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A phase I/II, open-label study of the novel checkpoint IGSF8 inhibitor GV20-0251 in patients with advanced solid tumors

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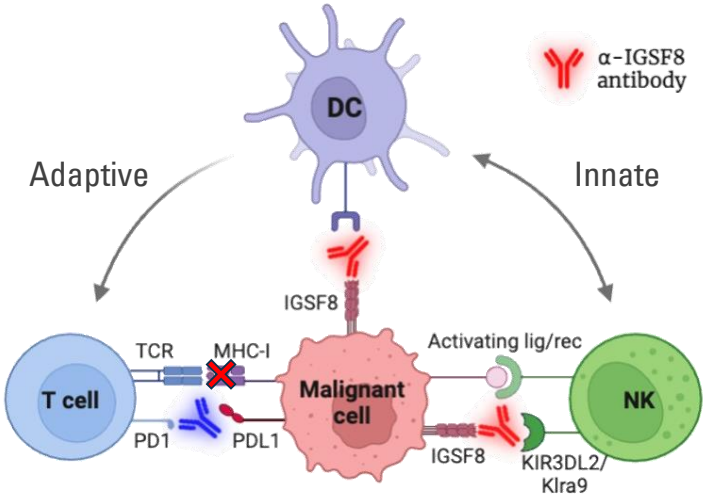
Declaration of Interests

Kristopher Wentzel MD:

No disclosures and no conflicts.

GV20-0251 is a Monoclonal Antibody Against a Novel Immune Checkpoint IGSF8 to Activate Innate and Adaptive Immunity

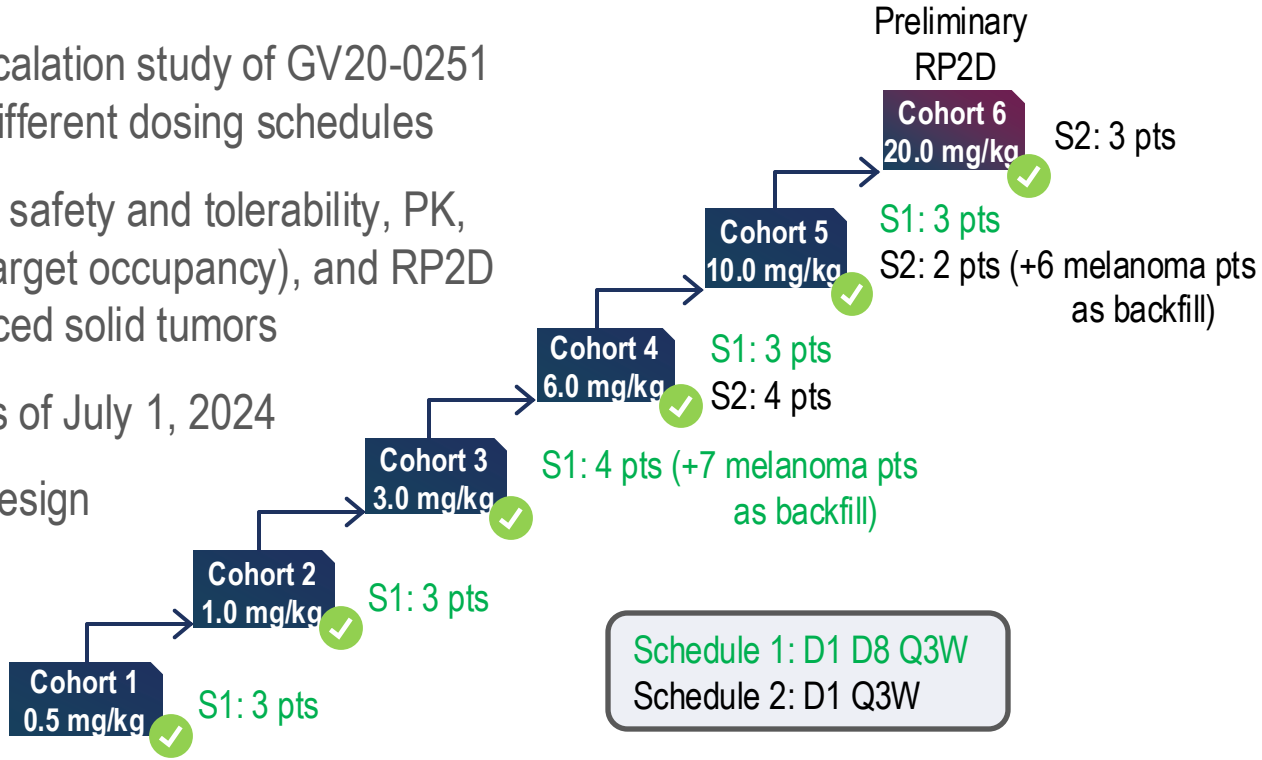
- IGSF8 is a newly discovered immune checkpoint that suppresses NK cells and dendritic cells in antigen presentation deficient tumors which are often resistant to immune checkpoint inhibitors
- GV20-0251 is a cross-species reactive, Fc-attenuated IgG1 antibody against IGSF8 and is the first clinical stage, AI-designed antibody therapeutic against an AI-predicted target
- Blocking IGSF8 with GV20-0251 enhances NK cell-mediated cytotoxicity, upregulates antigen presentation, and activates antigen-specific T cells



