May 7, 2020

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Reason for report:

PROPRIETARY INSIGHTS

BIOPHARMA / IMMUNO-ONCOLOGY

TIGIT & PVRIG Preview Heading into Catalyst-Rich Month

• **Bottom Line:** In concert with our Compugen (OP) initiation (LINK), we further interrogated the scientific rationale behind PVR-nectin / DNAM-1 axis targeting, including TIGIT and PVRIG antagonism. Our work leaves us more enthusiastic that these checkpoints (with TIGIT in the lead) in combination with PD-(L)1 antagonism will emerge as a second Immuno-Oncology / Immuno-Oncology (IO/IO) therapy. While the scientific rationale and pre-clinical evidence are strong for these novel checkpoints, Ph1 clinical efficacy has been modest. This could all change shortly, as Roche (RHHBY, not covered) shares data from their randomized, Ph2 CITYSCAPE trial in PD-L1+ treatment-naïve (1L) non-small cell lung cancer (NSCLC) at the American Society of Clinical Oncology (ASCO) virtual meeting (5/29-5/31) and large Ph1 basket trial at the American Association for Cancer Research (AACR) virtual annual meeting II (6/22 – 6/24). We expect Compugen and Arcus (RCUS, OP: Geoff Porges) will continue to benefit from anticipation of the data and positive results. An unclear / mixed signal will likely deflate enthusiasm and M&A speculation in both stocks.

• **Sections in the note include:**

• **Immuno -suppressive and -stimulatory functions in the PVR-nectin family / DNAM-1 axis**

• **Fc-FcγR controversy—will it matter in humans?**

• **Clinical data with anti-TIGIT and anti-PVRIG**

• **Building TIGIT expectations ahead of near-term catalysts, including a preview of data we expect at ASCO and AACR II**

• **Updated table of TIGIT and PVRIG clinical trials**

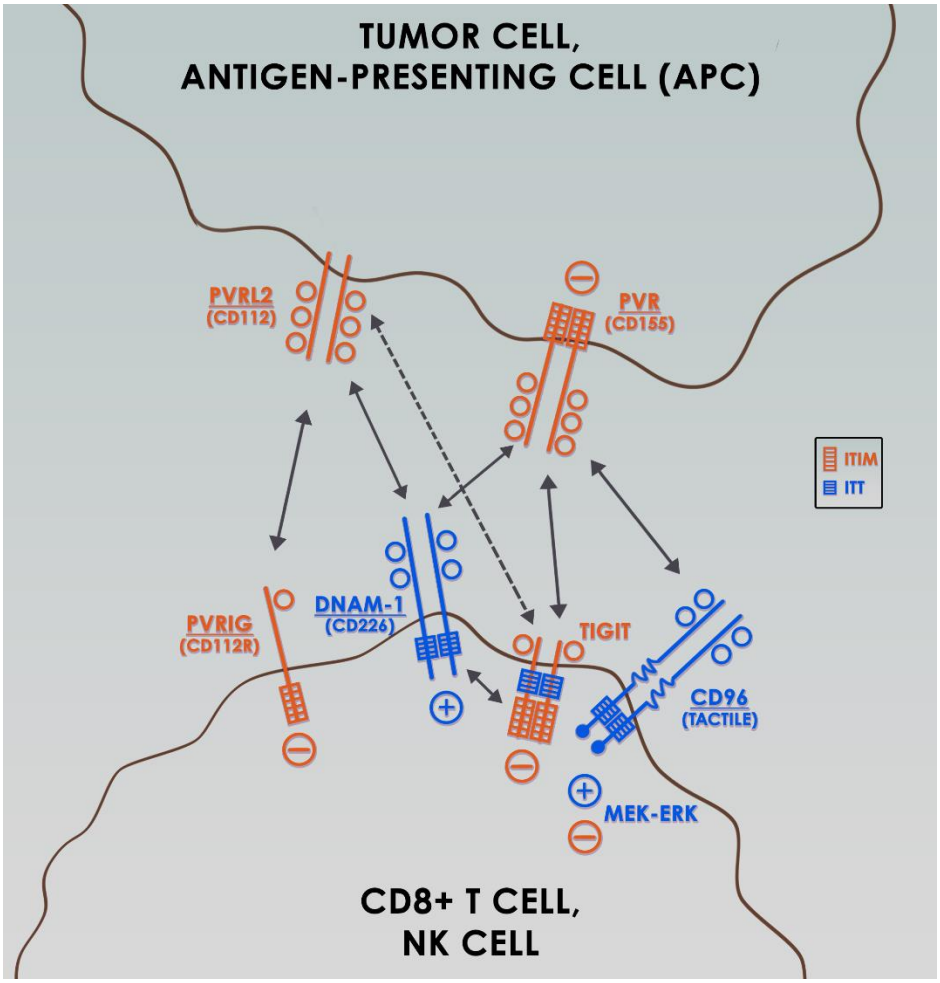
S&P 500 Health Care Index: **1,198.14**

Companies Highlighted:
BMY, CGEN, MRK, RCUS

Immuno -Suppressive and -Stimulatory Functions in the PVR-Nectin Family / DNAM-1 Axis

TIGIT and PVRIG (CD112R) are receptors found on T and natural killer (NK) cells that act through multiple mechanisms to inhibit anti-tumor immunity when engaged by their receptors, PVR (CD155) and PVRL2 (CD112). PVR and PVRL2 expression on tumor and antigen-presenting cells is high in many human tumors.

