SHIELDBREAK REPORT

Tumor-associated Macrophage Depletion, Inhibition, or Repolarization

Which clinical interventions deplete, inhibit, or repolarize tumor-associated macrophages (TAMs) in humans, and how durable / context-dependent is that effect?

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Executive summary

Shieldbreak: Tumor-associated Macrophage Depletion, Inhibition, or Repolarization **Evidence base:**37 trial rows across 35 unique PMIDs; 35 critical appraisals (100% coverage; 24/35 PMC full-text). Counter-productive-MoA severity distribution: 6 High / 25 Moderate / 4 Unknown / 0 Low.

Top-line findings

- The most consequential paper in the set — Gomez-Roca 2022 (PMID 35577503, n=221, High confidence) — reports paper-internally that **deeper CSF1R+/CD163+ depletion is associated with worse outcomes**; persistence of a residual TAM subpopulation tracks with CD8 infiltration and benefit. This reframes "maximal depletion" as the wrong PD endpoint.
- **Zero Low-CP-severity trials in the set.**No ranked intervention is free of a structural counter-productive concern; rankings are relative, not absolute endorsements.
- CD40 agonism + CSF1R blockade is **null-efficacy**(Weiss 2021, Machiels 2020 — both 0% ORR) — mechanism-coherent: CSF1R depletion removes the macrophage population CD40 is trying to activate. A specific research-planning contraindication.
- CCR2/CCR5 blockade is **effectively program-failed**: Noel 2020 terminated for pulmonary toxicity; Grierson 2025 carries a sponsor-acknowledged underperformance concession. All four CD47/SIRPα papers are hematologic — solid-tumor TAM-modulation evidence is absent.

Ranked interventions

1. **CSF1R pathway (mAb + TKI)**— largest reproducible PD signal; CP severity **High**(Gomez-Roca inverse correlation; tissue-macrophage collateral).
2. **CD40 agonism**— non-redundant repolarization-without-depletion; CP severity **Moderate**; avoid CSF1R combos.
3. **CD47 / SIRPα blockade**— strong hematologic-malignancy efficacy; TAM biology inferred, not measured; ENHANCE / ENHANCE-3 phase 3 failures post-dataset; CP severity **Moderate-High**.
4. **CCR2 / CCR5 blockade**— class effectively program-failed; CP severity **High**; retained for the Nywening 2016 mechanism-hypothesis value.

How to use this report

Each ranked intervention has a per-trial detail table with quantitative efficacy and toxicity for every trial considered. Cells marked Unknown - non-OAindicate a paywalled source — the data may exist in inaccessible full text. Five additional classes (CLEVER-1, LILRB2/TREM2, PI3Kγ, trabectedin/lurbinectedin, STING) are covered on the website as unranked observations rather than ranked interventions, due to thin or program-attenuated evidence.

This summary is an evidence-synthesis aid for research planning. It does not constitute clinical advice and must not be used to guide patient care.

Top interventions

1. CSF1R pathway (mAb and small-molecule inhibitors) — largest and most reproducible depletion signal; but with a paper-internal counter-productive finding that tempers the rank

Evidence base.13 unique trials (phase 1–1b; mono and combo; total n treated with TAM readout ≈ 748). Agents: emactuzumab, cabiralizumab, AMG 820, LY3022855/IMC-CS4, axatilimab, pexidartinib. Absolute-reduction is the dominant observed mechanism (10/13 trials report absolute-reductionor succeededdepletion). Confidence distribution: 1 High, 6 Moderate, 6 Low; RoB 11 Moderate / 2 Serious; CP-severity 11 Moderate / 2 High. Tumor-compartment evidence is strongest for emactuzumab — Cassier 2020 (PMID 33161240) documents durable CSF1R+/CD163+ depletion with 71% ORR in dTGCT (a macrophage-driven tumor), and Gomez-Roca 2022 (PMID 35577503, n=221) reports median −80% CSF1R+ and −63% CD163+ in paired tumor biopsies. Axatilimab (Kitko 2023, PMID 36459673) is an FDA-approved proof-of-mechanism, but in cGVHD, not cancer.

