Strategy, efficacy and safety of combination regimens using immunotherapy

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Disclosures

• Advisory Board: Clovis, AstraZeneca, VBL, Janseen, Tesaro
Combination opportunities in cancer immunotherapy

Enhance antigen presentation and T-cell activation
- EGFR inhibitors
- ALK inhibitors
- BRAF inhibitors
- MEK inhibitors
- Chemotherapy
- HDAC
- Radiotherapy
- Anti-CD40
- IFN-γ
- Oncolytic viruses
- Neo-epitope vaccine
- Anti-CEA-IL2v
- Anti-FAP-IL2v
- Anti-OX40
- Anti-CTLA4
- Anti-CD27
- Anti-41BB
- PARPi

Increase T-cell trafficking and infiltration into tumors
- Anti-VEGF

RECRUIT/INFILTRATE (vasculature)
- TCBs
- ImmTACs
- CAR-T
- BiTes
- Anti-PDL1
- Anti-PD1
- Anti-CSF-1R
- IDO inhibitors
- Anti-TIGIT
- Anti-TIM3
- Anti-LAG3

ACTIVATE (central)
- Non-Inflamed
- Inflamed

KILL CANCER CELLS (tumour)
- Non-Inflamed
- Inflamed

Block immunosuppression within the tumor microenvironment and enhance tumor cell death

Chen & Mellman. Immunity 2013
Novel combination strategies in development

• VEGFi + T cell modulators

• PARPi + I/O agents
  ➢ PARP inhibition may increase immunogenicity

• I/O + chemotherapy

• I/O + I/O

• Triple Combos
I/O + VEGFi
Rationale for combining cancer immunotherapy with anti-VEGF

Induces abnormal tumor vasculature
- Reducing T-cell trafficking and infiltration into the tumor bed

Reduces lymphocyte adhesion to vessel walls
- Decreases immune-cell recruitment to the tumor site

Inhibits dendritic cell function
- Drives them into an immature state

Directly inhibits T-cell function
- Binds to VEGFR2 on T cells

Indirectly inhibits T-cell function
- Kills T cells by tumor endothelium-produced FasL

Stimulates immunosuppressive regulatory T cells

Pre-clinical data for combining anti-PD-L1 and VEGF blockade

Combined treatment with these two agents synergistically inhibited tumour growth in the Cloudman mouse tumour model.

Irving. 1st Annual Expert Forum on Immuno-oncology, 2013
**Immunotherapy with bevacizumab**

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>Roche Atezolizumab (PDL1)</td>
<td>Safety expansion cohort in 2L+ PR ovarian added in July, 2015. DLT Dec 2018</td>
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<tr>
<td></td>
<td>Atezo + bev</td>
<td>2L+ PR ovarian, CRC, RCC, NSCLC, TNBC, gastric n=240</td>
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<td></td>
<td>Vanucizumab + atezo</td>
<td>2L+ AST incl. PR/Ref ovarian n= 132</td>
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<td>Atezo ± bev ± aspirin vs. bev vs. atezo</td>
<td>2-4L PR ovarian n=160</td>
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<td>Lynparza + durvalumab</td>
<td>2L+ AST n=421</td>
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<td></td>
<td>Durvalumab + cediranib</td>
<td>NCI-sponsored; originally ovarian only (N=112); NSCLC, SCLC, mCRPC, TNBC and CRC cohorts added in Dec 2015; ORR Dec 2018</td>
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<tr>
<td></td>
<td>Pembro + aflibercept (VEGF-Trap)</td>
<td>EORTC-sponsored; 2-3L patients must have been exposed to an anti-VEGF; 6 mth-PFS Jan 2021</td>
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<td></td>
<td>Pembro + nintedanib</td>
<td>PEMBIB pembro + nintedanib</td>
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<td></td>
<td>Pembro + bev + CTX</td>
<td>2L+ ovarian n=40</td>
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<tr>
<td></td>
<td>Nivo + bev</td>
<td>2-4L ovarian n=38</td>
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**Legend**
- Phase 1 = hashed
- Phase 2 or 3 = solid
- Pivotal = red border
I/O + chemo
Chemotherapy can enhance antigen presentation

