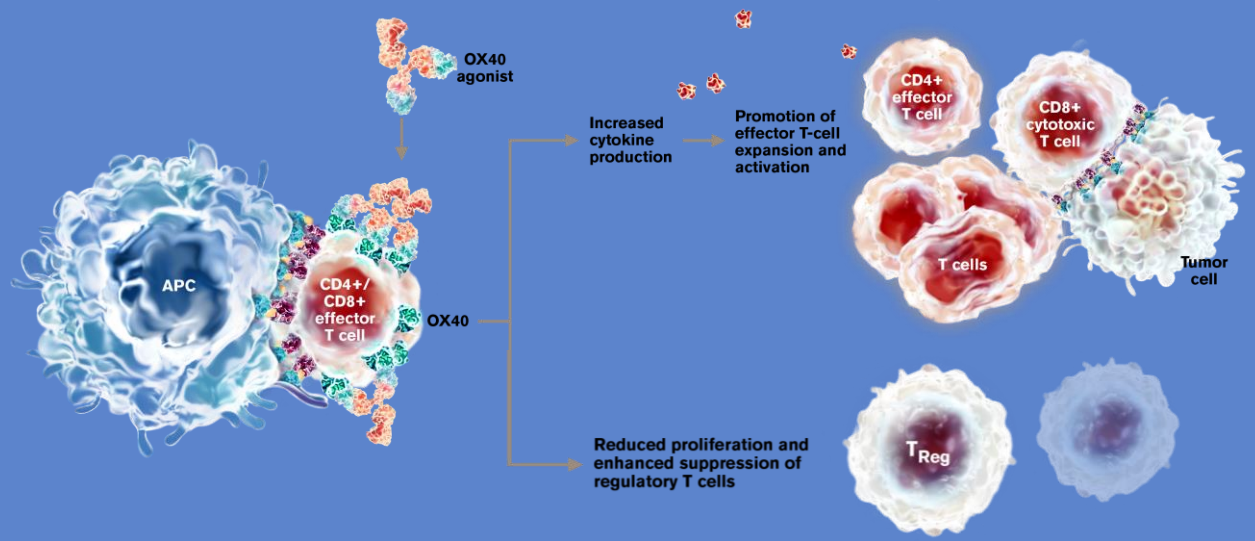
CT150

A First-in-Human Phase I Study of the OX40 Agonist GSK3174998 (GSK998) +/- Pembrolizumab in Patients (Pts) With Selected Advanced Solid Tumors (ENGAGE-1)

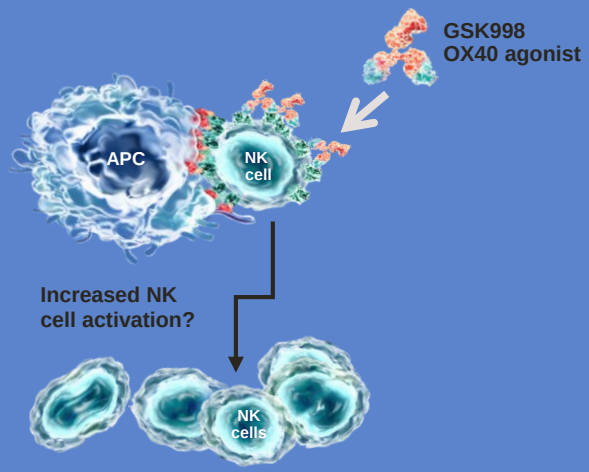
Sophie Postel-Vinay[1], Vincent K. Lam[2], Willeke Ros[3], Todd M. Bauer[4], Aaron R. Hansen[5], Daniel C. Cho[6], F. Stephen Hodi[7], Jan H.M. Schellens[3], Jennifer K. Litton[2], Sandrine Aspeslagh[1], Karen A. Autio[8], Frans L. Opdam[3], Meredith McKean[4], Neeta Somaiah[2], Stephane Champiat[1], Mehmet Altan[2], Anna Spreafico[5], Osama Rahma[7], Elaine M. Paul[9], Christoph M. Ahlers[10], Helen Zhou[10], Herbert Struemper[9], Shelby A. Gorman[10], Maura Watmuff[10], Kaitlin M. Yablonski[10], Niranjan Yanamandra[10], Michael J. Chisamore[11], Emmett V. Schmidt[11], Axel Hoos[10], Aurélien Marabelle[1], Jeffrey S. Weber[6], John V. Heymach[2]

