CAR T Applicazioni cliniche

Dr Daniele Avenoso

Consultant Haematologist

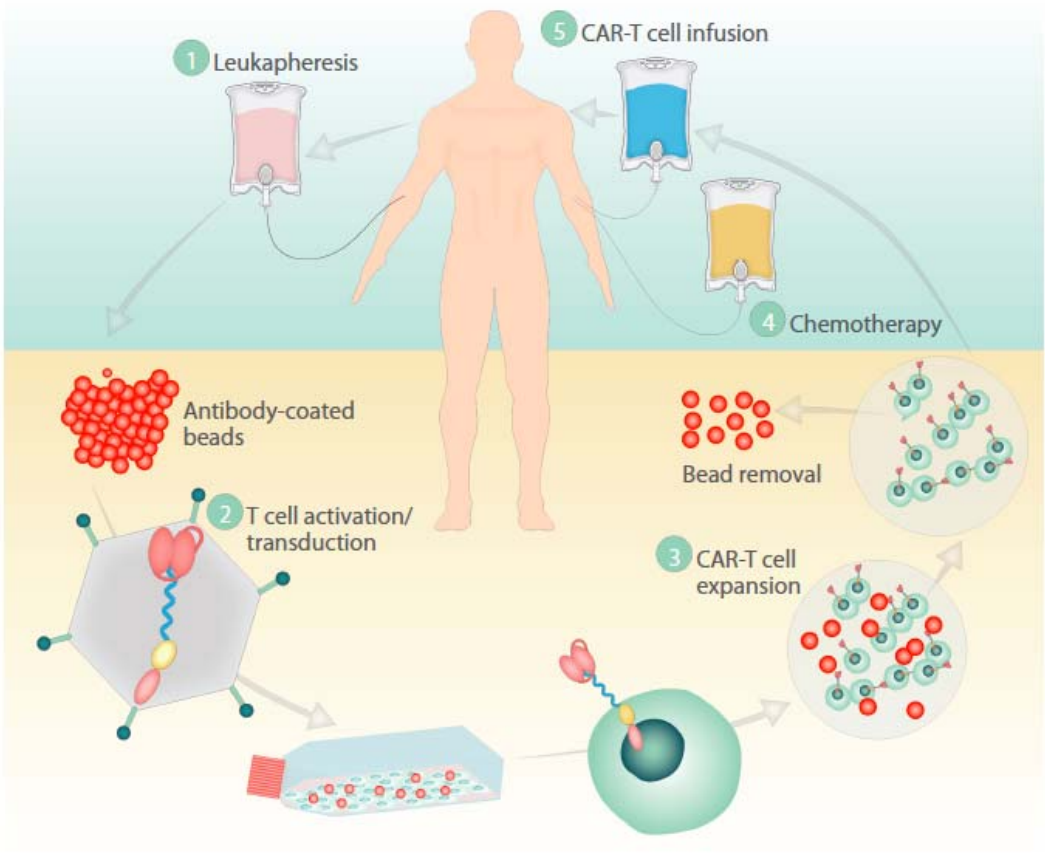
King’s College Hospital

KING'S HEALTH PARTNERS

An Academic Health Sciences Centre for London

Pioneering better health for all

Manufacturing of CAR-T



Citation: Buechner J, Kersten MJ, Fuchs M, Salmon F, Jäger U. Chimeric Antigen Receptor-T Cell Therapy: Practical Considerations for Implementation in Europe. *HemaSphere*, 2018;2:1. http://dx.doi.org/10.1097/HS9.0000000000000018

