Alloplex Biotherapeutics

SCIENTIFIC MONOGRAPH

The Pooled Clinical Safety Database of Clinically Tested NK and NKT-like Cell Therapies

The Aggregate Toxicity Record

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ABOUT THIS DOCUMENT

- *A quantitative evaluation of the entire published clinical safety experience with natural killer (NK) and natural killer T-like (NKT-like) cell products available at the time of writing, assembled to support the class safety argument. The document establishes a defensible, pooled denominator from published systematic reviews and meta-analyses that supports SUPLEXA™ use in early-intervention and precursor indications such as SMM for multiple myeloma and MDS for AML.*
- *It tabulates the aggregate incidence of graft-versus-host disease, cytokine release syndrome, neurotoxicity, and routine adverse events, and then performs the analysis that matters most for regulatory purposes: an attribution audit that assigns each reported severe toxicity in the class either to the cell product or to one of three non-cell components commonly used in combination — lymphodepleting conditioning, exogenous cytokine support, and host-versus-graft allo-rejection. It is important to note that none of these toxicities apply to the SUPLEXA treatment paradigm due to its autologous, non-engineered nature.*
- *Section 4.2 partitions that clinical dataset into three architectural categories — non-engineered autologous, non-engineered allogeneic or otherwise HLA-disparate, and CAR-engineered. It shows that the autologous category SUPLEXA occupies is devoid of every toxicity displayed in the broader NK/NKT-like cell drug class.*

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SECTION 1

Executive summary

A safety argument for a cellular therapy in an early-intervention indication cannot rest on a single Phase 1 data set. In the case of the single SUPLEXA-101 study, that evidence is bounded by the 220 doses of SUPLEXA administered. To provide the necessary regulatory assurance, the argument must also rely on the safety of the cell drug class. This document assembles the entire published clinical experience with NK and NKT-like cell products, establishes what that experience does and does not demonstrate, and converts a favorable empirical record into a mechanistic argument fit for regulatory consideration.

The conclusion in one sentence. Across approximately 1,700 to 1,900 documented patients and on the order of 2,400 to 2,700 individual doses, the NK/NKT-like cell class, both autologous and allogeneic combined, has produced one case of GvHD, a CRS-and-neurotoxicity rate of roughly 3% at low grade, no severe-grade signal that remains attributable to the cells once lymphodepletion, exogenous cytokine support, and allo-rejection are accounted for, and no genotoxic hazard of the kind that generated a class boxed warning for engineered T cells — which means the class safety record is favorable.

Partitioning the NK/NKT-like cell class further into subsets places SUPLEXA in the most favorable subset. The non-engineered autologous category carries no reported toxicities beyond three self-resolving grade 3 events in a single study.

Why this matters for the regulatory argument requesting permission to treat early-stage patients. The standing objection to early-intervention and precursor indications in hematologic malignancies is that an asymptomatic patient should not be asked to accept the uncertain toxicity profile of a new therapy. That understandable objection is addressed in two ways: indirectly by the drug class data presented here, and directly by the SUPLEXA Phase 1 clinical trial data — 35 patients, more than 220 doses, no SAEs — which remains the primary safety evidence.

The argument is based on nine components.

1 – The drug class denominator is large enough to inform regulatory decisions. Three independent systematic reviews establish the countable exposure. A 2025 systematic review of two decades of NK cell trials in AML and adjacent hematologic malignancies captured 48 trials and 798 patients, of which only two trials used engineered cells [1]. A 2024 meta-analysis restricted explicitly to unmodified NK cells in solid tumors captured 31 trials and 600 patients [2]. A disease-specific meta-analysis in advanced NSCLC captured 199 NK-treated patients across nine trials, five of them randomized and controlled [3]. The defensible, indexed figure is on the order of 1,400 to 1,600 patients treated with non-engineered NK cells, with a further 250 to 350 treated with NKT-like products. Including unindexed Chinese, Korean, and Japanese series, the true global figure is plausibly two to three times larger (modeled).

2 – Every severe toxicity signal in the class is attributable to something other than the cells. The one documented exception to the clean CRS record for NK cells traces to the cytokine, not the product. After lymphodepletion, subcutaneous dosing of recombinant human IL-15 prolongs drug exposure, thereby producing CRS and neurotoxicity—an effect not seen with intravenous dosing [8]. The mechanism was subsequently resolved in the cytokine-induced memory-like NK program, where CRS at days 10 to 14 correlated with expansion of activated recipient CD8 T cells bearing a CD38-positive, HLA-DR-positive phenotype — indicating host-versus-graft allo-rejection, rather than graft-mediated toxicity [9]. Section 8 audits every reported severe event in the class against three non-cell attribution channels: lymphodepleting conditioning, exogenous cytokine support, and allo-rejection. None survives assignment to the cells themselves.

3 – Partitioning that denominator by category rather than by disease is what makes it instructive, and the non-engineered autologous category to which SUPLEXA belongs has the best safety profile. Section 4.2 divides the whole class into three categories: non-engineered autologous, non-engineered allogeneic or otherwise HLA-disparate, and CAR-engineered. The autologous category — approximately 73 patients on a strict adoptive-transfer count, or 108 if autologous α-GalCer-pulsed antigen-presenting cell products are included [12,13,14,15,16,17,39] — carries no graft-versus-host disease, no host-versus-graft rejection, no cytokine release syndrome, no neurotoxicity, no dose-limiting toxicity, and no genotoxic hazard. Its entire severe-event record is three grade 3 events in a single hepatocellular carcinoma study, all of which resolved without treatment [12]. The allogeneic category, at roughly 1,300 to 1,500 patients, carries one GvHD event, an approximately 3%

low-grade CRS and neurotoxicity rate, one dose-limiting toxicity, and the whole of the class's allo-rejection signal. The CAR-engineered category carries 7% CRS for CAR-NK and 67% for CAR-T, with a class boxed warning attaching to the latter [6,7,20].

4 – Of the toxicity parameters identified, two do not apply to SUPLEXA, by virtue of its autologous status. Zero GvHD and zero host-versus-graft rejection in an autologous product are not findings but consequences of the architecture: with no HLA disparity, no HLA driven rejection is possible. In any case, graft-versus-host disease is effectively absent from the class, and this is the most robust finding in the database. In the pooled AML analysis of 406 patients, a single patient showed any sign of GvHD [1]; the 2026 AML meta-analysis reports GvHD across its 607 patients at 0 to 8% [52]. The absence holds in HLA-mismatched allogeneic settings, which is where the finding has force: allogeneic NK cells are administered across HLA barriers without the T-cell-receptor-driven alloreactivity that makes allogeneic T cells dangerous [4,5]. A reviewer reading the source systematic review must be warned that the 37.3% acute and 23.7% chronic GvHD rates it reports for the transplant-setting cohort are the GvHD of the transplant, not of the NK infusion; the two cohorts must not be pooled. The third parameter is different in kind. Zero CRS is a genuine empirical observation, and at 73 to 108 patients the rule of three bounds an unobserved event rate only at approximately 2.8% to 4.1% — which brackets the roughly 3% rate observed in the allogeneic category. On cytokine release syndrome the autologous category is therefore consistent with being cleaner but is not yet statistically separated from the allogeneic one.

5 – Counting exposure in doses, as well as in patients, shows that SUPLEXA-101 is the densest study in the class. Patient counts understate cellular exposure because most trials gave more than one infusion. The 2026 AML meta-analysis reports per-study infusion schedules for all 29 included trials, permitting a trial-level reconstruction: approximately 1,041 infusions across 607 patients, a mean of 1.71 doses per patient [52] (derived; see Section 4.2). Applied across the wider non-engineered NK denominator this implies on the order of 2,400 to 2,700 cellular exposures. Against that baseline, SUPLEXA-101 delivered more than 220 doses to 35 patients — 6.3 doses per patient, roughly 3.7-fold the class mean. Repeat dosing is the thinnest part of the class database, and it is the part to which SUPLEXA contributes most.

6 – Cytokine release syndrome and neurotoxicity in the NK/NKT-like cell class, engineered and non-engineered alike, occur at roughly one-tenth to one-twentieth the rate seen with engineered T cells, and severe grades are essentially absent. Across 406 AML patients, 13 experienced any adverse event of the CRS or neurotoxicity type — approximately 3%, ungraded [1]. The comparator is stark: a systematic review of 1,193 patients receiving CD19 CAR-T for diffuse large B-cell lymphoma found 67% with CRS of some grade, 10% grade 3 and 3% grade 4 [6]. Even CAR-NK, which adds a transgene to the same effector, reports no grade 3 or higher CRS and no ICANS or GvHD across 150 published patients [7].

7 – The routine adverse event profile is an infusion-reaction profile and nothing more. Fatigue is the most frequently reported event in the solid tumor pooled analysis [2]; transient chills, headache, low-grade fever, nausea, and bone pain dominate the hematologic series, grade 1 in most reports and resolving without hospitalization [10,11]. Maximum tolerated dose was not reached in the great majority of dose-escalation studies, including at doses above 10^9 cells per square meter and, in one iNKT study, at 10^{10} cells per square meter [12]. A class in which MTD is repeatedly not reached is telling regulatory agencies something specific about the shape of its dose-toxicity curve.

