Abstract: 777

Initial results from an open-label, phase 1b/2 study of RP1 oncolytic immunotherapy in solid organ and hematopoietic cell transplant recipients with advanced cutaneous malignancies (ARTACUS)

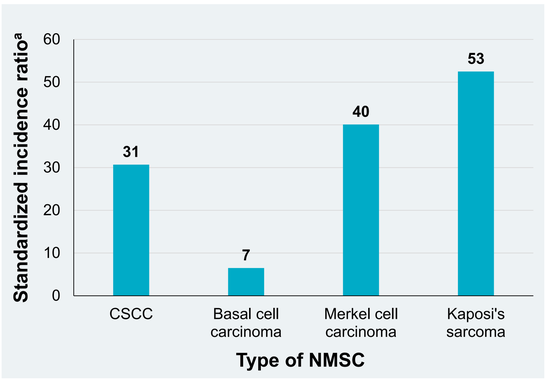
Michael R. Migden[1], Wanxing Chai-Ho[2], Gregory A. Daniels[3], Trisha M. Wise-Draper[4], Meenal Kheterpal[5], Jennifer C. Tang[6], Diana Bolotin[7], Claire Verschraegen[8], Andrew Poklepovic[9], Shaheer A. Khan[10], Sherrif F. Ibrahim[11], Nathalie C. Zeitouni[12], Theresa Medina[13], Katy K. Tsai[14], Chris Tucci[15], Susan Navia[15], Laxminarasimha Donthireddy[15], Praveen K. Bommareddy[15], Jeannie W. Hou[15], Diwakar Davar[16]

[1]MD Anderson Cancer Center, Houston, TX, USA; [2]UCLA David Geffen School of Medicine, Los Angeles, CA, USA; [3]Moores Cancer Center, University of California San Diego, La Jolla, CA, USA; [4]Division of Hematology-Oncology, University of Cincinnati, Cincinnati, OH, USA; [5]Department of Dermatology, Duke University Medical Center, Durham, NC, USA; [6]University of Miami Sylvester Comprehensive Cancer Center, Miami, FL, USA; [7]University of Chicago, Department of Medicine, Section of Dermatology, Chicago, IL, USA; [8]Division of Medical Oncology, Ohio State University Comprehensive Cancer Center, Columbus, OH, USA; [9]Department of Biochemistry and Molecular Biology, Medicine, Virginia Commonwealth University, Richmond, VA, USA; [10]Columbia University, New York, NY, USA; [11]Rochester Dermatologic Surgery, Victor, NY, USA; [12]University of Arizona College of Medicine and US Dermatology Partners, Phoenix, AZ, USA; [13]University of Colorado Cancer Center, Aurora CO, USA; [14]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; [15]Replimune, Inc., Woburn, MA, USA; [16]UPMC Hillman Cancer Center, Pittsburgh, PA, USA

Background

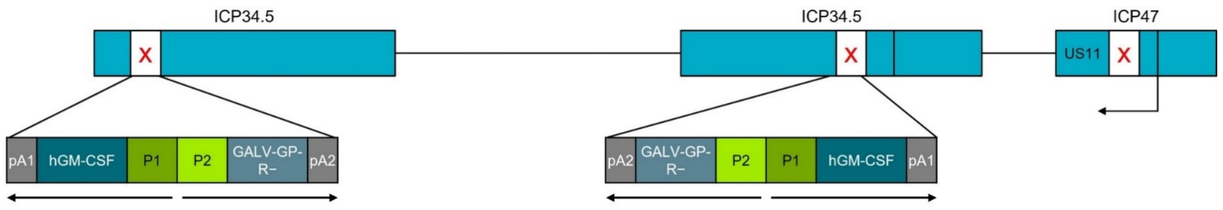
- Non-melanoma skin cancer (NMSC) is the most common post-transplant malignancy in solid organ transplant (SOT) recipients and occurs at a 7–53x higher incidence vs the general population (**Figure 1**)[1]
  - Over 90% of NMSC in SOT recipients is cutaneous squamous cell carcinoma (CSCC) and basal cell carcinoma[1,2]
  - Systemic immune checkpoint blockade is contra-indicated in the setting of SOT-associated NMSC given the documented risk of allograft rejection[3,4]
- Optimal management of NMSC in SOT is not well established[3,4]
- RP1 is an oncolytic immunotherapy (herpes simplex virus type 1) that expresses granulocyte-macrophage colony-stimulating factor and a fusogenic glycoprotein (gibbon ape leukemia virus glycoprotein with the R sequence deleted [GALV-GP-R−]; **Figure 2**)[5]
  - When used in combination with intravenous nivolumab, intratumoral RP1 demonstrated a high rate of deep and durable responses in non-SOT patients with advanced skin cancers (IGNYTE study)[6]
- **Objective:** To assess the safety and efficacy of single-agent RP1 in SOT and hematopoietic cell transplant patients with skin cancers (NCT04349436)

Figure 1. Population-based cohort study in SOT recipients[1]



[a]Standardized incidence ratios were calculated by dividing the observed number of NMSC cases by the expected number of cases based on the general population. NMSC, non-melanoma skin cancer; SOT, solid organ transplant.