Clinical Process for CAR-T

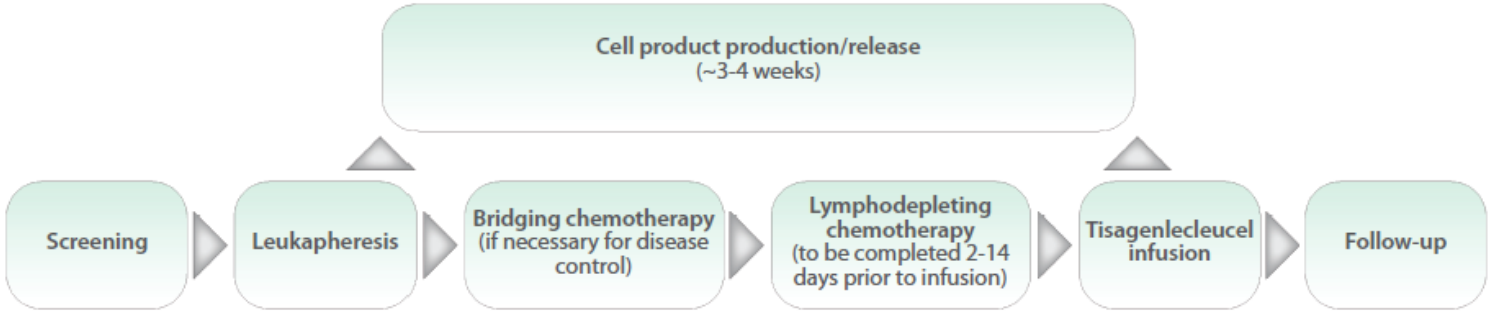
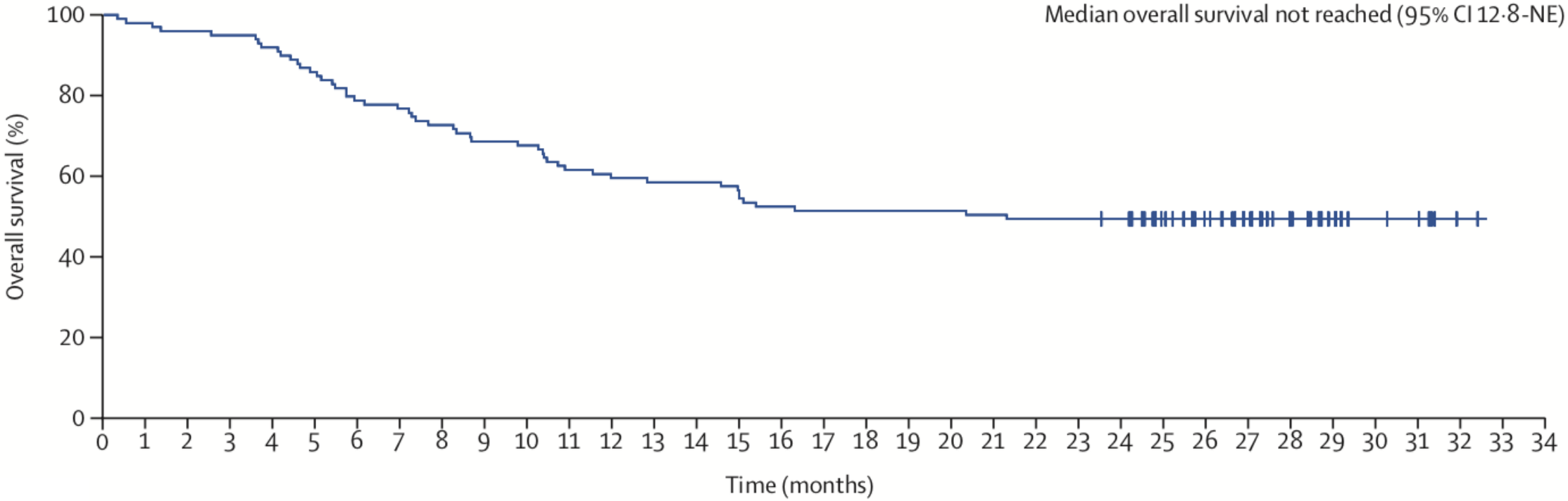


Figure 3. Clinical process flow of tisagenlecleucel therapy.

Citation: Buechner J, Kersten MJ, Fuchs M, Salmon F, Jäger U. Chimeric Antigen Receptor-T Cell Therapy: Practical Considerations for Implementation in Europe. *HemaSphere*, 2018;2:1. http://dx.doi.org/10.1097/HS9.0000000000000018