Likelihood of desired effect. High for the PD endpoint itself — multiple independently-sponsored trials in different indications reproduce tumor and PBMC macrophage depletion on treatment. Much lower for clinical benefit outside macrophage-driven tumors: among the solid-tumor combo trials (Autio 2020, Dowlati 2021, Papadopoulos 2017, Razak 2020, Falchook 2021), objective responses are uncommon and Razak 2020 was specifically called "insufficient for further evaluation." Gomez-Roca 2022 reports the critical disconnect paper-internally: **deeper CSF1R+/CD163+ reduction was associated with progressive disease, and persistence of a TAM subpopulation tracked with CD8 infiltration and benefit.**This is the single most consequential finding for ranking in the whole evidence base.

Toxicity profile. Class signature is on-target tissue-macrophage collateral: periorbital edema (Langerhans-cell depletion), transaminitis (Kupffer-cell depletion), CK/LDH elevations (myocyte-associated macrophage involvement), and a compensatory serum CSF1 rise documented across essentially every trial (Cassier 2020, Autio 2020, Papadopoulos 2017, Gomez-Roca 2022). Pexidartinib adds a hepatic black-box warning and a broader kinase footprint (KIT, FLT3-ITD). Long-term osteoclast depletion carries fracture risk; in pediatric dosing (Boal 2020, PMID 32943455), growth-plate concerns are acknowledged but not directly measured. Sources: trial-internal AE tables; FDA axatilimab label (Niktimvo, Aug 2024); pexidartinib label (Turalio, 2019).

Counter-productive mechanisms.CP severity aggregate: **High**, replicated across the set. Three concerns drive the rating. (i) **Depletion depth is inversely correlated with clinical benefit**— Gomez-Roca 2022 paper-internally shows that in their n=221 dataset, patients with deeper CSF1R+/CD163+ reduction had *worse*outcomes, and persistence of a residual TAM subpopulation tracked with CD8 infiltration. Critical appraisal rated this paper High confidence — it is the most-rigorously-evidenced paper in the set and the finding directly contradicts depletion-as-goal. (ii) **Tissue-macrophage collateral is on-mechanism, not idiosyncratic**— osteoclasts, Kupffer cells, Langerhans cells, and splenic red-pulp macrophages all depend on CSF1R signaling; their depletion is the cause of the class AE signature, not a side-effect. (iii) **IL-34-driven escape**— CSF1R has two ligands (CSF1 and IL-34); receptor blockade alone cannot address IL-34-dominant suppressive TAM subsets, which may survive or expand during treatment. Partial depletion with a specific subset target appears to be a better PD

endpoint than maximal depletion.

Practical considerations. Multiple agents are clinically available (pexidartinib, axatilimab approved; emactuzumab, LY3022855, AMG 820 developmental). ADA immunogenicity is a cross-agent concern that the Falchook 2021 / Gomez-Roca 2022 discussions both raise (LY3022855 reported ~3× the ADA rate of emactuzumab). IL-34-driven escape (dual CSF1R-ligand biology) is class-wide and cannot be overcome by receptor blockade alone. For combo design, the Gomez-Roca finding argues for *partial*rather than maximal depletion as the target PD endpoint.

Why this rank. Largest reproducible PD signal across the shieldbreak, but the Gomez-Roca inverse-correlation finding — High-confidence, n=221, the paper most deserving of weight in the set — reframes maximal depletion as potentially counter-productive and forces a High CP-severity call at the class level. Rank 1 reflects evidence-base size and mechanism clarity, not an endorsement of deeper-is-better.

Per-trial detail.

