Objective

• Identify an approach to the treatment of melanoma in light of novel agents available
Case 1

• 45 year old male patient presents with a pigmented lesion on thigh, progressively increasing in size and changing color over the last 4 months

• Initial biopsy:
  – Breslow thickness 1.4 mm
  – Clark level 4
  – Mitotic rate 5/mm
  – Ulcerated
Case 1

- Undergoes wide local excision and sentinel lymph node biopsy
- Pathology:
  - No residual melanoma
  - 1 of 4 SLN involved with metastatic disease
- PET/CT negative for distant metastases
- Final stage: Stage (pT2bN1aM0) IIIb
High Risk Melanoma

- Melanoma with at least a 40% risk of recurrence or death after complete surgical excision
- Thought to be related to micrometastases
- Ulcerated lesions, high mitotic score and regional LN involvement portend worse prognosis
- Traditionally, AJCC stage IIb- IIIc
- Adjuvant therapy is standard of care

Adjuvant Therapy for High Risk Melanoma

- FDA approved adjuvant systemic therapy for high risk melanoma:
  - High dose Interferon-alfa (IFN-alfa)
  - Ipilimumab (CTLA-4 inhibitor)
IFN-alfa

- E1684 trial - One year high-dose IFN-alfa with improved PFS
  - Approved in the United States in 1995
- EORTC 18991 Pegylated IFN-alfa
  - Approved in the United States in 2011
# Trials of High Dose IFN-Alfa

- One year of adjuvant high-dose IFN-alfa
- Demonstrated 25-30% reduction in risk of relapse
- E1684 and E1694 noted significant reduction in risk of death

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Comparison</th>
<th>Follow-up (y)</th>
<th>RFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1684</td>
<td>N=287 T4, N+</td>
<td>IFN vs. obs</td>
<td>6.9 12.6</td>
<td>0.61 (0.001) 0.72 (0.02) 0.67 (0.01) 0.82 (0.18)</td>
<td></td>
</tr>
<tr>
<td>E1690</td>
<td>N=642 T4, N+</td>
<td>IFN 1y or 2 y vs. obs</td>
<td>4.3 6.6</td>
<td>0.78 (0.05) 0.81 (NS) 1.0 (NS) 1.0 (NS)</td>
<td></td>
</tr>
<tr>
<td>EORTC 18991</td>
<td>N=1256 N1-2</td>
<td>Peg IFN 5 y vs. obs</td>
<td>3.8 7.6</td>
<td>0.82 (0.011) 0.87 (NS) 0.98 (NS) 0.96 (NS)</td>
<td></td>
</tr>
</tbody>
</table>

Toxicity Profile of IFN-Alfa

• Toxicities limit use
• Common side effects:
  – Fatigue (18%)
  – Nausea and/or vomiting (5-9%)
  – Fever (18%)
  – Myelosuppression (26-60%)
  – Transaminitis (14-29%)
  – Neuropsychiatric symptoms (2-10%)
• Toxicities with PEGylated IFN similar

Checkpoint Inhibitors
Ipilimumab: EORTC 18701

- Phase 3 randomized, double-blind study
- 951 patients with high-risk stage IIIA, IIB or IIC
- No in-transit or satellite metastases

**RANDOMIZE**

**INDUCTION (N=475)**
Ipilimumab 10 mg/kg
Every 3 wk x 4 doses

**INDUCTION (N=476)**
Placebo every 3 wk X 4 doses

**MAINTENANCE**
Ipilimumab 10 mg/kg
Every 12 wk ≥ 3y

Placebo every 12 wk x ≥ 3y

Primary end point was RFS
Stratification
- By stage (IIIA vs. IIIB vs. IIIC 1-2 LN vs. IIC ≥ 4 LN)
- By region (North America, European countries, Australia)