[1]Gustave Roussy, Villejuif, France; [2]The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; [4]Sarah Cannon Research Institute/TN Oncology, Nashville, TN; [5]Princess Margaret Cancer Centre, Toronto, ON, Canada; [6]Perlmutter Cancer Center at NYU Langone Medical Center, New York, NY; [7]Dana-Farber Cancer Institute, Boston, MA; [8]Memorial Sloan Kettering Cancer Center, New York, NY; [9]GlaxoSmithKline, Research Triangle Park, NC; [10]GlaxoSmithKline, Collegeville, PA; [11]Merck & Co., Inc, Kenilworth, NJ

OX40 Agonism Results in Stimulation of Immune Effector T Cells and Attenuation of the Function of T_{reg} Cells[1-3]



OX40 Agonism may Increase NK Cell Activation



1. Croft M. Ann Rev Immunol. 2010;28:57–78; 2. Weinberg AD, et al. Immunol Rev. 2011;244:218–31; 3. Voo KS, et al. J Immunol. 2013;191:3641–50.APC, antigen-presenting cell, NK, natural killer; T_{reg}, regulatory T-cell

Disclosures

- **S. Postel-Vinay**: Gustave Roussy, Merck KGaA, Roche, Boehringer Ingelheim. **V.K. Lam**: GSK, BMS, Takeda, Adaptimmune, Achilles Therapeutics**. W. Ros**: None. **T.M. Bauer**: Moderna Therapeutics, Pfizer, Guardant Health, Loxo Pharmaceuticals, Exelexis, Ignyta, Bayer; Institutional: Daiichi Sankyo, Medpacto, Inc., Incyte, Mirati Therapeutics, MedImmune/AZ, Abbvie, Leap Therapeutics, MabVax, Stemline Therapeutics, Merck, Eli Lilly, GSK, Novartis, Genentech/Roche, Deciphera, Merrimack Pharmaceuticals, Immunogen, Millennium Pharmaceuticals, Calithera Biosciences, Kolltan Pharmaceuticals, Principa Biopharma,Peleton, Immunocore, Aileron Therapeutics, Bristol-Myers Squibb, Amgen, Sanofi, Boehringer Ingelheim, Astellas Pharma, Five Prime Therapeutics, Jacobio, Top Alliance BioScience, Janssen Pharmaceuticals, Clovis Oncology, Takeda, Karyopharm Therapeutics, Onyx Pharmaceuticals, Phosplati Therapeutics, Foundation Medicine. **A.R. Hansen**: Genentech/Roche, Merck, GSK, Bristol-Myers Squibb, Novartis, Boston Biomedical, Boehringer-Ingelheim, AstraZeneca, Medimmune. **D.C. Cho**: Nektar, Pfizer, Puretech, Torque, HUYA**. F. Hodi**: Novartis, BMS, Genentech, Merck, Sanofi, EMD Serono, Verastem, Pfizer, Bayer, Aduro, Amgen., Apricity, Bicara, Boston, Pharma, Pionyr, 7 Hills, Torque, Takeda, Compass**. J.H. Schellens**: share and patent holder on oral taxanes; Modra Pharmaceuticals. **J.K. Litton**: The University of Texas, MD Anderson Cancer Center, GSK, Novartis, Medivation/Pfizer, Genentech, EMD-Serono, Astra-Zeneca, Medimmune, Zenith, Ayala, Up To Date review panels for NCCN, ASCO, NIH PDQ, Medlearning, Physicians Education Resource, Prime Oncology, Medscape, Clinical Care