8 – The NKT-like cell sub-database is an order of magnitude smaller but points the same way. Cumulative iNKT exposure is on the order of 250 to 350 patients across roughly two decades, concentrated in the Chiba University program in NSCLC and head and neck cancer and in a scatter of single-center Phase 1 studies [13,14,15,16,17]. One review tallies only five treatment-related adverse events of grade 2 or higher across the entire early adoptive iNKT literature [18]. The one dose-limiting toxicity on record in the modern era — a grade 3 skin rash — occurred with an allogeneic iPSC-derived product, not with an autologous or peripheral-blood-derived one [19].

9 –The boxed-warning risk category that now attaches to gene-modified cell therapies does not apply to SUPLEXA due to its non-engineered status. In April 2024 the FDA required a boxed warning for T-cell malignancies on all approved BCMA- and CD19-directed autologous CAR-T products and called for lifelong secondary-malignancy monitoring [20,21]. That risk is a consequence of transgene integration. A product carrying no

transgene carries no insertional-mutagenesis hazard, is not subject on that basis to the 15-year gene-therapy long-term follow-up expectation and is the only cell-therapy architecture for which a precursor-disease risk-benefit calculation can be made without that hazard.

SECTION 2

Document scope and method of assembly

There is no registry of NK or NKT-like cell exposure. No sponsor, consortium, or regulator maintains a pooled safety database for this class in the way that CIBMTR maintains one for transplant and cellular therapy. The denominator therefore must be constructed from public information, and the construction must be transparent enough that a reviewer can check it.

Method. The pooled figure in Section 4 is assembled from published systematic reviews and meta-analyses rather than from primary trial reports, for three reasons. Systematic reviews apply pre-registered inclusion criteria, which prevents the denominator from being padded with favorable series. They report their own PRISMA exclusions, which allows the overlap between reviews to be estimated. And they are the artifact a reviewer will reach for independently, so building on them removes an argument about selection. Primary trial reports are then used in Sections 5 through 8 to characterize individual events, because reviews report events in aggregate and the attribution analysis requires the case-level detail.

Overlap handling. The three principal reviews partition cleanly by disease: hematologic malignancy [1], solid tumors [2], and a disease-specific NSCLC analysis [3] that is largely subsumed by the second. The older tally that circulates in regulatory documents — more than 500 patients across 30 completed allogeneic NK studies, sourced to a 2017 review [4] — is almost entirely contained within the first two and is not added to the total. It is retained in Table 2 because of its provenance rather than its arithmetic: it appears verbatim in IND protocols that have cleared FDA review [22], which establishes that the FDA has already accepted this framing of the class record.

Labeling convention. Figures drawn directly from a published review are stated without qualification. Figures obtained by netting overlap across reviews are labeled *estimated*. Figures obtained by extrapolating beyond the indexed English-language literature are labeled *modeled* and are never used as the basis of a claim; they appear only to indicate the direction and rough magnitude of the undercount. Where a category is small enough that its counting rule changes the number materially, both a *strict* count (adoptive transfer of

the effector cell itself) and an *inclusive* count (adding autologous cell products that act by mobilizing the endogenous effector, principally α-GalCer-pulsed antigen-presenting cells) are given, and the strict count is used in any load-bearing statement.

What is deliberately excluded. Trials of NK-directed antibodies, cytokines, checkpoint agents, and engagers are excluded even though they act on the same effector population, because their toxicity is pharmacological rather than cellular. Trials in which NK cells were a component of an unfractionated donor lymphocyte infusion are excluded because the exposure cannot be attributed specifically to NK cells.

SECTION 3

Class boundaries: establishing what is included in the pooled database

The term "NK cell therapy" covers products that differ in cell source, manufacturing route, genetic status, and accompanying regimen. Those differences matter to safety, and a pooled analysis that ignores them will be attacked. Table 1 sets the boundaries used here.

TABLE 1

Product taxonomy and inclusion boundaries for the pooled database

PRODUCT CLASS	CELL SOURCE	GENETIC STATUS	IN DENOMINATOR	RATIONALE
Autologous non-engineered NK/NKT-like	Patient peripheral blood	Unmodified	**Yes**	Closest architectural match to SUPLEXA; no allo-rejection channel, no GvHD channel
Allogeneic haploidentical NK	Related-donor peripheral blood	Unmodified	**Yes**	Largest single body of evidence; carries allo-rejection and theoretical GvHD channels, so it bounds risk from above
Cord blood / CD34-derived NK	Umbilical cord blood	Unmodified	**Yes**	Differentiated ex vivo; unmodified genome
Cytokine-induced memory-like NK	Donor PB, IL-12/15/18 preactivated	Unmodified	**Yes**	Unmodified but functionally reprogrammed; most informative attribution data comes from this program
NK-92 cell line	Immortalized NK lymphoma line	Unmodified but irradiated	**Yes, flagged**	Malignant-origin line requiring irradiation before infusion; safety record relevant but architecture is not comparable
iPSC-derived NK/iNKT	Induced pluripotent stem cells	Often unmodified at CAR locus	**Yes, flagged**	Included where no CAR is present; reprogramming raises distinct questions

PRODUCT CLASS	CELL SOURCE	GENETIC STATUS	IN DENOMINATOR	RATIONALE
CAR-NK, CAR-NKT	Any	Transgene-modified	**No**	Excluded from denominator; retained as comparator in Sections 6 and 11
Unfractionated DLI, CIK, LAK	Donor or patient	Unmodified	**No**	NK exposure not separable from T cell exposure; toxicity not attributable
NK-directed antibodies, cytokines, engagers	n/a	n/a	**No**	Pharmacological rather than cellular exposure

Shading: green = architecture comparable to SUPLEXA; blue = included and mechanistically informative; amber = included with a stated caveat; red = excluded.

The strength of the SUPLEXA position depends on being an autologous, non-engineered NK/NKT-like therapy. That architecture removes graft-versus-host and host-versus-graft issues from consideration, as well as the risk of insertional mutagenesis. Beyond that, obtaining the starting cells from a simple blood draw, with no chemotherapy preconditioning and no supportive cytokines, substantially narrows the range of safety risks to be considered. Including CAR-NK in the denominator would inflate the count and while simultaneously weakening the argument, because once a transgene enters the product the genotoxicity question reopens.

SECTION 4

The pooled denominator

4.1 The countable exposure by source

Table 2 sets out the countable exposure by contributing source, with overlap handled explicitly. The arithmetic is deliberately conservative: where two reviews may have captured the same trial, the patients are counted once, and where a review's scope is uncertain its contribution is discounted rather than added.

TABLE 2

The pooled denominator by contributing source

SOURCE	SCOPE	TRIALS	PATIENTS	WEIGHT	TREATMENT IN THE POOLED TOTAL
Systematic review of two decades of NK trials in AML [1]	AML and adjacent hematologic malignancy, inception to April 2024	48 (46 non-engineered)	**798**	HIGHEST	Counted in full. 342 in transplant settings, 456 in non-transplant settings
NK adoptive transfer in AML: systematic review and meta-analysis [52]	Non-genetically-modified NK in AML only; searched to Dec 2024, published Mar 2026	29	**607**	**HIGHEST**	The post-cutoff update. Overlaps [1] substantially and is not added to the total; contributes the trial-level infusion schedules from which the dose denominator is derived, and independently confirms GvHD at 0–8%
Meta-analysis of unmodified NK in solid tumors [2]	Solid tumors, to May 2024; explicitly unmodified product only	31	**600**	Moderate	Counted in full. No disease overlap with [1]
Disease-specific NSCLC meta-analysis [3]	Advanced NSCLC, to August 2024; 5 randomized, 4 Phase 1	9	199 NK-treated (325 total with controls)	Low	Largely subsumed by [2]. Not added. Retained because it contributes the only controlled comparisons in the class

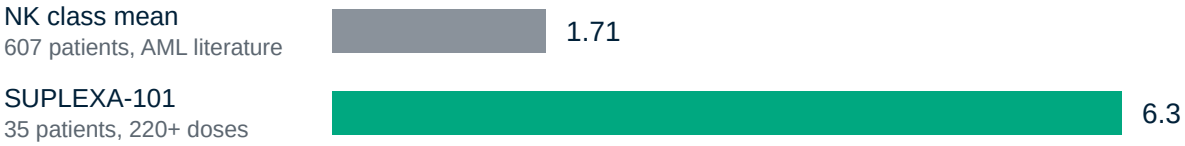
SOURCE	SCOPE	TRIALS	PATIENTS	WEIGHT	TREATMENT IN THE POOLED TOTAL
Allogeneic NK tally carried in FDA-reviewed IND protocols [4,22]	Completed allogeneic NK studies to 2017	30	>500	Low	Not added — substantially contained within [1] and [2]. Retained for provenance
NK-92 cell line trials [23,24]	Irradiated NK-92 in solid tumors and heme malignancy	~4	~50	Low	Counted, flagged. Architecture not comparable but exposure is real
Non-oncology NK trials [25,26,27]	COVID-19 pneumonia, viral respiratory disease	~4	~40	Moderate	Counted, flagged. See Section 10
NKT-like / iNKT sub-database [13–19,28]	Cancer and ARDS, 2006 to 2025	~14	250–350 (estimated)	Moderate	Counted separately. See Section 9
DEFENSIBLE INDEXED TOTAL	**Non-engineered NK, all settings**	**~90**	**1,400–1,600 (estimated)**	—	**The figure to use in a submission**
DOSE DENOMINATOR	**Reconstructed from the per-study infusion schedules in [52], Tables 1–4**	**29**	**~1,041 doses / 607 patients mean 1.71 doses per patient (derived)**	**HIGHEST**	**Scaled to the full non-engineered NK denominator: ~2,400–2,700 cellular exposures (modeled)**
DEFENSIBLE INDEXED TOTAL, NK + NKT-like	**Whole non-engineered class**	**~104**	**1,700–1,900 (estimated)**	—	**The class figure**
Extrapolated global exposure	Including unindexed Chinese, Korean, Japanese hospital and registrational series	—	3,500–5,500 (modeled)	—	Directional only. Never load-bearing