Li et al, Cell 2024

GV20-0251-100 Study Design

- Monotherapy dose escalation study of GV20-0251 administered on two different dosing schedules
- Objectives: Determine safety and tolerability, PK, pharmacodynamics (target occupancy), and RP2D in patients with advanced solid tumors
- 38 patients enrolled as of July 1, 2024
- 3+3 dose escalation design



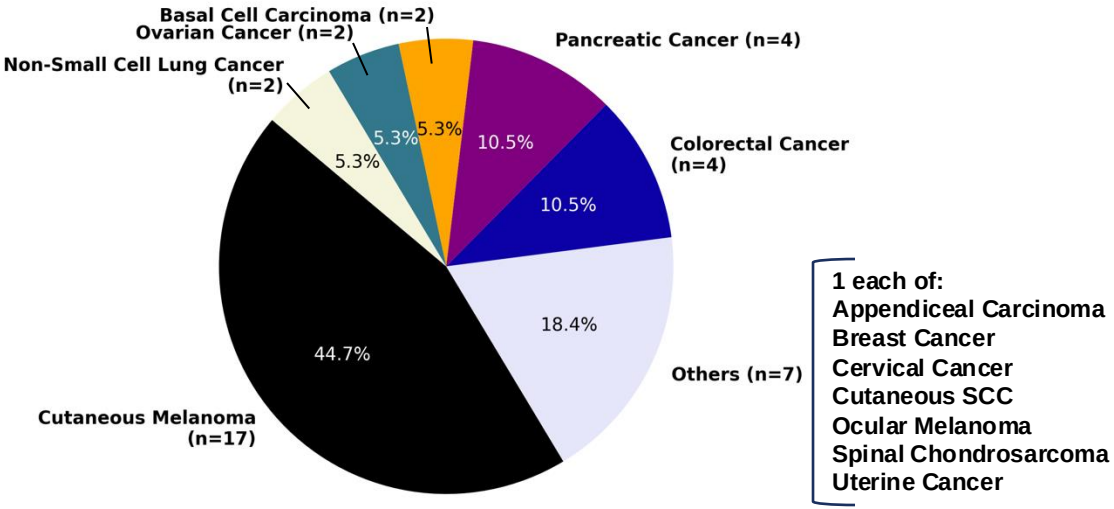
Data cut-off date: July 1, 2024 (ongoing and preliminary)

Key Inclusion & Exclusion Criteria:

