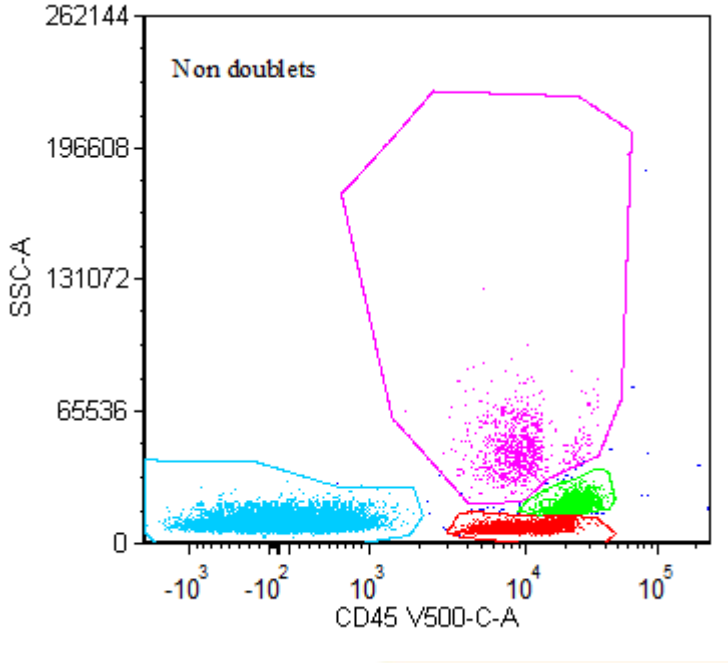
| ABS COUNT | |
|---|---|
| NEUTROPHIL ABSOLUTE | 58.86 |
| PMN ABS (AUTO) | |
| PMN ABS | |
| LYMPHS ABS | |
| LYMPHOCYTE ABSOLUTE | 258.65 |
| EOS ABS | |
| EOSINOPHIL ABSOLUTE | |
| MONOS ABS | |
| MONOCYTE ABSOLUTE | 12.44 |
| BASOS ABS | |
| BASOPHIL ABSOLUTE | |

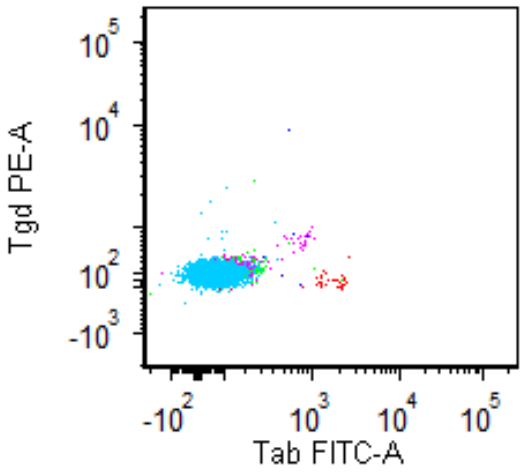
| CHEM 1 | |
|---|---|
| SODIUM | 143 |
| POTASSIUM | 3.6 |
| CHLORIDE | 106 |
| CARBON DIOXIDE | 26 |
| BUN | 21 |
| CREATININE | 2.30 |
| GLUCOSE | 103 |
| ANION GAP | 11 |
| BUN/CREAT RATIO | 9 |
| ESTIMATED GLOMERUL... | 21 |
| CALCIUM | 9.7 |
| MAGNESIUM | 2.0 |
| PHOSPHORUS | 1.8 * |
| URIC ACID | 5.6 |

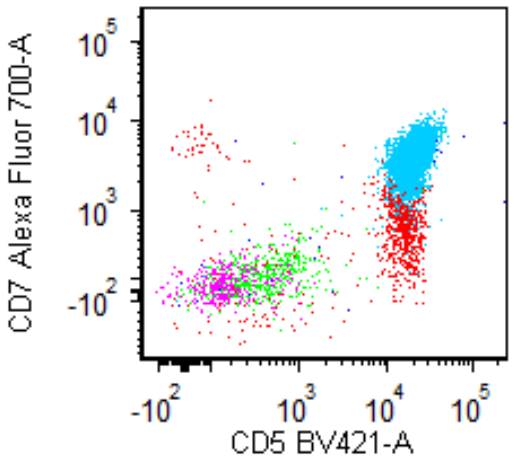
| LIVER/PANCREAS FUN... | |
|---|---|
| TOTAL PROTEIN | |
| ALBUMIN | 3.6 |
| BILIRUBIN, TOTAL | 3.1 * |
| BILIRUBIN,CONJUGATED | |
| AST (SGOT) | 161 |
| ALT (SGPT) | 122 |
| ALKALINE PHOSPHATASE | 426 |
| LDH | 2,077 |
| LIPASE | 81 |

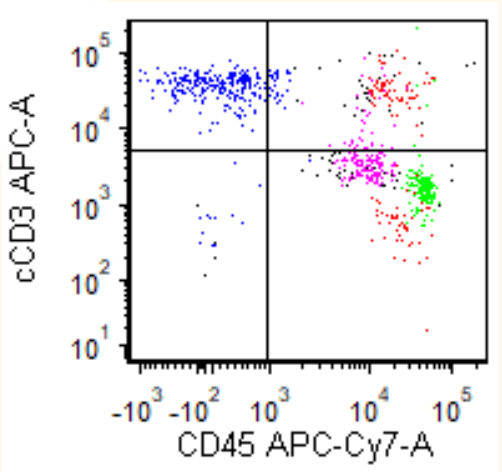
# Case 3b, C.P.


