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Anti-TIGITs

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An emerging class of therapies but facing setbacks

Emerging class of therapies faces multiple setbacks due to mixed clinical performance; lung & GI cancers being the most targeted

Landscape snapshot

- TIGIT & PD-1 are often co-expressed on CD8+ T cells, NK-cells or T-regs. Blocking both PD-1 & TIGIT may have potential synergies and could remove the block on activation and proliferation of T cells
- 20+ clinical-stage molecules (the majority are mAbs) and several more preclinical-stage molecules are in development. I/O players like Roche's tiragolumab, Merck's vibostolimab, Arcus' domvanalimab and BeiGene's ociperlimab are being investigated in late-stage pivotal trials. AstraZeneca's rilvegostomig & GSK/iTeos's belrestotug were the latest entrants to Phase 3
- AZ's rilvegostomig (anti-TIGITxPD-1) is the first bsAb to enter the Phase 3 trial while many bispecifics are also in early/mid-stage trials
- Lung cancer remains the most targeted indication, followed by GI-related tumors
- TIGIT + PD(L)1 immunotherapy combo trials (doublet) are targeting PD-(L)1+ve settings, while broader all-comers trials have additional chemo (triplet)

Multiple setbacks

- While TIGITs remains a key emerging class of therapies, it faced multiple setbacks due to disappointing efficacy
- Earlier investigations of TIGITs proved no efficacy in lateline disease settings. But, Roche's tiragolumab consecutive negative Phase 3 data in 1L settings (SCLC & 1L PD-L1 NSCLC [PFS]) seen as a big setback to class
- The setbacks continued even now when tiragolumab again failed in all-comers, 1L NSCLC Phase 3 trial. This failure was very concerning considering tiragolumab regimen (+ chemo + Tecentriq) performed worse *vs.* the Keytruda regimen (treatment arm pts had a higher risk of death). A PoC trial of tiragolumab failed in cervical cancer
- Regarding other molecules, vibostolimab (failed in Phase 3 melanoma trial), ociperlimab (negative data in 3 Phase 2 trials - AdvanTIG-203 [2L ESCC]; AdvanTIG-206 [1L HCC]; AdvanTIG-202 [2L+ cervical]), BMS-986207 (discontinued due to safety issues) had its own hurdles

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Intense interest from I/O players; most using TIGIT + PD-(L)1s combinations as part of their LCM strategy

Some positives

- Although Roche's tiragolumab regimen (+ Tecentriq) failed to meet the PFS endpoint in 1L, PD-L1+ve NSCLC, Phase 3 trial (SKY-01) continued for OS data. As hoped by Roche, an interim data leak of this trial in Aug 2023, showed OS benefit (HR: 0.81). Before this, in late 2022, the most anticipated Arcus' domvanalimab showed promising Ph 2 (ARC-7) results in a similar setting. These results brought back hopes in the TIGIT space
- Among GI cancer, in ESCC, tiragolumab (+ Tecentriq + chemo) improved OS in the Phase 3 trial (Asian), although an outdated control arm (chemo alone) was a key concern. Similarly, Arcus' domvanalimab (zimberelimab + chemo) showed promising ORR (~59%) in 1L mG/GEJC in small Phase 2 trial (n=41) and its further evaluation in Phase 3 trial (STAR-221) ongoing
    - In uHCC, tiragolumab (+ Tecentriq + Avastin) showed impressive ORR (~42% vs. 11% with SoC) in Phase 2 trial (n=58). Further evaluation of this regimen Phase 3 trial ongoing

What to expect

- I/O established players are dominating the space. Many are using TIGIT combinations as part of their LCM strategy and creating FDCs with their PD-1/PD-L1s
- Considering TIGITs vary in molecular characteristics (FC silent vs. intact; mAb vs. bsAb) and the developers are employing different combinations, targeting different indications & biomarkers, the molecules may succeed and emerge as a new class of therapies (while adding value to current anti-PD-(L)1s therapies)
- In the earliest case, the first TIGIT approval possible in 2026 as Roche expects tiragolumab's BLA submission in 2025 for 1L, PD-L1+ve NSCLC

