4th MEETING ON
INNOVATIVE IMMUNOTHERAPIES
FOR LYMPHOID MALIGNANCIES

Società Italiana di Ematologia

Presidents
Paolo Corradini
Marco Ruella
Pier Luigi Zinzani

# The Evolving Role of Checkpoint Inhibitors in Non-Hodgkin Lymphomas

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MILANO, STARHOTELS ROSA GRAND
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# Disclosures of John Kuruvilla

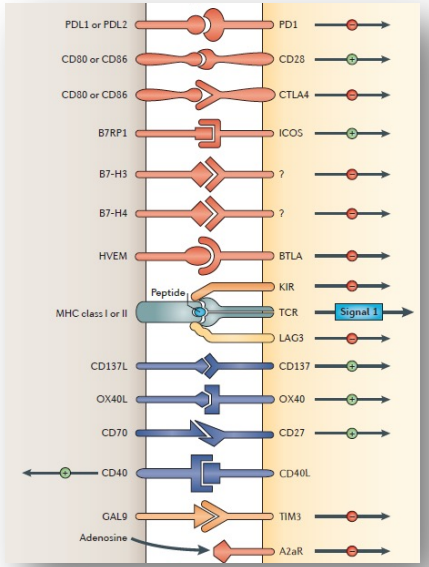
- Consultancy: AbbVie, AstraZeneca, BMS, Gilead, Karyopharm, Merck, Pfizer, Roche
- Honoraria: AbbVie, Amgen, AstraZeneca, Arvinas, BMS, Eli Lilly, Genmab, Gilead, GSK, Incyte, Janssen, Karyopharm, Merck, Novartis, Pfizer, Roche
- Membership on a Board or Advisory Committee: Karyopharm, Lymphoma Canada (Chair)
- Research Funding: AstraZeneca, Canadian Institutes of Health Research, Leukemia and Lymphoma Society Canada, Merck, Roche

# Objectives

- Review current rationale behind use of checkpoint inhibitors (CPI) in Non-Hodgkin Lymphoma (NHL)
- Highlight key data supporting current usage of CPI in NHL
- Discuss further development of CPI in NHL

# Role of the Immune Checkpoint

- Controls needed on this system
  - Activate immunosurveillance for infection/tumour
  - Maintain tolerance and prevent injury to self tissue
- The immune checkpoint is the series of inhibitory signals for this system




**Cancer Cell** **T-cell**

Pardoll , 2012*, Nat Rev Can*, **5**, 252-265

# THE CPI story in NHL is… unfortunate

- Anti-PD1 antibodies are not particularly active in DLBCL, FL or PTCL
- Additional checkpoint inhibitors (LAG3, TIGIT, TIM3) have also been evaluated in lymphoma with at most modest activity
- Broad activity does not appear to be present in common lymphoma subtypes
  - Could there be activity in subgroups where biology may support this?
  - Stealing from the genomics of cHL – what about PMBCL?
  - Given what we know about EBV – what NKT cell lymphomas?
  - What about subsets of DLBCL?

# Primary Mediastinal B-cell lymphoma (PMBCL)

- Clinically, PMBCL can have a similar presentation to cHL
- Mediastinal mass, typically young women
- Curable with primary chemotherapy (R-CHOP; DA-EPOCH-R)
- Outcomes of salvage therapy and ASCT are inferior to those of RR-DLBCL
  - ORR 25% versus 48%; 2-year OS: 15% versus 34%
- CAR-T cell registrational studies have included CAR-T failure
- Frequently exhibits 9p24.1/PD-L1/PD-L2 copy number alterations and rearrangements with associated PD-L1 and/or PD-L2 overexpression
- Drug development historically has not demonstrated activity for many typical agents considered in DLBCL (lenalidomide, ibrutinib etc.)



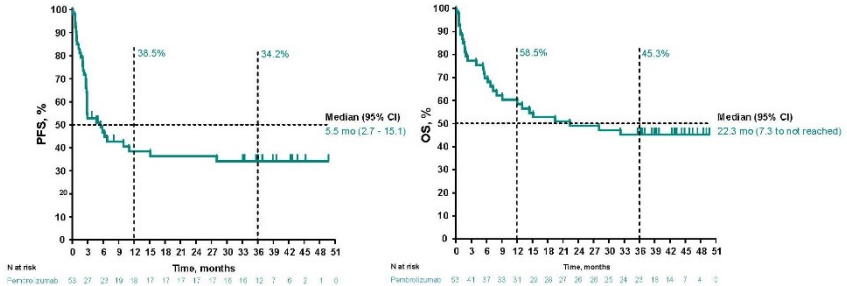
Kuruvilla Leuk Lymph 2008

# Pembrolizumab in RR-PMBCL

| Study (n) | ORR (CR) % | PFS (median) | OS (median) | Toxicity / irAE |
|---|---|---|---|---|
| Keynote-13 (21) | 48 (33) | 10.4 m | 31.4 m | 14% Grade 3-4 ANC<br>1 Grade 3-4 myositis |
| Keynote-170 (53) | 45 (13) | 5.5m (38% @ 12m) | Not Reached | 13% Grade 3-4 ANC<br>1 Grade 3-4 pneumonitis |