CD8 PE-A
CD3 BV605-A

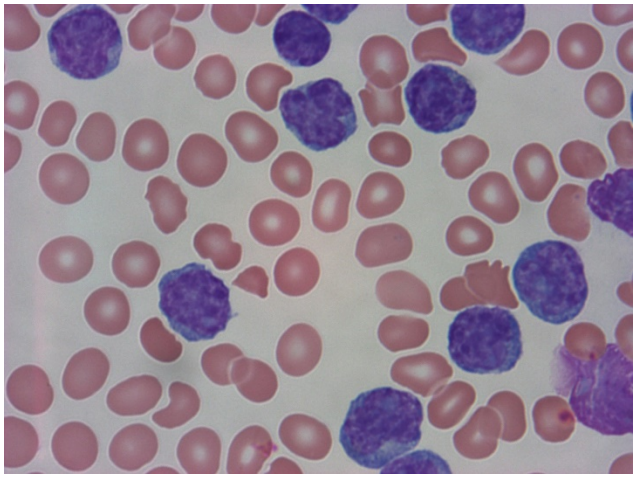

Non doublets
SSC-A
CD45 V500-C-A

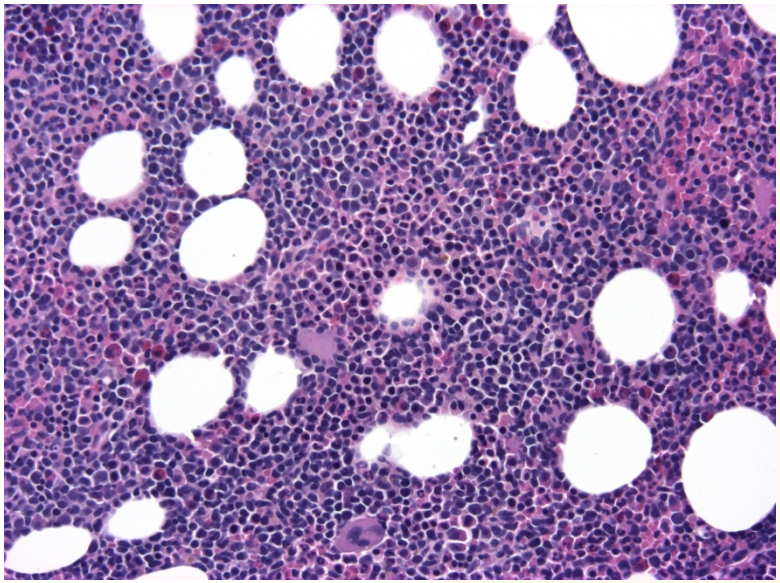

Tgd PE-A
Tab FITC-A

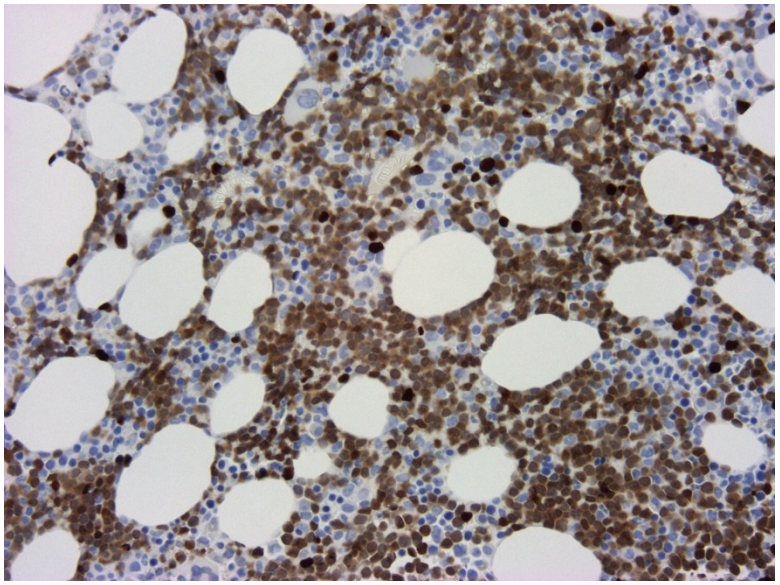

CD7 Alexa Fluor 700-A
CD5 BV421-A

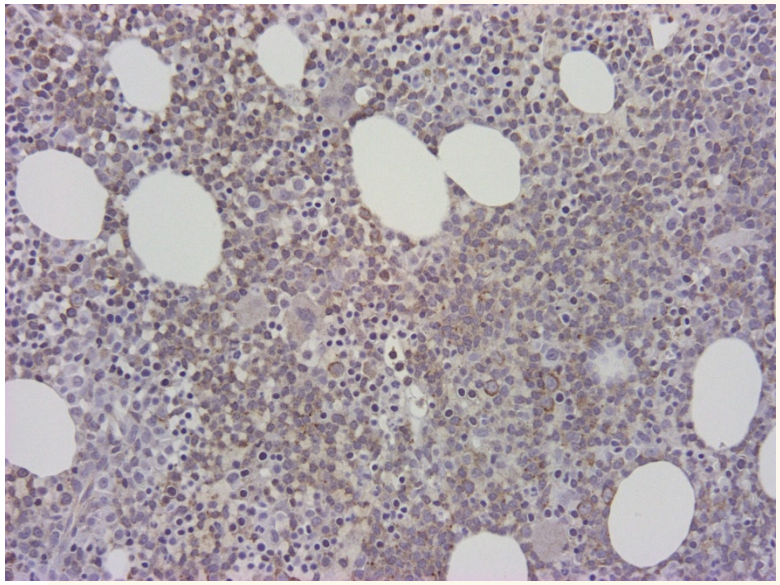

cCD3 APC-A
CD45 APC-Cy7-A

# Case 3b, C.P.









# Case 3a/3b

- T-PLL is a rare mature T-cell neoplasm, accounting for up to one-third of mature T-cell malignancies with a leukemic presentation, but these account for only a very small percentage of all lymphoid malignancies.

- Clinicians will often only see a case of T-PLL once every 5 to 10 years, which makes recognition of the disorder difficult yet essential because the treatment approach is specifically tailored to T-PLL and not well adopted for other T-cell malignancies.

- A minority of patients (15%) may be asymptomatic at diagnosis, and this “inactive” phase can persist for a variable length of time, which may extend to several years. However, progression is inevitable and may be very rapid when it occurs.

- There is usually a marked peripheral lymphocytosis, often in excess of 100 $10^9$/L with greater than 90% of the circulating cells being prolymphocytes. Serology and/or DNA analysis for HTLV I and II are consistently negative, and these retroviruses are not implicated in the pathogenesis of the disease.

- Confirmation of the diagnosis requires a systematic approach and careful integration of the results of morphology with specialized diagnostic tests, including immunophenotyping and cytogenetics.[1]



*Dearden, Claire. “How I treat prolymphocytic leukemia.” Blood 120.3 (2012): 538-551. Web. 26 Sept2019.*

# Case 3a/3b

- **Morphology**

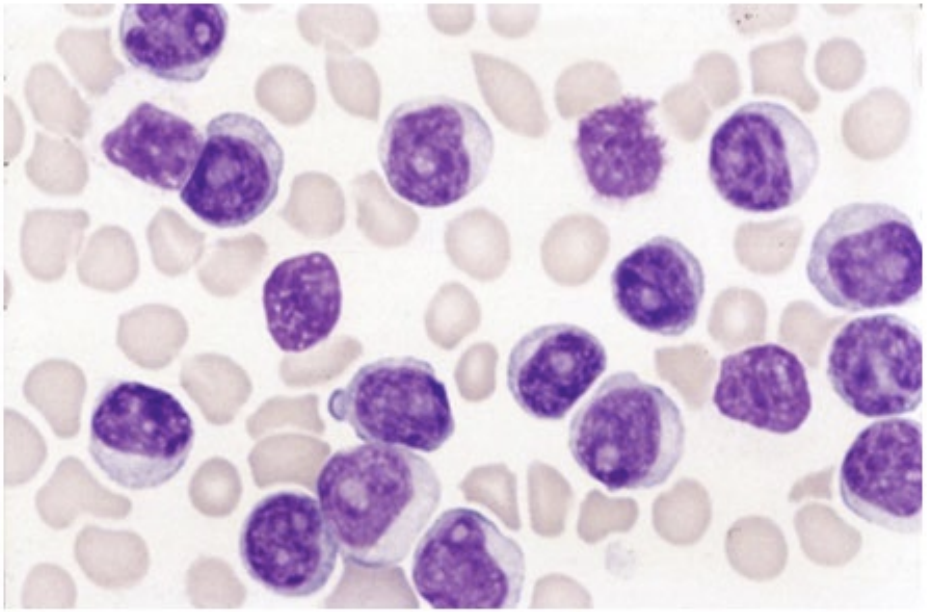


**Figure 2. PB morphology from a typical case of T-PLL showing medium-sized lymphoid cells with a regular nuclear outline, single nucleolus, and intense basophilic cytoplasm.** An occasional cell shows a cytoplasmic protrusion.

Examination of the PB film is a key diagnostic test and will often provide the first clue to the diagnosis. Morphology of other tissues (eg, BM and lymph nodes) is less informative and may not clearly discriminate between this and other peripheral T-cell malignancies.



*Dearden, Claire. "How I treat prolymphocytic leukemia." Blood 120.3 (2012): 538-551. Web. 26 Sept2019.*

## Mature T-cell neoplasms

*Leukemic or disseminated*

- T-cell large granular lymphocytic leukemia†
- Chronic lymphoproliferative disorders of NK cells†
- T-cell prolymphocytic leukemia
- Aggressive NK-cell leukemia
- Adult T-cell leukemia/lymphoma
- Systemic EBV-positive T-cell lymphoproliferative disorders of childhood

*Extranodal*

- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-type T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract
- Breast implant-associated anaplastic large-cell lymphoma

*Cutaneous*

- Mycosis fungoides†
- Sézary syndrome†
- Primary cutaneous CD30⁺ T-cell lymphoproliferative disorder†
- Primary cutaneous CD4⁺ small/medium T-cell lymphoma†
- Primary cutaneous acral CD8⁺ T-cell lymphoma†
- Primary cutaneous anaplastic large cell lymphoma†
- Lymphomatoid papulosis
- Subcutaneous panniculitis-like T-cell lymphoma
- Primary cutaneous γδ T-cell lymphoma
- Primary cutaneous CD8⁺ aggressive epidermotropic cytotoxic T-cell lymphoma
- Hydroa vacciniforme-like lymphoma

*Nodal*

- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Follicular T-cell lymphoma
- Nodal peripheral T-cell lymphoma with TFH phenotype
- Anaplastic large-cell lymphoma, ALK positive
- Anaplastic large-cell lymphoma, ALK negative

# Case 3a/3b

- **<u>Immunophenotyping</u>**
- Flow cytometry demonstrates the postthymic T-cell nature (TdT- , CD1a-, CD5+, CD2+, CD7+) of the prolymphocytes.
- T-prolymphocytes express CD7 with strong intensity in contrast to other mature T-cell leukemias, where this marker is often weakly positive or negative. CD52 is expressed at high density, explaining to some degree the in vivo sensitivity to the anti-CD52 monoclonal antibody alemtuzumab.

**Table 2. Differential diagnosis of mature T-cell leukemias by immunophenotype**

| Immunophenotype | T-PLL | T-LGL | SS | ATLL |
|---|---|---|---|---|
| CD2 | + | + | + | + |
| CD3 | + | + | + | ± |
| CD7 | + (strong) | ± | ± | − |
| CD4 | + (in 60%) | − (rarely +) | + (most) | + (most) |
| CD8 | + (15%) | + | Rare | Rare |
| CD4/CD8 coexpression | + (25%) | Rare | Rare | Rare |
| Other antigen expression | | CD 57/CD16 (often) | | CD25 in most cases |

T-PLL indicates T-cell prolymphocytic leukemia; T-LGL, T-large granular lymphocytic leukemia; SS, Sezary syndrome; and ATLL, adult T-cell leukemia lymphoma.



*Dearden, Claire. "How I treat prolymphocytic leukemia." Blood 120.3 (2012): 538-551. Web. 26 Sept2019.*

# Case 3a/3b

- **Cytogenetics**

- Recurrent chromosomal abnormalities involving chromosome 14 are present in almost 75% of T-PLL cases, with inversion 14 being the commonest. Tandem translocations between the 2 chromosomes 14, t(14;14), are also present in some cases. Both rearrangements result in activation and expression of the protooncogene *TCL-1.* It is also possible to test for TCL-1 protein expression using a flow cytometry technique, which confirms positivity in the majority of T-PLL cases.

- Trisomy 8 or iso8q is seen in up to two-thirds of cases (Figure 4A).15 The *C-MYC* localized at 8q24 is not rearranged in these cases, but the encoded protein may be overexpressed.

- The combination of such distinctive clinical, morphologic, immunophenotypic, and cytogenetic features usually means that the diagnosis, once entertained, is relatively straightforward.



