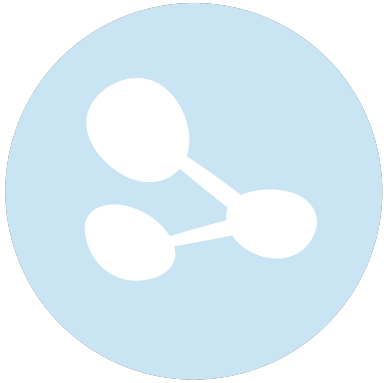

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TRANSLATING THE BIOLOGY OF DIFFUSE LARGE B-CELL LYMPHOMA INTO TREATMENT

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SELECTED HIGHLIGHTS

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January 2022

Danilov AV, et al. The Oncologist 2022;oyab004

CONFLICT OF INTEREST AND FUNDING

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The authors have received financial support/sponsorship for research support, consultation, or speaker fees from the following companies:

- **Prof. Alexey Danilov:** Research funds from Takeda Oncology, Gilead Sciences, TG Therapeutics, Bayer Oncology, Bristol Meyers Squibb, SecuraBio, Genentech. Honoraria from Genentech, Bristol-Myers Squibb, AstraZeneca, Bayer, Abbvie, TG Therapeutics, Beigene, Bristol-Meyers Squibb, Pharmacyclics, Morphosys
- **Dr. Massimo Magagnoli:** Honoraria from AstraZeneca, Sanofi
- **Dr. Matthew Matasar:** Research funds from Genentech, Roche, GlaxoSmithKline, IGM Biosciences, Bayer, Pharmacyclics, Janssen, Rocket Medical, Seattle Genetics, Immunovaccine Technologies. Stock/other ownership interests from Merck. Honoraria from Genentech, Roche, GlaxoSmithKline, Bayer, Pharmacyclics, Janssen, Seattle Genetics, Immunovaccine Technologies, Takeda. Consulting/advisory roles for Genentech, Bayer, Merck, Juno Therapeutics, Roche, Teva, Rocket Medical, Seattle Genetics, Daiichi Sankyo, Takeda. Reimbursement for travel/accommodation/expenses from Genentech, Roche, Seattle Genetics, Bayer

SUMMARY AND IMPLICATIONS FOR PRACTICE

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- Diffuse large B-cell lymphoma (DLBCL) is a **heterogenous disease** with a high relapse rate and poor outcomes in the relapsed/refractory (R/R) setting
- Assessing the **molecular profile** is fundamental to the diagnosis but can also **guide treatment decisions**
- Advanced understanding of DLBCL biology has facilitated the development of **novel drugs** in this area
- Sophisticated **classification** methods that incorporate molecular characteristics and other prognostic indicators are likely to transform the management of DLBCL and improve the outcomes for patients
- The paper provides an **overview of recent advances in DLBCL biology** and how they can be **translated into clinical care**

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STRATIFICATION OF DLBCL

- The various **clinical indices** used with the goal of risk-stratification in DLBCL, including the (revised) IPI and NCCN-IPI, do not routinely lead to a qualitative change in the chemotherapy backbone
  - Integrating molecular features into prognostic models could better characterise high-risk patients

- **Gene expression profiling** classifies DLBCL into:
  - Germinal centre B-cell-like (GCB), the most prevalent subtype
  - Activated B-cell-like (ABC)
  - Unclassified or type 3 subtype (neither GCB nor ABC)

- Suggested **alternative approaches** to classifying DLBCL include methods based on the metabolic program, stromal gene signatures and immunohistochemistry-based approaches

ABC, activated B-cell-like; DLBCL, diffuse large B-cell lymphoma; GCB, germinal centre B-cell-like; IPI, International Prognostic Index; NCCN, National Comprehensive Cancer Network

