Rasha Cosman, MD

MBBS, FRACP, Medical Oncologist

The Kinghorn Cancer Centre
St Vincent Hospital, Sydney, Australia

Dr. Rasha Cosman has obtained her Medical Degree from the University of New South Wales and completed her fellowship in Medical Oncology at the Royal Australasian College of Physicians in 2012. She underwent a Clinical Research Fellowship at the National Health and Medical Research Council in Sydney and is currently working at the Precision Medicine Unit/ Phase I Clinical Trials at The Kinghorn Cancer Centre, St Vincent Hospital, and is a Conjoint Lecturer at the University of New South Wales.

She has special interests in Head & Neck cancer and Melanoma and has conducted many Clinical Trials, from Phase I to Phase III. She is well experienced in Oncology drug development and First In Human Trials.

Preliminary Safety and Pharmacokinetics (PK) from a Phase I Study of CS1002, an Anti-Cytotoxic T-lymphocyte Antigen-4 (CTLA-4) Monoclonal Antibody (mAb) in Patients with Advanced Solid Tumors

Rasha Cosman

St Vincent's Hospital, Sydney, Australia

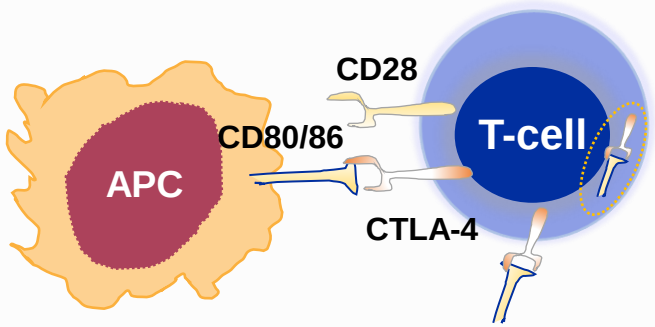
20th Sep, 2019

Dusan Kotasek[1], Morteza Aghmesheh[2], Amy Prawira[3], Rasha Cosman[3], Ning Li[4], Wenyi Sun[4], Ruijie Gu[4], Yiru Wang[4], Ying Pan[4], Archie N Tse[4], Xiaolu Tao[4]

1. Ashford Cancer Centre Research, Adelaide, Australia
2. Southern Medical Day Care Centre, Wollongong, Australia
3. St Vincent's Hospital, Darlinghurst, NSW, Australia
4. CStone Pharmaceuticals（Suzhou）Co., Ltd, Suzhou, China

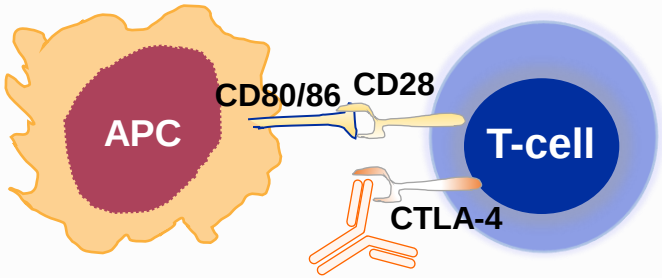
CS1002: A Full-Length, Fully Human IgG_1 Monoclonal Antibody Against CTLA4

- **CS1002: identical to ipilimumab (Yervoy) in term of amino acid sequence**
- **Mechanism of Action**
  - CTLA-4 blocks and removes B7 (CD80/86) leading to T cell inhibition
  - CS1002 binds to CTLA-4 and blocks the interaction between CTLA-4 and CD80/86, resulting in T-cell activation and proliferation