Options, Medpage. **S. Aspeslagh**: UZbrussel, BSMO, ESMO, personal fees for oral presentations; MSD, BMS, Astra Zeneca, Amgen, Roche, Sanofi, Pfizer and Novartis. **K.A. Autio:** Institution: GSK, Pfizer, Astra-Zeneca, CytomX, Amgen, Tizona. **F.L. Opdam**: Netherlands Cancer Institute. **M. McKean**: Institution: Epizyme, Exelexis, Genentech, GSK, Infinity, Jacobio, Moderna, Regeneron, Tizona, Prelude, Ascentage Pharma, Ideaya Biosciences, Ikena Oncology, Array Biopharma, publication support to institution; Novartis. **N. Somaiah**: None. **S. Champiat**: Amgen, AstraZeneca, BMS, Janssen, MSD, Novartis and Roche, As part of Gustave Roussy Drug Development Department (DITEP): Principal/sub-Investigator of Clinical Trials; Abbvie, Adaptimmune, Aduro Biotech, Agios Pharmaceuticals, Amgen, Argen-X Bvba, Arno. **M. Altan**: GSK, Genentech, Nektar Therapeutics, Merck, Novartis, Jounce Therapeutics, BMS, Eli Lilly. **A. Spreafico**: University Health Network and Assistant Professor University of Toronto, MERCK, BMS, Novartis, Oncorus, Janssen, Institution: Novartis, Bristol-Myers Squibb, Symphogen AZ/Medimmune, Merck, Bayer, Surface Oncology, Northern Biologics, Janssen/J&J, Roche, Regeneron, Alkermes, Array Biopharma, GSK. **O. Rahma**: GSK, Merck, Celgene, Five Prime, GFK, Bayer, Roche/Genentech, Puretech, Imvax. **E.M. Paul**: GSK. **C.M. Ahlers**: GSK. **H. Zhou**: GSK. **H. Struemper**: GSK. **S.A. Gorman**: GSK. **M. Watmuff**: GSK. **K.M. Yablonski**: GSK. **N. Yanamandra**: GSK. **M.J. Chisamore**: Merck & Co. Inc. **E.V. Schmidt**: Merck & Co. Inc. **A. Hoos**: GSK. **A. Marabelle**: Pfizer, Roche/Genentech, Astra Zeneca/Medimmune, BMS. **J.S. Weber**: Nextcure, Biond, Celldex, Protean, CytoMx, Altor, BMS, GSK, Merck, Novartis, Amgen, Genentech, Astra Zeneca, Incyte, Named on a CTLA-4 biomarker patent by Moffitt,and a PD-1 biomarker by Biodesix; Moffitt, Biodesix. **J.V. Heymach**: GSK, Astra Zeneca, Patent; Spectrum Pharmaceuticals, Checkmate Pharmaceuticals, Brightpath Biotherapeutics, Eli Lilly & Co, Kairos Venture Investments, Triptych Health Partners, NIH/NCI, American Cancer Society, Cancer Prevention & Research Institute of Texas, AACR Johnson & Johnson Lung Cancer.

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ENGAGE-1: Phase I Study (NCT02528357)[1,2]

Safety, Tolerability, PK, PD, and Clinical Activity of GSK998 Alone or in Combination With Pembrolizumab for up to 2 Years

Part 1A: Escalation → **Part 1B: Expansion**

GSK998 Q3W

Not initiated

GSK998 Dose, mg/kg (patients, n)							
0.003 (1)	0.01 (1)	0.03 (8)	0.1 (10)	0.3 (10)	1.0 (4)	3.0 (7)	10.0 (4)