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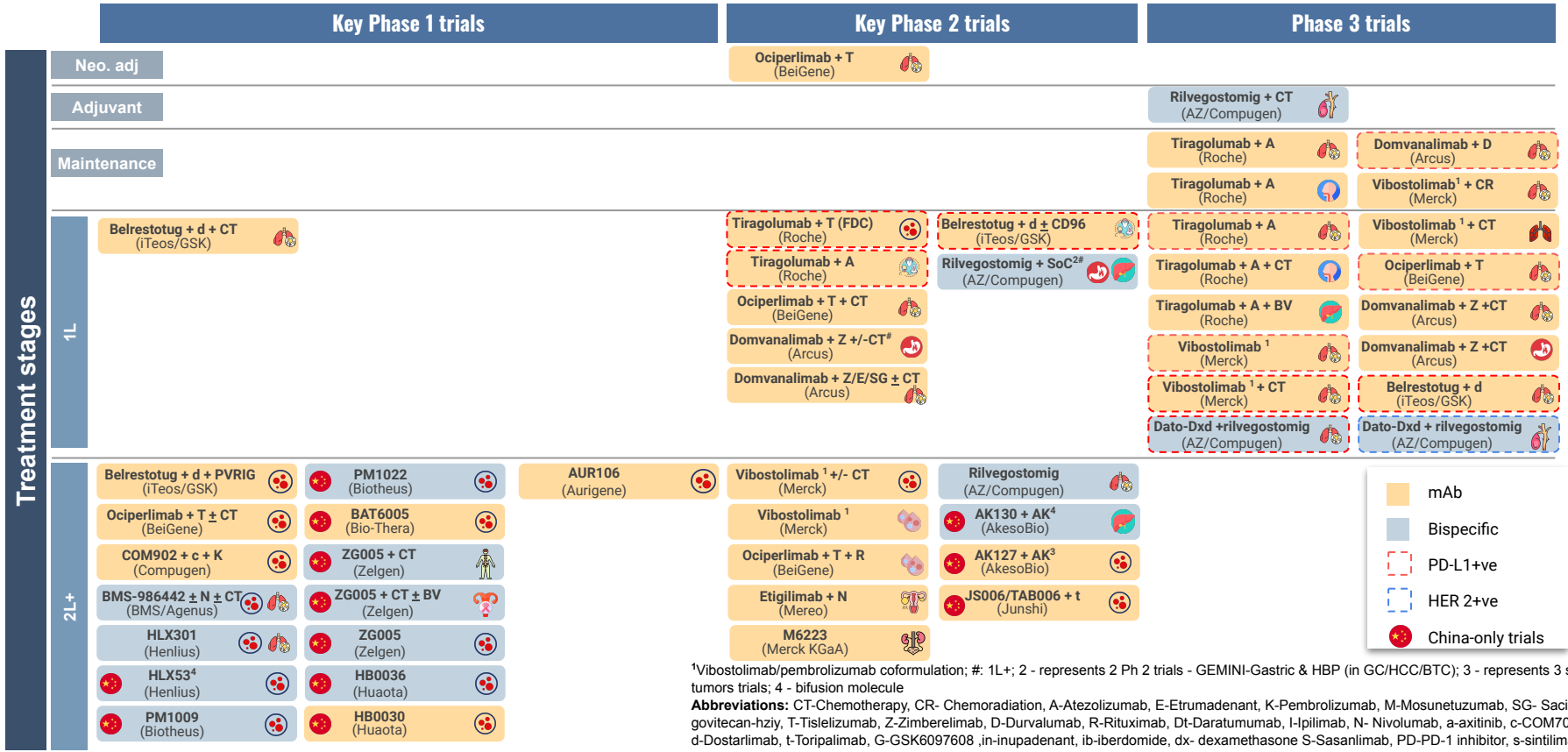
Roche has an extensive TIGIT program in multiple tumors; Merck, Arcus, BeiGene, AZ and GSK are also in the pivotal stage



[1]Vibostolimab/pembrolizumab coformulation; #: 1L+; 2 - represents 2 Ph 2 trials - GEMINI-Gastric & HBP (in GC/HCC/BTC); 3 - represents 3 solid tumors trials; 4 - bifusion molecule