APC: antigen-presenting cells

T-cell inhibition



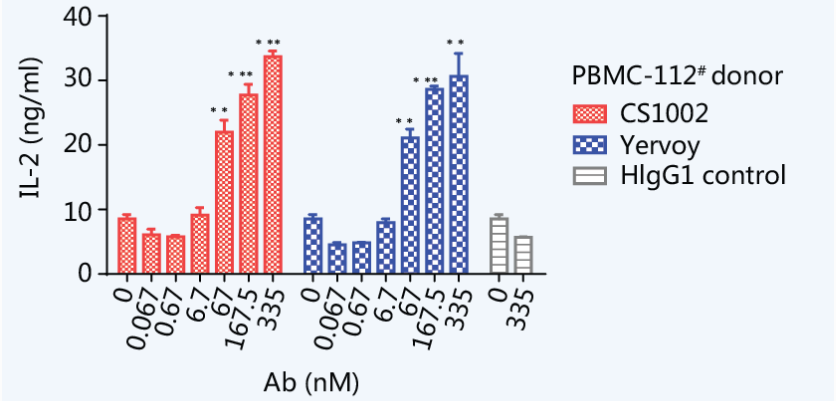
CS1002

Restoration of T-cell activation, proliferation

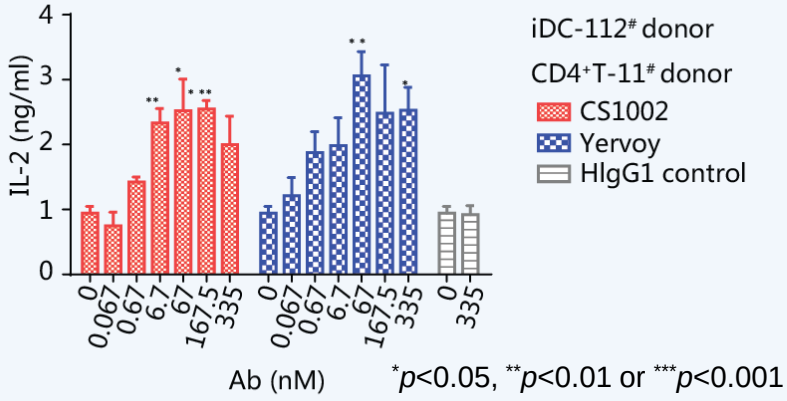
CS1002: Preclinical Efficacy Profile Comparable to that of Ipilimumab

In vitro: Cell Based Functional Assay

Staphylococcal enterotoxin B (SEB)-stimulated PBMCs



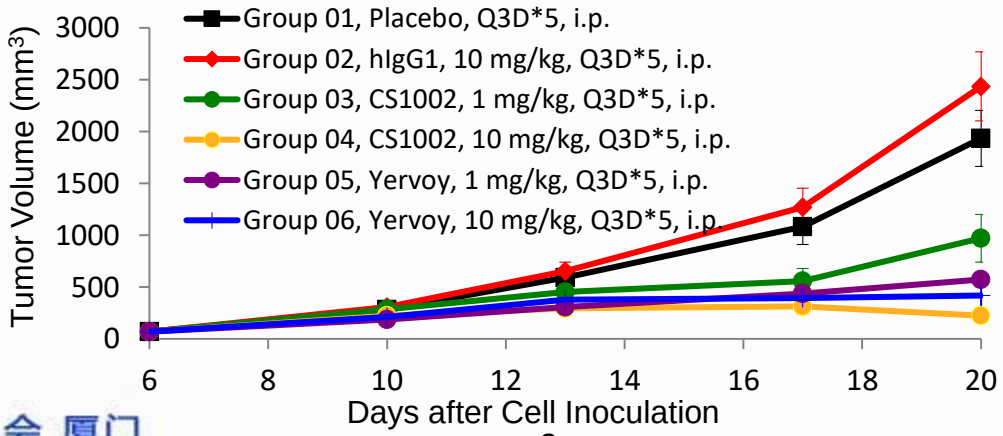
Allogeneic mixed lymphocyte reaction



*p<0.05, **p<0.01 or ***p<0.001

In vivo Efficacy

In mouse colon cancer MC38 tumor model

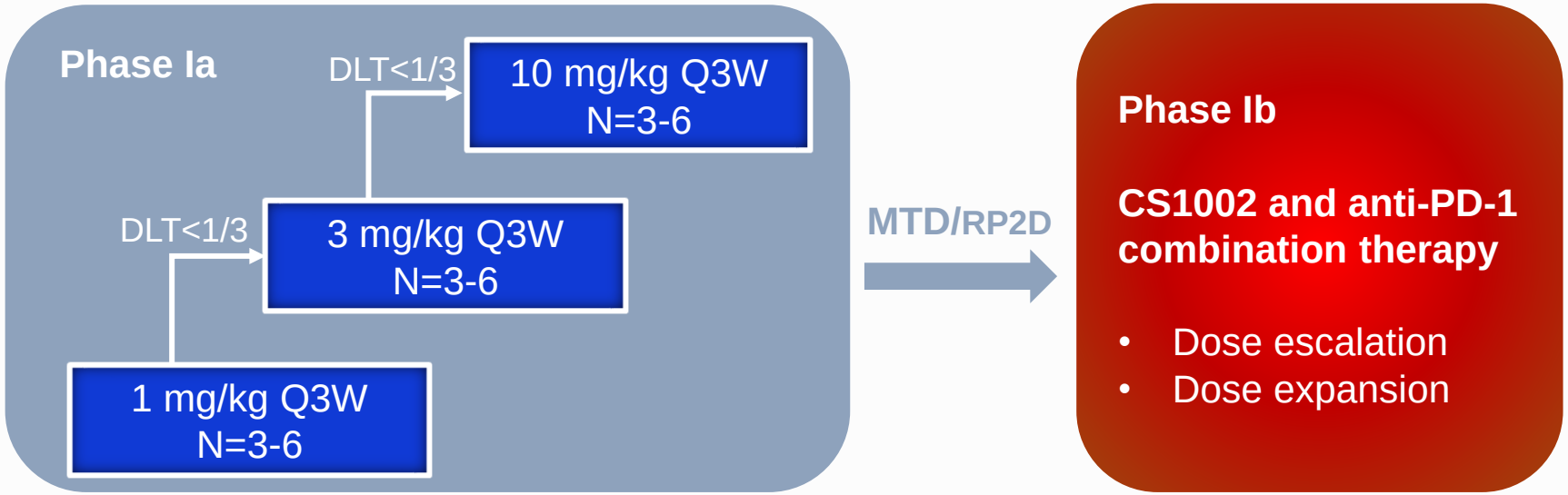


CS1002 Phase I Study Design

Objectives (Phase Ia)