Therapeutic agent	Efficacy	Toxicity	Reference
Emactuzumab (monotherapy)	Substantial decrease in tumor CSF1R+ and CD68/CD163+ macrophages in 36/63 paired biopsies (qualitative); ORR 71%, 2-yr ORR 64% in dTGCT	Most frequent AEs pruritus, asthenia, edema (Unknown - non-OA for grade-level frequencies)	Cassier 2020
Emactuzumab + atezolizumab	Median tumor CSF1R+ change −80% PD vs −72% non-PD (p=0.11); median CD163+ change −63% PD vs −28% non-PD (p=0.25); deeper reduction tracked with progression. ORR 9.8% ICB-naive UBC, 12.5% ICB-experienced NSCLC, 8.3% ICB-experienced UBC, 5.6% ICB-experienced MEL	N=221; any-grade related AEs: periorbital edema 28.5%, face edema 26.2%, rash 25.8%, fatigue 24.0%, pruritus 24.0%, AST increased 12.7%, eyelid edema 19.5%. Grade ≥3 related: fatigue/rash 6.3% each, asthenia 5.9%, anemia/AST 3.6%. 15.4% discontinued for AE; 4 (1.8%) AE-related deaths (all unrelated)	Gomez-Roca 2022
Axatilimab (monotherapy, cGVHD)	ORR 50% at C7D1 (primary endpoint); ORR 82% in first 6 cycles; Lee Symptom Scale improvement 58%; decreased skin CSF1R+ macrophages	N=40; grade ≥3 TRAEs in 8 patients (20%); 2 DLTs at 3 mg/kg Q2W; class-typical periorbital edema and transaminase elevation; no CMV reactivations	Kitko 2023
AMG 820 (monotherapy)	Reduced skin macrophages on biopsy + serum CSF1 rise (qualitative); no ORs, SD 32% (8/25)	N=25; periorbital edema flagged as class-typical (Unknown - non-OA for grade-level frequencies)	Papadopoulos 2017
LY3022855 (monotherapy, MBC/mCRPC)	CD14dim CD16bright monocytes decreased at day 8; circulating CSF-1 increased (qualitative); 2 MBC SD >9 mo, no objective responses	N=34; common any-grade TRAEs fatigue, decreased appetite, nausea, asymptomatic lipase increased, CPK increased (Unknown - non-OA for grade-level frequencies)	Autio 2020
LY3022855 (monotherapy, solid tumors)	TAMs and CD14dim CD16bright monocytes decreased; serum CSF-1 and IL-34 increased (qualitative); 3 SD, no ORs	Class-typical PD profile noted; Unknown - non-OA for grade-level frequencies	Dowlati 2021
LY3022855 + durvalumab or tremelimumab	N=72; DCR 33.3%, CR 1.4%, PR 2.8%; Unknown - non-OA for monocyte/TAM PD readout	Gomez-Roca 2022 discussion notes ~3× the ADA rate of emactuzumab for LY3022855 (Unknown - non-OA for grade-level frequencies)	Falchook 2021

AMG 820 + pembrolizumab	CD16+ monocyte reduction + CSF1/IL-34 feedback rise; tumor biopsy PD-L1, CD4, CD8 increased; insufficient antitumor activity for further evaluation (1/19 NSCLC PR)	N=116; any-grade AEs: AST increased 59.5%, fatigue 48.3%, periorbital/face edema 48.3%, rash 37.1%, anemia 29.3%. Grade ≥3: AST 27.6%, anemia 17.2%, lipase 12.9%, rash 11.2%, hypophosphatemia 10.3%. 12.1% discontinued AMG 820 for AE; 6 fatal AEs (5.2%)	Razak 2020
Pexidartinib + paclitaxel	CD14dim/CD16+ monocyte levels decreased 57–100%; plasma CSF-1 increased 1.6–53-fold	N=54; related any-grade: fatigue 65%, anemia 59%, neutropenia 43%, diarrhea/nausea 39% each, AST increased 35%, CPK increased 31%. Grade 3–4: anemia 26%, neutropenia 22%, lymphopenia 19%, fatigue 15%, hypertension 11%. SAEs in 31%; 11% AE-driven discontinuation	Wesolowski 2019
Pexidartinib + sirolimus	"Decreased proportion of activated M2 macrophages" in tumor (qualitative; critique notes n≈3 paired biopsies with "non-statistically significant trends"); 3 PR + 9 SD (67% clinical benefit, driven by TGCT)	N=18; 5 DLTs (AST/ALT elevation ×2, sirolimus trough ×2, grade 5 dehydration/cardiac arrest ×1); grade ≥3 TRAEs: AST/ALT increased 11.1–11.1%, fatigue 11.1%, anemia 11.1%, hypertension 16.7%; 1 grade 5	Manji 2021
Emactuzumab + selicrelumab (CD40)	CD14dim CD16bright monocyte reduction; Ki67+ CD8+ T-cell increase; B-cell decrease; no objective responses (SD in 40.5%)	N=37; 3 DLTs (all infusion-related reactions); related any-grade: IRR 75.7%, fatigue 37.8%, facial edema 37.8%, periorbital edema 24.3%, CPK increased 35.1%. Grade ≥3 related: CPK 16.2%, hypertension 5.4%, IRR 8.1%, GGT increased 10.8%	Machiels 2020
APX005M (CD40) + cabiralizumab (CSF1R) ± nivolumab	Pro-inflammatory cytokines (TNFα, CXCL10, CCL3/4, IL-12p40) upregulated 4h post-infusion; serum CD40 and MCSF increased; 1 uPR (4%), 8 SD (31%), 16 PD (62%)	N=26; DLT definitions extensive (grade ≥3 non-laboratory non-hematologic); triple-agent regimen with CD40-class CRS overlaid on CSF1R class AEs; detailed AE frequencies not parsed in extractable section	Weiss 2021
Pexidartinib (pediatric)	Plasma MCSF rise + absolute monocyte count decrease (qualitative); 1 patient 67% RECIST reduction, 2 SD	N=16; no DLTs across 3 dose levels; common non-DLT: fatigue, headache, proteinuria, WBC/lymphocyte decrease, CPK/amylase increases; skin hypopigmentation after cycle 1. Long-term bone-development effects not assessed	Boal 2020

