

Investor science conference call from ESMO 2014

Madrid, 29 September 2014



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Introduction

Karl Mahler, Head of Investor Relations, Roche

Agenda

Introduction

Dr. Karl Mahler, Head of Investor Relations

Update on key oncology data

Stefan Frings MD, Medical Director, Roche Germany

Breast cancer

- Avastin in 1st line maintenance and treatment through multiple lines HER2-neg. mBC: phase III IMELDA and TANIA
 - Perjeta in 1st line HER2-pos. mBC: final overall survival data phase III CLEOPATRA
-

Metastatic melanoma

- Combination of cobimetinib and Zelboraf in BRAF-mutated metastatic melanoma frontline setting: phase III coBRIM
-

Update on cancer immunotherapy

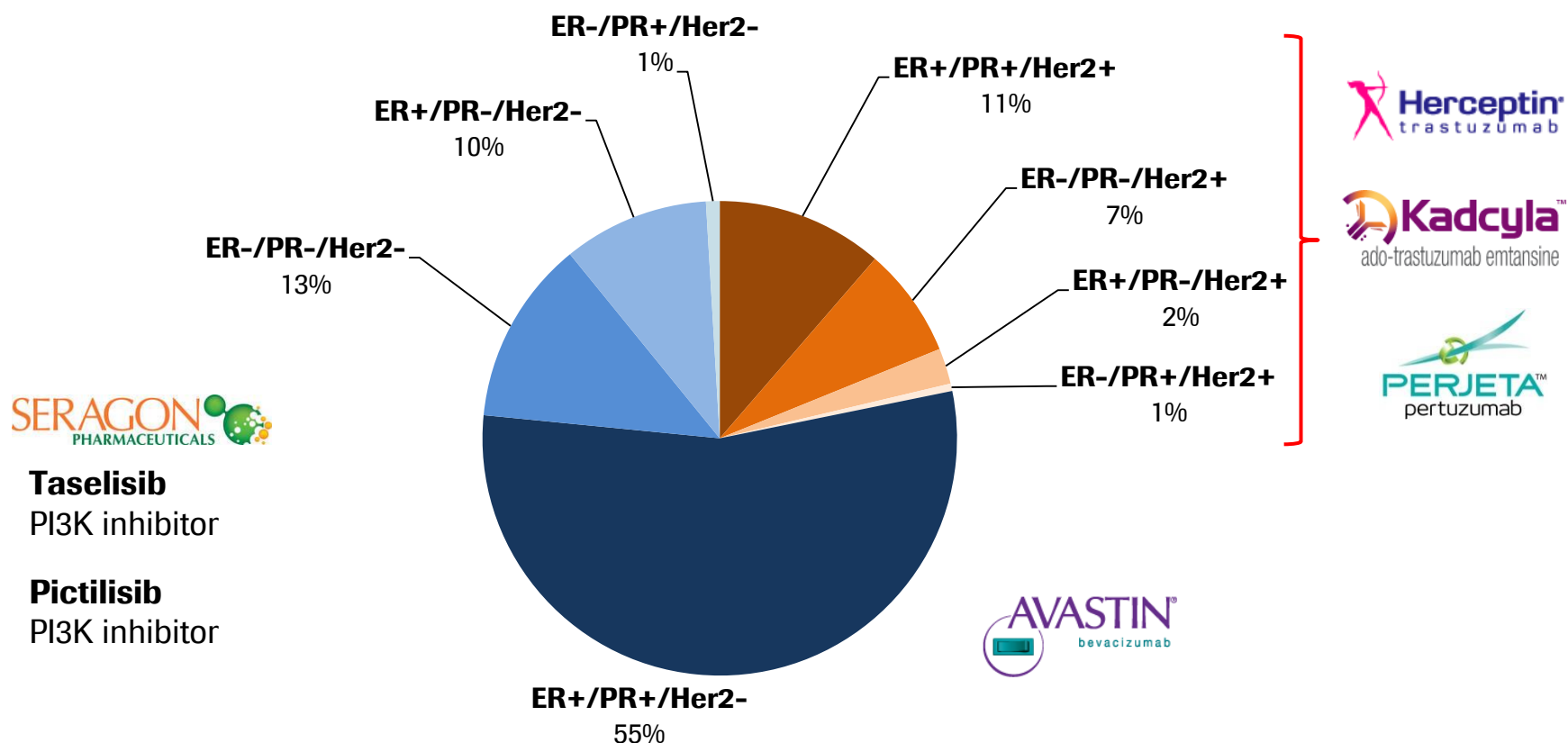
Cathi Ahearn, Lifecycle Leader anti-PDL1, Genentech

MPDL3280A (anti-PDL1) in solid tumors

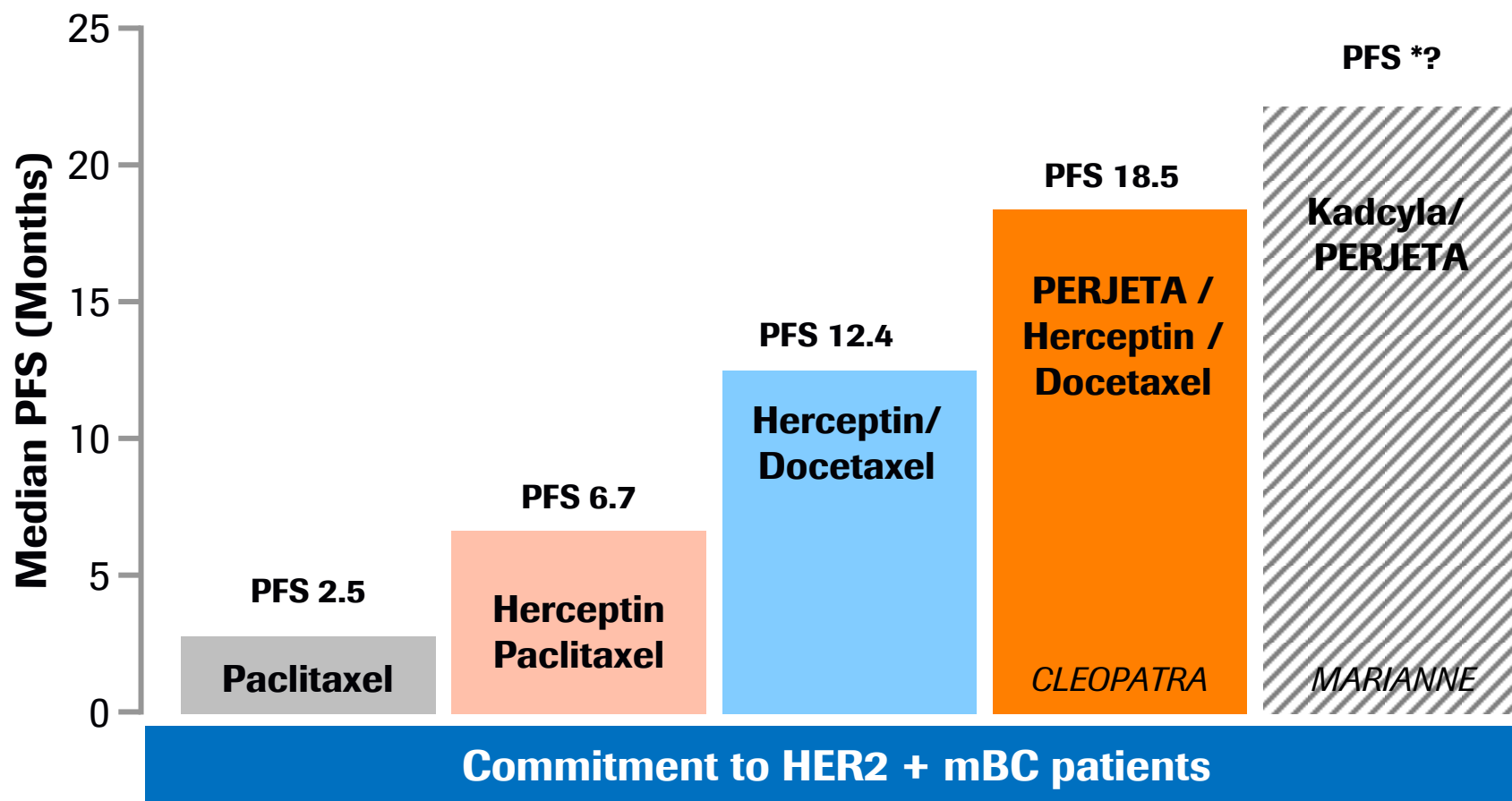
- Phase I combination with Avastin +/-chemo, monotherapy RCC, update bladder cancer
-

Breast cancer: Still high unmet medical need

Roche proposing solutions for most segments

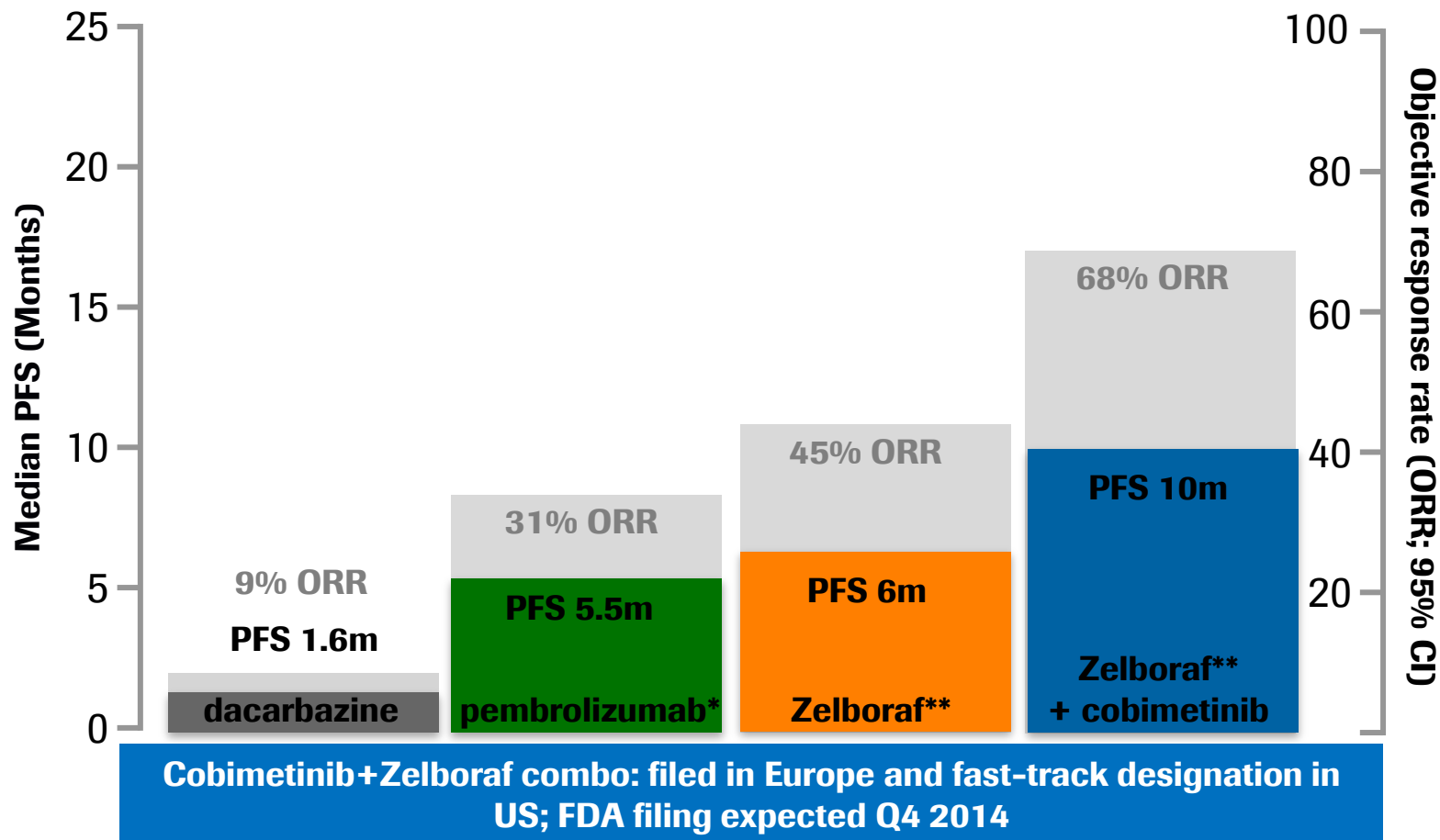


Continuing to raise the efficacy bar in HER2-positive metastatic breast cancer



- *Illustrative. MARIANNE trial ongoing, results are not yet available.

Continuing to raise the efficacy bar in metastatic melanoma



* ipilimumab pre-treated patients

**BRAF-mutation positive patients

Roche in cancer immunotherapy

A comprehensive program

| <i>Compound</i> | <i>Indication</i> | Phase | | |
|------------------|--------------------------------|--------------|----------|----------|
| | | 1 | 2 | 3 |
| <i>PDL1</i> | Lung: mono/combo | ✓ | ✓ | ✓ |
| <i>PDL1</i> | Bladder | ✓ | ✓ | ✓ |
| <i>PDL1</i> | Renal: mono/combo | ✓ | ✓ | |
| <i>PDL1</i> | Melanoma | ✓ | | |
| <i>PDL1</i> | Other solid tumors: mono/combo | ✓ | | |
| <i>PDL1</i> | CRC | ✓ | | |
| <i>PDL1</i> | Hematology/combo | ✓ | | |
| <i>CSF1R</i> | Solid tumours/PVNS | ✓ | ✓ | |
| <i>CEA IL-2v</i> | Solid tumours | ✓ | | |
| <i>Ox 40</i> | Solid tumours | ✓ | | |
| <i>CD40</i> | Solid tumours | ✓ | | |
| <i>INO</i> | Solid tumours | ✓ | | |

✓ Study ongoing

✓ Study planned

PDL1 in bladder: A strong set of data

ASCO 2014: N= 65
Mai /June 2014

| PD-L1 IHC (n) | ORR (95% CI) | Dx+ vs Dx- ORR (95% CI) |
|------------------|--------------------|-------------------------------|
| IHC 3 (n=10) | 50% (22-78) | 43% (26-63) |
| IHC 2 (n=20) | 40% (22-64) | |
| IHC 1 (n=23) | 13% (4-32) | 11% (4-26) |
| IHC 0 (n=12) | 8% (0.4-35) | |

- After 6 weeks follow-up
- 2 complete responses in PD-L1+
- 16/17 responders continuing to respond

ESMO 2014: N=70*
September 2014

| PD-L1 IHC (n) | ORR (95% CI) | Dx+ vs Dx- ORR (95% CI) |
|------------------|--------------------|-------------------------------|
| IHC 3 (n=10) | 60% (27-85) | 52% (34-69) |
| IHC 2 (n=23) | 48% (27-68) | |
| IHC 1 (n=24) | 17% (6-37) | 14% (6-28) |
| IHC 0 (n=12) | 8% (0-35) | |

- Median of 6 months follow-up
- 3 complete responses in PD-L1+
- 19/22 responders continuing to respond

*1 pt has unknown IHC (IC) status

Update on key oncology data

Stefan Frings MD, Medical Director, Roche Germany

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Breast cancer

Avastin in 1st line maintenance and treatment through multiple lines HER2-neg. mBC: phase 3 IMELDA and TANIA

