IN PURSUIT OF *YOUR CURE.*™

Relapsed /Refractory Hodgkin Lymphoma 2023

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NCI Cancer Center
A Cancer Center Designated by the National Cancer Institute

Disclosures

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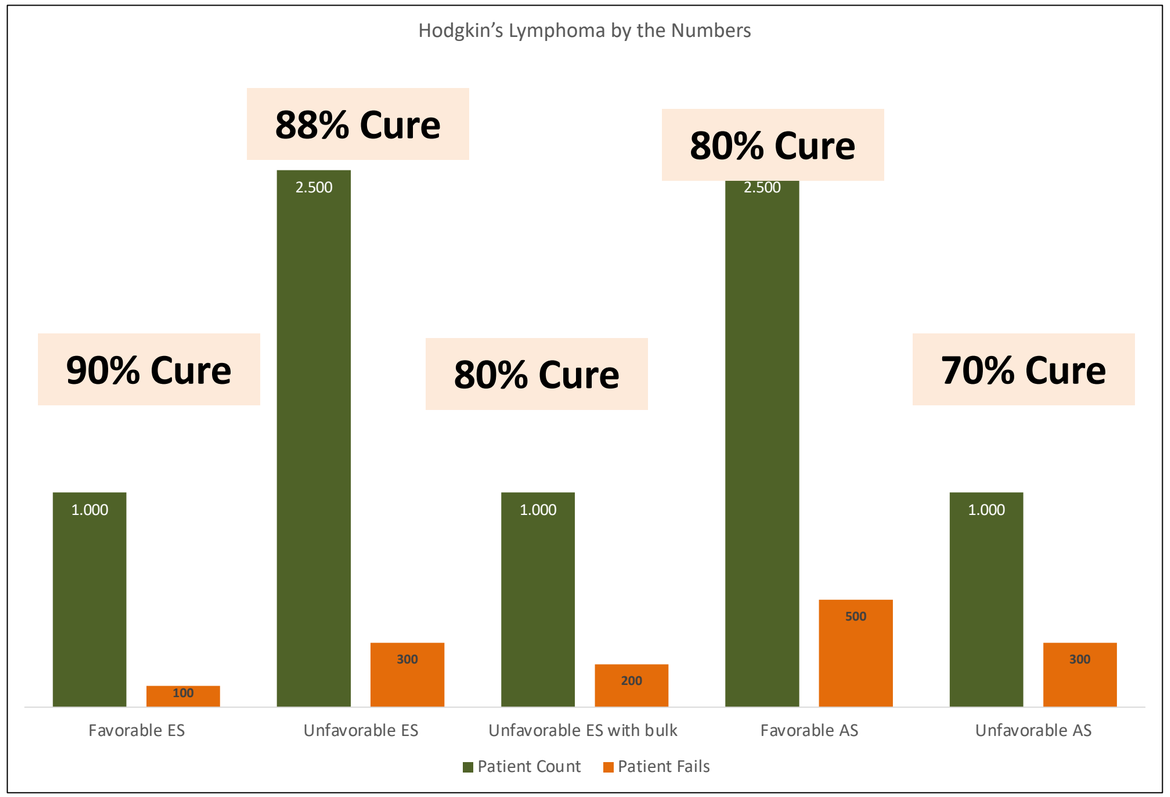
Scientific Advisory Board-ADC therapeutics, Merck, Takeda, Merck, Seattle Genetics, Astra Zeneca, Incyte, Genmab

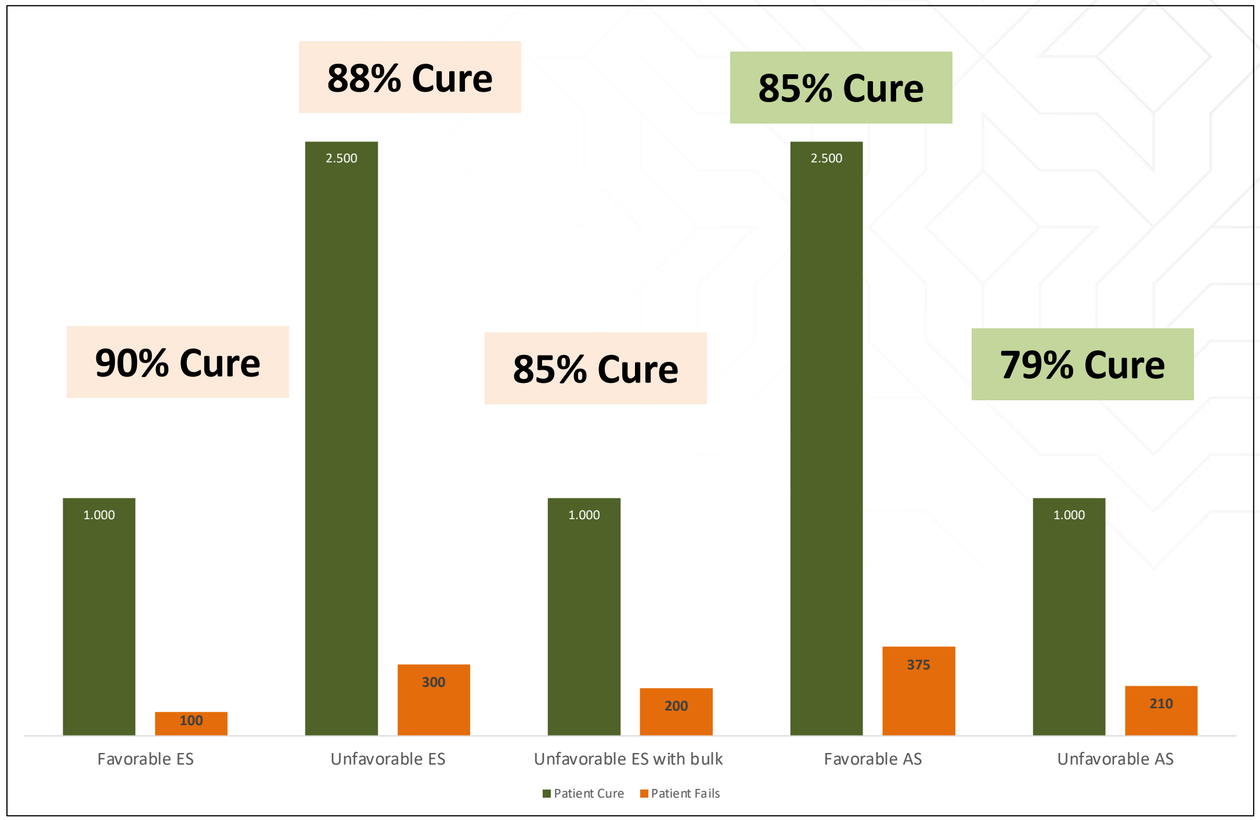
Hodgkin Lymphoma by the Numbers

Optimal upfront treatment 8,500 patients (Pre BV)



1400 pts need SLT

Optimal upfront treatment 8,500 patients (post BV)



1135 pts need SLT

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700 patients ≥70 excluded

Management changes in untreated HL

Standard treatment for HL now in US

- 3-4 cycles of ABVD without RT early stage without tumor bulk
- 6 cycles of ABVD without RT if PET negative post treatment is common for bulky disease
- BV-AVD is becoming for standard of ASHL

Standard treatment at time of HL randomized ASCT study in 2000 in US

- 4-6 cycles of ABVD or MOPP/ABV+/-D and Rt standard management for ESHL without tumor bulk
- 6 cycles and RT for bulky disease
- 6 cycles of ABVD or MOPP/ABV hybrid; other hybrid regimens for ASHL

Has clinical research gone in the wrong direction?

- **With optimal therapy in each cohort, less pts with ASHL need SLT/ASCT**
- **With less treatment for ESHL and the near elimination of ISRT, more pts are relapsing**
- **Clinical research has moved in a direction to maintain the cure rate of patients with HL and decrease long term side effects**
- **Luckily in the second-line setting we are curing more patients!**
- **Don’t we want to cure more pts upfront?**

Why is this topic so important?

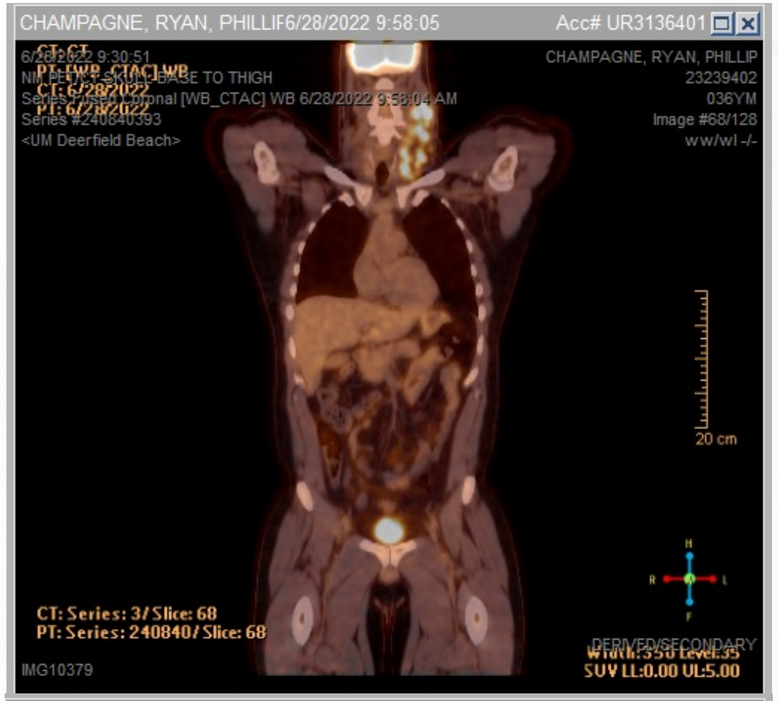
In 2023 the cure rate of relapsed/refractory HL is > untreated ABC-DLBCL and is approaching that of untreated ASHL

One wonders if we are overtreating some patients

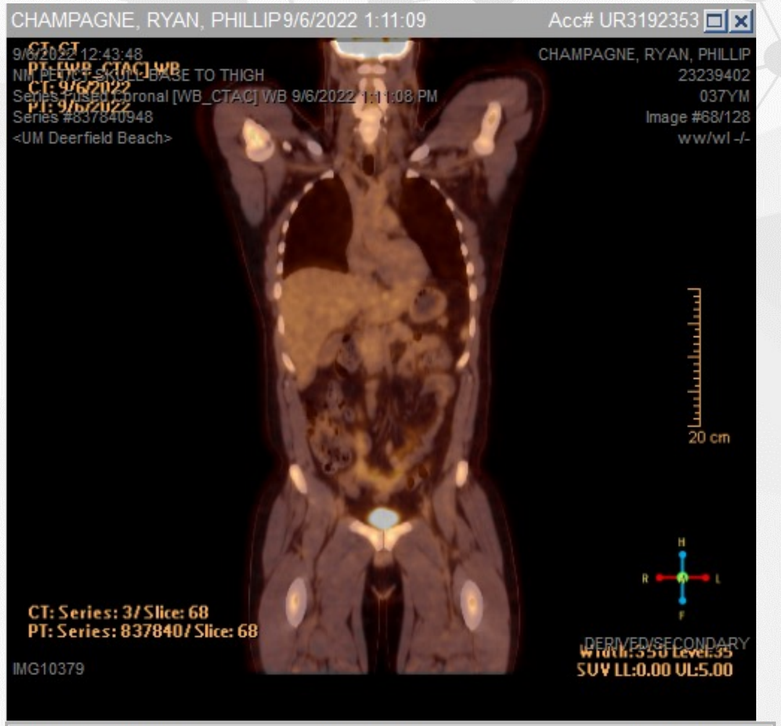
Primary refractory Favorable ESHL

- 26 year-old male presents with stage 2 ESHL; ESR 40
- Largest nodal mass 4.6 cm in left neck
- DLCO 71%; history of smoking 1PPD
- Treatment as per CALGB, 4 cycles PET adapted however BV substituted for bleomycin
- PET 2-Deauville 3
- PET 4-Deauville 3
- Patient calls 6 weeks later with new node; on exam about 1 cm
- Repeat PET 6 weeks later-POD; bx cHL
- Does this pt need HDT/ASCT?