*Dearden, Claire. "How I treat prolymphocytic leukemia." Blood 120.3 (2012): 538-551. Web. 26 Sept2019.*

# Case 3a/3b

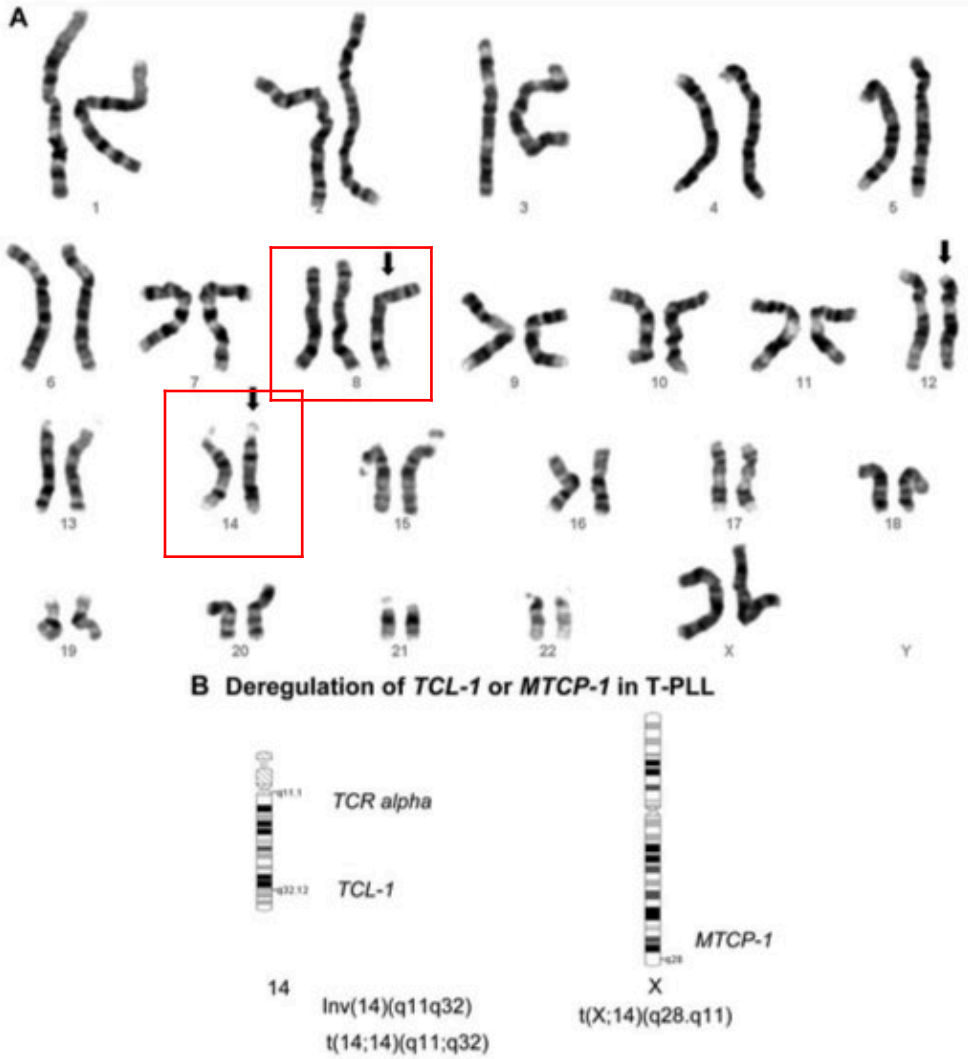



**Figure 4. Genetics in T-PLL.** (A) Complex karyotype from a case of T-PLL showing the characteristic abnormalities of inversion 14 and trisomy 8 [gain of whole chromosome rather than i(8q)]. The karyotype is 47,XX, +8, del12(p13.1p13.3), inv(14) (q11q32). (B) The deregulation of the oncogenes *TCL-1* (chromosome 14) and *MTCP-1*(X chromosome) through translocations involving the *TCR alpha* locus on chromosome 14. Courtesy of John Swansbury (Royal Marsden Hospital).



*Dearden, Claire. "How I treat prolymphocytic leukemia." Blood 120.3 (2012): 538-551. Web. 26 Sept2019.*

# Case 3a/3b

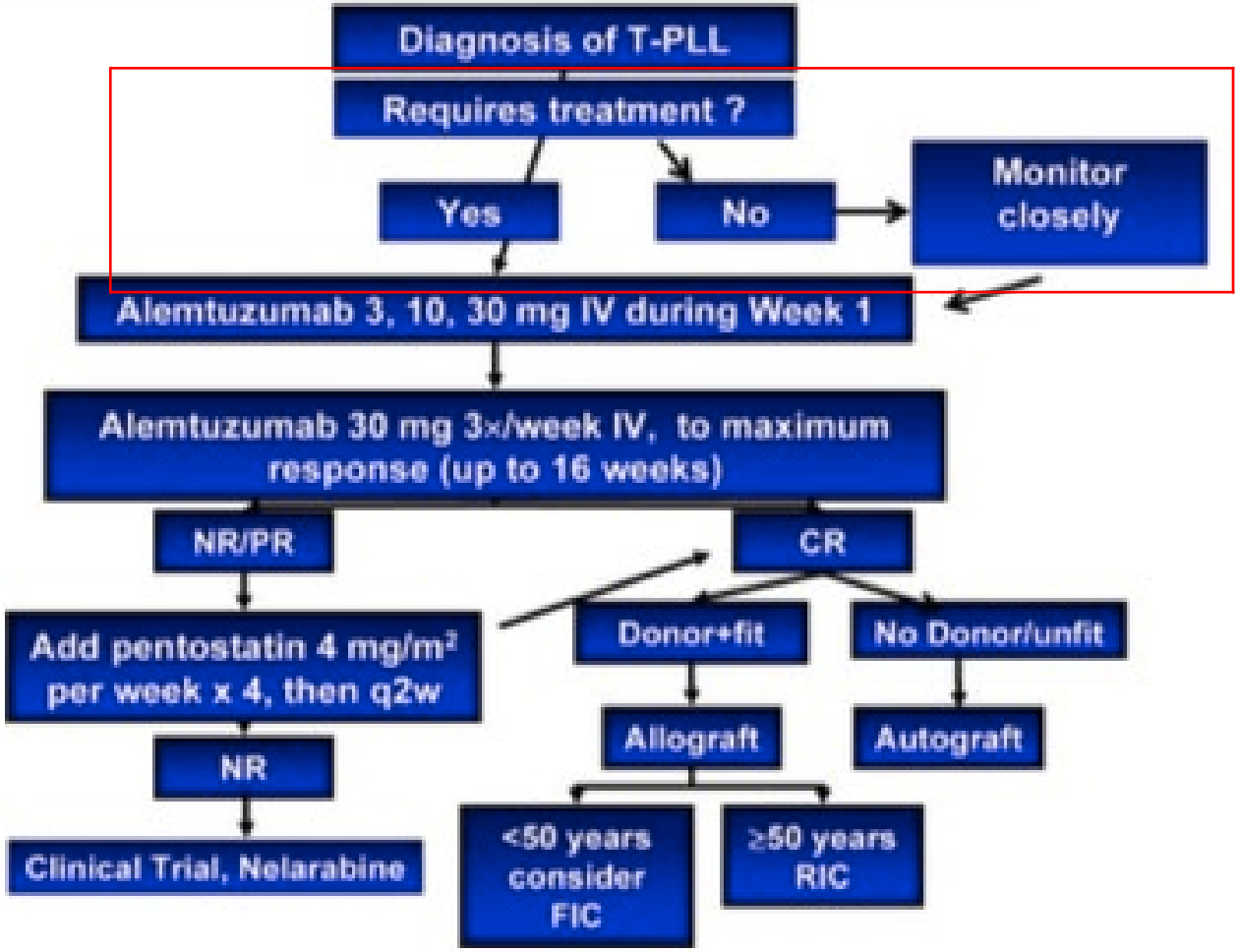



Figure 5. Treatment algorithm for T-PLL.



*Dearden, Claire. "How I treat prolymphocytic leukemia." Blood 120.3 (2012): 538-551. Web. 26 Sept2019.*

# Consensus criteria for diagnosis, staging, and treatment response assessment of T-cell prolymphocytic leukemia (T-PLL)

Philipp B. Staber, Marco Herling, Mar Bellido, Eric D. Jacobsen, Matthew S. Davids, Tapan Mahendra Kadia, Andrei Shustov, Olivier Tournilhac, Emmanuel Bachy, Francesco Zaja, Kimmo Porkka, Gregor Hoermann, Ingrid Simonitsch, Claudia Haferlach, Stefan Kubicek, Marius Mayerhoefer, Georg Hopfinger, Ulrich Jaeger, and Claire Dearden

Blood 2019 :blood.2019000402; doi: https://doi.org/10.1182/blood.2019000402

# Case 3a/3b

- Requires Treatment?
- Currently no evidence that asymptomatic T-PLL patients with “inactive disease” benefit from early treatment, it should be restricted to patients with “active” or symptomatic disease.

Table 4. Criteria for staging and indication of treatment in T-PLL

| Staging: At least 1 criterion defines "Active T-PLL" (=indication for treatment) | |
|---|---|
| **Disease related constitutional symptoms** | Significant fatigue: ECOG ≥ 2<br>Unintentional weight loss of > 10% of normal body weight in ≤ 6 months<br>Drenching night sweats, without evidence of infection<br>Fever greater than 38°C, without evidence of infection |
| **Symptomatic bone marrow failure** | Hemoglobin < 10 g/dL<br>Platelet count < 100 x $10^9$/L |
| **Rapidly enlarging lymph nodes, spleen, and liver** | > 50% in 2 month; diameter doubling < 6 month<br>Symptomatic enlarged lymph node, spleen, or liver |
| **Increasing lymphocytosis** | If > 30 x $10^9$/L: > 50% in 2 months; Lymphocyte doubling time < 6 month |
| **Extranodal involvement** | Organ infiltration; peritoneal or pleural effusion, central nervous system involvement |



*Staber, Philipp B. et al “Consensus criteria for diagnosis, staging, and treatment response assessment of T-cell prolymphocytic leukemia (T-PLL).” Blood (2019): blood.2019000402. Web. 27 Sept2019.*