Abbreviations: CT-Chemotherapy, CR- Chemoradiation, A-Atezolizumab, E-Etrumadenant, K-Pembrolizumab, M-Mosunetuzumab, SG- Sacituzumab govitecan-hziy, T-Tislelizumab, Z-Zimberelimab, D-Durvalumab, R-Rituximab, Dt-Daratumumab, I-Ipilimab, N- Nivolumab, a-axitinib, c-COM701, d-Dostarlimab, t-Toripalimab, G-GSK6097608 ,in-inupadenant, ib-iberdomide, dx- dexamethasone S-Sasanlimab, PD-PD-1 inhibitor, s-sintilimab, t-toripalimab; AK-AK104/AK112, B-BAT1706; SoC - standard of care; BV - Bevacizumab

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20+ clinical stage competitors with mostly being mAbs; Several preclinical assets yet to enter clinic

Preclinical*		Phase 1		Phase 2	Phase 3
AI-030 (AcroImmune)	SLD2435 (TIGITxPVRI) (Simcere Pharma)	COM902 (Compugen)	BMS-986442 (TIGITxCD96) (BMS/Agenus)	Tiragolumab[2,3] (Roche)	Tiragolumab (Roche)
PH-804[5] (Phio)	MG1131 (Mogam)	IBI-939[4] (Innovent Bio)	IBI-321[4] (TIGITxPD-1) (Innovent Bio)	Vibostolimab[1,2] (Merck)	Vibostolimab[1] (Merck)
SL-9258 (Shattuck Labs)	YH29143 (Yuhan)	PM1021 (Biotheus)	PM1009 (TIGITxPVRIG) (Biotheus)	Ociperlimab[2] (BeiGene)	Ociperlimab (BeiGene)
DSP502 (Kahr Medical)	TJ-L1T6 (PD-L1xTIGIT) (I-Mab)	BAT6005 (Bio-Thera)	PM1022 (TIGITxPD-L1) (Biotheus)	Domvanalimab[2] (Arcus)	Domvanalimab (Arcus)
AET2023 (Biocytogen)	Anti-TIGIT mAb (Oricell)	HB0030 (Huaota)	HLX301(TIGITxPD-L1) (Henlius)	Rilvegostomig[2] (PD-1xTIGIT)/AZ	Rilvegostomig (PD-1xTIGIT)/AZ
GB265 (PD-L1xTIGIT) (Ab Therapeutics)	Anti-TIGIT mAb (Immunoah)	AUR106 (Aurigene)	HLX53 (TIGIT bifusion) (Henlius)	Belrestotug (GSK/iTeos)	Belrestotug (GSK/iTeos)
TIGIT bsAb (Compass)	Anti-TIGIT Ab (Ampsource)		ZG-005 (TIGITxPD-1) (Zelgen)	Etigilimab (Mereo BioPharma)	
LP010 (Lepu Biopharma)	Anti-TIGIT Ab (Bioray)		BC008-1A (Buchang)	JS006 (Junshi)	
YBL-012 (Y-Biologics)	TIGITxPVRIG (Hengrui)		SIM0348(TIGITxPVRI) (Simcere Pharma)	AK130 (TIGITxTGF-□) (Akesobio)	
TIGITxCD112RxPD-L1 (Amgen)	TIGITxPD-1 (Eli Lilly)		HB0036 (TIGITxPD-L1) (Huaota)	AK127 (Akesobio)	
				M6223 (Merck KGaA)	

NSCLC, SCLC, Esophageal, Melanoma, GC/GEJ, UC & BC, Pancreatic, Ovarian, Neuroendocrine, TNBC, Rectal, Glioblastoma, Hepatocellular (HCC), Cervical, Head & Neck, Solid tumors, Hematological malignancies, Biliary tract

mAb, Bispecific, Unknown, Other, China-only trials

1- Vibostolimab is being evaluated as a co-formulation with KEYTRUDA in trials; 2- Multiple Ph 2 trials (both as basket or umbrella trial) running in multiple solid and hematological malignancies. Hence, key indications are shown here. 3- Ph 2 trial underway for FDC
4 No further evaluation detected; 5 RNAi
*Only key preclinical assets are added

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