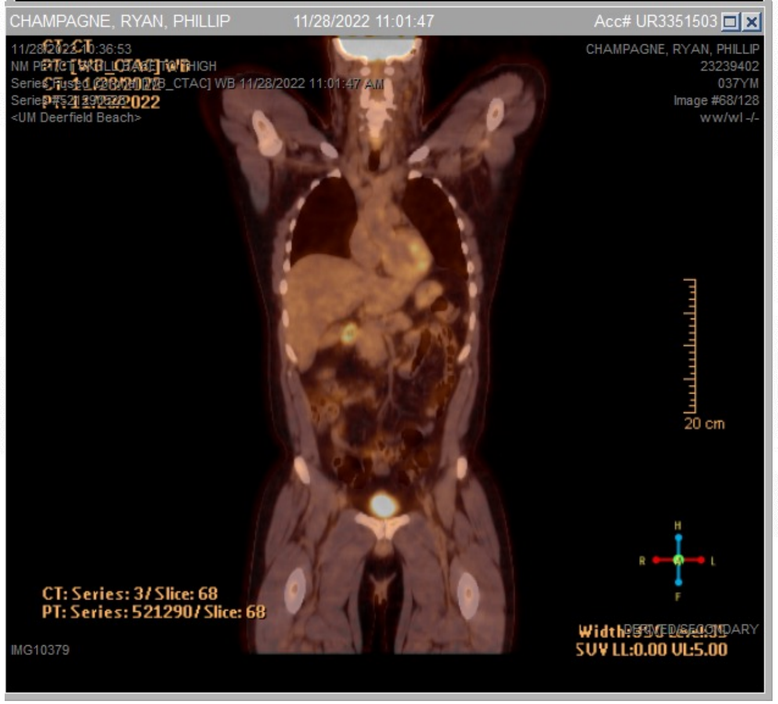
Baseline PET



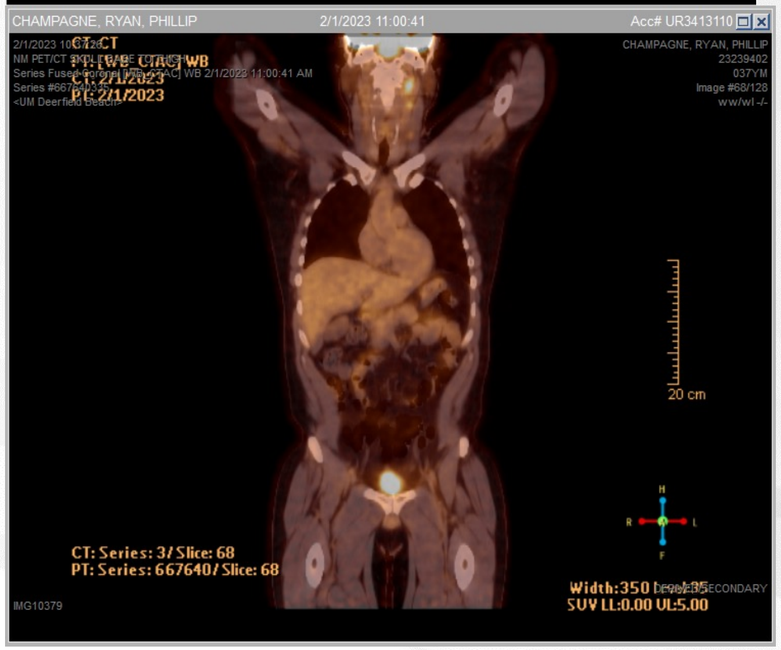
PET2



EOT scan (after 4 cycles)

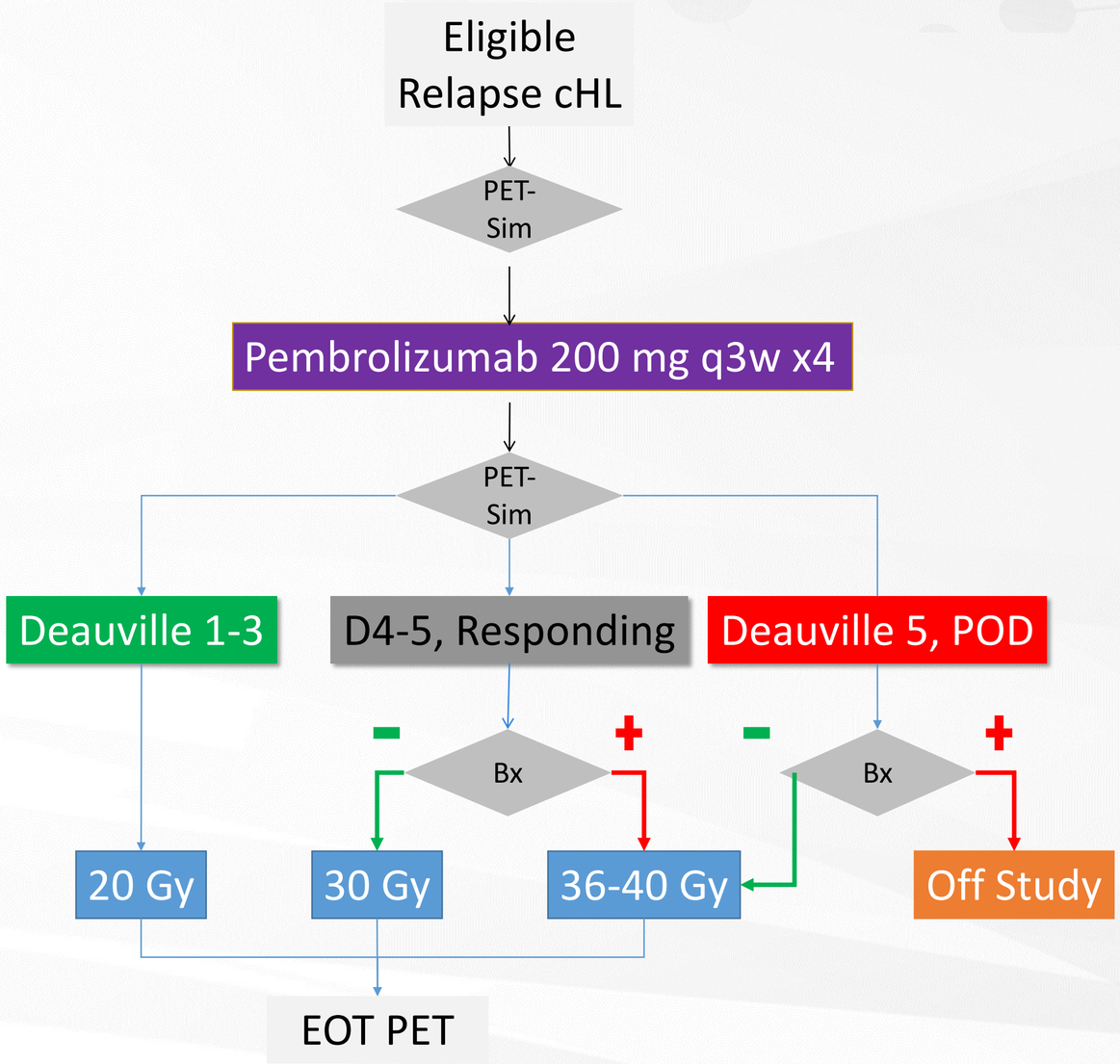


~3 months post treatment



Phase II Study of Pembrolizumab + ISRT for Relapsed ES HL

Eligiblity
Histologically confirmed cHL
Initial stage: I-IIA
Prior therapy: Chemo only or CMT with relapse outside field
Relapse stage: I-II (1 radiation port)
No bulk > 10 cm
ECOG 0-1



Moskowitz C, personal communication

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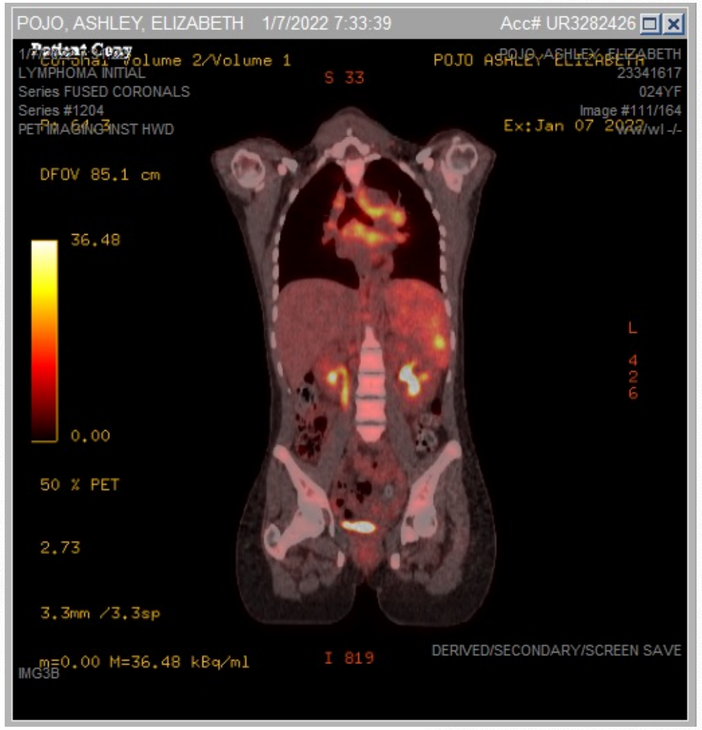
Primary Refractory Favorable ASHL

- 24 year-old female presents with stage 3 ASHL; ESR 66
- Largest nodal mass 5.1 cm in anterior mediastinum
- Active B symptoms
- Treated with 6 cycles of BV-AVD
- PET 2-Deauville 3
- PET 6-Deauville 4; referred at this time, decided to repeat PET again in 8-10 weeks
- Clear POD; endobronchial bx confirms cHL
- Does this pt require HDT/ASCT?

Baseline PET

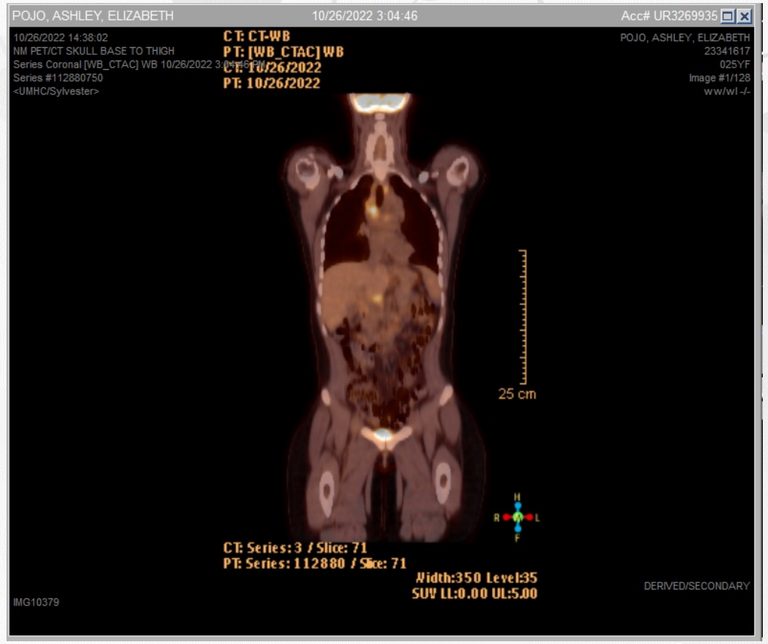
(prior to BV AVD

Initial tx)



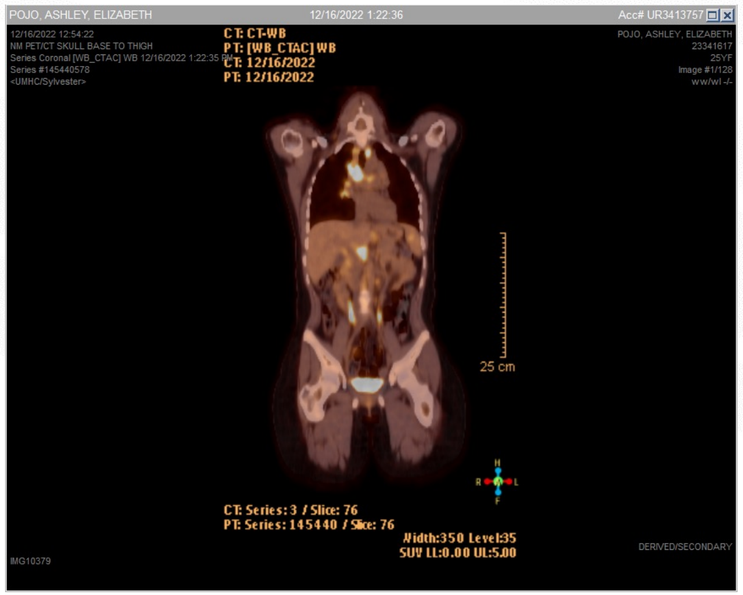
Baseline PET

(prior to pembro GVD)



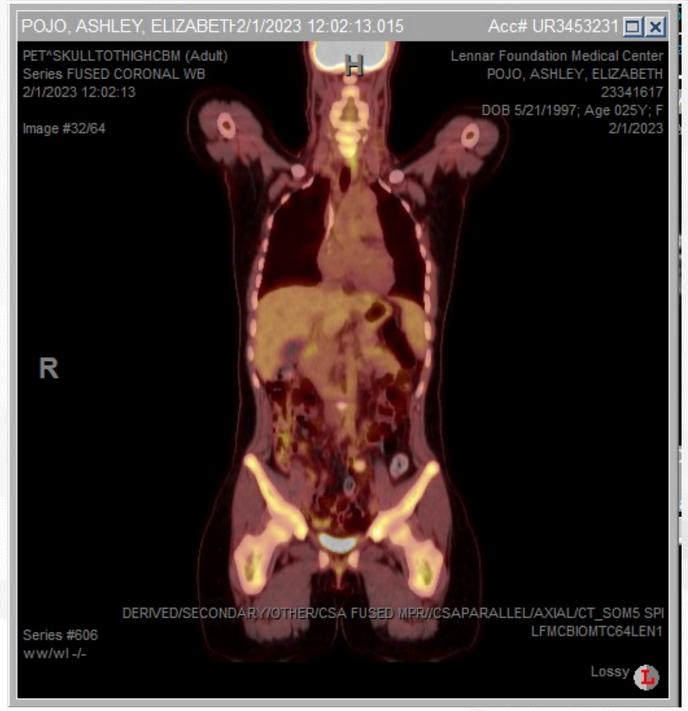
Baseline PET #2

(prior to Pembro GVD)