- **Inclusion Criteria:**
  - *Previously treated, histologically confirmed advanced solid malignancy with progressive disease*
  - *Refractory or intolerant to SOC therapies or have no SOC therapies available*
  - *Measurable disease per RECIST version 1.1*
  - *ECOG Performance Status 0 or 1*
  - *Adequate organ function per protocol-specified ranges for hematology and chemistry parameters*
  - *Recovered from all TRAEs of prior anticancer therapies to ≤ Grade 1*
  - *Disease-free of active secondary or prior malignancies for ≥ 2 years*
- **Exclusion Criteria:**
  - *CNS malignancy*
  - *CNS metastasis unless stable and not requiring steroids*
  - *Anti-cancer treatment (other than immune modulators) within 14 days (or 5 half-lives) prior to first dose*
  - *Anti PD-1 or other immune modulators within 28 days prior to first dose*
  - *Investigational agent within 28 days (or 5 half-lives) prior to first dose*
  - *Major surgery within 28 days prior to first dose*
  - *Active autoimmune disease or other medical conditions requiring chronic systemic steroid or immunosuppressive therapy within 6 months prior to first dose*

Demographics and Disease Characteristics

Demographics	n=38
Age, years	
Median	62
Range	21-84
Sex, n (%)	
Male	15 (39)
Female	23 (61)
Race, n (%)	
Asian	3 (8)
Black or African American	3 (8)
White	30 (79)
Other	2 (5)
ECOG performance status, n (%)	
0	20 (53)
1	18 (47)



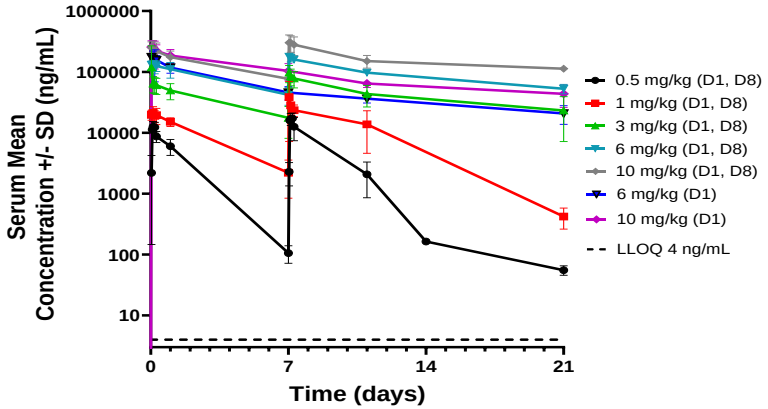
Prior systemic therapies	Median=4, Range(0-11)
Prior immunotherapy*	33 patients
Prior PD1/PDL1 inhibitor	26 patients
Prior CTLA4 inhibitor	15 patients

*** Includes α-PD1, α-PDL1, α-CTLA4, α-LAG3, IL-2, TIL, etc.**

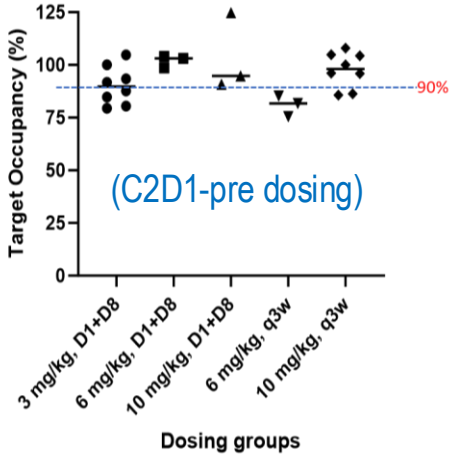
PK Profile and Target Occupancy

- Dose proportional pharmacokinetics (PK) ≥ 3mg/kg with **half-life ~25.6 days**
- Full target occupancy achieved in the peripheral blood at dose levels ≥ 3mg/kg
- No significant signals in serum cytokine and anti-drug antibody (ADA) analyses
- Characterization of immune effects in paired biopsy samples (pre- and on-treatment) is ongoing