Zinzani KN170 ASH 2020

## Survival

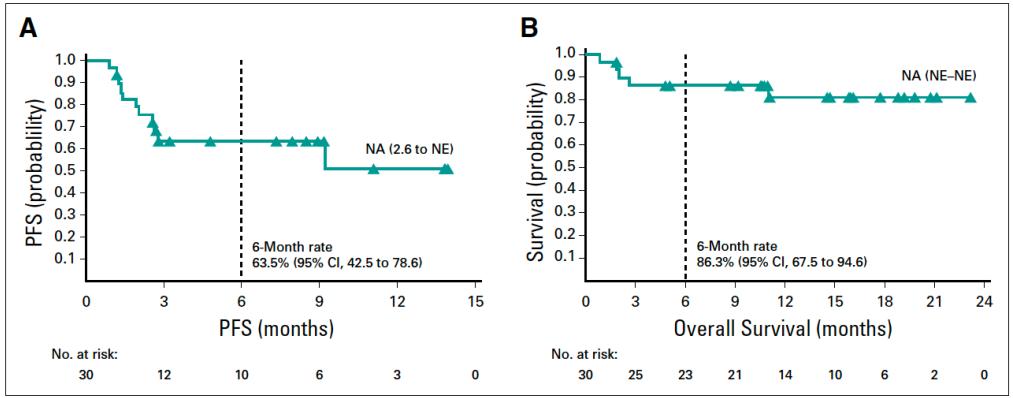



PFS by IWG per central review; Data cutoff date: May 7, 2020.

Zinzani Blood 2017; Armand JCO 2019

# Novel regimens in RR-PMBCL: CPI with BV

| Study (n) | ORR (CR) % | PFS | OS (median) | Toxicity / irAE |
|---|---|---|---|---|
| Italian BV phase 2 (15) | 13 (0) | N/R | N/R | 1 Grade 2 AF; 2 Grade 2 liver,1 grade 2 anemia, 1 Grade 3 fatigue |
| | | | | |
| Checkmate 436 (nivo+BV) (30) | 70 (43) | 6m: 63.5%<br>median: NR | 6m: 86.3%<br>Median: NR | 9 Grade 3-4 ANC, 3 Grade 3-4 PLT, 3 Grade 3-4 PN |




Zinzani Blood 2017; Armand JCO 2019

# Pembrolizumab (Pembro) plus R-CHOP is efficacious as first-line therapy for Primary Mediastinal B-cell lymphoma (PMBL) with high rates of ctDNA negativity – interim efficacy analysis of the ALLG-PACIFIC (NHL35) trial

**Katharine L Lewis,**[1,2] Piers Blombery,[3] Nagendraprasad Sungala,[4] Pratyush Giri,[5] Tamara Marconi,[6] Tara Cochrane,[7,8] Roslyn J Francis,[2] SzeTing Lee,[9] Chun-Kei-Kris Ma,[10,11] Vinay Vanguru,[12] Kate Manos,[13,14] Colm Keane,[15,16] Sally Hunter,[3] Melissa Burgess,[15] Sushmitha Kannan,[3] Julia Carlson,[17] Mannu Walia,[17] Belinda Butcher,[18] Chan Y Cheah[1,2]