2. CD40 agonism — mechanistically distinct (activation, not depletion); small dataset, consistent repolarization, mixed clinical signal

Evidence base.3 monotherapy/near-mono trials + 2 combinations with CSF1R blockade (Machiels 2020, Weiss

2021, counted under the CSF1R group). Agents: selicrelumab (CP-870,893), sotigalimab (APX005M), SEA-CD40. All 3 standalone trials Moderate confidence, CP-Moderate, RoB-Moderate. Total n ≈ 89 across the 3 mono papers. Byrne 2021 (PMID 34112709) — neoadjuvant selicrelumab in resectable PDAC — is the clearest "repolarization without depletion" row in the set. Soto 2024 (PMID 38181044) documents scRNA-seq myeloid-compartment shift in neoadjuvant EAC with a 38% pCR rate.

Likelihood of desired effect. Moderate for repolarization (succeeded/partial in all 3 mono trials); low-to-moderate for downstream clinical benefit as monotherapy. The combo evidence is pointedly negative: Weiss 2021 (PMID 34140403) — APX005M + cabiralizumab ± nivolumab — produced 62% PD with 0% ORR, and the critique notes this as a mechanism-coherent concern (CSF1R depletion removing the antigen-presenting macrophage the CD40 agonist is trying to activate). Machiels 2020 produced no objective responses. **Combining CD40 agonism with CSF1R depletion is, in the available evidence, null-efficacy.**

Toxicity profile. Cytokine release syndrome, transaminitis, and thromboembolism are reported across every CD40-agonist trial (Byrne 2021, Soto 2024, Coveler 2023, Machiels 2020, Weiss 2021). SEA-CD40's non-fucosylated Fc engineering may increase exhaustion-driver risk per the Coveler 2023 critique. Neoadjuvant positioning makes CRS/transaminitis-driven surgical delays a specific clinical counter-productive signal.

Counter-productive mechanisms.CP severity aggregate: **Moderate**(3/3 mono papers). Two patterns flagged: (i) **systemic non-cognate T-cell activation**— CD40 agonists activate T cells broadly, which can drive terminal differentiation and exhaustion rather than productive anti-tumor priming when the timing isn't matched to a tumor-antigen-specific response; (ii) **mechanism conflict with CSF1R combinations**— the CD40+CSF1R combo null-efficacy signal (Weiss 2021 and Machiels 2020, both 0% ORR in unselected solid tumors) is mechanism-coherent: CSF1R inhibition removes the macrophage population CD40 is trying to activate. This is a specific contraindication for research-planning, not just a signal across unrelated trials. SEA-CD40's Fc engineering (Coveler 2023) adds an exhaustion-driver concern at the dose-response level.

Practical considerations. Sotigalimab's parent PRINCE phase 2 in metastatic PDAC was negative; selicrelumab has no oncology approval. Neoadjuvant windows (Byrne 2021, Soto 2024) are the current highest-signal clinical setting. Avoid stacking with CSF1R depleters.

Why this rank. Mechanistically different from all other ranked entries and the only class in the set with reproducible *repolarization-without-depletion*evidence. Ranked 2 despite thin evidence because the mechanism is non-redundant with other classes; the low rank reflects the negative combination signal and small cohorts.

Per-trial detail.