Figure 1. Overview of PVR-nectin family / DNAM-1 axis signaling



(-) Immuno-inhibitory; (+) Immuno-stimulatory
ITIM = immunoreceptor tyrosine-based inhibitory motif; ITT = immunoglobulin tail tyrosine
Source: Murter, B. et al., 2019; Johnston, R. et al., 2014; Chiang, E. et al., 2020; Levy, O. et al., AACR 2017; illustration by Jeremy Cook

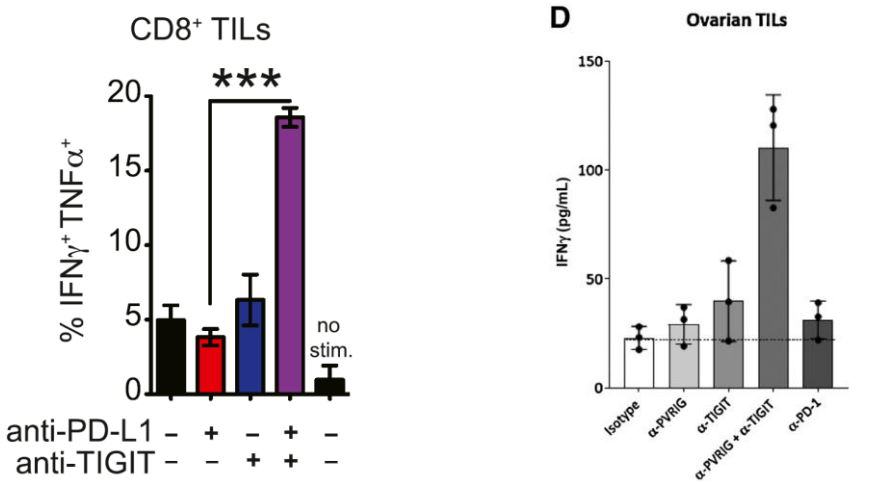
TIGIT negatively regulates anti-tumor immunity through several mechanisms; monoclonal antibodies antagonizing TIGIT could reverse this immunosuppression. Somewhat uniquely in immuno-oncology (IO), all the known mechanisms point in the same direction—TIGIT being immuno-suppressive and anti-TIGIT being immuno-stimulatory.

1. TIGIT engaging PVR induces dendritic cells to a tolerogenic phenotype, increasing IL-10 and decreasing IL-12 expression (Genentech: Yu, X *et al.,* 2008)
2. With relatively higher affinity, TIGIT competes with DNAM-1 and CD96 for PVR, preventing CD8+ T cell co-stimulation through PVR-DNAM-1 and PVR-CD96 signaling (Genentech: Johnston, R. *et al.,* 2014; Chiang, E. *et al.,* 2020)
3. Intracellularly, TIGIT inhibits DNAM-1 dimerization *in cis* and/or directly signals through ITIM domains to prevent CD8+ T cell co-stimulation (Genentech: Johnston, R. *et al.,* 2014)
4. TIGIT inhibits activation of NK cells through DNAM-1 inhibition and/or direct ITIM signaling (Compugen: Stanietsky, N. *et al.,* 2009)
5. TIGIT maintains Treg cells and shifts macrophages toward an immuno-suppressive M2 polarization (Manieri, N. *et al.,* 2017)

Though less well characterized, PVRIG seems to inhibit T and NK cell stimulation though multiple mechanisms. It also competes with DNAM-1 for a second stimulatory ligand, PVRL2 (CD112) and directly inhibits T and NK cell function through its intracellular ITIM domain (Compugen: Murter, B. et al., 2019, Li, J *et al.,* 2019; Zhu, Y *et al.,*. 2016). Investors should also note that mice express PVRIG to a lesser extent than humans, indicating murine results may underestimate clinical benefit.

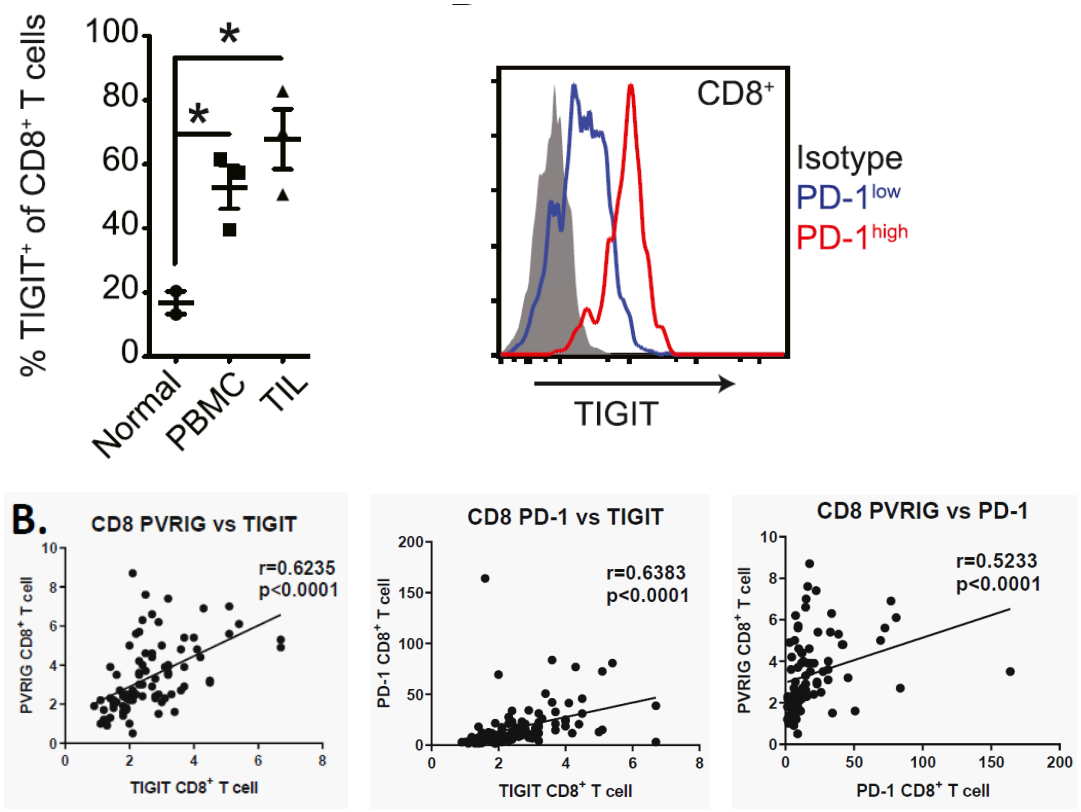
Theoretically, scientists have hypothesized targeting TIGIT and PVRIG may be more fruitful than other "second-generation" checkpoints like LAG-3 and TIM-3 (Johnston, R. et al., 2015). TIGIT and PVRIG are involved directly in regulating CD8+ cell lytic function (Figure 2) and co-expressed with PD-1 on exhausted CD8+ tumor infiltrating lymphocytes (TILs) from cancer patients (Figure 3). TIGIT's mechanism is analogous to PD-1, acting both to inhibit dendritic cell priming and T cell activity. PD-1 intracellular signaling also inhibits DNAM-1 T cell activation. Both anti-PVRIG and anti-TIGIT have anti-tumor activity in murine models when combined with anti-PD(L)1 (Figure 4).