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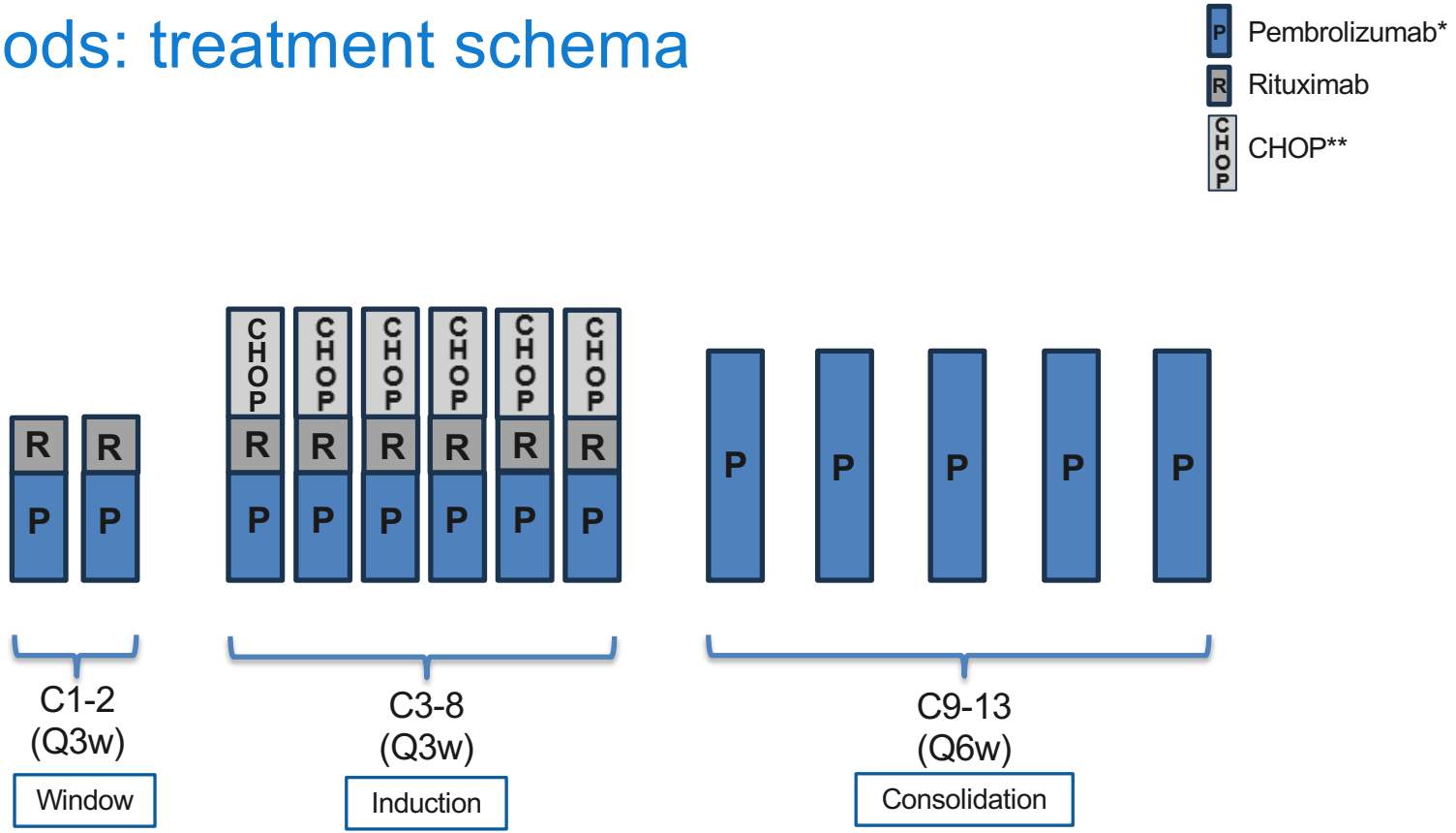
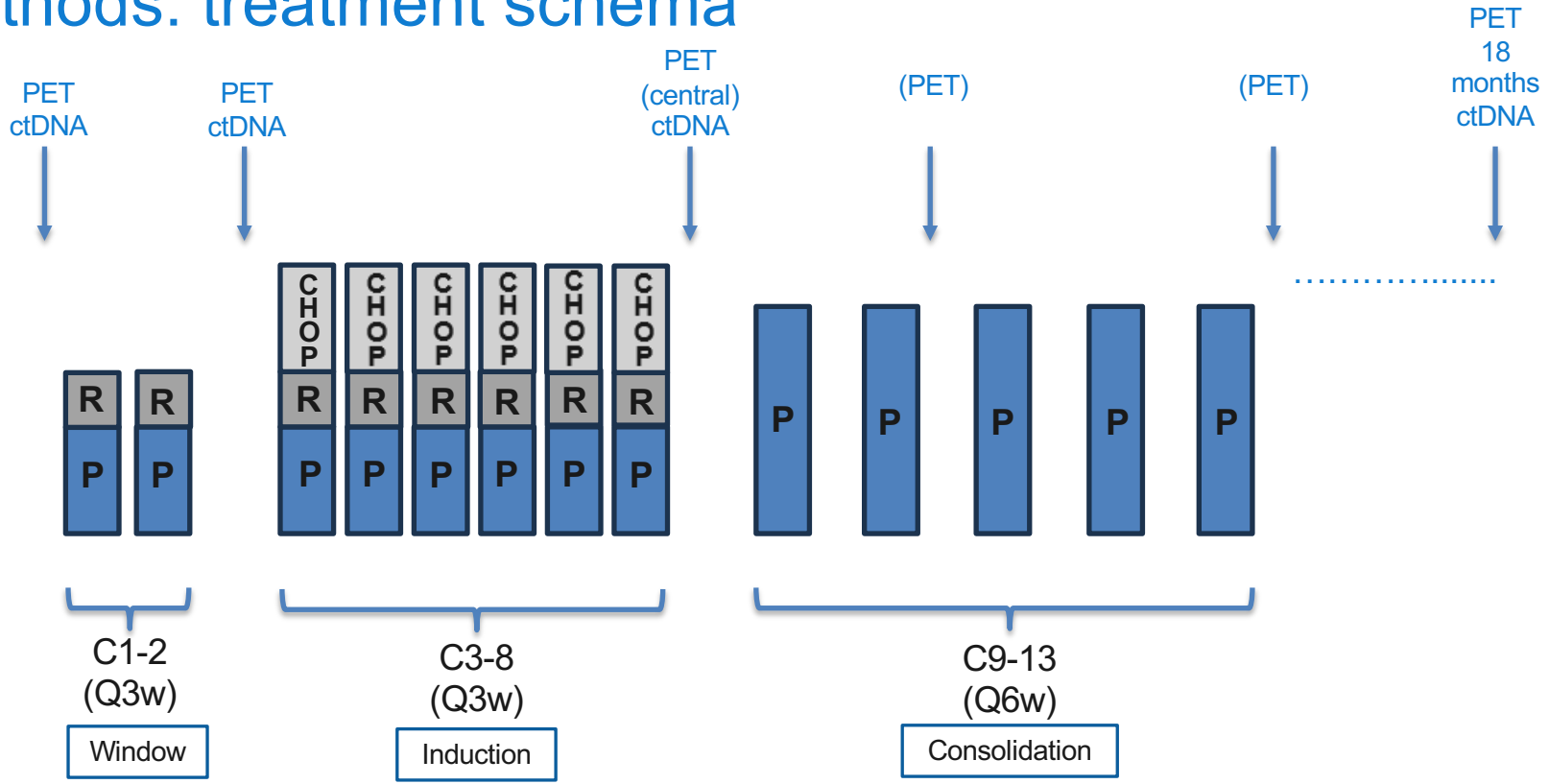
# Methods: treatment schema