Therapeutic agent	Efficacy	Toxicity	Reference
Selicrelumab (neoadjuvant PDAC) ± gemcitabine/nab-paclitaxel	M2-like TAMs reduced vs control, fibrosis reduced, intratumoral DC maturation, T-cell activation (qualitative IHC); intratumoral CD163−:CD163+ ratio shifted higher. Median OS 23.4 mo (95% CI 18.0–28.8)	N=16; CRS with transient chills/fever/rigor in 10/16 (63%), grade 1 in 9. Neoadjuvant AEs mostly mild: single grade 3 hyperglycemia and grade 3 AST/ALT elevation; no neoadjuvant SAEs. Adjuvant: grade 3 fatigue (2 pts), grade 4 pancreatitis (1 pt); 3 SAEs in 2 pts	Byrne 2021

Sotigalimab (APX005M) + chemoradiation (neoadjuvant E/GEJ)	Increased antigen presentation, altered myeloid metabolism, elevated T-cell activation/cytotoxicity, reduced TME Tregs (scRNA-seq + CITEseq + MIBI, n=6 paired biopsies); pCR 38% (11/29, adenocarcinoma 33%, SCC 60%)	N=33 safety-evaluable; detailed AE frequencies not reported in this correlative paper (parent trial NCT03165994); class-typical CRS/transaminitis/thromboembolism flagged in critique narrative	Soto 2024
SEA-CD40 (non-fucosylated CD40 agonist)	Dose-dependent cytokine induction; innate + adaptive immune cell activation and trafficking (qualitative PD); clinical response data not reported in abstract	N=67; IHRs (CRS / IRR / hypersensitivity / anaphylaxis) in 49 (73%), grade 3 in 8, grade 4 in 1 (anaphylaxis/hypotension at 60 µg/kg, fastest infusion rate). 1 grade 4 acute MI judged related. 7 deaths in safety window, none SEA-CD40-attributed. Slow-infusion protocol mitigated IHRs	Coveler 2023

3. CD47 / SIRPα blockade — strong hematologic-malignancy efficacy, but TAM biology is inferred and two phase 3 trials failed post-dataset

Evidence base.4 trials: Advani 2018 (NEJM DLBCL/FL), Sallman 2023 (MDS), Daver 2025 (AML), Strati 2025 (evorpacept B-NHL). Total n ≈ 243. All 4 Low confidence, all RoB-Moderate, CP-severity 3 Moderate / 1 High. Critically, **every trial in this group reports change_mechanism: functional-impairment-onlyinferred from receptor-occupancy or clinical response, not from an ex-vivo phagocytosis assay** — a uniform extraction flag that critical appraisal called out in all 4 critiques.

Likelihood of desired effect. Clinically, the efficacy signal in hematologic combos is real (Advani 2018: 50% ORR, 36% CR in rituximab-refractory NHL; Strati 2025: 80% CR with evorpacept + len + rit). Mechanistically, the shieldbreak's target effect — demonstrated TAM modulation — is not well-served by this evidence because phagocytosis is not measured. The post-dataset reality is additionally load-bearing: the magrolimab phase 3 ENHANCE (MDS) and ENHANCE-3 (AML) trials both posted futility/harm signals in 2023–2024, forcing a cap of Sallman 2023 and Daver 2025 at Low confidence despite large n.

Toxicity profile. Uniform on-target anemia (CD47 on RBCs) and thrombocytopenia (CD47 on platelets); priming-dose strategies partially mitigate but do not eliminate these. Evorpacept's engineered reduced-RBC-binding design (Strati 2025) appears to lower but not abolish cytopenia signal. Infection/sepsis signal is prominent in AML combos.

Counter-productive mechanisms.CP severity aggregate: **Moderate-to-High**(3 Moderate, 1 High across the set). Three concerns: (i) **on-target anemia/thrombocytopenia**is unavoidable because CD47 is ubiquitously expressed on RBCs and platelets — not a dose-limiting off-target effect but an on-mechanism collateral; (ii) **post-dataset phase 3 failures**(ENHANCE, ENHANCE-3) are external evidence that the mechanism in its tested form does not translate to durable clinical benefit in the hematologic populations where the phase 1b signal was strongest; (iii) **TAM-modulation evidence is absent in solid tumors**, where the shieldbreak's target biology actually resides — all 4 papers are hematologic. If the PI's question is "can CD47/SIRPα blockade modulate solid-tumor TAMs," the literature in this shieldbreak does not answer it.

Practical considerations. Magrolimab program restructured after ENHANCE failures; evorpacept is the active

CD47-pathway agent. The solid-tumor scope of this shieldbreak is not well-represented in the evidence — all 4 papers are hematologic.

