Plasma cell tumours - choice of systemic therapy

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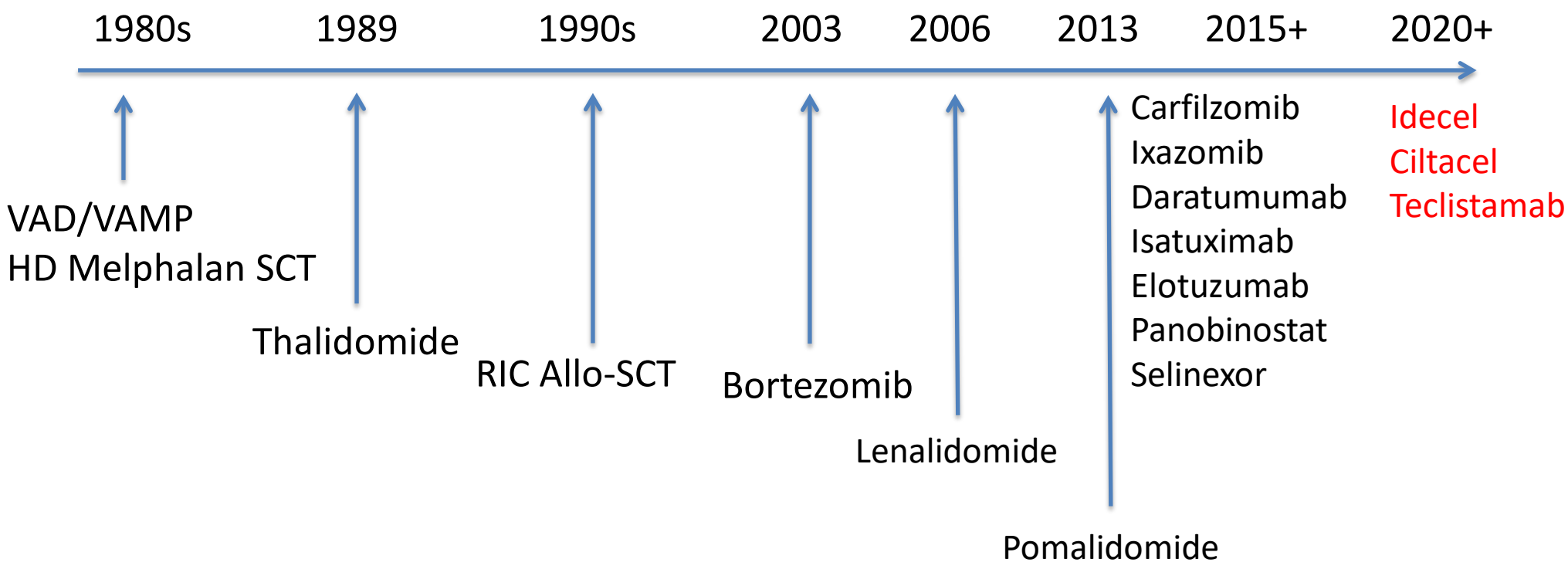
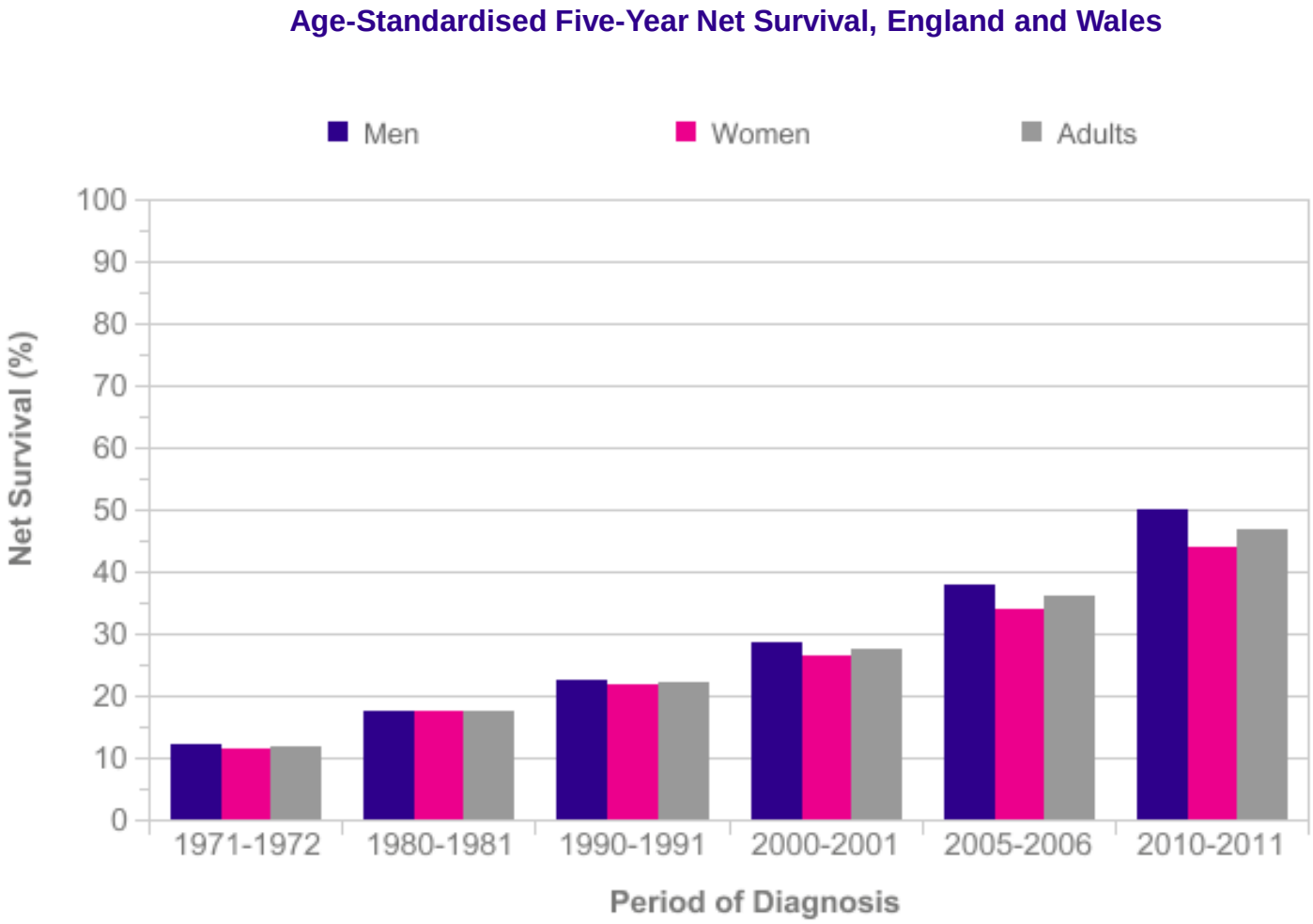
Timeline of treatment advances for MM