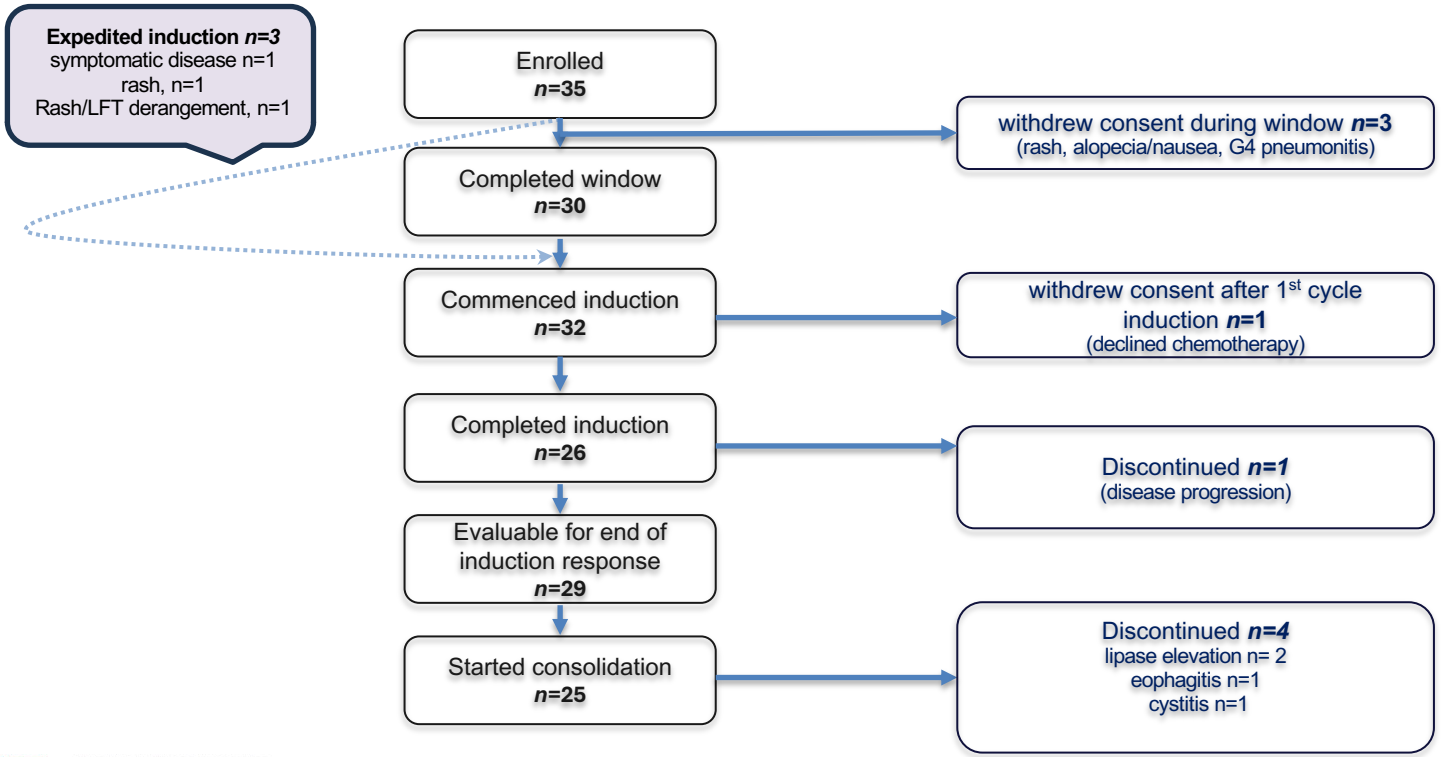



*200mg window and induction; 400mg consolidation
**cyclophosphamide, doxorubicin, vincristine, prednisolone