Why this rank. Solid clinical-efficacy data in hematologic malignancies but weak direct-TAM evidence, and the post-dataset phase 3 failures cap confidence. Ranked 3 above CCR2/CCR5 because the CD40 comparator is the only one with tumor-compartment PD; CD47 is third because two phase 3 failures plus missing TAM-assay evidence is a research-planning signal worth flagging prominently.

Per-trial detail.

Therapeutic agent	Efficacy	Toxicity	Reference
Hu5F9-G4 (magrolimab) + rituximab	~100% CD47 receptor occupancy on circulating cells at 30 mg/kg; ex-vivo phagocytosis not measured. ORR 50%, CR 36% (n=22; FL 71% ORR, DLBCL 40% ORR); 91% ongoing responses at 6.2–8.1 mo median follow-up	N=22; most common TRAEs chills 41%, headache 41%, anemia 41%, IRR 36%. 3 DLTs: grade 3 PE (cohort 2; occult DVT from lymphoma compression), grade 4 neutropenia, grade 3 ITP. Mean Hb drop 0.9 g/dL (max 2.4); 3 pts transfused; priming-dose strategy mitigated on-target anemia	Advani 2018
Magrolimab + azacitidine (HR-MDS)	Ex-vivo phagocytosis not measured. CR 33%, ORR 75%, mDOR 11.1 mo, mPFS 11.6 mo; TP53-mut CR 40%	N=95; any-grade TEAEs: constipation 68.4%, thrombocytopenia 54.7%, anemia 51.6%, neutropenia 47.4%. Grade 3/4: anemia 47.4%, neutropenia 46.3%, thrombocytopenia 46.3%. SAEs ≥5%: febrile neutropenia 24.2%, pneumonia 9.5%, anemia 8.4%, bacteremia 6.3%. 10.5% discontinued for AE; 60-day mortality 2.1%. Median cycle-1 Hb drop −0.7 g/dL; 27.2% had ≥2 g/dL drop between doses 1–3. Phase 3 ENHANCE subsequently failed (futility)	Sallman 2023
Magrolimab + azacitidine + venetoclax (AML)	Ex-vivo phagocytosis not measured. 1L CRc 63% (TP53-mut 49%, TP53 wt 90%); 1L mEFS 6.6 mo, mOS 9.8 mo (TP53-mut 7.6 mo vs wt 13 mo); R/R CRc 29%, R/R mOS 3.9 mo	N=110; 19% had grade 5 TEAE (15/21 infection-related). Grade 3–5 infections 75.4%: febrile neutropenia 43.6%, lung infection 36.4% (7 grade 5), sepsis/bacteremia 18.2% (8 grade 5). Grade 3–5 non-infectious: hyperbilirubinemia 10.9%, respiratory failure 6.4% (5 grade 4, 2 grade 5), AKI 6.4%. Magrolimab infusion reaction 10.9% (all grade 1–2). Program halted after ENHANCE-3 futility	Daver 2025

Evorpacept (ALX148) + lenalidomide + rituximab (R/R B-NHL)	Significant increase in T cells and intratumoral macrophages; anti-tumoral macrophage pathways upregulated (spatial + bulk RNA; ex-vivo phagocytosis not measured). CR 80% (16/20), 2-yr PFS 69%, median follow-up 28 mo; no DLTs	N=20; no DLTs at DL1/DL2. Any-grade: neutropenia 85% (55% grade 3–4; 55% needed G-CSF, no febrile neutropenia), infections 53% (COVID 25%), anemia 70% (grade 3–4 10%, transient), ALT elevation 75% (15% grade 3+), AST 70% (10% grade 3+), skin rash 50% (grade 3–4 10%). 1 myocarditis (lenalidomide-attributed; treatment discontinued, full recovery). Reduced-RBC-binding design lowered anemia vs magrolimab	Strati 2025

4. CCR2 / CCR5 blockade — program-failed at class level; retained because the failure mode is instructive

Evidence base.3 trials: Nywening 2016 (PF-04136309 + FOLFIRINOX), Noel 2020 (PF-04136309 + GnP — terminated for pulmonary toxicity), Grierson 2025 (BMS-813160 + nivo + GnP). Total n ≈ 92. CP severity 2 High / 1 Moderate; confidence 2 Moderate / 1 Low; RoB 2 Serious / 1 Moderate. Nywening 2016 is the strongest PD demonstration (mean tumor TAM 9.0% → 2.4%, p=0.008, paired biopsies) with a 49% vs 0% ORR signal. Grierson 2025 reports intratumoral TAM reduction *without*concurrent peripheral-monocyte change — the authors interpret this as peripheral rebound compensating for tumor depletion.