Perjeta in 1st line HER2-pos. mBC: final overall survival data phase 3 CLEOPATRA

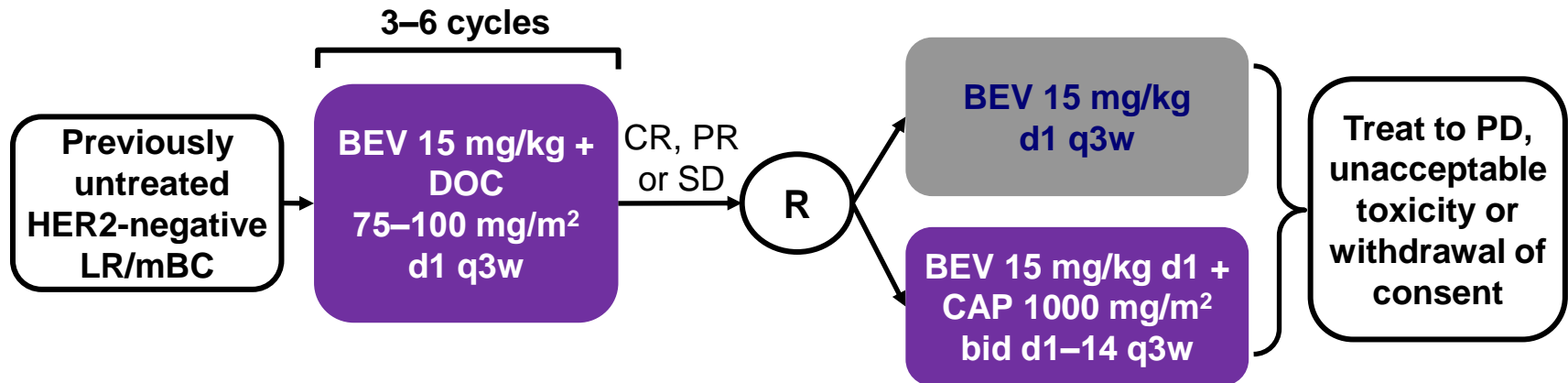
Melanoma

Cobimetinib + Zelboraf in metastatic BRAF-mutated melanoma frontline setting: phase 3 coBRIM

IMELDA:

Open-label randomised phase III trial

Published online in Lancet Oncology



Stratification factors

- ER status (positive vs negative), visceral metastasis (present vs absent), stable disease/response/non-measurable disease, LDH concentration (≤ 1.5 vs $> 1.5 \times$ ULN)

Primary endpoint (maintenance population)

- PFS from the time of randomisation to progression/death

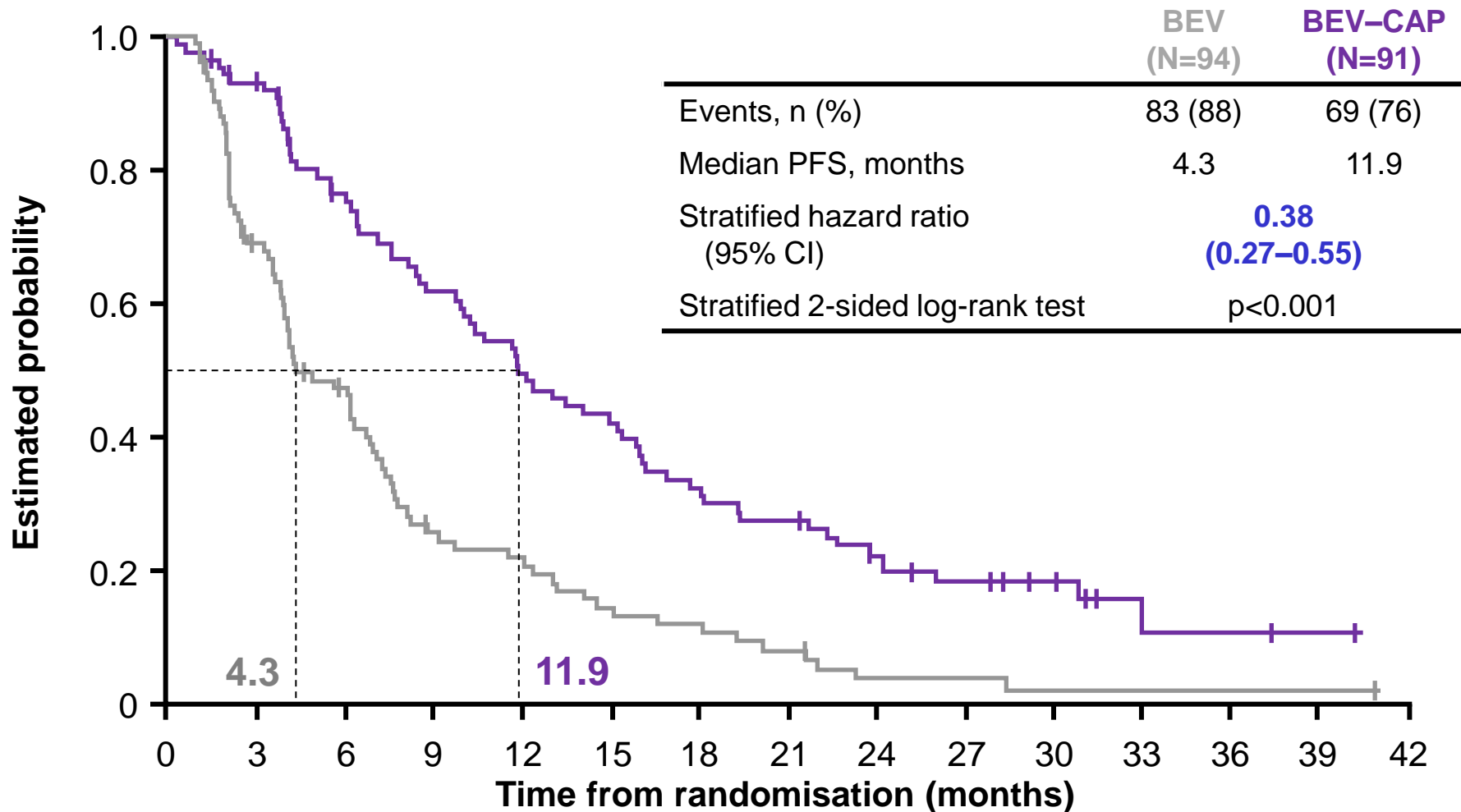
Key secondary endpoints

- Overall response rate (ORR), clinical benefit rate, time to disease progression, overall survival (OS)

BEV = bevacizumab; CAP = capecitabine; CR = complete response; DOC = docetaxel; ER = oestrogen receptor; LDH = lactate dehydrogenase; LR/mBC = locally recurrent/metastatic breast cancer; PD = progressive disease; PR = partial response; SD = stable disease; R = randomisation; ULN = upper limit of normal.

* Avastin is licenced by EMA for 1L therapy of metastatic Breast Cancer combination with paclitaxel or capecitabine, but not in combination with Docetaxel

Primary endpoint: PFS from time of randomisation

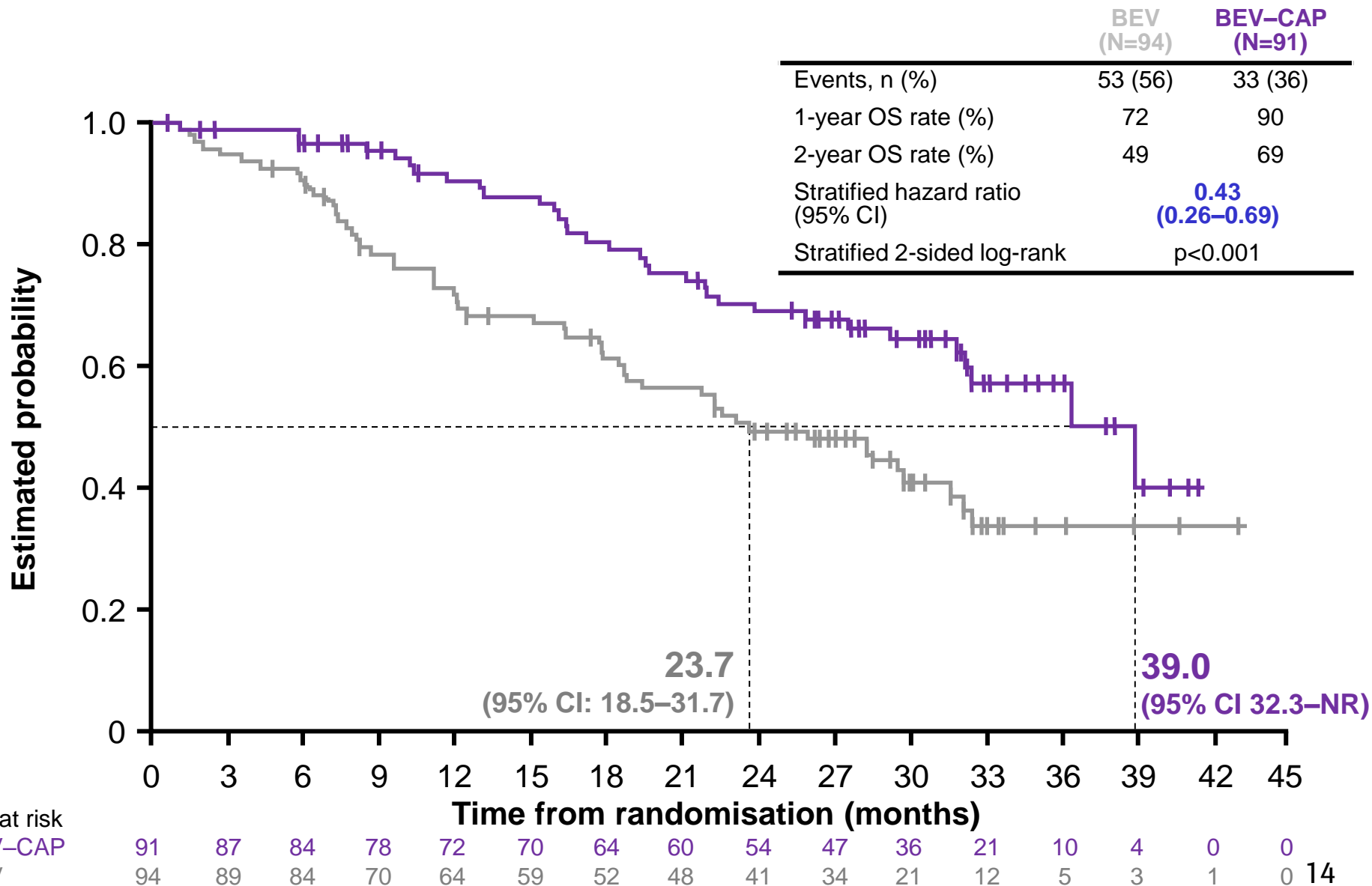


No. at risk
BEV-CAP
BEV

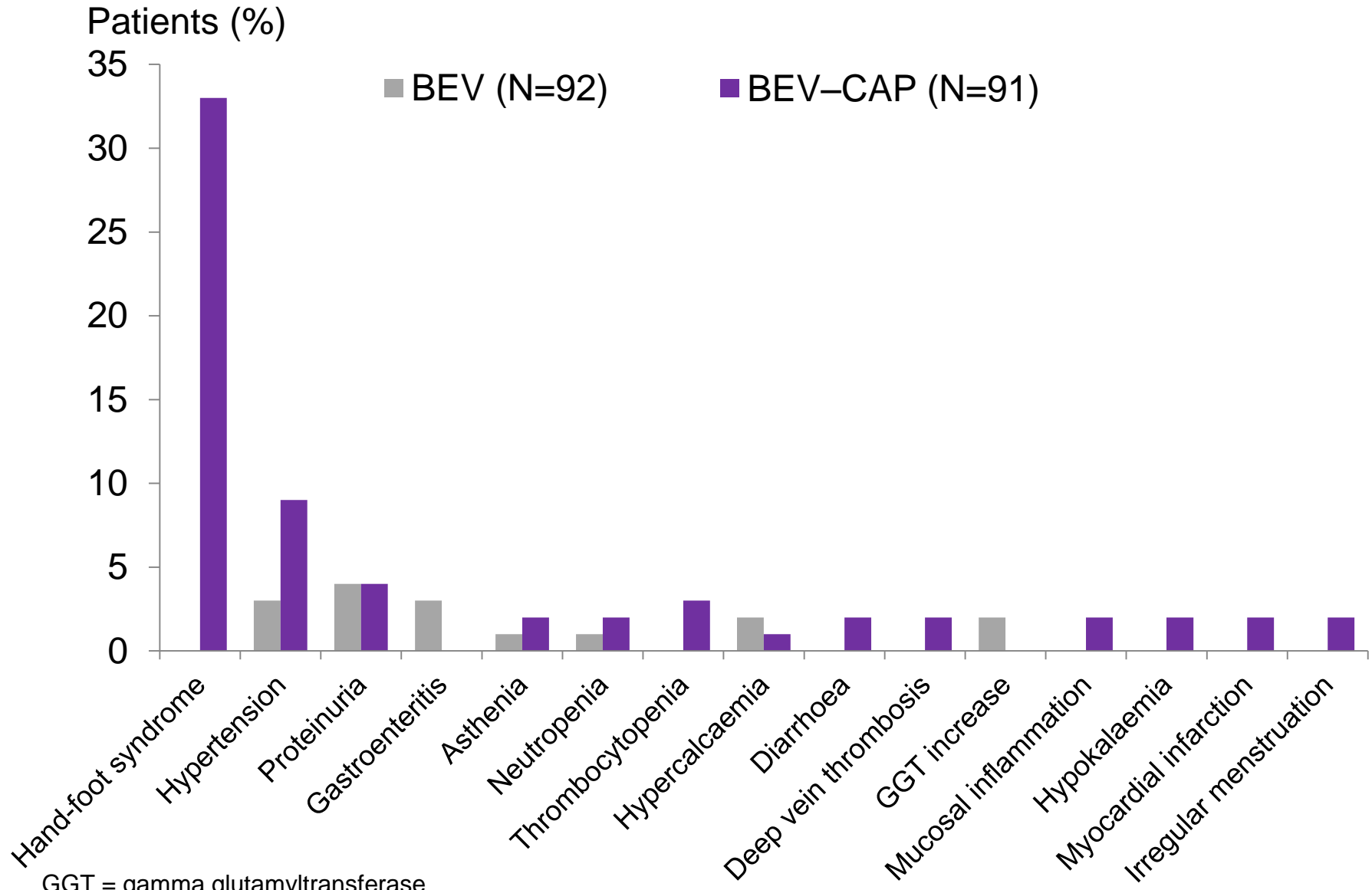
| | | | | | | | | | | | | | | |
|----|----|----|----|----|----|----|----|----|----|---|---|---|---|---|
| 91 | 80 | 62 | 50 | 40 | 34 | 26 | 22 | 16 | 12 | 8 | 2 | 2 | 1 | 0 |
| 94 | 60 | 40 | 20 | 17 | 11 | 9 | 6 | 2 | 2 | 1 | 1 | 1 | 1 | 0 |

Stratification factors: ER status, visceral metastasis, stable disease/response/non-measurable disease, LDH concentration

Secondary endpoint: OS from time of randomisation



Most common grade ≥ 3 AEs ($\geq 2\%$ of patients in either arm)