# Case 3a/3b

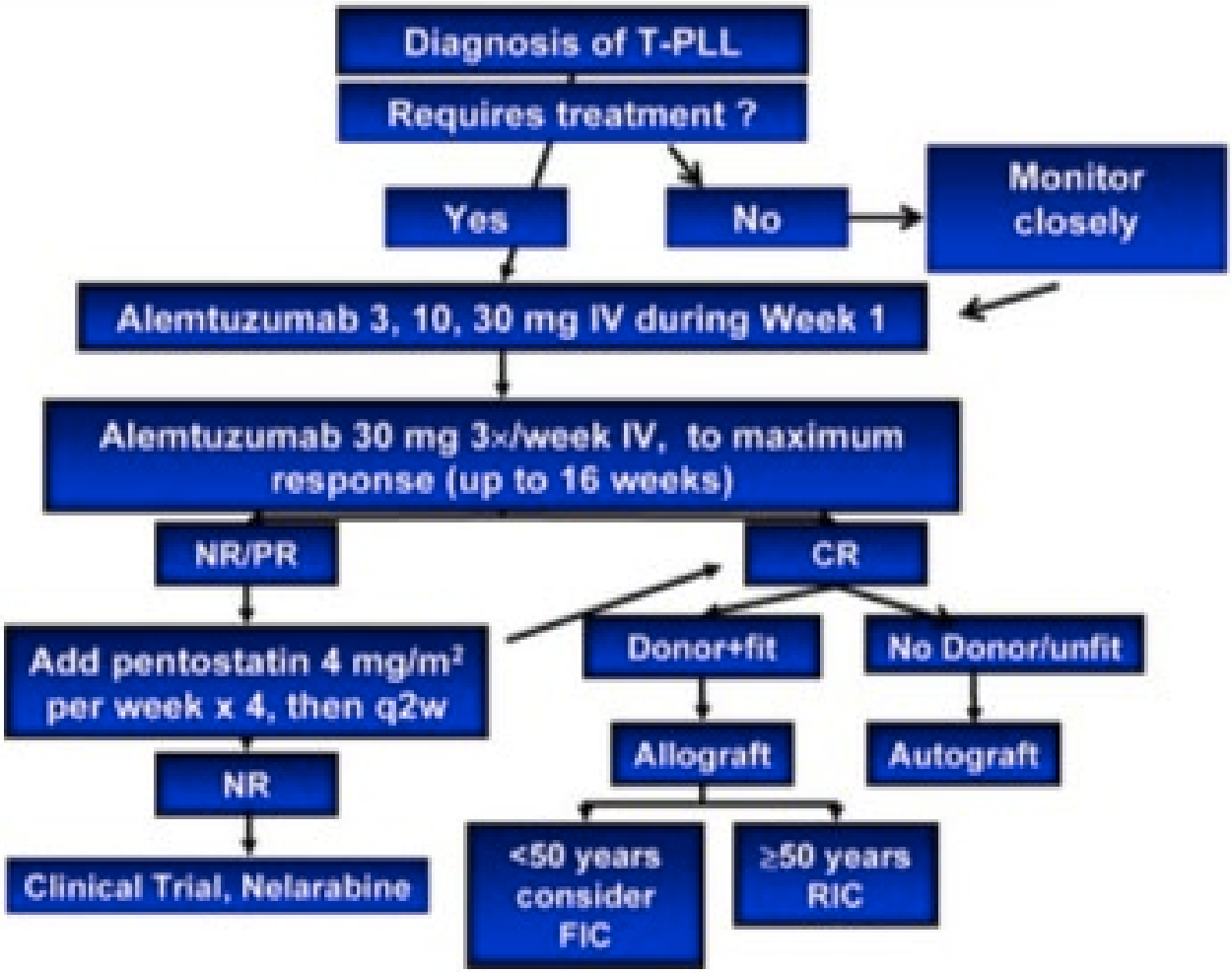



Figure 5. Treatment algorithm for T-PLL.



*Dearden, Claire. "How I treat prolymphocytic leukemia." Blood 120.3 (2012): 538-551. Web. 26 Sept2019.*

# Case 3a/3b

**Table 3. Treatment of T-PLL comparing patients treated first line, either with IV or SC alemtuzumab, with those treated with relapsed or refractory disease (N = 86)[22]**

| | First-line IV | First-line SC | Relapsed/refractory IV |
|---|---|---|---|
| No. of patients | 32 | 9 | 45 |
| ORR, % | 91 | 33* | 74 |
| CR, % | 81 | 33* | 60 |
| PFS at 12 mo, % | 67 | 67 | 26 |
| HSCT, % | 50 | 55 | 30 |
| OS at 48 mo, % | 37 | 33 | 18 |

IV indicates intravenous; SC, subcutaneous; CR, complete remission; PR, partial remission; ORR, overall response rate; PFS, progression-free survival; HSCT, hematopoietic stem cell transplant; and OS, overall survival.

*Increased to 67% when changed to IV and/or pentostatin added, but 2 of 9 patients died while on treatment.



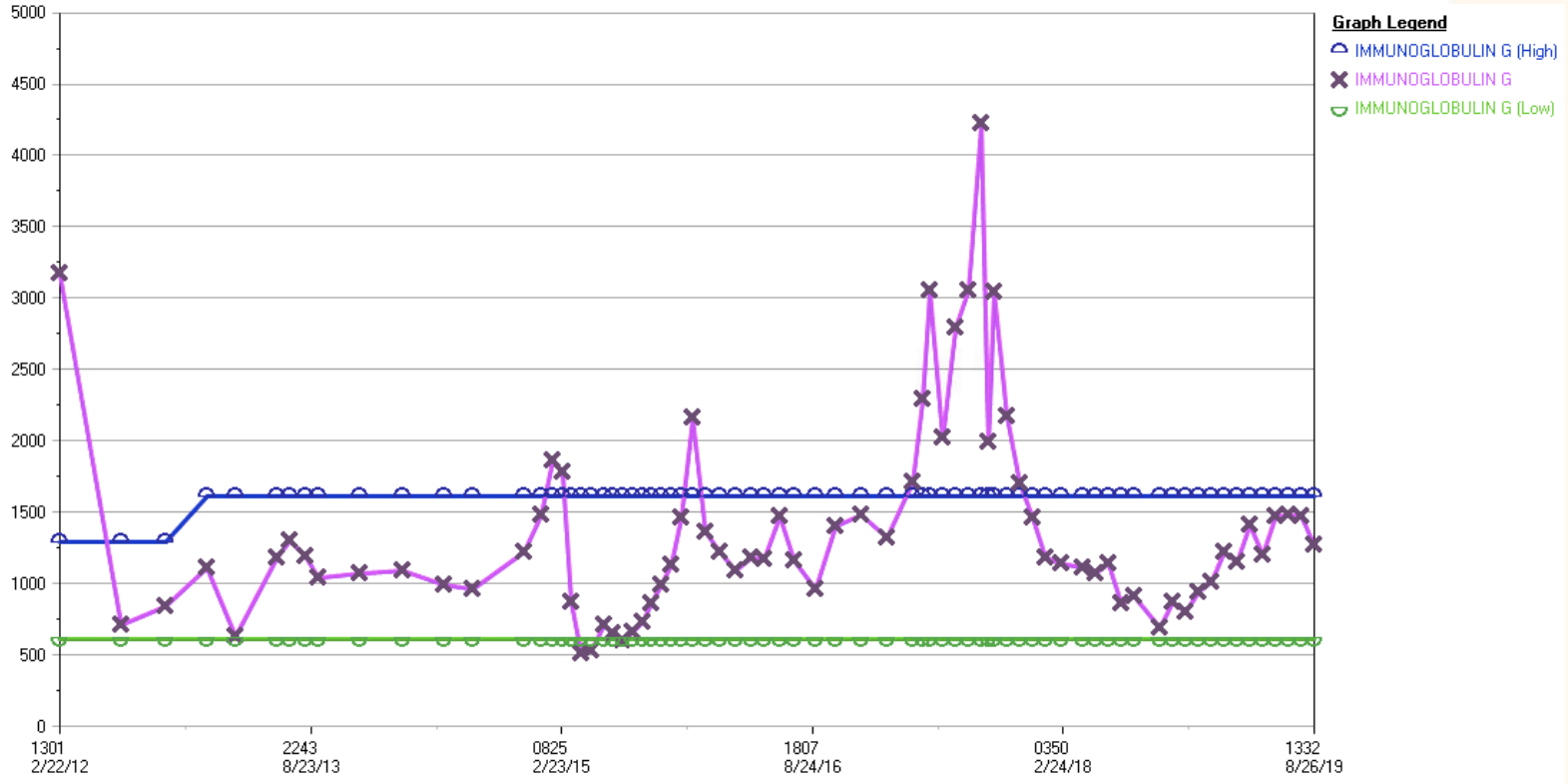
*Dearden, Claire. "How I treat prolymphocytic leukemia." Blood 120.3 (2012): 538-551. Web. 26 Sept2019.*

# Case 4, M.H.

- **HPI:** 65 yo female first diagnosed with ISS stage III IgG kappa MM in 2012.
  - Front line- VRD , followed by tandem auto HCT, followed by lenalidomide maintenance *(on clinical trial)*
  - *Progression at Day +846 from 1st transplant.*
  - Second line- Clinical trial with VD
  - *Progression at C12*
  - Third line- Pomalidomide + dexamethasone
  - *Progression at C14*
  - Fourth line – Daratumumab/Lenalidomide/Dexamethasone
  - *Progression at C4*
  - Fifth line- Carfilzomib/cyclophosphamide/dexamethasone
  - Progression at C25
  - ***Sixth line- ?????***
- **PMH, PSH:** MM, empyema
- **SH:** Retired preschool teacher, Non smoker, non drinker