GV20-0251 Serum PK



IGSF8 Occupancy on CD3+ T cells



GV20-0251 Safety Profile

Generally well tolerated; no dose limiting toxicities

Treatment-Related Adverse Events (TRAEs) in ≥ 2 patients

	Max Grade (CTCAE v5)			Overall (n=38)
	1 (n=38)	2 (n=38)	3 (n=38)	
Any GV20-0251 Related TEAE	9 (24%)	9 (24%)	1 (3%)	19 (50%)
Rash†	1 (3%)	4 (11%)	0	5 (13%)
Anaemia	3 (8%)	0	0	3 (8%)
Fatigue	1 (3%)	2 (5%)	0	3 (8%)
Pruritus	0	3 (8%)	0	3 (8%)
Arthralgia	0	2 (5%)	0	2 (5%)
Diarrhoea	0	2 (5%)	0	2 (5%)
Dyspnoea	0	2 (5%)	0	2 (5%)

† Includes dermatitis acneiform, rash, rash maculo-papular, rash pruritic

One patient with Grade 3 pneumonitis (6 mg/kg, Schedule 2; all other TRAEs were Grade 1 or Grade 2)

GV20-0251 Preliminary Efficacy (n=29)

2 PRs and 14 SDs in 29 evaluable* patients (ORR 6.9%; DCR 55.2%)

Summary of RECIST 1.1 Overall Response Rate by GV20-0251 Dose and Schedule

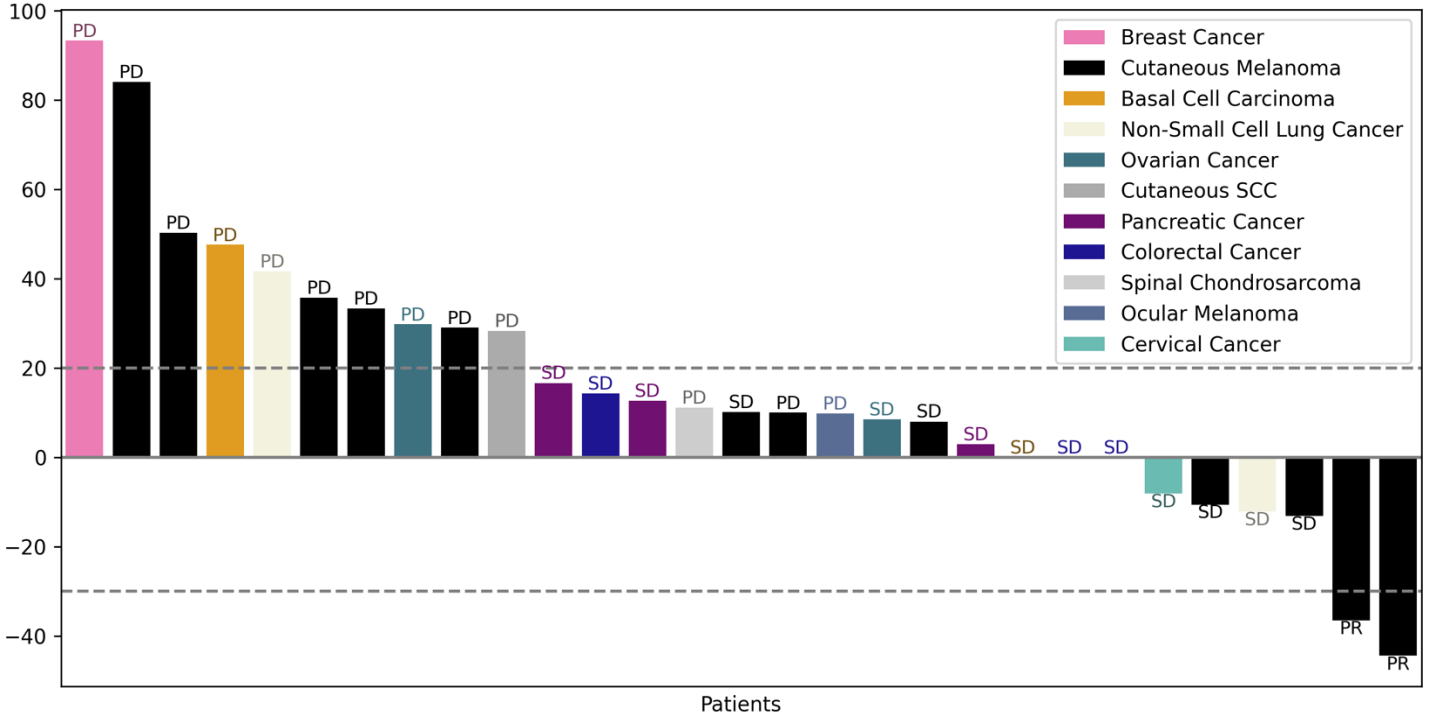
RECIST V1.1 Response	Schedule 1					Schedule 2			Overall n=29* (%)
	0.5 mg/kg n=2	1 mg/kg n=2	3 mg/kg n=10	6 mg/kg n=2	10 mg/kg n=3	6 mg/kg n=3	10 mg/kg n=7	20 mg/kg n=0	
Complete Response	0	0	0	0	0	0	0	0	0
Partial Response	0	0	1	0	0	0	1†	0	2 (6.9)†
Stable Disease	2	1	5	1	2	1	2	0	14 (48.2)
Progressive Disease	0	1	4	1	1	2	4	0	13 (44.8)
Discontinued prior to first tumor assessment	1	1	1	1	0	1	0	0	5
Pending first tumor assessment	0	0	0	0	0	0	1	3	4