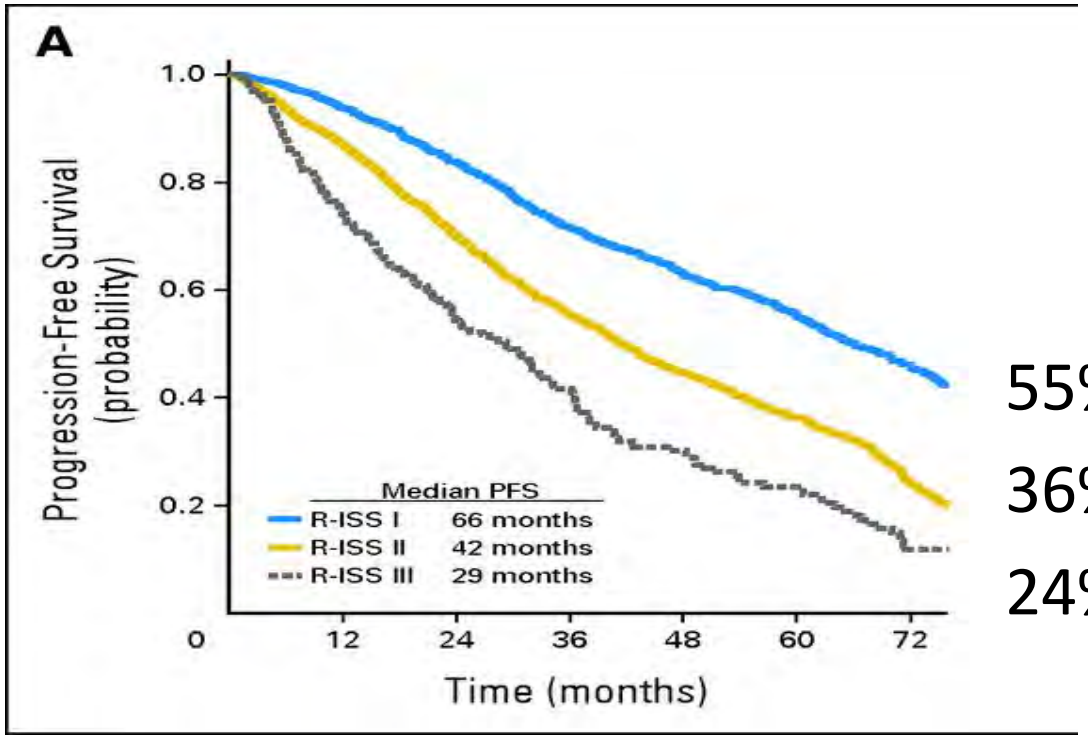


5 year overall survival in MM 1971-2011



CANCER RESEARCH UK

Myeloma outcomes based on R-ISS

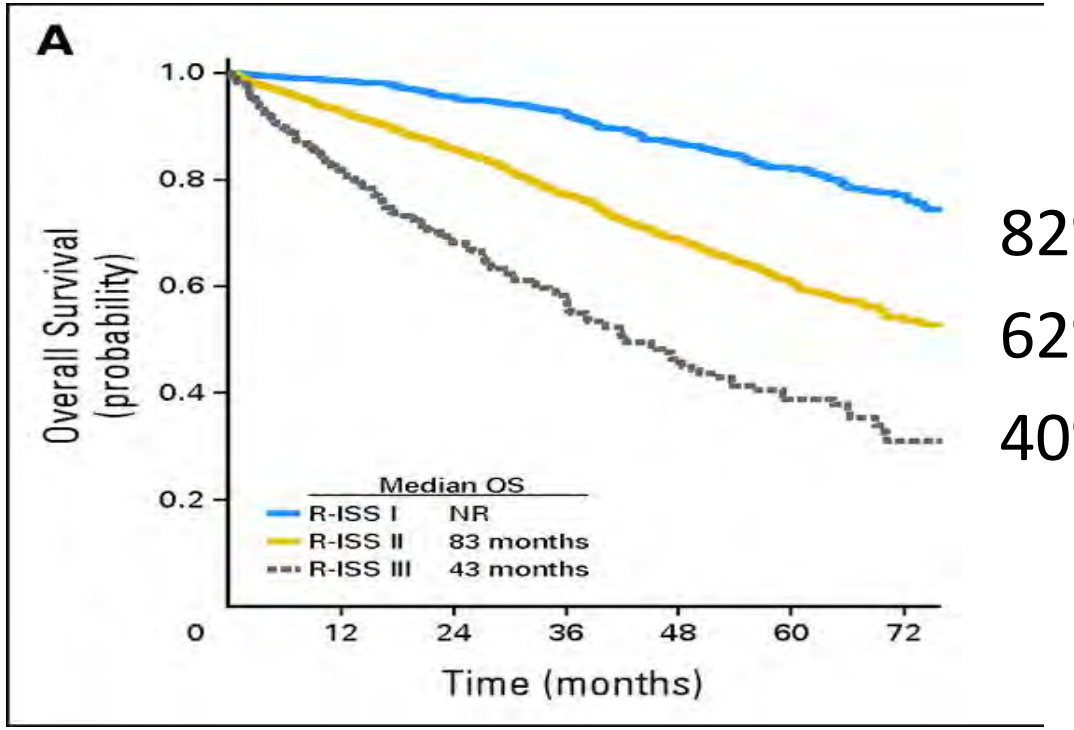


55%

36%

24%

5 year Progression free survival



82%

62%

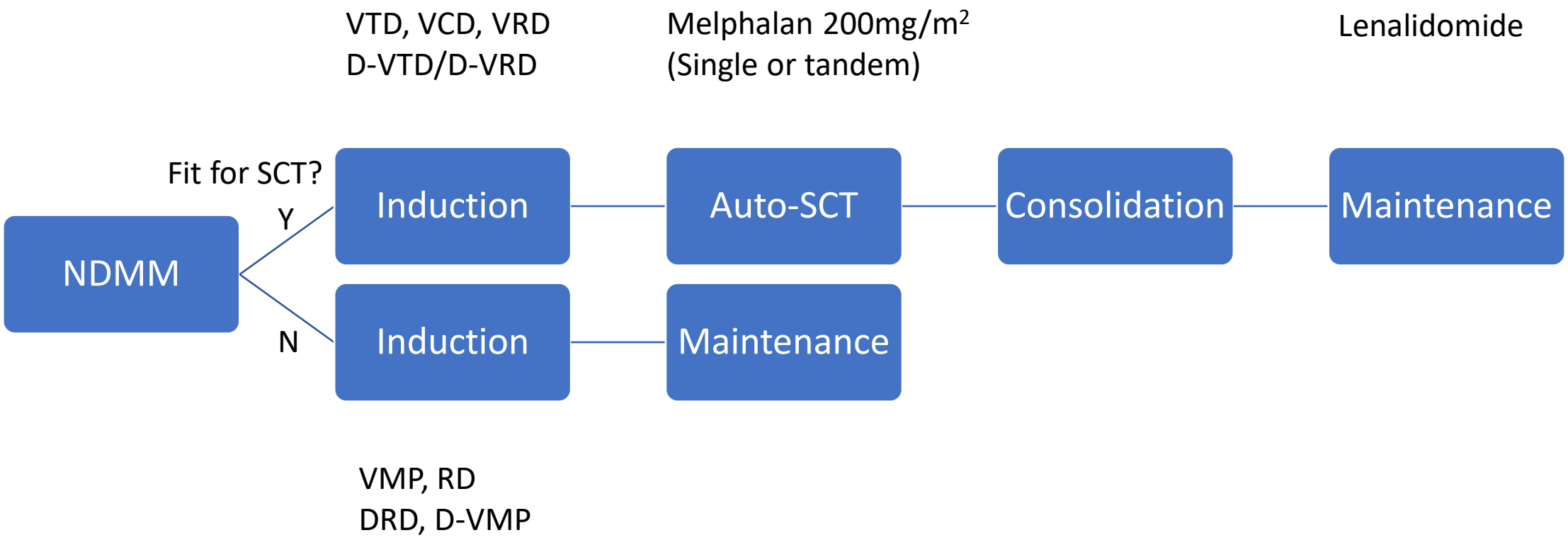
40%

5 year Overall survival

Choice of therapy in multiple myeloma

- Determined by whether patient is fit to undergo HD Melphalan Auto-SCT
- Age, Performance Status, Cytogenetic risk, Comorbidities, Organ function also considered
- Treatment consists of Induction, (Transplant, Consolidation), Maintenance phases
- Doublet, triplet or quadruplet chemo-immunotherapy regimens containing an IMiD, PI, Alkylator, Steroids, anti-CD38 antibody

Choice of initial therapy in MM



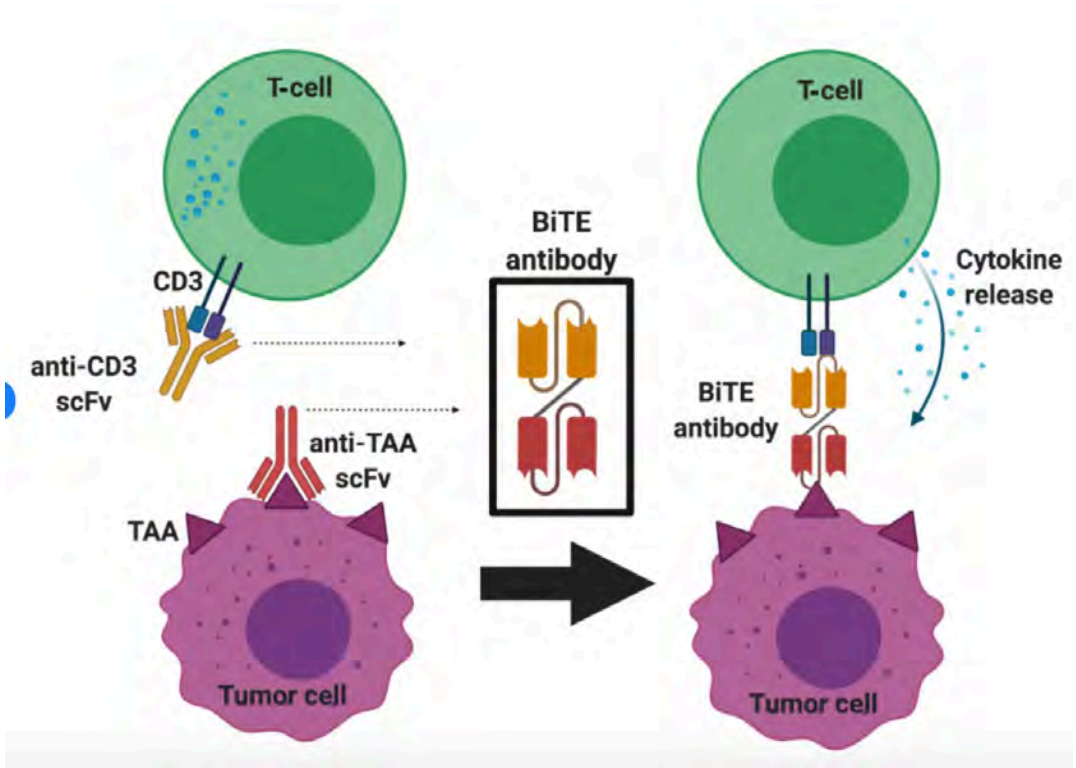
Progression free survival post treatment in MM

Line of Treatment	Regimen	median PFS
• First	VRD/Auto/Len	3-5 years
• Second	KRD, DRD, DVD	24+ mths
• Third	IRD	18-24 mths
• Fourth	IsaPomD	12 mths
• Fifth	PomD, VPanoD	<6 mths

Immunotherapy options for MM

