New and emerging Treatments in Lymphoma

Lymphoma Action Conference
12th May 2018
Dr Adam Gibb
Clinical Research Fellow- Lymphoma
The Christie

Certain slides credited to:
- CRUK
- Dr Kim Linton
- Professor Tim Illidge
The Present

2000-2016
HODGKIN LYMPHOMA
Hodgkin 10-year Survival

Age-Standardised Ten-Year Net Survival, England and Wales

[Graph showing trends in 10-year net survival for men, women, and adults across different periods of diagnosis (1971-1972 to 2010-2011).]
Hodgkin: Unmet Need

- About 20% of Hodgkin patients die within 10yr
  - 50/50 from Hodgkin/late effects of chemo or radiotherapy
- Can we make treatment less toxic?
  - PET scan enable doctors to omit radiotherapy in selected patients-
    The UK has lead the way with the RAPID and RATHL trials
Hodgkin: Unmet Need

• Can new drugs save patients with lymphoma resistant to standard chemo?

• Until recently there were no new drugs in Hodgkin in over 50 years!
Overall Survival by Time to Relapse After Transplant

90% of patients who relapse after ASCT die
71% in year 1
90% year 2
Median prognosis 1.3 years

Brentuximab vedotin

Brentuximab vedotin (SGN-35) ADC
- Monomethyl auristatin E (MMAE), potent antimicrotubule agent
- Protease-cleavable linker
- anti-CD30 monoclonal antibody

1. ADC binds to CD30
2. ADC–CD30 complex traffics to lysosome
3. MMAE is released
4. MMAE disrupts microtubule network
5. G2/M cell cycle arrest
6. Apoptosis
PET Scans: Baseline Vs C4 BV monotherapy in a chemorefractory patient
Study SG035-0003 Phase II pivotal study of brentuximab vedotin in patients with R/R HL post ASCT

R/R, relapsed/refractory; ASCT, autologous stem cell transplantation; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; IRF, independent review facility

Study SG035-0003: Improved PFS strongly correlated with PET-negative disease at Cycle 4

Median PFS: 4.8 months versus 29.2 months

PFS, progression free survival; PET, positron emission tomography; R/R, relapsed/refractory; HL, Hodgkin lymphoma; ASCT, autologous stem cell transplant

Adapted from Chen R et al. ASH 2012 (Abstract 3689)
Development of Brentuximab Vedotin

- Addition to frontline chemotherapy in advanced disease
  - ECHELON-1: A-BV-VD vs ABVD
  - Better than ABVD/less toxic than BEACOPP?
- Sparing radiotherapy in early stage disease
  - UK NCRI RADAR study
- Addition to salvage chemotherapy
  - BRAVE
  - More autologous/fewer allogeneic transplants
The future of Hodgkin lymphoma treatment 2016 and Beyond
Immune checkpoint blockade
T cell re-activation

PD-1
- Nivolumab
- Pembrolizumab
- Pidilizumab

PDL-1
- Avelumab
- Durvalumab

CTLA-4
- Ipilimumab
- Tremelimumab

Nivolumab in HL | Phase 1b (ongoing)

- N=23 pts; median age 35; 78% previous BV; 78% relapsed post ASCT; 17% EN disease
- **Nivolumab (3 mg/kg) every 2 weeks** (dose expansion cohort)
- ORR 87%; PR 70%; **CR 17%**
- PFS 86% @ 24 weeks; 6 patients (26%) bridged to alloSCT (n=5) or ASCT (n=1)

**Change in tumour burden**

- 100% clinical benefit
- 50% decrease

Pembrolizumab in HL | KEYNOTE-013
phase 1b trial

- N=31 pts; median age 32; 100% previous BV, 71% previous ASCT, 26% ineligible for ASCT
- Pembrolizumab 10 mg/kg every 2 weeks
- ORR 65% (90% CI 48-79%); PR 49%; CR 16% (90% CI 7-31%),
- PFS 69% at 24 weeks, 46% at 52 weeks; 3 patients (10%) bridged to alloSCT

