

Supplemental Table 1. Early Intervention (EI) Strategy for CRS Management

| Symptom related to CRS | Suggested Intervention |
|--|--|
| Fever of $\geq 38.3^{\circ}\text{C}$ | Acetaminophen (12.5 mg/kg) PO/IV up to every 4 hours |
| Persistent fever of $\geq 39^{\circ}\text{C}$ for 10 hours that is unresponsive to acetaminophen | Tocilizumab (8-12 mg/kg) IV |
| Persistent fevers $\geq 39^{\circ}\text{C}$ after Tocilizumab | Dexamethasone 5-10 mg IV/PO up to every 6-12 hours with continued fevers |
| Recurrence of symptoms 48 hours after initial dose of Tocilizumab | Tocilizumab (8-12 mg/kg) IV |
| Hypotension | Fluid bolus, target hematocrit $>24\%$ |
| Persistent/recurrent hypotension after initial fluid bolus (within 6 hours) | Tocilizumab (8-12 mg/kg) IV |
| Use of low dose vasopressors for hypotension for longer than 12 hours | Dexamethasone 5-10 mg IV/PO up to every 6 hours with continued use of vasopressors |
| Initiation of higher dose vasopressors or addition of a second pressor for hypotension | Dexamethasone 5-10 mg IV/PO up to every 6 hours with continued use of vasopressors |
| Initiation of oxygen supplementation | Tocilizumab (8-12 mg/kg) IV |
| Increasing respiratory support with concern for impending intubation | Dexamethasone 5-10 mg IV/PO up to every 6-12 hour |
| Recurrence/Persistence of symptoms for which tocilizumab was given ≥ 48 hours after initial dose was administered | Tocilizumab (8-12 mg/kg) IV |

Supplemental Table 2. Diversity of CRS grading scales

| CRS Symptom | Grading Scale | Grade 2 | Grade 3 | Grade 4 |
|-------------------------------------|----------------------------|--|---|---|
| Hypotension | CTCAEv4/PLAT-02 | Single fluid bolus | Multiple fluid boluses | Use of vasopressors |
| | Lee criteria ¹¹ | Low dose pressors or IV fluids | High dose or multiple pressors | Life Threatening |
| | UPENN ¹⁶ | | Multiple fluid boluses or low-dose vasopressors | High-dose vasopressors |
| | ASTCT ²⁴ | Not requiring vasopressors | Requiring a vasopressor with or without vasopressin | Requiring multiple vasopressors (excluding vasopressin) |
| Hypoxia | CTCAEv4/PLAT-02 | | Supplemental Oxygen | Requirement for Ventilator support |
| | Lee criteria ¹¹ | Oxygen requirement <40% FiO2 | Oxygen requirement ≥ 40% FiO2 | Requirement for Ventilator support |
| | UPENN ¹⁶ | | Supplemental Oxygen | Mechanical ventilation |
| | ASTCT ²⁴ | Low-flow nasal cannula or blow-by | High-flow nasal canula, facemask, nonrebreather mask, or Venturi mask | Requiring positive pressure (eg CPAP, BiPAP, intubation and mechanical ventilation) |
| Organ Toxicity (graded per CTCAEv4) | CTCAEv4/PLAT-02 | GRADED SEPARATELY FROM CRS | | |
| | Lee criteria ¹¹ | Any Grade 2 organ toxicity attributed to CRS | Any Grade 3 organ toxicity attributed to CRS or grade 4 transaminitis | Grade 4 organ toxicity (excluding transaminitis) attributed to CRS |
| | UPENN ¹⁶ | Grade 2 creatinine or Grade 3 LFTs | Grade 3 creatinine and Grade 4 LFTs | |
| | ASTCT ²⁴ | GRADED SEPARATELY FROM CRS | | |

CRS, cytokine release syndrome; CTCAEv4, Common Terminology Criteria for Adverse Events version 4; PLAT, pediatric leukemia adoptive therapy; UPENN, University of Pennsylvania; ASTCT, American Society for Transplantation and Cellular Therapy; FiO2, Fraction of inspired oxygen; CPAP, continuous positive airway pressure; BiPAP, bilevel positive airway pressure, LFTs, liver function tests