Part 2A: Escalation → **Part 2B: Expansion***

Pembrolizumab 200 mg Q3W + nCRM

GSK998 Q3W

Pembrolizumab 200 mg Q3W

GSK998 0.3 mg/kg Q3W

GSK998 Dose, mg/kg (patients, n)							
0.003 (5)	0.01 (5)	0.03 (10)	0.1 (12)	0.3 (36)	1.0 (12)	3.0 (12)	10.0 (4)

Inclusion

- Locally advanced, recurrent or metastatic solid malignancy progressed after standard therapy for specific tumor type
- Melanoma, NSCLC, RCC, bladder cancer, HNSCC, STS, TNBC, CRC MSI-h
- ≤5 prior lines of therapy
- ECOG PS 0-1
- Life expectancy ≥12 weeks

Exclusion

- Prior TNFR agonist treatment
- Prior bone marrow or solid organ transplant
- Brain metastases
- Active autoimmune disease

Assessments & Endpoints

- **Safety:** AEs, SAEs (NCI-CTC v4.0), DLT (4-week time frame), changes in laboratory parameters and immunogenicity
- **PK:** GSK998 concentrations in plasma and PK parameters including C_{max}, AUC(0-τ), and C_{min}
- **PD:** Receptor occupancy (CD3+); exploratory tumor and blood biomarkers
- **Disease assessments:** Q12W until progression then OS follow-up Q12W
- **Tumor response:** immune-related RECIST (primary) and RECIST v1.1
- **Endpoints:** ORR and DCR (CR+PR+SD ≥12 weeks)

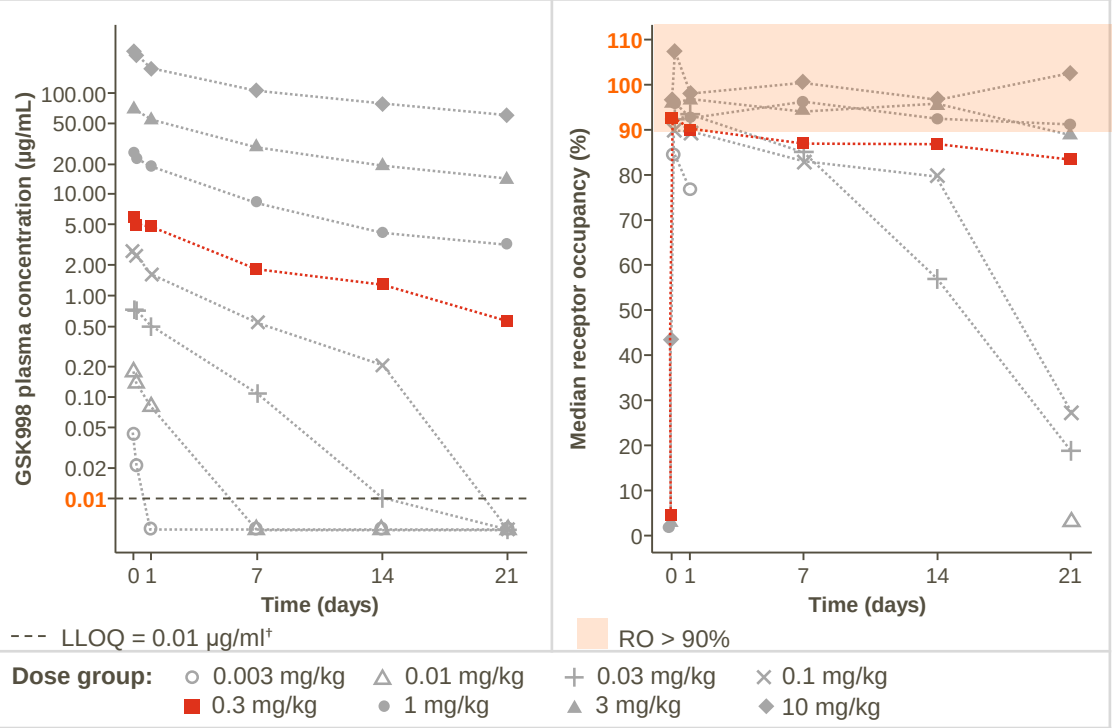
* Melanoma (n=8) soft tissue sarcoma de-differentiated liposarcoma (n=8) non-small cell lung cancer (n=5) || 1. US Clinical Trial Registry (https://www.clinicaltrials.gov). 2. Infante JR et al. Poster presentation, ASCO 2016; Abstract TSP31 || AE, adverse event; AUC, area under the curve; C_{max}, maximum concentration; C_{min}, minimum concentration; CR, complete response; CRM, continual reassessment method; DCR, disease control rate; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; HNSCC, head and neck squamous cell carcinoma; CRC MSI-h, colorectal cancer displaying high microsatellite instability; NCI-CTC, National Cancer Institute Common Toxicity Criteria; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD, pharmacodynamics; PK, pharmacokinetics; PR, partial response; Q3W, every 3 weeks; Q12W every 12 weeks; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria In Solid Tumors; RO, receptor occupancy; SAE, serious adverse event; SD, stable disease; STS, soft tissue sarcoma; TNBC, triple-negative breast cancer; TNFR, tumor necrosis factor receptor.

