Table S1. Overview of routine and additional risk minimization measures and pharmacovigilance activities for approved CAR T cell products

Routine risk minimisation measures
Risk communication and recommendations in the Summary of Product Characteristics (SmPC) and Package Leaflet (PL)
Additional risk minimization measures
i. Educational program a. Healthcare professional information pack (Training program focussing on identification and treatment of CRS and NT, necessity of patient education and reporting of adverse reactions) b. Material for patients (incl. Patient Alert Card to be carried at all times,) ii. Controlled distribution program (treatment centre qualification) To ensure that only qualified treatment centres that have completed the educational program and with immediate access to tocilizumab will be supplied
Routine pharmacovigilance activities
ADR reporting, signal detection
Additional pharmacovigilance activities
i. Registry-based post-authorisation safety study (PASS) as condition of marketing authorisation (MA) ii. Long-term follow-up of clinical trial patients exposed to CAR-T-cell therapy and/or continuation of clinical trials

CRS cytokine release syndrome, *NT* neurotoxicity. Information extracted from the EMA – European public assessment reports for Yescarta, Kymriah and Tecartus [1-3].

References Supplementary Material

1. EMA. Human medicine European public assessment report (EPAR): Kymriah. https://www.ema.europa.eu/en/medicines/human/EPAR/kymriah. Accessed 14 Dec 2020.
2. EMA. Human medicine European public assessment report (EPAR): Yescarta. https://www.ema.europa.eu/en/medicines/human/EPAR/yescarta. Accessed 14 Dec 2020.
3. EMA. Human medicine European public assessment report (EPAR): Tecartus. https://www.ema.europa.eu/en/medicines/human/EPAR/tecartus. Accessed 20 Aug 2021.

Table S2. Key changes in CRS or NT management guidelines introduced with an investigator's brochure (IB) update

Treatment	IB before 06/2017	IB since 06/2017
Cytokine release syndrome (CRS)		
Grade 1		• Not improving after 3 days: Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800mg)
Grade 2	• If elderly or com-morbidities, consider tocilizumab (8mg/kg) ± corticosteroids	• Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800mg). • Repeat tocilizumab every 4 to 6 hours as needed if not responsive to IV fluids or increasing supplemental oxygen; maximum of 3 doses in a 24-hour period. • If no improvement within 24 hours after starting tocilizumab, manage per Grade 3, which includes Methylprednisolone 1 mg/kg IV
Grade 3	• Consider tocilizumab (8mg/kg) ± corticosteroids	• Tocilizumab as per grade 2. Methylprednisolone 1 mg/kg IV
Neurotoxicity (NT)		
Grade 1		
Grade 2	• Consider tocilizumab 8mg/kg IV over 1 hour (not to exceed 800mg) if other co-morbid conditions (e.g. Grade 2 or greater CRS)	<u>No concurrent CRS:</u> • Dexamethasone at 10 mg IV every 6 h. Tocilizumab not indicated. <u>Concurrent CRS:</u> • Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg) • Repeat tocilizumab every 4 to 6 hours as needed if not responsive to IV fluids or increasing supplemental oxygen; maximum of 3 doses in a 24-hour period. • If no improvement within 24 hours after starting tocilizumab, give dexamethasone 10 mg IV every 6 h • If not improving: Manage as Grade 3
Grade 3	• Consider tocilizumab 8mg/kg IV over 1 hour (not to exceed 800mg) • Repeat tocilizumab q4-6hrs if symptoms have not stabilized or improved • Consider corticosteroids (e.g., dexamethasone 10 mg IV q6hrs, methylprednisolone 1mg/kg BID) for worsening symptoms despite tocilizumab	• Dexamethasone at 10 mg IV every 6 h. • Tocilizumab as per grade 2. • If not improving: Manage as Grade 4

CRS cytokine release syndrome, *NT* neurotoxicity