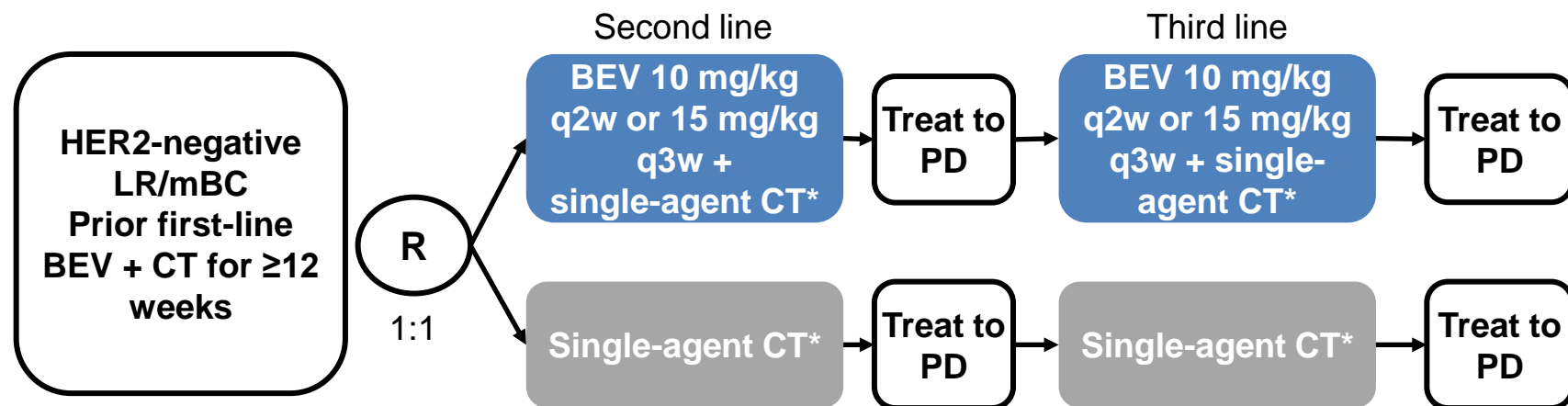


Conclusions

- **Adding CAP to BEV maintenance after initial BEV + taxane demonstrated statistically significant and clinically meaningful improvements in PFS (primary endpoint) and OS**
 - Sample size smaller than planned
 - Insufficient duration of follow-up for OS → low event rate for OS (secondary endpoint) especially in the BEV–CAP arm
- **No unexpected safety signals**
 - Long-term bevacizumab-containing therapy was well tolerated
 - CAP was associated with an increase in hand-foot syndrome (grade 3: 33% vs 0%)
- **Ongoing evaluation:**
 - Collection of anti-cancer treatment after study therapy
 - Patient-reported outcomes
- **In patients benefiting from first-line BEV-containing therapy, continued BEV with oral chemotherapy improves efficacy**

TANIA: Open-label randomised phase III trial

Published online in Lancet Oncology



Stratification factors

- Hormone receptor status, time to first progression (<6 vs ≥6 months), choice of chemotherapy (taxane vs non-taxane vs vinorelbine), LDH concentration (≤1.5 vs >1.5 × UNL)

Primary endpoint

- 2nd-line PFS

Key secondary endpoints

- 2nd-line best overall response rate, 2nd- and 3rd-line PFS, OS, 3rd-line PFS

Final OS: ≥24 months' follow-up since randomisation in all patients (or death, withdrawn consent or lost to follow-up)

CT = chemotherapy; LDH = lactate dehydrogenase; nab = nanoparticle albumin-bound; PD = disease progression; R = randomisation; UNL = upper normal limit

*CT options (investigator's choice, doublets not allowed): paclitaxel, nab-paclitaxel, docetaxel, capecitabine, gemcitabine, pegylated liposomal doxorubicin, non-pegylated liposomal doxorubicin, doxorubicin, epirubicin, vinorelbine, cyclophosphamide, ixabepilone (and in 3rd line only: eribulin)

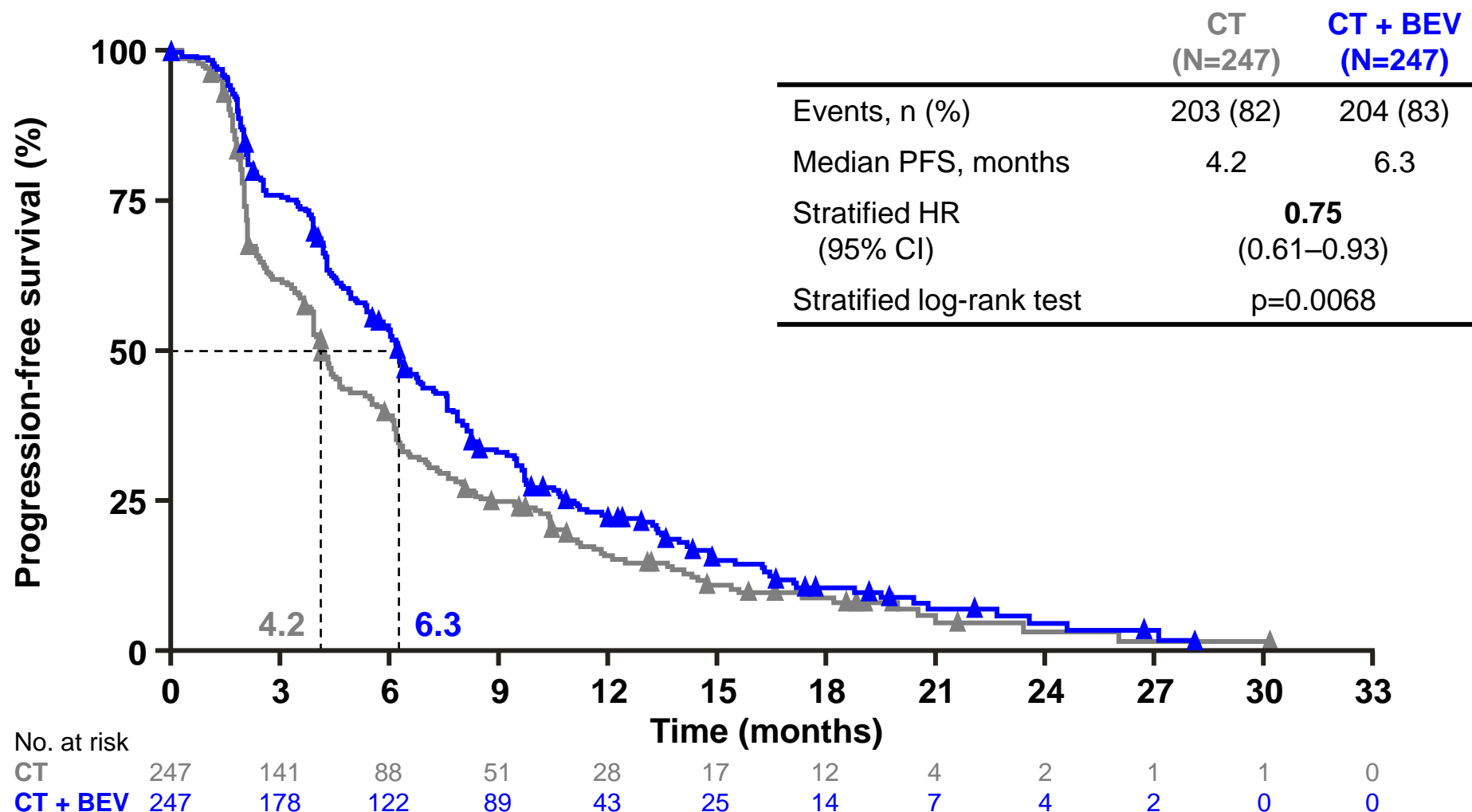
§ Avastin is licenced by EMA for for 1L therapy of metastatic Breast Cancer until progression of the disease but not for second or third line use nor for use beyond disease progression

Investigator-selected second-line chemotherapy

| Second-line CT, n (%) | CT (N=238) | CT + BEV (N=245) |
|-------------------------------------|-------------------|-------------------|
| Taxane* | 25 (10.5) | 24 (9.8) |
| Paclitaxel | 11 (4.6) | 16 (6.5) |
| Nab-paclitaxel | 8 (3.4) | 4 (1.6) |
| Docetaxel | 6 (2.5) | 4 (1.6) |
| Anthracycline | 34 (14.3) | 36 (14.7) |
| Non-pegylated liposomal doxorubicin | 20 (8.4) | 17 (6.9) |
| Pegylated liposomal doxorubicin | 8 (3.4) | 7 (2.9) |
| Doxorubicin | 2 (0.8) | 7 (2.9) |
| Epirubicin | 4 (1.7) | 5 (2.0) |
| Other | 179 (75.2) | 184 (75.1) |
| Capecitabine | 142 (59.7) | 148 (60.4) |
| Vinorelbine* | 26 (10.9) | 29 (11.8) |
| Gemcitabine | 10 (4.2) | 5 (2.0) |
| Cyclophosphamide | 1 (0.4) | 2 (0.8) |

*Stratification factors: taxane, vinorelbine, the rest (non-taxane)

Primary endpoint: Second-line PFS



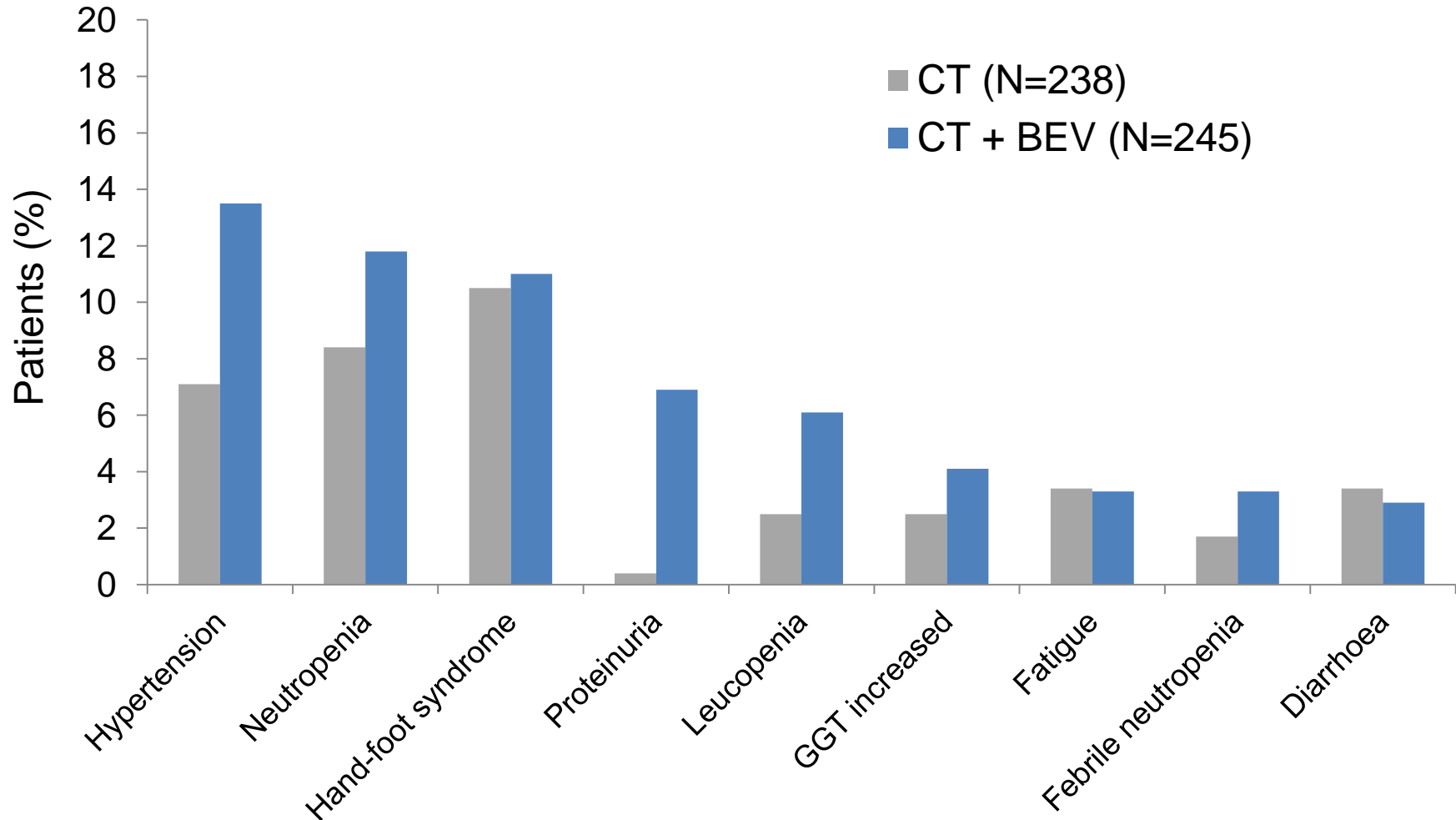
Median duration of follow-up: 15.9 months (CT) vs 16.1 months (CT + BEV)

Secondary endpoints: Best response* (second-line treatment from randomisation)

| Endpoint | CT (N=185) | CT + BEV (N=182) |
|--------------------------------------|-----------------------------------|---------------------|
| Overall response rate, % (95% CI) | 16.8 (11.7–22.9) | 20.9 (15.2–27.5) |
| Difference (95% CI) | 4.1 (–4.2 to 12.4) p=0.3457 | |
| Stable disease, % | 33.5 (26.8–40.8) | 48.9 (41.4–56.4) |
| Disease progression, % | 41.1 (33.9–48.5) | 24.2 (18.1–31.1) |
| Duration of response | (N=31) | (N=38) |
| Median, months (95% CI) | 10.6 (4.4–16.7) | 8.3 (6.1–10.3) |

*Response Evaluation Criteria in Solid Tumors version 1.0






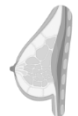

Most common grade ≥ 3 AEs ($\geq 3\%$, second-line safety population)



Conclusions

- The primary objective of TANIA was met
 - Statistically significant improvement in second-line PFS with further BEV in BEV-pretreated LR/mBC
 - Continuous VEGF suppression appears to be important, consistent with findings in metastatic colorectal cancer
- Effect of second-line BEV on PFS in BEV-pretreated patients (TANIA) appears similar to effect in BEV-naïve patients (RIBBON-2; HR 0.78 [95% CI 0.64–0.93])
- No new safety signals seen; long-term BEV-containing therapy was generally well tolerated
- Biomarker and patient-reported outcomes analyses are ongoing
- Final OS, PFS from randomisation to third-line progression/death and third-line safety results are anticipated in mid 2015

Avastin: Standard of care in multiple tumor types with the largest breadth of data

| | Indication | US | EU | New data 2014 |
|---|-------------------------|-----------------|-------|--|
|  | Colorectal | ✓ | ✓ | CALGB 80405: Avastin only biologic with proven OS in 1 st , 2 nd L and TML ¹ irrespective of Ras status |
|  | Lung | ✓ | ✓ | JO 25567 in EGFRmut.+ patients: Significant PFS benefit of A+T over Tarceva single agent |
|  | Ovarian | Priority Review | ✓ | US Priority review in Pt-resistant patients; EU approval, label extension Pt-resistant Aug '14 |
|  | Renal | ✓ | ✓ | Promising early data in combination with MPDL3280A (anti-PDL1): ORR 40% |
|  | Brain | ✓ ² | Filed | Negative CHMP opinion Sep '14 |
|  | Breast, HER2-neg | | ✓ | Positive phase 3 data in 1st line maintenance (IMELDA) and 2nd line TML settings (TANIA) |
|  | Cervical | ✓ | Filed | US approval Aug '14, based on significant OS benefit of Avastin over chemotherapy |

¹Treatment through multiple lines of therapy, ²Accelerated approval in recurrent GBM; 2012 US sales CHF ~170 m