Patient and Disease Characteristics, Pharmacokinetics and Receptor Occupancy

GSK998 0.3 mg/kg dose was threshold for linear PK and peripheral RO saturation over 3-week dose interval

	GSK998 (n=45)	GSK998 + Pembrolizumab (n=96)*
Age, years; median (range)	63.0 (27-78)	63.5 (25-86)
Sex, n (%)		
Female	27 (60)	44 (46)
Male	18 (40)	52 (54)
ECOG PS, n (%)		
0	20 (44)	38 (40)
1	25 (56)	58 (60)
Tumor Types, n		
NSCLC	12 (27)	17 (18)
Melanoma	3 (7)	20 (21)
STS	10 (22)	8 (8)
CRC MSI-h	1 (2)	13 (14)
RCC	8 (18)	9 (9)
Bladder	2 (4)	11 (11)
HNSCC	2 (4)	7 (7)
TNBC	7 (16)	11 (11)
Prior anticancer regimens, n (%)		
1	10 (22)	19 (20)
2	9 (20)	23 (24)
3	7 (16)	22 (23)
4	7 (16)	13 (14)
>4	10 (22)	14 (15)
Prior PD-1/PD-L1 therapy, n (%)	13 (29)	41 (43)

GSK998 demonstrated target binding in the periphery as evidenced by PK and receptor occupancy (RO)



0.3 mg/kg dose was selected for further clinical evaluation in melanoma, STS-DDLS, and NSCLC in Part 2B (expansion)

*Part 1A = 45 pts; *Part 2A = 75 pts (3 pts crossed over from Part 1A); *Part 2B = 21 pts: Melanoma (8), STS (8), and NSCLC (5)
†Samples reported below the LLQ (0.01 µg/mL) were assigned a value of 0.005 µg /mL for the purposes of this graphical summary
ECOG PS, Eastern Cooperative Oncology Group performance status; HNSCC, head and neck squamous cell carcinoma; LLOQ, lower limit of quantitation; CRC-MSI-h, colorectal cancer displaying high microsatellite instability; NSCLC, non-small cell lung cancer; PK, pharmacokinetics; RCC, renal cell carcinoma; RO, receptor occupancy; STS, soft tissue sarcoma (DDLS = de-differentiated liposarcoma); TNBC, triple-negative breast cancer; TNFR, tumor necrosis factor receptor.