- Safety and tolerability
- MTD and Recommended phase II dose (RP2D) / Recommended combination dose

Study Design



- *3+3 dose escalation design*
- *Dosage: induction Q3W, up to 4 doses; maintenance Q12W, up to 2 years*
- *DLT evaluation conducted during the first cycle (21 day)*

DLT : dose-limiting toxicity ; MTD: maximum tolerated dose; Q3W : once every 3 weeks; Q12W: once every 12 weeks

Demographics and Baseline Characteristics in Phase Ia

Characteristics	Safety Analysis Set (N=13)
Age (years), median (range)	58 (48-75)
Sex, n (%)	
Male	4 (30.8)
Female	9 (69.2)
Baseline ECOG, n (%)	
0	7 (53.8)
1	6 (46.2)
Prior anti-cancer therapy regimen, median (range)	3.0 (1-6)

Colorectal cancer was the major cancer type enrolled in Ph Ia (n = 4); other enrolled cancer types included unknown primary metastatic adenocarcinoma (n = 2); oesophageal adenocarcinoma, pleural mesothelioma, cholangiocarcinoma, pancreatic adenocarcinoma, prostate cancer, hepatocellular carcinoma, and gastrointestinal stromal tumor (n = 1 each)

All the Phase Ia data presented: Cut-off by Apr 25th , 2019

Study Status and Patients Disposition

- 13 patients have been treated, and 2 patients are still on treatment
- Phase Ia dose escalation DLT observation has been completed
- DLT was not observed and MTD was not reached

	1 mg/kg (N=6) n (%)	3 mg/kg (N=3) n (%)	10 mg/kg (N=4) n (%)	Total (N=13) n (%)
Treated	**6 (100)**	**3 (100)**	**4 (100)**	**13 (100)**
Treatment ongoing	**0**	**0**	**2 (50.0)**	**2 (15.4)**
Discontinued from study treatment	**6 (100)**	**3 (100)**	**2 (50.0)**	**11 (84.6)**
Adverse event	0	0	0	0
Radiographic disease progression	3 (50)	2 (66.7)	1 (25.0)	6 (46.2)
Symptomatic deterioration without radiographic evidence	0	0	1 (25.0)	1 (7.7)
Subject decision	2 (33.3)	1 (33.3)	0	3 (23.1)
Death	1 (16.7)	0	0	1 (7.7)
Discontinued from study	**4 (66.7)**	**3 (100)**	**2 (50.0)**	**9 (69.2)**
Death*	1 (16.7)	1 (33.3)	2 (50.0)	4 (30.8)
Withdrawal by subjects	3 (50.0)	1 (33.3)	0	4 (30.8)
Other**	0	1 (33.3)	0	1 (7.7）

*: *Four patients died due to disease progression*

**: *Subject didn't want to participate in follow-up or any study procedures and didn't want to sign withdrawal of consent*

Treatment-Emergent Adverse Events (TEAEs) in Phase Ia (all Grades ≥10% or any Grade ≥3)

Event, n (%)	1 mg/kg (N=6)	3 mg/kg (N=3)	10 mg/kg (N=4)	Total	
				All grades (N=13)	Grade ≥3 (N=13)
Nausea	1 (16.7)	2 (66.7)	1 (25.0)	4 (30.8)	0
Diarrhoea	0	3 (100)	0	3 (23.1)	1 (7.7)
Fatigue	1 (16.7)	1 (33.3)	1 (25.0)	3 (23.1)	0
Vomiting	0	2 (66.7)	1 (25.0)	3 (23.1)	0
Abdominal pain	1 (16.7)	1 (33.3)	0	2 (15.4)	1 (7.7)
Alanine aminotransferase increased	0	0	2 (50.0)	2 (15.4)	1 (7.7)
Aspartate aminotransferase increased	0	0	2 (50.0)	2 (15.4)	0
Blood creatinine increased	0	1(33.3)	1 (25.0)	2 (15.4)	0
Cancer pain	1 (16.7)	1 (33.3)	0	2 (15.4)	1 (7.7)
Lower respiratory tract infection	1 (16.7)	0	1 (25.0)	2 (15.4)	0
Headache	1 (16.7)	1 (33.3)	0	2 (15.4)	0
Anaemia	1 (16.7)	0	0	1 (7.7)	1 (7.7)
Blood alkaline phosphatase increased	0	0	1 (25.0)	1 (7.7)	1 (7.7)
Gamma-glutamyltransferase increased	0	0	1 (25.0)	1 (7.7)	1 (7.7)
Pleural effusion	1 (16.7)	0	0	1 (7.7)	1 (7.7)
Upper respiratory tract infection	1 (16.7)	0	0	1 (7.7)	1 (7.7)

Treatment-Related TEAEs in Phase Ia

- **Treatment-related TEAEs were reported in 4 patients, including diarrhoea (15.4%), fatigue (15.4%), alanine aminotransferase increased (7.7%) and aspartate aminotransferase increased (7.7%)**