90% clinical benefit

Nivolumab appears most effective in lymphomas

Amplification of chromosome 9p24.1 is a recurrent genetic abnormality in HL

1 Ansell et al, NEJM 2015; 2 Lesokhin et al, JCO 2016; 3 Weber at al, Lancet Oncol 2015 (Checkmate 037); 4 Motzer et al, NEJM 2015; 5 Brahmer et al, NEJM 2015 (Checkmate 017)
### CheckMate 205B: PFS and OS

<table>
<thead>
<tr>
<th>Event</th>
<th>Probability</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (24/80 events)</td>
<td>98.7%</td>
<td>6</td>
</tr>
<tr>
<td>OS (3/80 events)</td>
<td>76.9%</td>
<td>6</td>
</tr>
<tr>
<td>PFS rate at 6 months (95% CI)</td>
<td>76.9% (65%–85%)</td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td>Not reached</td>
<td></td>
</tr>
<tr>
<td>OS rate at 6 months (95% CI)</td>
<td>98.7% (91%–100%)</td>
<td></td>
</tr>
</tbody>
</table>

**Median follow-up (range):** 8.9 months (1.9–11.7)

**Median PFS (95% CI):** 10.0 months (8.41–NA)

High responses but apparently not curative

**Nivolumab in HL**
- Median PFS ~ 1 year

**Pembrolizumab in HL**
- Median PFS ~ 10 months

**Pidilizumab + Rituximab in FL**
- Median PFS ~ 18 months

---

Safety of PD-1 inhibitors in lymphoma

5-20% of patients affected at all grades

- Most toxicities are grade 1-2 constitutional and gastrointestinal events
- With the exception of thrombocytopenia, haematological toxicity is rare and infection rates are low
- Infusion related reactions rare
- Grade 3 or higher toxicities generally immune-related
  - Pancreas, lung, GI tract, skin, bone marrow, liver, thyroid
- Rarely severe and fatal

Pseudo-progression

Response to immune checkpoint inhibitor treatment with brief increase in tumor size (pseudoprogression)

- Pseudoprogression

Tumor Size

Activated T cells enter tumor

Start of treatment

Time

Tumor cell

T cell
Scans may initially look worse

Baseline May 2016

After 4 cycles August 2016
Patient clinically better!

After 6 cycles Sept 2016

DS 5
‘new’ left hilar node

DS 4
↓ left hilar node

Line tip!
Single Agent Activity of Novel Agents in Relapsed HL

Response rate (%)

Nivolumab
Brentuximab... GVD
Retreatment BV
Pembrolizumab
Everolimus +...
Everolimus
Panobinostat
Mocetinostat
Lenalidomide
Idelalisib
Vorinostat
SGN30

HL, Hodgkin lymphoma; CR, complete response; PR, partial response

Updated from Betlevi and Younes, Hematology Am Soc Hematol Educ Program 2013.
Relapsed and Refractory HL Combination Strategies

ADC
Brentuximab Vedotin

Immunotherapy
PD1/PDL1

Targeted Therapy
PI3Ki/mTORi HDACi

Chemotherapy
Bendamustine

HDACi, histone deacetylase inhibitors; PD1, programmed death-1; PDL, programmed death ligand; PI3K, phosphoinositide 3-kinase inhibitor; mTOR, mammalian target of rapamycin; MoAb, monoclonal antibody
Non-Hodgkin Lymphoma

- Much commoner than Hodgkin
- Diverse group of diseases:
  - Diffuse Large B-cell Lymphoma (DLBCL)
    - Commonest lymphoma in the UK
    - Aggressive
  - Follicular Lymphoma
    - Patients now living longer
The future of non-Hodgkin lymphoma treatment

2016 and Beyond
R-CHOP is the standard of care for DLBCL

- Intensified regimens not superior to CHOP in pre-Rituximab era and convincing randomised data favouring RCHOP as the standard of care for all ages and IPI scores

Fisher RI et al NEJM 1993; 328, 1002

updated results GELA study, Coiffier, 2007
Non-Hodgkin Lymphoma Survival

Age-Standardised Ten-Year Net Survival, England and Wales
Age-standardised (European) mortality rates, Non-Hodgkin lymphoma, by sex, UK, 1971-2008

- **Trials**: The years 1995 and 1998 are marked as the years when trials were conducted.
- **NICE approved**: The years 2001 and 2004 are marked as the years when NICE approved the use of Rituximab.