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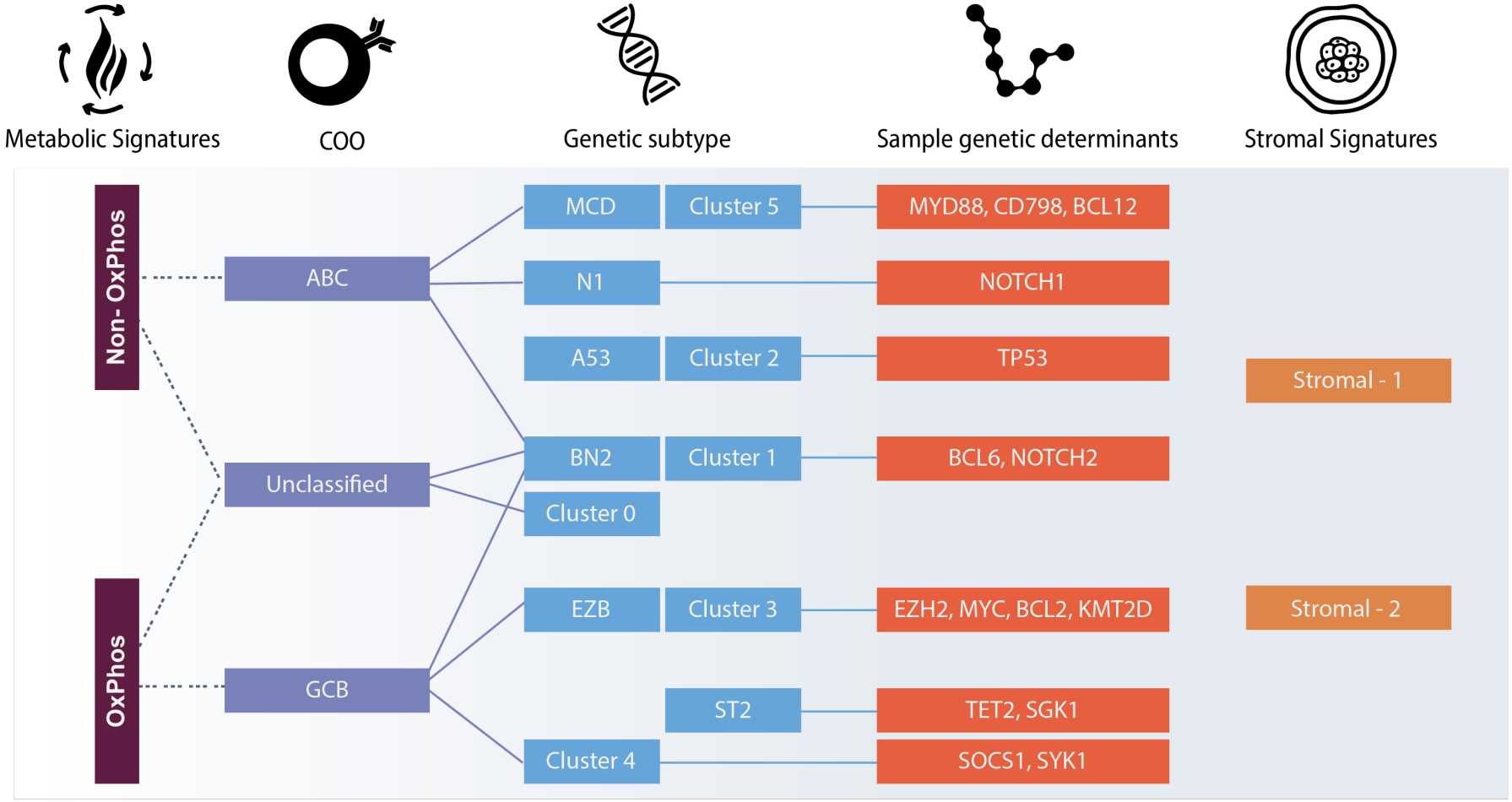
GENE EXPRESSION PROFILING-BASED CLASSIFICATIONS, NOVEL GENETIC SUBTYPE CLASSIFICATIONS AND POSSIBLE INTERFACE BETWEEN THEM



ABC, activated B-cell; COO, cell of origin; DLBCL, diffuse large B-cell lymphoma; GCB, germinal centre B-cell

Danilov AV, et al. The Oncologist 2022;oyab004. Chapuy B, et al. Nat Med 2018;24:679-90. Schmitz N, et al. J Clin Oncol 2016;34:3150-6. Wright GW, et al. Cancer Cell 2020;37:551-568 e514. Caro P, et al. Cancer Cell 2012;22:547-60; Lenz G, et al. N Engl J Med 2008;359:2313-23

CURRENT STANDARD OF CARE IN DLBCL TREATMENT

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Newly diagnosed DLBCL

- **R-CHOP** remains the standard of care
- No survival benefit of escalating therapy or other anti-CD20 monoclonal antibodies
  - Except dose-intensive R-ACVBP in patients <60 years with low-intermediate risk IPI DLBCL