Figure 2. Antagonizing TIGIT, PVRIG, and PD-(L)1 increases function of CD8 TILs



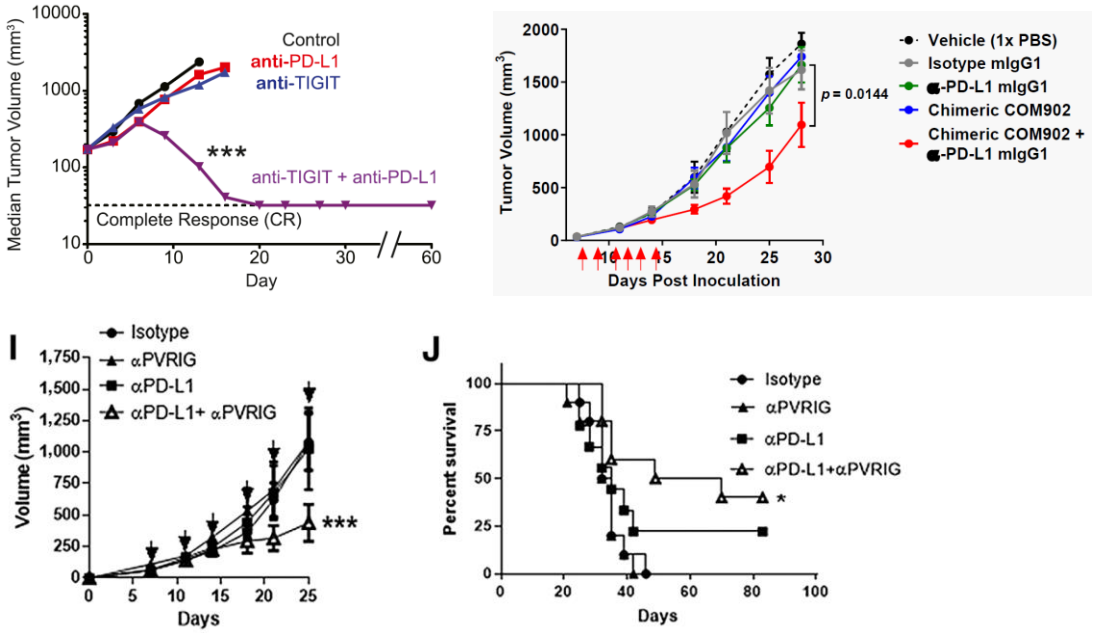
Left panel: BALB/C mice with CT26 colorectal tumors, treated as described and TILs harvested and analyzed by flow cytometry on day 7 (Johnston, R. et al., 2014); Right panel: Human ovarian cancer TILs stimulated in vitro with Mel-624 OKT3, a modified Mel-624 tumor cell line expressing surface-bound anti-CD3 scFv (OKT3) (Murter, B. et al., 2019)

Figure 3. Correlated expression of TIGIT, PVRIG, and PD-1 on CD8+ TILs



Top: Lymphocytes from human NSCLC tumors, tumor-matched peripheral blood, and normal donor peripheral blood (Johnston, R. et al., 2014); Bottom: CD8+ T cells from human dissociated tumors (Logronio, K et al., 2019 SITC)

Figure 4. Activity of anti-TIGIT and anti-PVRIG in murine CT26 tumor models

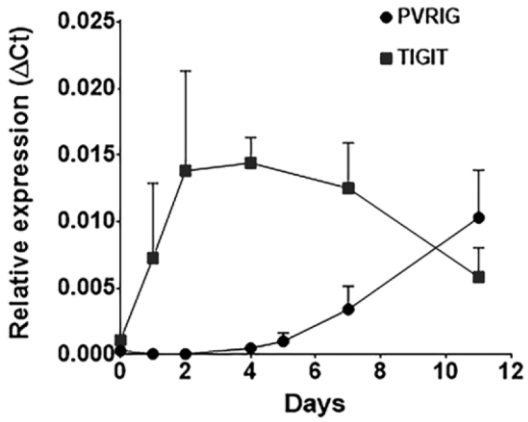


Top left: Genentech: Johnston, R. et al., 2014); Top right: Compugen (COM902 = anti-TIGIT): Logronio, K et al., 2019 SITC; Bottom: Compugen: Murter, B. et al., 2019

Though PVRIG and TIGIT have many similarities, scientists have reported distinct differences that indicate the pathways are independent and parallel. TIGIT is expressed on CD8+ T cells early after antigen priming and anti-TIGIT increases T stem-like memory cells (like anti-PD1), while PVRIG arises late on exhausted Teffector cells and does not seem to have a role in priming or formation of memory T cells (Figure 5 and 2020 Genentech investor meeting). Though they do not yet understand the physiological relevance, Compugen has also shown PVRIG rapidly internalizes upon activation of NK cells and antigen-specific stimulation of T cells, while TIGIT levels remain flat or increase (Li, J *et al.,* 2019; Whelan, S. *et al.,* 2019). While we believe both targets have potential, we are more excited about anti-PD(L)1 doublets with anti-TIGIT, given TIGIT's role early in T cell priming and in formation of T stem-like memory cells.