# Methods: treatment schema



# Results: Interim efficacy analysis

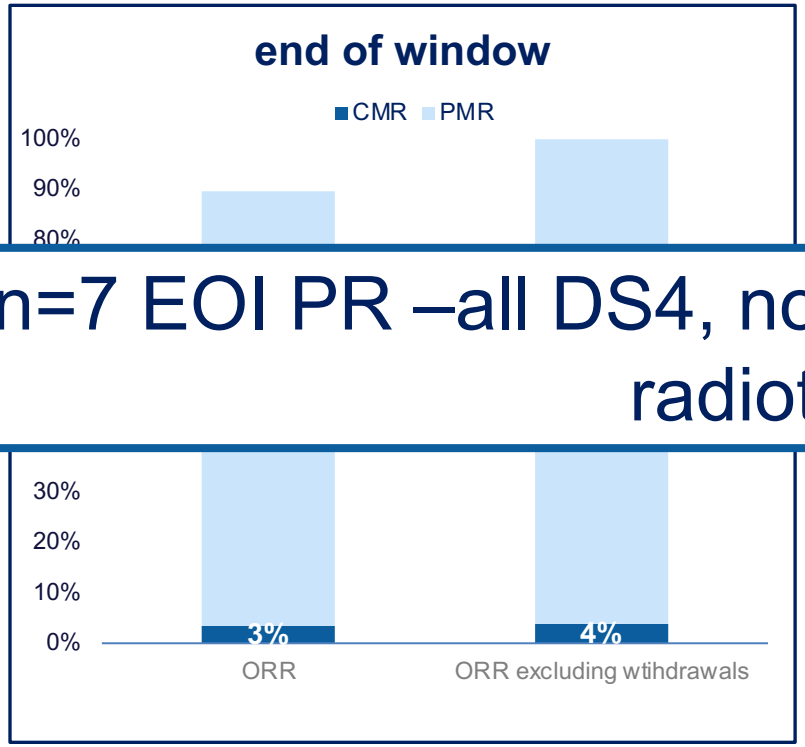


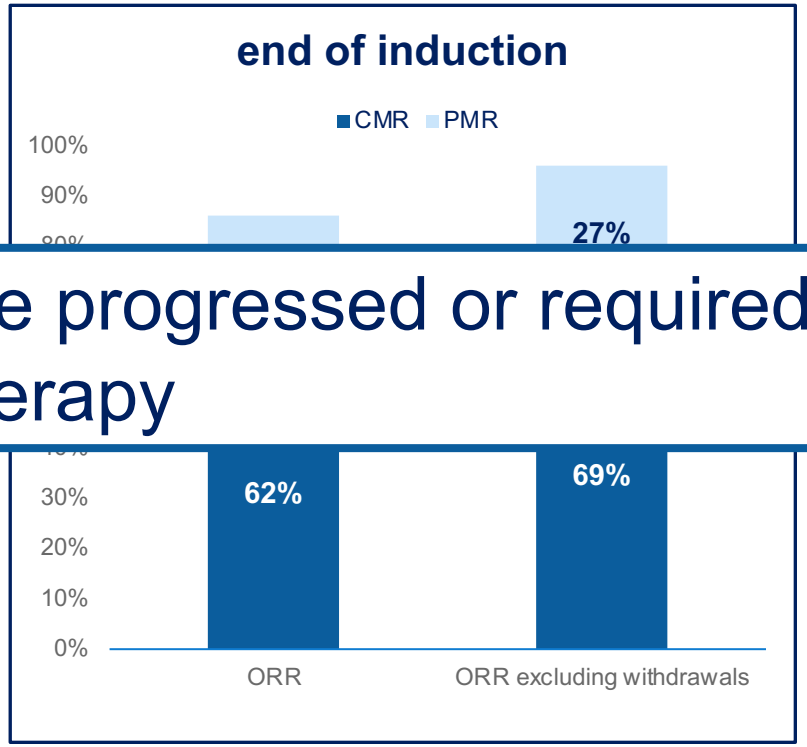
# Results: baseline patient characteristics

**n=35**

| Characteristic | Results |
|---|---|
| Median age, years (range) | 34 (19-71) |
| Female n (%) | 22 (63%) |
| ECOG performance status<br>0<br>1 | <br>25 (71%)<br>10 (29%) |
| Median baseline total MTV (range) | 447.7ml (68.0-1366.9) |
| Median baseline $SUV_{max}$ (range) | 22.7 (16.0-32.9) |
| Median baseline reporter variants (range) | 193 (46-610) |