Agenda

Update on key oncology data

Breast cancer

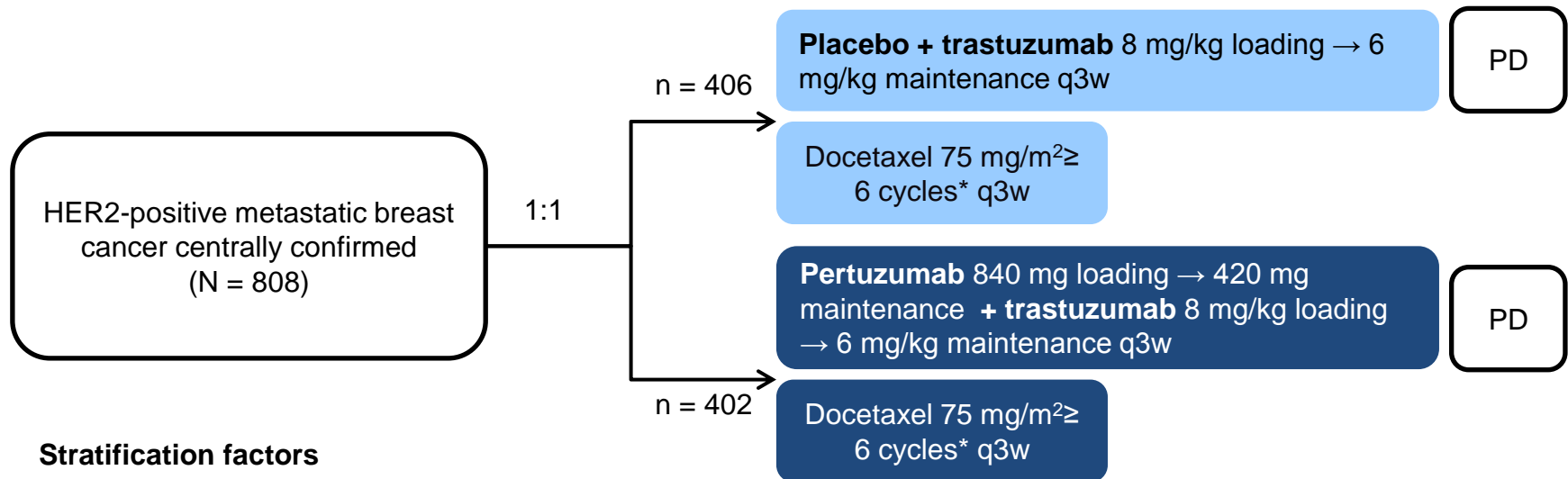
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phase 3 CLEOPATRA

Melanoma

Cobimetinib + Zelboraf in metastatic BRAF-mutated melanoma frontline setting: phase 3 coBRIM

CLEOPATRA Study Design



Stratification factors

- Geographic region and neo/adjuvant chemotherapy

Primary endpoint

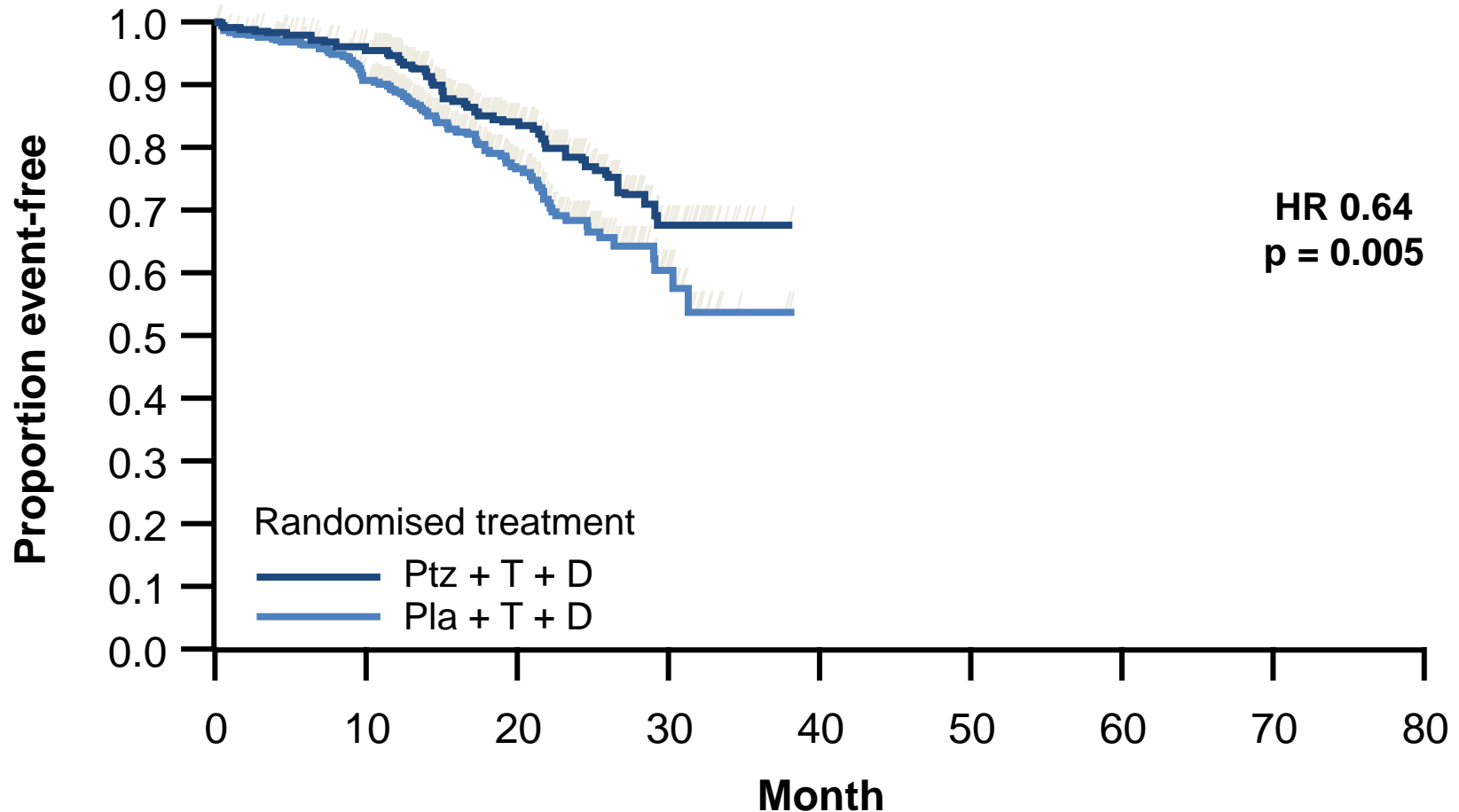
- Independently assessed PFS at 381 events

Secondary endpoints

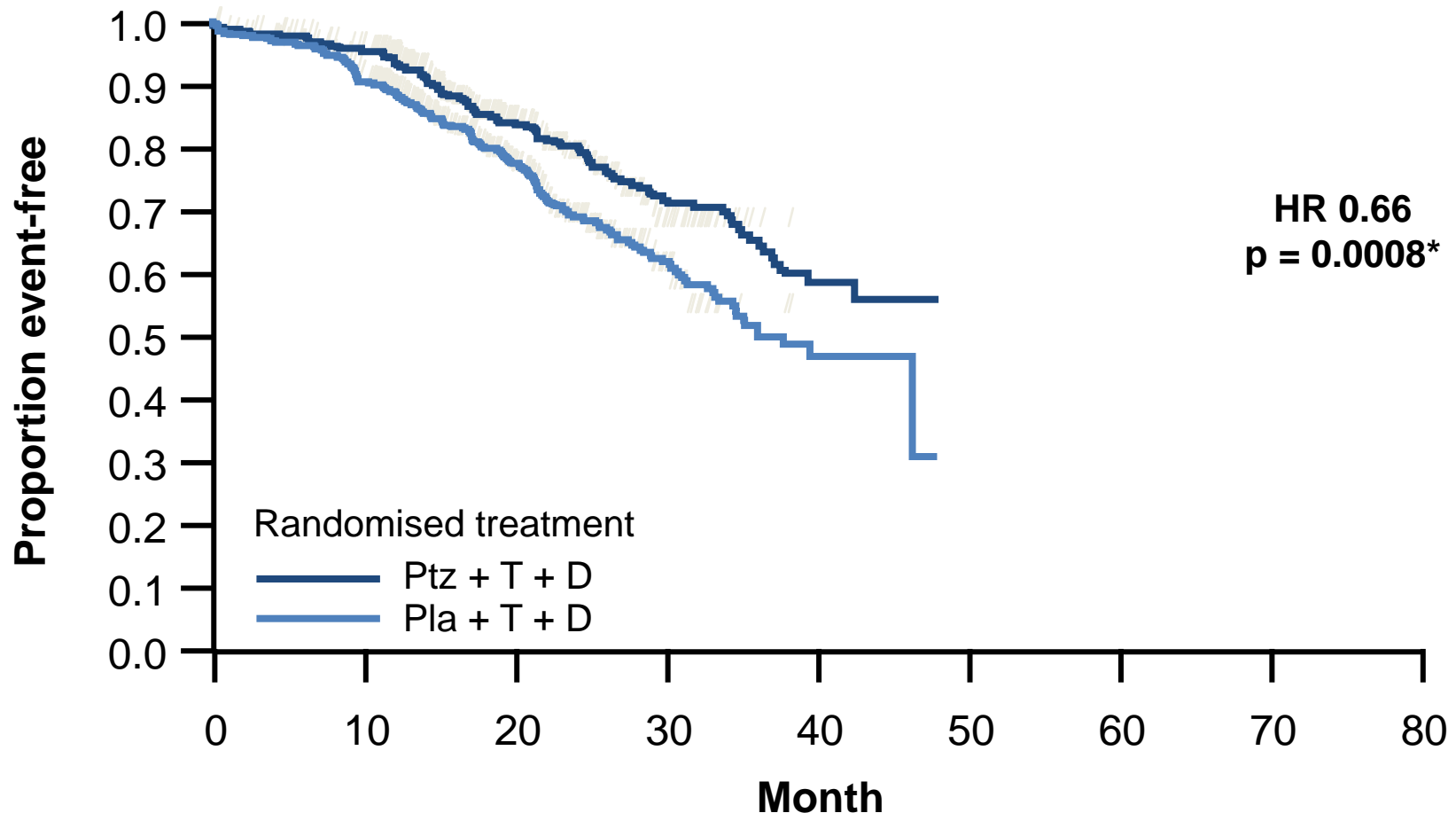
- Investigator-assessed PFS, objective response rate, safety, OS, final analysis planned at 385 deaths, with two interim analyses at 165 and 267 deaths

* < 6 cycles allowed for unacceptable toxicity or PD; > 6 cycles allowed at investigator discretion. Dose escalated to 100mg/m² if tolerated
HER2, human epidermal growth factor receptor 2; PD, progressive disease.

Overall survival 1st interim analysis: May 2011

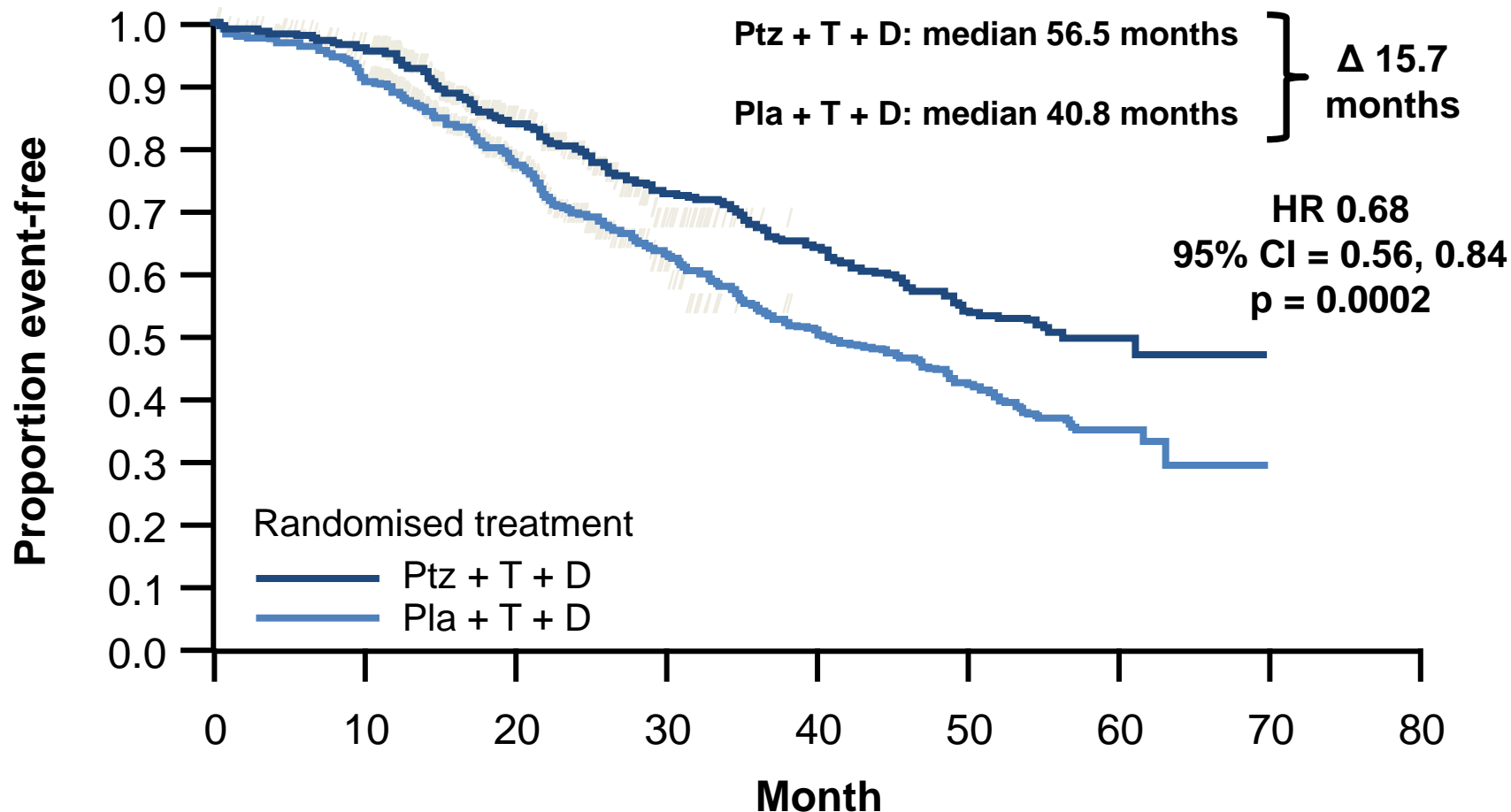


Overall survival 2nd interim analysis: May 2012



* Crossed the prespecified O'Brien-Fleming stopping boundary ($HR \leq 0.739$; $p \leq 0.0138$)

Overall survival final analysis: Feb 2014



Median follow-up of 50 months (range 0–70 months) at final analysis

Grade ≥ 3 Adverse Events

Incidence $\geq 5\%$

| Safety population | Placebo + T + D (n = 396), % | Pertuzumab + T + D (n = 408), % |
|---------------------|------------------------------------|---------------------------------------|
| Neutropenia | 46.2 | 49.0 |
| Leukopenia | 14.9 | 12.3 |
| Febrile neutropenia | 7.6 | 13.7 |
| Diarrhea | 5.1 | 9.3 |