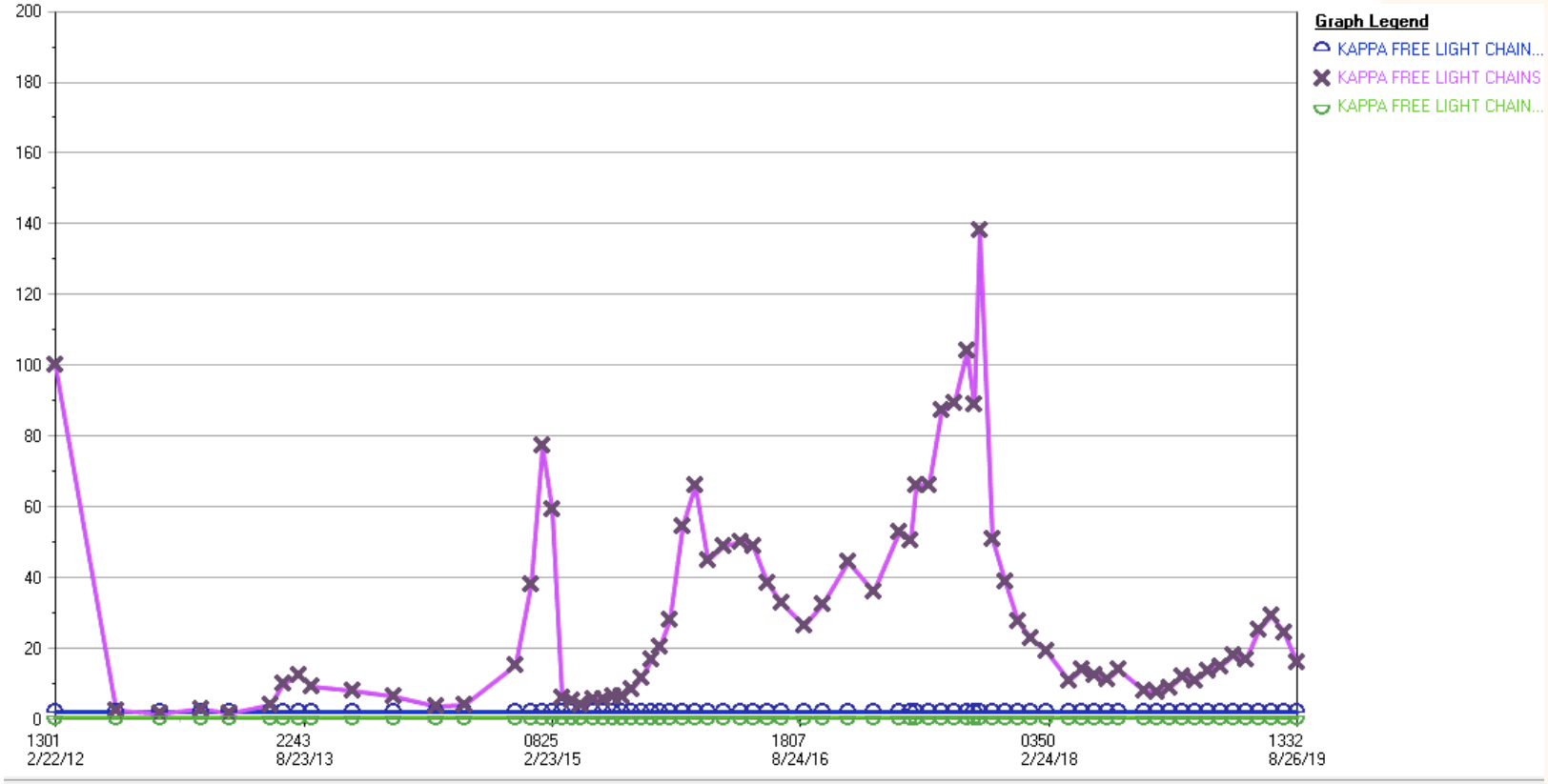
# Case 4, M.H.

- **Clinical course and w/u:**

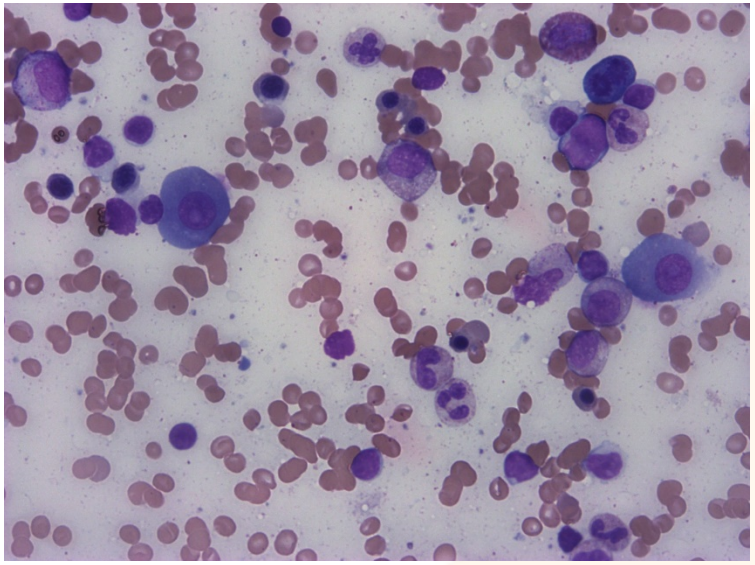


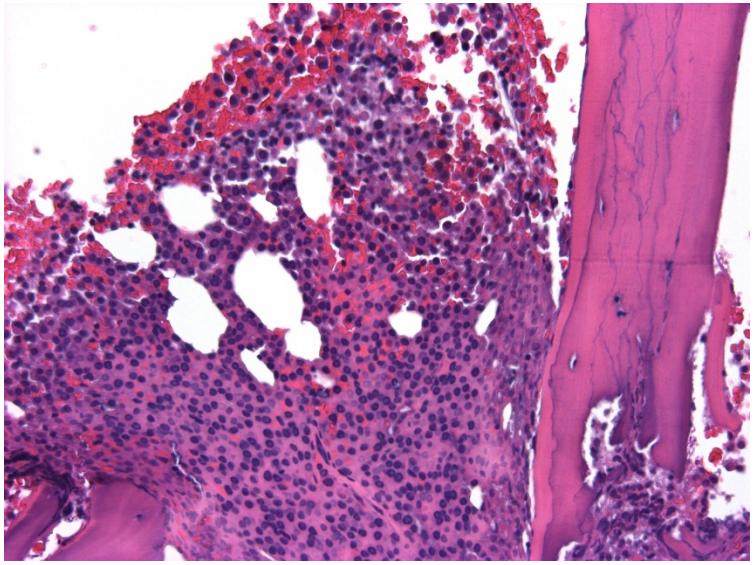
# Case 4, M.H.

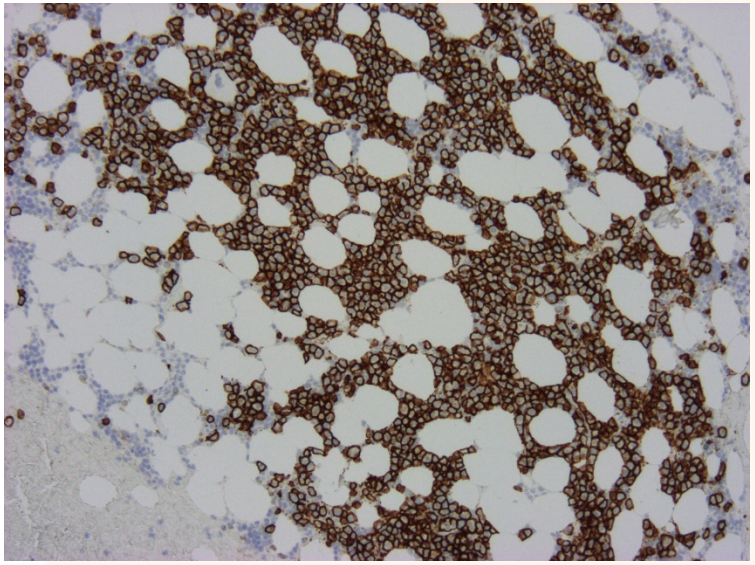
- **Clinical course and w/u:**



# Case 4, M.H.







REVIEW ARTICLE

# Current and New Therapeutic Strategies for Relapsed and Refractory Multiple Myeloma: An Update

**Inger S. Nijhof[1] · Niels W. C. J. van de Donk[1] · Sonja Zweegman[1] · Henk M. Lokhorst[1]**

# Case 4, M.H.

- Multiple myeloma remains an incurable malignancy with most patients experiencing relapse and requiring additional therapy.

- In particular, the prognosis of MM patients who have received at least 3 prior lines of therapy, who have become double refractory to IMiDs and PIs and who have been exposed to an alkylating agent, is very poor with EFS and OS of only 5 and 13 months respectively.