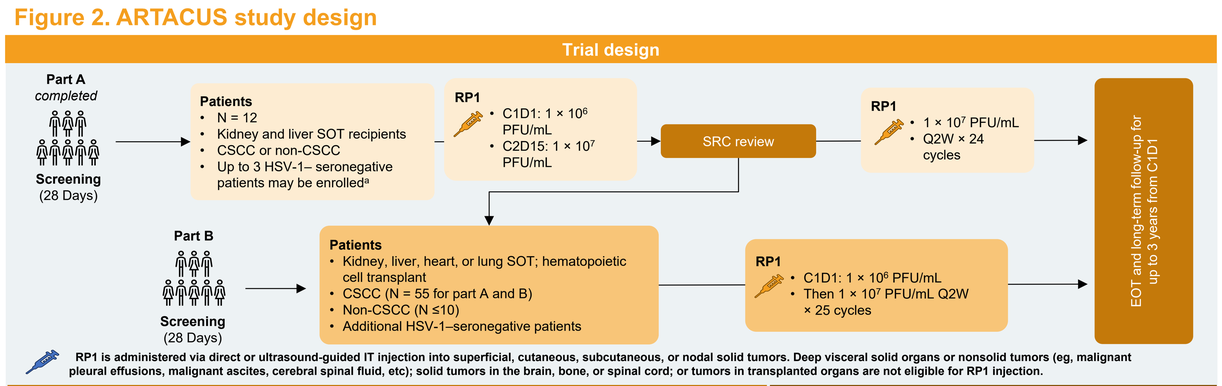
Figure 2. RP1 backbone



GALV-GP-R–, gibbon ape leukemia virus glycoprotein with the R sequence deleted; hGM-CSF, human granulocyte-macrophage colony-stimulating factor; ICP, infected cell protein; pA, polyA signal; X, denotes inactivation of viral protein.

Methods

Figure 2. ARTACUS study design



Key eligibility criteria

Inclusion
- Solid organ or hematopoietic cell transplant recipients with recurrent, locally advanced, or metastatic cutaneous malignancies including CSCC, BCC, Merkel cell carcinoma, and melanoma
- At least 1 measurable tumor ≥1 cm in longest diameter or ≥1.5 cm in shortest diameter for lymph nodes and injectable lesions that, in aggregate, comprise ≥1 cm in longest diameter
- ECOG PS ≤1 and adequate hepatic, renal, and hematologic function
- Stable allograft function including allograft cfDNA
- No more than 1 prior systemic therapy for cutaneous malignancy

Exclusion
- Prior treatment with an oncolytic therapy
- Active significant herpetic infections or prior complications of HSV-1 infection
- A history of transplant-related viral infections requiring treatment or modification to immunosuppression, such as BKV, EBV, or CMV, within 3 months of study entry
- Patients with visceral metastases
- Other active malignancy (other than the disease under study) within 3 years of the first dose of RP1

Key endpoints

Primary
- Investigator-assessed ORR per modified RECIST 1.1
- Safety and tolerability

Secondary
- Duration of response, complete response rate, disease control rate, and progression-free survival by investigator review; 1-year and 2-year overall survival rate
- Quality of life score using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30

Exploratory
- Biomarker analysis

[a]After 3 seronegative patients were enrolled, safety in this population was assessed by SRC, who approved continued enrollment of seronegative patients.
One cycle = 2 weeks. The treatment period is up to 52 weeks (one year).
BCC, basal cell carcinoma; BKV, BK virus; C, cycle; CMV, cytomegalovirus; CSCC, cutaneous squamous cell carcinoma; D, day; EBV, Epstein-Barr virus; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; HSV-1, herpes simplex virus type 1; IT, intratumoral; ORR, objective response rate; PFU, plaque-forming unit; Q2W, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SOT, solid organ transplant; SRC, safety review committee.