GSK998 +/- pembrolizumab was well tolerated

GSK998 0.003–10.0 mg/kg IV Q3W +/- pembrolizumab 200 mg

AE, n (%)	Monotherapy (n=45)	
	All Grades	G ≥3*
Any AE (all causality)	45 (100)	18 (40)
Any TR-AE	23 (51)	3 (7)
TR-AE in ≥5% patients		
Diarrhea	5 (11)	0
Fatigue	5 (11)	0
Nausea	4 (9)	0
Decreased appetite	3 (7)	0
Myalgia	3 (7)	0
TR-AE leading to treatment delay	3 (7)	2 (4)
TR-AE leading to IP discontinuation	0	0
DLT	0	0

AE, n (%)	Combination (n=96)†	
	All Grades	G ≥3*
Any AE (all causality)	95 (99)	34 (35)
Any TR-AE	61 (64)	8 (8)
TR-AE in ≥5% patients		
Fatigue	23 (24)	3 (3)
Nausea	10 (10)	0
Pruritis	7 (7)	0
Arthralgia	6 (6)	0
Pyrexia	6 (6)	0
Diarrhea	5 (5)	1 (1)
Rash	5 (5)	0
Rash (maculopapular)	5 (5)	0
TR-AE leading to treatment delay	6 (6)	1 (1)
TR-AE leading to IP discontinuation	3 (3)	2 (2)
DLT	2 (2)	2 (2)

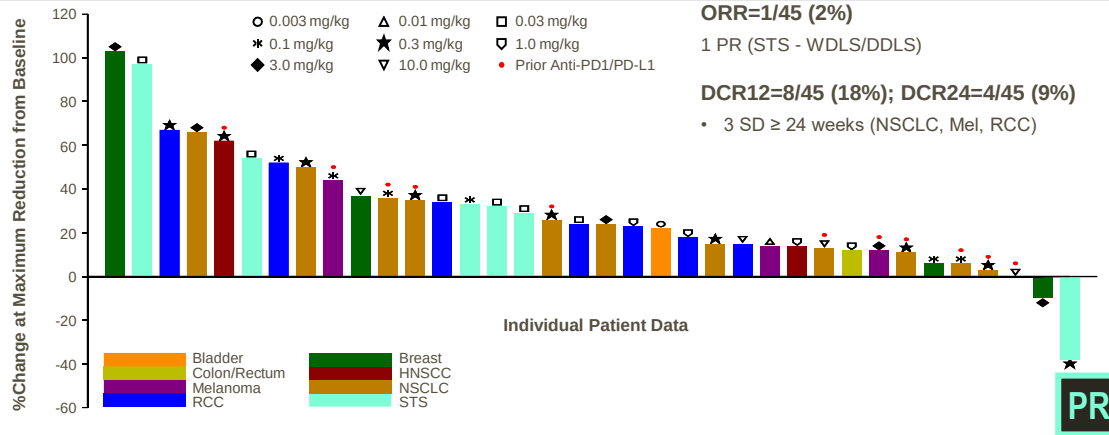
- **No dose-relationship for AEs**
- **No MTD established**
- **DLTs**
  - Combination therapy only, n=2
  - G3 non-malignant pleural effusion (0.03 mg/kg); G1 myocarditis with G3 troponin increase (10 mg/kg)
- **No Grade 4 or 5 TR-AEs**
- **TR-AEs leading to IP discontinuation**
  - Combination therapy only, n=3
  - G1 myocarditis with G3 troponin increase; G3 infusion reaction; G2 fatigue
- **Immunogenicity**
  - GSK998 ADA in 38% (49/130) patients (monotherapy, 21/45; combination 28/85), of whom 3 had infusion reactions

*No treatment-related Grade 4 or 5 AEs. †Includes 75 pts from Part 2A and 21 pts from Part 2B: Melanoma (8), STS – De-differentiated liposarcoma (8), and NSCLC (5)
ADA, anti-drug antibody; AE, adverse event; CVA, Cerebrovascular accident; DLT, dose-limiting toxicity; g, grade; IP, investigational product; MTD, maximally tolerated dose; TR-AE, treatment-related AE.