Rituximab is a monoclonal antibody used in the treatment of various lymphomas, including Non-Hodgkin lymphoma.
DLBCL- Treatment Failure

- Approximately 40% of patients with DLBCL will ultimately relapse following 1st line R-CHOP

- Risk-of-relapse can be stratified by the International Prognostic Index:
  - Age >60
  - Stage 3 or 4 (or advanced!)
  - Lactate Dehydrogenase > ULN
  - Performance Score >2
  - Extranodal Sites >1
Overall Survival Following R-CHOP by International Prognostic Index

- Age >60
- Stage 3 or 4
- LDH >ULN
- Performance Score >2
- Extranodal Sites >1

Ziepert et al, JCO 2010; IPI derived for 1062 RCHOP-treated patients from 3 clinical trials
DLBCL- Salvage

- This scenario was looked at in several large studies including:
  - Parma
  - CORAL
  - ORCHARRD
Parma Study

Survival in CORAL

A. Overall Survival (years)

B. Progression-Free Survival (years)

C. Event-Free Survival (years)

D. Event-Free Survival (years)

P = .4899

P = .4416

P = .0010

P = .1124
Non-Hodgkin Lymphoma: Unmet need

- Relapsed DLBCL following initial R-CHOP
  - Few survivors even with transplant
  - Many patients can’t consider transplant

- Multiply relapsed FL
  - Some patients become resistant to rituximab
  - Not everyone wants more chemo!
Unmet Need

• ~50% of IPI 3-5 pts will fail R-CHOP
• Conventional salvage followed by autologous transplant will ‘cure’ only 1 in 6 of these
• SCHOLAR-1 (r/r DLBCL then next line of tx):  
  • ORR 26% CRR 7% mOS 6.3 mo 2yrOS 20%
• There are no currently licensed efficacious agents for these pts
  • Although various ADCs look promising (loncastuximab tesirine, polatuzumab vedotin)
New Drugs in Refractory DLBCL

• Many have been tried from other types of blood cancer:
  • Lenalidomide, ibrutinib, brentuximab,

• Most have not (yet) shown promise…

• Could new directions hold the key?
  • Cellular therapy
  • NHL-specific ADCs
ADCT402

- Now known as loncastuximab tesirine
- Produced by ADC Therapeutics, Lausanne, Switzerland
- A novel anti-CD19/pyrrolobenzodiazepine dimer antibody-drug conjugate
- CD19 is ubiquitous on the cell surface of B-NHL
- PBD dimers are extremely potent cytotoxics
ADCT-402 PBD Molecular Structure

Humanized monoclonal antibody specific for human CD19 of the immunoglobulin G1 (IgG1) kappa isotype

8-polyethylene glycol

Protease-sensitive valine-alanine linker

Para-aminobenzoic acid

Maleimide
Linker component

SG3199
PBD dimer

Self-immolative group

CD19-specific IgG1

Tesirine/SG3249
PBD linker comprising the PBD dimer SG3199 and all linker components (stochastic conjugation)

Courtesy of ADC Therapeutics
ADCT-402 Mechanism of Action

ADCT-402 binds to the CD19 antigen on the tumor cell surface.

Following internalization of the ADC, the protease-sensitive linker is cleaved and the cytotoxic PBD dimer is released inside the cell.

The free PBD dimers bind in the minor groove of the cell DNA and form potent cytotoxic DNA cross-links in a sequence-selective fashion.

The cross-links result in a stalled DNA replication fork, blocking cell division and causing cancer cell death.