Event, n (%)	1 mg/kg (N=6)	3 mg/kg (N=3)	10 mg/kg (N=4)	Total (N=13)
Number of Subjects with at Least One Event	1 (16.7)	2 (66.7)	1 (25.0)	4 (30.8)
Diarrhoea	0	2 (66.7)	0	2 (15.4)
Fatigue	1 (16.7)	1 (33.3)	0	2 (15.4)
Alanine aminotransferase increased	0	0	1 (25.0)	1 (7.7)
Aspartate aminotransferase increased	0	0	1 (25.0)	1 (7.7)

Diarrhoea (one was Grade 1, the other was Grade 3); fatigue (one was Grade 1, the other one was Grade 2); alanine aminotransferase increased (Grade 3); aspartate aminotransferase increased (Grade 1)

Immune-Related Adverse Events (irAEs) in Phase Ia

- **Two irAEs were reported in 2 patients, one was diarrhoea (7.7%, Grade 3), the other was fatigue (7.7%, Grade 2)**

Event, n (%)	1 mg/kg (N=6)	3 mg/kg (N=3)	10 mg/kg (N=4)	Total (N=13)
Number of Subjects with at Least One Event	0	2 (66.7)	0	2 (15.4)
Diarrhoea	0	1 (33.3)	0	1 (7.7)
Fatigue	0	1 (33.3)	0	1 (7.7)

Summary of Safety Data in Phase Ia

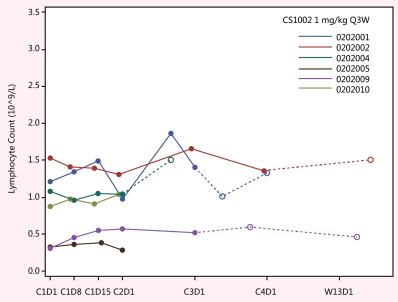
- Treatment-related TEAEs reported in 4 patients, including diarrhoea (15.4%), fatigue (15.4%), alanine aminotransferase increased (7.7%) and aspartate aminotransferase increased (7.7%)
- Treatment-related Grade 3-5 TEAEs reported in 2 patients, diarrhoea (7.7%, Grade 3), and alanine aminotransferase increase (7.7%, Grade 3)
- irAEs reported in 2 patients, diarrhoea (7.7%), and fatigue (7.7%)
- No treatment-related SAE
- No treatment-related death
- No treatment-related AE leading to drug discontinuation

Pharmacodynamics and Efficacy of CS1002 in Phase Ia

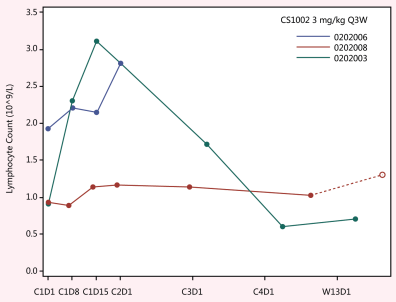
- **CS1002 induced an early increase in absolute lymphocyte count (ALC) during treatment (similar to Ipilimumab)**
  - Early increase of ALC across all dose groups, indicating CS1002 functions similarly to ipilimumab

CS1002

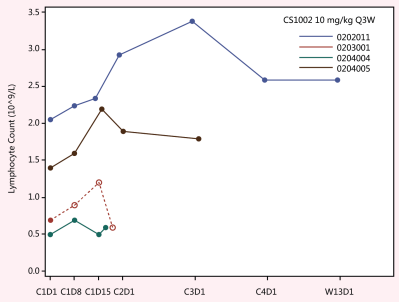
1 mg/kg (N=6)



3 mg/kg (N=3)

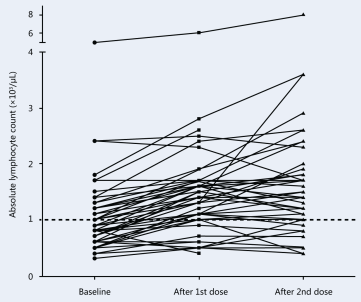


10 mg/kg (N=4)