Ipilimumab: EORTC 18701 Data

• Met primary end point of RFS
• Significant reduction in recurrence with Ipi
  – Median RFS 26 months vs. 17 months
  – 3-y RFS rates 47% vs. 35%
  – HR 0.75 (95% CI, 0.64-0.90; p=0.0013)
• Improved RFS with Ipi across all subgroups
  – Microscopic involvement and ulcerated melanoma associated with more favorable outcomes
• OS data pending

Future Directions In Adjuvant Therapy
US Intergroup E1609

**Randomize**

**Induction**
- Ipilimumab 10 mg/kg
  - Every 3 wk ≤ 4 doses

**Maintenance**
- Ipilimumab 10 mg/kg
  - Every 12 wk ≤ 4 cycles

**Induction**
- High-dose IFN

**Maintenance**
- High dose IFN x 48 wk

**Induction**
- Ipilimumab 3 mg/kg
  - Every 3 wk ≤ 4 doses

**Maintenance**
- Ipilimumab 3 mg/kg
  - Every 12 wk ≤ 4 cycles

Accrual complete August, 2014
Primary end points: OS and RFS
Secondary end points: QOL and toxicity

Clinicaltrials.gov
# Phase 3 Adjuvant Therapy Trials

Adjuvant Therapy Trials for Resected High-Risk Melanoma

<table>
<thead>
<tr>
<th>Trial (NCT)</th>
<th>Regimen</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRIM8 (NCT01667419)</td>
<td>Vemurafenib 960 mg twice daily vs placebo for 52 wk</td>
<td>• <em>BRAF</em>-positive Stage IIC-III</td>
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<tr>
<td></td>
<td></td>
<td>• N = ~500 (open)</td>
</tr>
<tr>
<td>CheckMate 238</td>
<td>Nivolumab 3 mg/kg every 2 wk vs ipilimumab 10 mg/kg every 3 wk for 4 doses, then up to 1 y maintenance</td>
<td>• Stage III B, III C, or IV</td>
</tr>
<tr>
<td>(NCT02388906)</td>
<td></td>
<td>• N = ~800 (closed)</td>
</tr>
<tr>
<td>COMBI-AD (NCT01682083)</td>
<td>Oral dabrafenib 150 mg twice daily + oral trametinib 2 mg/d vs placebo for 12 mo</td>
<td>• <em>BRAF</em>-positive Stage III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• N = ~852 (closed)</td>
</tr>
<tr>
<td>KEYNOTE 054 (NCT02362594)</td>
<td>Pembrolizumab 200 mg on d 1 of a 21-d cycle vs placebo for up to 1 y</td>
<td>• Stage III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• N = ~900 (open)</td>
</tr>
<tr>
<td>USI S1404 (NCT02506153)</td>
<td>Standard high-dose IFN-α2b regimen vs pembrolizumab 200 mg every 3 wk for up to 1 y</td>
<td>• Stage III-IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• N = ~1378 (open)</td>
</tr>
</tbody>
</table>
Case 1

- Patient participating in S1404 clinical trial of adjuvant Ipilimumab/IFN alfa vs. pembrolizumab
- Pending randomization at this time
Case 2

- 64 year old man presents with new pulmonary nodules
- Originally diagnosed with melanoma 4 years ago
- Completed 1 year of adjuvant high dose IFN-Alfa
- Had solitary pulmonary metastasis 2 years ago, which was resected
- Now noted to have bilateral pulmonary nodules on routine surveillance imaging. Asymptomatic
- Biopsy confirms metastatic melanoma
Approach to Systemic Therapy for Metastatic Melanoma

- Initial multidisciplinary evaluation
  - Is the patient a candidate for metastasectomy?
    - Yes: Metastasectomy
    - No:
      - Recurrent disease
        - Systemic therapy: Is a targetable driver mutation present (e.g., BRAF, MEK, KIT)?
          - Yes: Checkpoint inhibition immunotherapy or molecularly targeted therapy
            - PD: Second-line checkpoint inhibition immunotherapy or molecularly targeted therapy; choice based upon initial therapy
              - PD: Clinical trials or chemotherapy
          - No: Checkpoint inhibition immunotherapy
            - PD: Clinical trials or chemotherapy
Targetable Driver Mutations
Targetable Driver Mutations