Chemotherapy can increase susceptibility to immune attack

Chemotherapy can enhance immunogenicity (release of adjuvants by cells)

DAMPs, danger-associated molecular patterns; DC, dendritic cell; PDT, photodynamic therapy

Garg et al. Biofactors 2013
Pre-clinical evidence for chemotherapy and anti-PDL1

The synergism of nab-paclitaxel plus anti-PDL1 has been demonstrated in a MC38 mouse tumour model.

Treatment with platinum agents or taxanes increased the percentage of CD8+ tumour-infiltrating lymphocytes in immunocompetent mouse models.

1. Adams et al. SABCS 2015
2. Jeong Kim, Genentech; unpublished data
Javelin 100

- **Chemotherapy**
  - Arm A: Chemotherapy
  - Arm B: Chemotherapy
  - Arm C: Chemotherapy + Avelumab Q3W

- **Maintenance**
  - Observation
  - Avelumab Q2W

**Primary endpoint:**
PFS from randomization (A vs B, A vs C)

**Secondary endpoints:**
Maintenance PFS, OS, ORR, duration of response, pCR, PFS2, PROs, safety, PK

Chemotherapy: Choice of carboplatin + q3w, paclitaxel, OR carboplatin + weekly paclitaxel
Maintenance avelumab up to 24 months
I/O + PARPi
Scientific rationale for PARPi in combination with PD-1 inhibitor

Preclinical models exhibit synergy with combination PARPi + anti-PD-1 agents regardless of BRCA mutation status or PD-L1 expression

• Unrepaired DNA damage resulting from niraparib treatment leads to the abnormal presence of DNA in the cytoplasm, which activates the stimulator of interferon gene (STING) pathway

• Activation of the STING pathway leads to increased expression and release of type 1 interferons, subsequent induction of γ-interferon, and intratumoral infiltration of effector T cells

NCT02657889
Konstantinopulos et al. SGO 2018
Treatment with either olaparib or anti-PD-L1 alone restricted tumour growth, but the combined treatment demonstrated enhanced therapeutic benefit.

# I/O + PARPi clinical trials

<table>
<thead>
<tr>
<th>Year</th>
<th>AstraZeneca Lynparza</th>
<th>Tesaro Niraparib</th>
<th>BeiGene BGB-290</th>
<th>Clovis Rucaparib</th>
<th>Pfizer Talazoparib</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>Durvalumab + Lynparza</td>
<td>Topacio (KN162)</td>
<td>BGB-290 + BGB-A317 (PD1)</td>
<td>COUPELT</td>
<td>Javelin Parp Medley</td>
</tr>
<tr>
<td></td>
<td>Durvalumab + cediranib</td>
<td>pembro + niraparib</td>
<td></td>
<td>Rucaparib + atezo</td>
<td>talazoparib + avelumab</td>
</tr>
<tr>
<td>2013</td>
<td>2L+ AST incl. ovarian; N=421</td>
<td>TSR-042 + niraparib or pac/carb vs. TSR-042 + niraparib + bev vs. TSR-042 + bev + pac/carb</td>
<td>Expansion cohort in BRCAm/HRD+ 1-4L TNBC (n~20); ORR Apr 2019</td>
<td>Dose escalation in 2L+ ovarian &amp; endometrial (n=6-18); FM CDx; Safety Jan 2019</td>
<td>1L mtx all-comers n~1,000</td>
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<tr>
<td>2014</td>
<td>2L PR or PPSR ovarian; N=68</td>
<td>Safety Sep 2018</td>
<td>Preliminary data presented at ASCO 2017</td>
<td>Expansion cohort in BRCAm/HRD+ 1-4L TNBC (n~20); ORR Apr 2019</td>
<td>1L mtx all-comers n=700</td>
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<tr>
<td>2015</td>
<td>2L+ gBRCAm ovarian; N=50</td>
<td>No enrichment for PDL1+ or HRD+ pts but the biomarkers will be assessed; ORR May 2018 ORR 25% (3% CR) in 2-6L PRR ovarian. Data update at ASCO 2018</td>
<td>Safety Sep 2018</td>
<td>Safety Jan 2019</td>
<td>Q2 2018 start</td>
</tr>
<tr>
<td>2016</td>
<td>1L gBRCAm ovarian; N=148</td>
<td>1L mtx &amp; mtx n=927</td>
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<tr>
<td>2017</td>
<td>Durvalumab + tremelimumab + Lynparza</td>
<td>Sponsored by MRK.; Details TBD</td>
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<tr>
<td>2018</td>
<td>PSR/PRR BRCAm ovarian; N=39</td>
<td>Results Q4 2021</td>
<td></td>
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<tr>
<td>2019</td>
<td>1L mtx &amp; mtx n=927</td>
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<td>2020</td>
<td>ESR. PRR PFS/ PSR PFS Aug 2019</td>
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<td>2021</td>
<td>ESR. PR or PSR pts eligible; ORR Feb, 2018</td>
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<td>2022</td>
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</table>