Ipilimumab

10 mg/kg



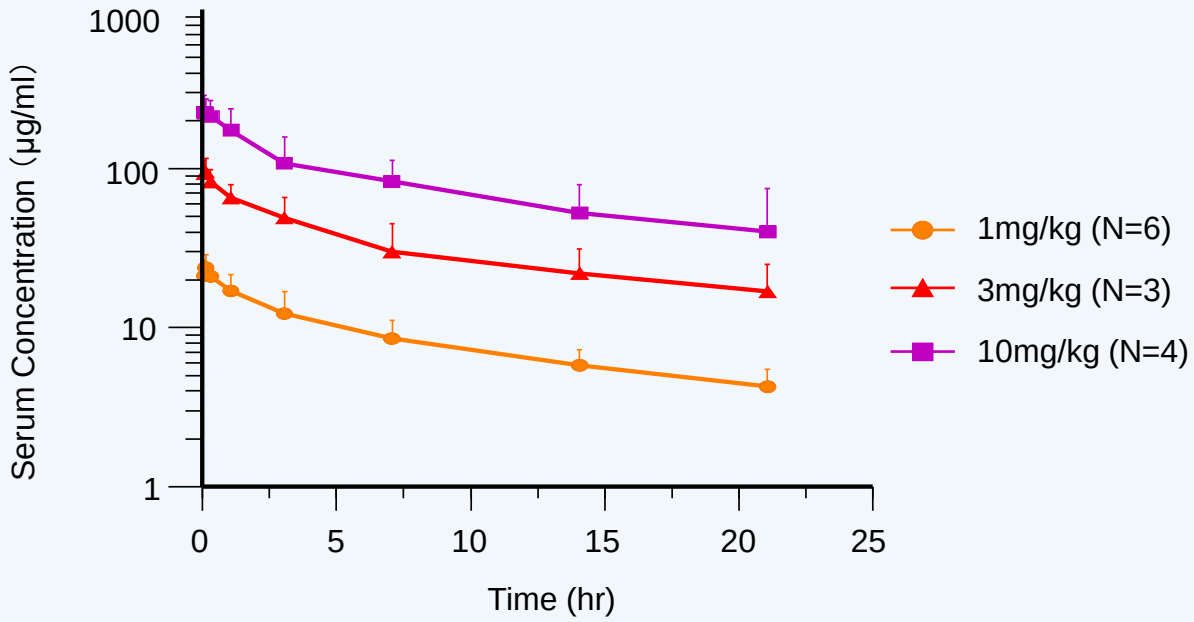
Martens A, *et al*. Clin Cancer Res. 2016, 22(19): 4848
Bjoern J, *et al*. OncoImmunology. 2016
Ku GY, *et al*. Cancer. 2010(116):1767

- **9 patients were included for the tumor assessment in Phase Ia**
  - No complete response (CR) or partial response (PR), 2 stable disease (SD)
  - One cholangiocarcinoma patient is still on treatment with SD for 11 months since Oct. 2018

Pharmacokinetic Profile of CS1002 in Phase Ia

- CS1002 demonstrated dose-proportional PK profile across 3 dose levels
- $T_{1/2}$ is 12~15 days

Log Geometric Mean Serum CS1002 Concentration vs. Time (Cycle 1)



Conclusions

- This was a first-in-human study initiated in Australia in May 2018
- As of April 25th of 2019, 13 patients have been treated
- CS1002 was well tolerated across dosage levels from 1 mg/kg to 10 mg/kg Q3W, with no reported DLT and treatment-related SAE
- MTD was not reached
- No clinical response was observed based on current data (not unexpected from anti-CTLA4 monotherapy)
- CS1002 demonstrated dose-proportional PK profile with $T_{1/2}$ of 12~15 days
- Overall clinical profile is consistent with that of ipilimumab
- Future development will focus on combination with CS1003 (anti-PD-1 antibody) in subjects with solid tumors (Phase Ib)