Limited monotherapy and modest combination clinical activity

MultiOmyx™ data from tumor biopsies suggested increased NK/decreased Treg involvement in some responders

Monotherapy (Part 1A) n=45



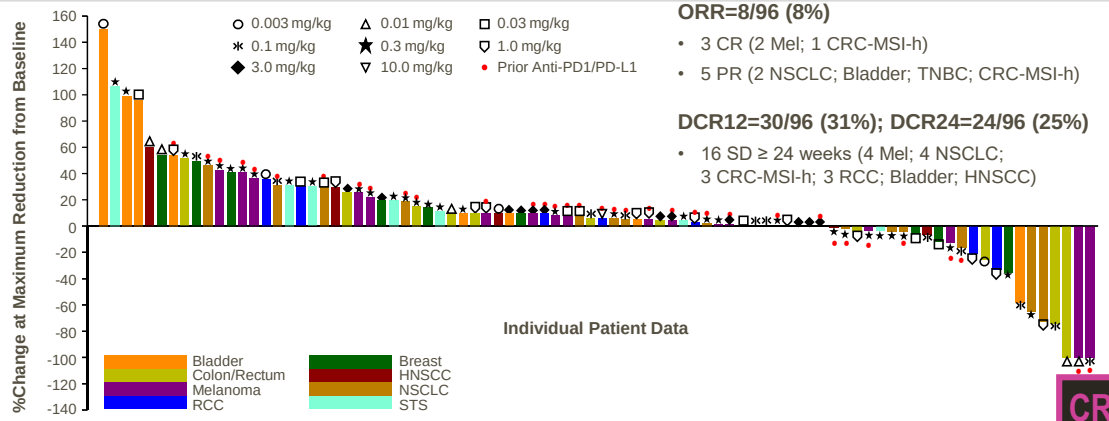
ORR=1/45 (2%)

1 PR (STS - WDLS/DDLS)

DCR12=8/45 (18%); DCR24=4/45 (9%)

- 3 SD ≥ 24 weeks (NSCLC, Mel, RCC)

Combination (Part 2A and 2B) n=96

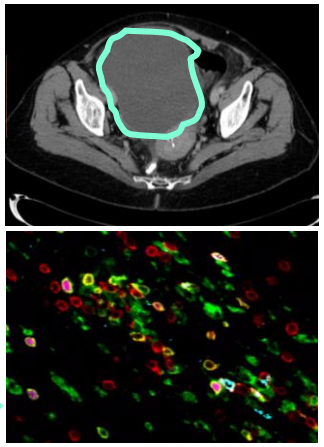
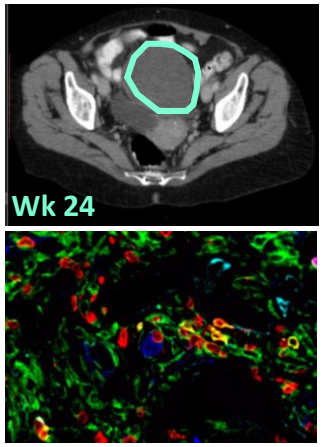
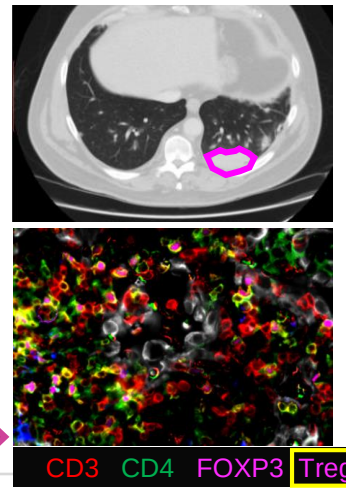
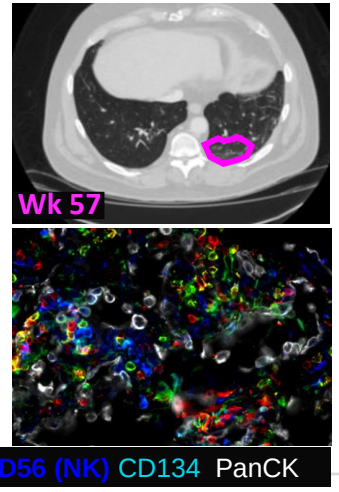