## Legend
- **Phase 1** = hashed
- **Phase 2 or 3** = solid
- **Pivotal** = red border
- **Potential to support registration = red dashed line**

## Notes
- NCI-sponsored; originally ovarian only (N=112); NSCLC, SCLC, mCRPC, TNBC and CRC cohorts added in Dec 2015; ORR Dec 2018
- Safety endpoint
- Trial also recruiting gBRCAm HER2- BC, ATM- gastric and 2L+ SCLC; DCR, safety/tolerability Jun 2018
- Safety/tolerability Jun 2018
- No enrichment for PDL1+ or HRD+ pts but the biomarkers will be assessed; ORR May 2018 ORR 25% (3% CR) in 2-6L PRR ovarian. Data update at ASCO 2018
- Preliminary data presented at ASCO 2017
- Dose escalation in 2L+ ovarian & endometrial (n=6-18); FM CDx; Safety Jan 2019 RP2D is the full dose of both rucaparib and atezo, CLVS anticipates 2018 data presentation, but highlights that it is Genentech decision
- Basket study to provide PoC data, no registration intent suggested; ORR Mar 2020
Anti-PD1 and PARPi: TOPACIO/Keynote-162

Phase I/II study dose-finding combination study of niraparib plus pembrolizumab in patients with metastatic TNBC or recurrent platinum-resistant epithelial OC

<table>
<thead>
<tr>
<th>Evaluable patients*</th>
<th>Integrated Efficacy Analysis (combined phase 1+2) PROC Cohort N=60</th>
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<tbody>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>12 (20%)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>25 (42%)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>20 (33%)</td>
</tr>
<tr>
<td>ORR (CR+PR)</td>
<td>25%</td>
</tr>
<tr>
<td>Disease control rate (CR+PR+SD)</td>
<td>67%</td>
</tr>
</tbody>
</table>

~60% (9/15) of responders (CR or PR) remain on treatment as data continue to mature; duration of response and PFS will be presented at an upcoming conference

NCT02657889
Konstantinopoulos et al. ASCO 2018

*Two patients were not evaluable for efficacy; data are immature, responses include both confirmed and unconfirmed; evaluable pts had at least one on-treatment scan; data as of April 2, 2018
Anti-PD1 and PARPi: MEDIOLA

Initiation of therapy at the time of relapse

- PSR OC 2L+ gBRCAm PARPi and IO naïve
- Olaparib 300 mg po bid
- Durvalumab 1.5 g IV q4w
- Target DCR at 12 weeks: 90%*
  → N=31