**Table 2** Newer generations and classes of anti-myeloma drugs

| | Class | Mechanism of action |
|---|---|---|
| | *Immunomodulatory agents* | Direct antitumor activity, anti-angiogenic effects and indirect immunomodulatory effects |
| ★ | Thalidomide | |
| | Lenalidomide | |
| | Pomalidomide | |
| | *Proteasome inhibitors* | Proteasome inhibition leads to accumulation of proteins within the myeloma cell resulting in growth arrest and cell death |
| | Bortezomib | |
| ★ | Carfilzomib | |
| | Ixazomib | |
| | Marizomib | |
| | Oprozomib | |
| | *Histone deacetylase inhibitors* | Increased acetylation of histone (and some non-histone) proteins, which regulates gene expression of tumor suppressors, transcription factors and oncogenic proteins. Interference with protein degradation via the aggresome pathway, an alternative protein degradation process pathway to the proteasome pathway. Interference with the interaction of myeloma cells and the microenvironment |
| ★ | Panobinostat | |
| | Vorinostat | |
| | Romidepsin | |
| | *Monoclonal antibodies (mAbs)* | Direct induction of apoptosis via activation or inhibition of target molecules. CDC, ADCC, ADCP. Immunomodulation via altered immune subset activation. |
| ★ | Elotuzumab (anti-CS1/anti-SLAM7) | Other new developed mAbs are directed against cellular or non-cellular components of the microenvironment resulting in inhibition of angiogenesis, neutralization of growth factors, enhancing host antitumor immune responses, and modulation of mediators of bone disease |
| | Daratumumab (anti-CD38) | |
| | SAR650984 = isatuximab (anti-CD38) | |
| | MOR202 (anti-CD38) | |
| | Denosumab (anti-RANKL) | |
| | Siltuximab (anti-IL6) | |
| | IPH2101 (anti-KIR2DL1/2/3) | |
| | *Checkpoint inhibitors* | Checkpoint inhibitors target PD1 or PD-L1/PD-L2 whereby restoring T cell activity against tumor cells |
| ★ | i.e. Nivolumab | |
| | Pembrolizumab | |
| | *mTOR inhibitors* | Downstream mediator of the PI3 K/Akt pathway regulating translation of proteins involved in myeloma growth and survival |
| ★ | Everolimus | |
| | Temsirolimus | |
| ★ | *Akt inhibitors* | Prevention of cell cycle protein translation and inducement of G1 arrest |
| | Perifosine | |
| ★ | *MEK inhibitors* | Decreased proliferation and survival of MM cells as well as inhibition of osteoclast bone resorption |
| | Selumetinib | |
| ★ | *Kinesin spindle protein inhibitors* | To arrest cells in mitosis and to induce apoptosis due to degradation of the BCL2 family survival protein MCL-1 |
| | Array-520 | |
| | *BH3 mimetics* | Binds to anti-apoptotic BCL2 family members, whereby inhibiting the binding of pro-apoptotic proteins |
| | ABT-199 (venetoclax) | |
| ★ | ABT-263 (navitoclax) | |
| | Obatoclax mesylate | |
| | *Vaccines* | Cocktail of HLA-A2–specific peptides which can trigger HLA-restricted expansion and activation of MM-specific T cells |
| | PVX-410 | |
| | *CAR T* | Targeted T cell therapy directed against a cell-surface antigen on malignant cells |
| ★ | i.e. against CD19, CD38, CS1, BCMA | |
| | *Selective inhibitor of nuclear transport (SINE)* | Retention and activation of tumor-suppressor proteins (as NF-kB, p53 and FOXO), induction of the glucocorticoid receptor in the presence of steroids and also suppressing the oncoprotein expression as Myc and cyclin D |
| ★ | Selinexor | |

*CDC* complement-dependent cytotoxicity, *ADCC* antibody-dependent cellular cytotoxicity, *ADCP* antibody-dependent cellular phagocytosis, *SLAM7* signaling lymphocyte-activating molecule-related receptor family 7, *RANKL* receptor activator of nuclear factor kappa-B ligand, *IL6* interleukin 6, *PD1* programmed death 1, *PD-L1* programmed death-ligand 1, *PD-L2* programmed death-ligand 2, *mTOR* mammalian target of rapamycin, *MM* multiple myeloma, *CAR* chimeric antigen receptor, *BCMA B* cell maturation antigen



*Nijhof, I.S., van de Donk, N.W.C.J., Zweegman, S. et al. Drugs (2018) 78; 19.*

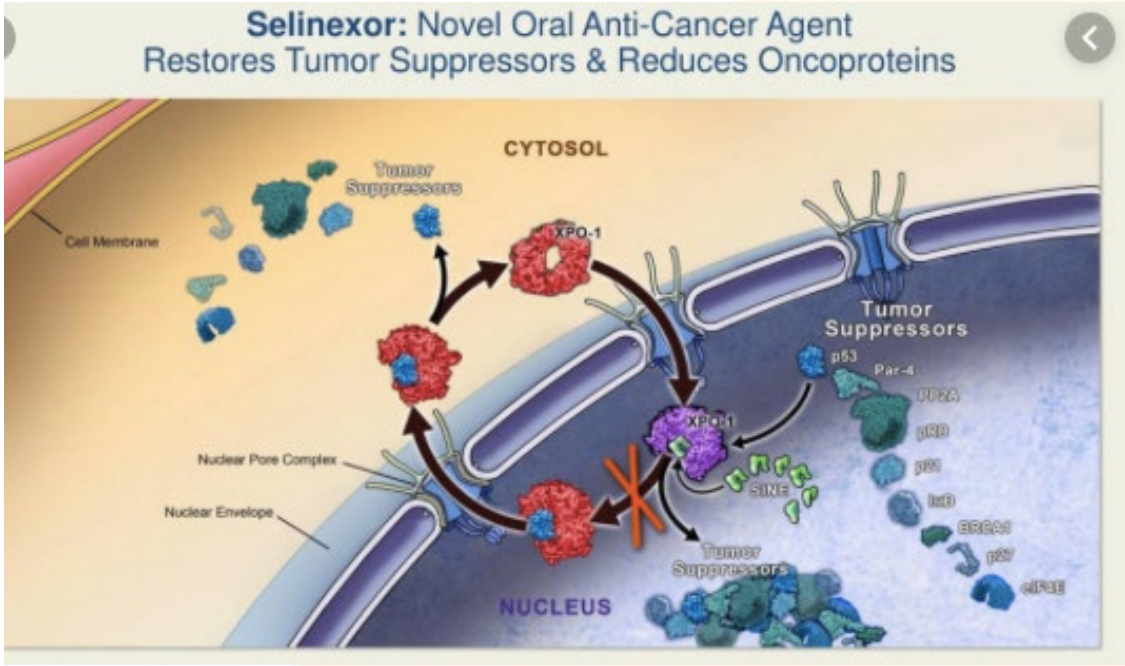
# Results of the Pivotal STORM Study (Part 2) in Penta-Refractory Multiple Myeloma (MM): Deep and Durable Responses with Oral Selinexor Plus Low Dose Dexamethasone in Patients with Penta-Refractory MM

Ajai Chari, Dan T. Vogl, Meletios A Dimopoulos, Ajay K Nooka, Carol Ann Huff, Philippe Moreau, Craig E. Cole, Joshua Richter, David Dingli, Ravi Vij, Sascha A Tuchman, Marc S Raab, Katja Weisel, Michel Delforge, David Kaminetzky, Robert Frank Cornell, A Keith Stewart, James Hoffman, Kelly N. Godby, Terri L Parker, Moshe Levy, Martin Schreder, Nathalie Meuleman, Laurent Frenzel, Mohamad Mohty, Choquet Sylvain, Andrew J. Yee, Maria Gavriatopoulou, Luciano J Costa, Jatin J. Shah, Carla Picklesimer, Jean-Richard Saint-Martin, Lingling Li, Michael G. Kauffman, Sharon Shacham, Paul Richardson, and Sundar Jagannath

Blood 2018 132:598; doi: https://doi.org/10.1182/blood-2018-99-116663

# Case 4, M.H.

- Selinexor is a novel, first in class, oral selective inhibitor of nuclear export (SINE) that blocks exportin 1 (XPO1). Resulting in nuclear accumulation and activation of tumor suppressor proteins, inhibition of NF-kB, and translation suppression of several oncoprotein mRNAs (c-myc, cyclin D.)






*Chari, A. et al "Results of the Pivotal STORM Study (Part 2) in Penta-Refractory Multiple Myeloma (MM): Deep and Durable Responses with Oral Selinexor Plus Low Dose Dexamethasone in Patients with Penta-Refractory MM." Blood (2018) 132:598*

# Case 4, M.H.

- Granted accelerated approval by FDA in July 2019 based on efficacy from Part 2 of the STORM study. Part 1 of the STORM trial enrolled both quad (bort, carfil, len, pom) and penta-refractory (+dara) MM and demonstrated an ORR of 21%. Part 2 was initiated with the enrollment of  an additional cohort of 122 patients.

- Pts with penta-refractory MM were treated with 80mg selinexor plus 20mg dexamethasone (Sd) twice weeky.

- Median of 7 prior regimens with 53% of patients consider high risk cytogenetics.

- ORR found at 26.2% with 6.5% atleast VGPR.
- PFS of 3.7 months and OS 8.0 months.

- Treatment related AEs included (all grades, grades 3/4); Thrombocytopenia (67%, 53%), nausea (67%, 10%), fatigue (68%, 21%) and hyponatremia (30.9%, 16.3%)



*Chari, A. et al "Results of the Pivotal STORM Study (Part 2) in Penta-Refractory Multiple Myeloma (MM): Deep and Durable Responses with Oral Selinexor Plus Low Dose Dexamethasone in Patients with Penta-Refractory MM." Blood (2018) 132:598*

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*Leuk Lymphoma*. 2018 September ; 59(9): 2056–2067. doi:10.1080/10428194.2017.1393668.

# CAR T cell therapy for multiple myeloma: Where are we now and where are we headed?

**Arnab Ghosh**[a], **Sham Mailankody**[b], **Sergio A. Giralt**[c,d], **C. Ola Landgren**[b], **Eric L. Smith**[b,d,#], and **Renier J. Brentjens**[d,e,#]

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[b]Myeloma Service, Memorial Sloan Kettering Cancer Center, New York, New York

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# Case 4, M.H.

CAR T cell therapies targeting CD19 have been the most widely used and successful among all the CARs to date.

However, the plasma cells of MM do not routinely express detectable CD19.

In addition, both k light-chain CAR T and CD 138 CAR T cells have been investigated with limited results.

