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MEETING SUMMARY
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HIGHLIGHTS ON
DIFFUSE LARGE B-CELL LYMPHOMA

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DISCLAIMER



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**CLINICAL IMPACT OF IBRUTINIB
WITH R-CHOP IN UNTREATED
NON-GCB DLBCL CO-EXPRESSING
BCL2 AND *MYC* GENES IN THE
PHASE 3 PHOENIX TRIAL**

Johnson P, et al. ASH 2019 Abstract #354

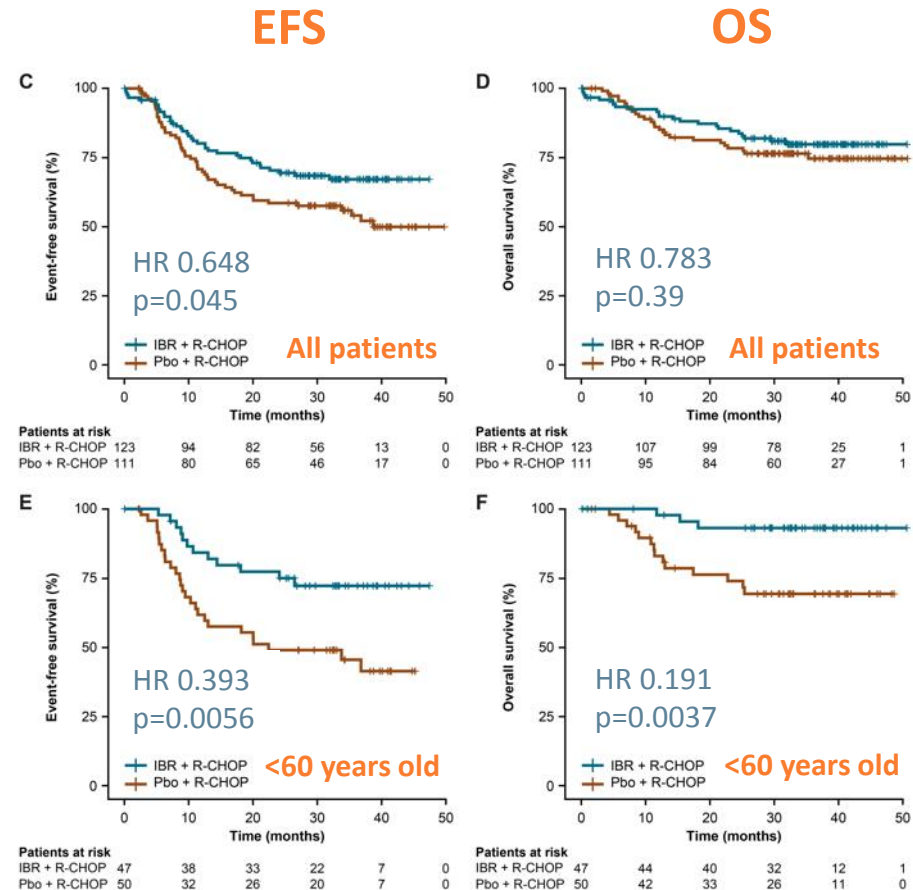
- The ITT analysis of the phase 3, double-blind, placebo-controlled **PHOENIX trial** previously showed no EFS improvement of adding ibrutinib to R-CHOP in 838 patients with non-GCB DLBCL (HR 0.934)¹
- Co-expression of *BCL2* and *MYC* by immunohistochemistry is associated with a worse outcome with R-CHOP²
- This analysis of data from the PHOENIX trial examined the **clinical prognostic effect of *BCL2* and *MYC***³
 - The median TPM values for *BCL2* and *MYC* gene expression analysed across all patients with RNAseq data (n=766) were used as cut-offs to define high and low expression rather than standard immunohistochemistry

RESULTS

- 30.5% of patients were *BCL2+MYC* high
- In the **placebo + R-CHOP arm**, ***BCL2+MYC* high** patients had **worse EFS** (HR: 1.820) **and OS** (HR: 1.662) versus those with low expression of *BCL2* and/or *MYC*
 - This is consistent with the known poor outcomes associated with these genes
- In the **ibrutinib + R-CHOP arm**, there was **no difference** between patients with high and low *BCL2/MYC* expression