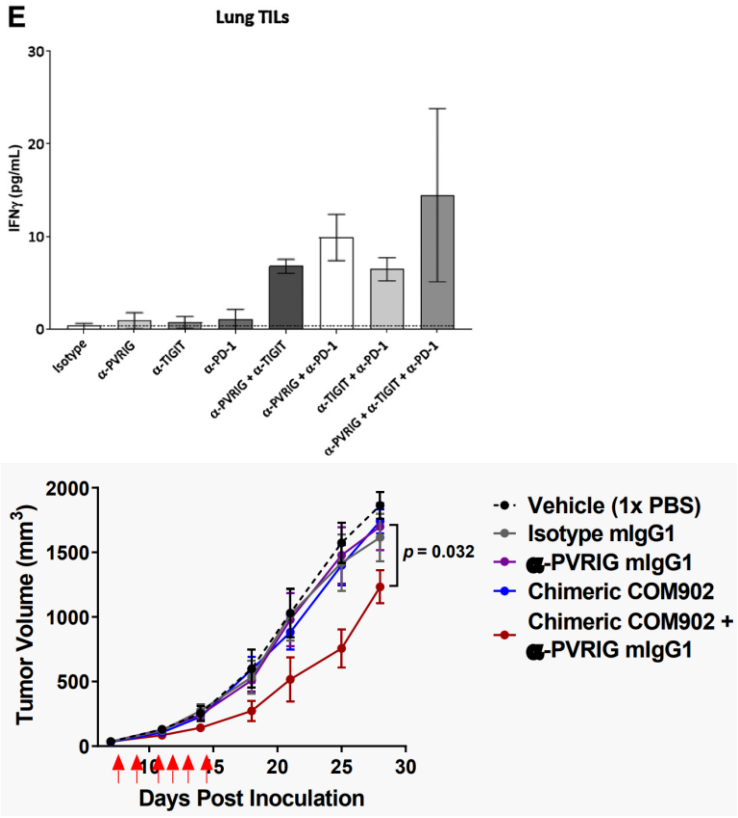
The independent role of TIGIT and PVRIG supports Compugen's doublet and triplet DNAM-1 targeting hypotheses (anti-PVRIG + anti-TIGIT +/- anti-PD-(L)1. In *in vitro* experiments in murine models and with human TILs, Compugen demonstrated synergistic restoration of CD8+ T cell function with the doublet and triplet (Figure 6). Anti-tumor activity of anti-PVRIG + anti-TIGIT was similar to that seen in the combination with anti-PD1 (Figure 6). Importantly, Compugen is the only company with anti-PVRIG in the clinic and, with BMY (not covered), will be the first to clinically test the triplet.

Figure 5. Temporal expression of TIGIT and PVRIG on CD8+ T cells after priming



Analyzed by RT-PCR (Murter, B. et al., 2019)

Figure 6. Additive / synergistic activity with DNAM-1 axis multi-targeting



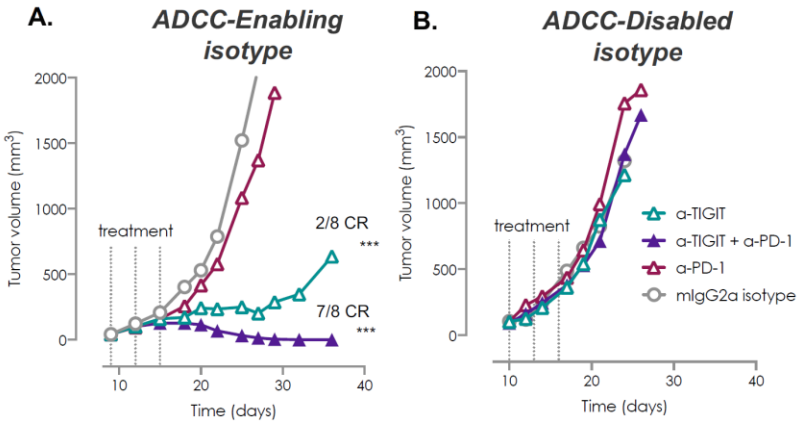
Top: In vitro restoration of CD8+ activity of TILs from lung cancer patients (Whelan, S. et al., 2019); Bottom: Synergistic anti-tumor activity of anti-TIGIT (COM902) combined with anti-PVRIG in the CT26 murine model (Logronio, K et al., 2019 SITC)

While TIGIT, PVRIG, and PD-1 expression on CD8+ T cells is highly correlated (Figure 3), variable ligand (PVR, PVRL2, PD-L1) expression in tumor and infiltrating immune cells suggests potential niches for various combinations of DNAM-1 targeting therapies. It is no surprise Genentech, Merck (OP), and Arcus (OP) are exploring anti-TIGIT + anti-PD(L)1 based therapies in lung cancer, as TIGIT is highly expressed on TILs and PVR is expressed on antigen-presenting cells (APCs) and tumor cells. For their triplet (anti-PVRIG + anti-TIGIT + anti-PD1), Compugen and BMY are planning to pursue indications with PVRL2+ and PVRL2+PVR+ expression on tumor and associated monocyte/macrophages: endometrial, ovarian, and tumor agnostic PVRL2+. See Logronio, K et al., 2019 SITC, Whelan, S. et al., 2019, Johnston, R. et al., 2014 , and Wald, N *et al.,* AACR 2019 for extensive expression analyses.

Fc-FcɣR Controversy—Will It Matter in Humans?

FcɣR engagement maximizes anti-TIGIT activity in murine tumor models. A nice illustration of these data is the comparison of clinical activity from Roche and iTeos (IgG1, Fc-FcɣR strong / ADCC-enabling) and Compugen (IgG4, weak Fc-FcɣR) in the CT26 murine model (Figure 4 top and Figure 7). This is consistent with Genentech management commentary in a 2020 investor meeting: *"We had preclinical evidence that the Fc domain was important, which is why we kept it in."*

Figure 7. Comparison of efficacy in the murine CT26 model using surrogate mouse anti-TIGIT

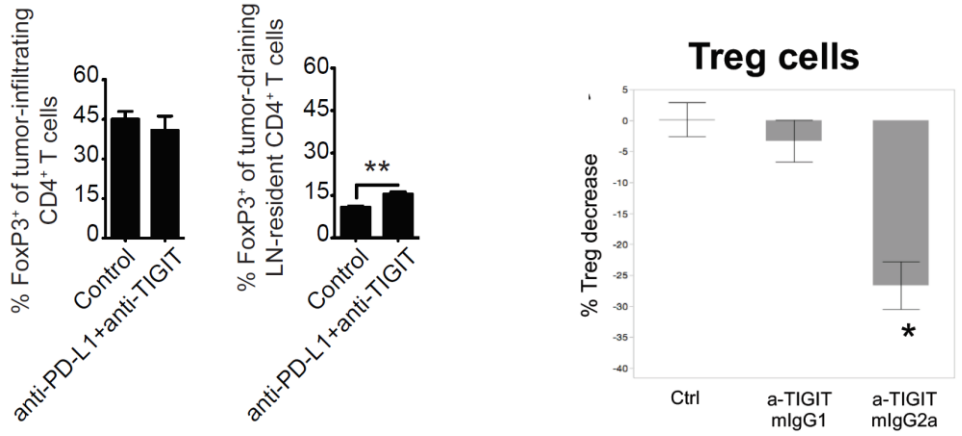


Source: Preillon, J et al., AACR 2019 (iTeos)