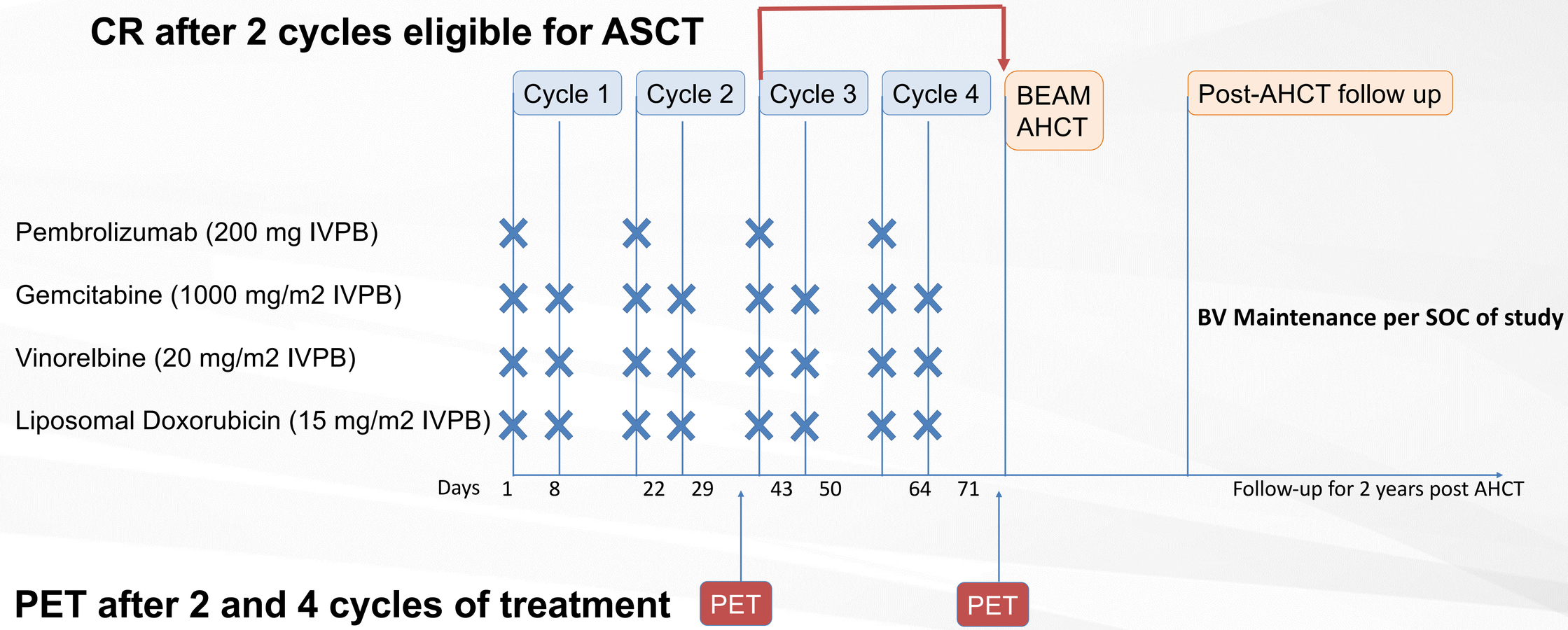
PET2

(s/p 2 cycles Pembro GVD)



Phase II study of pembro-GVD as second-line therapy for cHL

- **Eligibility**: relapsed or refractory cHL following 1-line of therapy
- **Primary endpoint**: CR (by Deauville 3) rate after 2-4 cycles



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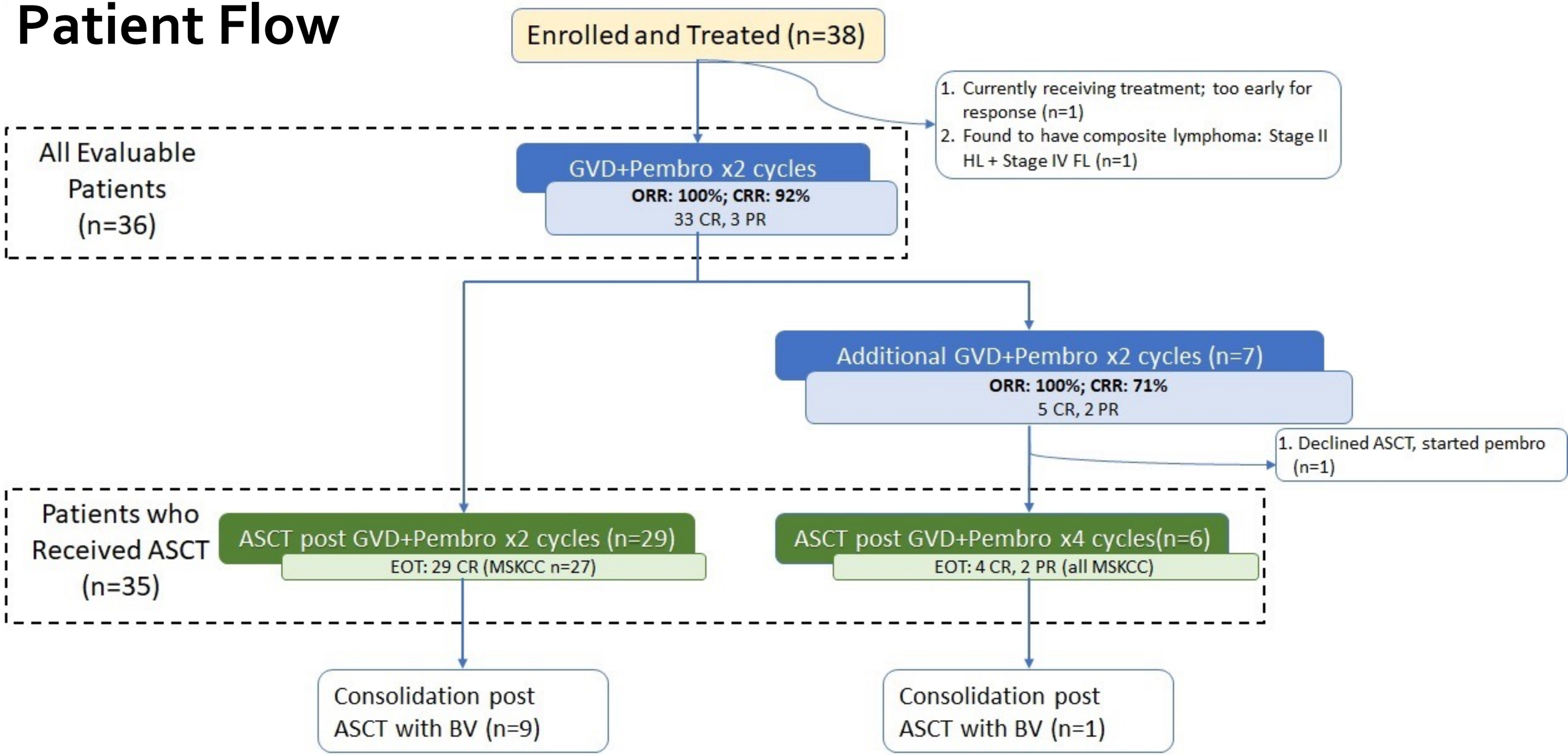
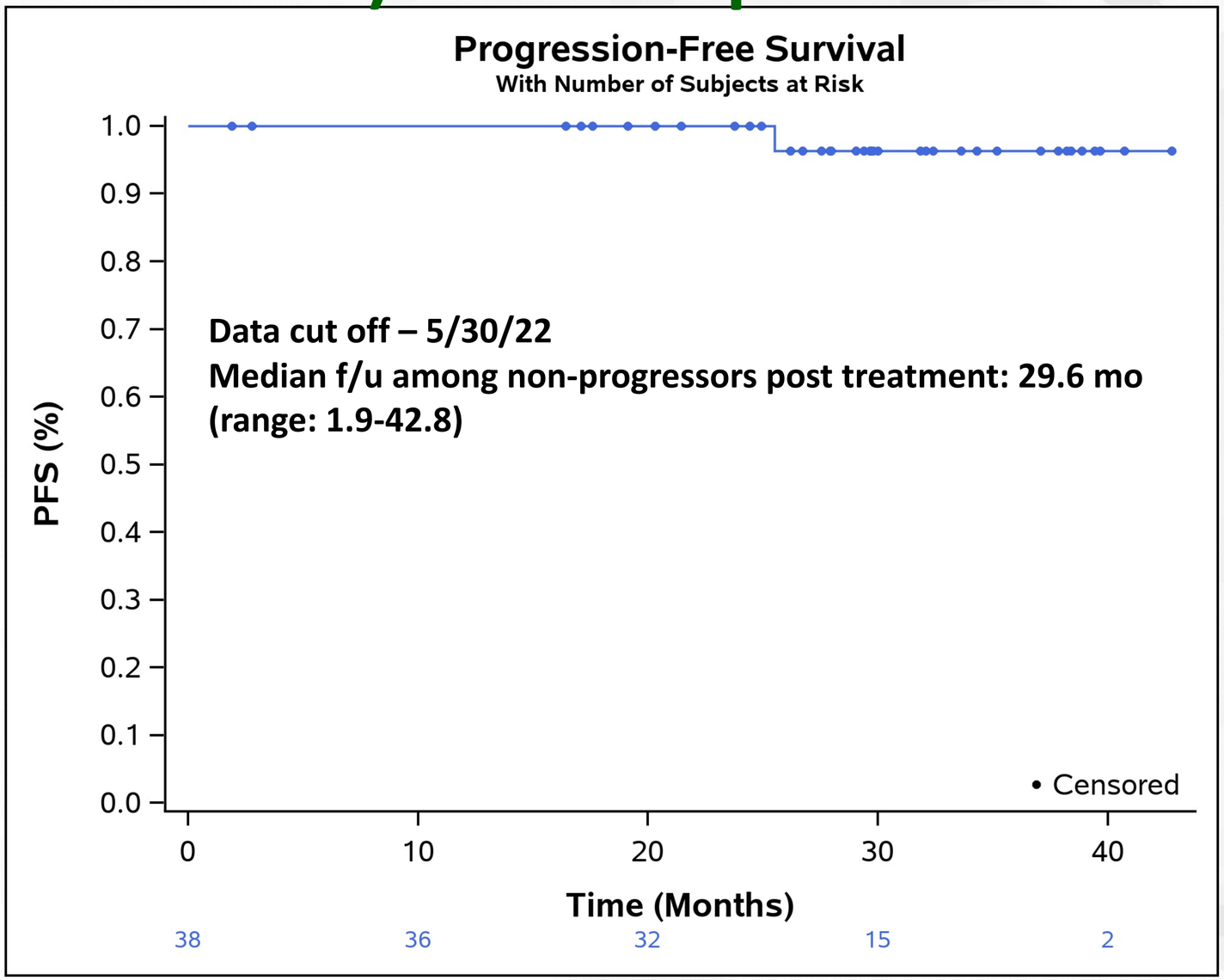
NCT03618550

Patient Flow



ITT Curve (Transplant Cohort): Follow up

- n=38 evaluable patients
- ORR: 100%
- CR: 95% (92% after 2 cycles)
- 1 relapse



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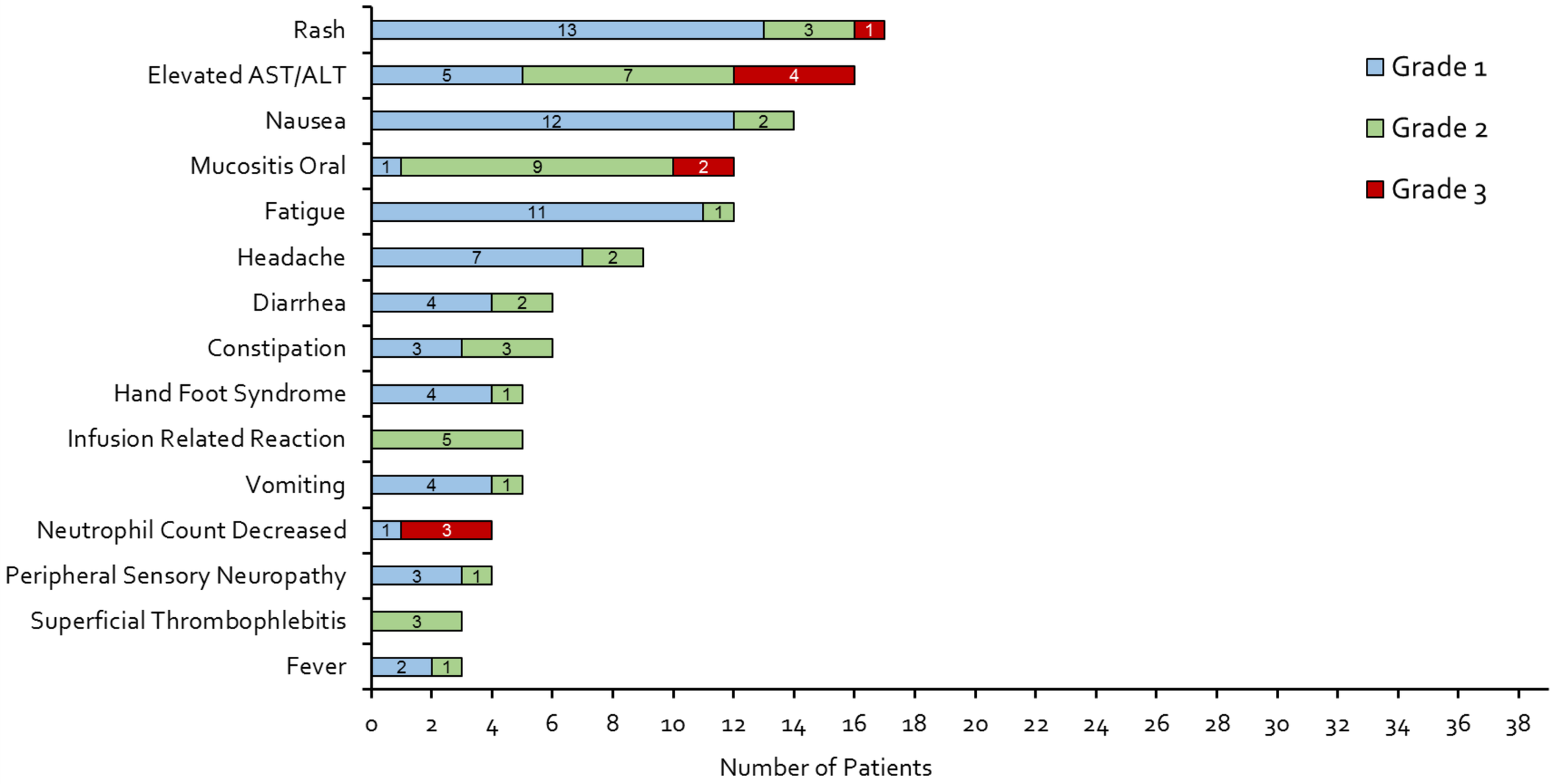
Tolerable Side Effects with Pembro-GVD (n=38)