RESULTS

- Patients with *MYC+BCL2* high had better EFS with ibrutinib + R-CHOP versus placebo + R-CHOP
 - Overall, there was no significant difference in OS
- Patients <60 years of age (n=97) with high expression did have an improved EFS and OS



AUTHORS' CONCLUSIONS AND CLINICAL INTERPRETATION

- In this exploratory analysis, ibrutinib + R-CHOP was associated with **improved EFS** compared with placebo + R-CHOP in patients with *MYC*-high + *BCL2*-high expression in the **ITT population** of patients with non-GCB DLBCL
 - OS was not improved in the ITT population
- In **patients aged <60 years**, both **EFS and OS were significantly better** with ibrutinib
 - No significant difference was seen in older patients (≥60 years)
- **These data suggest that the addition of ibrutinib to R-CHOP may particularly benefit patients with *MYC*-high + *BCL2*-high-expressing lymphomas**
 - This hypothesis warrants validation in other DLBCL cohorts

**PIVOTAL SAFETY AND EFFICACY
RESULTS FROM TRANSCEND NHL 001,
A MULTICENTER PHASE 1 STUDY OF
LISO-CEL IN R/R LARGE B CELL
LYMPHOMAS**

Abramson JS, et al. ASH 2019 Abstract #241

- CAR T-cell therapies have demonstrated high response rates in patients with rel/ref B-cell NHL
 - **Liso-cel** is an investigational anti-CD19, defined composition, 4-1BB CAR T-cell product administered at target doses of CD4+ and CD8+ CAR T cells
- This analysis showed long-term data from patients with **rel/ref DLBCL** treated with liso-cel in the **phase 1 TRANSCEND NHL 001 study**
 - TRANSCEND included patients with DLBCL NOS (incl. transformed from any indolent lymphoma), HGBCL with MYC and BCL2 and/or BCL6 rearrangements or PMBCL or FL3B
 - Patients were heavily pre-treated and had aggressive disease
- Liso-cel was administered at **three target dose levels**
 - 50×10^6 viable CAR+ T cells
 - 100×10^6 viable CAR+ T cells → target dose level for dose confirmation
 - 150×10^6 viable CAR+ T cells
- **Primary endpoints:** TEAEs and ORR (independent review by Lugano criteria)

RESULTS

SAFETY

- **The study met all primary and secondary efficacy endpoints**
- As outcomes were similar between dose levels, data were pooled
- 79% of patients had **grade ≥ 3 TEAEs**
 - Primarily cytopenias (neutropenia, 60%; anaemia, 37%; thrombocytopenia, 27%)
 - Four grade 5 TEAEs occurred (diffuse alveolar damage, pulmonary haemorrhage, multiple organ dysfunction syndrome, cardiomyopathy)

TEAEs of special interest, n (%)	All liso-cel treated patients N=268	
	Any Grade	Grade ≥ 3
CRS	113 (42)	6 (2)
Time to onset, median (range) days	5 (1–14)	6.5 (3–12)
NE	80 (30)	27 (10)
Time to NE onset, median (range) days	9 (1–66)	9 (2–44)
Any tocilizumab	52 (19)	
Tocilizumab alone	18 (7)	
Any corticosteroids	56 (21)	
Corticosteroids alone	22 (8)	
Both tocilizumab and corticosteroids	34 (13)	
Infections	110 (41)	33 (12)
Prolonged grade ≥ 3 cytopenia ^a	–	100 (37)
Tumor lysis syndrome	2 (1)	2 (1)

^a Prolonged cytopenias were defined as grade ≥ 3 laboratory assessments at study Day 29
CRS, cytokine release syndrome; NE, neurological events; TEAE, treatment-emergent adverse event
Abramson JS, et al. ASH 2019 Abstract #241.

RESULTS

EFFICACY

Response	Evaluable patients, n	ORR, n (%)	CR, n (%)
DLBCL cohort, all patients	225	186 (73)	135 (53)
DLBCL NOS	131	89 (68)	63 (48)
Transformed from FL	57	48 (84)	36 (63)
Transformed from indolent lymphoma	18	11 (61)	7 (39)
PMBCL	14	11 (79)	7 (50)
HGBCL	33	25 (76)	20 (61)
FL3B	2	2 (100)	2 (100)
Age ≥65 years	107	83 (78)	65 (61)
LDH ≥500 U/L	57	36 (63)	23 (40)
SPD ≥50 cm ²	69	43 (62)	23 (33)
Chemosensitive	85	66 (78)	46 (54)
Chemorefractory	170	120 (71)	89 (52)
Received prior HSCT	87	68 (78)	55 (63)
Received bridging therapy	150	101 (67)	67 (45)