- IMiDs - thalidomide, lenalidomide, pomalidomide
- CELMoDs - iberdomide, mezigdomide
- Monoclonal antibodies - daratumumab, isatuximab, elotuzumab
- Allogeneic SCT
- Bispecific T-cell engagers (BiTEs) - teclistamab, elranatamab, talquetamab
- CAR-T cells - idecel, ciltacel

Bispecific T-cell engagers (BiTEs)



Antibody that binds tumour and T cell

Teclistamab for RRMM

- anti-BCMA/anti-CD3 BiTE
- approved for RMM after 3 (EMA) or 4 prior lines of therapy (FDA)
- **MajesTEC-1 study**
  - N=165, median of 5 prior lines, 77% triple refractory disease
  - ORR 63%, 39% CR, 26% MRD-ve
  - median PFS 11.3 mths, median DoR 18.4 mths
  - CRS 72% (G≥3 0.6%), ICANS 3% (G1-2)
  - Infections 76.4% (G≥3 44.8%)

- Teclistamab + Dara *(TRIMM-2 study, MajesTEC-3 study)*
- Teclistamab + Dara + Len *(MajesTEC-2 study)*

Moreau et al, NEJM 2022

BiTEs for RRMM

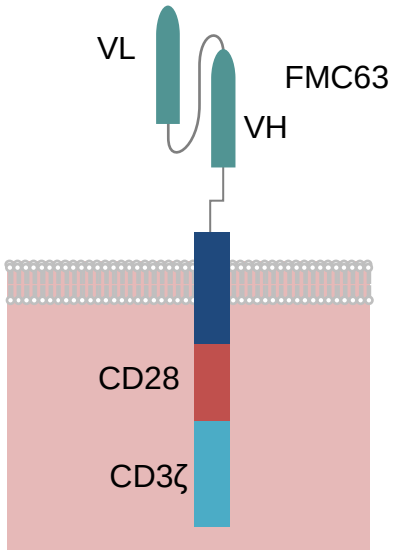
- **Elranatamab** (anti-BCMA/anti-CD3) in **MagnetisMM-2** study
  - N=123, median 5 prior lines
  - ORR 61%, CR 35%, 15 mth PFS 57%
  - CRS 57% (no G≥3), ICANS 3.4% (G1-2)
  - Infections 69.9% (G≥3 39.8%)