* Evaluable: patient had baseline and at least one on-treatment tumor scan assessment

† Second PR with 28% and 36% target lesion reductions on first 2 tumor assessments, respectively, and treatment is ongoing

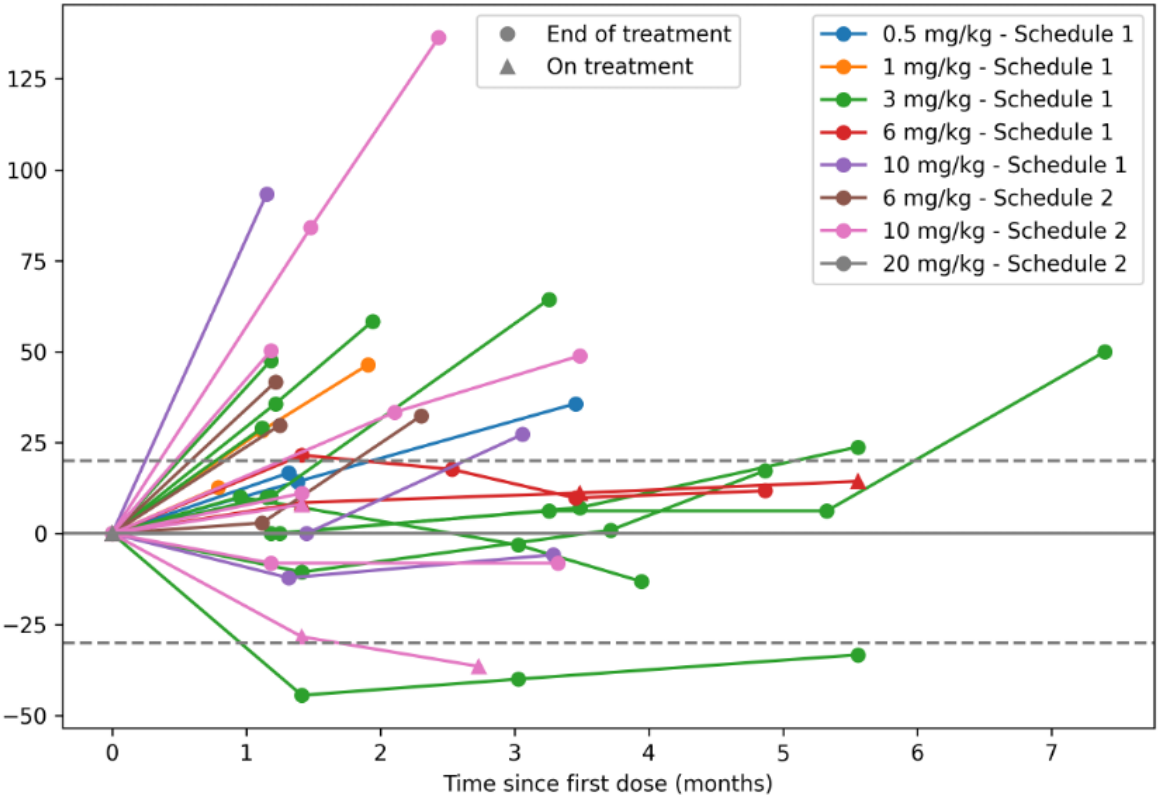
GV20-0251 Preliminary Efficacy (n=29)