Despite the murine data, we heard skepticism from Genentech on whether ADCC-activity is important for anti-TIGIT activity in humans*: "We had pre-clinical evidence that the Fc domain was important, which is why we kept it in. At the time, the hypothesis has to do with depletion of T regulatory cells. I don't know if that's true. Subsequently, there is some data in-house and elsewhere that, since TIGIT is also expressed in myeloid cells, there may*

be some level of myeloid cell reprogramming or skewing that accompanies the use of TIGIT, but I think that will emerge from biomarker studies." Further, in murine models, Genentech showed anti-TIGIT + anti-PD-L1 efficacy was not dependent on Treg depletion from TILs (Figure 4 for efficacy; Figure 8); iTeos did see Treg depletion with their surrogate mouse anti-TIGIT (Figure 8).

Figure 8. Impact of anti-TIGIT and anti-PD-L1 on Treg in tumors (CT26 murine model)



Left panel: Impact on TILs measured after 7 days of treatment with anti-TIGIT reactive against mouse and human TIGIT and cloned into a murine IgG2a isotype (Genentech: Johnston, R. et al., 2014); Right panel: Impact on TILs measured 1 day after 3-cycles of treatment with a surrogate anti-TIGIT, IgG2a isotype (iTeos: Preillon, J et al., AACR 2019)

Fc-FcɣR engagement could play an important role other than in ADCC-depletion of Tregs, as investigators have demonstrated in murine models and human *in vitro* experiments with anti-CTLA-4 and anti-TIGIT (Waight, J. *et al.,* 2018). The authors hypothesize this is facilitated through engagement with FcɣR on a population of dendritic cells. Running with the analogy, though ipilimumab (anti-CTLA-4) depletes Tregs in murine models, that mechanism may not be at all relevant in humans where investigators have shown no decreases in absolute TME Treg numbers following treatment with ipilimumab (Sharma, A. *et al.,* 2018). Results with the non-fucosylated ipilimumab (BMS-986218) that more tightly binds FcɣR, combined with careful biomarker analysis, could be informative for anti-TIGIT.

Though there is a risk of T-effector and NK cell depletion with active TIGIT-directed antibody-dependent cellular cytotoxicity (ADCC) upon Fc-FcɣR engagement, those companies that retain ADCC activity also argue there is little downside. TIGIT-ADCC activity may be biased toward Treg over T-effector and NK cells, as TIGIT expression is higher on Treg cells (Wald, N *et al.,* AACR 2019; Kumar, S. *et al.,* 2017). Analogous, other ADCC-enabling monoclonal antibodies (ipilimumab, avelumab) are efficacious despite target expression on stimulatory immune cells.

Comparison of randomized data from AB-154 (Arcus' anti-TIGIT, lacks strong Fc-FcɣR engagement) to tiragolumab in 1L NSCLC may help resolve the debate. We are waiting for further clinical data from both approaches before assuming an advantage for one.

Clinical Data With Anti-TIGIT and Anti-PVRIG

Top-line single-agent efficacy for anti-TIGIT and anti-PVRIG from Ph1 dose escalation studies has been modest (Table 1). None of the signals meets our bar for proof-of-concept (PoC) in a single-arm trial; Roche may have seen something similar leading them to look for PoC in a randomized Ph2.

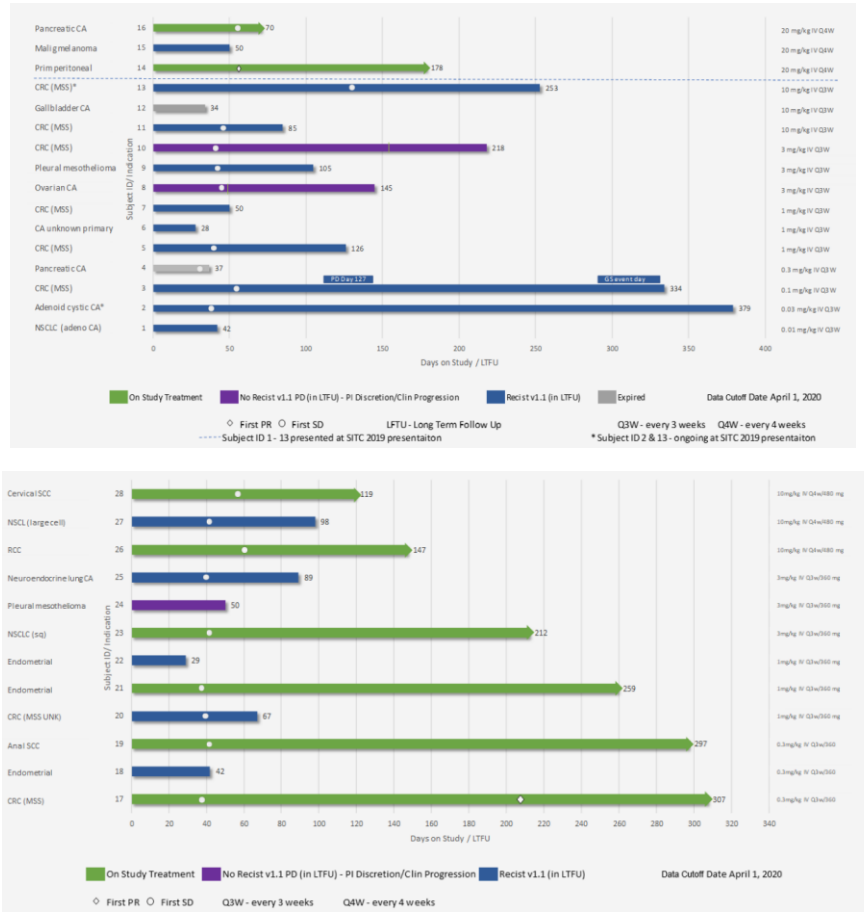
Table 1. Top-line data from dose escalation trials of anti-TIGIT and anti-PVRIG