Weight reflects relevance to the intended indications, which are hematologic. The two AML-anchored reviews [1,52] are weighted highest because they are the only sources whose population matches MGUS/SMM and MDS/AML development. Trial counts are approximate where reviews overlap. Patient counts within each cited

review are exact as published; the totals are estimates because overlap cannot be resolved without patient-level data.

FIGURE 1

Doses per patient: class mean against SUPLEXA-101



Class mean derived from the per-study infusion schedules in [52]. SUPLEXA-101 delivers roughly 3.7-fold the class mean.

Two features of the denominator deserve emphasis.

- The first is that the class experience is historically overwhelmingly non-engineered. In the AML review only two of 48 trials used engineered cells [1]; the field evolved unmodified and only recently added transgenes. That means the safety record being cited is the record of the same architecture that SUPLEXA employs, not a record from which the engineered cases must be subtracted.
- The second is that dose exposure substantially exceeds patient exposure**.** In the non-transplant AML cohort patients received one to six infusions each, at doses reaching 21.48×10^9 cells per dose [1]; the pediatric and consolidation studies gave repeated cycles; the NK-92 trial gave up to six monthly cycles of three infusions each [23]. The true infusion-level denominator is therefore several thousand exposures, which matters because infusion reactions are per-exposure events while the durable toxicities of interest are per-patient events.

4.2 The denominator partitioned by architecture

Partitioning by disease, as Table 2 does, is conventional but it is not the appropriate partition for this argument. Disease determines the population's baseline event rate; it does not determine which toxicity channels are available to the product. Three attributes determine the potential toxicity of a cellular product — whether an HLA disparity exists

between product and recipient, whether a transgene has been integrated, and what is given alongside the cells — and the first two partition the class cleanly into three categories. Table 3 performs the partition.

TABLE 3

The three architectural categories, their exposure, and their aggregate toxicity

ATTRIBUTE	CATEGORY 1: NON-ENGINEERED AUTOLOGOUS	CATEGORY 2: NON-ENGINEERED ALLOGENEIC OR OTHERWISE HLA-DISPARATE	CATEGORY 3: CAR-ENGINEERED
Countable N	~73 strict ~108 inclusive of autologous α-GalCer-pulsed APC products [12–17,39]	~1,300–1,500 [1,2,23–28,34,52]	150 CAR-NK published [7]; 1,193 CAR-T in the DLBCL systematic review [6], carried as comparator only
Doses	≥135 strict, ≥170 inclusive, from reported schedules SUPLEXA-101 adds 220+ doses in 35 patients — 6.3 per patient, the highest density in the class	~1,041 doses across 607 patients in the AML literature alone, mean 1.71 per patient, reconstructed from the per-study schedules in [52] ~2,400–2,700 across the full category (modeled)	Predominantly single administration; CAR-T is given once by design
HLA disparity	**None by construction**	Present in essentially all exposure — haploidentical, cord blood, unrelated donor, immortalized line, iPSC-derived	Absent in autologous CAR-T; present in allogeneic CAR-NK
CRS, any grade	**None reported**	~3% ungraded across 406 [1]. In [52] all CRS was confined to the subcutaneous IL-15 cohort of one trial: 9 cases, 4 of grade ≥3 [8]	7% CAR-NK [7,42]; 67% CAR-T [6]
CRS, grade ≥3	**None reported**	Confined to the subcutaneous rhIL-15 arm [8,52]	0% CAR-NK [7]; 13% CAR-T (10% G3, 3% G4) [6]
Neurotoxicity / ICANS	**None reported**	Five cases, all in the subcutaneous IL-15 cohort [8,52]; one grade 4 event in an expanded-NK trial [32,52]	None reported in CAR-NK [7]; a defining CAR-T class toxicity [6,43]

ATTRIBUTE	CATEGORY 1: NON-ENGINEERED AUTOLOGOUS	CATEGORY 2: NON-ENGINEERED ALLOGENEIC OR OTHERWISE HLA-DISPARATE	CATEGORY 3: CAR-ENGINEERED
Dose-limiting toxicity	**None reported. MTD not reached wherever escalated, including an exploratory dose of 1×10^{10} cells/m² [12,39]**	1 (grade 3 skin rash, iPSC-derived allogeneic iNKT) [19]	Dose-limiting toxicity routine in CAR-T dose finding
Genotoxicity	**This channel does not exist for a non-engineered product**	None — no vector	Class boxed warning for T-cell malignancies; lifelong monitoring recommended [20,21]
Graft-versus-host disease	**This channel does not exist for an autologous product**	1 event in 406 non-transplant patients, ~0.25% [1,32]; 0–8% across 607 patients in [52]	0 in CAR-NK even in HLA-mismatched recipients [7,40]
Host-versus-graft rejection	**This channel does not exist for an autologous product**	Present. Source of the CIML NK day 10–14 CRS and of graft loss [9,48]	Present in allogeneic CAR-NK; drives limited persistence
Residual attributable to the cells	**Three grade 3 events, all in one HCC study, all resolving without treatment [12]. Everything else grade 1–2 infusional.**	One GvHD event, one DLT. All else assigns to conditioning, cytokine, or allo-rejection (Section 8)	The full engineered-cell toxicity architecture

Category 3 is not part of the class denominator (Section 3) and is carried here only so the gradient is visible. The 600-patient solid tumor pool [2] cannot be apportioned between categories 1 and 2 from the published source and is assigned to category 2 for conservatism, which understates category 1.

FIGURE 2

Toxicity channels by architectural category

	CAT. 1 AUTOLOGOUS	CAT. 2 ALLOGENEIC	CAT. 3 CAR-ENGINEERED
Graft-versus-host disease	○ Not possible	● ~0.25% (1 in 406)	● 0 in CAR-NK
Host-versus-graft rejection	○ Not possible	● Present	● Allogeneic CAR-NK
CRS, any grade	● None reported	● ~3%	● 7% CAR-NK · 67% CAR-T
CRS, grade ≥3	● None reported	● SC rhIL-15 arm only	● 0% CAR-NK · 13% CAR-T
Neurotoxicity / ICANS	● None reported	● IL-15 cohort; 1 grade 4	● Defining CAR-T toxicity
Dose-limiting toxicity	● None; MTD not reached	● 1 (iPSC iNKT)	● Routine in CAR-T
Genotoxicity	○ Not possible	● None; no vector	● Class boxed warning

○ Not possible by construction ● None reported ● Present, low rate or confined ● Present, substantial

Summary of Table 3. Category 3 is carried as a comparator only and is not part of the class denominator.

The table lists three attributes that are not applicable to autologous, non-engineered SUPLEXA. HLA disparity governs graft-versus-host disease and host-versus-graft rejection; it does not govern CRS magnitude. The transgene governs CRS magnitude and genotoxicity; it does not govern GvHD, which is why CAR-NK produces none, even in mismatched recipients [7,40]. Effector lineage sets the ceiling on the transgene's effect, which is why the same CAR architecture yields 7% CRS on an NK backbone and 67% on a T cell backbone [6,7]. Category 1 is the only cell of the matrix that is clean on both axes at once. Presenting this as a single ordered ranking would be simpler and would invite a correct objection; presenting it as two orthogonal axes survives scrutiny.

4.3 What the autologous category demonstrates

The autologous category is the smallest of the three, and its contents should be laid out patient by patient rather than asserted in aggregate. Table 4 does so. Two counts are given, following the convention set in Section 2: a strict count restricted to adoptive transfer of the effector cell itself, and an inclusive count that adds autologous α-GalCer-pulsed antigen-presenting cell products. These are autologous, non-engineered cell therapies that act through the endogenous iNKT compartment rather than through an infused effector. Every load-bearing statement in this document uses the strict count.