Related Adverse Events (occurring in >10% of pts)



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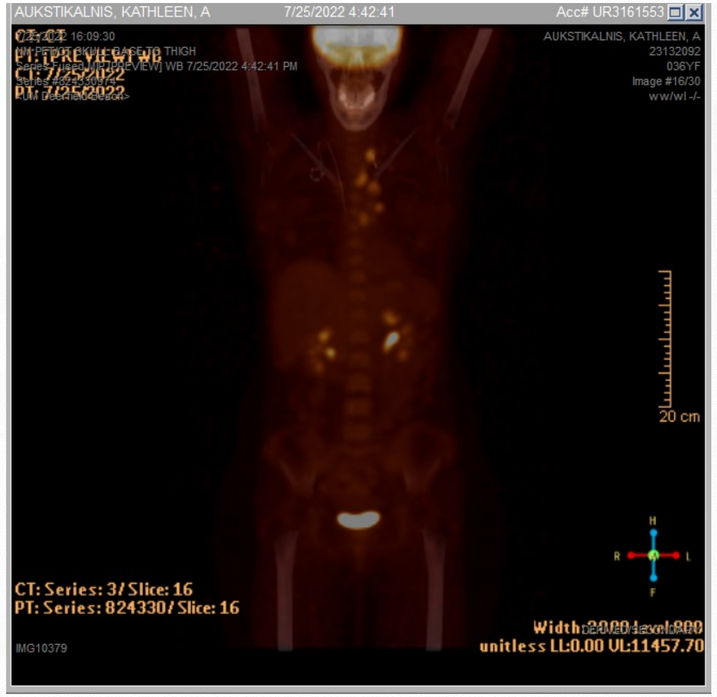
Unfavorable primary refractory ESHL

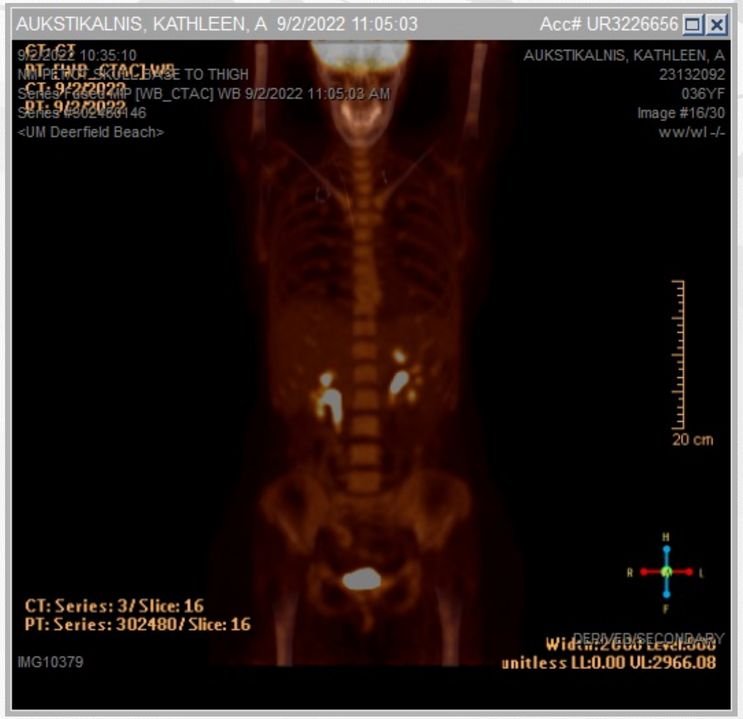
- 37 year old female presents with bilateral cervical and anterior mediastinal HL seen on telemedicine after cycle 2 of planned 4 cycles of ABVD; deauville score of 4 at biopsy site and no change after cycle 4 and I recommended completing 6 cycles of chemotherapy
- End of tx PET no change and on exam palpable node vs seroma; bx confirmed HL
- Does this pt need a transplant?

Baseline PET

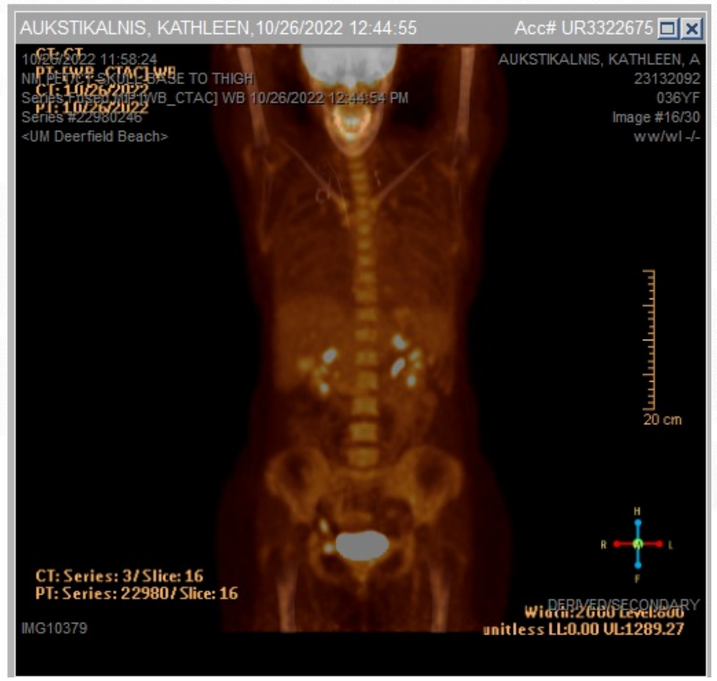
(Prior to P-GVD)



PET2

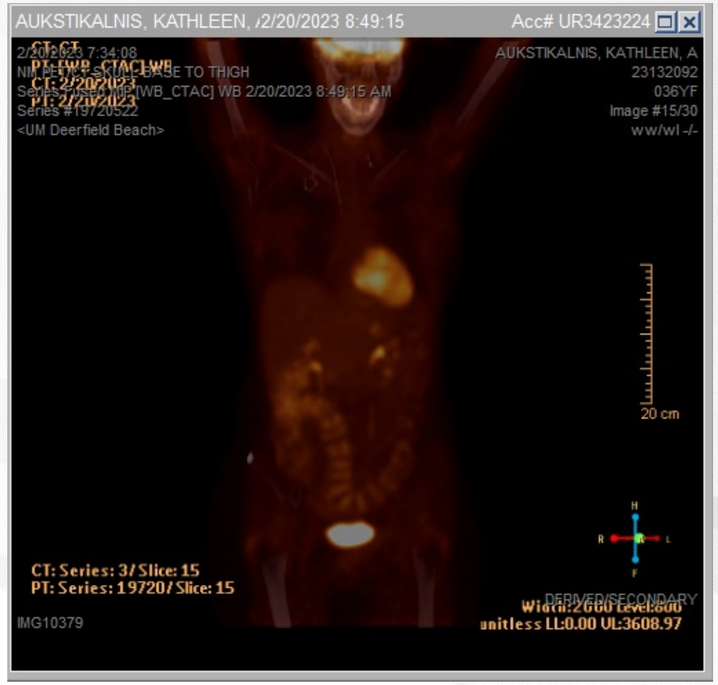


EOT scan (after 4 cycles)

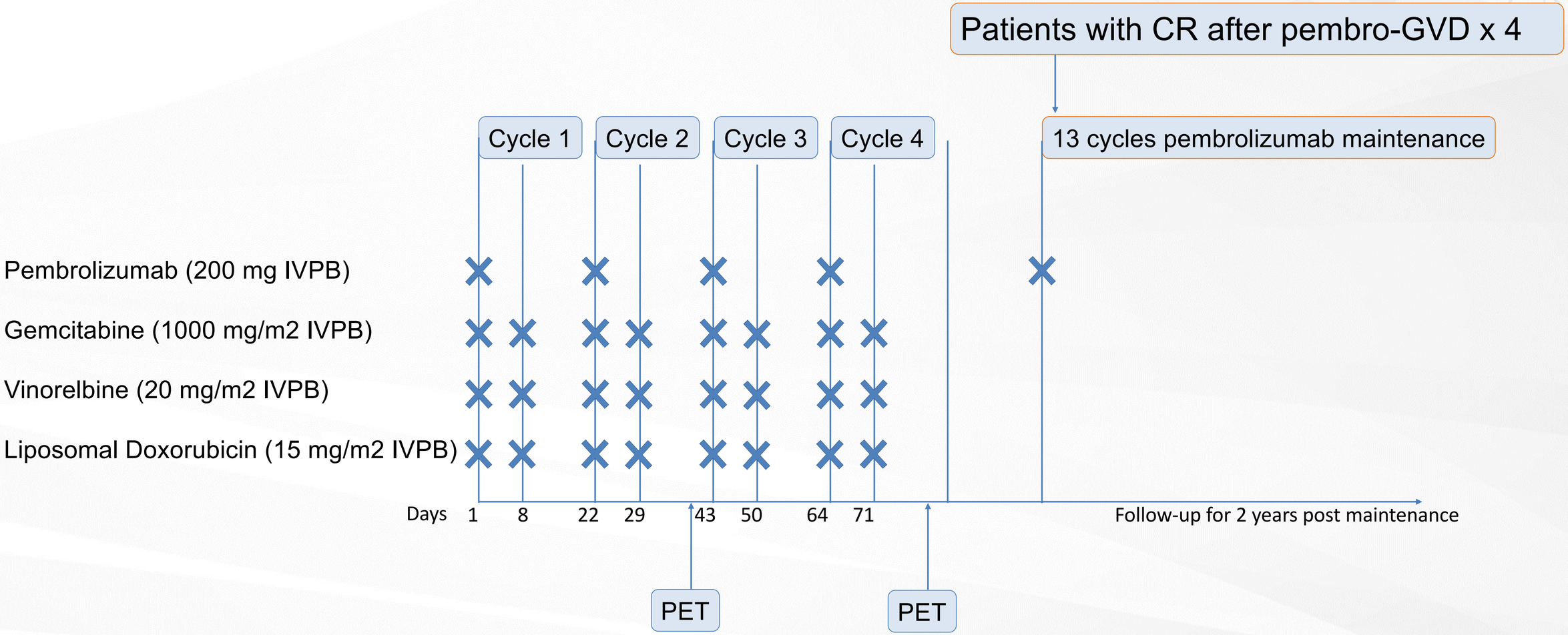


Day ~100 scan

s/p 2 cycles BV



Pembro Maintenance Cohort : Study Design



Exploratory: cytokines, immune-cell subsets, metabolic tumor volume, ctDNA, 9p24.1 amplification, IHC staining for MHC-I, MHC-II, pd-1, pd-l1, pd-l2, beta-2 microglobulin