Acknowledgements

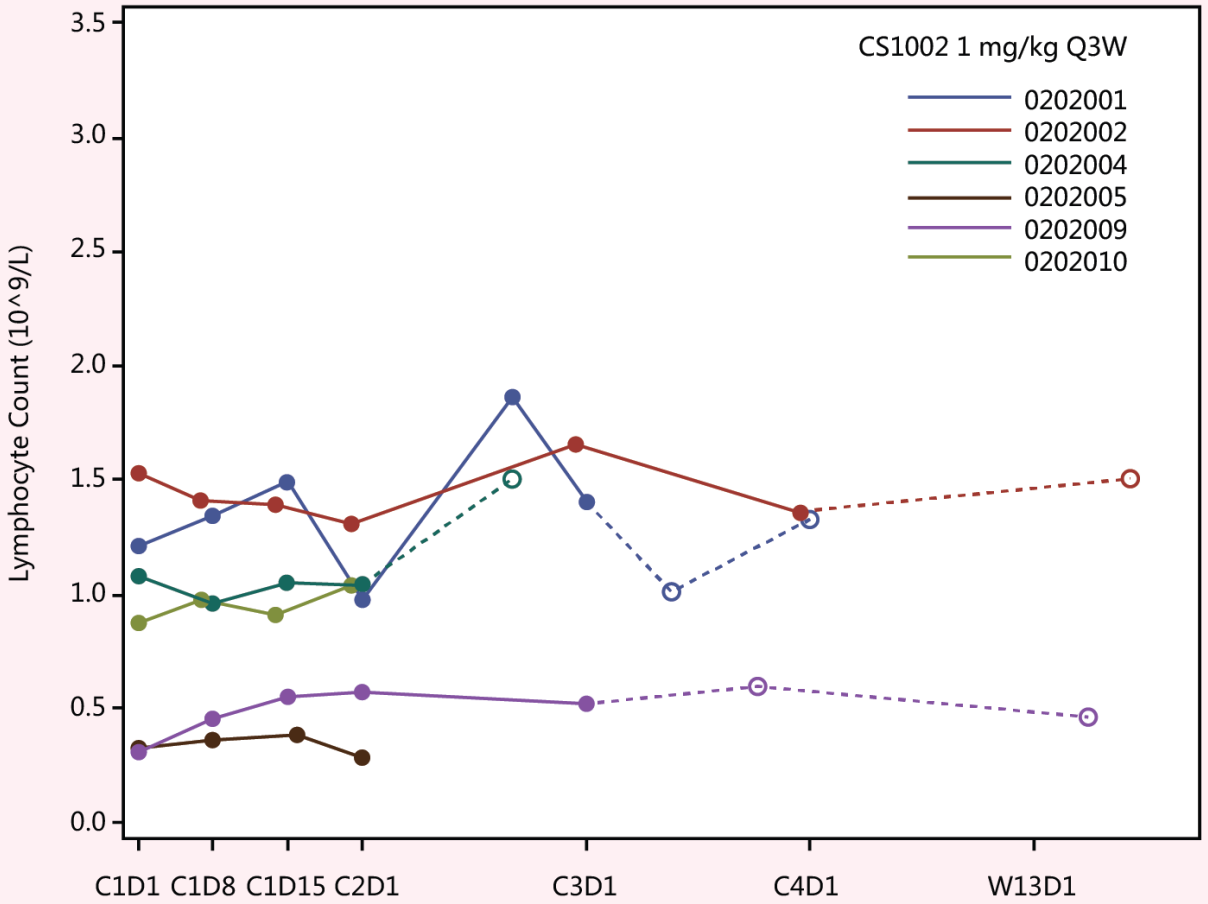
The patients and their families

Participating study investigators and clinical sites

This study is sponsored by CStone Pharmaceuticals Co., Ltd.

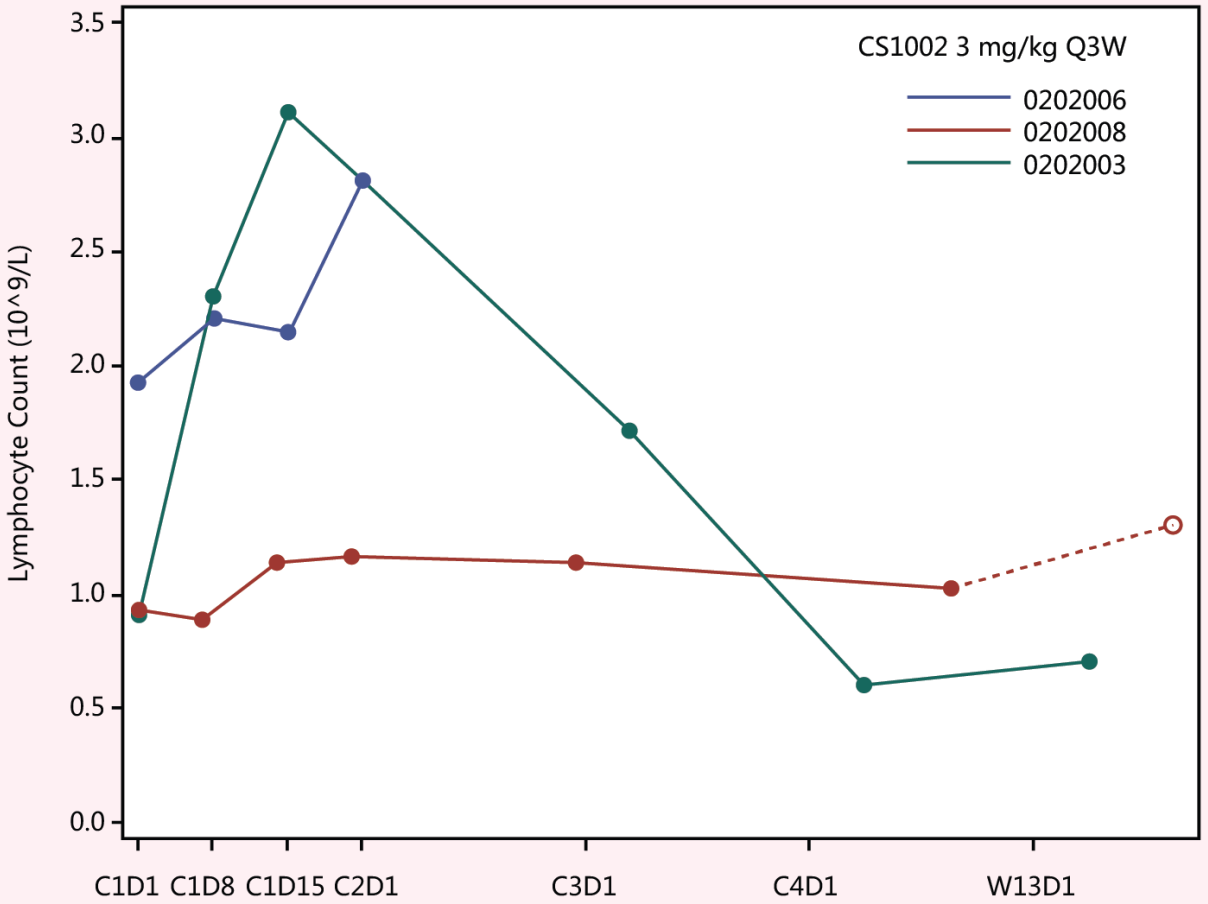
CS1002

1 mg/kg (N=6)