Data type	Vibostolimab (MK-7684)	Etigilimab	COM701
Characteristics	IgG1, anti-TIGIT	IgG1, anti-TIGIT	IgG4, anti-PVRIG
Trial	Ph 1, dose-escalation	Ph 1, dose-escalation	Ph 1, dose-escalation
Last update	SITC 2018	SITC 2018	AACR 2020
Single-agent ORR	3% (1/34)	0% (0/18)	6% (1/16)
Single-agent DCR	35%	39% (7/18)	69% (11/16)
Anti-PD(L)1 combo ORR	19% (8/43), *prior PD(L)1 exposure unclear*	N.A.	8% (1/12), *32% enrolled had progressed on PD(L)1*
Gr.3+ treatment-related AE rate, single-agent	6%	≥17%	6% 33% (TEAE)
Discontinuation due to AE, single-agent	0%	5%	0% 28% (TEAE)

TEAE: treatment-emergent adverse event (not deemed related to treatment by investigator)
Sources: Etigilimab (SITC 2018, poster), MK-7684 (SITC 2018, press release), AACR 2020

Digging further into the details of the data, we do see some signs to be more enthusiastic. For the COM701 trial, the two confirmed partial responses—with single-agent COM701 in primary peritoneal cancer and with combination COM701 + nivolumab in microsatellite stable (MSS) colorectal—were in indications typically unresponsive to anti-PD(L)1. Investigators enrolled many patients typically refractory to IO-therapy to this study, e.g., MSS colorectal cancer (CRC), patients who had progressed on checkpoints. Of the nine patients who had previously progressed on checkpoints, six had stable disease and of the six MSS-CRC patients treated with COM701 alone, five had stable disease (Figure 9). With the exception of MSS CRC, clinical benefit was in tumor types where Compugen expected benefit based on high expression of PVRL2, e.g., ovarian.

Figure 9. Swimmers plot of COM701 +/- nivolumab in Ph1 dose escalation



Top: Single agent COM701; Bottom: Combination of COM701 with nivolumab
Source: AACR 2020

Building TIGIT Expectations Ahead of Near-Term Catalysts

Investor and KOL excitement for TIGIT antagonism has been building over the last year, which is evident in the rising stock prices of "TIGIT-plays" Compugen and Arcus. Genentech (RHHBY, not covered) leadership highlighted the mechanism at major oncology conferences, suggested a positive randomized trial of their anti-TIGIT (tiragolumab) with Tecentriq (atezolizumab) in treatment-naïve non-small cell lung cancer (CITYSCAPE, ASCO oral), and announced their intent to move into eight registration-enabling trials with the combination (SKYSCRAPER programs). Despite playing down their excitement for anti-TIGIT on their Q1 2020 earnings call, we view Merck's (OP) strategy in clinicaltrials.gov as aggressive. First, they gave their anti-TIGIT (MK-7684) a name: vibostolimab. Second, they posted three new trials with vibostolimab and Keytruda (pembrolizumab) in melanoma, including triplet combinations with their own anti-CTLA-4. This is on top of a December 2019 start of a trial testing the triplet of vibostolimab with Keytruda and chemotherapy in NSCLC. Third, their Ph1 dose escalation trial has a new cohort aimed directly at Keytruda life-cycle management: fixed-dose of a co-formulated product of vibostolimab and pembrolizumab (MK-7684A). Across the industry, the list of ongoing anti-TIGIT trials is quite extensive, reminiscent of early-days with anti-PD(L)1 (Appendix Table 1).

The most important near-term catalysts for the class are two clinical readouts from Genentech's tiragolumab combined with Tecentriq at ASCO (randomized CITYSCAPE) and AACR (large Ph1 basket trial). Preliminary results from Arcus's ARC-7 study of AB-154, expected in 4Q, is another major data catalyst on our radar. ARC-7 results could help answer important scientific questions, including what benefit there is in disabling Fc-FcR engagement, as well as additive benefit from parallel targeting of PD-1, TIGIT, and adenosine signaling.

Table 2. Near-term clinical catalysts for anti-TIGIT class

Program	Event	Catalyst Details	Time
Tiragolumab (Roche)	Data	Efficacy and safety data from randomized Ph 2 CITYSCAPE trial in PD-L1+, 1L NSCLC	June 2020 (ASCO)
Tiragolumab (Roche)	Data	Biomarker, safety, and efficacy data from large Ph 1 basket trial (n=400)	June 2020 (AACR 2)
Tiragolumab (Roche)	Strategy	Disclosure of additional registration-enabling trials	2020
COM701 (Compugen)	Trial Start	Start of triple combination Ph 1/2 study of COM701 with Opdivo and BMY's anti-TIGIT	2H 2020
AB-154 (Arcus)	Data	Preliminary Ph 2 ARC-7 randomized data + anti-PD1 +/- $A_{2A}R/A_{2B}Ri$ in PD-L1+, 1L NSCLC	4Q 2020
BGB-A1217 (BeiGene)	Data	Ph 1 results	Late 2020 / early 2021
EOS-448 (iTeos)	Data	Initial safety and efficacy from Ph 1	1H 2021
COM902 (Compugen)	Data	Initial Ph 1 dose escalation data	2021
COM701 (Compugen)	Data	Data from Ph 1 monotherapy expansion cohorts	1H 2021

Sources: clinicaltrials.gov, company disclosures

In CITYSCAPE, we expect the combination of tiragolumab with Tecentriq will improve progression free survival (PFS, co-primary) over Tecentriq alone. While the preclinical data suggest objective response rate (ORR, co-primary) could improve, read-through from Merck's Ph1 data hints ORR improvement could be limited. Single-agent Tecentriq data from the Ph 3 IMpower110 and Ph2 BIRCH trials provide a gauge of how the control arm in CITYSCAPE might perform (Table 3). We will be looking closely at the results by PD-L1 expression level, as Roche decided to advance tiragolumab + Tecentriq in PD-L1 high (TC3 or IC3) NSCLC patients in the Ph3 SKYSCRAPER-01. We suspect this decision was strategic to enable a faster launch using Tecentriq alone as the control arm. That said, if the combination has efficacy only in PD-L1 high patients, this would suggest more narrow potential for anti-TIGIT. Data from the basket trial at AACR should further inform anti-TIGIT

potential by indication and biomarkers (including PD-L1 on tumor cells (TC) and/or immune cells (IC), PVR TC and/or IC, and TIGIT / PD-1 IC).