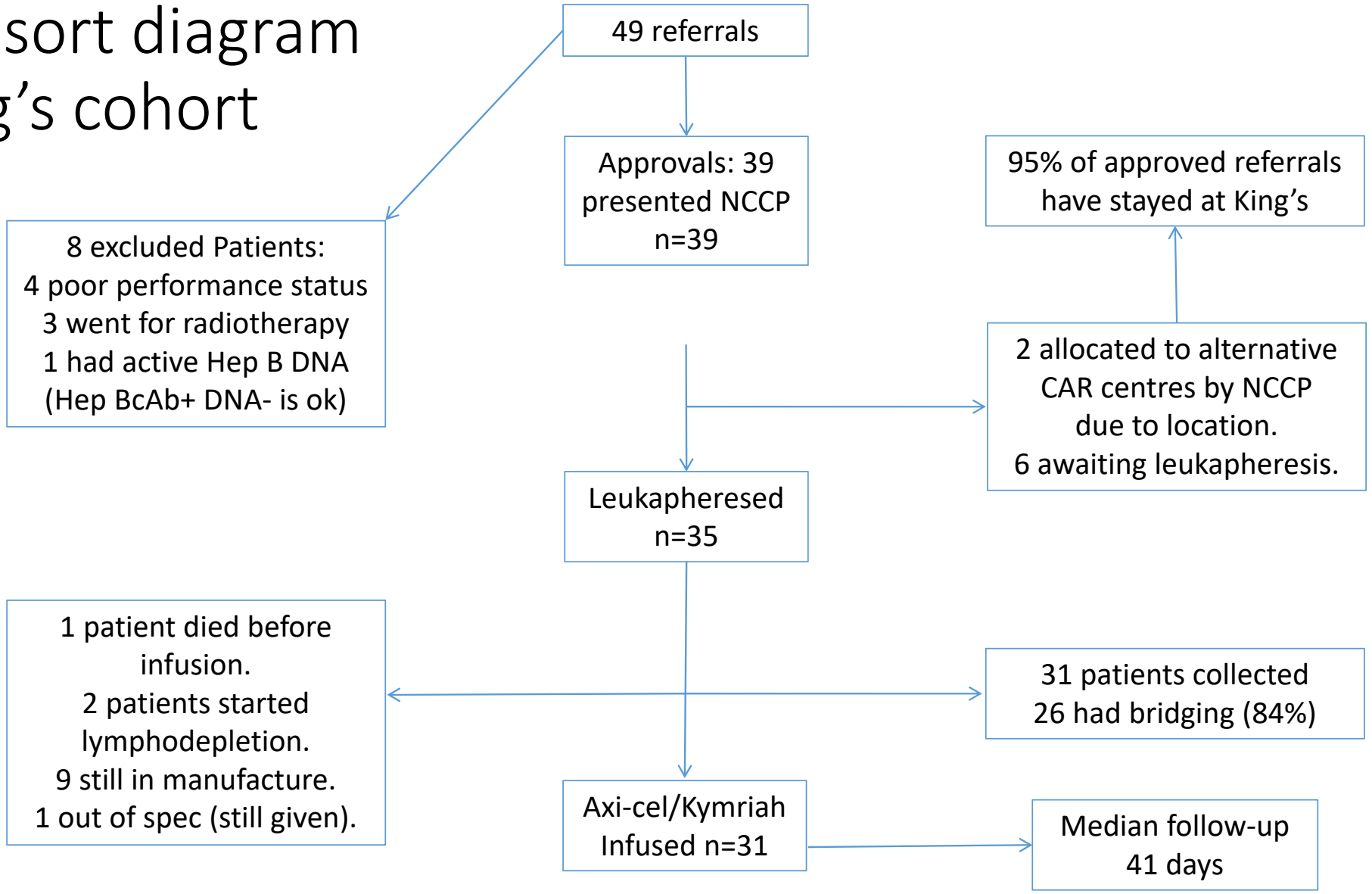
Benchmark Data: Real world vs ZUMA-1/JULIET

- Axi-cel (Yescarta™) and Tisagenlecleucel (Kymriah™) are approved in the US and EU, for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy.
- ZUMA-1 trial, 108[1] patients were treated with axi-cel:



[1]Locke et al. Lancet Oncol, 2018. [2]Schuster et al. NEJM, 2019. [3]Nastoupil et al. ASH abstract 91, 2018.

Consort diagram King's cohort

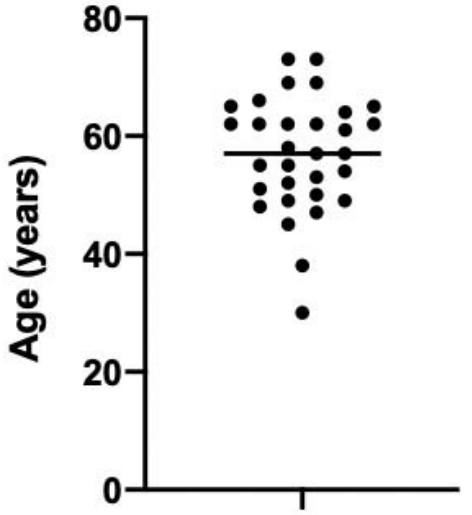


Manufacturing issues/Not infused

- 35 patients leukapheresed: 5 Tisagenlecleucel/Kymriah, 30 Axi-cel/Yescarta.
  - Manufacturing failure 0/35 = 0%.
  - Out of spec failure 1/35 = 3% (IFNg/cytotoxicity – not out of spec for ZUMA-1). Pt had grade 3 CRS and CMR at D+28.
  - Died before infusion 1/35 = 3%
- In ZUMA-1 detailed info not available but 11/119 patients were not infused.
- In JULIET 50/165 patients enrolled did not proceed after leukapheresis:
  - 12/165 due to manufacturing failure = 7%
  - 38/165 due to 'other reasons' = 23%
  - Other reasons = 16 died, 16 treating physician decided not to proceed, 2 patient decided not to proceed. All related to disease progression.
    - **Caution stricter trial criteria was likely enforced.**

Demographics – Patient characteristics

	King's Cohort	Real world axi-cel[2]	ZUMA-1[1]
Leukapheresed	35	295	119
Infused	31	274	108
Median age	57 (30-73)	60 (21-83)	58 (23-76)
>65 years (%)	23	33	25
Male (%)	68	65	68
Performance Status 0-1 (@NCCP)*	100%	81%	100%



*patient PS can deteriorate to 2 **after** leukapheresis to proceed.