Relapsed/refractory DLBCL

- **Younger, fit patients**: platinum-based salvage **chemoimmunotherapy (CIT) followed by ASCT**
- **Transplant-ineligible patients**: management tailored to the patient's tolerance
  - Poor outcomes and **high unmet need**

ASCT, autologous stem cell transplantation; DLBCL, diffuse large B-cell lymphoma; IPI, International Prognostic Index; R-ACVBP, rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; R-CHOP, rituximab, doxorubicin, vincristine, cyclophosphamide, prednisone

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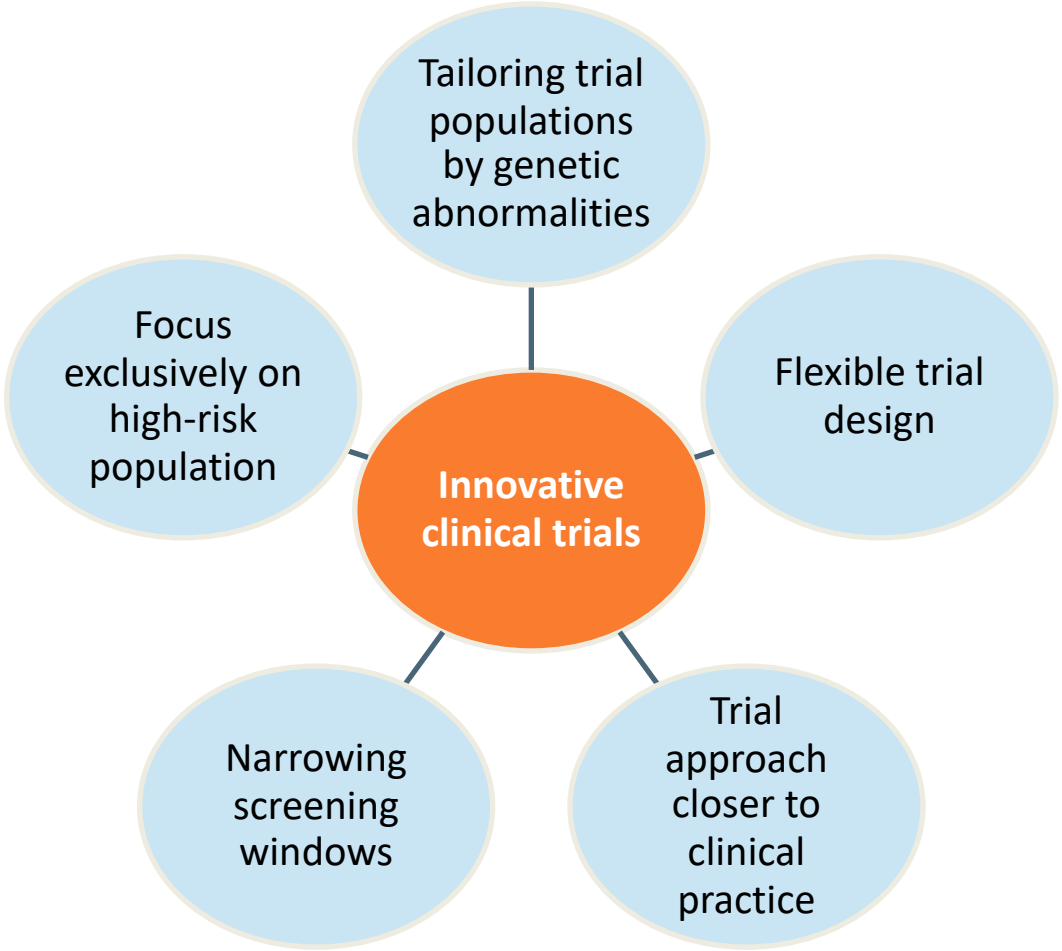
HOW TO BETTER LEVERAGE OUR UNDERSTANDING OF DLBCL BIOLOGY TO ADVANCE NOVEL THERAPIES IN FRONTLINE SETTING



DLBCL, diffuse large B-cell lymphoma

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TRACTABLE TARGETS IN GCB DLBCL[1]