Best % change in sum of RECIST target lesion diameters



GV20-0251 Tumor Response and Duration

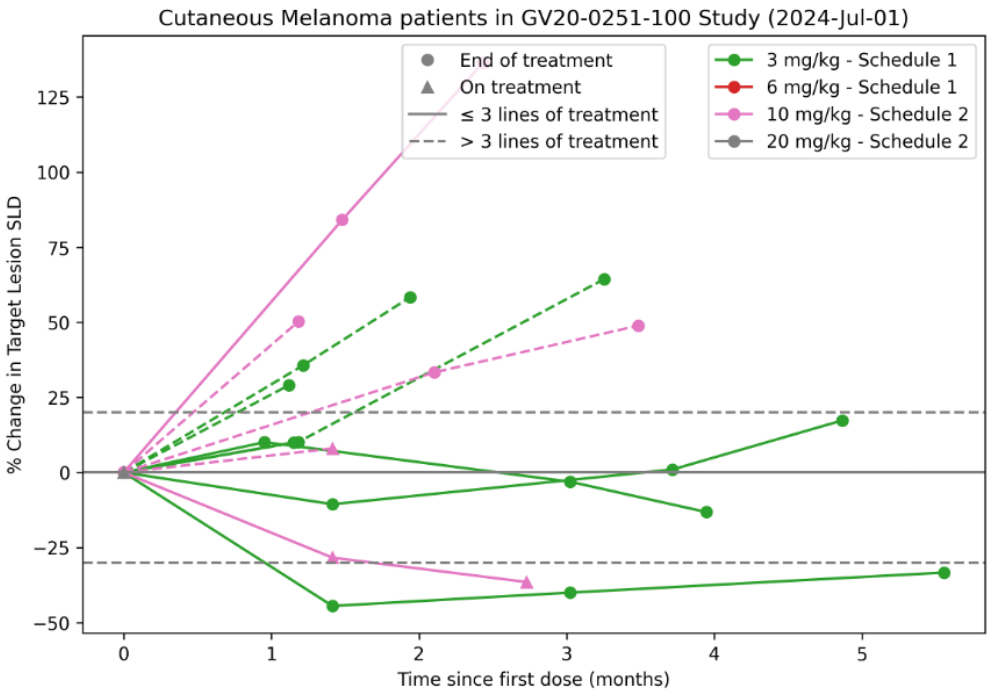
Percentage change in the sum of RECIST target lesion diameters over time



GV20-0251 Cutaneous Melanoma Population (n=12)