TABLE 4

What the autologous, non-engineered category contains

STUDY	PRODUCT	N	DOSES	REPORTED SAFETY OUTCOME
Autologous NK + trastuzumab [39]	Expanded activated autologous NK	22	22+ (schedule not fully reported)	Well tolerated across dose escalation; MTD not reached. The largest autologous NK exposure in the category
Exley et al., melanoma [16]	Autologous in vitro expanded iNKT	9	27 (3 each)	Three infusions each completed; only grade 1–2 toxicities
Autologous iNKT + PD-1^{+}CD8^{+} T cells, pancreatic [17]	Autologous iNKT	15 (9 completed ≥3 cycles; 59 courses)	59 courses	No side effects above grade 2. Fever peaking 2–4 h and reverting within 24 h without treatment
Chiba University Phase I [14]	Autologous ex vivo expanded Vα24 NKT	~9	~9	No severe treatment-related events
Kunii et al., HNSCC [15]	Autologous expanded NKT (intra-arterial) + α-GalCer-pulsed APC	8	8	NKT expansion in 7 of 8; no severe events
Gao et al., HCC [12]	Autologous α-GalCer-pulsed iNKT	10	10	No severe AEs related to infusion; three grade 3 events, all resolving untreated. Exploratory dose of 1 × 10^{10} cells/m² administered without dose-limiting toxicity — the entire severe-event record of the category

STUDY	PRODUCT	N	DOSES	REPORTED SAFETY OUTCOME
STRICT SUBTOTAL	**Adoptive autologous NK/NKT transfer**	**~73**	**≥135**	**0 GvHD, 0 allo-rejection, 0 CRS, 0 neurotoxicity, 0 DLT, 3 self-resolving grade 3 events**
Chiba University Phase II [13]	Autologous α-GalCer-pulsed APC (acts via endogenous iNKT)	35	35	No severe adverse events related to treatment; 32 of 35 completed
INCLUSIVE SUBTOTAL	**Adding autologous APC products**	**~108**	**≥170**	**Unchanged event record**
Unapportioned	Autologous fraction of the 600-patient unmodified solid tumor pool [2]	Indeterminate	Indeterminate	The published source does not separate autologous from allogeneic. Assigned to category 2 for conservatism; the true category 1 count is therefore higher than stated

The claim that survives this qualification. It is that a non-engineered autologous product is clean by construction on two of the three toxicity channels the class exhibits, clean in observation on the third, and free of the genotoxic hazard that generated a boxed warning in category 3. Zero graft-versus-host disease and zero host-versus-graft rejection follow from the absence of HLA disparity. They are not observations that a larger series could overturn — the channels do not exist, and no accumulation of counter-evidence is possible short of a manufacturing failure that introduced allogeneic material. Zero CRS and zero neurotoxicity are different in kind. They are real observations in a real series, but at 73 to 108 patients the rule of three bounds an unobserved event only at approximately 4.1% and 2.8% respectively, and the rate observed in category 2 is approximately 3%.

Two composition caveats should be noted. The first is that category 1 is NKT-weighted: on the strict count roughly 51 of 73 patients received an NKT or iNKT product and roughly 22 received autologous NK [39]. For a product containing both populations this is arguably the favorable composition, but the autologous NK column is thin and should not be represented otherwise.

The second is that the counterargument a reviewer will raise is not a safety argument at all: that the autologous category is clean because autologous effector cells recovered from a cancer patient are functionally impaired, and an inert product is trivially a safe one. This document carries no efficacy data and therefore cannot address that question. It belongs in the product response dataset and should be addressed separately in the material brought to the FDA meeting.

4.4 Representative individual trials

Table 5 lists the individual studies that carry most of the weight in Sections 5 through 9, with the category assignment of each made explicit so that no reader must infer it.

TABLE 5

Representative individual trials contributing to the database

TRIAL / PROGRAM	SETTING	N	PRODUCT	CATEGORY	SAFETY OUTCOME AS REPORTED
Miller et al., seminal haploidentical NK [5]	R/R AML	43	Haploidentical PB NK, IL-2 support	2	Established in vivo expansion and remission induction without GvHD
Bachanova et al. [29]	R/R AML, IL-2DT arm	57	Haploidentical NK + IL-2 diphtheria toxin	2	Improved clearance; toxicity attributable to conditioning and cytokine
Rubnitz et al., NKAML [10]	Pediatric AML consolidation	10	Haploidentical NK, CD3 depletion / CD56 selection	2	Safe and feasible; no GvHD
Nguyen et al. [11]	Pediatric AML consolidation, Phase II	21	Haploidentical NK	2	No severe toxicity attributed to product
Ciurea et al. [30]	Multiply R/R AML	13	mbIL-21 ex vivo expanded haploidentical NK	2	Tolerated at expanded doses
Fehniger et al., CNDO-109 [31]	High-risk AML in CR	15	Tumor-lysate-primed NK, no cytokine support	2	Feasible and safe; notable as a cytokine-free regimen

TRIAL / PROGRAM	SETTING	N	PRODUCT	CATEGORY	SAFETY OUTCOME AS REPORTED
Silla et al. [32]	R/R AML	9	Double-bright expanded NK	2	One GvHD event — the single case in the pooled AML series
Ahmadvand et al. [33]	AML, Phase I	10	Allogeneic PB NK	2	No grade 2–5 toxicity attributed to infusion; 4 patients grade 1 chills, headache, vomiting, bone pain
Dolstra et al. [34]	Older AML	10	Cord blood CD34-derived NK	2	No GvHD in HLA-mismatched setting
Berrien-Elliott / Bednarski / Shapiro, CIML NK [9,35,36]	AML, post-transplant relapse	~60 across program	IL-12/15/18 memory-like NK	2	Source of the definitive allo-rejection attribution data
Lee et al., randomized [37]	High-risk AML/MDS post haplo-HCT	Randomized	IL-15/IL-21 activated donor NK	2	One of the few randomized safety comparisons in the class
Jaiswal et al. [38]	Haplo-HCT with PTCy	10	CD56-enriched donor cells (NK + NKT-like retained)	2	Grade 2–4 acute GvHD 0% versus 50% in controls, p = 0.01
Autologous NK + trastuzumab [39]	HER2-positive refractory solid tumors	22	Expanded activated autologous NK	1	Well tolerated; MTD not reached
NK-92 Phase I [23]	R/R heme malignancy after auto-HCT	12	Irradiated NK-92 line, up to 6 monthly cycles	2	Toxicity entirely acute infusional: fever, chills, nausea, fatigue
Cooley et al., rhIL-15 [8]	Advanced AML	26	Haploidentical NK + subcutaneous rhIL-15	2	CRS and neurotoxicity — the one severe signal in the class. See Section 8

Category per Section 4.2. Green = clean safety outcome attributable to the cell product. Blue = clean outcome with an additional comparative or mechanistic finding. Amber = clean outcome, non-comparable architecture. Red = the trial carrying the class's severe toxicity signal. Note that fourteen of the fifteen studies below sit in category 2 — the individual-trial evidence base is overwhelmingly allogeneic, which is why the category view in Table 3 is necessary and the trial-by-trial view is not sufficient.

SECTION 5

Graft-versus-host disease

This is the strongest finding in the database, but notably it is not applicable to SUPLEXA. In the pooled AML analysis covering 406 patients, exactly one patient showed any sign of GvHD [1,32]. The finding is not an artifact of autologous product: the great majority of that exposure was allogeneic, much of it haploidentical, and the absence of GvHD holds in explicitly HLA-mismatched settings including cord-blood-derived product [34]. It also holds in the engineered arm of the field, where CD19 CAR-NK produced no GvHD even in HLA-mismatched recipients [40], which isolates the finding to the effector lineage rather than to the manufacturing route. Note that the entire GvHD record of the class sits in category 2 of Table 3; in category 1 the count is zero for the structural reason that there is no HLA disparity to react against, and that zero is a consequence of the architecture rather than a finding about it.

TABLE 6

Graft-versus-host disease across the non-engineered NK series

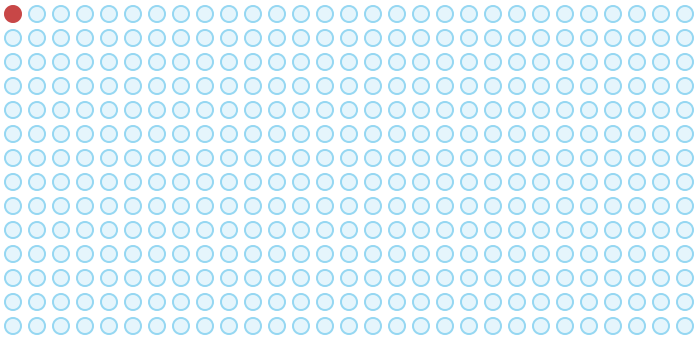
SETTING	PATIENTS	GVHD EVENTS	INTERPRETATION
Non-transplant NK infusion, pooled AML analysis [1]	406	**1**	The headline figure. Approximately 0.25%. This is the number to quote
HLA-mismatched cord-blood-derived NK [34]	10	**0**	No GvHD despite mismatch — the mechanistically decisive setting
CD19 CAR-NK, HLA-mismatched [7,40]	150 (engineered comparator)	**0**	Absence persists after transgene addition, isolating the finding to lineage
CD56-enriched donor infusion after PTCy [38]	10	**0 grade 2–4 acute**	Versus 50% in controls, p = 0.01. NKT-like cells retained by single-step CD56 selection and associated with reduced, not increased, GvHD

SETTING	PATIENTS	GVHD EVENTS	INTERPRETATION
Transplant-setting cohort, pooled AML analysis [1]	342	37.3% acute, 23.7% chronic	DO NOT POOL. These are the GvHD rates of the allogeneic transplant these patients received, not of the NK infusion. A reviewer reading Table 4a of the source review without this distinction will reach the wrong conclusion

The last row is included specifically so that the confounded figure is disclosed and disarmed rather than left to be discovered.