[1]Neelapu, Locke et al. *NEJM*. 2017;377(26): 2531-2544

[2]Nastoupil et al. Blood, ASH abstract 91, 2018

Disease characteristics

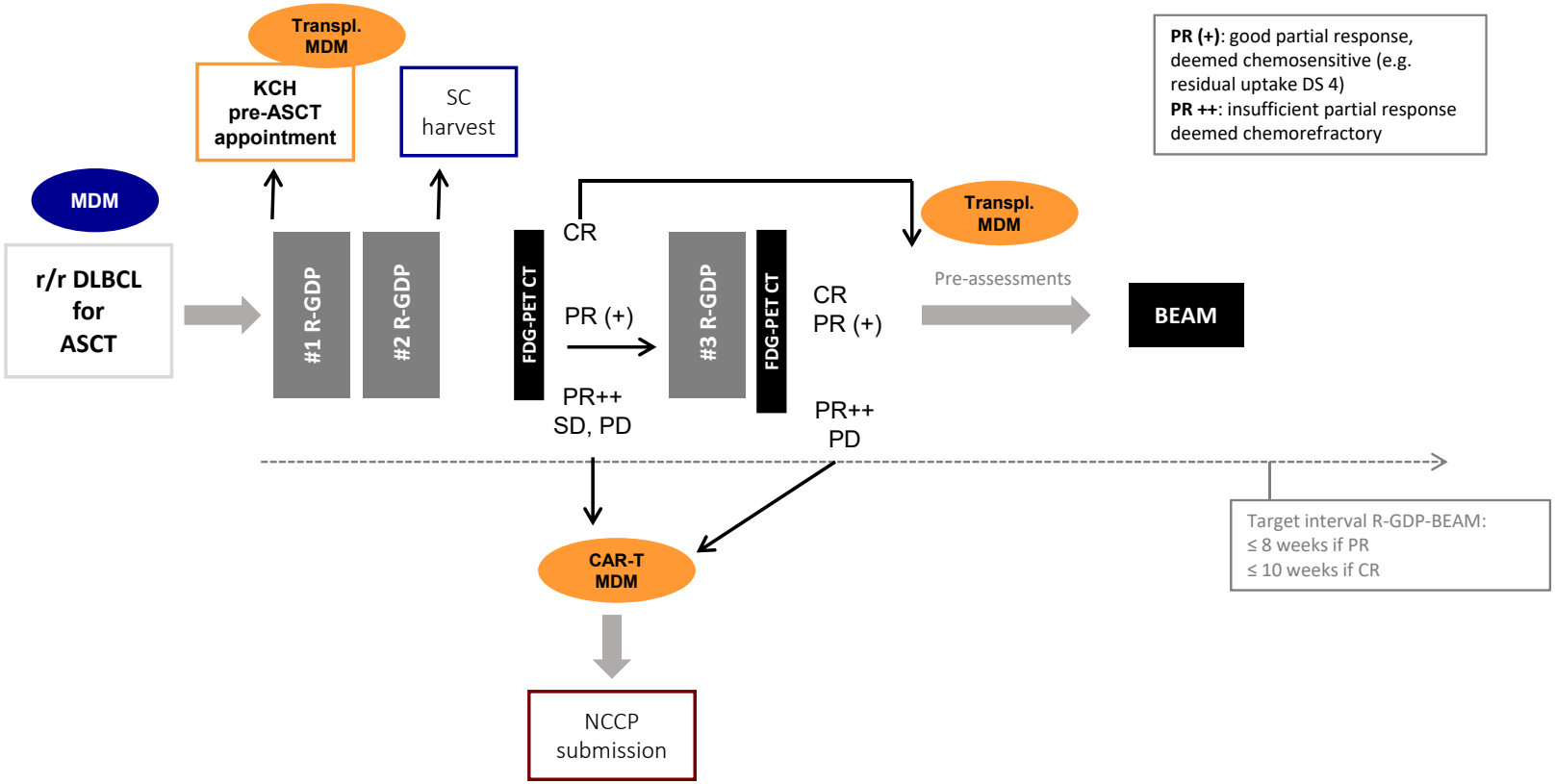
	King's Cohort	Real world axi-cel[1]	ZUMA-1[2]
DLBCL	19/31 (61%)	197 (68%)	77 (76%)
tFL	11/31 (35%)	75 (26%)	16 (15%)
PMBCL	1/31 (3%)	17 (6%)	8 (7%)
Primary Refractory	9/31 (29%)	100 (35%)	27 (25%)
Relapsed post auto	8/31 (26%)	95 (33%)	25 (33%)
Relapsed post allo	1/31 (3%)	not reported	n/a

% of leukapheresed patients.