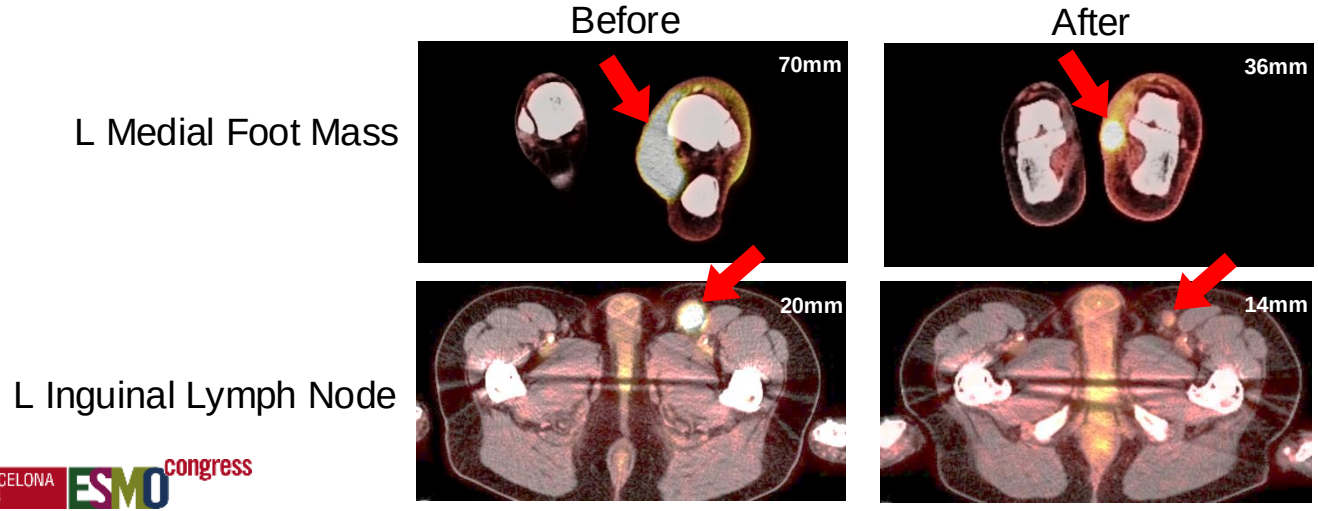
- All 12 melanoma patients had received anti-PD-1/PD-L1
- 11 out of 12 patients had received anti-CTLA4
- Median # prior lines: 3 (range, 1 – 11)

	All melanoma (n=12)	Melanoma with 1-3 prior lines (n=5)
PR	2 (17%)	2 (40%)
SD	4 (33%)	2 (40%)
ORR	2 (17%)	2 (40%)
DCR	6 (50%)	4 (80%)