• All advanced tumors assayed for the presence of a driver mutation at the V600 site in BRAF
• Testing for NRAS in patients with wild-type BRAF
• Testing for KIT in patients with:
  – Acral or mucosal primary tumor
  – Melanoma in an area of chronically sun-exposed skin that does not contain a BRAF mutation
BRAF Mutated Tumors

• Activating mutations in BRAF present in \( \sim 40 \text{-} 60 \% \) of advanced melanomas
• Single agent BRAF inhibitors result in non-sustained response
• BRIM-2 trial mechanisms of resistance
  – Reactivation of the MAP kinase pathway
  – \( NRAS^{Q61} \) mutation
  – \( MEK1 \) mutations
  – All relapse tumor specimens continued to demonstrate the \( BRAF^{V600} \) mutation
BRAF Inhibitors

- BRIM-3
- Phase III trial
- 675 patients randomly assigned to vemurafenib or dacarbazine
- Overall survival significantly prolonged with vemurafenib
  - 13.6 vs 9.7 months
  - HR 0.70 (95% CI 0.57-0.87)

BRAF Inhibitors

• Activity in brain metastases

• Most common toxicities include:
  – Dermatologic complications (rash, photosensitivity reactions, hyperkeratosis), arthralgia, fatigue, alopecia, nausea, and diarrhea
  – Reported in more than 15% of patients
MEK Inhibitors

• Significant clinical activity in melanoma with BRAFV600 mutation
• Now largely used in combination with BRAF inhibitors
• Use in BRAF wild-type patients with RAS-mutant tumors, as well as in those with variant BRAF mutations
MEK Inhibitors

• COMBI-d trial, phase III
• 423 patients were randomly assigned to either dabrafenib plus trametinib or dabrafenib plus placebo
• Overall survival was improved with the combination (median 25.1 vs 18.7 months)
• Overall survival rate at three years was prolonged with the combination (44 vs 32%)

Flaherty K et al. Genomic analysis and 3-y efficacy and safety update of COMBI-d. Abstract 9502 American Society of Clinical Oncology meeting.
NRAS-MUTATED TUMORS

- Binimetinib- MEK inhibitor studied in NRAS mutations
- Phase III trial
- Mutation at the NRAS Gln61 site
- Binimetinib or Dacarbazine
- PFS prolonged with binimetinib compared with dacarbazine (2.8 vs 1.5 months)
- No OS benefit
- Binimetinib not currently approved for use outside of a clinical trial setting

KIT-MUTATED TUMORS

• Mutations in \textit{c-kit} are seen in \textasciitilde 15 to 20\% of acral or mucosal melanomas and in a smaller percentage of melanomas arising in areas of chronic skin damage

• KIT inhibitors have useful clinically activity in some patients with activating mutations of the \textit{c-kit} gene

• Activity of Imatinib noted in nearly half patients
  – Typically PR
MAPK Pathway

Inhibitors
- Imatinib
- Nilotinib
- Dasatinib

Inhibitors
- Vemurafenib
- Dabrafenib
- Encorafenib

Inhibitors
- Trametinib
- Selumetinib
- Binimetinib

Melanoma cell

Mutant KIT

Other RTKs

RAS

Mutant BRAF

CRAF

MEK

ERK

Cyclin D1

Growth and survival
Approach to Systemic Therapy for Metastatic Melanoma

Initial multidisciplinary evaluation
Is the patient a candidate for metastasectomy?

Yes
- Metastasectomy

No
- Recurrent disease

Systemic therapy:
Is a targetable driver mutation present (e.g., BRAF, MEK, KIT)?