[1]Neelapu, Locke et al. *NEJM*. 2017;377(26): 2531-2544

[2]Nastoupil et al. Blood, ASH abstract 91, 2018

Diffuse large B-cell lymphoma –
First relapse for autologous transplant



Bridging (therapy between leukapheresis and infusion)

- Overall 84% had bridging therapy

- 19 with steroids (my preference is pulses of dex not continuous prednisolone).
- 14 with chemotherapy:
  - 3x R-IVE
  - 2x R-Gem-Ox
  - 2x High dose methotrexate
  - 2x Rituximab Bendamustine
  - 2x PMiTceBo
  - 1x R-GDP
  - 1x R-CHOP
  - 1x R-ICE
- 4 with radiotherapy – plus more patients as holding pre leukapheresis.

Remember:
2 week chemo/radiotherapy free for leukapheresis.
1 week off steroids pre leukapheresis.

Most patients will need bridging. Opportunity for service development +/- national guidelines.

Safety

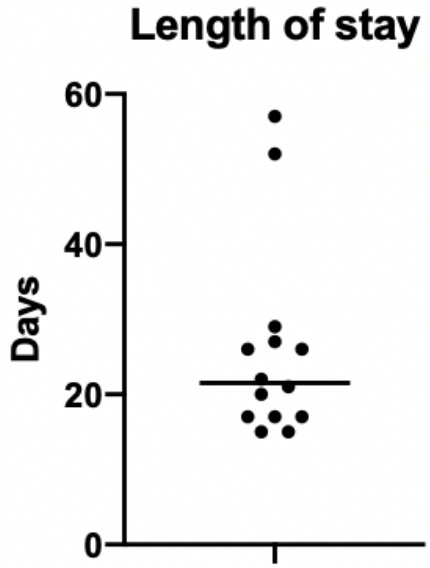
	King's Cohort	Real world axi-cel[2] n=274	ZUMA-1[1] n=108
All grades CRS (%)	18 (100%)	240 (92%)	108 (93%)
Grade ≥3 (%)	4 (22%)	18 (7%)	14 (13%)
Median time of onset		3 days	2 days
All grades ICANS (%)	4 (22%)	181 (69%)	70 (65%)
Grade ≥3 (%)	2 (11%)	85 (33%)	33 (31%)
Median time of onset		6 days	5 days
Median time to first dose of tocilizumab	5 days		

[1]Neelapu, Locke et al. *NEJM*. 2017;377(26): 2531-2544

[2]Nastoupil et al. Blood, ASH abstract 91, 2018

Hospitalization

	King's Cohort	Real world axi-cel[2]	ZUMA-1[1]
Tocilizumab usage	14/18 (78%)	63%	45%
Corticosteroid usage	6/18 (33%)	55%	29%
Median hospital stay	21 days	14 days	Not available
ICU stay (%)	6/18 (33%)	85 (32%)	Not available
Treatment mortality	0 (0%)	7* (3%)	4 (4%)
CAR related mortality	0 (0%)	2** (1%)	2 (2%)



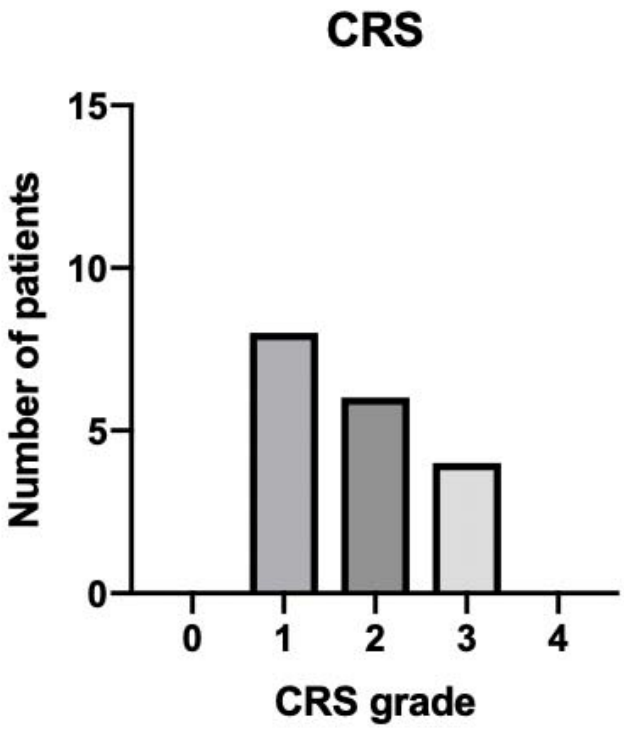
* = Infection (n=5; infection, sepsis, fungaemia, candidaemia, pneumonia).
** = HLH (n=1), cerebral oedema (n=1).