# Results – efficacy



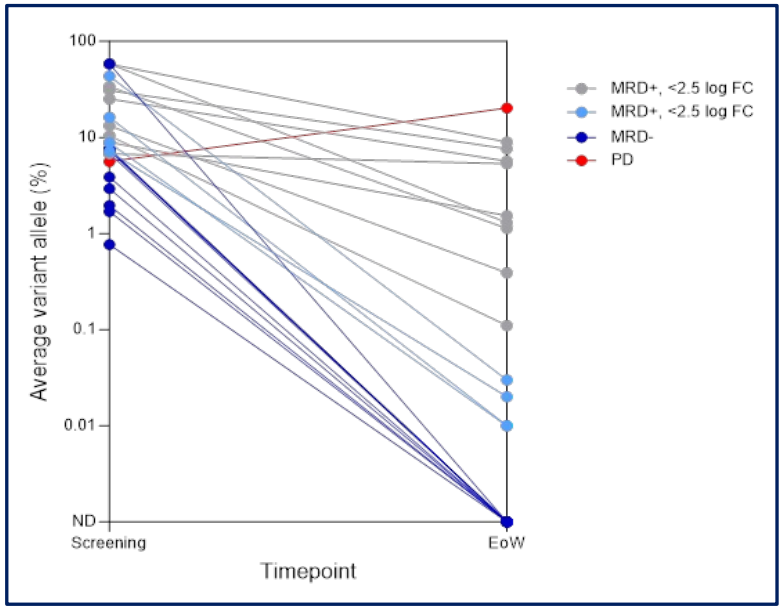




n=7 EOI PR –all DS4, none progressed or required radiotherapy

# Results: ctDNA at EOW

2 cycles of rituximab and pembrolizumab
**NO** cytotoxic chemotherapy

## 44% patients were ctDNA negative at EOW



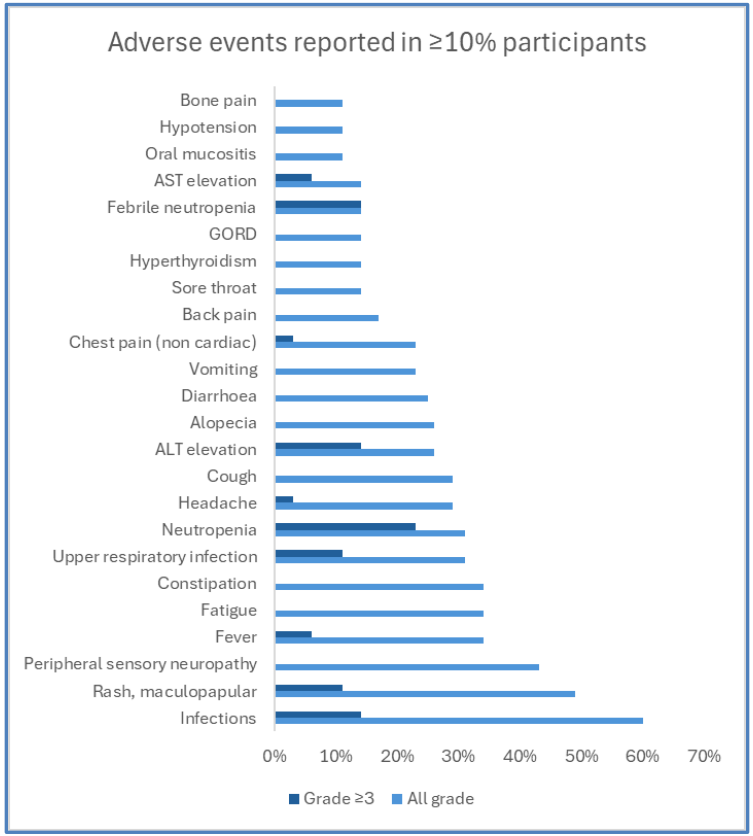

- Median VAF FC reduction (all): 2.7
- Median VAF FC reduction MRD + : 1.5



FC = fold change; VAF = variant allele frequency

# Safety: adverse events

No grade 5 adverse events



# Potential immune related adverse events (n=24)

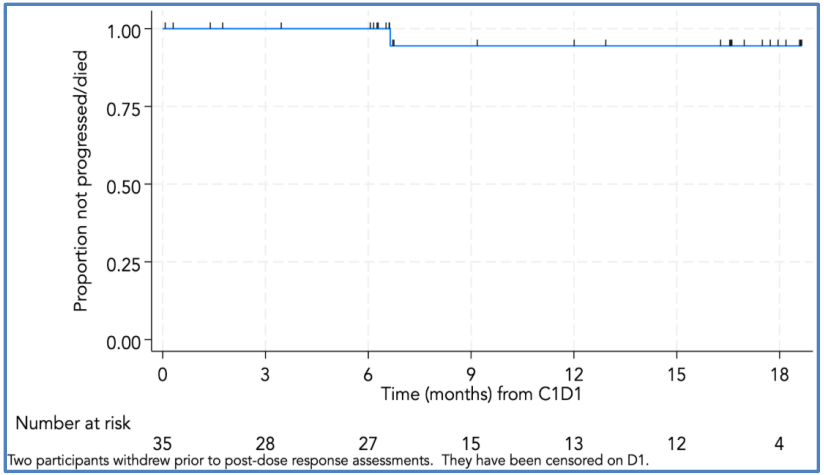
| Adverse event | All grade, n(%) | Grade ≥3, n(%) |
|---|---|---|
| Rash | 6 (17%) | 4 (11%) |
| Alanine aminotransferase elevation | 2 (6%) | 5 (14%) |
| Lipase elevation | - | 2 (6%) |
| Pneumonitis | - | 1 (3%) |
| Cystitis | - | 1 (3%) |
| Esophagitis | 1 (3%) | - |
| Hyperthyroidism | 1 (3%) | - |
| Hypothyroidism | 1 (3%) | - |

# Immune related adverse events leading to pembrolizumab discontinuation (n=5)

| Adverse event | Grade | Timing of onset | Timing of pembro discontinuation | Clinical course |
|---|---|---|---|---|
| Pneumonitis | 4 | Window (C1D11) | Post C1 | Fever, rash, hypotension, respiratory failure, ground glass changes in lungs. Steroids, IVIG, Toci. Resolved. |
| Cystitis | 3 | Consolidation | Post C10 | Symptomatic cystitis. Ongoing |
| Lipase elevation | 3 | Consolidation | Post C9 | Asymptomatic enzyme elevation, treated with steroids. Resolved |
| Lipase elevation | 3 | Consolidation | Post C12 | Asymptomatic enzyme elevation. Resolved |
| Esophagitis | 2 | Induction | Post C10 | MH-NSAID induced gastritis, recurrent symptoms during induction with FDG uptake EOI PET; gastroscopy lymphocytic esophagitis histologically. Resolved |