Results

Patients

- The trial enrolled 27 transplant recipients with skin cancers (median age, 68.0 years; **Table 1**)

Table 1. Patient demographics and baseline disease characteristics[a]

Characteristic	All patients (N = 27)
Age, years, median (range)	68.0 (48–86)
Male, n (%)	21 (77.8)
Race, n (%)	
White	26 (96.3)
Native Hawaiian/ Pacific Islander	1 (3.7)
Allograft type, n (%)	
Kidney	22 (81.5)
Liver	4 (14.8)
Lung	1 (3.7)
Heart	0
Cutaneous malignancies, n (%)	
CSCC	24 (88.9)
MCC	3 (11.1)
Stage at study baseline, n (%)	
Locally advanced	15 (55.6)
Metastatic[b]	12 (44.4)
Primary tumor location, n (%)	
Skin	26 (96.3)
Lymph node	1 (3.7)

[a]Data cutoff: September 18, 2023. [b]Per protocol, metastatic to skin, soft tissue, or lymph nodes.
CSCC, cutaneous squamous cell carcinoma; MCC, Merkel cell carcinoma.

Efficacy

- The objective response rate (ORR) for the 23 evaluable patients was 34.8%, with 5 patients (21.7%) achieving a confirmed complete response (CR; **Table 2**)

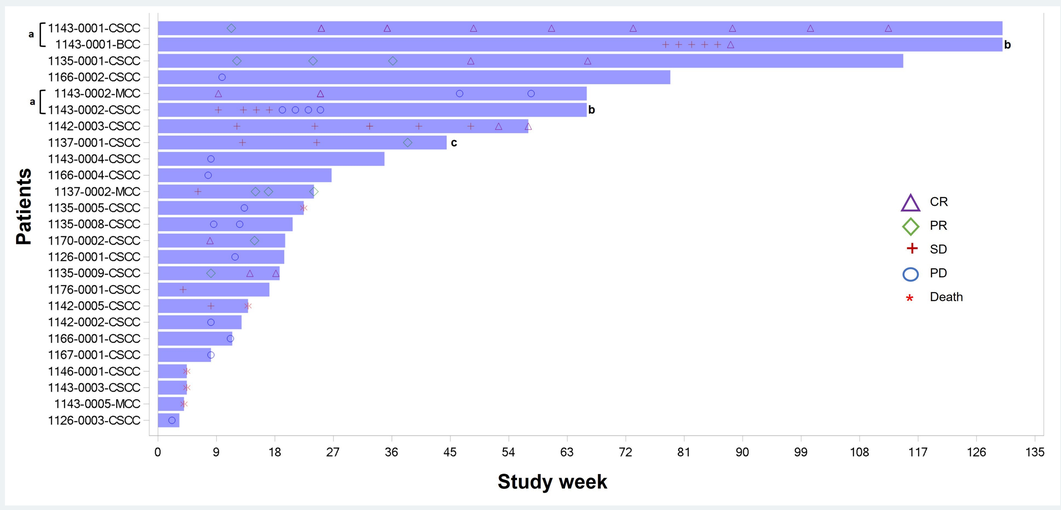
Table 2. Efficacy: Best response and responder characteristics

	Evaluable patients[a] (N = 23)
Best overall response (modified RECIST 1.1)	n (%)
CR	5 (21.7)[b]
PR	3 (13.0)[c]
SD	1 (4.3)
PD	14 (60.9)
ORR (CR + PR)	8 (34.8)
DCR (CR + PR + SD)	9 (39.1)

	Responders (n = 8)
Characteristics of responders	n
Tumor type	
CSCC	6
MCC	2
Stage at study baseline	
Locally advanced	6
Metastatic	2