*Target based on olaparib monotherapy efficacy

Tumor assessments

Optional biopsies

Primary endpoints: DCR at 12 weeks, safety
Secondary endpoints: DCR at 28 weeks, ORR, DoR, PFS, OS, PD-L1 expression
Exploratory endpoints: TILs

NCT02734004
Drew et al. SGO 2018

DCR, disease control rate; DoR, duration of response; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; po, oral; TILs, tumor-infiltrating lymphocytes
MEDIOLA: tumor responses

<table>
<thead>
<tr>
<th>Best Response</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>6 (19)</td>
</tr>
<tr>
<td>PR</td>
<td>17 (53)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (9)</td>
</tr>
<tr>
<td>PD</td>
<td>3 (9)</td>
</tr>
<tr>
<td>NE</td>
<td>3 (9)</td>
</tr>
</tbody>
</table>

Best percentage change in target lesion size

- 1 prior line of chemotherapy
- 2 prior lines of chemotherapy
- 3 or more prior lines of chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>1 prior (2L)</th>
<th>2 prior (3L)</th>
<th>3+ prior (4L)</th>
<th>All lines</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>10/13=77%</td>
<td>6/9=67%</td>
<td>7/10=70%</td>
<td>23/32=72%</td>
</tr>
<tr>
<td>95% CI</td>
<td>(46%, 95%)</td>
<td>(30%, 93%)</td>
<td>(35%, 93%)</td>
<td>(53%, 86%)</td>
</tr>
</tbody>
</table>
PD-L1 and TILs in archival tissue: association with clinical response

No statistically significant associations were observed between PD-L1 TC positivity or CD3 and CD8 TILs and positive BOR.

However, a trend was observed where higher PD-L1 and increased TIL densities were observed in archival samples in patients who had SD/PR/CR – this was not seen in patients with PD.

Higher PD-L1 (TC) was observed in patients with DCR at 12 weeks.

Dotted lines indicate CD3 (1000 cells/mm²) and CD8 (400 cells/mm²) ‘hot/cold’ thresholds established from unpublished data. Error bars present the median ± interquartile range.

BOR, best objective response; TC, tumor cell; TILs, tumor infiltrating lymphocytes; Y, Yes; N, No.
Dual signals control immune function

The immune system is governed by stimulatory and suppressive interactions.

I/O + I/O
TURN UP the GOOD and TURN DOWN the BAD

Immunosensitive

Immunoresistant

Epithelial Ovarian Cancer

CD8 T cell
CD103 T cell
CD27 T cell

Chemokines

IDO

Treg

FOXP3

TNFR2

CD28

OX40

GITR

CD137

CD27

HVEM

Agonistic antibodies

Activating receptors

CCL22

MDSC

NK

T cell

IDO

Treg

FOXP3

TNFR2

CD8

CD103

CD27

CCL5

CXCL9

CCL12

CXCL10

Chemokines

CD8

CD103

CD27

T cell

CD8

CD103

CD27

T cell

CD8

CD103

CD27

T cell

CD8

CD103

CD27

T cell

CD8

CD103

CD27

T cell

CD8
NRG GY003: nivo vs nivo/ipi

• Phase II trial in recurrent ovary CA
• Hypothesis: enhancing CD8 T cell accumulation and activity will reduce the population of T_{reg} cells and promote anti-tumor activity
• Dual blockade of PD-1 and CTLA-4:
  ➢ Tumor reactive TILs contain both
  ➢ Mice model showed that dual blockade reversed CD8^{+} TIL dysfunction and increased multiple immunogenic markers (↑Ag specific CD8+, CD4+, cytokine release, ↓suppressive Treg cell function, etc)

NCT#02498600
DART: Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (central and peripheral attack)