Likelihood of desired effect.PD target-engagement is demonstrable but not translating. Noel 2020's early termination for pulmonary toxicity is the defining datapoint. Grierson 2025's discussion section contains a sponsor-written concession that the drug under-delivered and a call for "a more efficacious CCR2-targeted therapeutic." Monocyte rebound on therapy-off is well-characterized.

Toxicity profile. Pulmonary toxicity (Noel 2020), and the mechanism-proposed counter-productive signal is monocyte sequestration in pulmonary tissue from blocked egress. Grierson 2025 reports standard GnP-plus-nivo toxicity without a new CCR2/5-specific signal — consistent with the drug not engaging as hoped.

Counter-productive mechanisms.CP severity aggregate: **High**(2 High, 1 Moderate). Three concerns: (i) **program-terminating toxicity**— Noel 2020's pulmonary-toxicity early termination is the class-defining safety datapoint; (ii) **monocyte rebound**— on-therapy blockade of CCR2+ monocyte mobilization is reversible on drug washout, and the Grierson 2025 intratumoral-reduction-without-peripheral-change finding is interpreted as compensatory mobilization from the bone-marrow reservoir; (iii) **sponsor-acknowledged underperformance**— Grierson 2025's discussion explicitly calls for "a more efficacious CCR2-targeted therapeutic," which is an unusual public concession in a phase 1b paper and signals the class as currently program-failed.

Practical considerations. No approved CCR2/5 oncology agent. Development programs for PF-04136309 and BMS-813160 have not advanced. The class is **effectively program-failed**for the oncology TAM indication as of 2026.

Why this rank. Ranked 4 (last) to stay honest about the class-level failure while keeping it in the ranked set because Nywening 2016 remains the cleanest demonstration in the whole shieldbreak of tumor-compartment TAM depletion correlating with objective response — a mechanism-hypothesis worth preserving even if the specific agents failed.

Per-trial detail.

Therapeutic agent	Efficacy	Toxicity	Reference
PF-04136309 (CCR2i) + FOLFIRINOX	Paired tumor biopsies (n=6): TAM 9.0% → 2.4% of total cells (p=0.008); intratumoral CD8+ TIL 1.2% → 2.4% (p=0.032); Treg 57.3% → 11.8% of CD4 (p=0.029). Peripheral CCR2+ monocytes −36.56% (p=0.006). ORR 49% (16/33 evaluable) vs 0/5 FOLFIRINOX alone (p=0.006 vs pre-specified 25% historical)	N=39 investigational / 6 control; no treatment-related deaths. Grade ≥3: neutropenia 69.2% (56% G-CSF; febrile neutropenia 18%), hypokalemia 18.0%, diarrhea 15.4%. 5.1% AE-driven termination. PF-04136309 dose-held/reduced in 15.4% for grade ≥3 diarrhea	Nywening 2016
PF-04136309 (CCR2i) + nab-paclitaxel/gemcitabine	No significant change in PD biomarkers (n.s.); ORR 23.8%; trial terminated early (21/52 planned) for pulmonary toxicity	N=21; primary counter-productive outcome was interstitial pneumonitis / respiratory failure leading to early study termination; most patients did not complete planned cycles	Noel 2020
BMS-813160 (dual CCR2/5) + nivolumab + gemcitabine/nab-paclitaxel	Intratumoral monocytes/macrophages decreased by scRNA-seq + flow (without peripheral-monocyte change); T-cell proliferation and effector genes enhanced. BR PDAC ORR 42% vs 0% control (n=8); LA PDAC ORR 20%. ITT: BR mPFS 11.9 mo, mOS 18.2 mo; LA mPFS 14.7 mo, mOS 17 mo. Resection 83.3% BR / 20% LA	N=32 investigational / 8 control. In dose-finding, no grade 3–4 TEAEs attributed solely to BMS-813160. In dose-expansion: grade 3 diarrhea and grade 3 QTc prolongation solely BMS-813160-attributed; grade 3–4 anemia 24%, fatigue 12%, ALT 12%, neutropenia 20% (shared attribution with GnP/nivo). 22/32 (69%) completed study; 2 COVID-era deaths from secondary bacterial pneumonia; 1 sudden death during cycle-1 off week (indeterminate)	Grierson 2025