- **Talquetamab** (anti-GPRC5D/anti-CD3) in **MonumenTAL-1** study
  - N=232, median 6 prior lines
  - ORR 70%, median DoR 10.2 mths (405 mcg dose), CRS 77% (G≥3 3%)
  - ORR 64%, median DoR 7.8 mths (800 mcg dose), CRS 80% (G≥3 0%)
  - Skin & nail adverse events, dysgeusia

Lesokhin et al, Nat Med 2023
Chari et al, NEJM 2023

Approved CAR T cell products (FDA/EMA)

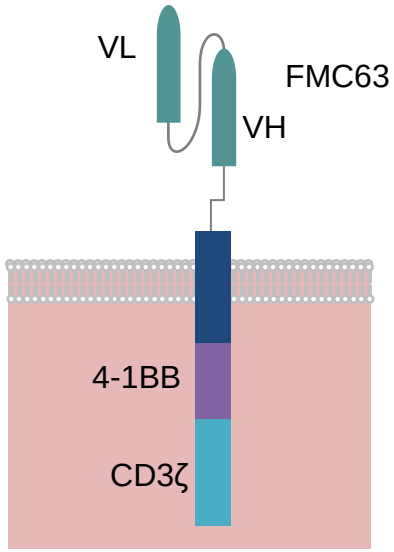
Axicabtagene ciloleucel (Kite)



Gammaretrovirus

Adult patients with R/R DLBCL and PMBCL, after ≥2 lines of systemic therapy

Tisagenlecleucel (Novartis)

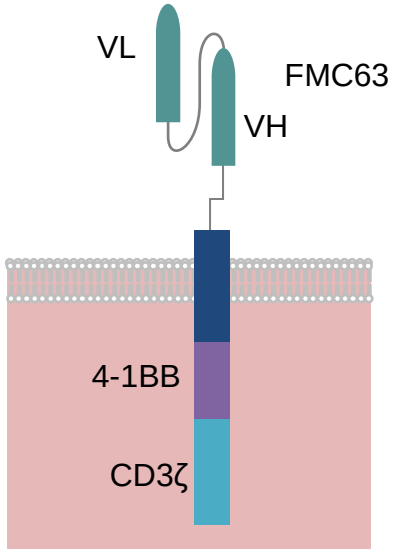


Lentivirus

Adult patients with R/R DLBCL after ≥2 lines of systemic therapy

R/R B-ALL ≤ 25yrs

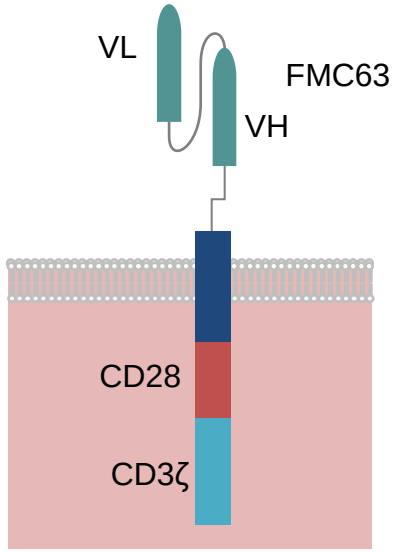
Lisocabtagene maraleucel (BMS)



Lentivirus

Adult patients with R/R DLBCL after ≥2 lines of systemic therapy

Tecartus (Kite)

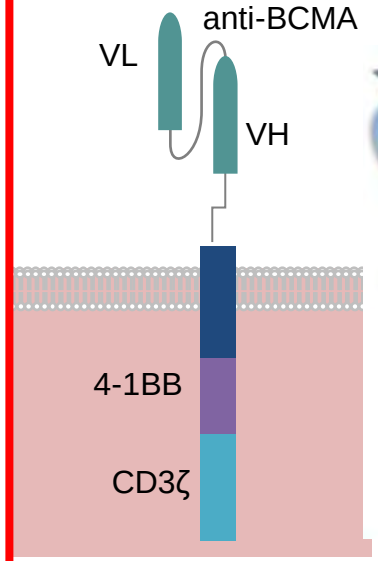


Gammaretrovirus

Adult patients with R/R MCL after ≥2 lines of systemic therapy including a BTKI

R/R Adult B-ALL

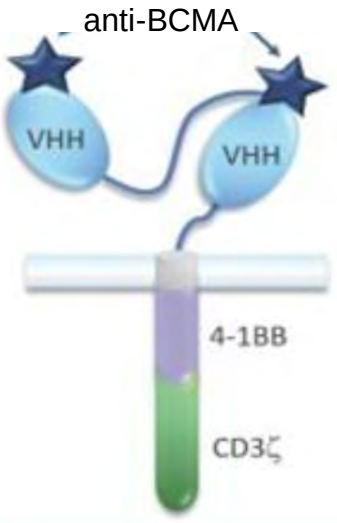
Idecabtagene vicleucel (BMS)



Lentivirus

R/R MM after ≥4* lines of systemic therapy including PI, ImiD, anti-CD38 Ab

Ciltacabtagene autoleucel (Janssen)

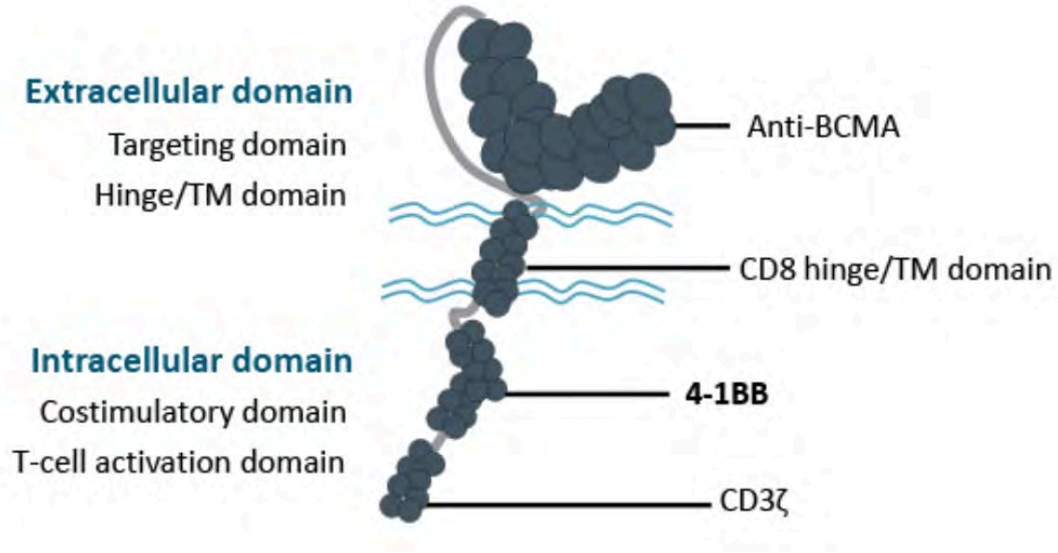


Lentivirus

R/R MM after ≥4* lines of systemic therapy incl PI, ImiD, anti-CD38 Ab

*** ≥3 lines - EMA license**

Idecabtagene Vicleucel (bb2121, Abecma)