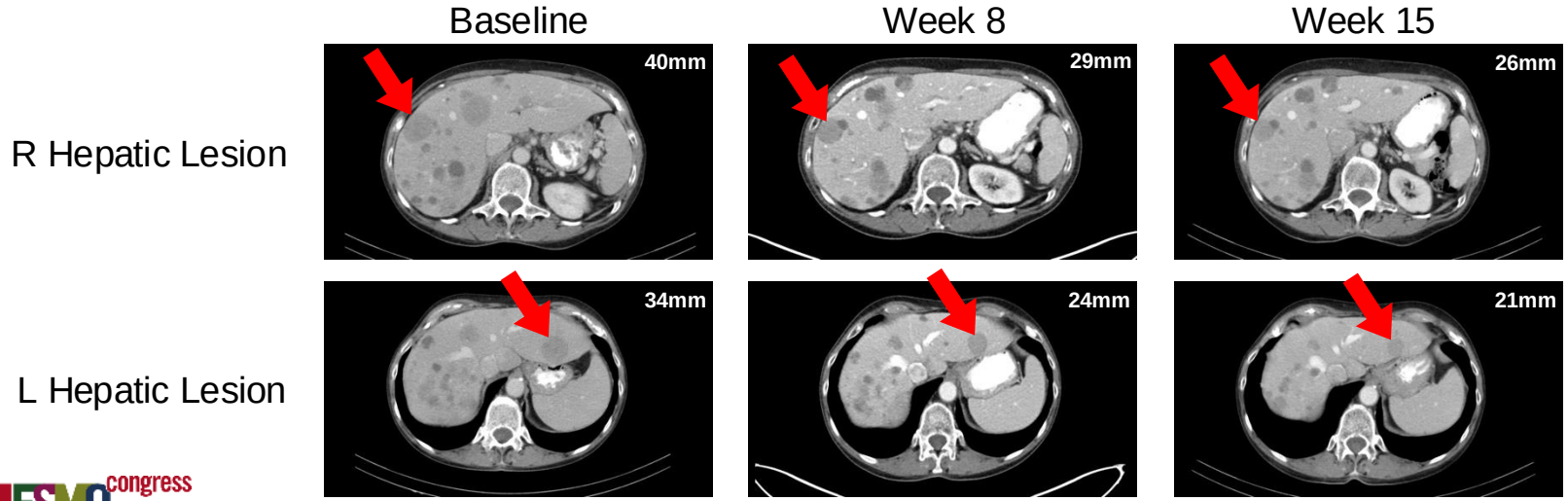
Case Report #1: Cutaneous Melanoma

- 66-year-old male diagnosed in Jan 2022 with left foot skin lesion. Received surgery followed by adjuvant pembrolizumab (Apr to Dec 2022). Tumor recurred while on adjuvant therapy and was switched to ipilimumab (Mar to Jun 2023) the progressed with pelvic/inguinal lymph nodes (Jun 2023)
- Started GV20-0251 at 3mg/kg dose on Schedule 1 (D1, D8 Q3W) in Sep 2023
- Achieved partial response after 5 weeks with 44% reduction in target lesions; response lasted for 4 months
- Underwent surgery and continued to receive GV20-0251, for total duration of treatment of 8.6 months



Case Report #2: Cutaneous Melanoma

- 71-year-old female diagnosed in Oct 2023 with liver metastases. Received Ipilimumab and Nivolumab combination therapy (Dec 2023 to Jan 2024) and progressed in Jan 2024
- Started GV20-0251 at 10mg/kg dose on Schedule 2 (D1 Q3W) in Mar 2024
- Achieved partial response after 15 weeks with 36% reduction in target lesions
- Treatment ongoing and awaiting further CT scans to confirm the partial response



Conclusions:

- GV20-0251, a first-in-class antibody against a novel immune checkpoint IGSF8, activates both innate and adaptive immunity
- Well-tolerated up to 20 mg/kg Q3W; no DLTs
  - Grade 1 AE (24%), Grade 2 AE (24%) Grade 3 AE (3%); only 1 immune-related adverse event
- Preliminary efficacy as monotherapy, 17% ORR in cutaneous melanoma
- Safety, PK, and target occupancy support preliminary RP2D at 20mg/kg Q3W
- Planned initiation of enrollment of GV20-0251 in combination with pembrolizumab

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GV20-0251 Monotherapy Safety Profile Supplementary

Generally well tolerated; no dose limiting toxicities

Treatment-Related Adverse Events (TRAEs) in ≥ 2 patients

	Schedule 1					Schedule 2			Overall (n=38)
	0.5 mg/kg (n=3)	1 mg/kg (n=3)	3 mg/kg (n=11)	6 mg/kg (n=3)	10 mg/kg (n=3)	6 mg/kg (n=4)	10 mg/kg (n=8)	20 mg/kg (n=3)	
Any GV20-0251 Related TEAE	1 (33%)	1 (33%)	6 (55%)	1 (33%)	3 (100%)	3* (75%)	4 (50%)	0	19 (50%)
Rash†	0	0	1 (9%)	1 (33%)	1 (33%)	0	2 (25%)	0	5 (13%)
Pruritus	0	0	1 (9%)	0	1 (33%)	0	1 (12%)	0	3 (8%)
Fatigue	0	0	2 (18%)	0	1 (33%)	0	0	0	3 (8%)
Anemia	0	0	1 (9%)	1 (33%)	0	1 (25%)	0	0	3 (8%)
Diarrhea	0	0	2 (18%)	0	0	0	0	0	2 (5%)
Arthralgia	1 (33%)	0	0	0	1 (33%)	0	0	0	2 (5%)
Dyspnea	1 (33%)	0	1 (9%)	0	0	0	0	0	2 (5%)

† Includes dermatitis acneiform, rash, rash maculo-papular, rash pruritic

* All TRAEs were Grade 1 or Grade 2, with exception of 1 patient with Grade 3 pneumonitis (6 mg/kg, Schedule 2)