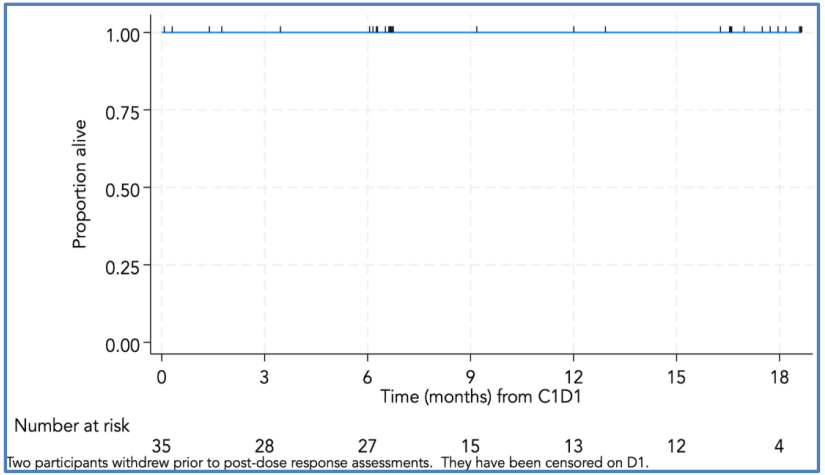
# PFS and OS

## Progression free survival



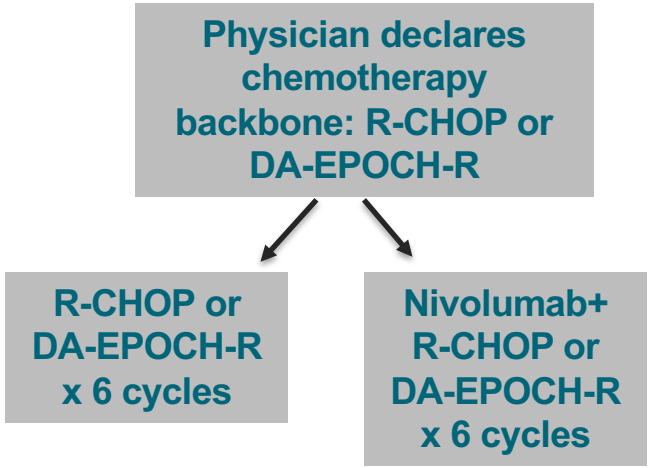

Median follow up 6.7 months

## Overall survival




Median follow up 8.9 months

# COG ANHL1931: Randomized phase III trial evaluating nivolumab in primary treatment of PMBCL




**Consolidative RT permitted only in the following circumstances:**

1) Physician declares R-CHOP + RT regardless of EOT imaging
2) + biopsy at EOT

Will be open NCTN wide
No age restriction

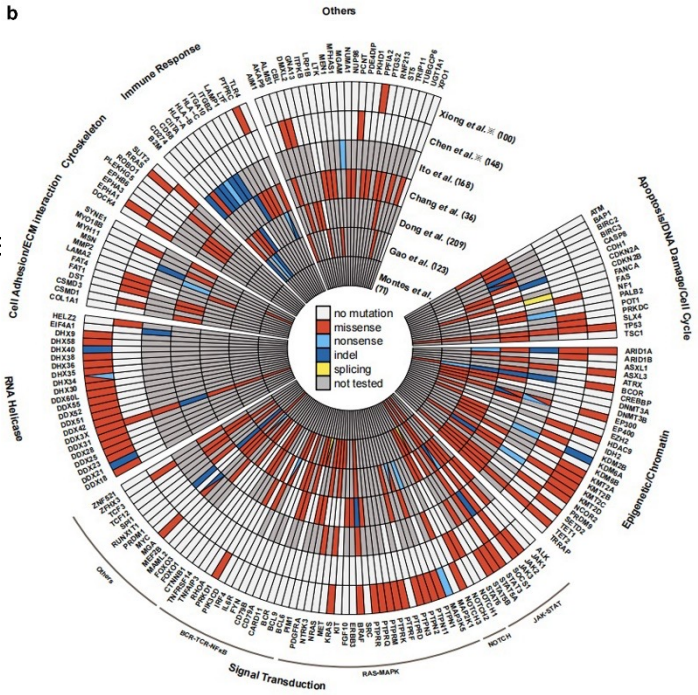
Primary Endpoint: PFS

# CPI in PMBCL

- Active in relapsed/refractory disease
  - Appears superior to historical results with chemotherapy
  - CPI/BV could be used prior to CAR-T/ASCT as bridging or salvage
- Primary treatment data show feasibility
  - Awaiting results of RCT – suspect this will be practice changing given biology and single agent activity

# ENKTCL

- Arises from NK or cytotoxic T cells
- Predilection for East Asian and indigenous South/Central American populations, accounting for 28.6%–31% of T/NK lymphomas in Asia, but only 8% in Europe and North America
- Majority present with nasal disease involving the upper aerodigestive tract.  Other extranodal sites may be common
- Strong association with EBV, which occurs in the tumour cells in a clonal episomal form and exhibits a type II latency pattern characterized by positive expression of LMP1, LMP2A and EBNA1
- More recent work has identified 3 molecular subtypes: tumor suppressor-immune modular (TSIM), MGA-BRDT (MB), and HDAC9-EP300-ARID1A (HEA) subtypes




Chan Lancet Western Pacific 2025

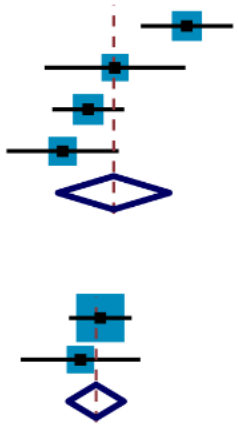
# ENKT Cell Lymphoma

- Meta-analysis of 13 studies
- 460 patients; 297 stage III-IV
- Mixture of primary treatment and relapsed/refractory disease
- N=125 treated with monotherapy; n=234 treated with combination