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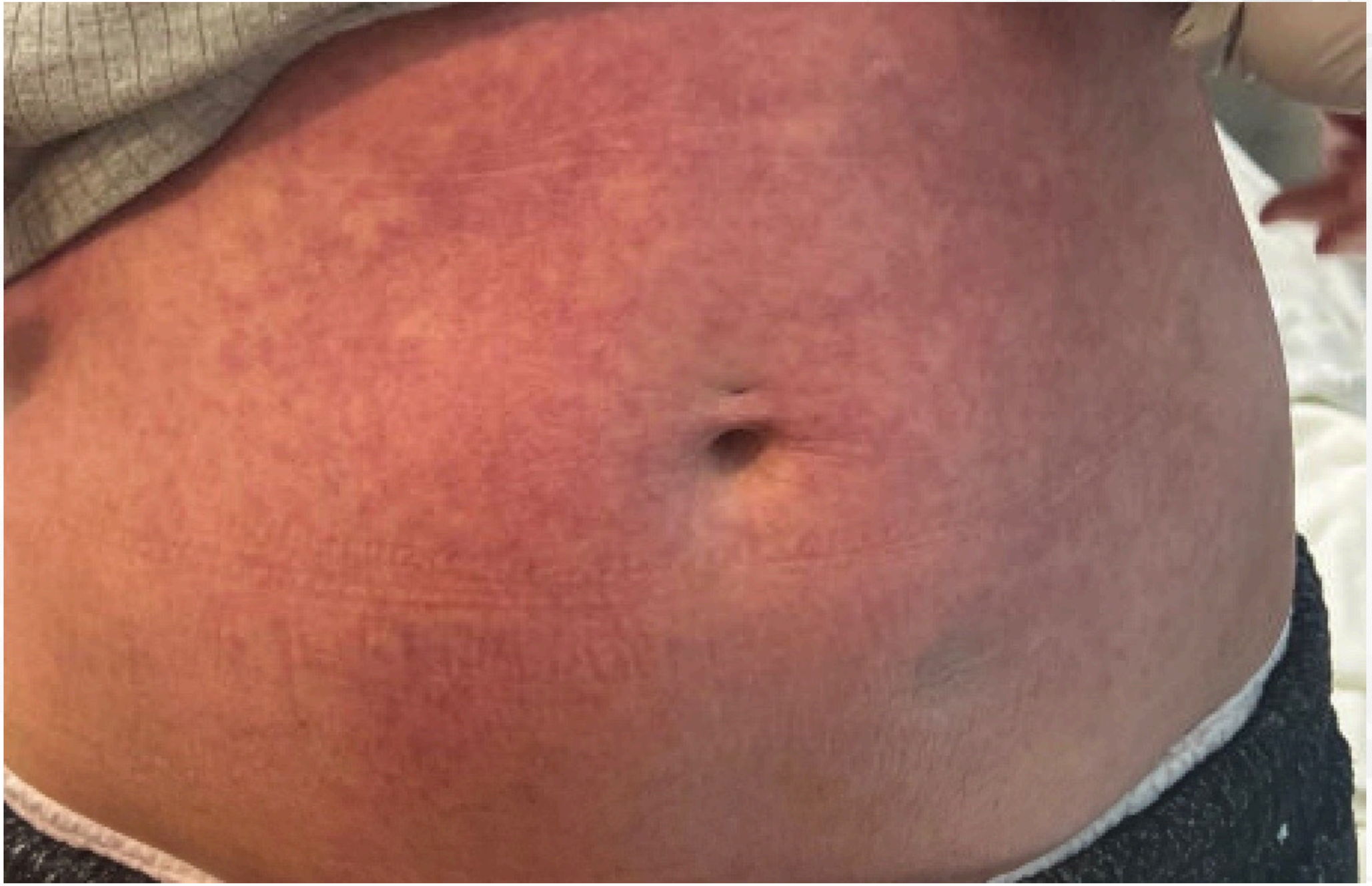
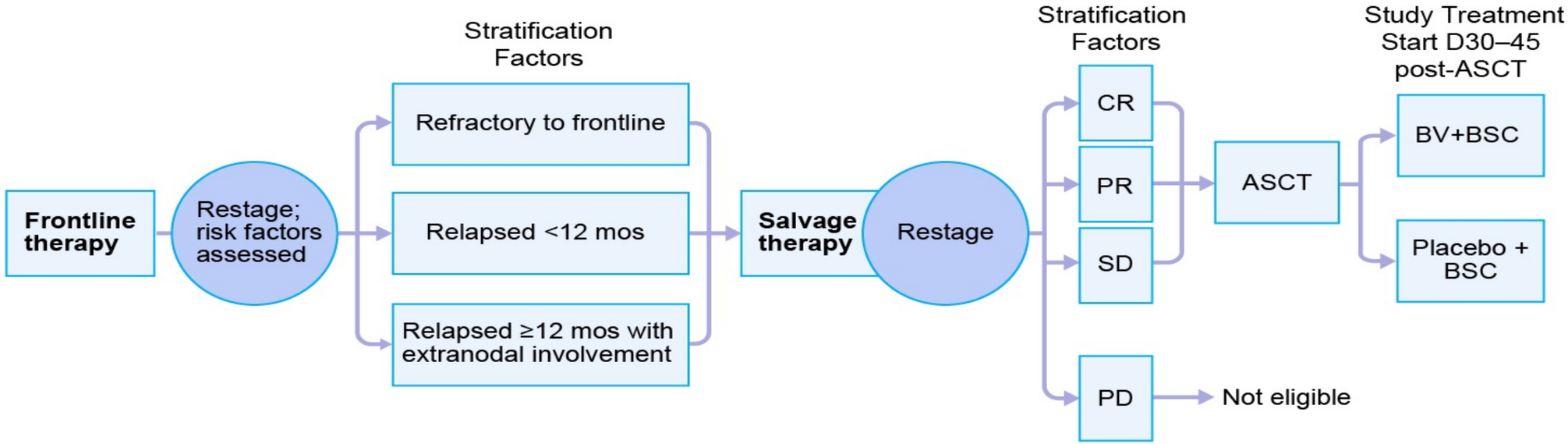


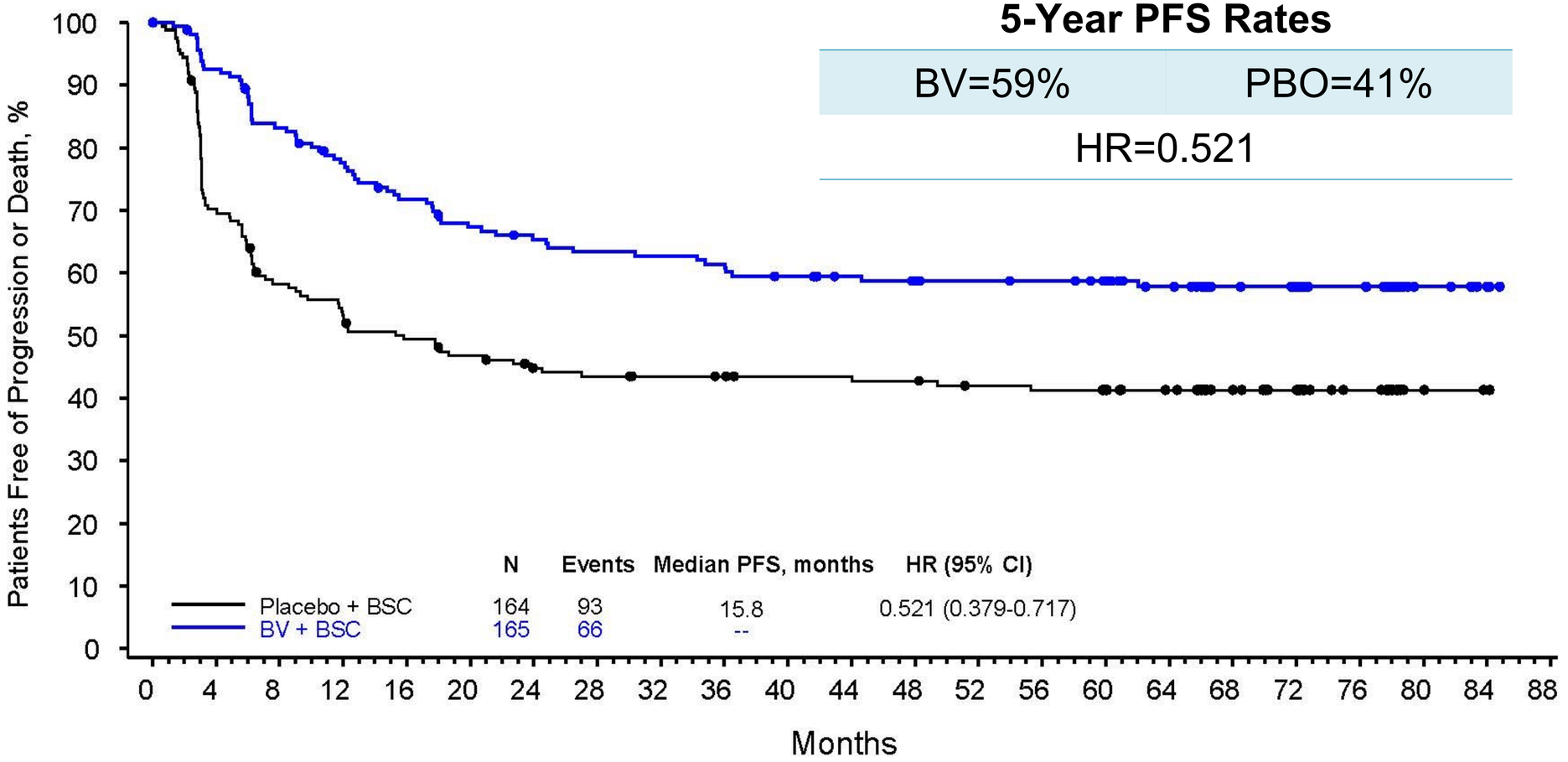
AETHERA Trial Design



- Randomization was stratified by:
  - Risk factors after frontline therapy
  - Best clinical response to salvage therapy before ASCT
- 329 patients randomized to BV 1.8 mg/kg IV and BSC or PBO + BSC for up to 16 cycles, starting 30–45 days after ASCT
- Patients on the PBO+BSC arm with progressive disease had access to BV subsequent therapy on a separate study

5-Year PFS per Investigator: All Patients (N=329)

5-Year PFS Rates	
BV=59%	PBO=41%
HR=0.521	



No. at risk (events)

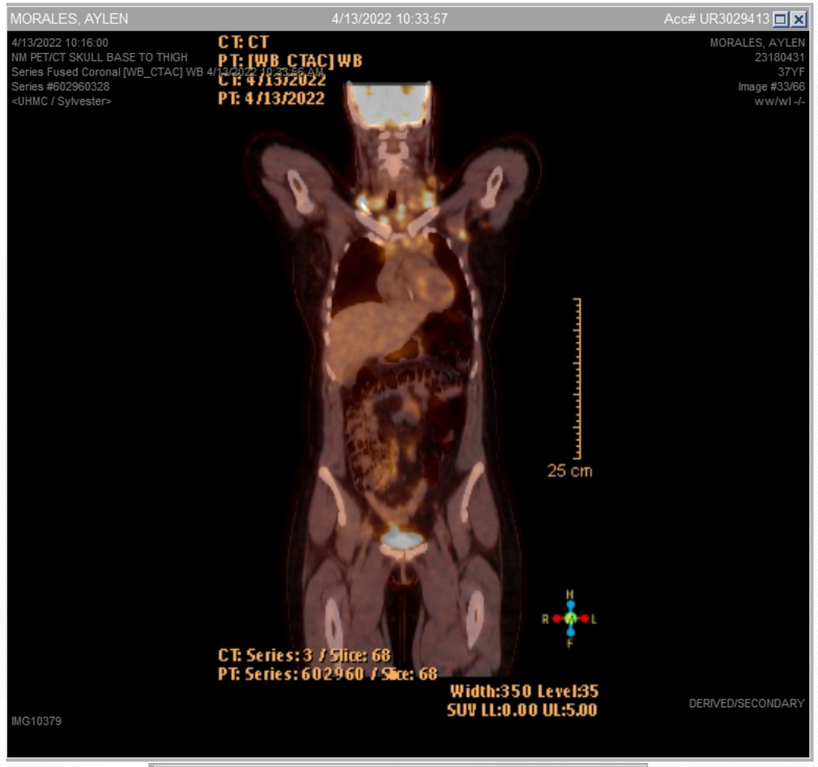
Pla+BSC	164 (0)	113 (48)	92 (67)	83 (76)	77 (81)	72 (85)	66 (88)	64 (90)	62 (90)	61 (90)	59 (90)	58 (91)	58 (91)	55 (92)	54 (93)	52 (93)	44 (93)	32 (93)	27 (93)	17 (93)	2 (93)	1 (93)	0 (93)
BV+BSC	165 (0)	149 (12)	133 (27)	122 (36)	112 (45)	104 (52)	100 (55)	97 (58)	96 (59)	94 (61)	90 (64)	87 (64)	84 (65)	83 (65)	82 (65)	78 (65)	66 (66)	47 (66)	43 (66)	26 (66)	7 (66)	3 (66)	0 (66)

Early relapse unfavorable ESHL

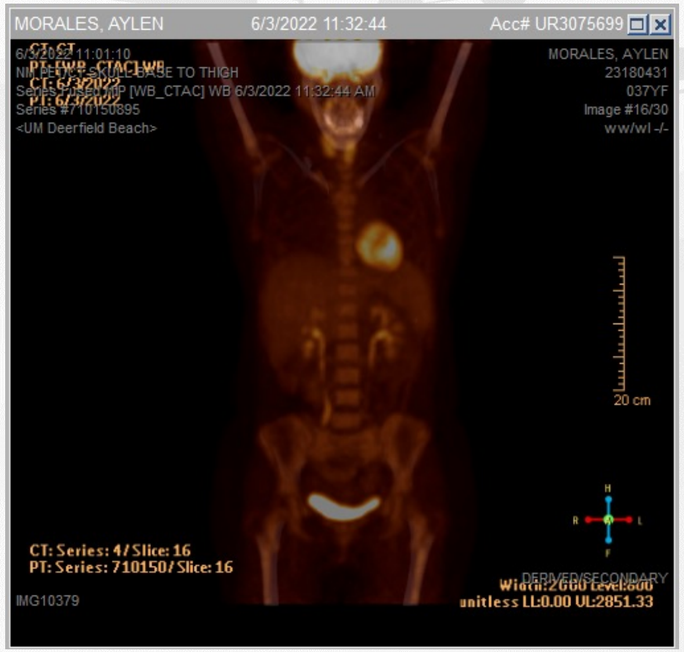
- 38 year old internist presented 4 months post ABVD x 4 with new cervical node
- Biopsy confirmed cHL
- She has pruritis but no B symptoms

Baseline PET

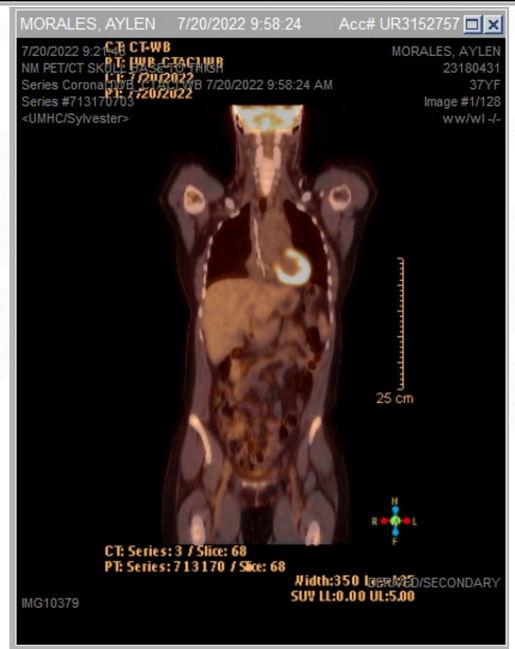
(prior to P-GVD)