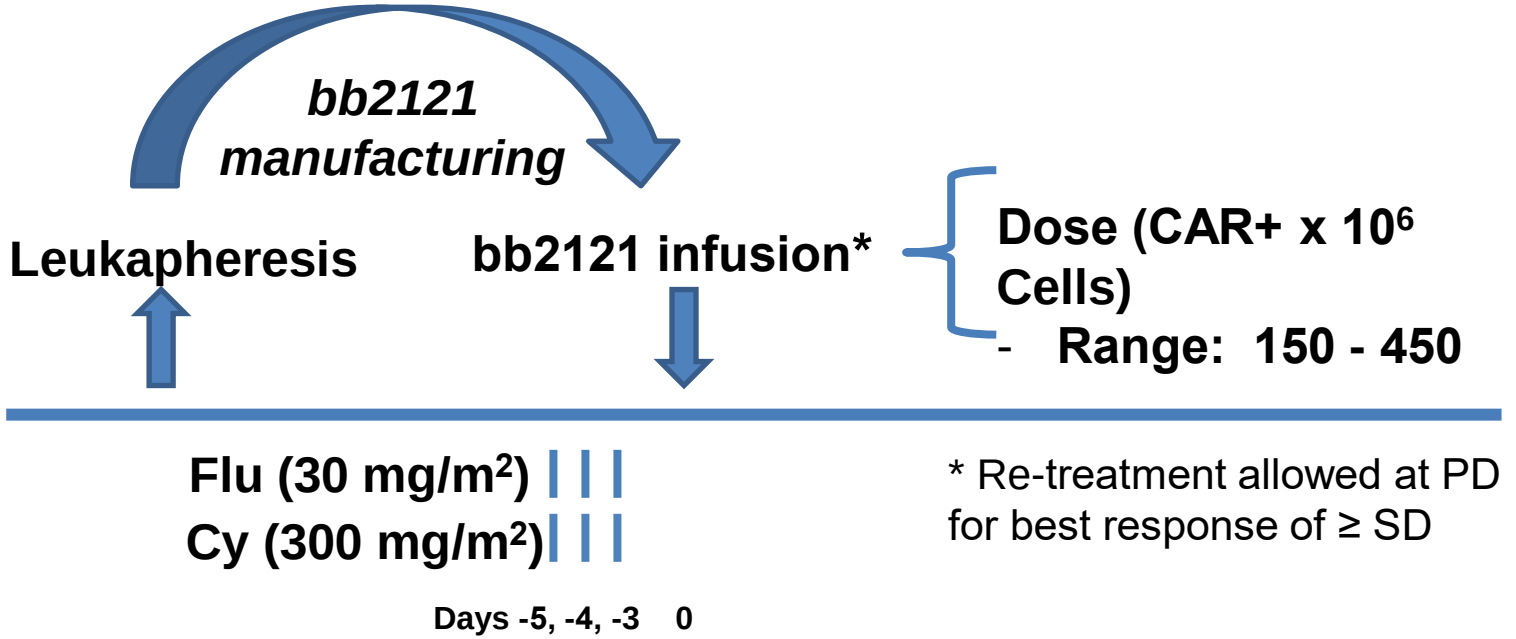
- CRB-401 phase 1 *Raje et al NEJM 2019*
- KarMMa phase 2 *Munshi et al NEJM 2021*

- FDA approval Mar 2021 for RRMM after ≥4 lines incl PI, IMiD, anti-CD38 Ab
- EMA approval Aug 2021 for RRMM after ≥3 lines incl PI, IMiD, anti-CD38 Ab

KarMMa Clinical Study Design

Pivotal phase 2 single arm Study (N=140)

RRMM:
- ≥3 prior treatment regimens with ≥2 consecutive cycles each
- received prior IMiD agent, PI and anti-CD38
- refractory (per IMWG) to last treatment regimen



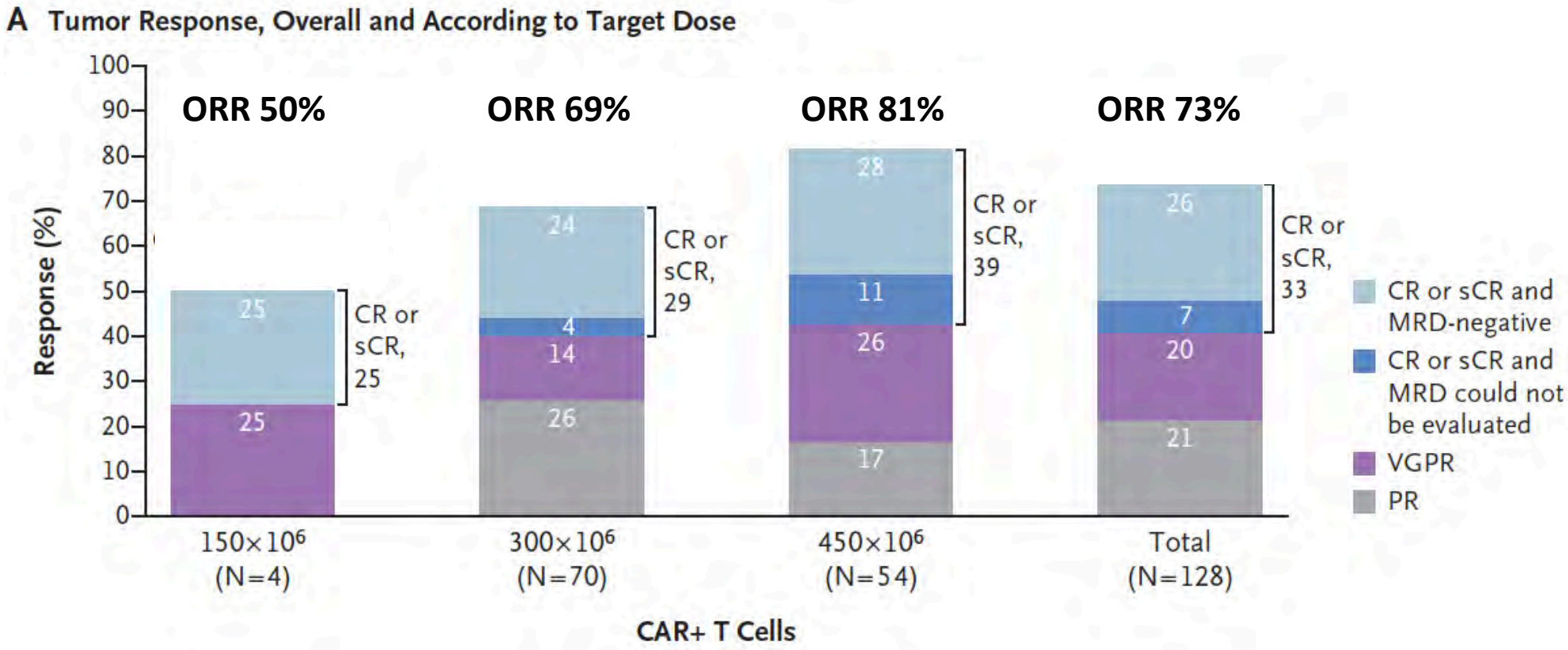
Endpoints:
- **Primary**: ORR
- **Secondary**: CR (Key Secondary), TTR, DOR, PFS, TTP, OS, Safety, bb2121 expansion and persistence, MRD (genomic and flow assays), QOL, immunogenicity, cytokines
- **Exploratory**: BCMA expression/loss, T cell immunophenotype, GEP in BM, HEOR