Yang BMC Cancer 2025

# Activity of anti-PD1 or anti-PD-L1 monotherapy

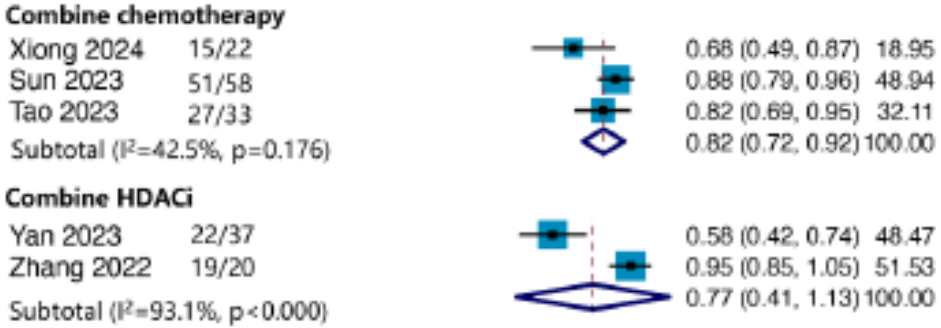
| Study | Sample size | Effect (95% CI) | % Weight |
|---|---|---|---|
| **PD-1 Monotherapy** | | | |
| Tao 2021 | 21/28 | 0.75 (0.59, 0.91) | 26.29 |
| Chan 2023 | 8/16 | 0.50 (0.26, 0.74) | 21.20 |
| Lee 2023 | 24/59 | 0.41 (0.28, 0.53) | 28.28 |
| Bachy 2023 | 7/22 | 0.32 (0.12, 0.51) | 24.23 |
| Subtotal ($I^2$=79.7%, p=0.002) | | 0.50 (0.30, 0.69) | 100.00 |
| **PD-L1 Monotherapy** | | | |
| Huang 2023 | 36/80 | 0.45 (0.34, 0.56) | 78.39 |
| Kim 2020 | 8/21 | 0.38 (0.17, 0.59) | 21.61 |
| Subtotal ($I^2$=0.0%, p=0.564) | | 0.43 (0.34, 0.53) | 100.00 |



ORR for PD-1: 50% (30-69); 1Y PFS (2 studies): 30%

ORR for PD-L:1: 43% (34-53)

# PD-1 or PD-L1 Combination studies




- ORR with chemotherapy: 82% (72-92); 1 year PFS: 74%
- ORR with HDACi: 77 (41-1.13) 1-year PFS: 91%

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# ENKT Cell Lymphoma and CPI

- Difficult to interpret – meta-analyses are only as good as the dataset
- Small trials, heterogeneity, inconsistency of reporting

BUT

- Anti-PD-1 and anti-PD-L1 antibodies appear to be active in this lymphoma
  - Prediction (ie. PD-1/PD-L1 expression, EBV etc.) is incompletely studied

What do we need?

- Well designed prospective trials to evaluate these agents
- Patient population remains challenging with poor outcomes and use of complex/intensive chemotherapy and allografting

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# NCT05700448: Gemstone 301

- A Phase III, Randomized, Double-Blind, Multicenter Study of Sugemalimab (CS1001) Plus PGemOx Regimen Versus Placebo Plus PGemOx for Subjects With Relapsed or Refractory Extranodal NK/T-Cell Lymphoma (R/R ENKTL)
- N=150
- Planned to start now?  CStone is pharma sponsor
- Aim for primary completion June 2028

# ASH 2025 Plenary: SETD2, inflammation and exhaustion

- SETD2 mutations and other DNA damaging genes are more frequent in African Americans
  - SETD2 mutations disrupt repair of AICDA-mediated DNA damage in GC B cells leading to DLBCLs with genomic instability
- Multiplex spatial proteomics (CODEX) studies demonstrated the presence of an inflamed environment enriched for exhausted CD4+ and CD8+ T cells
- In 4 independent datasets, there was enrichment of SASP (senescence-associated secretory phenotype) biomarkers of this phenotype in 70% of patients
- SASP+ lymphoma cells secrete cytokines that recruit CD4+ T cells that become exhausted and can negatively interact with CD8+ CTLs
- In preclinical models, depleting these CD4+ cells, reverses tumour growth
- In murine SETD2+ models, CPIs can induce durable responses

Shah ASH 2025

# Potential implications of this work

- Is there an “inflamed” subset of DLBCL that can be defined based on biomarkers identified from this study?
- Are they more likely to benefit from CPI (and or other immunotherapies)?
  - Requires prospective evaluation
- Is this generalizable to other lymphoma subtypes?
  - Are there other inflamed/exhausted populations to test agents in specific subsets?

# Conclusions: Evolving Role of CPI in NHL

- CPI do not demonstrate broad activity in common lymphoma subtypes
  - Newer agents beyond anti-PD-1 / anti-PD-L1 have also not appeared too promising
- CPI have activity in certain NHL subtypes
  - Identification of specific subsets that derive benefit remain challenging
- Randomized studies on the way
  - PMBCL study could change primary therapy
  - ENKTCL will better demonstrate potential value of anti-PD1 in this subtype
- The inflamed tumour environment may represent a biomarker that could inform future clinical trial design to better target immune active agents