FIGURE 3

Graft-versus-host disease in non-transplant NK infusion



1 of 406

patients showed any sign of GvHD, approximately 0.25%.

Each dot is one patient in the pooled AML non-transplant cohort [1,32]. Transplant-setting GvHD rates are excluded; see Table 6.

The NKT-like observation in the fourth row is worth more than its sample size suggests. Single-step CD56 positive selection retains CD56-positive CD3-positive NKT-like cells that two-step CD3-depletion-then-CD56-selection discards. The trial that retained them saw less acute GvHD, not more [38], consistent with the older observation that CD8-expressing NKT-like cells produce IL-4 and promote regulatory T cell expansion [41]. For a product containing both NK and NKT-like populations, this is the relevant literature: the NKT-like fraction is associated with GvHD suppression rather than GvHD risk.

SECTION 6

Cytokine release syndrome and neurotoxicity

CRS and immune effector cell-associated neurotoxicity are the toxicities that define the risk-benefit of engineered CAR-T cell therapy and the toxicities that most directly obstruct any argument for treating early-stage patients, where watch-and-wait may be the standard of care. The class record here is favorable for the NK/NKT-like cell class by an order of magnitude, and the residual signal is fully attributable to other components of the therapy.

TABLE 7

CRS and neurotoxicity: NK/NKT-like against engineered-cell benchmarks

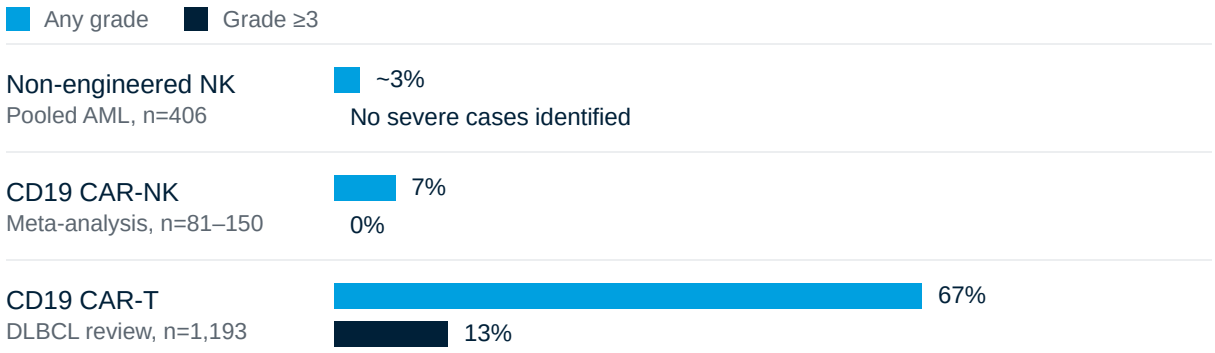
PRODUCT CLASS	PATIENTS	CRS ANY GRADE	CRS GRADE ≥3	NEUROTOXICITY
Non-engineered NK, pooled AML [1]	406	**~3% (13 events, CRS and neurotoxicity combined, ungraded)**	**Not reported as a distinct category**	Included in the 13; no severe cases identified
Unmodified NK, solid tumors [2]	600	Not a leading event; fatigue predominates	Not reported	Not reported
iNKT, cumulative early literature [18]	~250–350	Five grade ≥2 treatment-related AEs of any type across the whole literature	None reported	None reported
CD19 CAR-NK, meta-analysis [7,42]	81–150	7%	**0%**	None; no GvHD
CD19 CAR-T in DLBCL, systematic review [6]	1,193	**67%**	**13% (10% G3, 3% G4)**	Substantial; ICANS a defining class toxicity
CD19 CAR-T, field-wide range [43]	—	50–90%	10–20%	Substantial

PRODUCT CLASS	PATIENTS	CRS ANY GRADE	CRS GRADE ≥3	NEUROTOXICITY
Haploidentical NK + subcutaneous rhIL-15 [8]	26	**Significant**	**Present**	Present — the class exception, attributed to the cytokine (Section 8)

Grading heterogeneity is a genuine limitation: trials predating the 2019 ASTCT consensus [44] used institutional criteria. The direction and magnitude of the difference are nonetheless not in dispute.

FIGURE 4

Cytokine release syndrome: NK class against engineered-cell benchmarks



Sources [1,6,7,42]. NK figure combines CRS and neurotoxicity events and is ungraded. Scale 0–100%.

The mechanistic reason the class does not produce CRS. The cytokine storm of CAR-T is IL-6-dominated and driven by monocyte and macrophage activation downstream of massive, antigen-driven, exponentially expanding T cell activity. NK cells secrete IFN-γ and IL-15 rather than driving an IL-6-dominated cascade, do not undergo comparable in vivo exponential expansion, and persist for weeks rather than years [43]. The same biology that limits NK persistence — the field's central efficacy problem — is what limits its toxicity. A product intended for early intervention is on the favorable side of that trade.

SECTION 7

The routine adverse event profile

Stripped of chemotherapy preconditioning and cytokine support, what remains in the class is an infusion-reaction profile, shown in Table 8.

TABLE 8

The routine adverse event profile of NK and NKT-like infusion

EVENT	TYPICAL GRADE	TIMING	REPRESENTATIVE SOURCE AND COMMENT
Fatigue	1–2	Days	Most common AE in the 600-patient solid tumor pooled analysis [2]
Fever / chills	1–2	Hours; resolving within 24 h	Peaks 2–4 h post-infusion and reverts within 24 h without treatment [17]; grade 1 transient chills in the AML Phase I [33]
Influenza-like syndrome (headache, myalgia, arthralgia)	1–2	Hours to 1–2 days	Reported in a minority of patients across cancer iNKT series [17]
Nausea / vomiting	1–2	Peri-infusional	Acute infusional only in the NK-92 series [23]
Bone pain	1	Peri-infusional	Reported in 4 of 10 patients, no hospitalization required [33]
Injection-site reactions	1–2	Immediate	Where intradermal or submucosal routes used [45]
Transient transaminase elevation	1–2	Days	Minor LFT abnormality, symptomatically managed [45]
Grade 3 events, iNKT HCC series	3	Days	3 grade 3 events in 10 patients, all resolved without treatment [12]
Grade 3 skin rash	3	Second dose	Single DLT in the iPSC-derived allogeneic iNKT trial; no other severe AE in that study [19]

EVENT	TYPICAL GRADE	TIMING	REPRESENTATIVE SOURCE AND COMMENT
Cytopenias, febrile neutropenia, infection	3–4	Days 5–21	Present wherever Cy/Flu lymphodepletion is used. Attributable to conditioning, not to cells (Section 8)

Premedication with acetaminophen and an antihistamine is standard in this class and is sufficient to manage the grade 1–2 infusional profile [26].

Maximum tolerated dose is repeatedly not reached. This is a pattern rather than an isolated result: MTD was not reached in the autologous NK-plus-trastuzumab dose escalation at 22 patients [39], in the NK-92 escalation through 5×10^9 cells per square meter given on three days of each of six monthly cycles [23], and in the iNKT hepatocellular carcinoma study, where an exploratory dose of 1×10^{10} cells per square meter — more than a hundred-fold above the escalation range — was administered [12]. A dose-toxicity curve that stays flat across two to three logs is a different regulatory object from one that has a defined ceiling, and it is the correct empirical basis for arguing that cell dose is not the risk variable in this class. Two of the three studies establishing the pattern sit in category 1.

SECTION 8

Attribution of toxicities

Here, toxicity can be assigned to the individual components of a cell therapy, including the cell product itself, and the primary literature by the investigators has already made those assignments. The 2026 AML meta-analysis makes the assignment explicit at trial level: across its 607 patients, all reported cases of cytokine release syndrome and neurotoxicity were confined to the subcutaneous IL-15 cohort of a single study — nine CRS cases, four of grade 3 or above, and five neurotoxicity cases — with one further grade 4 neurotoxicity event in an expanded-NK trial [52,8,32].

Three non-cell factors account for the entire severe-toxicity signal in the class. Table 9 sets out the architecture; Table 10 audits the individual events.