KarMMa - baseline characteristics

	Total (n=128)
Median age, years	61 (33-78)
Male	59%
R-ISS Stage I II III unknown	 14 (11%) 90 (70%) 21 (16%) 3 (2%)
High risk FISH del17p t(14;16) t(4;14) 1q+	45 (35%) 23 (18%) 6 (5%) 23 (18%) 45 (35%)
Median prior treatment lines	6 (3-16)
Prior Auto SCT	120 (94%)

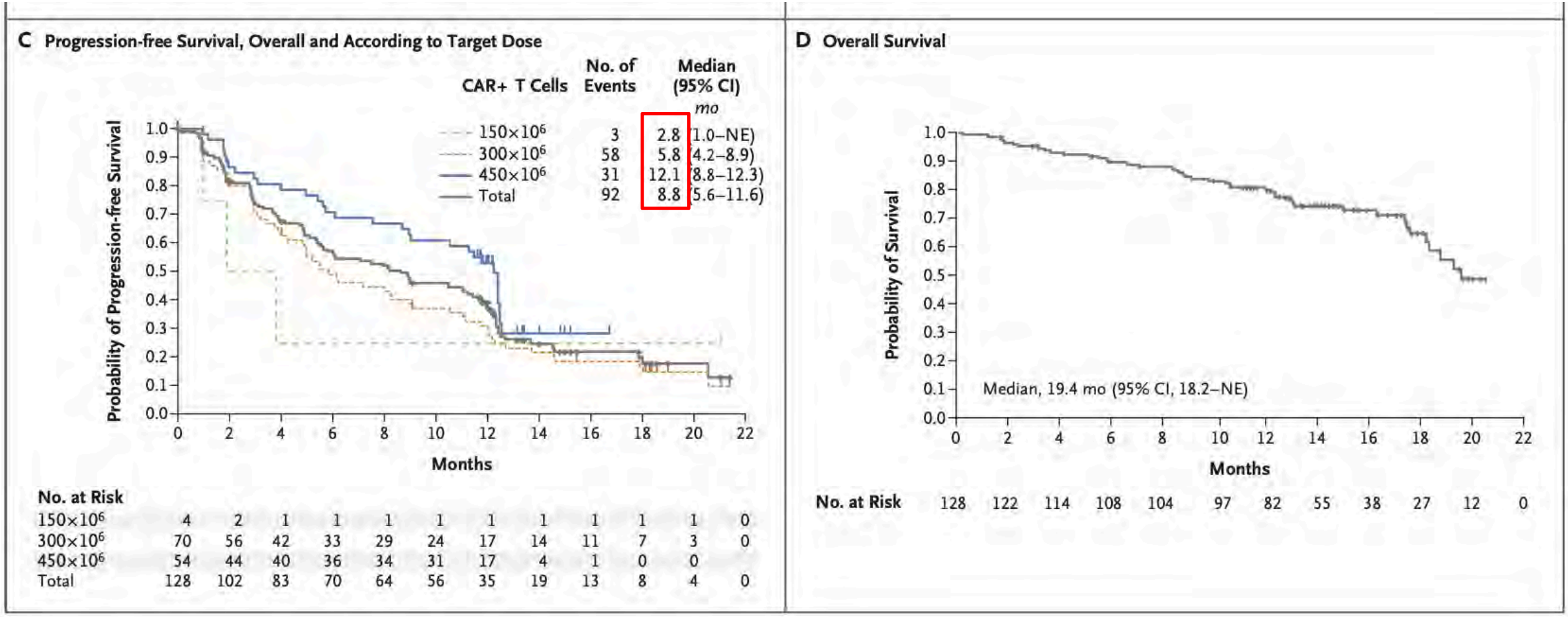
KarMMa Trial
Munshi et al, NEJM 2021

Overall Response Rate post Ide-cel



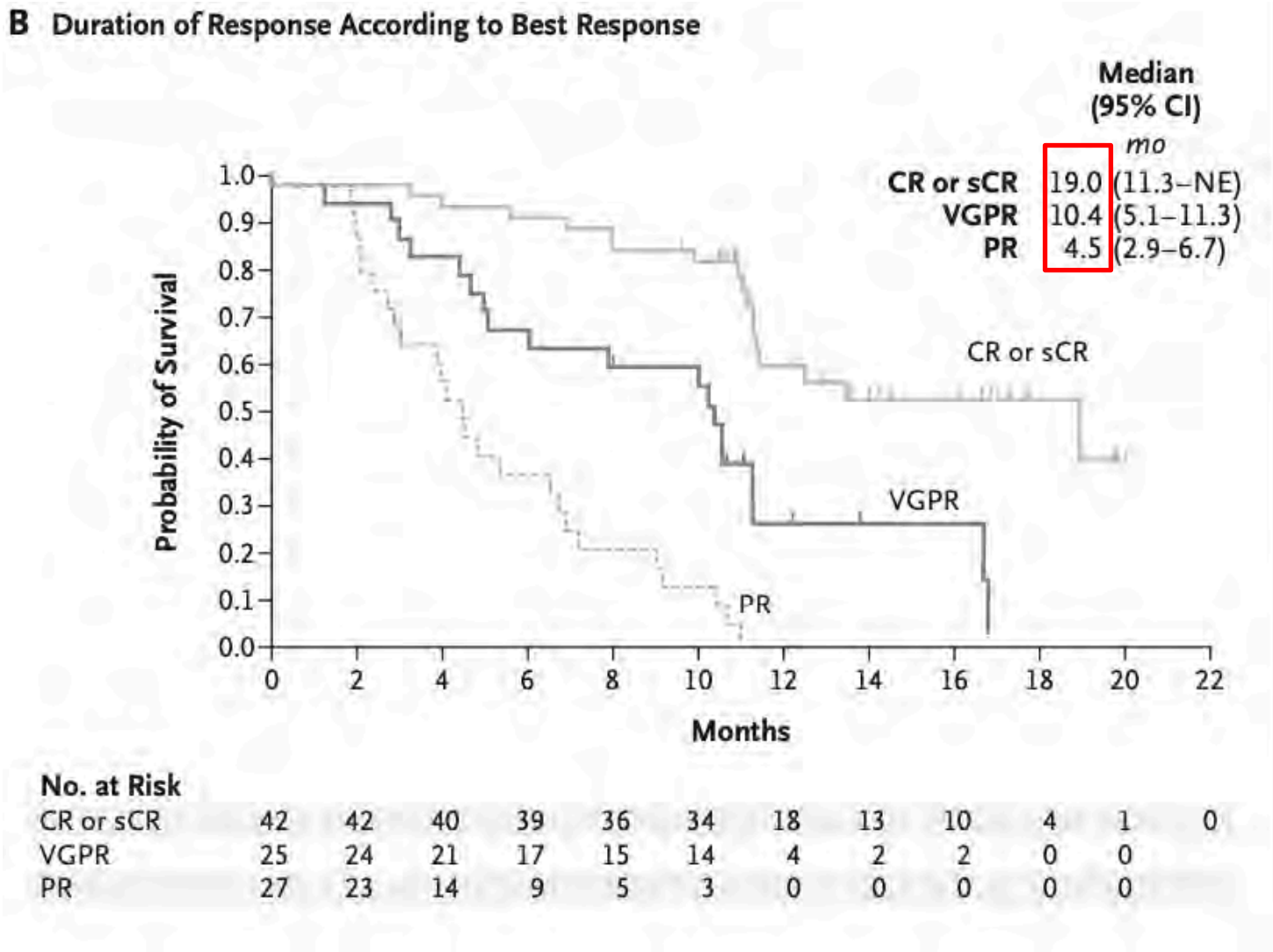
KarMMa Trial
Munshi et al, NEJM 2021

Outcomes post Ide-cel - PFS and OS



Munshi et al, NEJM 2021

Outcomes post Ide-cel and depth of response



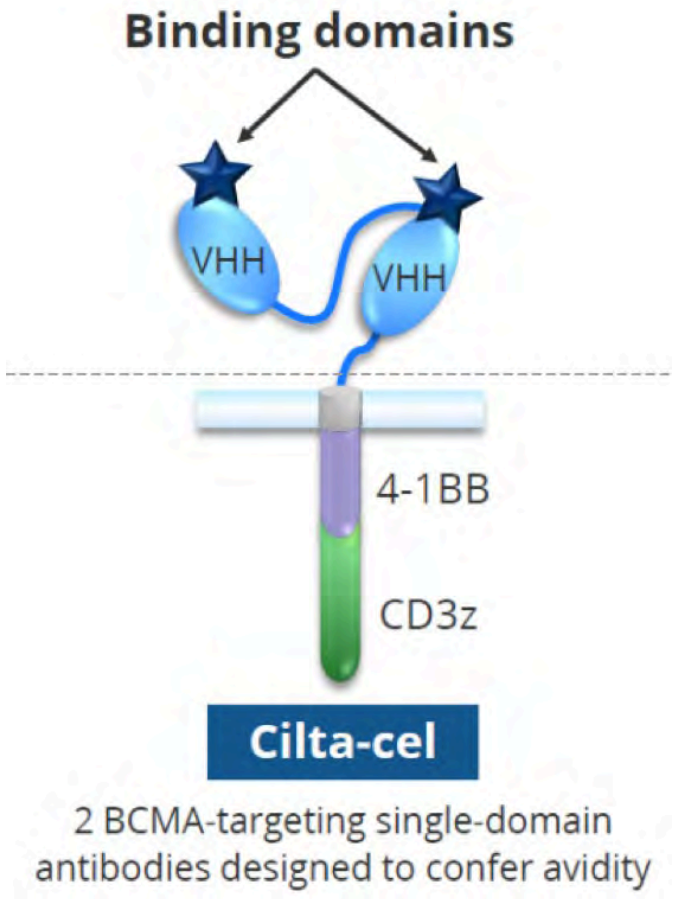
Munshi et al, NEJM 2021

Ide-cel toxicity

Adverse event	Any Grade No (%)	Grade 3 - 4 No (%)
Neutropenia	117 (91)	114 (89)
Thrombocytopenia	81 (63)	67 (52)