Supplemental Figure Legends

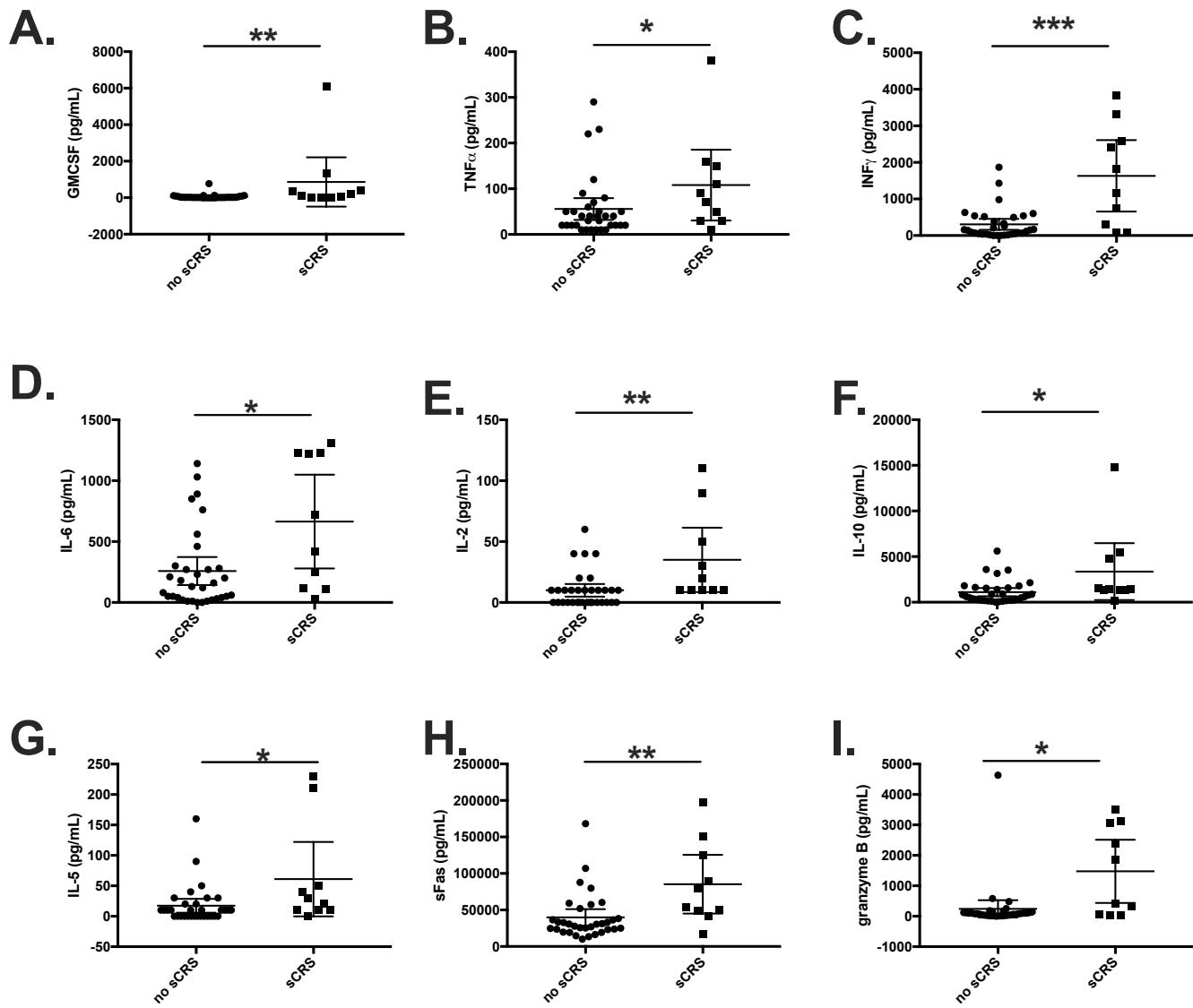
Supplemental Figure 1. Serum cytokines are impacted by occurrence of sCRS. Serum cytokines in the peripheral blood are noted by the maximum value following CAR T cell infusion through day 28, grouped by those who did and did not develop sCRS. (P values: *=<0.05; ** = <0.005; *** = <0.0005)

Supplemental Figure 2. Serum cytokines are impacted by occurrence of sCRS in all subjects who received tocilizumab. Serum cytokines in the peripheral blood are noted by the maximum value following CAR T cell infusion through day 28, grouped analyzing all

subjects that received tocilizumab and comparing those who did and did not develop sCRS.
(P values: *= <0.05 ; ** = <0.005 ; *** = <0.0005)