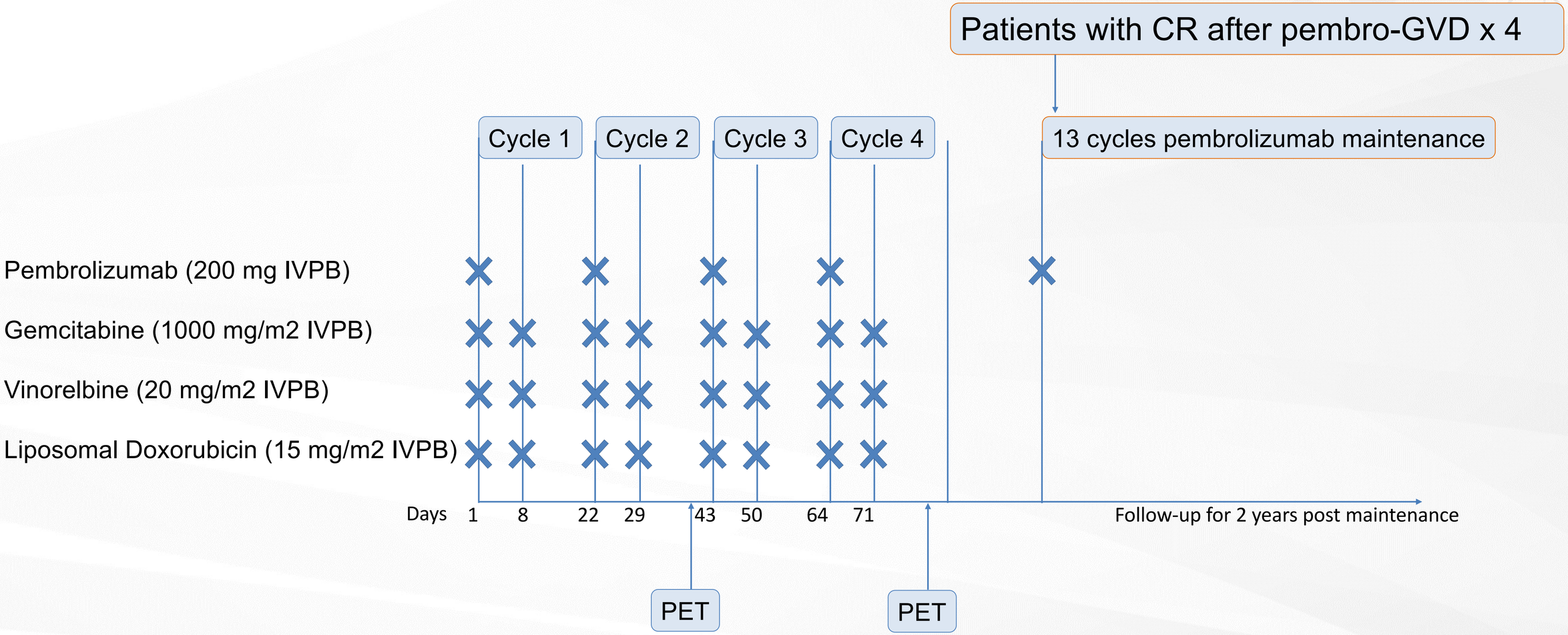
PET2



Baseline PET #4



Pembro Maintenance Cohort : Study Design



Exploratory: cytokines, immune-cell subsets, metabolic tumor volume, ctDNA, 9p24.1 amplification, IHC staining for MHC-I, MHC-II, pd-1, pd-l1, pd-l2, beta-2 microglobulin

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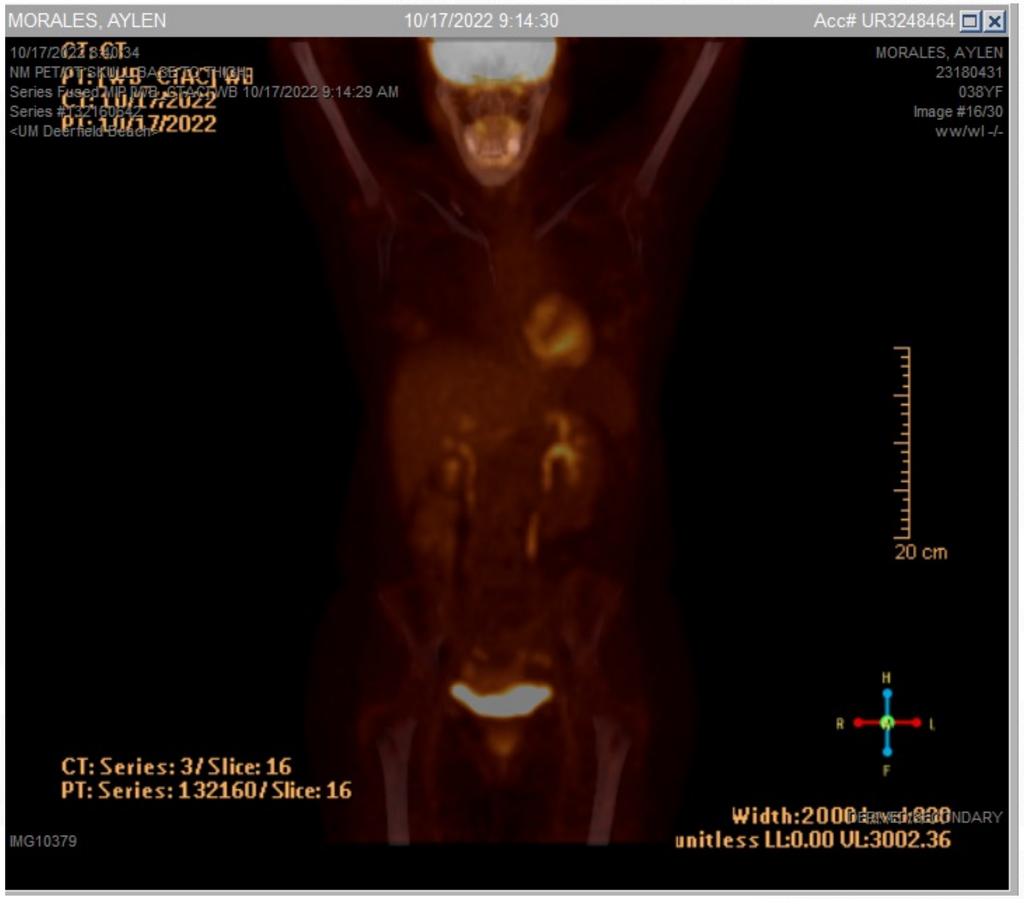
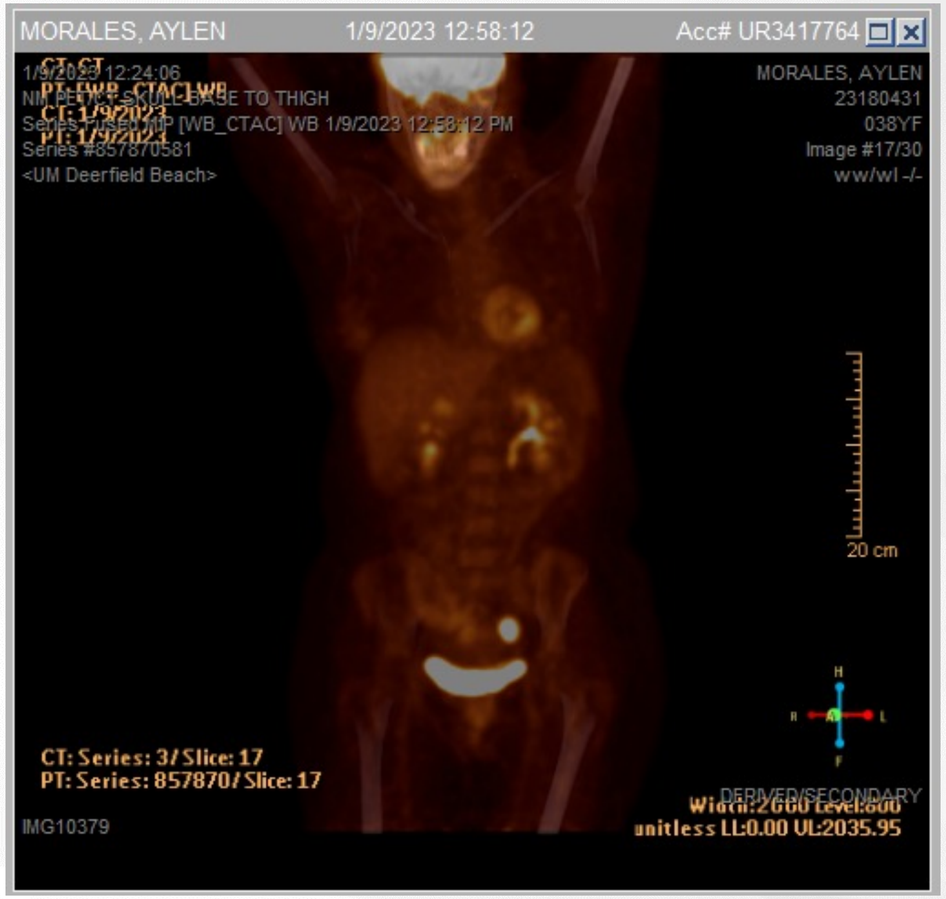
Aylen Morales