- No cumulative toxicities

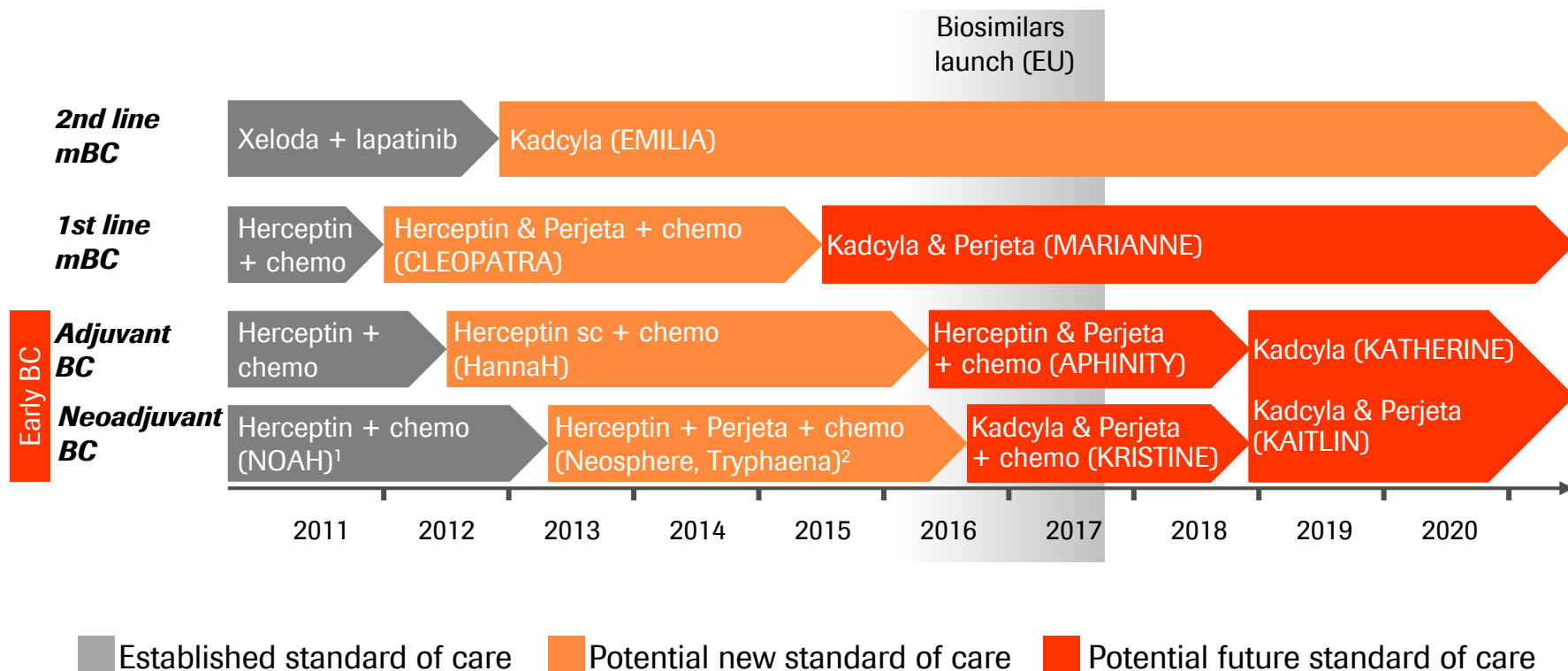
CLEOPATRA Conclusions

- First-line treatment with pertuzumab, trastuzumab, and docetaxel significantly improved OS for patients with HER2-positive MBC compared with placebo, trastuzumab, and docetaxel
 - Median OS increased by 15.7 months from 40.8 to 56.5 months
 - Survival benefit consistent across subgroups
 - Investigator-assessed PFS benefit maintained
- No new safety concerns seen with longer follow-up
 - No evidence of cumulative or late toxicity
 - Long-term cardiac safety maintained

The 56.5-month median OS is unprecedented in this indication and confirms the pertuzumab regimen as first-line standard of care for patients with HER2-positive MBC

HER2 franchise update

Improving standard of care in HER2-positive breast cancer in all lines of treatment



NEOSPHERE study filed for neoadjuvant breast cancer indication in EU

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Melanoma

Cobimetinib + Zelboraf in metastatic BRAF-mutated melanoma frontline setting: phase 3 coBRIM

Safety and efficacy of cobimetinib + Zelboraf vs Zelboraf alone

coBRIM study design

Published online in the New England Journal of Medicine; Larkin et al., Combined Vemurafenib and Cobimetinib in BRAF-Mutated Melanoma

Primary endpoint:

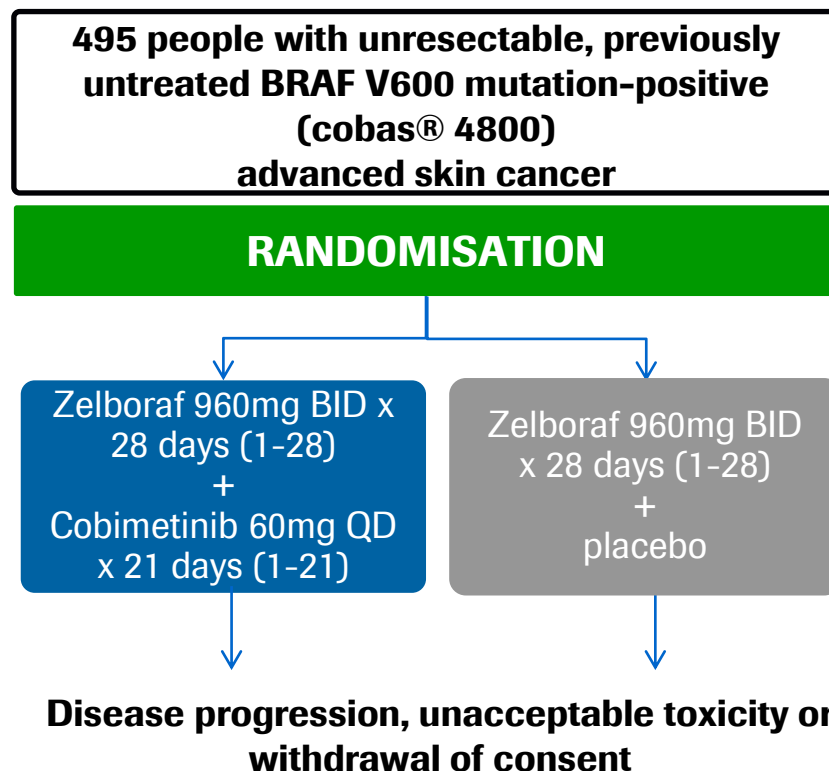
- Investigator-assessed progression-free survival (PFS)

Key secondary endpoints:

- Overall survival (OS)
- Independent Review Committee assessed PFS
- Objective response rate (ORR)

Stratification:

- Geographic region and extent of disease (M1c vs. other)



coBRIM: Cobimetinib plus Zelboraf significantly improved PFS

| | Vemurafenib + placebo | Vemurafenib + cobimetinib |
|---|------------------------------|------------------------------|
| No. of PFS events | 128 | 79 |
| Median PFS, months (95% CI), by investigators | 6.2 (2.6, 7.4) | 9.9 (9.0, NE) |
| Hazard ratio (95% CI) p value | 0.51 (0.39, 0.68) <0.0001 | |
| Median PFS, months (95% CI), IRC*-assessed | 6.0 (5.6, 7.5) | 11.3 (8.5, NE) |
| Hazard ratio (95% CI) p value | 0.60 (0.45-0.79) 0.0003 | |

- Cobimetinib plus Zelboraf combo: filed in Europe
- Fast-track designation in US; FDA filing expected Q4 2014

coBRIM: Overall Survival and overall response rates

| | Vemurafenib + placebo | Vemurafenib + cobimetinib |
|-------------------------------------|----------------------------|------------------------------|
| No. of OS events | 51 | 34 |
| Median OS | NE | NE |
| Hazard ratio (95% CI) p value | 0.65 (0.42, 1.00) 0.046 | |
| Confirmed ORR - %* (95% CI) | 45 (38.5, 51.2) | 68 (61.4, 73.4) |
| Complete Response, n (%) | 11 (4) | 25 (10) |

Cobimetinib plus Zelboraf combination regimen has a competitive ORR

coBRIM: Overall safety summary

Safety profile of combination consistent with previous studies

| | Zelboraf + Placebo (n=239) | Zelboraf + Cobimetinib (n=254) |
|---|----------------------------------|--------------------------------------|
| Total number of patients with at least 1 adverse event (AE), n (%) | 233 (98) | 250 (98) |
| Total number of patients with at least 1 of the following: | | |
| Grade \geq 3 AE, n (%) | 142 (59) | 165 (65) |
| Grade 5 AE, n (%) | 3 (1) | 6 (2) |
| Serious AE, n (%) | 60 (25) | 75 (30) |
| AE leading to withdrawal of vemurafenib, n (%) | 32 (13) | 35 (14) |
| AE leading to withdrawal of cobimetinib/placebo, n (%) | 33 (14) | 42 (17) |
| AE leading to withdrawal of both cobimetinib and vemurafenib, n (%) | 28 (12) | 37 |

coBRIM: Summary and conclusions

Combined BRAF and MEK inhibition results in improved clinical outcomes

Efficacy

- The combination of cobimetinib plus Zelboraf compared to Zelboraf alone resulted in:
 - 49% reduction in risk of progression (HR = 0.51; 95% CI, 0.39 to 0.68; P<0.0001)
 - A median PFS of 9.9 months vs 6.2 months
 - The frequency of complete and partial response of 68% versus 45% (P<0.0001)
 - Interim OS showed a reduction in risk of death - *magnitude to be disclosed this afternoon*

Safety

- The addition of cobimetinib to Zelboraf was tolerable and consistent with the adverse event profile of the combination
 - The frequency of grade ≥ 3 AEs was 65% vs 59%
 - There was no difference in the rate of study drug discontinuation between arms
 - The frequency of secondary cutaneous neoplasms decreased

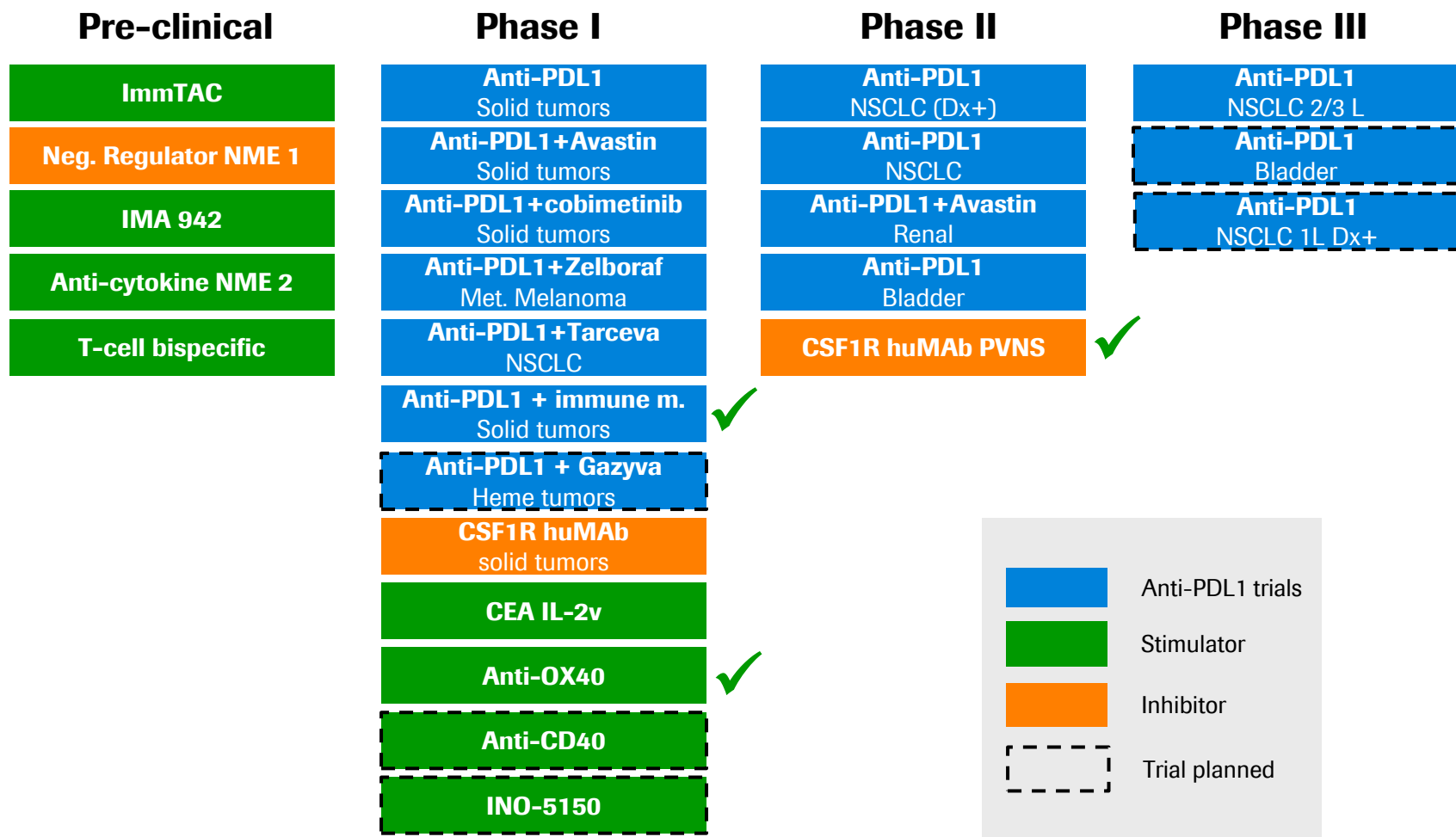
- **Strong clinical benefit supported filing**
- **Mature OS data expected 2015**
- **Metastatic melanoma treatment options are expanding rapidly**

Update on cancer immunotherapy

Cathi Ahearn, Lifecycle Leader anti-PDL1, Genentech

Cancer immunotherapy at Roche

Pipeline overview



Note: Anti-PDL1 is listed as MPDL3280A in clinicaltrials.gov

MPDL3280A - The present and the future

Monotherapy

Phase I results

- mUBC
- mRCC
- Loc adv /mNSCLC

Active clinical trials

- mRCC (Ph II)
- mUBC (Ph II)
- Loc adv /mNSCLC (Ph II 'BIRCH', 'POPLAR', 'FIR', Ph III 'OAK')
- Solid tumours & heme (Ph I)

Planned clinical trial

- Ph III Dx+ 1L NSCLC
- Ph III mUBC

Immune doublets

Active clinical trial

- Loc adv/ metastatic solid tumours with ipilimumab or Interferon alfa-2b (Ph I)

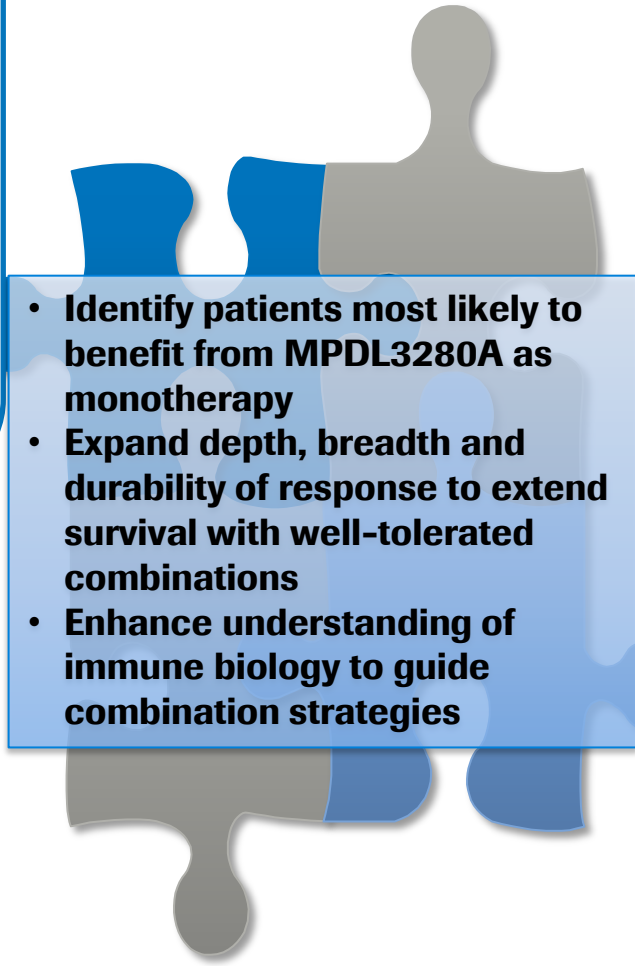
Combination with chemotherapy

Phase Ib results

- mCRC with Avastin + FOLFOX

Active clinical trial

- Loc adv /metastatic solid tumours: with Avastin +/- chemotherapy (Ph Ib)