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BCL2

- CAVALLI study showed promising efficacy and safety of 1st-line **venetoclax + R-CHOP or G-CHOP**[2,3]
  - Particularly in double expressors
- Randomised phase 2/3 study of 1st-line **venetoclax + CIT** in patients with MYC/BCL2 double-hit and double expressing lymphomas is ongoing (NCT03984448)

EZH2

- First-line tazemetostat + R-CHOP (**Epi-R-CHOP**) is under investigation in first line (NCT02889523)

MYC

- Oral BET inhibitor **CC-90010** is in early development in DLBCL (NCT03220347)

CDK9

- **AZ4573** is in early clinical development in DLBCL (NCT03263637)
- **A-1592668 + venetoclax** demonstrated synergistic activity *in vitro* and *ex vivo*[4]

BCL2, B-cell lymphoma 2; BET, bromodomain and extra-terminal motif; CDK, cyclin-dependent kinase; CIT, chemoimmunotherapy; DLBCL, diffuse large B-cell lymphoma; EZH2, enhancer of zeste homolog 2; GCB, germinal centre B-cell-like; G-CHOP, obinutuzumab, doxorubicine, vincristine, cyclofosfamide, prednison; R-CHOP, rituximab, doxorubicin, vincristine, cyclophosphamide, prednisone

1. Danilov AV, et al. The Oncologist 2022;oyab004. 2. Zelenetz AD, et al Blood 2019;133:1964-197. 3. Morschhauser F, et al. Blood 2021;137:600-9. 4. Phillips DC, et al. Leukemia 2020;34:1646-57

TRACTABLE TARGETS IN ABC DLBCL[1]

FRONT-LINE OPTIONS IN CLINICAL DEVELOPMENT

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BTK

- PHOENIX showed improved overall survival among patients <60 years treated with **ibrutinib + R-CHOP** vs R-CHOP alone[2]
- **Acalabrutinib + R-CHOP** is under investigation in patients <65 years (ESCALADE; NCT04529772)

Proteasome inhibitors

- In phase 2 **bortezomib** showed higher efficacy in ABC vs GCB DLBCL[3]
  - However, the phase 3 REMoDL-B trial found no significant improvement in efficacy of **bortezomib + R-CHOP** vs R-CHOP in GCB or ABC DLBCL[4]
- First-line **bortezomib + R-CHOP** is studied in phase 1/2 (ImbruVeRCHOP; NCT03129828)

PI3K-AKT pathway

- **Copanlisib**
  - First-line **copanlisib + R-CHOP** is under investigation in phase 2 (Copa-R-CHOP; NCT04263584)
  - In the R/R setting
    - **Single-agent copanlisib** showed activity in phase 2[5]
    - **Copanlisib + venetoclax** is under investigation in phase 1/2 (NCT04572763)
    - **Copanlisib + nivolumab** is under investigation (NCT03484819; NCT03884998).
- **Umbralisib**
  - In R/R DLBCL, **umbralisib + ublituximab** is under investigation in phase 2b (UNITY-NHL; NCT02793583)[6]

ABC, activated B-cell-like; AKT, protein kinase B; BTK, Bruton's tyrosine kinase; DLBCL, diffuse large B-cell lymphoma; GCB, germinal centre B-cell-like; PI3K, phosphatidylinositol-3-kinase; R/R, relapsed/refractory; R-CHOP, rituximab, doxorubicin, vincristine, cyclophosphamide, prednisone

1. Danilov AV, et al. The Oncologist 2022;oyab004. 2. Younes A, et al. J Clin Oncol 2019;37:1285-95. 3. Dunleavy K, et al Blood 2009;113:6069-76. 4. Davies A, et al. Lancet Oncol 2019;20:649-62. 5. Lenz G, et al. Leukemia 2020;34:2184-97. 6. Lunning M, et al. Blood 2019; 134: 1811-20.