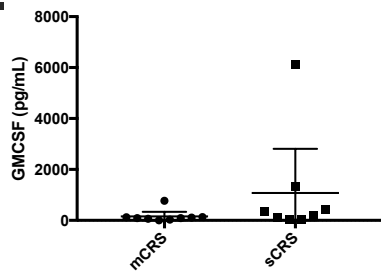
Supplemental Figure 3. Serum cytokines were not different between the CRS intervention strategy cohorts. A-I. Dose limiting toxicity (n=23) and early intervention (n=20) cohorts are noted for each analyzed cytokine that was significant when compared between sCRS and no sCRS. No significance was noted in any of the analytes.

Supplemental Figure 1

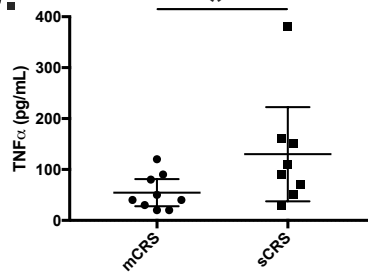


Supplemental Figure 2

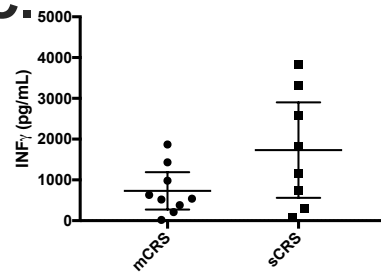
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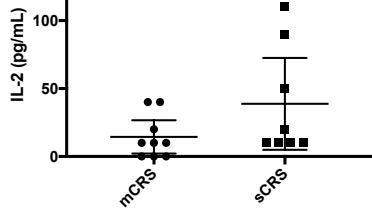
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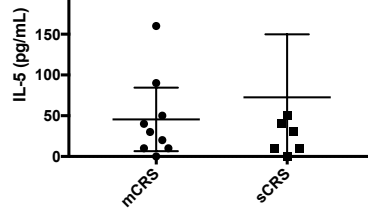
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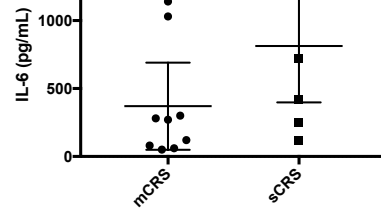
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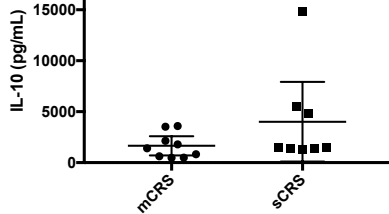
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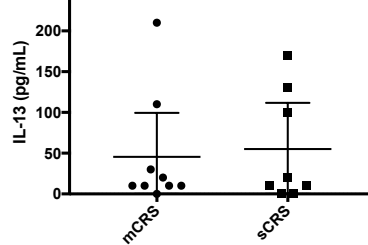
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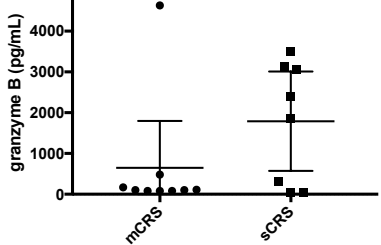
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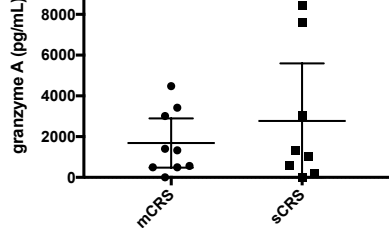
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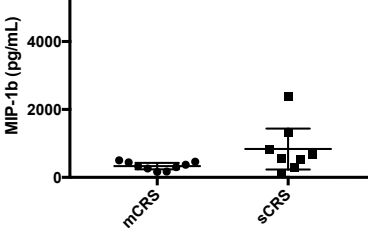
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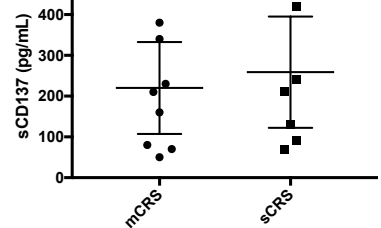
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K.



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M.