Table 3. Tecentriq single-agent efficacy in 1L NSCLC

Trial	Patients	Regimen	PD-L1* Population	ORR	DoR (mo)	mPFS (mo)	mOS (mo)
Ph 3 IMpower110	1L NSCLC	Tecentriq (n=277)	TC1/2/3 or IC1/2/3 (≥ 1% TC or IC)	29.2%	N.E. (1.8+ to 29.3+)	5.7	17.5
		Tecentriq (n=107)	TC3 or IC3 (≥ 50% TC or ≥ 10% IC)	38.3%	N.E. (1.8+ to 29.3+)	8.1	20.2
Ph 2 BIRCH	1L NSCLC subpopulation	Tecentriq (n=65)	TC3 or IC3 (≥ 50% TC or ≥ 10% IC)	31%	10.0	5.6	26.9

** Using VENTANA SP142 assay; TC = tumor cells and IC = tumor-infiltrating immune cells*
Source: BIRCH data from JCO, 2017; mOS is investigator assessment, other measures from independent review. IMpower110 data from ESMO 2019.

Appendix

Appendix Table 1. Ongoing clinical trial cohorts with anti-TIGIT and anti-PVRIG therapies

Shaded by company

Anti-TIGIT/ PVRIG drug	Fc-FcR engage-ment	Primary sponsor	Trial phase	NCT	Trial name	Start Date	Primary end date	# Pts	Treatment	Treatment mechanism	Setting
Tiragolumab	Yes	RHHBY	Ph 3	NCT04294810	SKYSCRAPER-01	2020-03	2022-08	500	Atezolizumab + Tiragolumab	PD-(L)1 antagonist + TIGIT antagonist	1L NSCLC, PD-L1 TPS>50%
		RHHBY	Ph 3	NCT04256421	SKYSCRAPER-02	2020-02	2023-08	424	Atezolizumab + Tiragolumab + Chemo	Chemotherapy + PD-(L)1 antagonist + TIGIT antagonist	1L SCLC
		RHHBY	Ph 2	NCT03563716	CITYSCAPE	2018-08	2019-06	135	Atezolizumab + Tiragolumab	PD-(L)1 antagonist + TIGIT antagonist	1L NSCLC, PD-L1+
		RHHBY	Ph 1/2	NCT04300647	SKYSCRAPER-04	2020-06	2021-08	160	Atezolizumab + Tiragolumab	PD-(L)1 antagonist + TIGIT antagonist	Cervical, PD-L1+
		RHHBY	Ph 1/2	NCT03869190	MORPHEUS mUC	2019-06	2020-09	305	Atezolizumab + Tiragolumab	PD-(L)1 antagonist + TIGIT antagonist	2L Bladder
		RHHBY	Ph 1/2	NCT03281369	MORPHEUS-Gastric & Esophageal	2017-10	2021-11	410	Atezolizumab + Tiragolumab + Chemo	Chemotherapy + PD-(L)1 antagonist + TIGIT antagonist	1L Esophageal
		RHHBY	Ph 1/2	NCT03281369	MORPHEUS-Gastric & Esophageal	2017-10	2021-11	410	Atezolizumab + Tiragolumab	PD-(L)1 antagonist + TIGIT antagonist	1L Esophageal
		RHHBY	Ph 1/2	NCT03193190	MORPHEUS Pancreatic	2017-07	2021-11	260	Atezolizumab + Tiragolumab + Chemo	Chemotherapy + PD-(L)1 antagonist + TIGIT antagonist	1L Pancreatic
		RHHBY	Ph 1	NCT04045028		2019-07	2021-07	52	Tiragolumab	TIGIT antagonist	DLBCL, FL, MM
		RHHBY	Ph 1	NCT04045028		2019-07	2021-07	52	Tiragolumab + Daratumumab	TIGIT antagonist + CD38 mAb	4L MM

Anti-TIGIT/ PVRIG drug	Fc-FcR engage-ment	Primary sponsor	Trial phase	NCT	Trial name	Start Date	Primary end date	# Pts	Treatment	Treatment mechanism	Setting
		RHHBY	Ph 1	NCT04045028		2019-07	2021-07	52	Tiragolumab + rituximab	TIGIT antagonist + CD20 mAb	3L DLBCL, 3L FL
		RHHBY	Ph 1	NCT02794571		2016-05	2022-11	300	Tiragolumab	TIGIT antagonist	Solid tumors
		RHHBY	Ph 1	NCT02794571		2016-05	2022-11	300	Atezolizumab + Tiragolumab	PD-(L)1 antagonist + TIGIT antagonist	Solid tumors
		RHHBY	Ph 1	NCT02794571		2016-05	2022-11	300	Atezolizumab + Tiragolumab + Chemo	Chemotherapy + PD-(L)1 antagonist + TIGIT antagonist	Solid tumors
Vibostolimab	Yes	MRK	Ph 2	NCT04165070	KEYNOTE substudy1A	2019-12	2032-02*	90	Vibostolimab + Pembrolizumab + Chemo	Chemotherapy + PD-(L)1 antagonist + TIGIT antagonist	1L NSCLC
		MRK	Ph 1/2	NCT04305054	KEYNOTE substudy2B	2020-07	2030-04*	200	Vibostolimab + Pembrolizumab	PD-(L)1 antagonist + TIGIT antagonist	1L Melanoma
		MRK	Ph 1/2	NCT04305041	KEYNOTE substudy2A	2020-07	2030-04*	200	Vibostolimab + Pembrolizumab + MK-1308	CTLA-4 antagonist + PD-(L)1 antagonist + TIGIT antagonist	2L Melanoma
		MRK	Ph 1/2	NCT04303169	KEYNOTE substudy2C	2020-07	2030-04*	65	Vibostolimab + Pembrolizumab	PD-(L)1 antagonist + TIGIT antagonist	Neoadj. Melanoma
		MRK	Ph 1	NCT02964013		Posted 2019-12	2022-06	432	MK-7684A (co-formulated Vibostolimab + Pembrolizumab)	TIGIT antagonist	Solid tumors
		MRK	Ph 1	NCT02964013		2016-12	2022-06	432	Vibostolimab	TIGIT antagonist	Solid tumors
		MRK	Ph 1	NCT02964013		2016-12	2022-06	432	Vibostolimab + Pembrolizumab	PD-(L)1 antagonist + TIGIT antagonist	Solid tumors
		MRK	Ph 1	NCT02964013		2016-12	2022-06	432	Vibostolimab + Pembrolizumab + Chemo	Chemotherapy + PD-(L)1 antagonist + TIGIT antagonist	Solid tumors