ORR=8/96 (8%)

- 3 CR (2 Mel; 1 CRC-MSI-h)
- 5 PR (2 NSCLC; Bladder; TNBC; CRC-MSI-h)

DCR12=30/96 (31%); DCR24=24/96 (25%)

- 16 SD ≥ 24 weeks (4 Mel; 4 NSCLC; 3 CRC-MSI-h; 3 RCC; Bladder; HNSCC)

Baseline	On treatment	
		**GSK998 0.3 mg/kg** • 66YO female patient • STS - WDLS/DDLS • Prior doxorubicin (15 mg/week x 2 mo) • Partial response (-38%) • On study - 39 weeks • MultiOmyx™ IHC: increased NK cells, decreased Treg
		**GSK998 0.1 mg/kg + pembrolizumab 200 mg** • 60YO male patient • Melanoma • Prior ipilimumab/ nivolumab (~14 mo) • Complete response (ongoing >18 mo) • On study - 3 years • MultiOmyx™ IHC: increased NK cells, decreased Treg

PR

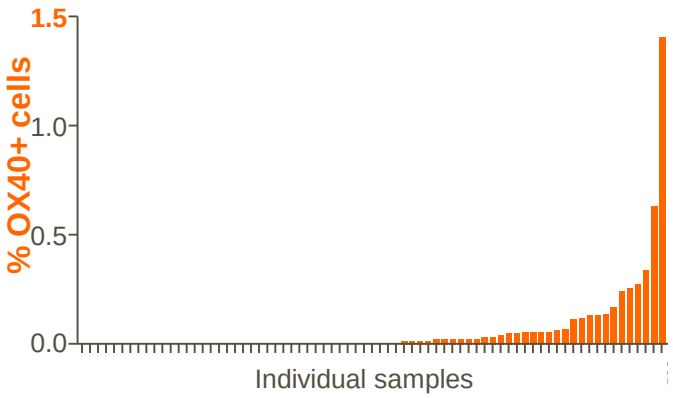
CR

irRECIST (Immune-related Response Evaluation Criteria In Solid Tumors) used to assess response; unconfirmed and confirmed responses included. CR, complete response; DCRX, DCR at X weeks (complete response + partial respons + stable disease ≥X weeks); HNSCC, head and neck squamous cell carcinoma; IHC, immunohistochemistry; mo, month; Mel, melanoma; CRC MSI-h, colorectal cancer displaying high microsatellite instability; NK, natural killer; NSCLC, non-small cell lung cancer; PD-L, Programmed death-ligand; PR, partial response; RCC, renal cell carcinoma; STS, soft tissue sarcoma (WDLS=well differentiated liposarcoma and DDLS=de-differentiated liposarcoma); TNBC, triple-negative breast cancer; Treg, regulatory T-cell; wk, week; YO, year-old

OX40 Expression, Summary and Conclusions

OX40 expression in tumor

MultiOmyx IHC: <2% total cells were OX40+



Both response rate and tumor OX40 expression were low; no correlation was observed between them

For questions please contact
Elaine Paul <elaine.m.paul@gsk.com>

Summary and Conclusions

Safety

- GSK998 well tolerated ≤ 10 mg/kg +/- 200 mg pembrolizumab
- ADA detected in 38% patients; 3 had infusion reactions

Dose

- GSK998 0.3 mg/kg selected for combination expansion:
  - Threshold for linear PK and peripheral RO saturation
  - Monotherapy and combination response observed

Efficacy

- Monotherapy activity did not support initiating expansion cohorts
- Combination activity not significantly greater than expected for pembrolizumab alone; did not support continued expansion

Exploratory Biomarkers

- Role for ↑NK cells/↓Treg in responses driven by OX40 agonism?
- Would ↑OX40 expression in tumor increase clinical activity?

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