Courtesy of ADC Therapeutics
Pyrrolobenzodiazepine
Comparison of Free Drug Potency

Free drug potency (IC50, M)

- PBD
- Auristatin
- Calicheamicin
- Maytansine
- Taxol/Taxotere
- Daunomycin
- Doxorubicin
- Vinblastine
- Methotrexate
ADCT402-101

- Phase 1 dose escalation/expansion single-arm study in r/r B-NHL
- Opened at The Christie on 28 Feb 2017
- 1st patient dosed 24 Apr 2017
- 21 patients screened, 15 treated
  - Out of a total 155 patients treated worldwide across 12 sites
  - 70 day target achieved
  - Sponsor happy with rapid site recruitment above target
Subject 31-003 FDG-PET-CT pre/post 2 cycles ADCT402 @200mcg/kg

Active Lymphoma

Normal activity
Interim Results of ADCT402-101

Nodal Regression – All Patients*
(Best Percentage Change From Baseline)

* All efficacy assessments to date have been investigator-determined
Chimeric Antigen Receptor T-Cells

• Not dissimilar in principle to checkpoint inhibition

• Gene-engineering patient T-cells to attack tumour cells

• Complex technology still in development
Building a CAR-T

- Select tumour cell-surface antigen
  - Should be highly-expressed on tumour but minimal/no expression on healthy cells
  - Construct a CAR that will recognise/bind this

- Insert the sequence for this CAR into a retrovirus

- Transduce sequence into patient T-cells obtained by apheresis
Building a CAR-T
Two week preparatory process

T cell collection, isolation, activation (by CD3 and CD28 antibodies), CAR transduction, expansion & QC/QA process makes CAR T cells within 1–2 weeks
Anti-Lymphoma Mechanism

Cytotoxicity of CD19-specific CAR-expressing T Lymphocytes against B Cell Lymphoma

CD19-CAR T cells, which are engineered to express extracellular single-chain immunoglobulin variable fragments to CD19, linked to cytoplasmic T cell activation domains including CD3-ζ, showed remarkable therapeutic benefits toward CD19+ B cell malignancies.

Image courtesy Prof. Keiya Ozawa
Generations of CAR-T
## Clinical efficacy of 2nd generation CAR-Ts in B-NHL

<table>
<thead>
<tr>
<th>Treating institute</th>
<th>No of patients</th>
<th>Conditioning therapy</th>
<th>Infused CAR T cell dose</th>
<th>% response rate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Cancer Institute</td>
<td>4*</td>
<td>FLU (25 mg/m² × 5 days)/CY (60 mg/kg × 2 days) + IV IL2 following CAR-T cell infusion</td>
<td>0.3–3 x 10⁷/kg</td>
<td>100 0 100 0</td>
<td>Kochenderfer et al 2012. Blood 119, 2709-20</td>
</tr>
<tr>
<td>National Cancer Institute</td>
<td>11*</td>
<td>FLU (25 mg/m² × 5 days)/CY (60 or 120 mg/kg × 2 days)</td>
<td>1–5 x 10⁶/kg</td>
<td>89 56 33 11</td>
<td>Kochenderfer et al 2015. J. Clin. Oncol. 33, 540-9</td>
</tr>
<tr>
<td>National Cancer Institute</td>
<td>9‡</td>
<td>FLU (30 mg/m² × 3 days)/CY (300 mg/m² × 3 days)</td>
<td>1 x 10⁶/kg</td>
<td>67 11 56 0</td>
<td>Kochenderfer et al 2014. Blood 124, abstract 550</td>
</tr>
<tr>
<td>Memorial Sloan Kettering</td>
<td>6‡</td>
<td>BEAM conditioning and autologous SCT</td>
<td>5–10 x 10⁶/kg</td>
<td>100 100 0 0</td>
<td>Schuster et al 2014. Blood 124, abstract 3087 (+ ASCO 2015)</td>
</tr>
<tr>
<td>University of Pennsylvania</td>
<td>8‡</td>
<td>EPOCH, CY, bendamustine, FLU/CY</td>
<td>3.7–8.9 x 10⁶/kg (median 5.8 x 10⁶/kg)</td>
<td>50 38 13 0</td>
<td>Sauter et al 2014. Blood 124, abstract 677</td>
</tr>
<tr>
<td>Fred Hutchinson</td>
<td>9‡</td>
<td>Lympho-depleting chemotherapy</td>
<td>2×10⁵/kg, 2×10⁶/kg, or 2×10⁷/kg</td>
<td>67 11 56 NA</td>
<td>Turtle et al 2014. Blood 124, abstract 384</td>
</tr>
</tbody>
</table>
Licensed CAR-T