Febrile neutropenia	21 (16)	20 (16)
Hypogammaglobulinaemia	27 (21)	1 (<1)
Cytokine release syndrome	**107 (84)**	**7 (5)**
Neurotoxicity	**23 (18)**	**4 (3)**

KarMMa Trial
Munshi et al, NEJM 2021

Ciltacabtagene autoleucel (Carvykti)



- LEGEND-2 phase 1 *Zhao J Hematol Oncol 2018*
- CARTITUDE-1 phase 2 *Berdeja Lancet 2021*

- FDA approval Feb 2022 for RRMM after ≥4 lines incl PI, IMiD, anti-CD38 Ab
- EMA approval May 2022 for RRMM after ≥3 lines incl PI, IMiD, anti-CD38 Ab

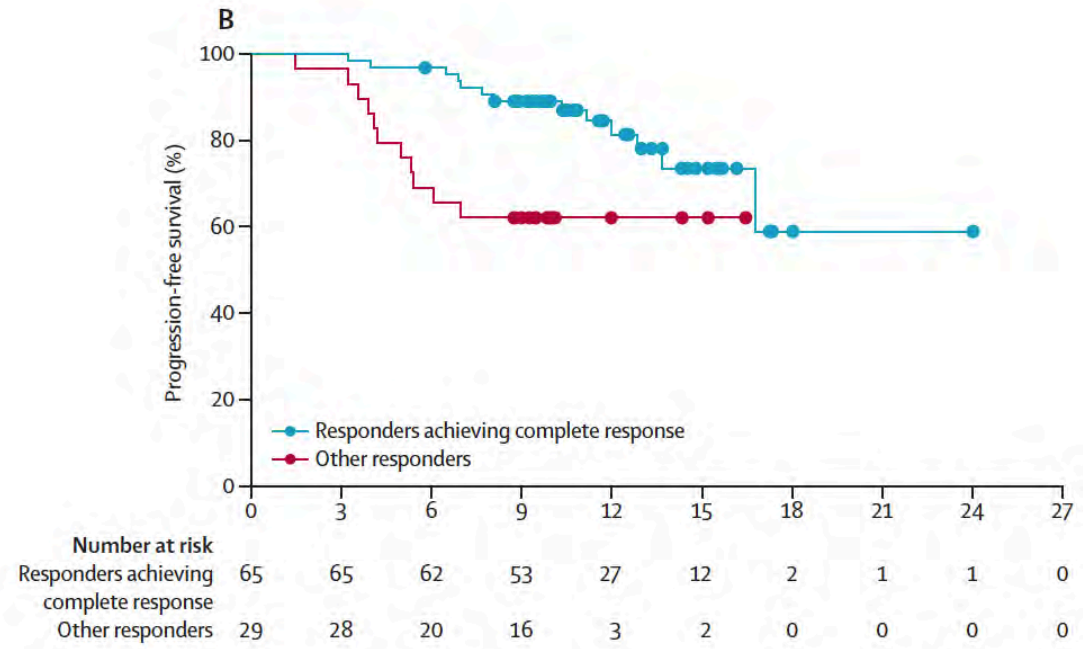
CARTITUDE-1 – baseline characteristics

	Total (n=97)
Median age, years	61 (56-68)
Male/Female	59% / 41%
<u>ISS Stage</u> I II III	 61 (63%) 22 (23%) 14 (14%
<u>High risk FISH</u> del17p t(14;16) t(4;14)	 19 (20%) 2 (2%) 3 (3%)
Median prior treatment lines	6 (4-8)
Prior SCT • Auto • Allo	 87 (90%) 8 (8%)