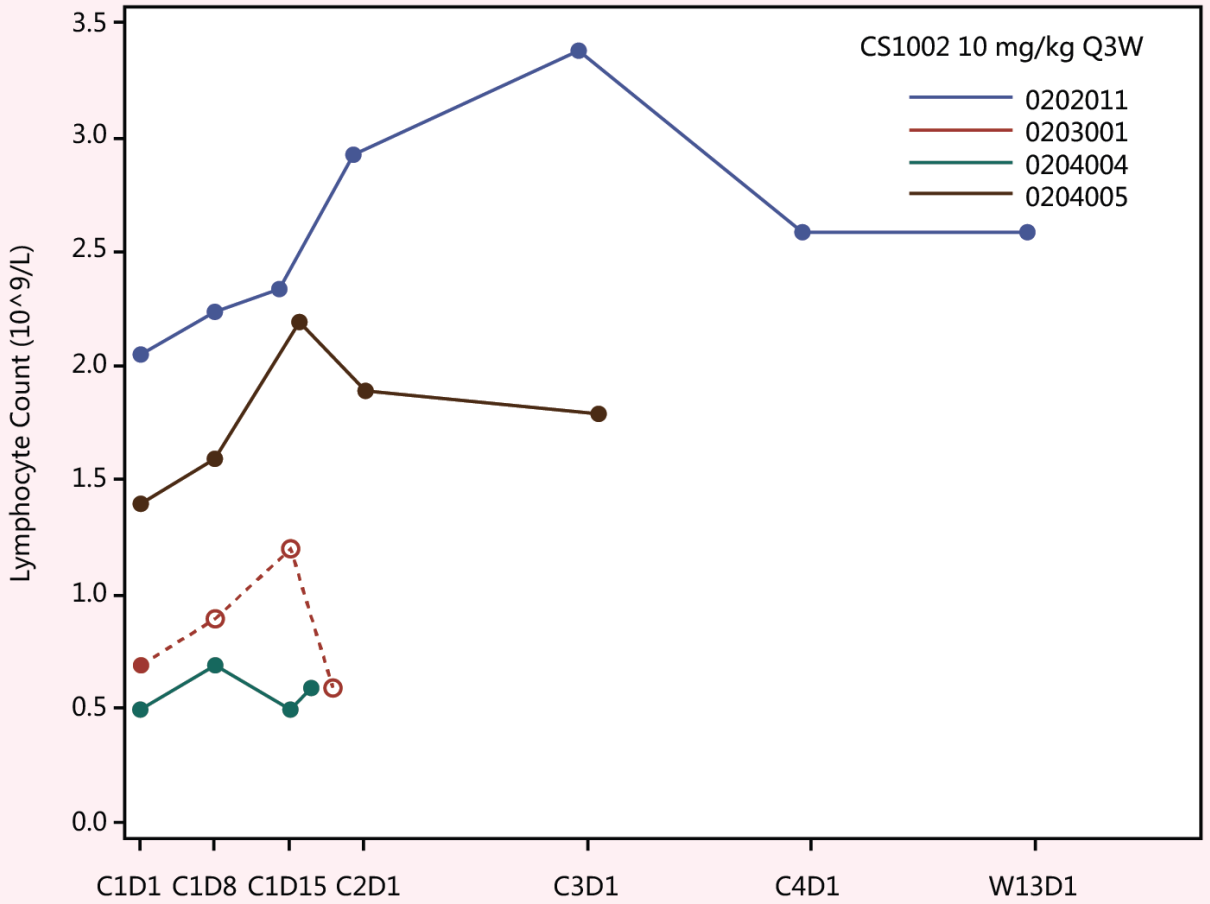
CS1002

3 mg/kg (N=3)