TRACTABLE TARGETS IN ABC DLBCL[1]

CLINICAL DEVELOPMENT IN THE R/R SETTING

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BTK

- **Ibrutinib**
  - Ibrutinib-containing therapy can improve outcomes in non-GCB DLBCL[2]
  - **Single-agent ibrutinib** and **ibrutinib + methotrexate + rituximab** have shown promising activity in R/R CNS lymphoma[3,4]
- **Pirtobrutinib** (LOXO-305)
  - Phase 1/2 BRUIN trial showed activity in B-cell malignancies[5]
- **ARQ 531**
  - Under investigation in phase 2 (NCT03162536)

Immunomodulation

- **Lenalidomide** modestly improved response rates and progression-free survival vs investigator-choice chemotherapy6
- After the inconclusive results from the ROBUST trial[7], **R-CHOP +/- lenalidomide** is investigated in newly diagnosed double-expressor DLBCL (NCT04164368)
- **Lenalidomide + tafasitamab** showed encouraging activity in phase 2 in R/R DLBCL (L-MIND; NCT02399085)
  - Now approved for R/R DLBCL

ABC, activated B-cell-like; BTK, Bruton's tyrosine kinase; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; GCB, germinal centre B-cell-like; R/R, relapsed/refractory; R-CHOP, rituximab, doxorubicin, vincristine, cyclophosphamide, prednisone

1. Danilov AV, et al. The Oncologist 2022;oyab004. 2. Hou K, et al. Crit Rev Oncol Hematol 2020;152:103010. 3. Grommes C, et al. Cancer Discov 2017;7:1018-29. 4. Grommes C, et al. Blood 2019;133:436-45. 5. Mato AR, et al. Lancet 2021;397: 892-901. 6. Czuczman MS, et al. Clin Cancer Res 2017;23:4127-37. 7. Vitolo U, et al. Hematol Oncol 2019;37:36-7

COO AGNOSTIC THERAPIES[1]

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Antibody drug conjugates

- **Polatuzumab vedotin (Pola)[2]**
  - **Pola + BR** is approved for R/R DLBCL after ≥2 prior therapies
  - Early phase 3 front-line data of **Pola + R-CHP** seem promising (POLARIX, NCT03274492)
  - Ongoing phase 3 studies in R/R DLBCL evaluate platinum-based CIT +/- Pola
    - POLARGO (NCT04182204) is assessing **RGemOx +/- Pola**
    - PolaR-ICE (NCT04665765) is evaluating **RICE + Pola** prior to autoSCT
- **Loncastuximab tesirine** is approved in R/R DLBCL
  - It is studied in phase 2 combined **with ibrutinib** (NCT03684694)[3]

CART-cell therapy

- **Axicabtagen ciloleucel** (axi-cel) and **tisagenlecleucel** are approved in R/R DLBCL[4,5]
  - In the pivotal trials, outcomes were not associated with COO
- Ongoing trials evaluate **CART vs. platinum-based second line therapy with planned auto transplant**
  - ZUMA-7 (NCT03391466)
  - BELINDA (NCT03570892)
  - TRANSCEND (NCT02631044)

Immune checkpoint inhibitors

- **Nivolumab**
  - Results as single agent were disappointing[6]
- **Durvalumab**
  - Front-line **durvalumab + R-CHOP** showed encouraging safety and efficacy in high-risk DLBCL, including double-hit lymphoma (NCT03003520)
- **Pembrolizumab**
  - Front-line **pembrolizumab + R-CHOP** showed encouraging efficacy[7]
  - **Pembrolizumab + MK-4280**, another PD-L1 inhibitor, is under investigation (NCT03598608)

ABC, activated B-cell-like; CIT, chemoimmunotherapy; COO, cell of origin; DLBCL, diffuse large B-cell lymphoma; GCB, germinal centre B-cell-like; PD-L1, programmed death ligand 1; Pola, polatuzumab vedotin; Pola-BR, polatuzumab vedotin + bendamustine + rituximab; R/R, relapsed/refractory; R-CHP, rituximab, doxorubicine,, cyclofosfamide, prednison; R-CHOP, rituximab, doxorubicin, vincristine, cyclophosphamide, prednisone; RGemOx, rituximab + gemcitabine + oxaliplatin; RICE, rituximab + ifosfamide + carboplatin + etoposide

1. Danilov AV, et al. The Oncologist 2022;oyab004. 2. Sehn LH, et al. J Clin Oncol 2020;38:155-65. 3. Kahl BS, et al. Clin Cancer Res 2019;25:6986-94. 4. Locke FL, et al. Lancet Oncol 2019;20:31-42. 5. Schuster SJ, et al. N Engl J Med 2019;380:45-56. 6. Ansell SM, et al. J Clin Oncol 2019;37:481-9. 7. Smith SD, et al. Br J Haematol 2020;189:1119-26.