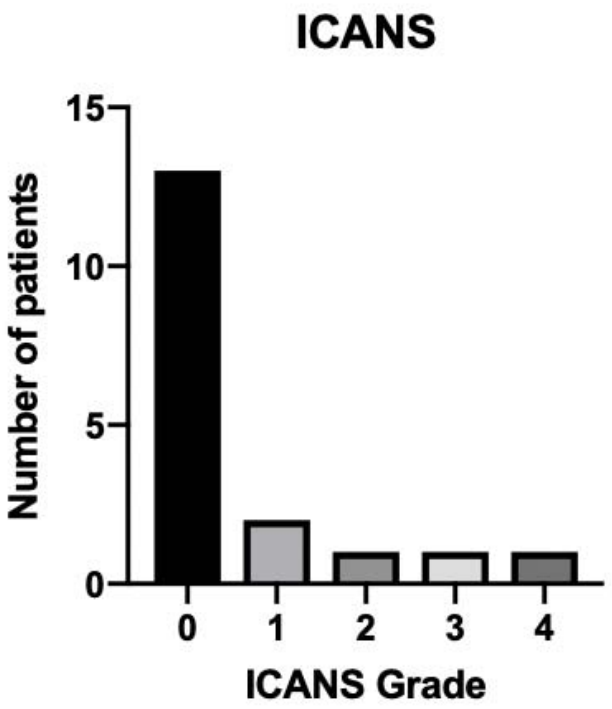
Two long length of stay patients – Secondary CNS progression post leukapheresis required CNS therapy first.
Other patient had grade 4 neurotoxicity, long ITU admission and rehabilitation on ward.

[1]Neelapu, Locke et al. *NEJM*. 2017;377(26): 2531-2544

[2]Nastoupil et al. Blood, ASH abstract 91, 2018

Cytokine Release Syndrome/Neurotoxicity





Immune effector cell associated neurotoxicity syndrome

Complications of CAR T cells

- Cytokine release syndrome (CRS)
  - Typically within 5 days and CRP best predictor
  - Exponential T cell proliferation leads to IL2, IL6, IFN
  - Can lead to macrophage activation syndrome and shock / organ failure
    - Treated with IL6 monoclonal antibodies (Tocilizumab)
      - Steroids are second line

Maude et al. Blood May 2015

Complications of CAR T cells

- Pancytopaenia (38% of patients); occasionally irreversible → allogeneic
- B Cell aplasia
  - Immunoglobulin replacement required to keep Ig > 500
- Encephalopathy
  - 6/30 patients in CTL019 ALL study
    - Unclear pathogenesis
    - Self limiting
    - No long term complications
    - CAR T cells in CSF in all patients

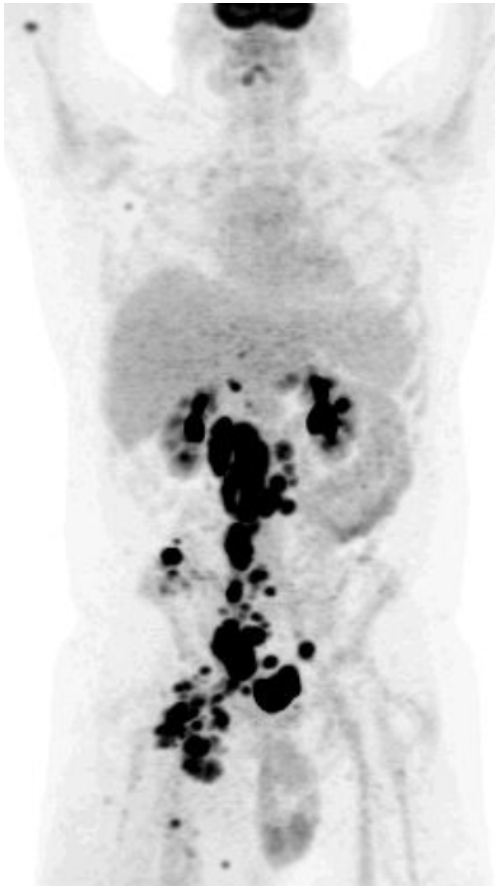
Responses (the good)

- 13 patients have had a D+28 disease assessment (11 with PET-CT).
- 7 CMR, 3 PR, 1 clinically responded, PET today.
- Best ORR 11/13 = 85% (real world 81%/ZUMA-1 83%).
- CR @D+28 is 7-8/13 = 54 or 62% (real world 47%/ZUMA-1 54%).
- In ZUMA-1 and real world data from ASH there was a proportion of patients that go from PR to CMR.

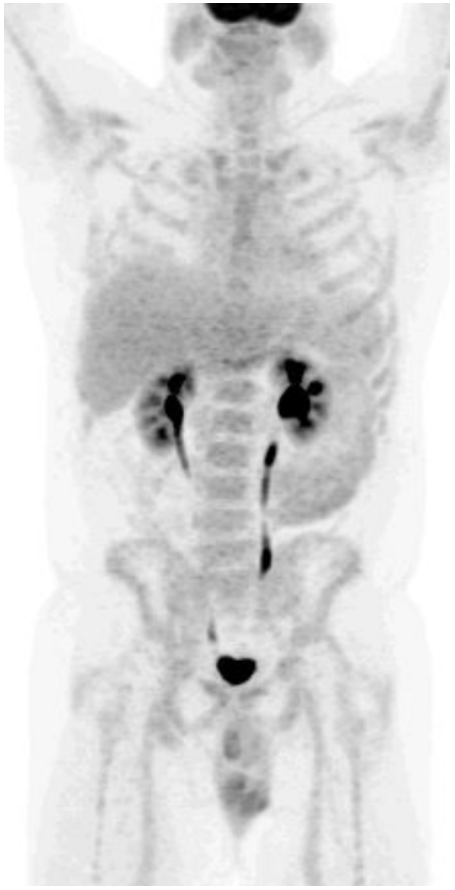
- D+100 responses are work in progress.