- 
- **Identify patients most likely to benefit from MPDL3280A as monotherapy**
 - **Expand depth, breadth and durability of response to extend survival with well-tolerated combinations**
 - **Enhance understanding of immune biology to guide combination strategies**

Combination with targeted therapy

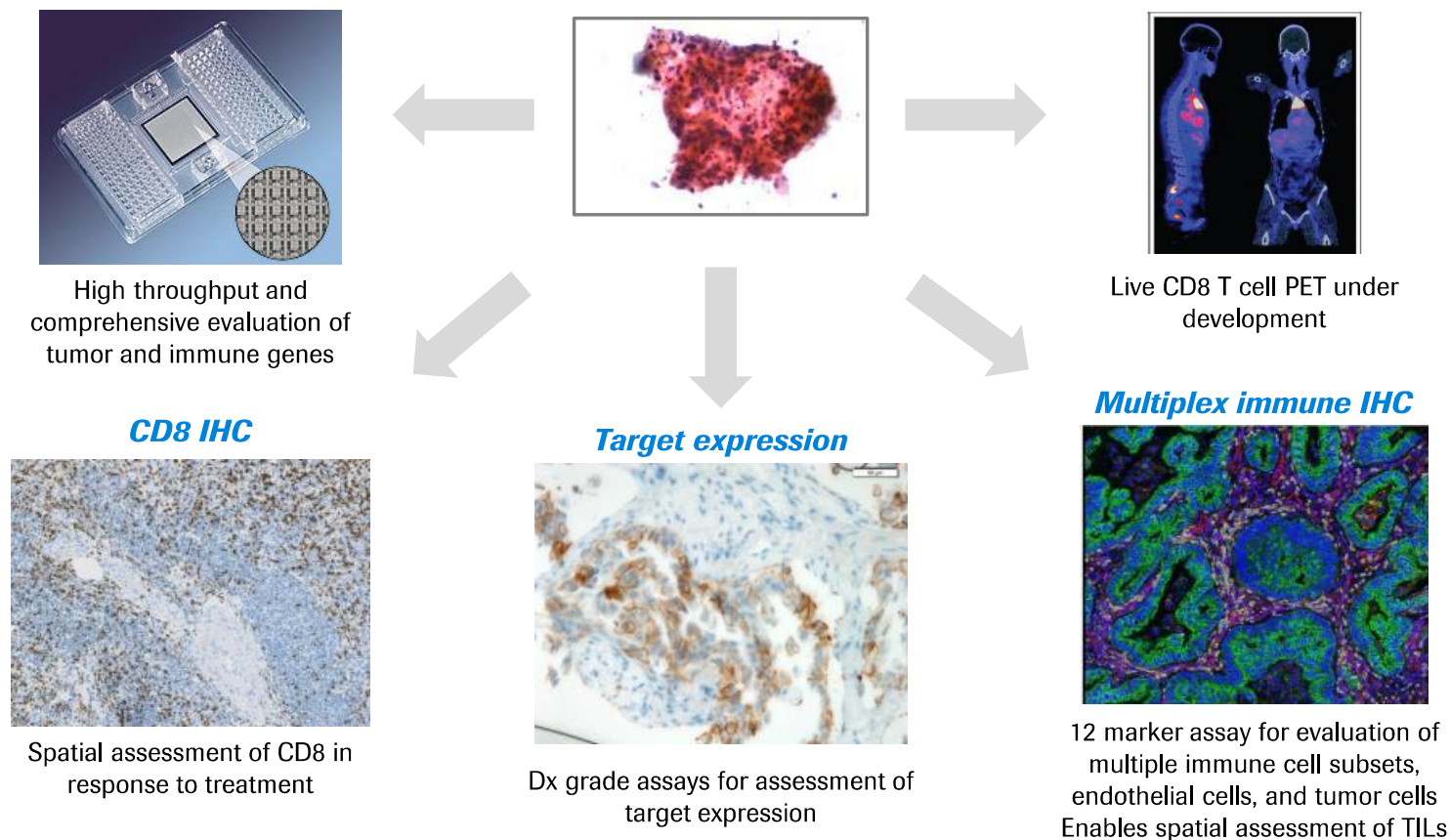
Phase I results

- mRCC with Avastin
- mCRC with Avastin

Active clinical trials

- mRCC with Avastin (Ph II)
- EGFR+ NSCLC w/Tarceva (Ph Ib)
- mMel with vemurafinib (Ph Ib)
- Solid tumours with Avastin (Ph Ib)
- Solid tumors w/cobimetinib (Ph Ib)
- Lymphoma with Gazyva (Ph Ib)

Comprehensive approach to biomarker discovery



- Identify the right indications to test our hypotheses
- Identify patients who may best respond to our therapies
- Understand what drives resistance to develop informed combination strategies

Agenda

Update on cancer immunotherapy

MPDL3280A (anti-PDL1) in solid tumors

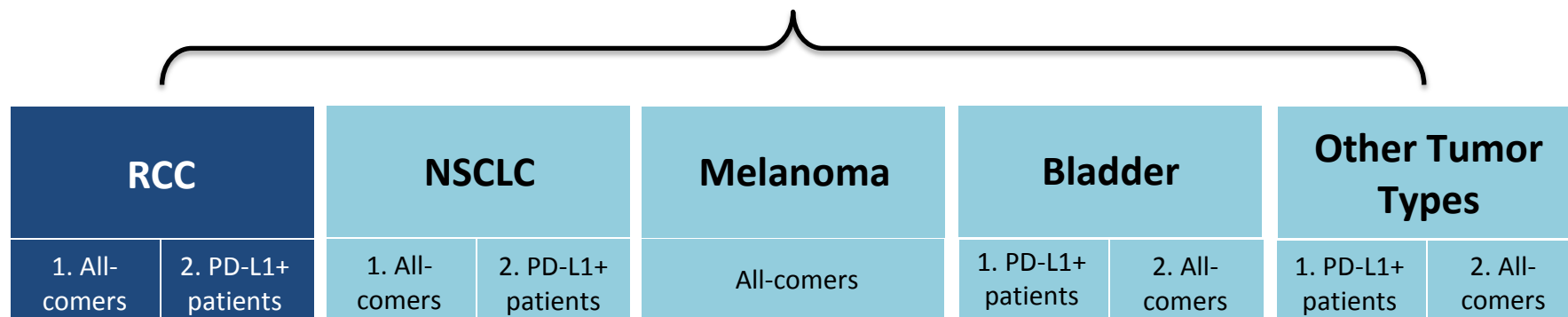
Metastatic renal cell carcinoma monotherapy (phase 1a) & combination with Avastin

Combination with Avastin +/- chemo (FOLFOX) in advanced solid tumors (phase 1b)

Clinical activity in metastatic urothelial bladder cancer (phase 1 update)

MPDL3280A Phase Ia

Phase Ia Expansion Ongoing



MPDL3280A administered by IV q3w for up to 16 cycles

Key Eligibility Criteria

Measurable disease per RECIST v1.1
ECOG PS 0 or 1

- First RCC patient was enrolled on Dec 12, 2011. Last RCC patient was enrolled on Jul 18, 2013

MPDL3280A: Treatment-Related Adverse Events

Safety-evaluable population with RCC in Phase I expansion

- Median duration of treatment was 239 days (21-834 days)
- 80% of patients experienced a treatment-related AE
- Treatment-related Grade 3 AEs occurred in 11 patients (16%), including anemia (4%), dehydration (3%), fatigue (3%) and hypophosphatemia (3%)
- No treatment-related Grade 4 AEs or deaths were reported

| Patients with RCC, N = 69 (Data cutoff Apr 21, 2014) | All Grade n (%) | Grade 3-4 n (%) |
|---|--------------------|--------------------|
| Fatigue | 15 (22%) | 2 (3%) |
| Decreased appetite | 11 (16%) | 0 |
| Arthralgia | 10 (15%) | 0 |
| Rash | 10 (15%) | 0 |
| Diarrhea | 8 (12%) | 0 |
| Pruritus | 8 (12%) | 0 |
| Pyrexia | 8 (12%) | 0 |
| Chills | 7 (10%) | 0 |
| Nausea | 7 (10%) | 0 |

Includes all grade events occurring in ≥ 7patients (10%).

McDermott et al., 26-30 September 2014, Madrid, Spain

MPDL3280A: Efficacy by PD-L1 IHC (IC)

Efficacy-evaluable population with clear cell RCC

| PD-L1 IHC - tumor-infiltrating immune cells (IC) ^a , n = 62 | ORR (95% CI), % |
|---|-----------------|
| Overall | 15% (8-25) |
| IHC (IC) 1/2/3 | 20% (9-37) |
| IHC (IC) 0 | 10% (2-30) |

- 24-week PFS rate was 51% (95% CI: 38-63)
- 1 CR (IHC [IC] 3)
- ORR for Fuhrman grade 4 or sarcomatoid clear cell RCC (n = 18) was 22% (95% CI: 8, 47)
- Higher response rate observed in MSKCC poor-risk patients with PD-L1 IHC 1/2/3 expression

^a A PD-L1+ cohort of patients was enrolled. 6 patients had unknown PD-L1 IHC (IC) status.

Investigator-assessed confirmed ORRs per RECIST v1.1.

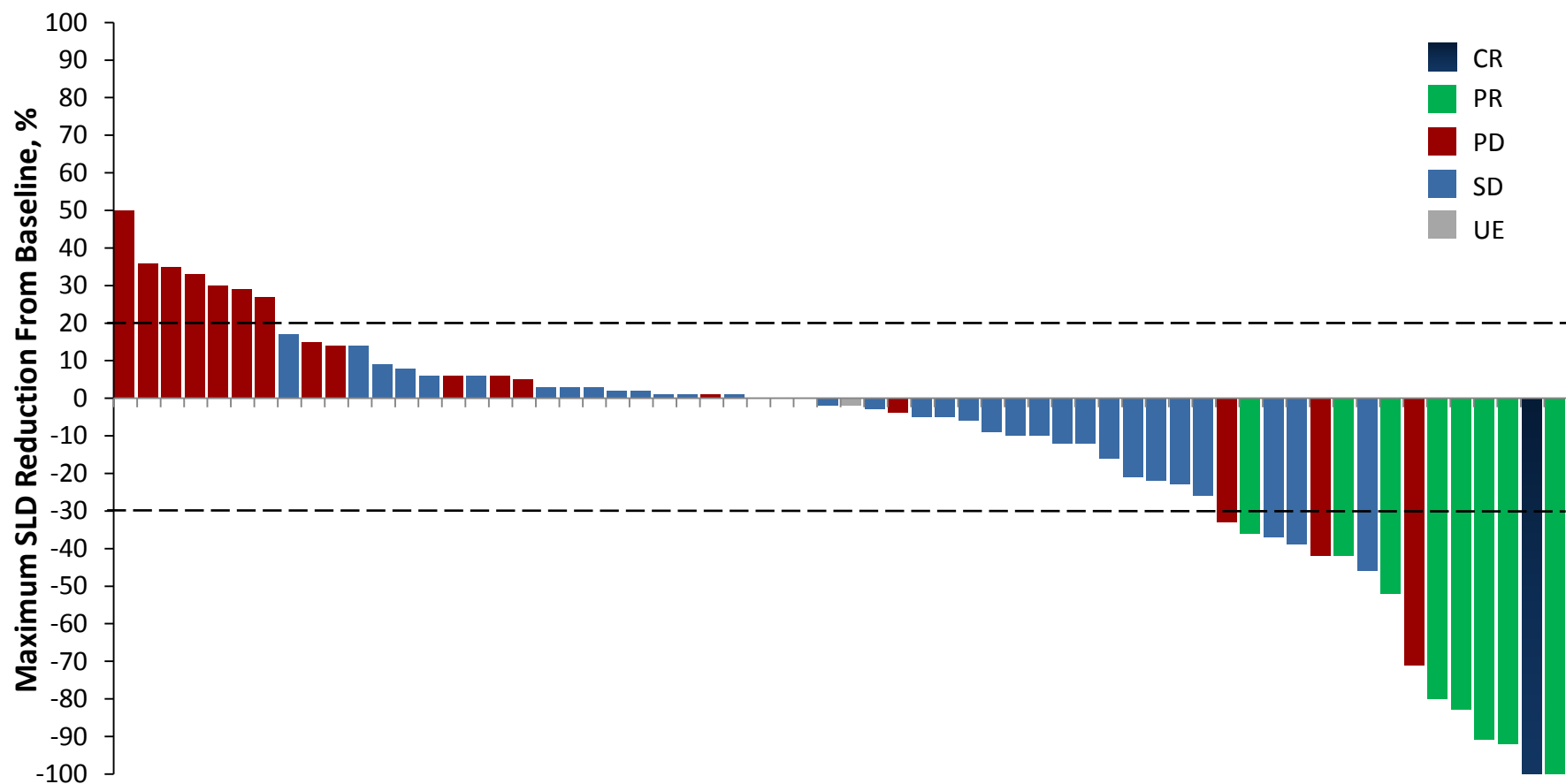
Patients dosed by Oct 21, 2013; data cutoff Apr 21, 2014.

IHC 3: ≥ 10% of ICs are PD-L1+; IHC 2: ≥ 5% but < 10% of ICs are PD-L1+; IHC 1: ≥ 1 % but < 5% of ICs are PD-L1+; IHC 0: < 1% are PD-L1+.