COO AGNOSTIC THERAPIES[1], CONT'D

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Bispecific antibodies

- **Blinatumomab**
  - Encouraging **single agent** results in R/R DLBCL and after front-line R-CHOP[2,3]
  - **Blinatumomab + pembrolizumab** is under investigation in R/R DLBCL (NCT03340766)
- **Mosunetuzumab**
  - Durable complete responses in phase 1[4]
- **Glofitamab**[5]
  - **Glofitamab +/- obinutuzumab** is under phase 1 investigation in R/R NHL (NCT03075696)
  - **Glofitamab + R-CHOP** is under phase 1 investigation in front line (NCT03467373)
  - **Glofitamab + gemcitabine/oxaliplatin** vs rituximab + gemcitabine/oxaliplatin in under phase 3 investigation the R/R setting (NCT04408638)

CD47 blockade

- **Magrolimab** (Hu5F9-G4)
  - Promising efficacy in R/R DLBCL in phase 1b[6]
  - Phase 2 trial of **magrolimab + rituximab** ongoing (NCT02953509)
  - Also evaluated **with other agents** targeting CD47, such as TTI-622 (NCT03530683
- Several **SIRPα inhibitors** are in development

XPO1 inhibition

- **Selinexor** is approved for R/R DLBCL
  - Based on the phase 2b SADAL study[7]

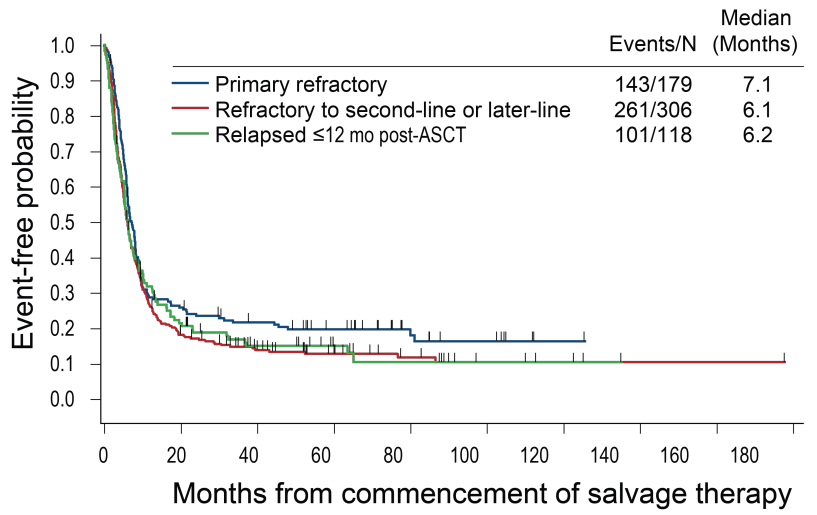
COO, cell of origin; DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma; R/R, relapsed/refractory; R-CHOP, rituximab, doxorubicin, vincristine, cyclophosphamide, prednisone; XPO-1, Exportin 1 (CRM1)

1. Danilov AV, et al. The Oncologist 2022;oyab004. 2. Viardot A, et al. Blood 2016;127:1410-6. 3. Katz DA, et al. Blood 2019;134:4077-7. 4. Schuster SJ, et al. Blood 2019;134: 6-6. 5. Hutchings 13 M, et al. J Clin Oncol 2021. 6. Advani R, et al. N Engl J Med 2018;379:1711-21. 7. Kalakonda N, et al. Lancet Haematol 2020;7: e511-e522.

FUTURE DIRECTIONS[1]

- With advanced understanding of its biology, **further parsing of DLBCL is poised to facilitate the development of novel agents** for patients with specific needs
- The fact that large phase 3 trials of novel targeted agents + CIT have been largely unsuccessful in showing improved outcomes **begs the question whether all-comer trials are still appropriate in DLBCL**
- Emerging data raise expectations for an **increasing role of genetic profiling in DLBCL**
- Informed and refined by novel classifications, prospective trials in the front-line setting might perform **molecular subtyping** during the initial cycle of R-CHOP and then **allocate patients to treatment with an appropriate targeted agent**, hence translating biology into individualised treatment

SCHOLAR-1 showed the futility of chemotherapy approaches in refractory DLBCL, highlighting the urgent medical need to improve standard of care, especially for molecularly defined subgroups at particularly high risk to exhibit resistance to first-line CIT[2]