S/p 4 cycles Pembro maintenance



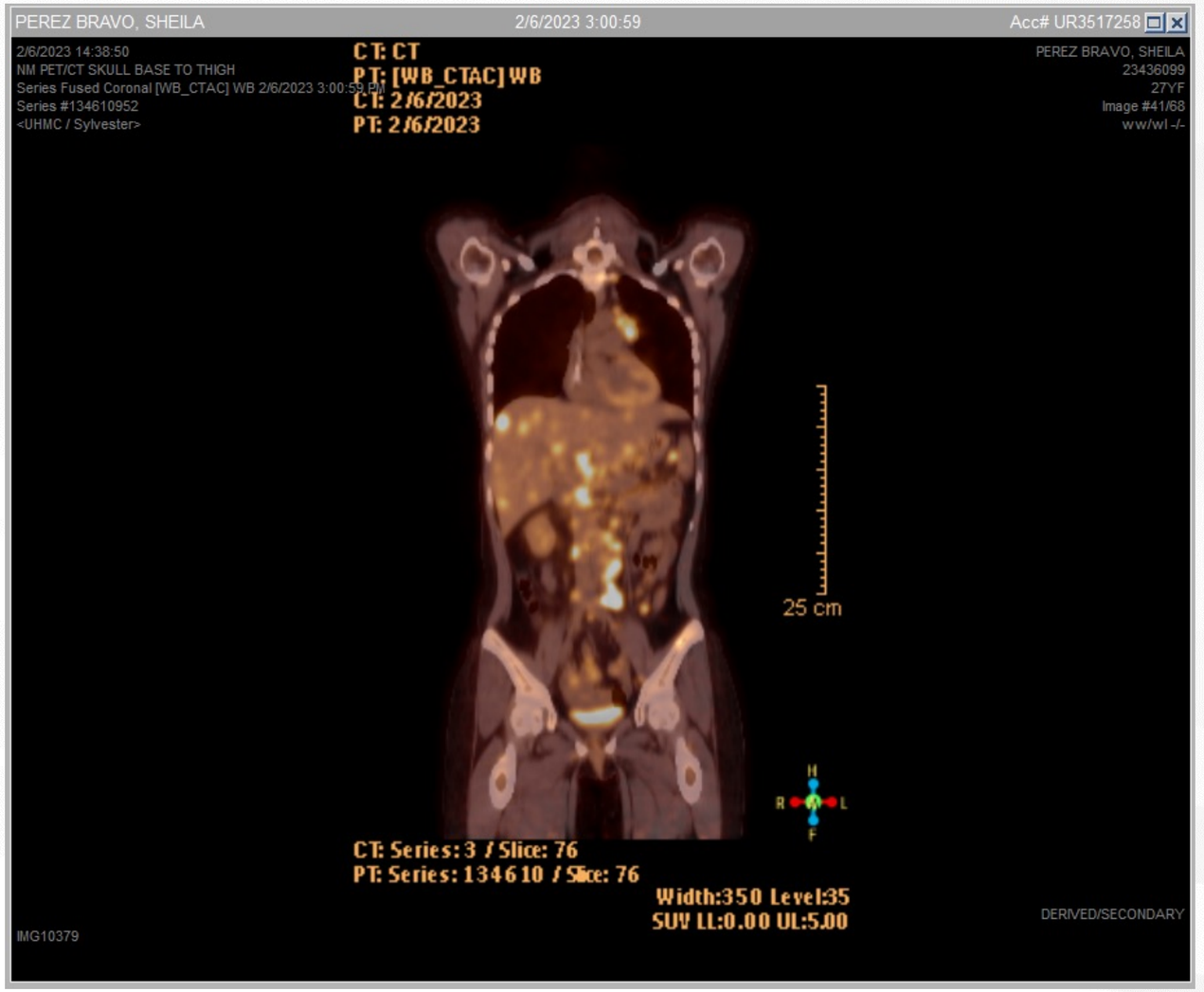
s/p 8 cycles pembro maintenance



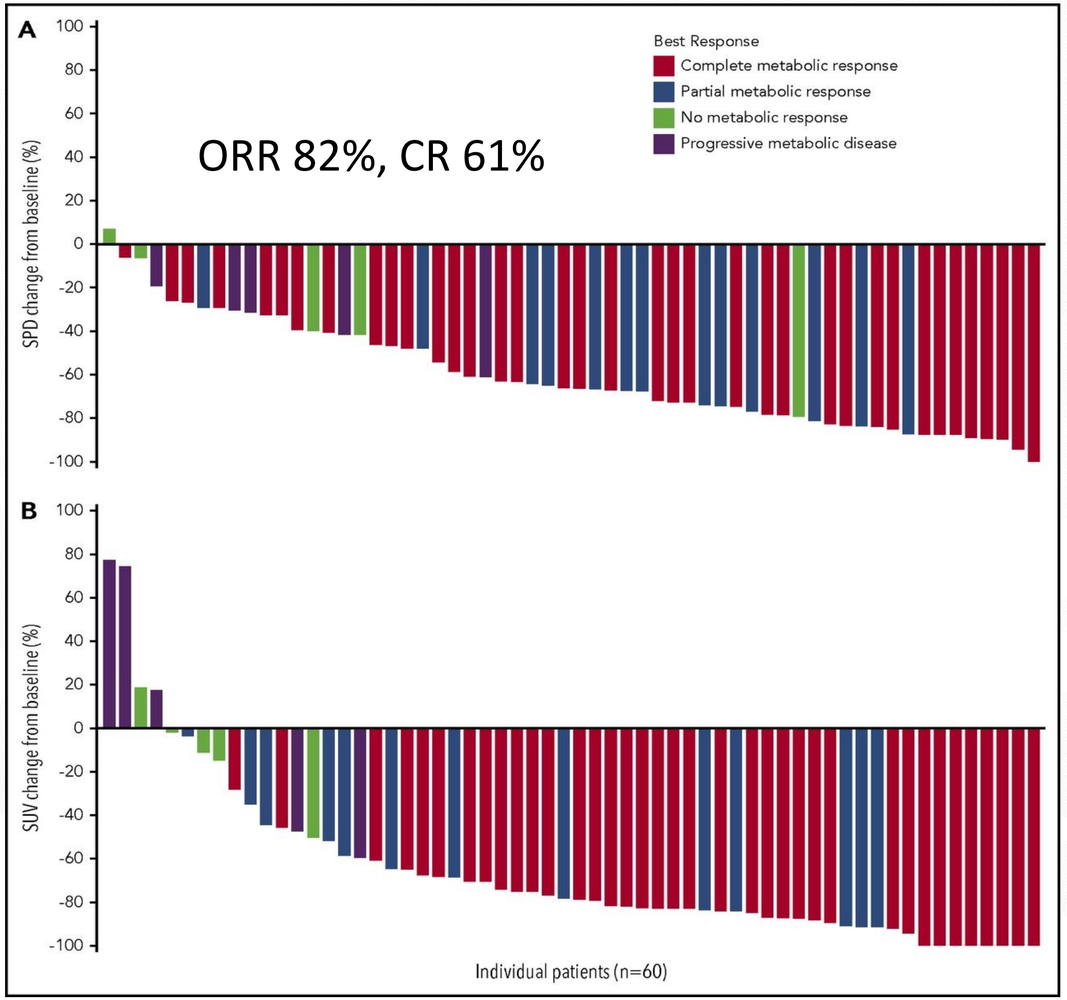
Primary refractory ASHL to multiple regimens

- 22 year-old female presents to me after receiving ABVD and BV-bendamustine for primary refractory HL
- Active B symptoms
- Imaging shows widespread nodal and extranodal disease

Baseline PET (prior to BV Nivo)

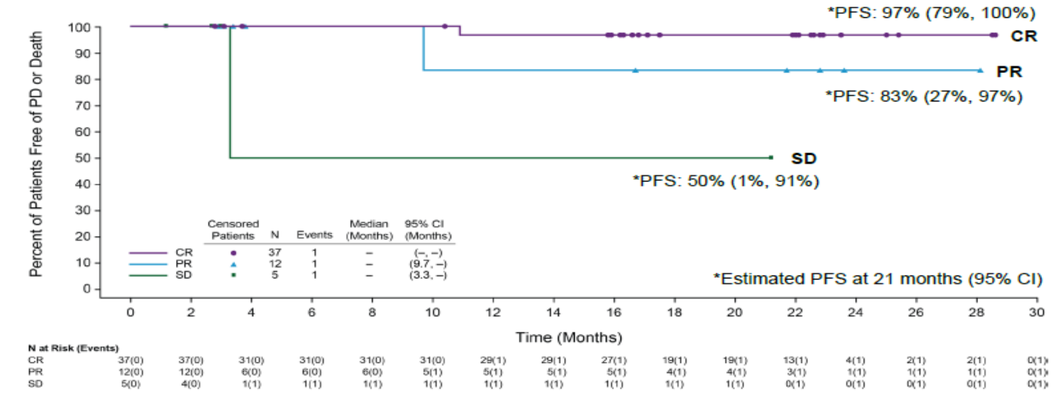


Phase I/II study BV + Nivolumab as 1st salvage

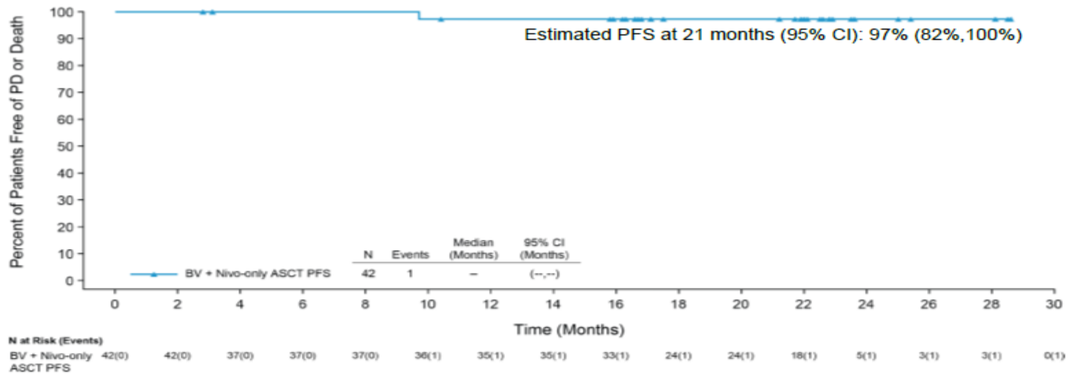


Advani et al Blood 2021

PFS by Response to Study Treatment

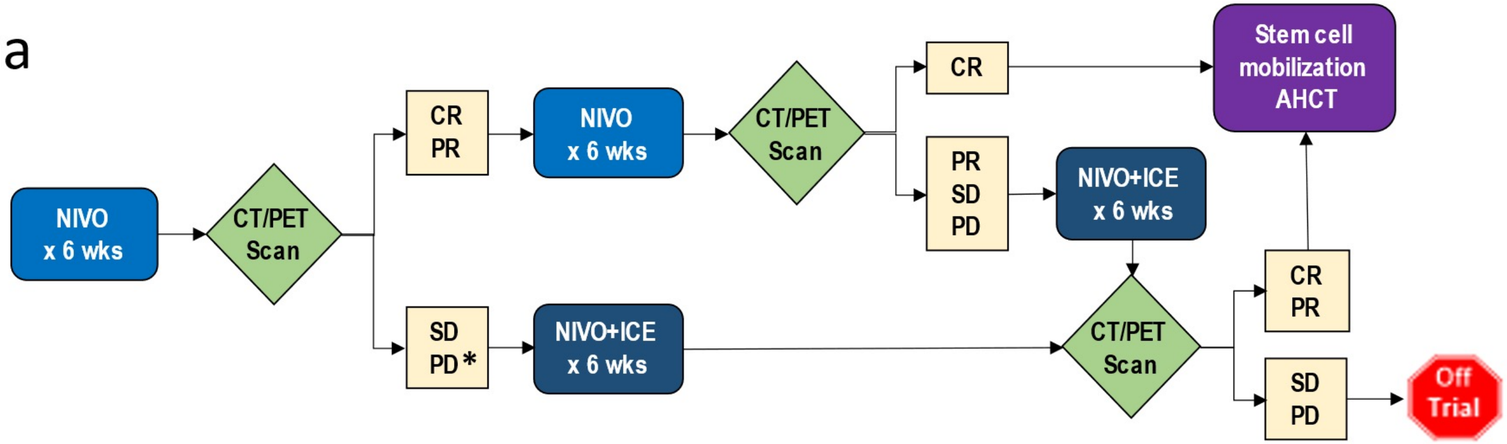


PFS: ASCT directly after BV + Nivo

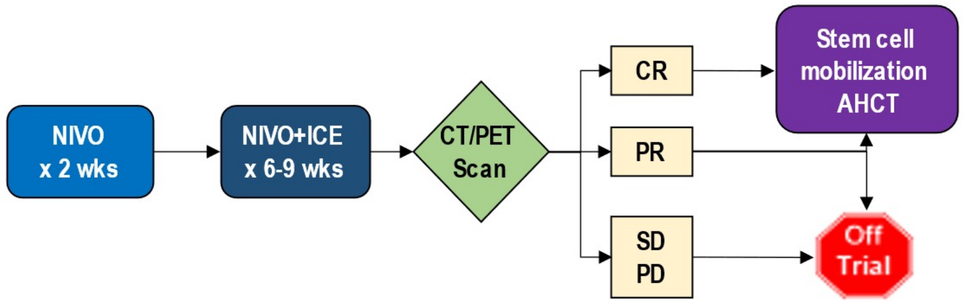


Cohort B: NICE Trial Treatment Schema

- Original Schema



- Cohort B Schema (12/31/19)



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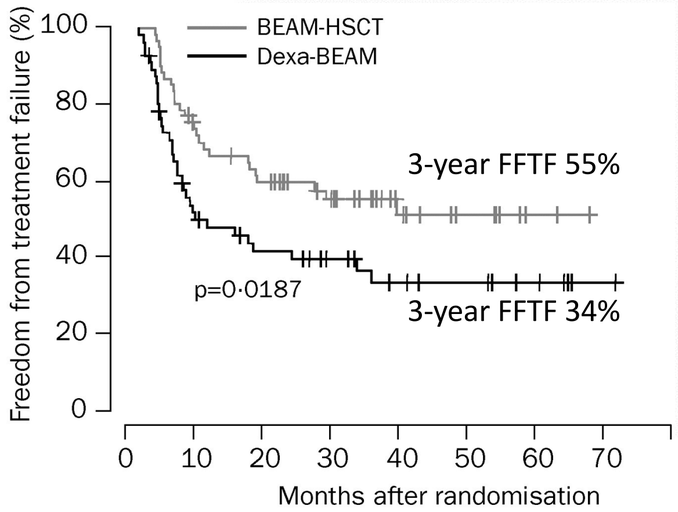
Why are we curing so many pts with Relapsed/Primary Refractory HL?