Yes
- Checkpoint inhibition immunotherapy or molecularly targeted therapy

No
- Checkpoint inhibition immunotherapy

PD
- Second-line checkpoint inhibition immunotherapy or molecularly targeted therapy; choice based upon initial therapy

PD
- Clinical trials or chemotherapy
Immunotherapy In Melanoma
Ipilimumab: Mechanism of Action

T-cell activation
- CTLA-4
- CD28
- TCR

T-cell inhibition
- CTLA-4

T-cell potentiation
- CTLA-4

Ipilimumab

• 676 patients with previously treated metastatic melanoma randomized to ipilimumab, ipi plus a gp100 vaccine, or the vaccine alone

• Median overall survival:
  – Ipi plus gp100 group: 10.0 months
  – Ipilimumab-alone group: 10.1 months
  – gp100-alone group: 6.4 months

Immunotherapy In Melanoma

• Programmed death 1 protein (PD-1)
• Immune checkpoint receptor expressed by activated T cells
• PD-1 binds to its ligands PD1-L1 and PD1-L2 expressed on tumor cells
• Thus causing immunosuppression and preventing the immune system from rejecting the tumor
**KEYNOTE-006**

- Phase 3 trial
- 834 patients
- Unresectable stage III or IV melanoma
- <1 prior line of therapy

**RANDOMIZE**

- Pembrolizumab 10 mg/kg every 2 wk
- Pembrolizumab 10 mg/kg every 3 wk
- Ipilimumab 3 mg/kg every 3 wk

<table>
<thead>
<tr>
<th></th>
<th>Pembro q2 wk</th>
<th>Pembro q3 wk</th>
<th>Ipi q3 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS at 6 m</td>
<td>47</td>
<td>46</td>
<td>27</td>
</tr>
<tr>
<td>ORR</td>
<td>34</td>
<td>33</td>
<td>12</td>
</tr>
<tr>
<td>OS at 12 m</td>
<td>74</td>
<td>68</td>
<td>58</td>
</tr>
</tbody>
</table>

HR 0.58 in both pembro arms compared to Ipi (p <0.001)

CheckMate-066

- Phase 3 trial
- 418 patients
- Previously untreated
- Stage III or IV without BRAF mutation

Randomize

Nivolumab 3mg/kg every 2 wk

Dacarbazine 1000 mg/m² every 3 wk

Survival End Points

A. Overall Survival

- **Hazard ratio for death**: 0.42 (99.79% CI, 0.25–0.73)
- **P**: 0.001

- **Nivolumab**: 100
- **Dacarbazine**: 100

- **Patients Who Died**
  - Nivolumab: 59/210
  - Dacarbazine: 96/208

- **Median Survival**
  - Nivolumab: Not reached
  - Dacarbazine: 10.8 (9.3–12.1)

- **No. at Risk**
  - Nivolumab: 210, 185, 150, 105, 45, 8, 0
  - Dacarbazine: 208, 177, 123, 82, 22, 3, 0

B. Progression-free Survival

- **Patients Who Died or Had Disease Progression**
  - Nivolumab: 108/210
  - Dacarbazine: 163/208

- **Median Progression-free Survival**
  - Nivolumab: 5.1 (95% CI: 3.5–10.8)
  - Dacarbazine: 2.2 (95% CI: 2.1–2.4)

- **Hazard ratio for death or disease progression**: 0.43 (95% CI, 0.34–0.56); **P**: 0.001

- **No. at Risk**
  - Nivolumab: 210, 116, 82, 57, 12, 1, 0
  - Dacarbazine: 208, 74, 28, 12, 0, 0, 0
CheckMate 037

• 405 previously treated patients
• Randomized 2:1 to Nivolumab or chemotherapy
• Median duration of response:
  – Not reached with nivo vs 3.5 mo for chemotherapy
• Responses seen in patients with BRAF mutations who had progressed on a prior BRAF inhibitor
• Appeared to be independent of benefit from prior ipilimumab

COMBINED ANTI-CTLA-4 AND ANTI-PD-1 IMMUNOTHERAPY
CheckMate 067

- Previously untreated
- Unresectable Stage III/IV
- N = 945

Nivo 1 mg/kg + Ipi 3 mg/kg q3w x 4 doses, then Nivo 3 mg/kg q2w (n = 314)