Anti-TIGIT/ PVRIG drug	Fc-FcR engage-ment	Primary sponsor	Trial phase	NCT	Trial name	Start Date	Primary end date	# Pts	Treatment	Treatment mechanism	Setting
BMS-986207	No	BMY	Ph 1/2	NCT04150965		2020-04	2022-03	104	BMS-986207 + Pomalidomide + Dex	TIGIT antagonist + IMiD + Steroid	4L Multiple Myeloma
		BMY	Ph 1/2	NCT02913313		2016-11	2022-12	170	BMS-986207	TIGIT antagonist	Solid tumors
		BMY	Ph 1/2	NCT02913313		2016-11	2022-12	170	BMS-986207 + Nivolumab	PD-(L)1 antagonist + TIGIT antagonist	Solid tumors
ASP-8374	No	Astellas	Ph 1	NCT03260322		2017-09	2021-07	363	ASP-8374	TIGIT antagonist	Solid tumors
		Astellas	Ph 1	NCT03260322		2017-09	2021-07	363	ASP-8374 ++ Pembrolizumab	PD-(L)1 antagonist + TIGIT antagonist	Solid tumors
AB-154	No	Arcus	Ph 2	NCT04262856	ARC-7	2020-01	2022-03	150	AB-154 ++ Zimberelimab	PD-(L)1 antagonist + TIGIT antagonist	1L NSCLC, PD-L1+
		Arcus	Ph 2	NCT04262856	ARC-7	2020-01	2022-03	150	AB-154 ++ Zimberelimab ++ AB-928	PD-(L)1 antagonist + TIGIT antagonist + A2aR/A2bR antagonist	1L NSCLC, PD-L1+
		Arcus	Ph 1	NCT03628677		2018-08	2020-07	66	AB-154	TIGIT antagonist	Solid tumors
		Arcus	Ph 1	NCT03628677		2018-08	2020-07	66	AB-154 ++ Zimberelimab	PD-(L)1 antagonist + TIGIT antagonist	Solid tumors
COM701, BMS-986207	No	Compugen	Ph 1/2			2H 2020			COM701 ++ Nivolumab ++ BMS-986207	PD-(L)1 antagonist + PVRIG antagonist + TIGIT antagonist	Solid tumors
COM902	No	Compugen	Ph 1	NCT04354246		2020-03	2021-10	45	COM902	TIGIT antagonist	Solid tumors, heme
COM701	No	Compugen	Ph 1	NCT03667716		2018-09	2021-06	140	COM701	PVRIG antagonist	Solid tumors
		Compugen	Ph 1	NCT03667716		2018-09	2021-06	140	COM701 ++ Nivolumab	PD-(L)1 antagonist + PVRIG antagonist	Solid tumors

Anti-TIGIT/ PVRIG drug	Fc-FcR engage-ment	Primary sponsor	Trial phase	NCT	Trial name	Start Date	Primary end date	# Pts	Treatment	Treatment mechanism	Setting
BGB-A1217	Yes	BeiGene	Ph 1	NCT04047862		2019-08	2021-04	39	Tislelizumab ++ BGB-A1217	PD-(L)1 antagonist + TIGIT antagonist	Solid tumors
EOS884448	Yes	iTeos	Ph 1	NCT04335253		2020-02	2021-04	30	EOS884448	TIGIT antagonist	Solid tumors
SGN-TGT	Yes	Seattle Genetics	Ph 1	NCT04254107		2020-04	8/2453	111	SGN-TGT	TIGIT antagonist	Solid tumors
		Seattle Genetics	Ph 1	NCT04254107		2020-04	8/2453	111	SGN-TGT ++ any PD-1	PD-(L)1 antagonist + TIGIT antagonist	Solid tumors
IBI-939	?	Innovent	Ph 1	NCT04353830		2020-05	2021-06	270	IBI-939	TIGIT antagonist	Solid tumors, heme
		Innovent	Ph 1	NCT04353830		2020-05	2021-06	270	IBI-939 ++ Sintilimab	TIGIT antagonist ++ PD-(L)1 antagonist	Solid tumors, heme

EOS884448 = EOS-448; vibostolimab = MK-7684; tiragolumab = RG-6058

** Umbrella trial design (e.g., will rotate through therapies); we assume anti-TIGIT cohort data will certainly be available before 2032.*

We are also tracking preclinical programs from Agenus (including a bispecific) and Phio Pharmaceuticals.

Sources: SVB Leerink Immuno-ONcology INdustry ANalytics (IONIAN) database, clinicaltrials.gov, company presentations

Note: After initial publication, we edited content to fix errors in the Appendix Table 1: NCT04150965 is in Multiple Myeloma, not Melanoma; NCT04305054 therapy does not include Merck's anti-CTLA-4; BMS-986207 does not have Fc-FcR engagement activity

Disclosures Appendix

Analyst Certification

I, Daina M. Graybosch, Ph.D., certify that the views expressed in this report accurately reflect my views and that no part of my compensation was, is, or will be directly related to the specific recommendation or views contained in this report.

Distribution of Ratings/Investment Banking Services (IB) as of 03/31/20

Rating	Count	Percent	IB Serv./Past 12 Mos. Count	IB Serv./Past 12 Mos. Percent
BUY [OP]	148	73.27	55	37.16
HOLD [MP]	54	26.73	4	7.41
SELL [UP]	0	0.00	0	0.00

Explanation of Ratings

Outperform (Buy): We expect this stock to outperform its benchmark over the next 12 months.

Market Perform (Hold/Neutral): We expect this stock to perform in line with its benchmark over the next 12 months.

Underperform (Sell): We expect this stock to underperform its benchmark over the next 12 months.

The degree of outperformance or underperformance required to warrant an Outperform or an Underperform rating should be commensurate with the risk profile of the company.

For the purposes of these definitions the relevant benchmark will be the S&P 600® Health Care Index for issuers with a market capitalization of less than $2 billion and the S&P 500® Health Care Index for issuers with a market capitalization over $2 billion.

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