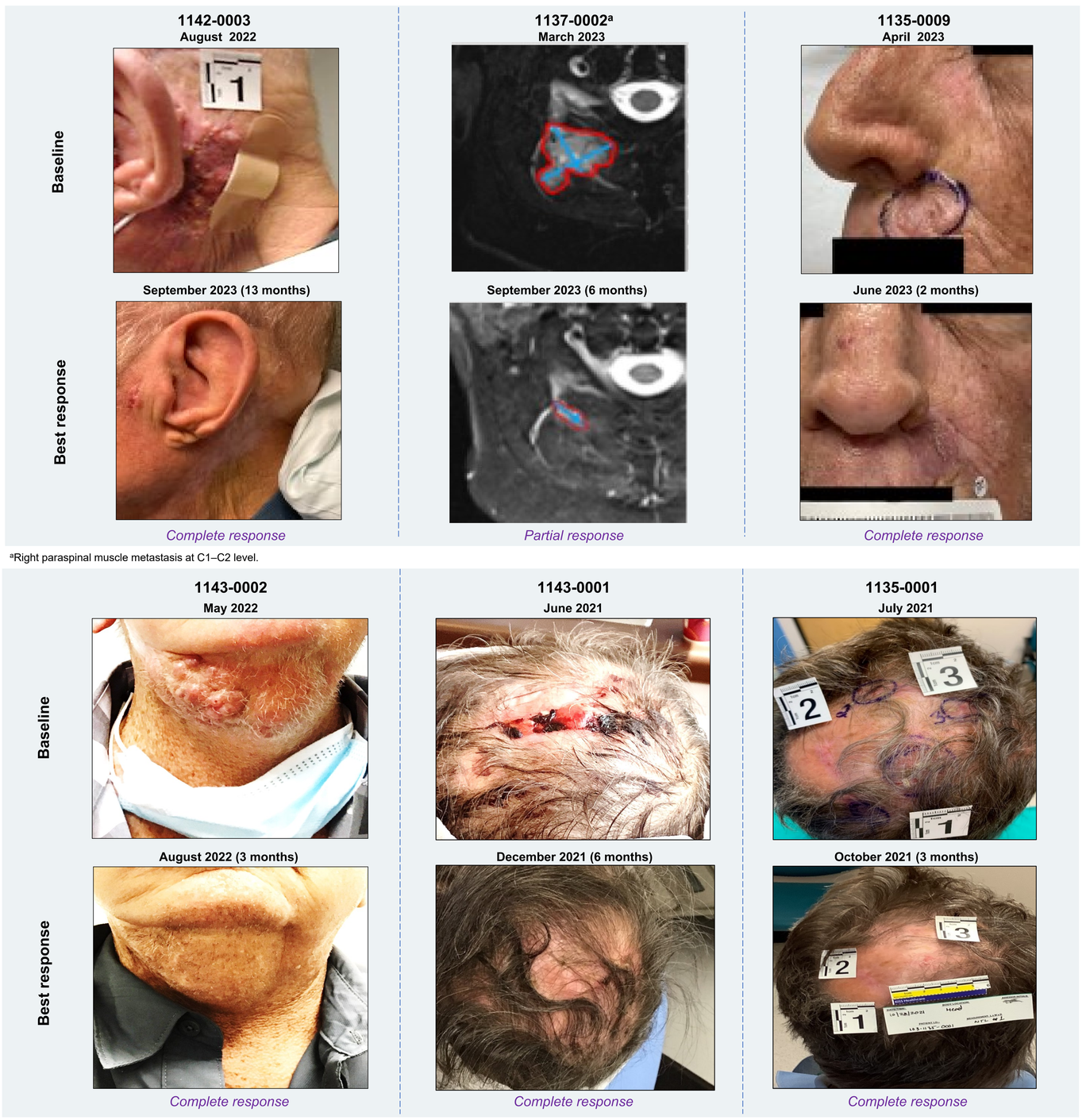
[a]Enrolled ≥3 months before the data cut; 4 patients who went off study for reasons unrelated to NMSC or RP1-related adverse events (1 death each from COVID-19, stroke, and pneumonia and 1 withdrawal because of injection pain) were excluded from the efficacy analysis. The median study follow-up time for all enrolled patients (N = 27) was 18.7 weeks as of September 18, 2023. [b]One patient with CSCC also had CR of a new primary BCC which appeared post baseline and was also treated with RP1. [c]One PR could not be confirmed because the patient withdrew consent; all other responses are confirmed.
BCC, basal cell carcinoma; CSCC, cutaneous squamous cell carcinoma; COVID-19, coronavirus disease 2019; CR, complete response; DCR, disease control rate; MCC, Merkel cell carcinoma; NMSC, non-melanoma skin cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Figure 3. Response profile over time



[a]A second primary skin cancer that developed on study was allowed to be treated with RP1, per protocol. [b]Second primary malignancy. [c]Withdrew consent.
CR, complete response; BCC, basal cell carcinoma; CSCC, cutaneous squamous cell carcinoma; MCC, Merkel cell carcinoma; PD, progressive disease; PR, partial response; SD, stable disease

Figure 4. Examples of patients with confirmed response



[a]Right paraspinal muscle metastasis at C1–C2 level.