Nivo 3 mg/kg q2w + Placebo (n = 316)

Ipi 3 mg/kg q3w x 4 doses + Placebo (n = 315)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. at Risk</th>
<th>Median PFS, Months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivo + Ipi (N= 314)</td>
<td>316 202 271 177 170 160 147 136 124 106 86 50 38 14 9 6 2 1 1 1 0</td>
<td>11.5 (8.9-16.7)</td>
</tr>
<tr>
<td>Nivo (N= 316)</td>
<td>314 203 275 199 208 191 173 164 163 151 137 116 65 54 18 11 7 2 1 0 0 0 0 0</td>
<td>6.9 (4.3-9.5)</td>
</tr>
<tr>
<td>Ipi (N= 315)</td>
<td>315 285 283 137 118 95 77 68 83 54 47 42 26 17 7 4 3 0 0 0 0 0 0 0 0 0 0</td>
<td>2.9 (2.8-3.4)</td>
</tr>
</tbody>
</table>

GM-CSF Combinations

• Addition of GM-CSF to ipilimumab may increase overall survival and decrease serious toxicity compared with ipilimumab alone
• Phase II trial conducted by ECOG
• OS significantly improved by the addition of GM-CSF to ipi
  – 17.5 vs 12.7 months
  – One-year survival rate 69 vs 53%, HR 0.64, p = 0.01
• GM-CSF now being studied in combination with nivo plus ipi (EA6141, NCT02339571)
Sequencing Treatment

ECOG-ACRIN EA16134 Study Design

- Primary end point: OS rate after 2 years of follow-up

STEP 1 → PD → STEP 2

ARM A
Nivolumab 1 mg/kg IV + ipilimumab 3 mg/kg IV on d 1 and 22 × 2 cycles followed by nivolumab IV 3 mg/kg on d 1, 15, and 29 for up to 84 wk

ARM B
Oral dabrafenib 150 mg twice daily + oral trametinib 2 mg/d on d 1 and 42 of each 6-wk cycle

ARM A
Nivolumab 1 mg/kg IV + ipilimumab 3 mg/kg IV on d 1 and 22 × 2 cycles followed by nivolumab IV 3 mg/kg on d 1, 15, and 29 for up to 84 wk

ARM B
Oral dabrafenib 150 mg twice daily + oral trametinib 2 mg/d on d 1 and 42 of each 6-wk cycle

- Phase 3 trial, randomized
- 300 patients
- BRAF+ melanoma
- Stage IIIc, M1a/b, or M1c
- ECOG PS 0 or 1

ClinicalTrials.gov. NCT02224781.
Talimogene laherparepvec (T-VEC)

• A herpes simplex virus type 1–derived investigational oncolytic immunotherapy
• Designed to induce local and systemic immune responses by:
  – Selectively replicating in cancer cells while producing GM-CSF at the site of injection
  – By lysing cancer cells, resulting in the release of tumor-derived antigens
  – By creating a microenvironment that promotes systemic immune responses against tumor-derived antigens
T-VEC Oncolytic Immunotherapy

1. Inside a healthy cell, the virus is unable to replicate, leaving the cell unharmed.

2. Inside a cancer cell, the virus replicates and secretes GM-CSF until the cell lyses, releasing more viruses, GM-CSF, and antigens.

3. GM-CSF attracts dendritic cells to the site, which process and present the antigens to T cells. The T cells are now "programmed" to identify and destroy cancer cells throughout the body.

Talimogene laherparepvec: proposed mechanism of action for systemic immunological effect.
Intralesional Injection

- The phase III OPTiM study of T-VEC in stage IIIB/IV melanoma.
- 295 patients treated with T-VEC and 141 treated with recombinant GM-CSF (Leukine) as the control arm.
- OPTiM met its primary endpoint of durable response, which was observed in 16.3% of the T-VEC arm and 2.1% of the control arm.
- The overall response rate was 26.4% and 5.7%, respectively.