McDermott et al., 26-30 September 2014, Madrid, Spain

MPDL3280A: Summary of ORR in Clear Cell RCC

Efficacy-evaluable population with clear cell RCC in Phase I expansion



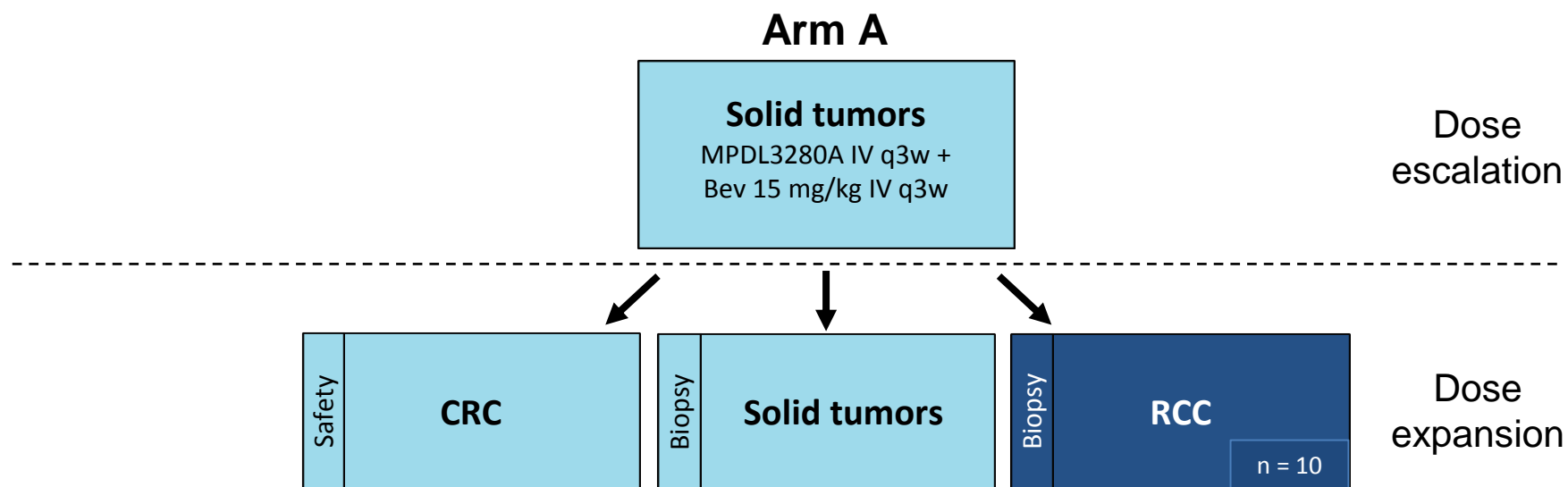
- Median duration of follow-up was 9 months (range, 1-27 months)

Patients dosed by Oct 21, 2013; data cutoff Apr 21, 2014. Investigator-assessed confirmed ORRs per RECIST v1.1.

CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease; UE, unable to evaluate.

McDermott et al., 26-30 September 2014, Madrid, Spain

MPDL3280A + Bevacizumab: Phase Ib Study Design Arm A^a

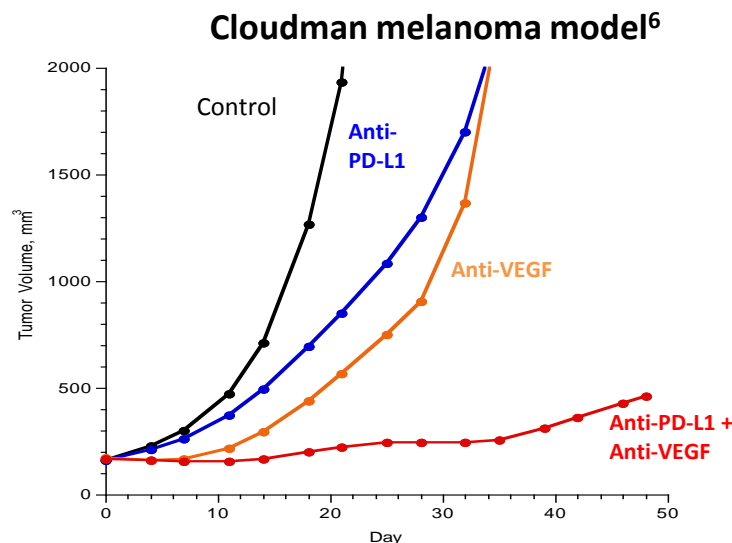


- Primary objectives: safety, tolerability, DLT and MTD
- Secondary objectives: preliminary anti-tumor activity and PK

^a Lieu et al., abstract 10490, presented Saturday.

Rationale to Combine MPDL3280A With Bevacizumab

- Single agent bevacizumab (10 mg/kg) has demonstrated a 10% ORR [95% CI: 2.9, 24.2] in RCC¹
- Anti-VEGF therapy has immunomodulatory properties
 - Increases trafficking of T cells into tumors^{2,3}
 - Reduces suppressive cytokines and infiltrating Tregs and MDSCs^{4,5}



MDSC, myeloid-derived suppressor cell; Tregs; regulatory T cells .

1. Yang. *NEJM*. 2003. 2. Manning. *Clin Cancer Res*. 2007. 3. Shrimali. *Cancer Res*. 2010. 4. Kutsmartsev. *J Immunol*. 2008. 5. Roland. *PLOS One*. 2009. 6. Genentech, data on file.

MPDL3280A + Bevacizumab: Summary of Phase Ib Results

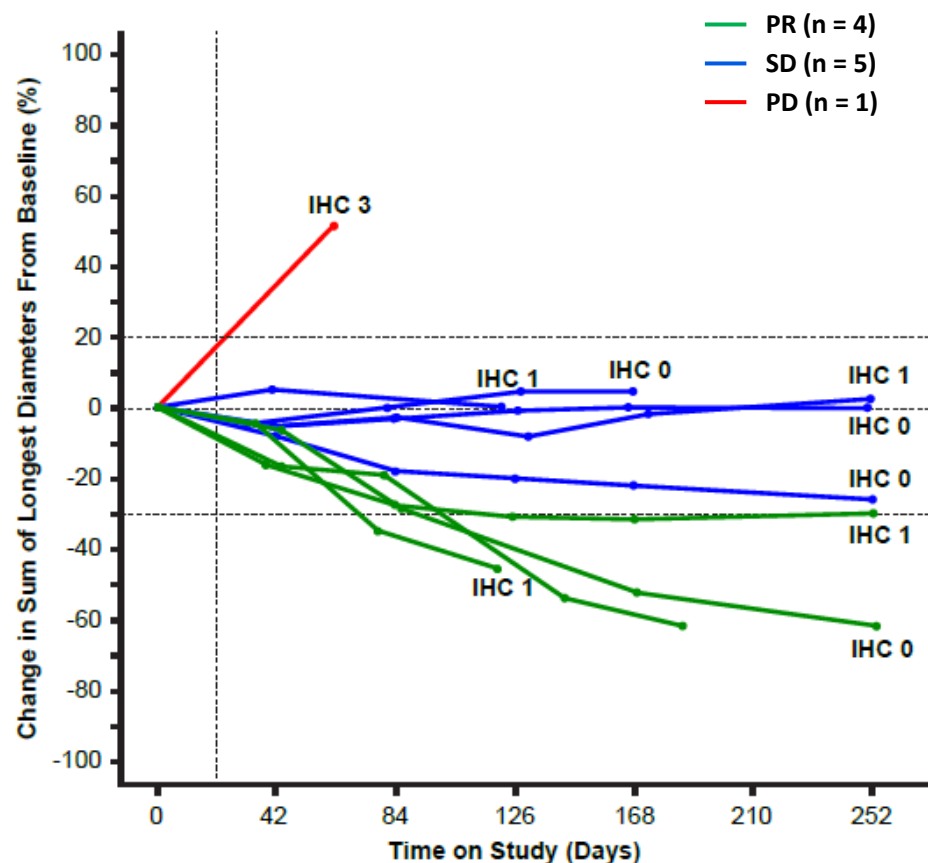
Safety and efficacy of patients in Arm A^a

- Safety

- All patients in Arm A (n = 35) experienced an AE, with 49% experiencing a G3-4 AE, regardless of attribution
- 1 MPDL3280A-related Grade 3 AE occurred (1 case of neutropenia in Arm A)
- No Grade 4 AEs or deaths were attributed to MPDL3280A

- Efficacy in patients with 1L clear cell RCC

- 4 of 10 patients demonstrated an objective response
- 5 of 10 patients experienced stable disease
- Responding patients included 2 with IHC (IC) 1, 1 with IHC (IC) 0 and 1 with IHC (IC) unknown



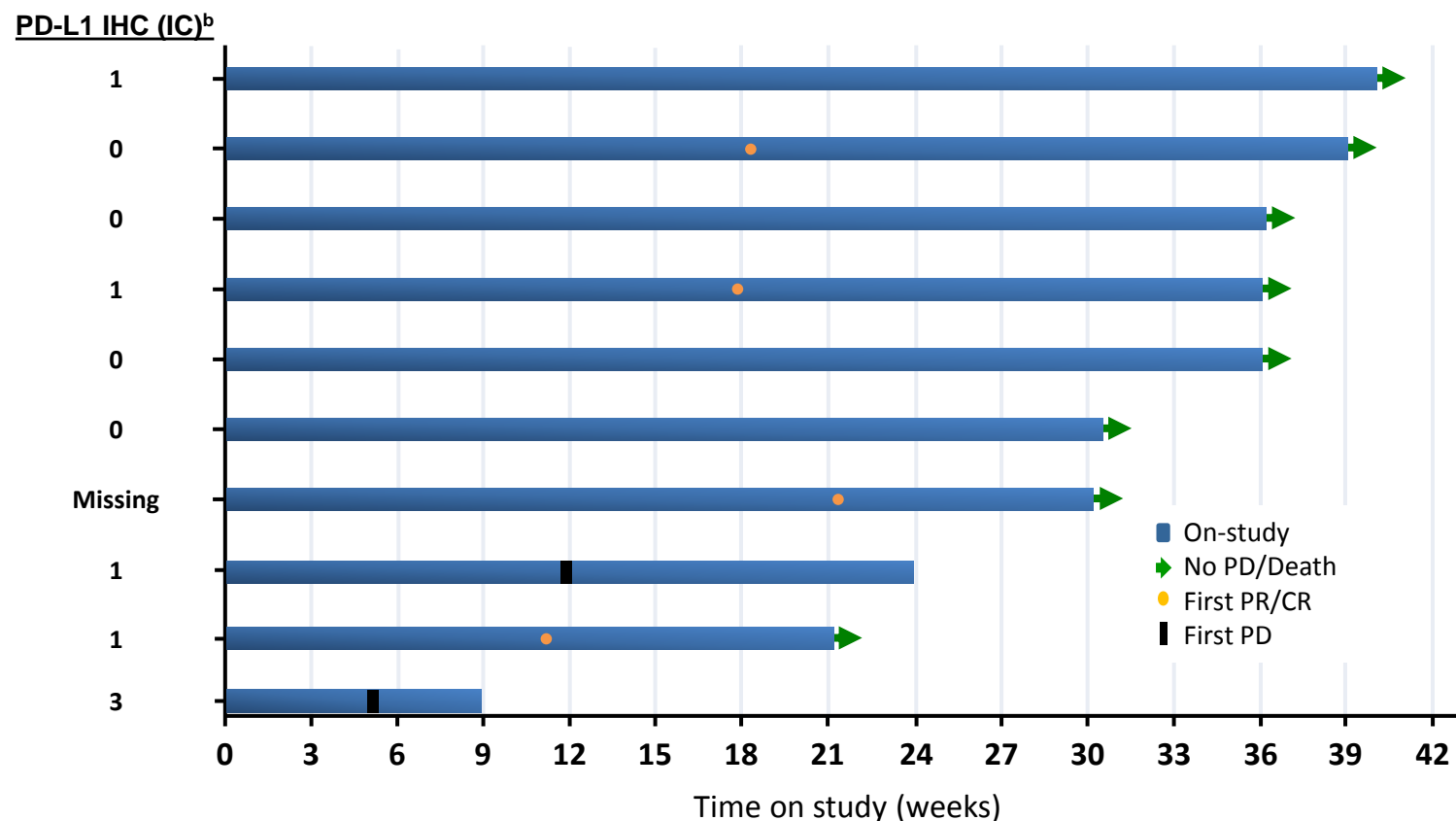
^a Lieu et al., abstract 10490, presented Saturday.

Patients dosed by Apr 7, 2014; data cutoff Jul 7, 2014; Unconfirmed best responses by RECIST v1.1.

IHC 3: ≥ 10% of ICs are PD-L1+; IHC 2: ≥ 5% and < 10% of ICs are PD-L1+. IHC 1: ≥ 1% and < 5% of ICs are PD-L1+; IHC 0: < 1% ICs are PD-L1+.

MPDL3280A + Bevacizumab: Duration of Treatment and Response in 1L RCC

Efficacy-evaluable population with 1L clear cell RCC in Arm A^a



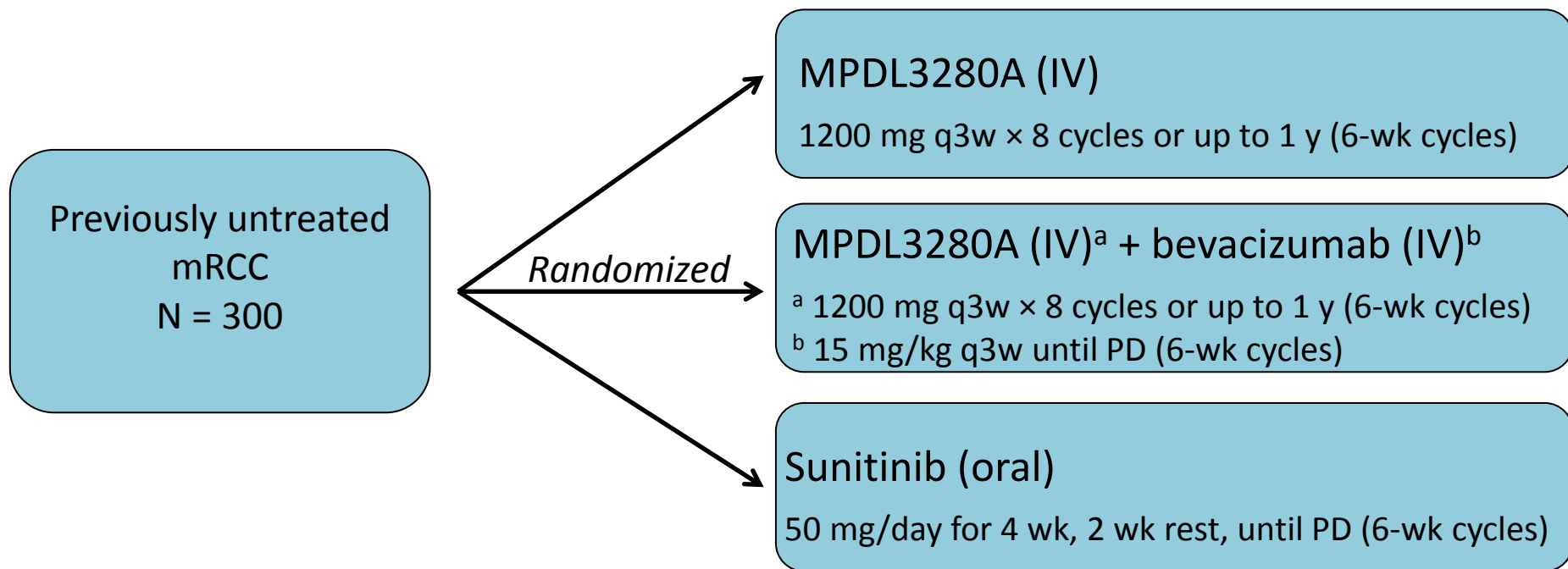
- SD \geq 24 weeks in 4 patients
- 9 of 10 patients with mRCC remain on study treatment

^a Lieu et al., abstract 10490, presented Saturday.

Patients dosed by Apr 7, 2014 who had at least 1 scan; data cutoff Jul 7, 2014.

^b IHC 3: \geq 10% of ICs are PD-L1+; IHC 2: \geq 5% and $<$ 10% of ICs are PD-L1+; IHC 1: \geq 1% and $<$ 5% of ICs are PD-L1+; IHC 0: $<$ 1% ICs are PD-L1+.