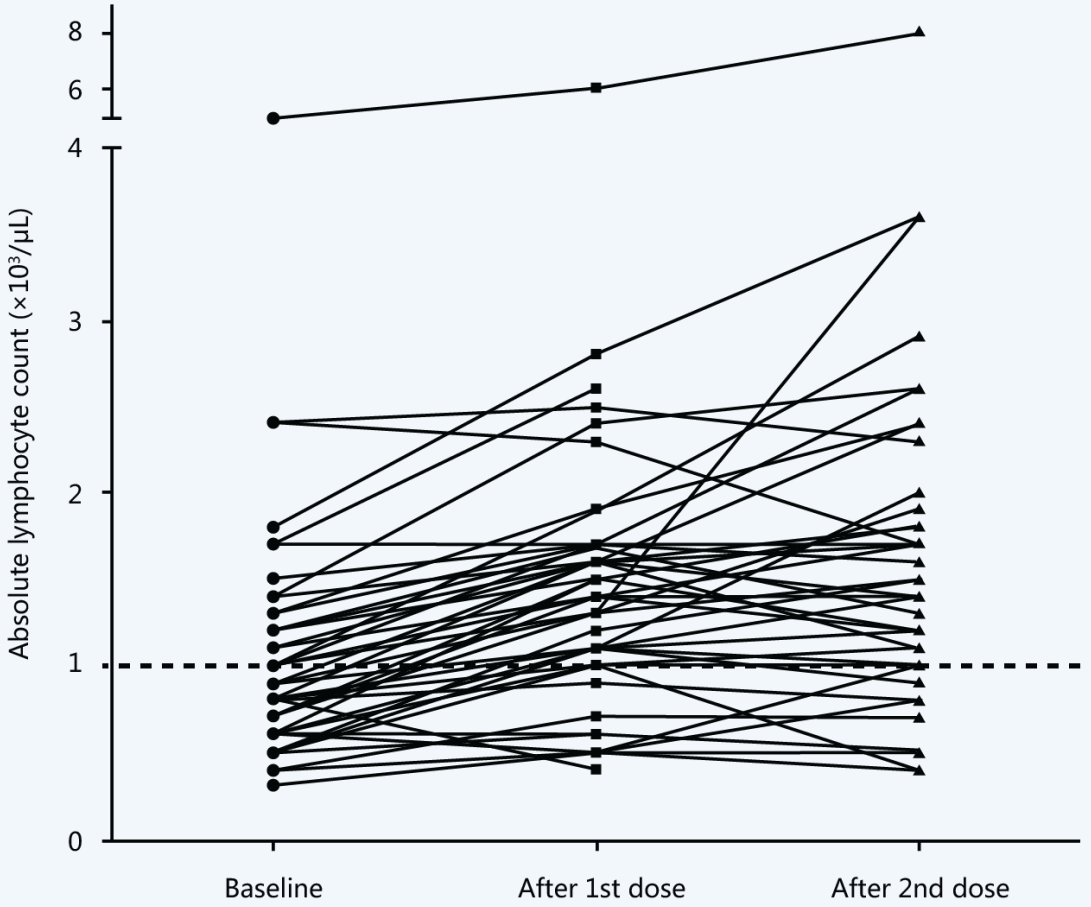
CS1002

10 mg/kg (N=4)



Ipilimumab

10 mg/kg



Backup: Ipilimumab Phase I study safety data

- **Ph I study of ipilimumab with or without one of two different chemotherapy regimens in patients with untreated advanced melanoma**
  - **3-arm/groups**
    - **Ipilimumab group: 10 mg/kg IV, Q3W, 4 doses**
    - **Ipilimumab + dacarbazine group**
    - **Ipilimumab + carboplatin/paclitaxel group**

	Ipilimumab (N=20) n (%)	Ipilimumab + dacarbazine (N=19) n (%)	Ipilimumab + carboplatin/paclitaxel (N=19) n (%)	Total (N=59) n (%)
Discontinued from study due to AEs	**5 (25.0)**	**7 (36.8)**	**6 (50.0)**	**18 (30.5)**
Treatment-related AEs	**18 (90.0)**	**19 (100)**	**20 (100)**	**57 (96.6)**
rash	16 (80.0)	9 (47.4)	15 (75.0)	40 (67.8)
pruritus	11 (55.0)	13 (68.4)	13 (65.0)	37 (62.7)
diarrhoea	12 (60.0)	11 (57.9)	10 (50.0)	33 (55.9)
fatigue	8 (40.0)	16 (84.2)	10 (50.0)	34 (57.6)
Treatment-related G3-5 AEs	**10 (50.0)**	**14 (73.7)**	**15 (75.0)**	**39 (66.1）**

Jeffrey W, et al. Cancer Immun. 2013, 13:7

Backup: Ipilimumab Phase I/II study safety data

- **Ph I /II study: Ipilimumab alone or in combination with radiotherapy in metastatic castration-resistant prostate cancer**
  - **Ipilimumab alone group: 3, 5, or 10 mg/kg, Q3W, 4 doses**

	Ipilimumab 3mg/kg (N=8) n (%)	Ipilimumab 5mg/kg (N=6) n (%)	Ipilimumab 10mg/kg (N=16) n (%)
Discontinued	**8 (100)**	**6 (100)**	**13 (91)**
Progression disease	6 (75)	4 (67)	10 (63)
AE	2 (25)	1 (17)	1 (6)
irAE	*1 (13)*	*1 (17)*	*0*
treatment-related death	0	1	1 (6)
Lost to follow-up	0	0	1 (6)
Treatment-related AEs (any grade/G3-4)	**8 (100)/ 2 (25)**	**5 (83)/3 (50)**	**16 (100)/10 (63)**
Immune-related AEs (any grade/G3-4)	**6 (75)/ 1 (13)**	**5 (83)/3 (50)**	**16 (100)/10 (63)**
AEs leading to study therapy discontinuation	**4 (50)**	**4 (67)**	**12 (75)**

Slovin SF, et al. Ann Oncol. 2013, 24(7):1813-1821