Andtbacka RI et al: OPTiM: A randomized phase III trial of talimogene laherparepvec (T-VEC) versus subcutaneous granulocyte-macrophage colony-stimulating factor (GM-CSF) for the treatment of unresected stage IIIB/C and IV melanoma. ASCO Annual Meeting
Combination Therapy

• Combining T-VEC, which promotes the release of tumor-derived antigens, with an immune checkpoint inhibitor that improves T-cell responses

• 19 previously untreated patients whose tumors were injected with up to 4 mL of T-VEC, dosed periodically until all injectable tumors disappeared or until progressive disease or intolerance.

• All responders received four doses of ipilimumab at 3 mg/kg every 3 weeks for 4 weeks, starting at week 6.

• Durable responses were observed in 10 of 18 (56%) evaluable patients, 33% being complete responses; the disease control rate was 72%.
Future Directions

• Clinical trials ongoing
• Significant interest in Melanoma vaccine trials
<table>
<thead>
<tr>
<th>Rank</th>
<th>Status</th>
<th>Study</th>
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<tbody>
<tr>
<td>1</td>
<td>Unknown</td>
<td>Vaccine Therapy With or Without Sargramostim in Treating Patients With High-Risk or Metastatic Melanoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Condition:</strong> Melanoma (Skin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Interventions:</strong> Biological: MAGE-10.A2; Biological: MART-1 antigen; Biological: NY-ESO-1 peptide vaccine; Biological: sargramostim; Biological: tyrosinase peptide</td>
</tr>
<tr>
<td>2</td>
<td>Terminated</td>
<td>Vaccine Therapy With or Without Interleukin-2 After Chemotherapy and an Autologous White Blood Cell Infusion in Treating Patients With Metastatic Melanoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Conditions:</strong> Recurrent Melanoma; Stage IV Melanoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Interventions:</strong> Drug: cyclophosphamide; Drug: fludarabine phosphate; Biological: therapeutic autologous lymphocytes; Procedure: in vitro-treated peripheral blood stem cell transplantation; Biological: gp100 antigen; Biological: MART-1 antigen; Biological: incomplete Freund's adjuvant; Biological: filgrastim; Biological: aldesleukin</td>
</tr>
<tr>
<td>3</td>
<td>Completed</td>
<td>Vaccine Therapy With or Without Interleukin-2 in Treating Patients With Metastatic Melanoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Conditions:</strong> Stage IV Melanoma; Recurrent Melanoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Interventions:</strong> Drug: gp100 antigen; Drug: interleukin-2</td>
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<tr>
<td>4</td>
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<td>Vaccine Therapy With or Without Interleukin-2 in Treating Patients With Metastatic Melanoma</td>
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<td><strong>Condition:</strong> Melanoma (Skin)</td>
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<tr>
<td></td>
<td></td>
<td><strong>Interventions:</strong> Biological: MART-1 antigen; Biological: aldesleukin; Biological: gp100 antigen; Biological: incomplete Freund's adjuvant</td>
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<td>5</td>
<td>Terminated</td>
<td>Vaccine Therapy in Treating Patients With Metastatic Melanoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Conditions:</strong> Recurrent Melanoma; Stage IV Melanoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Interventions:</strong> Biological: recombinant fowlpox-TRICOM vaccine; Other: laboratory biomarker analysis</td>
</tr>
<tr>
<td>6</td>
<td>Completed</td>
<td>Vaccine Therapy and Interleukin-12 in Treating Patients With Metastatic Melanoma</td>
</tr>
</tbody>
</table>
Case 2

- Patient was negative for BRAF/NRAS/KIT mutations
- Received ipilimumab + nivolumab, followed by nivolumab maintenance
- Noted to have CR after completion of combination therapy
References

Flatherty K et al. Genomic analysis and 3-y efficacy and safety update of COMBI-d. Abstract 9502 American Society of Clinical Oncology meeting.

Thank You