A

Transplant years: 1993-1997

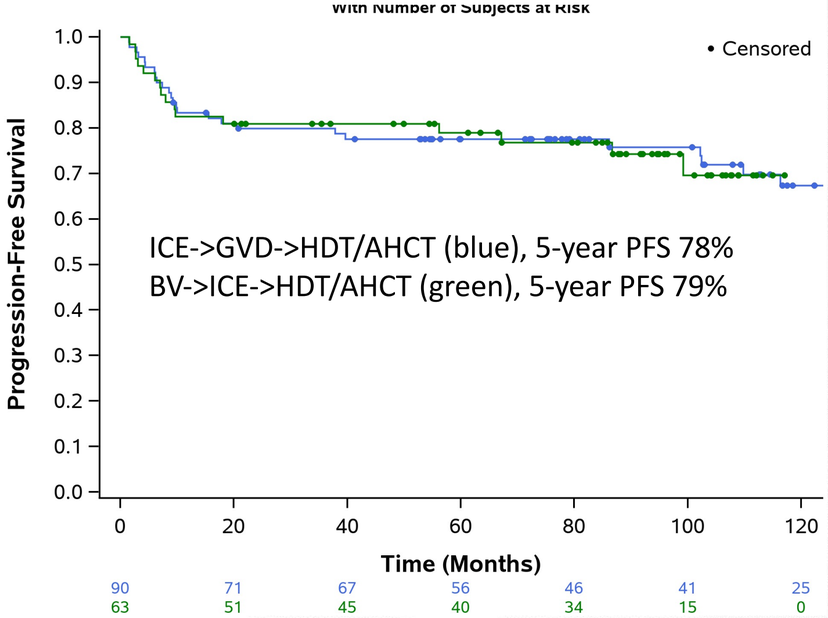


Number of patients

BEAM-HSCT	61	43	34	25	13	8	7	0
Dexa-BEAM	56	27	20	15	10	8	5	1

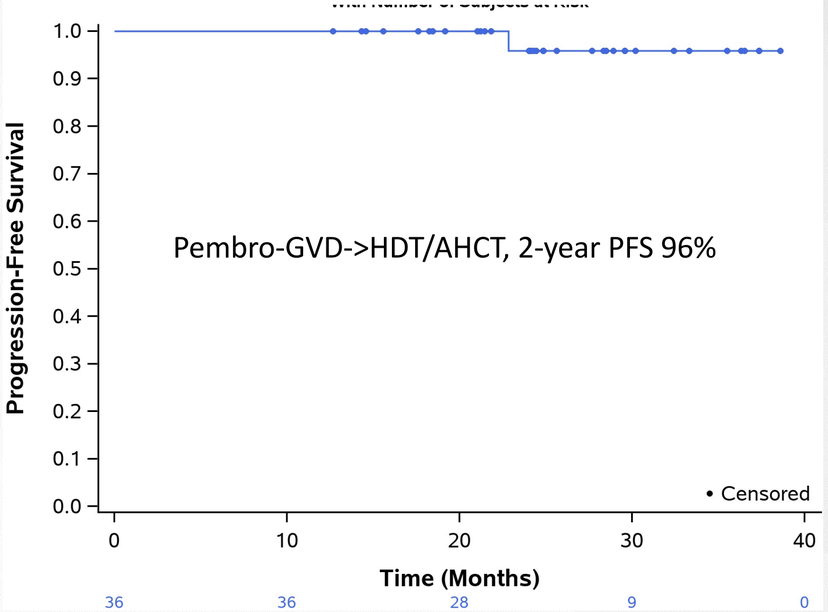
B

Transplant years: 2004-2014



C

Transplant years: 2018-2020



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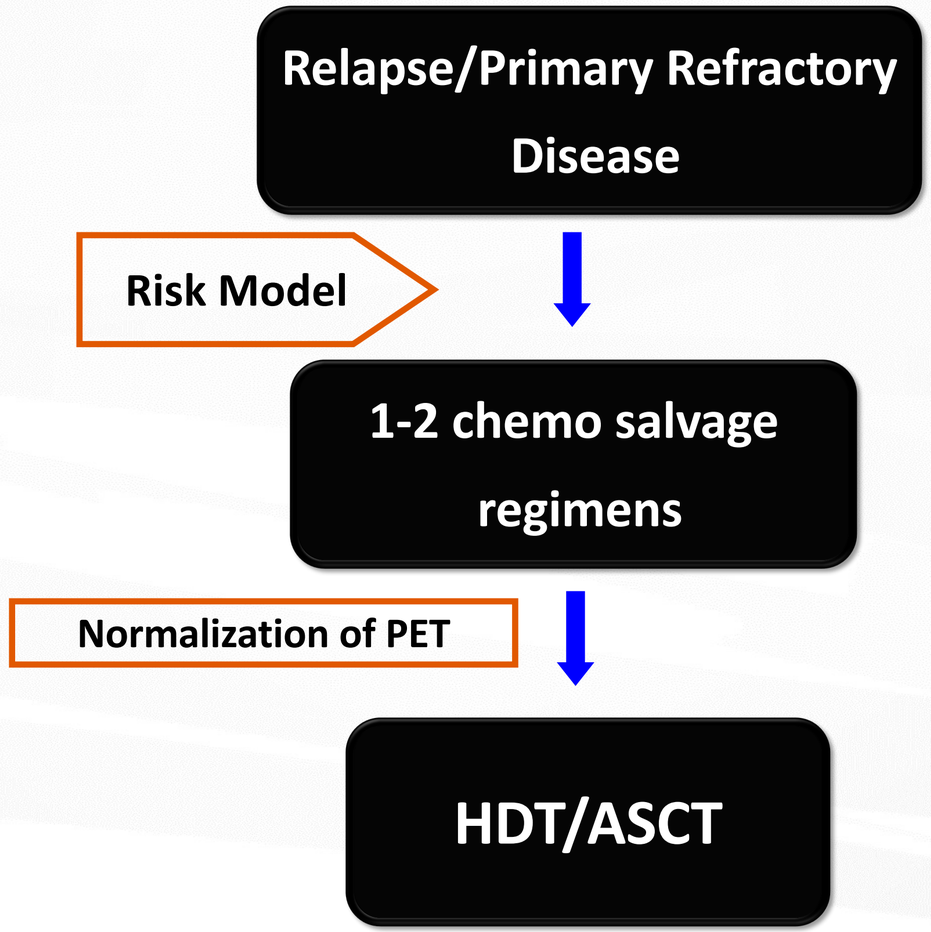
A reasonable approach to relapsed/refractory Hodgkin lymphoma era of maintenance



Pre-Tx Risk Actors?

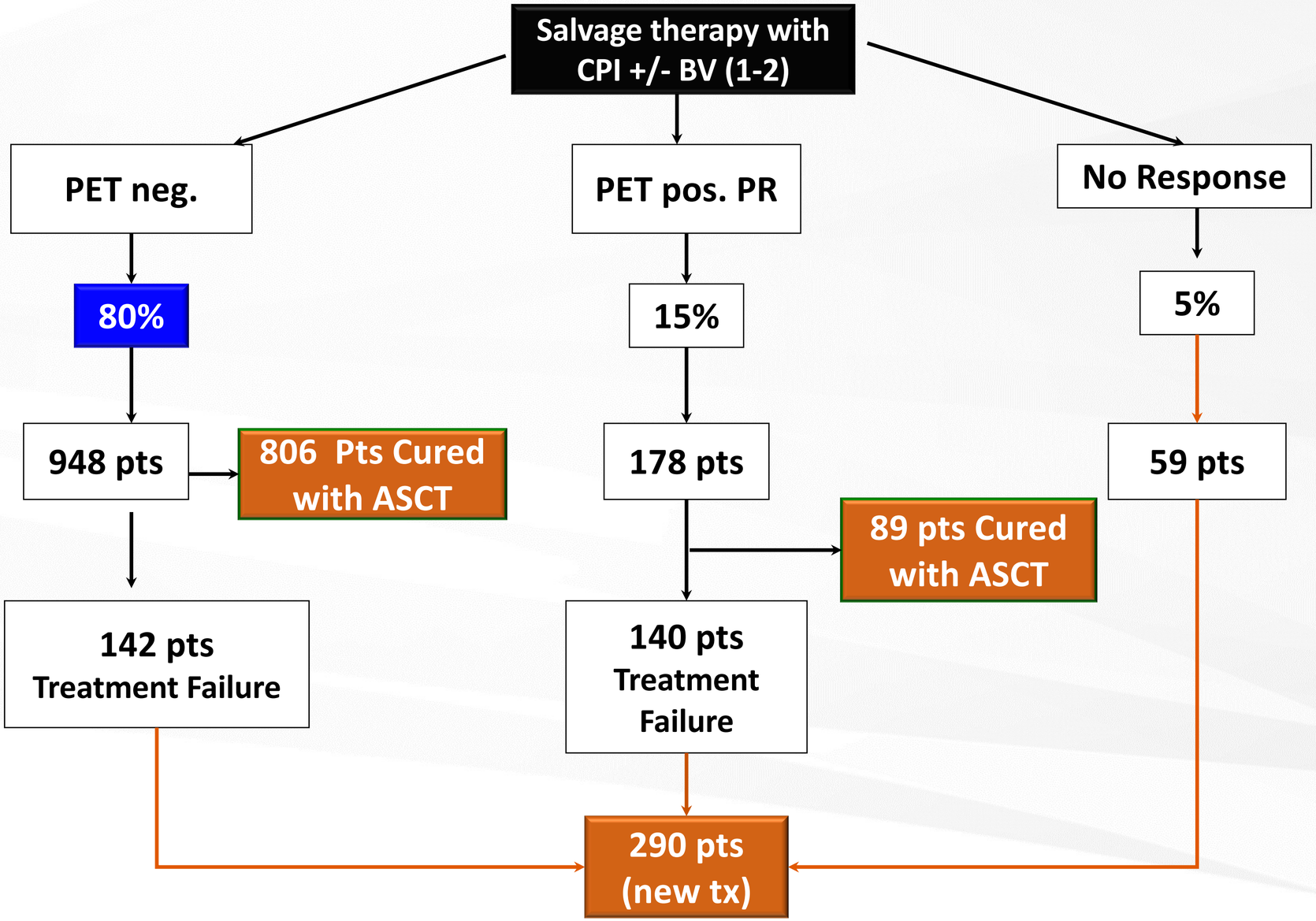
- B symptoms
- Extranodal disease
- Remission duration <1 yr
- Heavily pre-treated

Maintenance

If CR is not achieved

or multiple risk factors

Relapsed/Refractory HL: 1185 pts/year, era of modern salvage treatment



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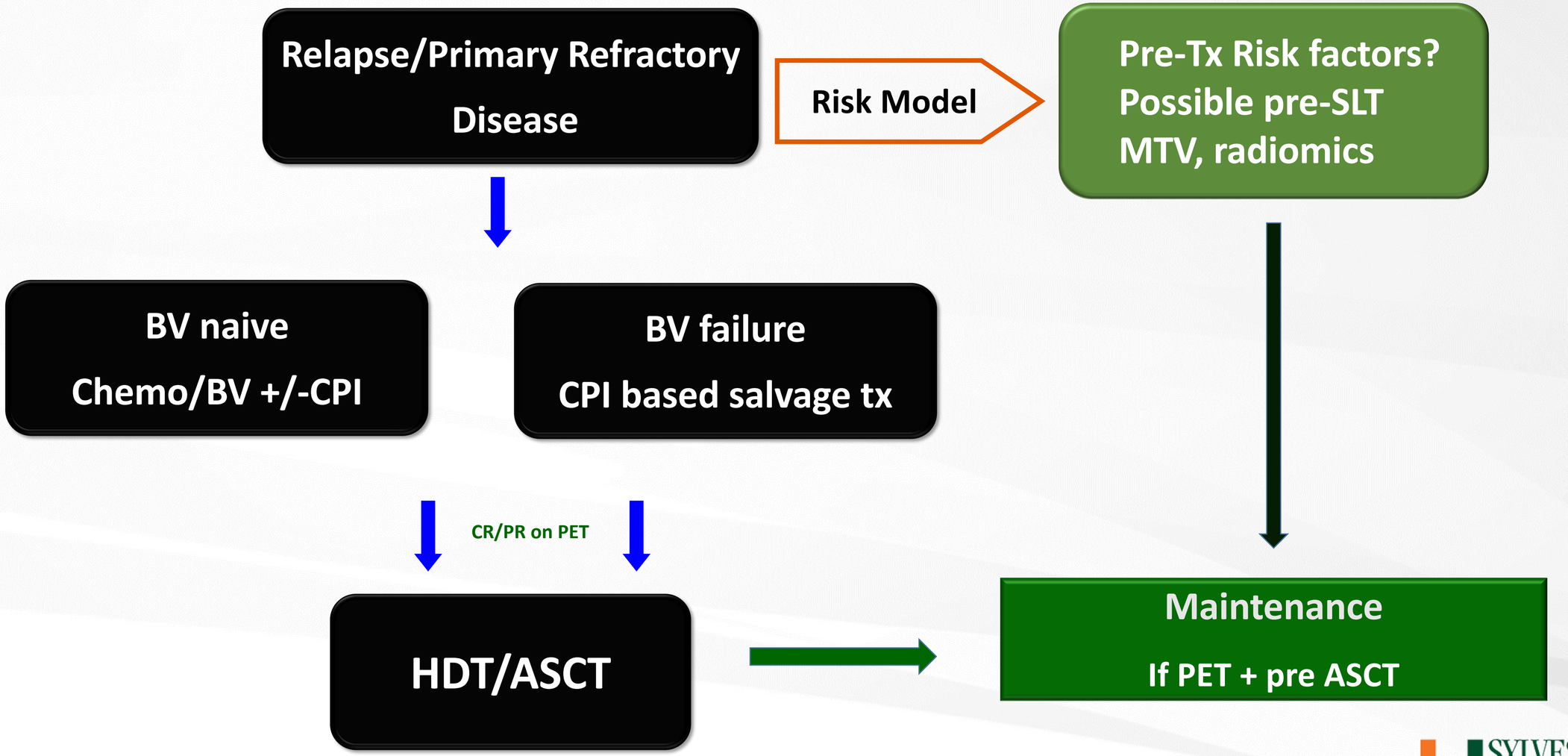
A reasonable approach to relapsed/refractory Hodgkin lymphoma-2023



BV-based frontline therapy and its affect in second-line approaches

- It is clear that with an OS advantage BV-AVD is the clear treatment for ASHL
  - Will BV be used again at the time of tx failure?
    - As part of salvage regimens?
    - Will the role of maintenance BV end?
    - The North American intergroup study comparing BV-AVD to N-AVD is complete, could we have a new standard of care when this conference meets again?
    - CPI work in BV failures, is the opposite true?

- The RADAR study is finally open comparing 3 cycles of BV-AVD to ABVD for stage I/II non-bulky cHL, hard to imagine this will be a negative study
  - The role of RT will be almost gone in ESHL if positive
  - Even in pts with tumor bulk a number of phase 2 studies suggests RT is not needed
  - RT can have a major role in second-line

When evaluating patients for SLT/ASCT in 2023 the most important issues are

- Did the patient receive BV-AVD as standard of care or on a research study
- Did the patient receive N/P-AVD on a research study
- If the patient had ESHL was short course chemo alone administered?
  - Does the patient have low volume stage I/II nodal disease

- Did the patient achieve a PET neg response after salvage chemotherapy
  - Was BV-based salvage chemotherapy used
  - Was CPI-based salvage chemotherapy used
  - Was BV/nivo salvage therapy used
  - Was standard platinum-based salvage chemotherapy used

Can the treatment paradigm be changed

- Not all salvage regimens are the same; consider efficacy, toxicity, easy of administration and cost
- Post-ASCT, BV should be standard for patients with multiple risk factors in BV naive pts or pts that have had a CR to BV based salvage but not 16 doses
- Research studies need to explore non-ASCT programs for favorable disease

- Off study I am in favor of withholding the salvage therapy/ASCT program until second relapse if patients have early stage disease that relapses as early stage, if all the disease can be encompassed into a reasonable RT field using a novel agent and RT consolidation

- Excluding ASCT for any other pt group should not be done off study!

I want to thank the patients for participating in these research studies over the past 30 years

Lymphoma faculty at MSKCC where I spent 25 years of my life especially Joachim Yahalom who was the co-PI of all the pre-BV studies and Alison Moskowitz the co-PI of all the studies before I left in mid 2018 and now I am her co-PI!

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