TABLE 9

Attribution architecture of severe toxicity in the NK/NKT-like class

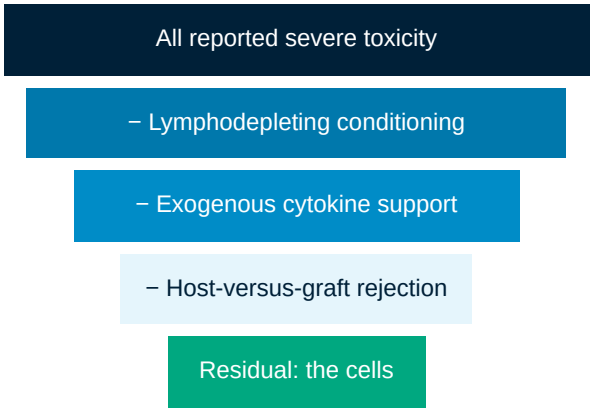
NON-CELL FACTOR	WHAT IT PRODUCES	EVIDENCE THAT IT, AND NOT THE CELLS, IS RESPONSIBLE
NON-CELL FACTOR 1 **Lymphodepleting conditioning (Cy/Flu)**	Grade 3–4 cytopenias, febrile neutropenia, infection, and the non-relapse mortality that follows from them	Present in every trial that lymphodepletes and absent from those that do not. The purpose of conditioning is stated in the literature as eliminating host T cells and inducing endogenous IL-15 and IL-7 [46] — it is a regimen component with its own well-characterized toxicity, imported wholesale from transplant practice
NON-CELL FACTOR 2 **Exogenous cytokine support (IL-2, rhIL-15, ALT-803/N-803)**	CRS, neurotoxicity, capillary leak, fever, skin infiltrates	The decisive evidence. Subcutaneous rhIL-15 after lymphodepletion prolongs drug exposure and produces CRS and neurotoxicity; intravenous dosing of the same cytokine does not [8,47]. Subcutaneous ALT-803 produced significant skin reactions from lymphoid infiltrate that were absent with rhIL-15 [8]. The toxicity tracks the cytokine and its route, not the cells

NON-CELL FACTOR	WHAT IT PRODUCES	EVIDENCE THAT IT, AND NOT THE CELLS, IS RESPONSIBLE
NON-CELL FACTOR 3 **Host-versus-graft allo-rejection**	CRS at days 10–14, loss of infused product, treatment failure	Resolved mechanistically in the CIML NK program: CRS-consistent fever and inflammatory markers at days 10–14 coincided with expansion of activated recipient CD8 T cells (CD38+ HLA-DR+), with donor NK numbers declining inversely. The investigators attributed the CRS to allo-rejection of the graft [9]. Systemic IL-15 was subsequently shown to promote allogeneic cell rejection directly [48]
RESIDUAL **Attributable to the cells themselves**	Grade 1–2 infusion reactions: fever, chills, fatigue, nausea, transient LFT changes	What remains after the three channels are removed. Self-limited, premedication-manageable, and not dose-limiting across two to three logs of cell dose

Read downward: each channel is removed in turn, and what survives at the bottom is the toxicity properly attributable to the cell product.

FIGURE 5

Attribution of severe toxicity: each non-cell factor removed in turn



Whole class, ~1,700–1,900 patients

Grade 3–4 cytopenias, febrile neutropenia, infection

CRS, neurotoxicity, capillary leak, skin infiltrates

Day 10–14 CRS, loss of infused product

Grade 1–2 infusion reactions; one GvHD event, one DLT

Summary of Tables 9 and 10. SUPLEXA uses none of the three non-cell factors.

TABLE 10

Attribution audit of every reported severe toxicity signal in the class

REPORTED SIGNAL	WHERE REPORTED	ASSIGNED TO	BASIS FOR THE ASSIGNMENT

REPORTED SIGNAL	WHERE REPORTED	ASSIGNED TO	BASIS FOR THE ASSIGNMENT
CRS and neurotoxicity	Haploidentical NK + subcutaneous rhIL-15, n=26 [8]	**NON-CELL FACTOR 2**	The trial report's own stated conclusion: subcutaneous dosing after lymphodepletion prolongs drug exposure leading to CRS and neurotoxicity. The comparator arm establishes route-dependence — intravenous rhIL-15 did not produce it [47]
CRS at days 10–14	CIML NK + ALT-803 lead-in, first 2 patients [9]	**NON-CELL FACTOR 3**	Correlative immunology showed recipient CD8 T cell expansion with activated phenotype and inverse decline in donor NK cells. Reducing ALT-803 exposure did not abolish it; the driver was rejection of the graft
Significant skin reactions from lymphoid infiltrate	Subcutaneous ALT-803 program [8]	**NON-CELL FACTOR 2**	Absent in the rhIL-15 study using the same cell product, establishing the cytokine rather than the cells as the cause
Grade 3–4 cytopenias, febrile neutropenia, infection	All lymphodepleted trials [1,5,29]	**NON-CELL FACTOR 1**	Toxicity of cyclophosphamide/fludarabine, characterized independently over decades of transplant practice
Capillary leak, fever, Treg expansion	IL-2-supported trials [5,29]	**NON-CELL FACTOR 2**	Established IL-2 toxicity. IL-2 was replaced by IL-15 in later trials specifically to avoid its Treg effect [46]
One GvHD event	Expanded double-bright NK, R/R AML [32]	**Cells (allogeneic product)**	The single event in 406 patients that cannot be assigned elsewhere. Retained as an attributable-to-product event for conservatism
Grade 3 skin rash (DLT)	iPSC-derived allogeneic iNKT, HNSCC [19]	**Cells (allogeneic iPSC product)**	The only modern DLT in the NKT-like literature. Occurred with an allogeneic reprogrammed product; does not read across to autologous peripheral-blood-derived product
Three grade 3 events	Autologous iNKT, HCC, n=10 [12]	**Cells (possible)**	All resolved without treatment

REPORTED SIGNAL	WHERE REPORTED	ASSIGNED TO	BASIS FOR THE ASSIGNMENT
DOSES CONSIDERED	**Whole class**	**—**	**~2,400–2,700 cellular exposures (modeled), of which ~1,041 are individually constructible from the per-study schedules in [52]. The severe events above arise from 26 patients in one cytokine cohort and two patients in a lead-in cohort — fewer than 40 exposures out of several thousand**
NET RESIDUAL	**Whole class, ~1,700–1,900 patients**	**Cells**	**One GvHD event, one grade 3 DLT, three self-resolving grade 3 events. Everything else assigns to conditioning, cytokine, or allo-rejection**

The audit is deliberately conservative: every event that cannot be affirmatively assigned to a non-cell channel is assigned to the cells, including events the original investigators considered unrelated.

Why the attribution analysis is the argument. A reviewer confronted with a low event rate in small single-arm studies will discount it, correctly, as possibly an artifact of sample size and short follow-up. A reviewer confronted with an attribution audit showing that the severe events which did occur are assigned by the investigators themselves to conditioning chemotherapy, to a subcutaneously dosed cytokine whose intravenous form does not produce the effect, and to host rejection of an allogeneic graft — cannot discount it on the same basis, because the analysis predicts which regimens will be toxic and which will not, and the prediction has already been tested within the class.

The corollary that matters. A non-engineered autologous product given without lymphodepleting conditioning and without exogenous cytokine support carries none of the three channels. Its expected toxicity is therefore limited to the residual: grade 1–2 infusion reactions. That is a mechanistic prediction, not an extrapolation from a favorable average.

SECTION 9

The NKT-like cell sub-database

The NKT-like record is roughly one-fifth the size of the NK record. Overstating it invites a correction that damages the rest of the document. The cumulative exposure to adoptively transferred NKT-like or invariant NKT-like cells is on the order of 250 to 350 patients (estimated), accumulated over two decades and concentrated in a small number of centers.

TABLE 11

The NKT-like clinical exposure record

PROGRAM	INDICATION	N	SAFETY OUTCOME AS REPORTED
Chiba University, α-GalCer-pulsed APC, Phase II [13]	Advanced/recurrent NSCLC	35	No severe adverse events related to treatment; 32 of 35 completed. Median survival 21.9 months
Chiba University, expanded NKT cells, Phase I [14]	Advanced/recurrent NSCLC	~6–12	First-in-human ex vivo expanded Vα24 NKT; no severe treatment-related events
Kunii et al., NKT + α-GalCer-pulsed APC [15]	Recurrent head and neck SCC	8	Intra-arterial infusion plus submucosal APC; NKT expansion in 7 of 8; no severe events
Exley et al., autologous expanded iNKT [16]	Stage IIIB–IV melanoma	9	Three infusions each completed in 9 patients, producing only grade 1–2 toxicities. Feasible and safe
Gao et al., autologous iNKT [12]	Advanced HCC (BCLC B/C)	10	No severe AEs related to infusion; most events grade 1–2 resolving within a week; three grade 3 events all resolving untreated. Exploratory dose of 1×10^{10} cells/m² administered
Autologous iNKT + PD-1^{+}CD8^{+} T cells [17]	Stage IV pancreatic cancer, post first-line failure	15 (9 completed ≥3 cycles; 59 courses)	Fever most common, peaking 2–4 h and reverting within 24 h without treatment. No side effects above grade 2

PROGRAM	INDICATION	N	SAFETY OUTCOME AS REPORTED
agenT-797, allogeneic donor-unrestricted iNKT [28]	Moderate–severe ARDS secondary to SARS-CoV-2	21 ventilated (5 on VV-ECMO)	No dose-limiting toxicities at doses to 10^9 cells. Anti-inflammatory systemic cytokine response; only transient donor-specific antibodies. The most acutely ill population ever given a cell therapy of this class
iPSC-derived allogeneic iNKT, Phase I [19]	Recurrent head and neck cancer	10	One grade 3 skin rash at second dose, identified as DLT. No other severe adverse events in any patient
Cumulative early adoptive iNKT literature [18]	NSCLC, HNSCC, HCC, pancreatic, melanoma	**~250–350 (estimated)**	**Only five treatment-related adverse events of grade ≥2 reported across the entire body of work**

Three observations from the NKT-like cell record are relevant for a combined NK/NKT-like cell product like SUPLEXA.