DLCBL – 1st patient treated in the UK

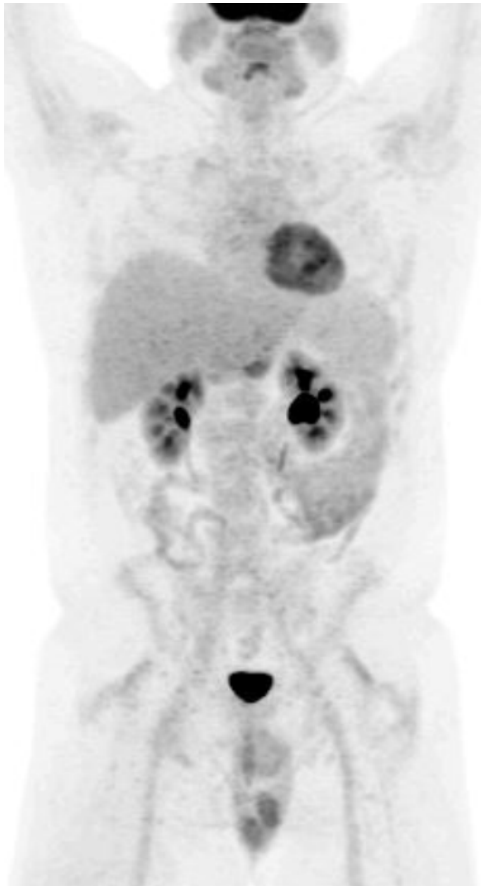
Pre CAR



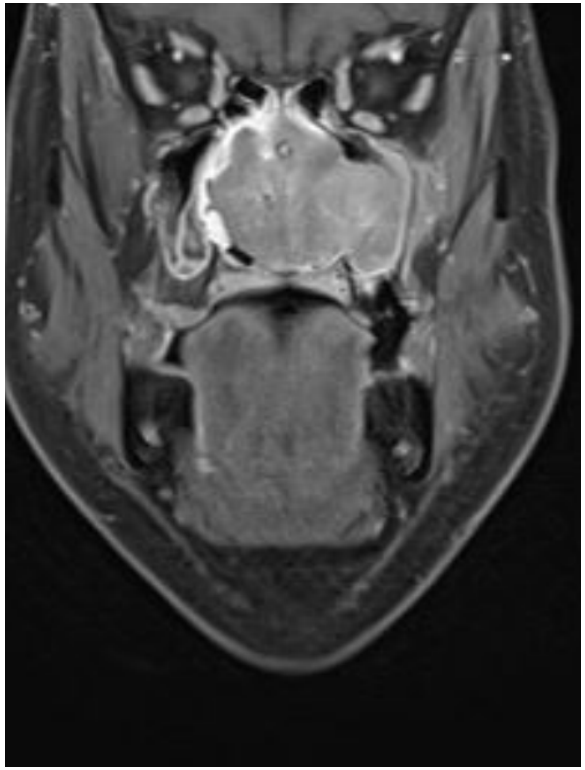
D+30



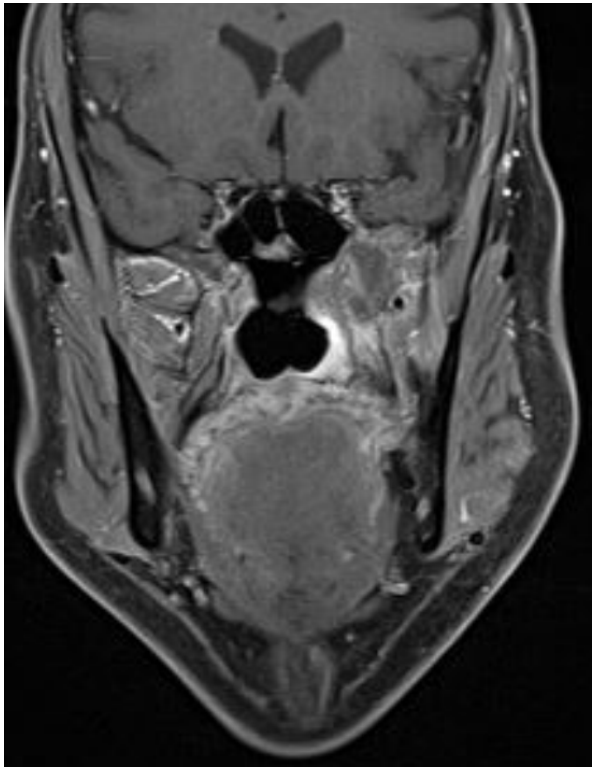
D+100



DLBCL with rhino-pharynx localisation



Pre CAR



D+30

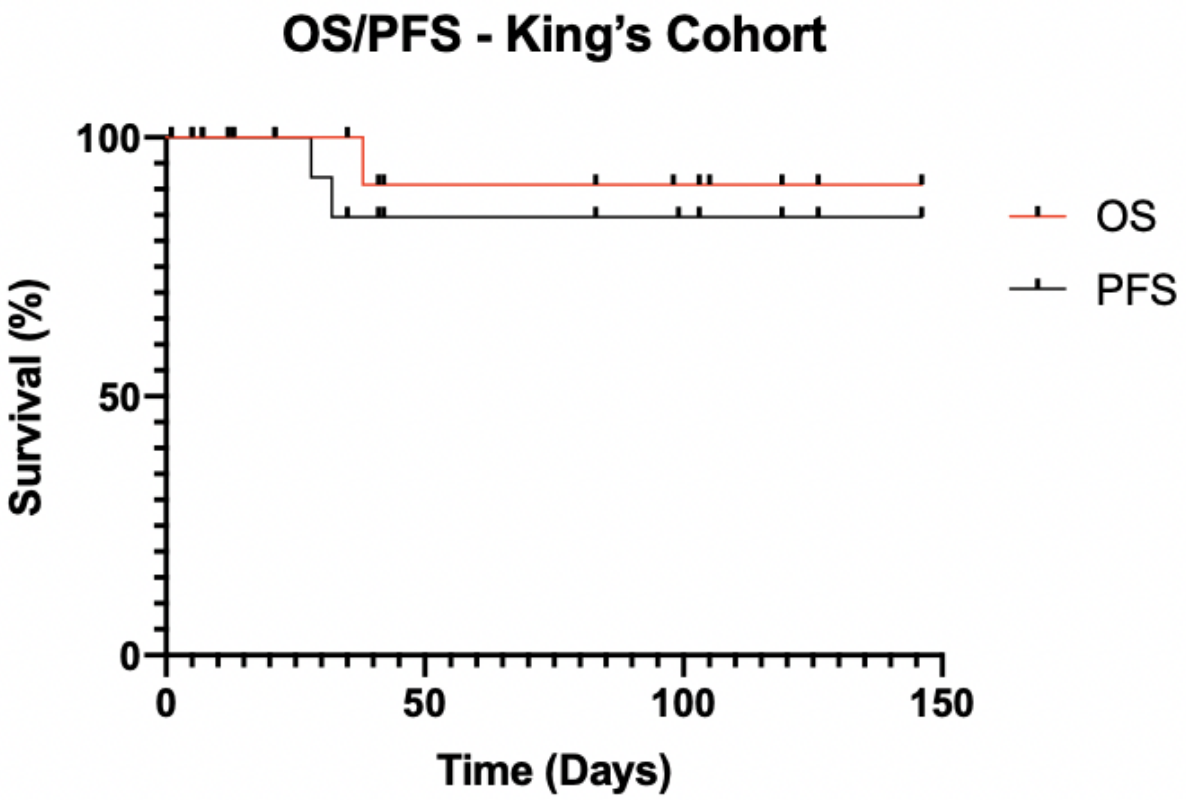
Longer follow up is needed

Responses (the bad)

- Two progressions by D+30, both were early so I would consider refractory rather than relapse.
- Both have proven to be CD19+ (implying CAR failure).
- One patient developed new CNS signs at D+21, his D+28 PET was actually CMR but with CD19+ clonal B cells in CSF. Patient is still alive being managed at local hospital.
- One patient was readmitted at D+30 with chest pain and a large pleural effusion. Flow on pleural fluid revealed CD5+CD19+ clonal B cells. Pt died at D+38.
- The CD19+/- status on progression is important data to collect.
- Double or triple hit not influence the outcome (?still small numbers ?really efficacy of CAR-T therapy

King’s Cohort 2019

- King’s has delivered this safely.
- Infused n=19
- First centre to infuse axi-cel in UK.
- First centre to infuse kymriah to a lymphoma patient in the UK.
- Only centre to have treated PMBCL.
- Performed most cases in UK (2nd largest in Europe).



KING'S HEALTH PARTNERS

An Academic Health Sciences Centre for London

Pioneering better health for all

Conclusions

- Effective in a population of R/R lymphoma
- Protean spectrum of toxicities
- Longer follow up is needed (?curative or bridge to allogeneic stem cell transplant)
- Early days for CAR-T therapy: new disease will be treated (i.e. MM or solid tumors); new CAR will be available (CAR-NK).