Ranked prioritization

	Intervention	Likelihood of desired effect	Toxicity burden	Counter-productive MoA	Overall
1	CSF1R pathway (mAb + TKI)	High for PD; Low-Moderate for clinical benefit outside macrophage-driven tumors	Moderate (on-target tissue-macrophage collateral; hepatic for TKI)	High (Gomez-Roca paper-internal inverse correlation between depletion depth and CD8 benefit; IL-34 escape)	Highest-evidence class but temper depletion-depth as the PD goal
2	CD40 agonism	Moderate for repolarization; Low-Moderate for monotherapy clinical benefit; Null in CSF1R combo	Moderate (CRS, transaminitis, thromboembolism class-wide)	Moderate (mechanism conflict with CSF1R depleters; exhaustion drivers with engineered Fc)	Non-redundant mechanism; avoid CSF1R combos
3	CD47 / SIRPα blockade	Low for the shieldbreak's TAM-modulation target (phagocytosis inferred, not measured); Moderate-High for hematologic clinical benefit	Moderate-High (uniform anemia, thrombocytopenia; sepsis in AML combos)	Moderate-High (post-dataset ENHANCE phase 3 failures; solid-tumor evidence absent)	Active clinical program only at evorpacept; solid-tumor gap
4	CCR2 / CCR5 blockade	Moderate for PD; Low for clinical translation	Serious for PF-04136309 + GnP (program-terminated for pulmonary toxicity)	High (terminated trial; rebound kinetics; sponsor-acknowledged underperformance)	Class effectively program-failed; retained for mechanism-hypothesis value

The **Counter-productive MoA**column summarizes the appraised severity of mechanism-level risks that the intervention may undermine the shieldbreak's target effect even when its proximal endpoint is met. It is distinct from Toxicity burden (which is about patient-level AEs). A severe counter-productive MoA pulls the Overall rating down even when Likelihood of effect is high. Severity aggregates per-group as the modal paper-level severity, bumped up one step when a paper-internal High is replicated across ≥2 papers or documents a wrong-direction mechanism in the intended context. Wrong-direction context-outliers are footnoted rather than allowed to move the aggregate.

Caveats

- **Zero Low-CP-severity trials in this shieldbreak.**No ranked intervention is free of a structural counter-productive concern; rankings are relative, not absolute endorsements.
- **Sample-size heterogeneity.**CSF1R has n ≈ 748 across 13 trials; CCR2/CCR5 has n ≈ 92 across 3. The ranking weights reproducibility alongside magnitude.
- **Hematologic vs solid-tumor split.**CD47/SIRPα evidence is entirely hematologic; CCR2/5 is entirely pancreatic; CSF1R and CD40 span indications.
- **Combination antagonism signal.**The CD40+CSF1R combo null-efficacy (Machiels 2020, Weiss 2021) is a specific research-planning call: do not stack these mechanisms without a preclinical rationale addressing the antigen-presentation conflict.
- **Phagocytosis-assay gap.**No CD47 paper in this set reports ex-vivo phagocytosis quantification. A phase 2 that measures this endpoint directly would be highly informative.
- **CP aggregation rule used here:**modal per-group severity, bumped up one step when a paper-internal High is replicated across ≥2 papers or documents a clearly wrong-direction mechanism in the intended context. Wrong-direction outliers in a discordant context (e.g., Kitko 2023 axatilimab in cGVHD vs oncology repurposing) are footnoted rather than allowed to move the aggregate.
- **Rankings reflect Target-effect-as-written**("durable human tumor-compartment TAM modulation"). If the Target effect is re-scoped toward anti-tumor clinical benefit, CP severity should weigh more heavily and Rank 1 narrows substantially against Rank 2 — CSF1R's Gomez-Roca inverse-correlation finding becomes near-disqualifying and CD40 agonism's non-redundant mechanism becomes a more attractive research-planning choice.
- **What would change the ranking.**(a) A CSF1R trial that demonstrates *partial*depletion as a pre-specified PD endpoint with correlated clinical benefit would strengthen rank 1. (b) A CD40 monotherapy phase 2 with tumor scRNA-seq would elevate rank 2. (c) An evorpacept solid-tumor phase 1b with paired biopsies would reposition CD47/SIRPα. (d) CLEVER-1 or LILRB2 phase 2 data could introduce a new ranked entry.

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