- The first is the ARDS study [28]: mechanically ventilated patients, five of them on veno-venous ECMO, received up to 10^9 allogeneic iNKT cells as a single infusion without dose-limiting toxicity, and the systemic cytokine response was anti-inflammatory rather than inflammatory. If **a donor-unrestricted iNKT product is tolerable** in that population, **the tolerability argument in an ambulatory precursor-disease patient is not a stretch**.
- The second is that the **NKT-like cell toxicity that does exist is concentrated in non-autologous, non-peripheral-blood architectures**. The only modern dose-limiting toxicity in the NKT-like literature occurred with an allogeneic iPSC-derived product [19]. The autologous peripheral-blood-derived series report grade 1–2 profiles almost uniformly [16,17]. This is the same architectural gradient seen on the NK side and it runs in SUPLEXA's favor.
- The third is that **NKT-like cells are associated with suppression of alloreactivity rather than with its induction**. The CD56-enriched infusion study, which by design retained NKT-like cells, reported 0% grade 2–4 acute GvHD against 50% in controls [38]. The mechanistic literature supports this: CD8-expressing NKT-like cells produce IL-4 and promote regulatory T cell expansion, and NKT-like cells preserve graft-versus-leukemia effect without increasing GvHD [41,49]. A product containing an NKT-like fraction should therefore not be assumed to carry additional alloreactive risk; the literature points the other way.

SECTION 10

Exposure outside advanced oncology

The thinnest part of the database is also the most relevant to an early-intervention indication. Nearly all NK and NKT-like exposure has been in patients with advanced, treatment-refractory malignancy — a population with high competing-risk mortality, in which mild toxicity is under-ascribed and late toxicity is never observed because the patients do not survive to it. The non-oncology exposure is small, but it is not zero, and its character is instructive.

TABLE 12

Exposure outside advanced oncology

SETTING	PRODUCT	N	OUTCOME
SARS-CoV-2 ARDS, mechanically ventilated [28]	Allogeneic ex vivo expanded iNKT (agenT-797)	21	No dose-limiting toxicities including in 5 patients on VV-ECMO; anti-inflammatory cytokine response; persistence with only transient donor-specific antibodies
COVID-19 pneumonia, RELEASE Phase I [25]	Memory NK from convalescent donors, $CD3^-/CD56^+$	6	No serious adverse events after infusion; no DLT identified at 1–2 × 10^6 cells/kg
Hospitalized COVID-19 [26]	Off-the-shelf allogeneic unmodified NK (DVX201)	9	Infusions well tolerated with no treatment-related adverse events and no inflammatory complications; median time to discharge 2 days
COVID-19 acute pneumonia [27]	Ex vivo expanded allogeneic NK	~10	Intravenous infusion safe and feasible; inflammatory parameters improved at discharge
Subtotal, non-malignant indications	**Unmodified NK and iNKT**	**~45–50**	**No serious product-attributable adverse events across the group**

The pattern in the non-oncology data is the one that most directly answers the advanced-disease-first objection. The concern about giving an immune effector product to a patient with viral pneumonia is precisely the concern about giving it to an asymptomatic

precursor-disease patient: that in the absence of a large tumor sink, systemic immune activation will manifest as toxicity. That assumption is not borne out by the literature. The cytokine response observed in the ARDS study was anti-inflammatory [28], and the COVID series recorded no inflammatory complications related to infusion [26]. The class does not behave as a systemic inflammatory agent when given to patients without bulky disease.

The gap that remains. There is no healthy-volunteer exposure to a non-engineered NK or NKT-like cell product, and none should be claimed. Healthy-volunteer cell therapy studies exist in adjacent product classes but not here. This is recorded in Section 12 as a genuine limitation rather than papered over.

SECTION 11

Genotoxicity, secondary malignancy, and the engineering boundary

The most consequential safety development in cell therapy since 2023 does not apply to the non-engineered autologous NK/NKT-like cell class of which SUPLEXA is a member. In November 2023 the FDA opened an investigation into reports of T-cell malignancies, including CAR-positive lymphoma, following BCMA- or CD19-directed autologous CAR-T treatment [20]. In January 2024 the FDA initiated class safety labeling changes, and on 18 April 2024 it required boxed warnings for T-cell malignancies on the approved products, together with a recommendation that patients be monitored lifelong for secondary malignancy [20,21]. CBER leadership framed the forward-looking mitigation in terms of targeted insertion of the CAR construct to specific loci to reduce the risk of cancers arising from integration at oncogenic loci [50].

TABLE 13

The engineering boundary and its regulatory consequences

ATTRIBUTE	TRANSGENE-MODIFIED CELL THERAPY	NON-ENGINEERED NK/NKT-LIKE
Insertional mutagenesis hazard	Present. Vector integration at or near oncogenic loci is a recognized mechanism; mitigation strategies now focus on site-directed insertion [50]	**Absent. No vector, no integration event, no locus to disrupt**
Secondary malignancy labeling	Class-wide boxed warning required April 2024 on all approved BCMA- and CD19-directed autologous CAR-T products [20,21]	**No class signal, no class warning**
Long-term follow-up expectation	Lifelong monitoring recommended, extending the previous 15-year mandatory follow-up [20,51]	**Standard cellular-product follow-up; the gene-therapy LTFU rationale does not attach**
Clonal expansion risk	CAR-positive clonal lymphoma documented in case reports [51]	**No engineered clonal marker; no reported clonal outgrowth in the class**

ATTRIBUTE	TRANSGENE-MODIFIED CELL THERAPY	NON-ENGINEERED NK/NKT-LIKE
Residual manufacturing considerations	Vector copy number, RCR/RCL testing, integration site analysis	Feeder-cell residuals and irradiation adequacy where feeder lines are used; cell line identity where an immortalized line is used
Consequence for precursor indications	A lifelong secondary-malignancy warning is very difficult to reconcile with treating an asymptomatic patient who may never progress	**The only cell-therapy architecture for which a precursor-disease risk-benefit calculation is straightforwardly constructible**

The argument still supports CAR-T, but only in a population with advanced disease. It is not that CAR-T is unsafe — the FDA concluded that the benefits of the marketed products continue to outweigh their risks for their approved uses [20]. Conversely, the risk-benefit arithmetic changes fundamentally when it involves an asymptomatic patient with a precursor condition, most of whom will not progress within the follow-up window. In that population a lifelong-monitoring secondary-malignancy warning is close to disqualifying, and the absence of the underlying hazard is not a marginal advantage but the entry condition.

SECTION 12

What the database does not establish

The value of this document to a regulatory interaction depends on its limitations being stated before a reviewer states them. Table 14 lists them and, for each, what it costs the argument and what mitigates it.

TABLE 14

Gaps in the pooled database and what each costs the argument

LIMITATION	WHAT IT COSTS	MITIGATION
The autologous category is small: ~73 patients on the strict count	Zero CRS and zero neurotoxicity in category 1 bound an unobserved rate only at ~4.1% by the rule of three, which brackets the ~3% observed in category 2. The two categories are not yet statistically separated on CRS	The two structural zeros — GvHD and allo-rejection — are unaffected, because they follow from the absence of HLA disparity rather than from observation. Only the CRS claim is underpowered, and it should be stated as consistent observation rather than established absence
Category 1 is NKT-like-weighted	On the strict count roughly 51 of 73 patients received an NKT-like or iNKT product against roughly 22 receiving autologous NK. The autologous NK column is thin	For a product containing both populations this is arguably the favorable composition, but it should be disclosed rather than left to be noticed
The 600-patient solid tumor pool cannot be apportioned by category	The published source [2] does not separate autologous from allogeneic exposure, so an unknown number of category 1 patients are counted in category 2	Assigned to category 2 for conservatism, which understates rather than overstates the autologous count
The counterargument to category 1 is an efficacy argument, not a safety one	A reviewer may hold that autologous effector cells recovered from a cancer patient are functionally impaired, and that an inert product is trivially safe	This document carries no efficacy data and cannot answer it. The answer belongs in the product response dataset and should be brought to the same meeting