- axicabtagene ciloleucel (Yescarta™)
  - Anti CD-19
  - R/R DLBCL, PMBCL, HGBL, TFL
- Was initially developed at NCI by Steven Rosenberg
- Later licensed to Kite Pharma
Licensed CAR-T

- tisagenlecleucel (Kymriah™)
  - Anti CD-19
  - R/R acute lymphoblastic leukaemia (ALL)
- Novartis
Upcoming CAR-T Studies

- JCAR017-BCM-001
- KTE-C19-107 (ZUMA-7)
- AUTO LT1
ZUMA1: Duration of Response

- Median follow-up of 8.7 mo

Practical Issues

• CAR-T is in general safe
  • Some institutions deliver in outpatient setting

• Nevertheless ~20-30% of patients will experience serious side effects
  • Infection
  • Cytokine Release Syndrome (CRS)
  • Neurological Events (NE)
CAR-T Toxicity:
Cytokine Release Syndrome and Neurological Events

- **Neurologic:**
  - Headaches
  - Changes in level of consciousness
  - Delirium
  - Aphasia
  - Apraxia
  - Ataxia
  - Hallucinations
  - Tremor
  - Dysmetria
  - Myoclonus
  - Facial nerve palsy
  - Seizures

- **Hepatic:**
  - Transaminitis
  - Hyperbilirubinemia

- **Hematologic:**
  - Anemia
  - Thrombocytopenia
  - Neutropenia
  - Febrile neutropenia
  - Lymphopenia
  - B-cell aplasia
  - Prolonged prothrombin time
  - Prolonged activated partial thromboplastin time
  - Elevated D-Dimer
  - Hypofibrinogenemia
  - Disseminated intravascular coagulation
  - Hemophagocytic lymphohistiocytosis

- **Constitutional:**
  - Fevers
  - Rigors
  - Malaise
  - Fatigue
  - Anorexia
  - Arthralgias

- **Cardiovascular:**
  - Tachycardia
  - Widened pulse pressure
  - Hypotension
  - Arrhythmias
  - Decreased left ventricular ejection fraction
  - Troponinemia
  - QT prolongation

- **Pulmonary:**
  - Tachypnea
  - Hypoxia

- **Renal:**
  - Acute kidney injury
  - Hyponatremia
  - Hypokalemia
  - Hypophosphatemia
  - Tumor lysis syndrome

- **Gastrointestinal:**
  - Nausea
  - Emesis
  - Diarrhea

- **Musculoskeletal:**
  - Myalgias
  - Elevated creatine kinase
  - Weakness

Figure 1. CRS toxicities by organ system. After infusion of CAR T cells, CRS toxicities affecting a wide variety of organs can occur. Professional illustration by Patrick Lane ScEYEence Studios.
Concept CARs...
Summary

- Exciting new technology
- Products already licensed and being given as SoC in the US
- Major NHS initiatives are underway to partake in the pivotal late-phase studies and integrate into SoC
- Key requirements:
  - Site infrastructure + staff education/training
  - Patient selection + referral pathways
Conclusion

- Much progress in the last 10 years
- But mainly in Hodgkin and low-grade lymphoma
- Little advance beyond rituximab for DLBCL
- Is the immune system the solution to resistant lymphomas?
Thank you

• Patients and families
  • Trials rely on brave volunteers

• Charities and other fundraisers
  • Lymphoma Action, Bloodwise
  • Much basic science relies upon these monies

• Pharmaceutical Industry
  • They produce experimental drugs and fund most clinical research
"If I have seen further than others, it is by standing upon the shoulders of giants."

— Sir Isaac Newton