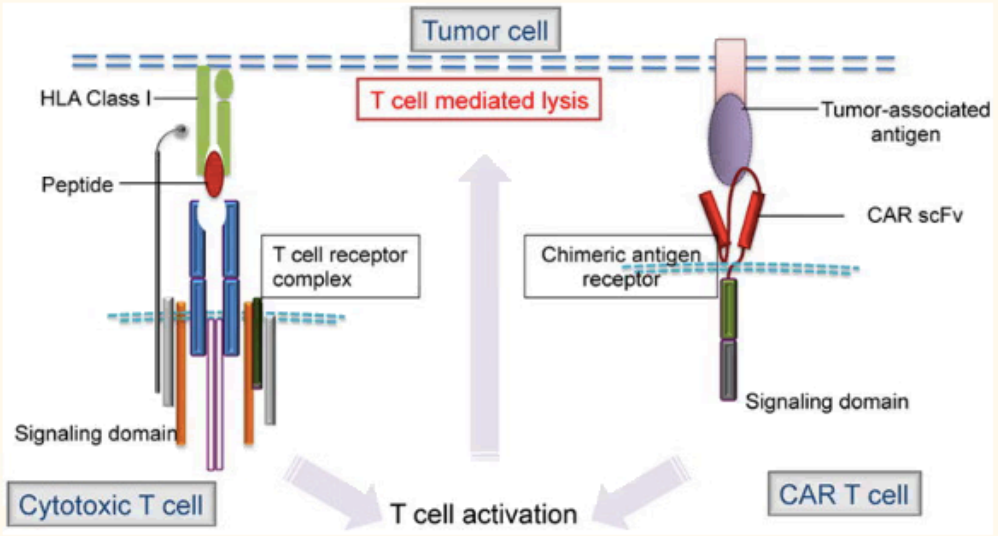


Figure 1

**Activation of TCR and CAR**

The TCR complex of a cytotoxic T cell binds to a peptide presented in the context of a HLA class- I molecule. This immunological synapse triggers a signaling cascade and in the presence of appropriate costimulatory signals cause activation of the cytotoxic T cells. A CAR is a synthetic fusion protein containing a single chain variable fragment (scFv) that can directly bind to target cell surface antigen. This engineered CAR synapse activates the immunoreceptor tyrosine-based activation motif (CD3e-ITAM) and, if present, costimulatory molecules causing activation of the CAR T cell.



*Ghosh, A. et al "CAR T Cell Therapy for Multiple Myeloma: Where are we now and where are we headed?" Leukemia & Lymphoma (2018), 59:9, 2056-2067*

# Case 4, M.H.

A particularly popular field of interest of late has been BCMA CAR T cells.

- B-cell maturation antigen (BCMA) is a TNF receptor superfamily 17 that plays a central role in regulating B-cell maturation and differentiation in plasma cells. It is not present on naïve B cells or hematopoietic stem cells, but is upregulated during B-cell differentiation into plasmablasts.

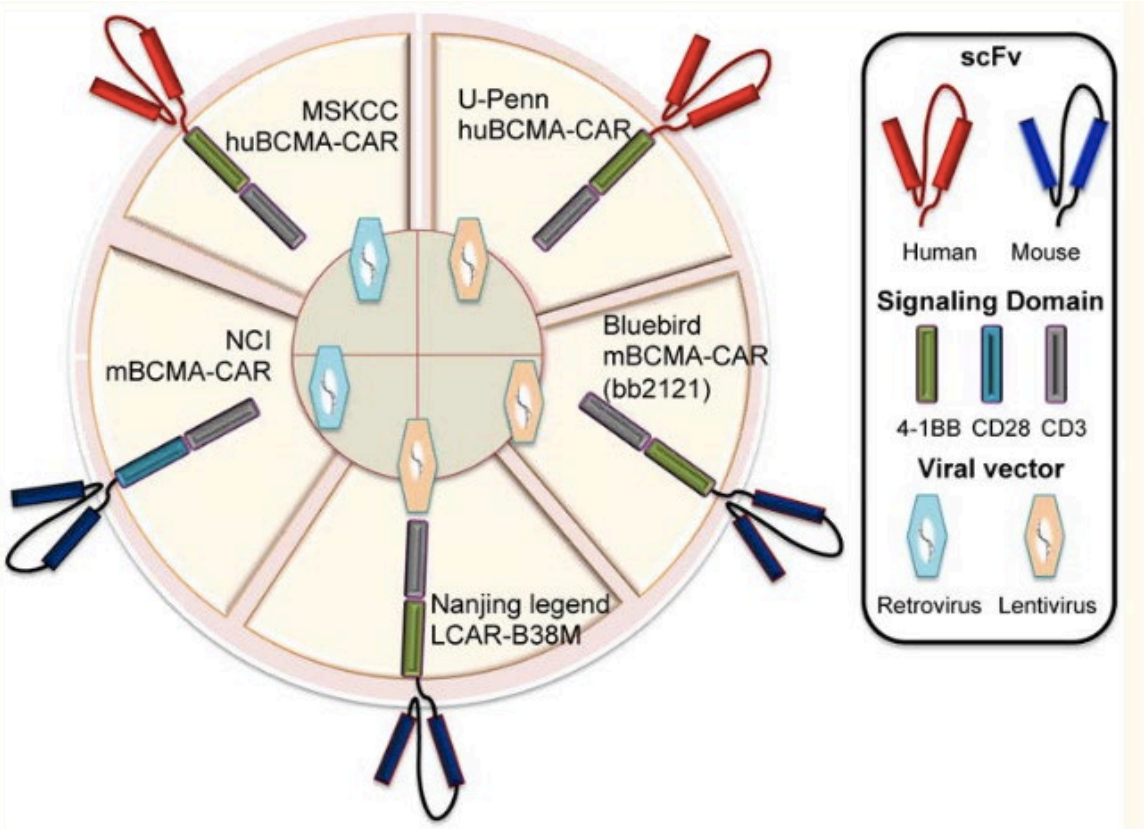


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Figure 2

**The components of BCMA-CAR T cells**

A schema depicting the components of the five BCMA targeted CARs currently being tested in clinical trials. NCI (National Cancer Institute); Bluebird (Bluebird Bio Multi-institutional trial of b2121): U Penn (University of Pennsylvania); MSKCC (Memorial Sloan Kettering Cancer Center)



*Ghosh, A. et al "CAR T Cell Therapy for Multiple Myeloma: Where are we now and where are we headed?" Leukemia & Lymphoma (2018), 59:9, 2056-2067*

# Case 4, M.H.

- The NCI derived BCMA- CAR T cells were the first demonstrated dramatic response in MM and subsequently three additional BCMA targeted CAR T cell trials for MM opened in the US and one internationally.

**Table 1**

Summary of the trial design of clinical trials with BCMA-CAR T cells.

| Institution/CAR | NCI mBCMA-CAR | Bluebird mBCMA-CAR (bb2121) | UPenn huBCMA-CAR | MSK huBCMA-CAR | Nanjing Legend LCAR-B38M |
|---|---|---|---|---|---|
| Clinicaltrials.gov Identifier | NCT02215967 | NCT02658929 | NCT02546167 | NCT03070327 | NCT03090659 |
| BCMA Ag screening | >50% | >50% | None | >1% | Clear expression |
| Conditioning (Day 0 denotes day of CAR T cell infusion) | Cyclophosphamide and fludarabine on days -5, -4, and -3 | Cyclophosphamide and fludarabine on days -5, -4, and -3 | *Cohort 1:* none<br>*Cohort 2, 3:* Cyclophosphamide on day-3 | *Cohort 1:* Cyclophosphamide on day –2<br>Cohort 2 onwards: Cyclophosphamide and fludarabine on days -4, -3, and -2 | Cyclophosphamide |
| Planned enrollment | 38 | 50 | 27 | 24 | 100 |



*Ghosh, A. et al "CAR T Cell Therapy for Multiple Myeloma: Where are we now and where are we headed?" Leukemia & Lymphoma (2018), 59:9, 2056-2067*

ORIGINAL ARTICLE

# Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma

Noopur Raje, M.D., Jesus Berdeja, M.D., Yi Lin, M.D., Ph.D., David Siegel, M.D., Ph.D., Sundar Jagannath, M.D., Deepu Madduri, M.D., Michaela Liedtke, M.D., Jacalyn Rosenblatt, M.D., Marcela V. Maus, M.D., Ph.D., Ashley Turka, Lyh-Ping Lam, Pharm.D., Richard A. Morgan, Ph.D., Kevin Friedman, Ph.D., Monica Massaro, M.P.H., Julie Wang, Pharm.D., Ph.D., Greg Russotti, Ph.D., Zhihong Yang, Ph.D., Timothy Campbell, M.D., Ph.D., Kristen Hege, M.D., Fabio Petrocca, M.D., M. Travis Quigley, M.S., Nikhil Munshi, M.D., and James N. Kochenderfer, M.D.

# Case 4, M.H.

- 33 patients received the trial BCMA CAR, median age of 60 and median time since diagnosis of 5 years.
- 45% patients with high risk cytogenetics defined as presence of del(17p), t(4,14), or t(14,16).
- Median of 7 previous regimens in dose-escalation cohort and 8 regimens in the expansion cohort.
- Doses of $50x10^6$, $150x10^6$, $450x10^6$ or $800x10^6$ total CAR-positive (CAR+) T cells were tested in the dose-escalation phase and $150x10^6$ to $450x10^6$ total CAR+ T cells in the expansion phase.