LIMITATION	WHAT IT COSTS	MITIGATION
Predominantly single-arm Phase 1/2 studies with small n	No control arms means no attributable-risk estimate; rare events are undetectable	The NSCLC meta-analysis contributes five randomized controlled comparisons showing similar adverse event rates between arms (OR 1.37, 95% CI 0.35–5.26) [3], and the CD56-enriched study is controlled [38]
Advanced, refractory populations with high competing-risk mortality	Late and subtle toxicity is systematically under-observed	Partly offset by the non-oncology exposure in Section 10 and by the pediatric consolidation studies, where patients were in remission and survived to observation [10,11]
Short follow-up; no long-term registry	No multi-year safety database exists for any product in this class	Genuine and unmitigated. Section 11 argues the genotoxic basis for long-term concern is absent, but absence of a mechanism is not the same as follow-up data
Heterogeneous adverse event grading	Trials predating the 2019 ASTCT consensus [44] used institutional CRS criteria; pooled rates are not strictly comparable	The magnitude of the difference against CAR-T (3% versus 67%) is far larger than any plausible grading artifact
The dose denominator is reconstructed, not reported	No source reports total cellular exposures. The ~1,041-dose figure is derived by multiplying per-study patient counts by the infusion schedules tabulated in [52], and the ~2,400–2,700 class figure extrapolates from it	The derivation is arithmetic on published table values and can be audited line by line. It is labeled derived and modeled respectively, and no claim rests on it alone
Repeat and chronic dosing exposure is thin	Most patients received 1–6 infusions; almost none received sustained or maintenance dosing	The NK-92 program gave up to six monthly cycles of three infusions [23]; the pancreatic iNKT study administered 59 courses across 9 patients [17]. SUPLEXA-101, with 220+ doses across 35 patients, materially adds to this specific gap
Autologous non-engineered exposure is smaller than allogeneic	The architecture closest to SUPLEXA has the thinner record	Reads across conservatively: allogeneic carries two toxicity channels that autologous does not (Section 3)
Publication bias in early-phase reporting	Negative safety outcomes in small, unregistered studies may be under-published	The systematic reviews used here searched gray literature, ClinicalTrials.gov, and ASH proceedings [1], which partly addresses this
No healthy-volunteer exposure	The cleanest possible demonstration is unavailable	Should not be claimed or worked around. State plainly

LIMITATION	WHAT IT COSTS	MITIGATION
Class data cannot substitute for product data	No pooled analysis licenses a safety claim for a specific product	This document establishes the prior. SUPLEXA-101 supplies the product-specific evidence. Neither is sufficient alone

One limitation deserves separate treatment because it is the strongest available counter-argument. A reviewer may say that a class record accumulated in patients with weeks-to-months life expectancy tells you nothing about what a living cell product does over the decades a precursor-disease patient will live. That limitation is real and cannot be resolved by the existing dataset. What can be said is that the concern is a concern about persistence and clonal behavior, and that NK cell persistence in vivo is measured in weeks to months rather than years [43] — the field's principal efficacy limitation is simultaneously the structural answer to its principal long-term safety question. Limited persistence correspondingly constrains the possibility of a late clonal event.

SECTION 13

Implications for SUPLEXA

The purpose of assembling this database is to establish what SUPLEXA inherits from its class and what it does not. Table 15 performs the read-across attribute by attribute.

TABLE 15

Read-across from the class database to SUPLEXA

CLASS ATTRIBUTE	CLASS RECORD	SUPLEXA STATUS	CONSEQUENCE
Architectural category	Category 1 carries no GvHD, no allo-rejection, no CRS, no neurotoxicity and no DLT across ~73 patients (Table 3)	**Category 1**	SUPLEXA sits in the cleanest of the three categories, not at the average of the pooled class
GvHD	1 event in 406 patients, predominantly allogeneic exposure [1]	**not relevant to SUPLEXA**	The residual class risk does not apply. No HLA disparity exists
Host-versus-graft allo-rejection (Channel 3)	Source of the CIML NK CRS signal at days 10–14 [9,48]	**not relevant to SUPLEXA**	The mechanism that produced the class's second severe signal cannot operate
Exogenous cytokine support (Channel 2)	Source of the class's only CRS/neurotoxicity signal, route-dependent [8,47]	**not relevant to SUPLEXA**	The mechanism that produced the class's principal severe signal cannot operate
Lymphodepleting conditioning (Channel 1)	Source of all grade 3–4 cytopenia, febrile neutropenia, infection in the class [46]	**not relevant to SUPLEXA**	The grade 3–4 hematologic toxicity of the class does not transfer
Transgene / insertional mutagenesis	Class-wide boxed warning and lifelong monitoring for engineered products [20,21]	**not relevant to SUPLEXA**	No genotoxic hazard; no basis for a secondary-malignancy warning
Manufacturing input	Leukapheresis standard across the class	**Peripheral blood draw**	Procedural risk of the class's collection step is itself removed — relevant when the patient is asymptomatic

CLASS ATTRIBUTE	CLASS RECORD	SUPLEXA STATUS	CONSEQUENCE
NKT-like fraction	Associated with reduced acute GvHD and preserved GVL, not with added alloreactivity [38,41,49]	**Present in product**	This is a favorable rather than a neutral feature
Dose density	Class mean 1.71 doses per patient across 607 patients in the AML literature [52]	**6.3 doses per patient**	Roughly 3.7-fold the class mean. SUPLEXA-101 is the densest repeat-dose experience in the class
Repeat-dose exposure	Thin: most patients 1–6 infusions	**220+ doses across 35 patients (SUPLEXA-101, NCT05237206)**	SUPLEXA contributes to the class's weakest area rather than relying on it
Residual attributable toxicity	Grade 1–2 infusion reactions: fever, chills, fatigue, nausea, transient LFT change	**The expected profile**	This is what should be predicted and what SUPLEXA-101 should be read against
Long-term follow-up data	Absent for the entire class	**Absent**	Shared limitation. Cannot be argued away; must be addressed by commitment rather than by data

The regulatory argument this supports. The non-engineered NK/NKT-like class has been given to approximately 1,700 to 1,900 patients with one GvHD event, a low-grade CRS and neurotoxicity rate near 3%, and no severe toxicity signal that survives attribution to lymphodepleting conditioning, exogenous cytokine support, or host-versus-graft rejection. When that denominator is partitioned by architecture, every one of those residual events falls in the allogeneic or engineered categories. The non-engineered autologous category — approximately 73 patients on the strict count — carries no GvHD, no allo-rejection, no CRS, no neurotoxicity, no dose-limiting toxicity and no genotoxic hazard, with an entire severe-event record of three self-resolving grade 3 events in one study. Two of those zeros are consequences of the architecture and cannot be overturned by further data; the CRS zero is an observation in a series still too small to separate statistically from the allogeneic category and should be stated as such. SUPLEXA occupies that category, uses none of the three toxicity channels, and its expected toxicity is the category residual — grade 1–2 infusion

reactions. The SUPLEXA-101 experience of more than 220 doses across 35 patients without a serious adverse event is what the categorized class database predicts rather than a fortunate outlier, and it roughly doubles the size of the category it belongs to.

The argument this does not support. Nothing here establishes beyond doubt that SUPLEXA is safe. What the totality of the direct evidence (the SUPLEXA-101 Phase 1 data) combined with the indirect evidence (this class analysis) establishes is that the risk-reward profile is favorable. It further demonstrates that this favorable profile is mechanistically explained rather than merely statistical, and that SUPLEXA sits on the clean side of every mechanistic boundary the class analysis identifies. That is the correct weight to place on it: it makes the product-specific dataset interpretable, and it removes the class-level safety objections, but the product-specific dataset still must carry the approval.

How this should be deployed against the advanced-disease-first objection. The objection holds that a therapy must first be shown safe and effective in advanced disease before it can be offered to asymptomatic patients. Sections 4.2, 8 and 11 answer the safety half directly: the toxicity that makes cell therapy inappropriate for asymptomatic patients is conditioning toxicity, cytokine toxicity, alloreactive toxicity, and genotoxicity, and a product carrying none of the four does not inherit that safety concern. The efficacy half of the objection is a separate argument and is addressed in the regulatory precedent stack, where the daratumumab smoldering-myeloma approval supplies the population precedent and the MRD-conversion decisions supply the endpoint precedent.

Recommended use of this document. Table 3 is the single exhibit to put in front of a reviewer; Sections 5 through 7 supply the supporting numbers for a briefing document or Type B meeting package. Section 8 should follow Table 3 rather than lead, because it explains the categorization rather than corroborating it. Section 12 should be included rather than omitted; a limitations table that anticipates the reviewer's objections is worth more than an additional favorable statistic, and the first five rows of Table 14 anticipate the specific objections to the category presentation. Section 13 should be read alongside the SUPLEXA class safety review and the RMAT position paper and should not be quoted without the qualification in Section 4.3 that two of category 1's zeros are deductive and one is not.

Maintenance of this document. The denominator moves. The three anchor reviews have search cut-offs in 2024. A literature check performed on 4 August 2026 identified one qualifying post-cutoff source, the March 2026 AML systematic review and meta-analysis [52], which is incorporated in this revision; no qualifying systematic review or meta-analysis of non-engineered NK or NKT-like cell safety published since then was found. The check should be repeated before any submission that quotes a total. The category 1 count is the figure most worth refreshing, because it is small enough that a handful of new autologous studies would materially change the rule-of-three bound on CRS and could convert the underpowered claim in Section 4.3 into a supported one. The attribution analysis in Section 8 is stable and should not need revision unless a new severe-toxicity signal appears that cannot be assigned to one of the three channels.

SECTION 14

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