CIT, chemoimmunotherapy; DLBCL, diffuse large B-cell lymphoma; R-CHOP, rituximab, doxorubicin, vincristine, cyclophosphamide, prednisone

1. Danilov AV, et al. The Oncologist 2022;oyab004. 2. Crump M, et al. Blood 2017;130:1800-8

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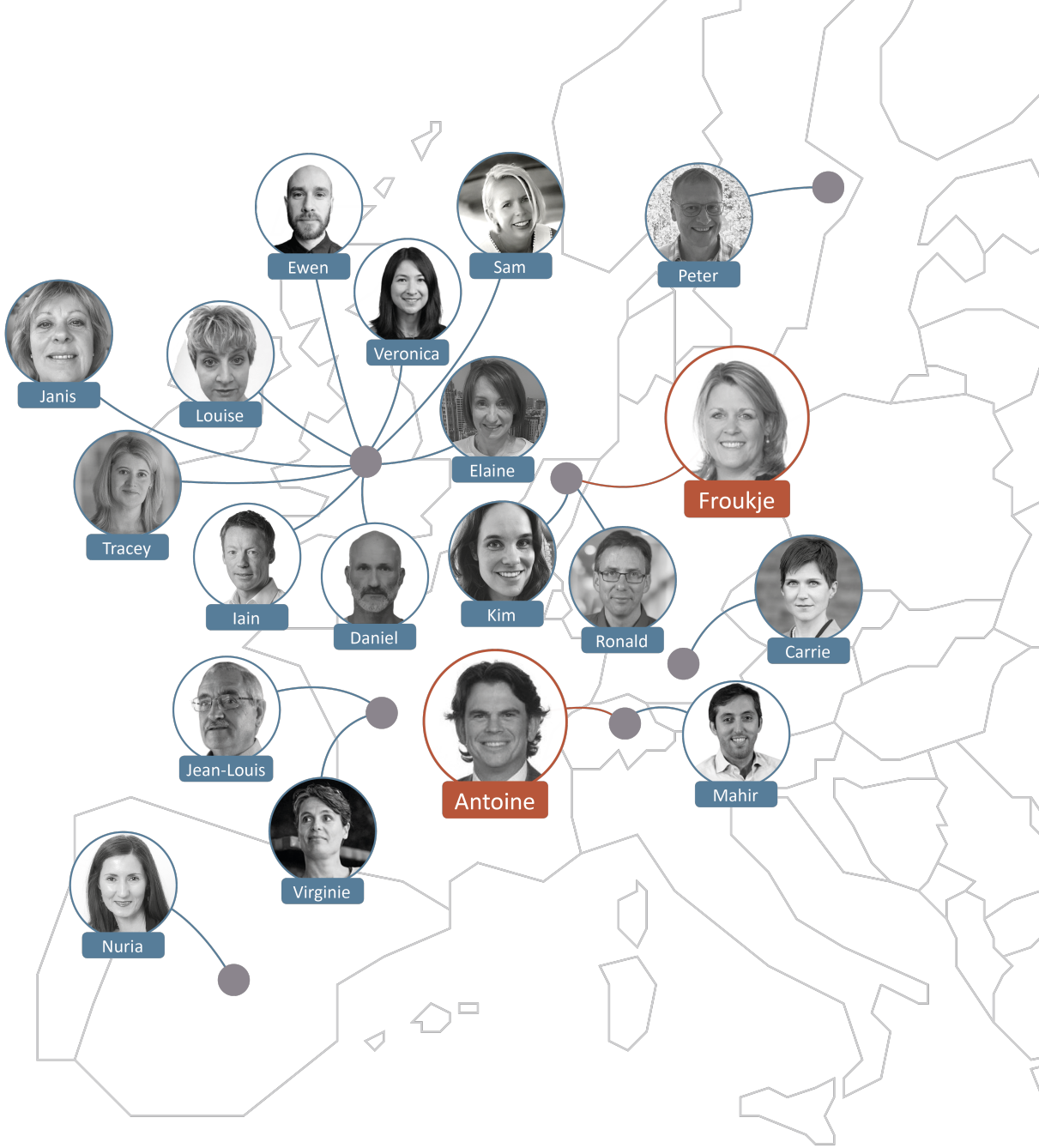

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