*Raje, N. et al "Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma." N Engl J Med 2019; 380:1726-37.*

# Case 4, M.H.

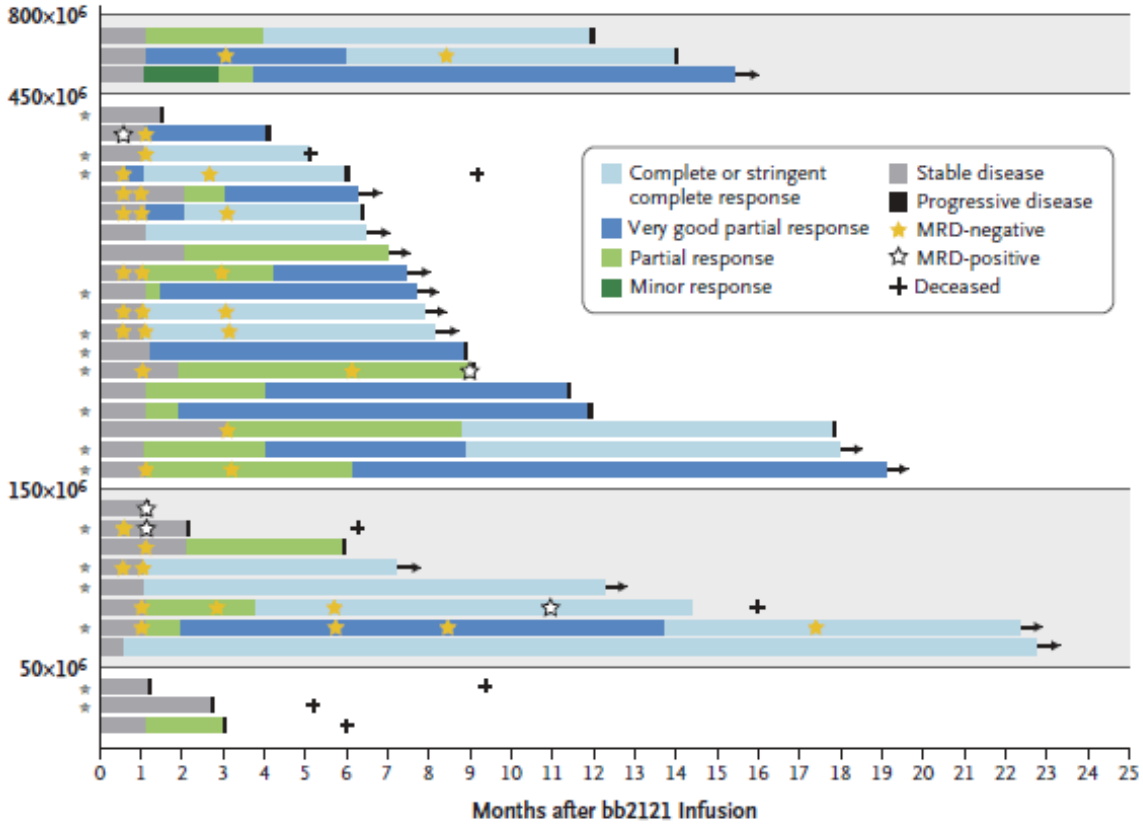


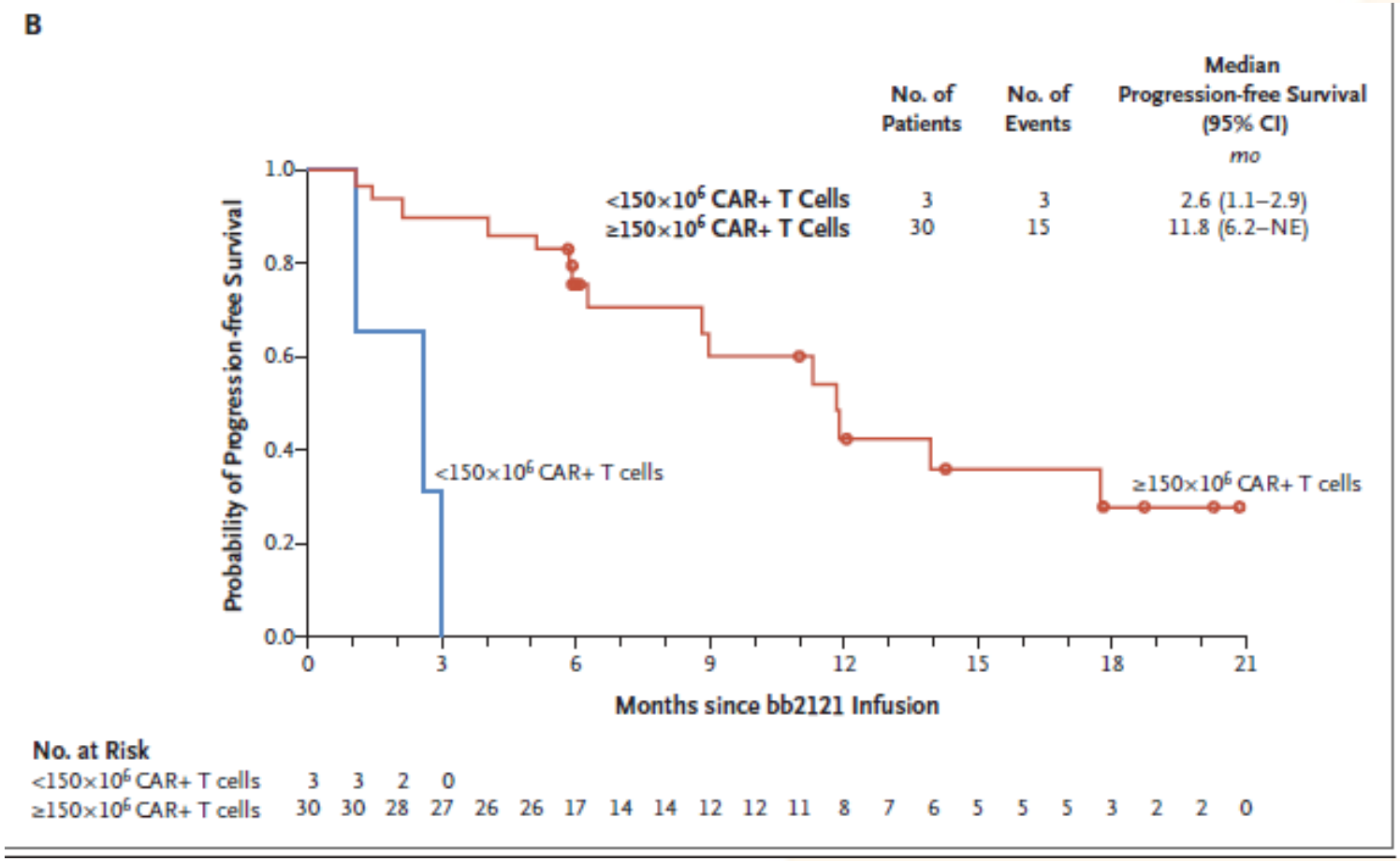

**Figure 1. Response to bb2121 Infusion.**

Shown are the best responses among individual patients according to dose ($50\times10^6$ to $800\times10^6$) of chimeric antigen receptor–positive (CAR+) T cells. All responses were confirmed and assessed according to the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma (details on the criteria for disease response are provided in the Supplementary Appendix). Asterisks indicate patients with a high tumor burden (≥50% bone marrow plasma cells). MRD denotes minimal residual disease.



*Raje, N. et al "Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma." N Engl J Med 2019; 380:1726-37.*

# Case 4, M.H.






*Raje, N. et al "Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma." N Engl J Med 2019; 380:1726-37.*

# Case 4, M.H.

**Table 2. Adverse Events, Cytokine Release Syndrome, and Neurologic Toxic Effects.**

| Variable | Total (N=33) | | |
|---|---|---|---|
| | Any Grade | Grade 3 | Grade 4 |
| | *number of patients (percent)* | | |
| Adverse event* | | | |
| Any | 33 (100) | 4 (12)† | 28 (85) |
| Hematologic | | | |
| Neutropenia | 28 (85) | 2 (6) | 26 (79) |
| Leukopenia | 20 (61) | 6 (18) | 13 (39) |
| Anemia | 19 (58) | 15 (45) | 0 |
| Thrombocytopenia | 19 (58) | 5 (15) | 10 (30) |
| Lymphopenia | 6 (18) | 3 (9) | 3 (9) |
| Gastrointestinal | | | |
| Constipation | 9 (27) | 0 | 0 |
| Nausea | 7 (21) | 0 | 0 |
| Diarrhea | 7 (21) | 0 | 0 |
| Vomiting | 6 (18) | 0 | 0 |
| Other | | | |
| Fatigue | 14 (42) | 1 (3) | 0 |
| Headache | 10 (30) | 0 | 0 |
| Hypocalcemia | 9 (27) | 0 | 0 |
| Pyrexia | 8 (24) | 1 (3) | 0 |
| Hypokalemia | 8 (24) | 0 | 0 |
| Hypophosphatemia | 7 (21) | 3 (9) | 0 |
| Peripheral edema | 6 (18) | 1 (3) | 0 |
| Hyperglycemia | 6 (18) | 1 (3) | 0 |
| Hypoalbuminemia | 6 (18) | 0 | 0 |
| Cough | 6 (18) | 0 | 0 |
| Dizziness | 6 (18) | 0 | 0 |
| Upper respiratory tract infection | 5 (15) | 0 | 0 |
| Sinus tachycardia | 5 (15) | 0 | 0 |
| Hypotension | 5 (15) | 2 (6) | 0 |
| Hyponatremia | 5 (15) | 2 (6) | 0 |
| Cytokine release syndrome‡ | 25 (76) | 2 (6) | 0 |
| Neurologic toxic effect§ | 14 (42) | 0 | 1 (3) |



*Raje, N. et al "Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma." N Engl J Med 2019; 380:1726-37.*

# Case 4, M.H.

- Other potential CAR targets
  - CD38
  - CD44v6
  - CD70

Other future directions

- Natural killer (NK) cells retrovirally transduced with CARs targeting SLAM7 (CS1), a glycoprotein expressed on normal and malignant plasma cells.
- Combining CAR T cells and immune checkpoint blockades
- Armored CAR (modifying CAR T cells to secrete IL12 and IL21)



*Ghosh, A. et al "CAR T Cell Therapy for Multiple Myeloma: Where are we now and where are we headed?" Leukemia & Lymphoma (2018), 59:9, 2056-2067*

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# Questions/Comments?