Berdeja Lancet 2021

Cilta-cel Outcomes

- **ORR 97%**
  - sCR 67% (MRD-ve 34%)
  - VGPR 26%
  - PR 4%
  - PD/NE 3%
- **median PFS 35 months**



Berdeja Lancet 2021
Updated ASCO 2022

Cilta-cel Toxicity

- CRS 95%
  - **G3-5 5%**
  - median time to onset 7 days, median duration 4 days
  - Toci 69%, steroids 22%, anakinra 19%

- ICANS 17%
  - **G3-4 2%**
  - median time to onset 8 days, median duration 4 days
  - Steroids 9%, toci 4%, anakinra 3%

- Other neurotoxicities 12%
  - median time to onset 27 days
  - Movement and neurocognitive symptoms

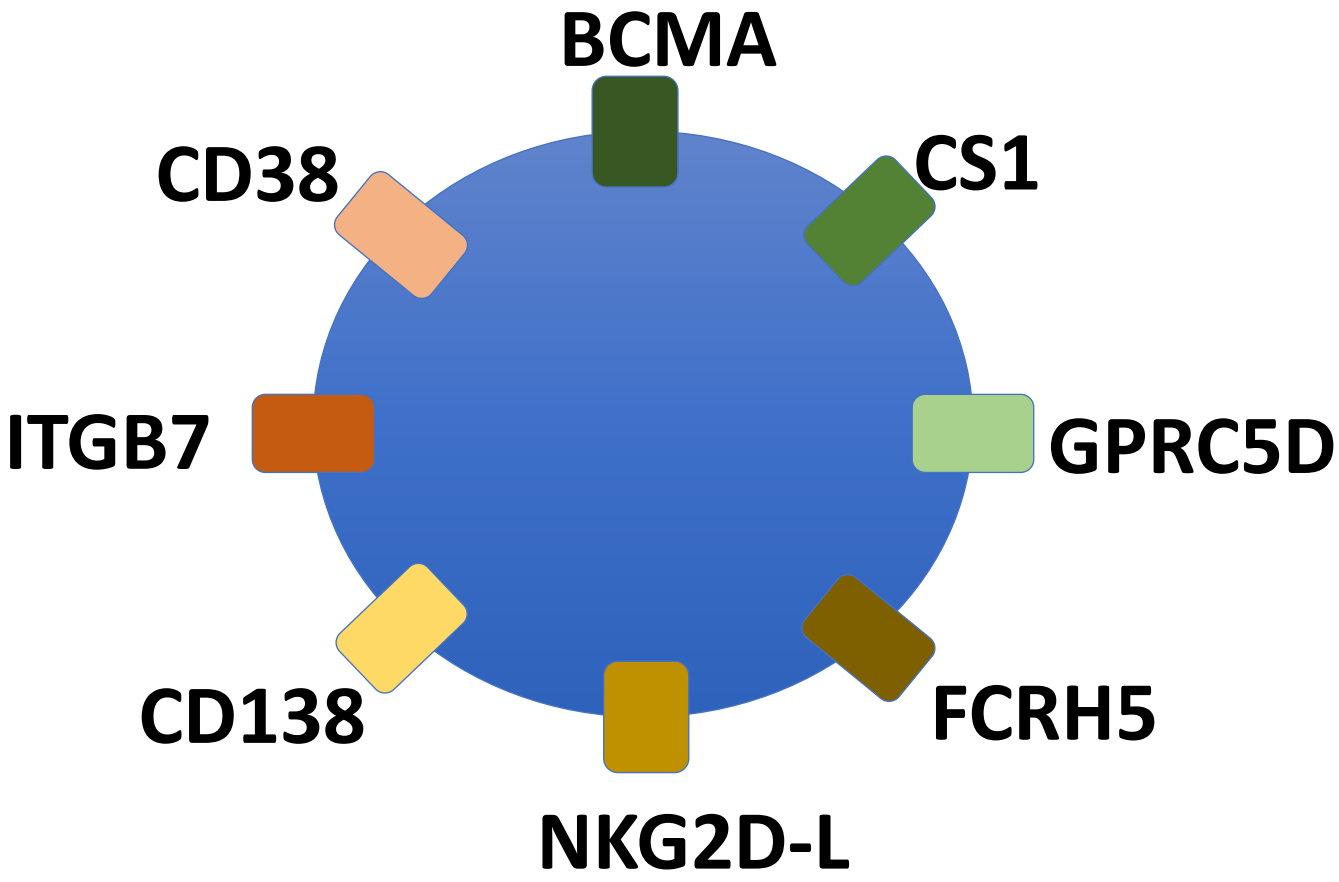
Berdeja Lancet 2021

Cilta-cel Toxicity

- Cytopenia
  - G3-4 neutropenia 95%
  - G3-4 thrombocytopenia 60%
- Infections 58%
  - G3-4 20%
- Secondary primary malignancies n=9
  - MDS n=5
  - AML n=2
  - Solid tumours n=2

Berdeja Lancet 2021

Antigen targets in myeloma for cellular immunotherapy



CAR T for myeloma – the future

- Earlier treatment with CAR T especially in high risk myeloma (Cartitude-2, Cartitude-5, KarMMa-9)
- Repeat infusions
- Combination treatment with IMiD or Gamma secretase inhibitors
- Alternative target antigen and dual antigen targeting
- Allogeneic CAR T cells
- Rapid, automated manufacturing process (Prodigy, Cocoon)

- How do we improve access to CAR T globally?
- How can we make CAR T affordable?

Supportive care

- **Bone disease** – Bisphosphonates, spinal bracing, physio, prophylactic pinning
- **Infections** – prophylactic antimicrobials, iv Immunoglobulins, vaccination
- **Pain relief** – neuropathic drugs, opiates, spinal injections, radiotherapy
- **Fatigue** – steroid dose modification, transfusions, erythropoietin
- **Psychosocial** – counselling, clinical nurse specialist, support groups

Future treatment paradigm in myeloma

- Risk adapted based on frailty, cytogenetic risk
- Early decision on whether fit for SCT, CAR-T or BiTE
- Continuous treatment except following CAR-T therapy
- MRD driven decision making

Myeloma - exciting times ahead !

"Treatment used to be simple, cheap and ineffective; now it is complex, expensive and effective"

Prof Sir Cyril Chandler