- Efficacy after a median follow-up of 10.8 months
 - Median **duration of response** was 13.3 months (95% CI, 8.2-NR)
 - Median **PFS** was 6.8 months (95% CI, 3.3-11.8)
 - Median **OS** was 19.9 months (95% CI, 10.9-NR)

AUTHORS' CONCLUSIONS AND CLINICAL INTERPRETATION

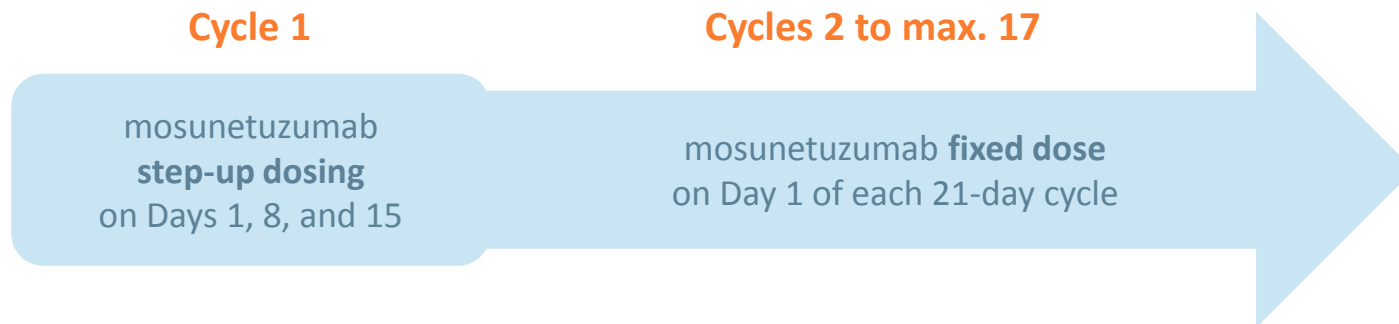
- Liso-cel demonstrated **durable clinical activity in rel/ref high grade B-cell NHLs across histologic subgroups and those with poor prognosis** including patients who were refractory, elderly, comorbid and/or had high tumour burden
 - This seems to be **comparable to other approved CAR-T therapies**
- **Lower toxicity profiles suggest that outpatient deliverability** will be possible for subsets of patients

**MOSUNETUZUMAB INDUCES COMPLETE
REMISSIONS IN POOR PROGNOSIS NHL
PATIENTS, INCLUDING THOSE WHO ARE
RESISTANT TO OR RELAPSING AFTER
CAR-T THERAPIES, AND IS ACTIVE IN
TREATMENT THROUGH MULTIPLE LINES**

Schuster SJ, et al. ASH 2019 Abstract #6

BACKGROUND AND METHODS

- Patients with B-cell NHLs who are rel/ref to CAR T-cell therapies have poor prognosis with limited treatment options
- Mosunetuzumab is a humanised IgG1 antibody targeting CD3 (on T cells) and CD20 (on B cells)
- **GO29781** is an ongoing open-label, multicentre **phase 1/1b** dose escalation and expansion study with mosunetuzumab in rel/ref B-cell NHL
- At ASH 2019, data from Group B was presented:



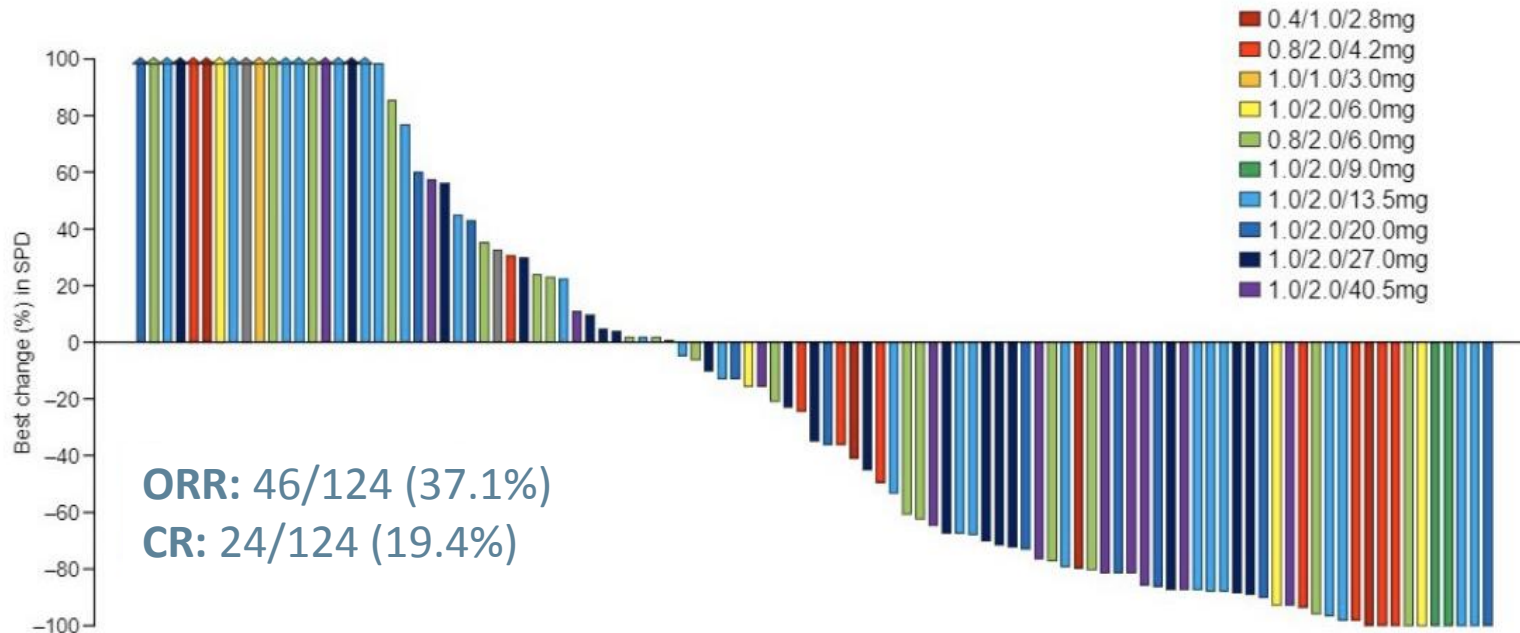
RESULTS

SAFETY

- 270 patients included, including 117 with DLBCL
 - Dose escalation is ongoing
- 95% of AEs occurred in cycle 1
 - No cumulative or chronic toxicity
- Neutropenia responded to GCSF
- Low rate of febrile neutropenia (3.3%)
- 5 fatal AEs: candida sepsis, large intestine perforation, pneumonia, volvulus and sepsis (n=1 each)

AEs, n (%)	Any grade (N=270)	Grade ≥3 (N=270)
≥1 TRAE	190 (70.4)	92 (34.1)
≥1 TRAE leading to treatment withdrawal	7 (2.6)	NR
≥1 TRAE leading to dose interruption/modification	54 (20.0)	NR
	Any grade AEs (>15% of patients)	Grade 3-4 AEs (>5% of patients)
Cytokine release syndrome	78 (28.9)	NR
Neutropenia	65 (24.1)	59 (21.8)
Fatigue	55 (20.4)	NR
Hypophosphataemia	52 (19.3)	36 (13.3)
Diarrhoea	45 (16.7)	NR
Pyrexia	44 (16.3)	NR
Headache	42 (15.6)	NR
Nausea	41 (15.2)	NR
Anaemia	NR	24 (8.9)

ORR in patients with aggressive NHL^a



- In the 30 patients who had prior CAR T-cell therapy, expansion of previously administered CAR-Ts after mosunetuzumab administration was detected
 - This is in line with the mechanism of action of mosunetuzumab

^a DLBCL, trFL, MCL, Richter's transformation, transformed MZL and FL (grade 3B)

CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle-cell lymphoma; MZL, marginal-zone lymphoma; NHL, non-Hodgkin lymphoma; ORR, overall response rate; SPD, sum of the product of diameters; trFL, transformed follicular lymphoma

Schuster SJ, et al. ASH 2019 Abstract #6

AUTHORS' CONCLUSIONS AND CLINICAL INTERPRETATION

- Mosunetuzumab has **favourable tolerability and durable efficacy** in patients with heavily pre-treated rel/ref B-cell NHL
- Preliminary data support the **possibility for re-treatment** with mosunetuzumab
- It is a particularly **promising option for patients who have not responded or progressed following CAR T-cell therapies**

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