• Phase II, single arm trial with 31 histologic cohorts
• 1º objective: evaluate ORR in pts with advanced rare tumors treated with nivo + ipi
• Given the impressive RR with combination nivo/ipi in melanoma (versus either as monotherapy), the combination therapy is expected to be the most efficient approach to testing immune checkpoint blockade efficacy across a variety of rare tumor types.
Triple Combos
Atezolizumab and bevacizumab: IMaGYN050

Double blinded, 1:1 randomized, placebo-controlled multi-center study

- Previously untreated epithelial ovarian, primary peritoneal, or fallopian tube cancer
- Stage III (sub-optimal/ optimal w/ macroscopic residual), Stage IV, or patients w/ advanced disease treated in the neo-adjuvant setting

Co-Primary endpoint: PFS & OS in all comers and Dx+ (IC 1+)

NCT03038100
## Other I/O combinations

<table>
<thead>
<tr>
<th>Year</th>
<th>Nivo + lirilumab (KIR)</th>
<th>BMS-986016 (LAG3) ± nivo</th>
<th>CM032 Nivo vs nivo + ipi (CTLA-4)</th>
<th>ECHO 204 Nivo + epacadostat (IDO1)</th>
<th>NRG-GY003 nivo vs. Nivo + ipi (CTLA-4)</th>
<th>Roche Atezolizumab (PDL1)</th>
<th>Merck Serono/Pfizer Avelumab (PDL1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>Ovarian, RCC, CRC, NSCLC and mel n=650</td>
<td>AST n=1,000</td>
<td>Ovarian, TNBC, gastric, bladder pancreatic, SCLC n=1,150</td>
<td>2-6L ovarian, NSCLC, mel, CRC, SCCHN n=175</td>
<td>2-4L PR or PPSR ovarian n=96</td>
<td>AST, n=15</td>
<td>Avelumab + defactinib (FAK) 4-7L ovarian, n=98</td>
</tr>
<tr>
<td>2011</td>
<td>N=16 patients in each cohort</td>
<td>Safety Jun 2019; Ovarian cohort only in the dose escalation arm</td>
<td>Signal finding for nivo + Ipi combo. Ovarian cohort added in Sept 2015; ORR Dec 2018</td>
<td>Incyte-sponsored; ORR/PFS Apr 2020</td>
<td>NCI-sponsored; currently suspended for recruitment, 2-step design suggest pts needed for the first step have been enrolled in the first 4-weeks, ORR Dec 2020</td>
<td>Safety Apr 2019</td>
<td>Avelumab + entinostat vs. avelumab (HDAC) 4-7L ovarian, n=138</td>
</tr>
<tr>
<td>2012</td>
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<td>Five Prime-sponsored; safety May 2019</td>
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### BMS Nivolumab (PD1)
- **ECHO 204** Nivo + epacadostat (IDO1)
  - 2-6L ovarian, NSCLC, mel, CRC, SCCHN n=175
  - Celldex-sponsored; ORR Apr 2019

### Roche Atezolizumab (PDL1)
- **NRG-GY003** nivo vs. Nivo + ipi (CTLA-4)
  - Nivo + IFN-γ:
    - 2L+ AST n=15
  - Nivo + WT1 (vaccine):
    - 2L+ maintenance ovarian n=11
  - ABBV-428 ± nivo (CD40):
    - 2L+ AST incl. ovarian n=172
  - Atezo + RO5509554 (CSF1R):
    - 1L+ ovarian, TNBC, gastric, bladder, sarcoma, n=310
  - Safety Nov 2018
  - Atezo + GDC-0919 (IDO1):
    - AST, n=158
    - DLT Dec 2018; ovarian cohort added in Aug 2016

### Merck Serono/Pfizer Avelumab (PDL1)
- **ECHO 204** Nivo + epacadostat (IDO1)
  - Nivo + varilumab (CD27):
    - 2-6L ovarian, NSCLC, mel, CRC, SCCHN n=175
  - Safety Apr 2019
  - NCI-sponsored; safety May 2019

### Other I/O combinations
- **AST, n=158**
  - NCI-sponsored; PFS Mar 2020

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