Safety

- The most common treatment-emergent adverse events (TEAEs) were fatigue (33.3%), chills (25.9%), and pyrexia (25.9%; **Table 3**)
  - No evidence of allograft rejection
  - Seventeen patients had ≥1 grade ≥3 AE, all unrelated to RP1
  - Eight deaths: Disease progression (n = 3); pneumonia (n = 2); sepsis, stroke, pulmonary hypertension (each n = 1); none were related to RP1

Table 3. All-grade TEAEs (>10% of patients)

	All patients (N = 27)		
TEAEs, n (%)	**Grade 1/2**	**Grade ≥3**	**Total**
Fatigue	9 (33.3)	0	9 (33.3)
Chills	7 (25.9)	0	7 (25.9)
Pyrexia	7 (25.9)	0	7 (25.9)
Anemia	2 (7.4)	3 (11.1)	5 (18.5)
Blood creatinine increased	5 (18.5)	0	5 (18.5)
Nausea	5 (18.5)	0	5 (18.5)
Urinary tract infection	3 (11.1)	2 (7.4)	5 (18.5)
Decreased appetite	4 (14.8)	0	4 (14.8)
Diarrhea	4 (14.8)	0	4 (14.8)
Headache	4 (14.8)	0	4 (14.8)
Injection-site pain	4 (14.8)	0	4 (14.8)
Cellulitis	2 (7.4)	1 (3.7)	3 (11.1)
Confusional state	3 (11.1)	0	3 (11.1)
Constipation	3 (11.1)	0	3 (11.1)
Facial pain	3 (11.1)	0	3 (11.1)
Hypercalcemia	3 (11.1)	0	3 (11.1)
Hyperglycemia	2 (7.4)	1 (3.7)	3 (11.1
Sepsis	0	3 (11.1)	3 (11.1)
Tumor pain	2 (7.4)	1 (3.7)	3 (11.1)

Other grade 3 TEAEs were encephalopathy and hyperkalemia (n = 2 each) and COVID-19, cerebrovascular accident, hematuria, hypertension, hyponatremia, mental status changes, tumor hemorrhage, aspiration, calciphylaxis, infusion-related reaction, lipase increased, pneumonia aspiration, staphylococcal infection, and *Pseudomonas* wound infection (n = 1 each). Grade 4 TEAEs were sepsis, cerebrovascular accident, mental status changes, COVID-19 pneumonia, and seizure (n = 1 each). Grade 5 TEAEs were disease progression (n = 2) and sepsis, cerebrovascular accident, and COVID-19 pneumonia (n = 1 each).
AE, adverse event; COVID-19, coronavirus disease 2019; TEAE, treatment-emergent AE.

Conclusions

- **This is the first clinical trial assessing single-agent intratumoral RP1 in solid organ/hematopoietic cell transplant patients on chronic immunosuppressive treatment with advanced skin cancer in whom systemic immunotherapy is typically contra-indicated**
- **RP1 monotherapy showed clear anti-tumor activity, with an ORR of 34.8% (5/23 [21.7%] confirmed CR) in evaluable patients, with most responses ongoing as of the data cutoff**
- **No allograft rejection was observed as of the data cutoff including in hepatic and lung allografts**
- **RP1 monotherapy was well tolerated, and the safety profile was similar to the profile in non-immunocompromised patients with advanced skin cancers (IGNYTE study)**

ARTACUS is now recruiting patients. To learn more about enrolling your patient, contact clinicaltrials@replimune.com or +1 (781) 222 9570.

Additional information can be obtained by visiting clinicaltrials.gov (NCT04349436).

Presenter disclosures:

MRM served as a paid advisor for Feldan, Regeneron, Replimune, Inc., Sanofi, Stamford Pharmaceuticals, and Sun Pharmaceuticals Industries Ltd. and received research funding from Regeneron, Replimune, Inc., Sanofi, and Senhwa.

Acknowledgments:

The authors would like to thank the patients for their participation in the trial. Medical writing and editorial support were provided by Hilary Durbano, PhD, of AlphaBioCom, a Red Nucleus company, and were funded by Replimune, Inc. (Woburn, MA, USA).

References:

1. Friman T, et al. *Int J Cancer.* 2022;150(11):1779-91.
2. Garrett G, et al. *JAMA Dermatol.* 2017;153(3):296-303.
3. Mittal A and Colegio O. *Am J Transplant.* 2017;17(10):2509-30.
4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Squamous Cell Skin Cancer. Version 1. 2023.
5. Thomas S, et al. *J Immunother Cancer.* 2019;7(1):214.
6. Milhem M, et al. *J Clin Oncol.* 2022;40(suppl 16):9553.

Study sponsor:

The study is sponsored by Replimune, Inc. (Woburn, MA, USA).

Presented at the Society for Immunotherapy of Cancer Annual Meeting 2023, November 1–5, 2023; San Diego, CA, USA