Study WO29074 MPDL3280A: Phase II Trial in mRCC (NCT01984242)



- Key objectives: evaluate efficacy of sunitinib vs MPDL3280A as monotherapy or in combination with bevacizumab
- Primary endpoint: PFS per RECIST v1.1
- Crossover allowed

MPDL3280A in RCC: Conclusions

- MPDL3280A was well tolerated in RCC
 - Both as a single agent and in combination with bevacizumab
- MPDL3280A demonstrated promising efficacy in previously treated clear cell mRCC
 - Median PFS = 24 weeks (5-98+)
 - ORR = 22% for Furhman grade 4 or sarcomatoid clear cell mRCC
- Preliminary data indicate that that patients with IHC 1/2/3 tumors had better efficacy vs patients with IHC 0 tumors
- MPDL3280A demonstrated clinical activity in combination with bevacizumab in 1L clear cell mRCC
 - ORR = 40%; SD = 50%

Agenda

Update on cancer immunotherapy

MPDL3280A (anti-PDL1) in solid tumors

Metastatic renal cell carcinoma monotherapy (phase 1a) & combination with Avastin

Combination with Avastin +/- chemo (FOLFOX) in advanced solid tumors (phase 1b)

Clinical activity in metastatic urothelial bladder cancer (phase 1 update)

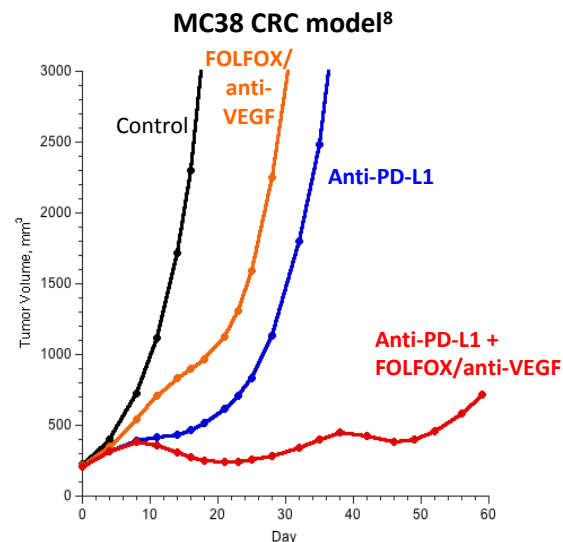
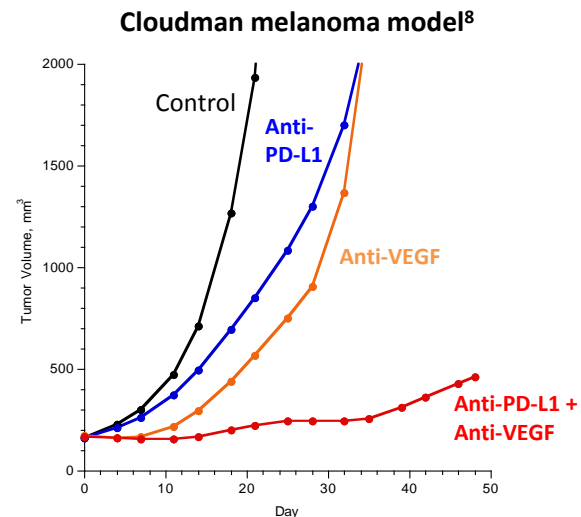
Rationale to Combine MPDL3280A With Bevacizumab and FOLFOX

- Anti-VEGF therapy has immunomodulatory properties
 - Increases trafficking of T cells into tumors^{1,2}
 - Reduces suppressive cytokines and infiltrating Tregs and MDSCs^{3,4}
- FOLFOX may have immunogenic effects
 - 5-FU reduces tumor-associated MDSCs and increases CD8 tumor-infiltrating lymphocytes⁵
 - Oxaliplatin induces immunogenic cell death (calreticulin exposure, release of ATP and HMGB1)^{6,7}

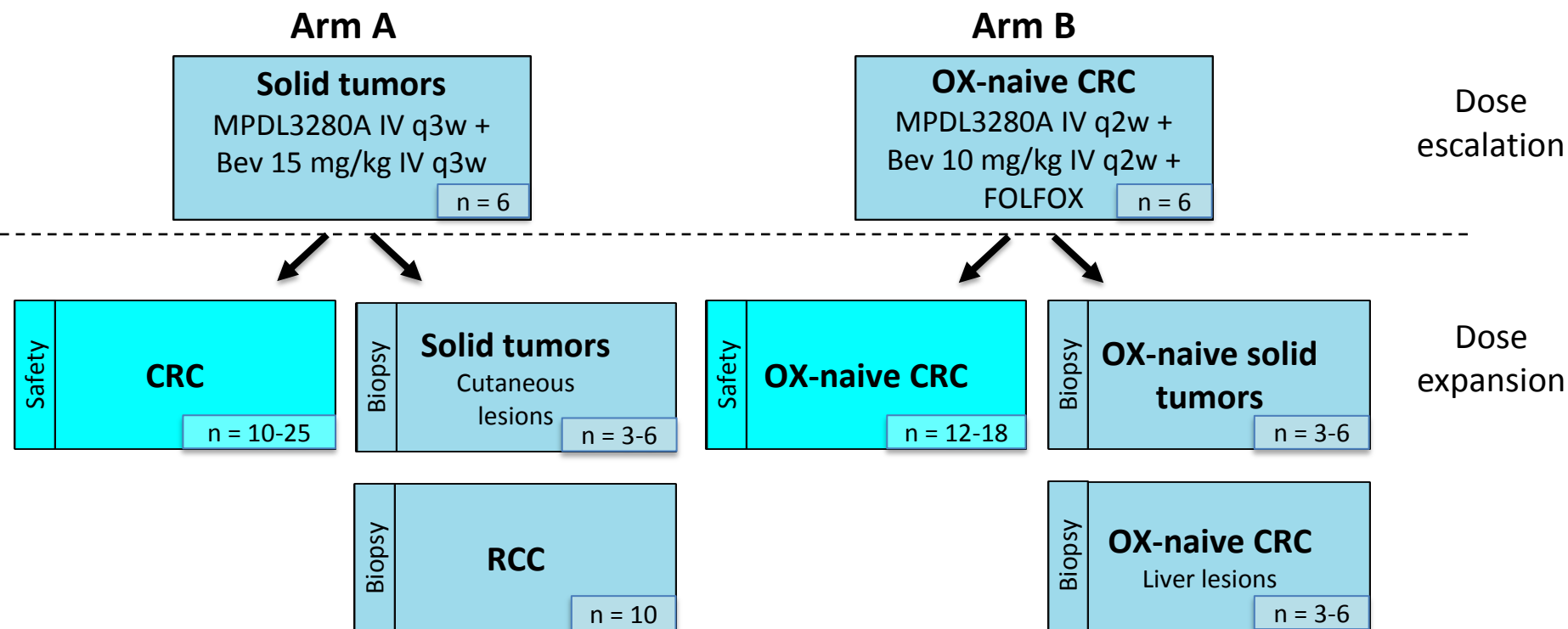
MDSC, myeloid-derived suppressor cell.

1. Manning. *Clin Cancer Res.* 2007. 2. Shrimali. *Cancer Res.* 2010. 3. Kutsmartsev. *J Immunol.* 2008. 4. Roland. *PLOS One.* 2009. 5. Vincent. *Cancer Res.* 2010. 6. Michaud. *Science.* 2011. 7. Tesniere. *Oncogene.* 2010. 8. Genentech, data on file.

Lieu et al., 26-30 September 2014, Madrid, Spain



Phase Ib Study Design



- Primary objectives: safety and tolerability, DLT and MTD
- Secondary objectives: preliminary anti-tumor activity and PK

n represent target enrollments.
Bev, bevacizumab; OX, oxaliplatin.

Adverse Events

- All Grade AEs attributed to MPDL3280A: Arm A 77%; Arm B 78%
- Grade 3 AEs attributed to MPDL3280A: Arm A 3%; Arm B 17%
- No Grade 4 AEs or deaths related to MPDL3280A

AEs Regardless of Attribution

| AEs in ≥ 13 patients in at least 1 Arm, n (%) | Arm A, n = 35 | | Arm B, n = 36 | |
|---|---------------|-----------|---------------|-----------|
| | All Grade | Grade 3-4 | All Grade | Grade 3-4 |
| All | 35 (100%) | 17 (49%) | 36 (100%) | 24 (67%) |
| Peripheral neuropathy | 2 (6%) | 0 | 25 (69%) | 0 |
| Fatigue | 16 (46%) | 0 | 24 (67%) | 1 (3%) |
| Diarrhea | 11 (31%) | 0 | 21 (58%) | 4 (11%) |
| Nausea | 13 (37%) | 0 | 18 (50%) | 0 |
| Temperature intolerance | 1 (3%) | 0 | 18 (50%) | 0 |
| Neutropenia | 1 (3%) | 1 (3%) | 16 (44%) | 14 (39%) |
| Decreased appetite | 9 (26%) | 0 | 15 (42%) | 0 |
| Pyrexia | 13 (37%) | 1 (3%) | 9 (25%) | 0 |
| Vomiting | 7 (20%) | 0 | 13 (36%) | 0 |

Grade 3-4 AEs Regardless of Attribution

| AEs in ≥ 2 patients in at least 1 Arm, n (%) | Arm A, n = 35 | Arm B, n = 36 |
|--|---------------|---------------|
| | Grade 3-4 | Grade 3-4 |
| All | 17 (49%) | 24 (67%) |
| Neutropenia | 1 (3%) | 14 (39%) |
| Diarrhea | 0 | 4 (11%) |
| Abdominal pain | 3 (9%) | 1 (3%) |
| Hypertension | 3 (9%) | 1 (3%) |
| Pneumonia | 3 (9%) | 0 |
| AST increased | 0 | 3 (8%) |
| ALT increased | 0 | 3 (8%) |
| Hyperbilirubinemia | 2 (6%) | 0 |
| Tumor pain | 2 (6%) | 0 |

Summary of Responses

MPDL3280A + Bevacizumab

| Indication | n | ORR |
|------------|----|-----|
| 1L RCC | 10 | 40% |
| CRC | 13 | 8% |

Minimum follow-up in Arm A: 2.1 months for 1L RCC and 1.9 months for CRC

MPDL3280A + Bevacizumab + FOLFOX

| Indication | n | ORR |
|------------|----|-----|
| CRC | 25 | 36% |
| 1L CRC | 18 | 44% |

Minimum follow-up in Arm B: 2.2 months for CRC

- Responses in other cohorts
 - Arm A: melanoma (1/4 PR), breast cancer (1/1 PR)
 - Arm B: RCC (1/1 CR), breast cancer (1/2 PR)

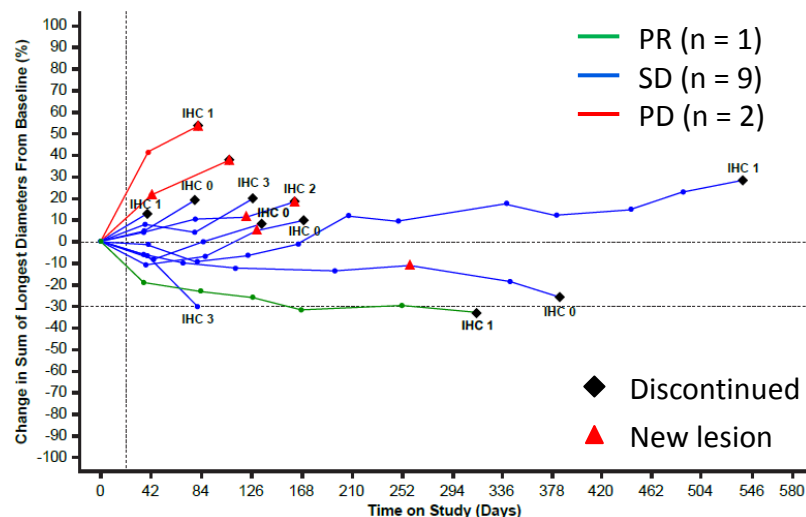
Investigator-assessed unconfirmed response per RECIST v1.1.

Efficacy evaluable patients dosed by April 7, 2014, who had at least 1 scan; data cutoff, July 7, 2014.

Lieu et al., 26-30 September 2014, Madrid, Spain

Tumor Burden Over Time in CRC

MPDL3280A + Bevacizumab



- SD \geq 24 weeks in 2 patients
- Median duration of follow-up: 5.6 months

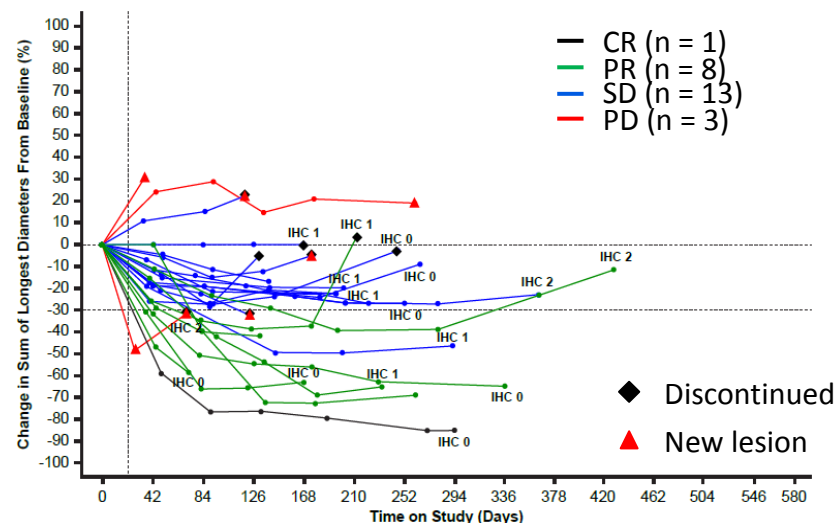
Investigator-assessed unconfirmed response per RECIST v1.1.

Does not include 2 patients: 1 patient did not have a scan post baseline and another patient had 1 target lesion that was not evaluable.

IHC 3, 2, 1, 0: $\geq 10\%$, $\geq 5\%$ and $< 10\%$, $\geq 1\%$ and $< 5\%$, $< 1\%$ tumor-infiltrating immune cells positive for PD-L1, respectively; IHC status not available for 1 patient.

Efficacy evaluable patients dosed by April 7, 2014, who had at least 1 scan; data cutoff, July 7, 2014.

MPDL3280A + Bevacizumab + FOLFOX



- SD \geq 24 weeks in 8 patients
- Several patients had PRs as early as 6 weeks (first scan)
- Median duration of follow-up: 8.8 months

Investigator-assessed unconfirmed response per RECIST v1.1. For 1 patient, the sum of longest diameters could not be computed after RECIST overall assessment of SD because one of the target lesions was unevaluable at TA2. A new lesion was also identified at this visit.

IHC 3, 2, 1, 0: $\geq 10\%$, $\geq 5\%$ and $< 10\%$, $\geq 1\%$ and $< 5\%$, $< 1\%$ tumor-infiltrating immune cells positive for PD-L1, respectively; IHC status not available for 9 patients.

Efficacy evaluable patients dosed by April 7, 2014, who had at least 1 scan; data cutoff, July 7, 2014.

Conclusions

- MPDL3280A combination therapy with bevacizumab and bevacizumab + FOLFOX was well tolerated without exacerbation of bevacizumab or chemotherapy-associated adverse events
- Responses were observed in a variety of tumor types, including RCC and CRC
- Increased PD-L1 expression or activated peripheral T cells were observed with both treatment regimens
- Additional clinical trials of MPDL3280A combination therapies are planned/ongoing
 - A Phase II trial of MPDL3280A \pm bevacizumab vs sunitinib in patients with previously untreated locally advanced or metastatic RCC is currently ongoing¹
 - A randomized trial (MODUL) investigating MPDL3280A in the 1L mCRC maintenance setting is expected to start later this year²

1. www.clinicaltrials.gov. NCT01984242.

2. Schmoll, et al. ESMO 2014, abstract 612TiP.

Agenda

Update on cancer immunotherapy

MPDL3280A (anti-PDL1) in solid tumors

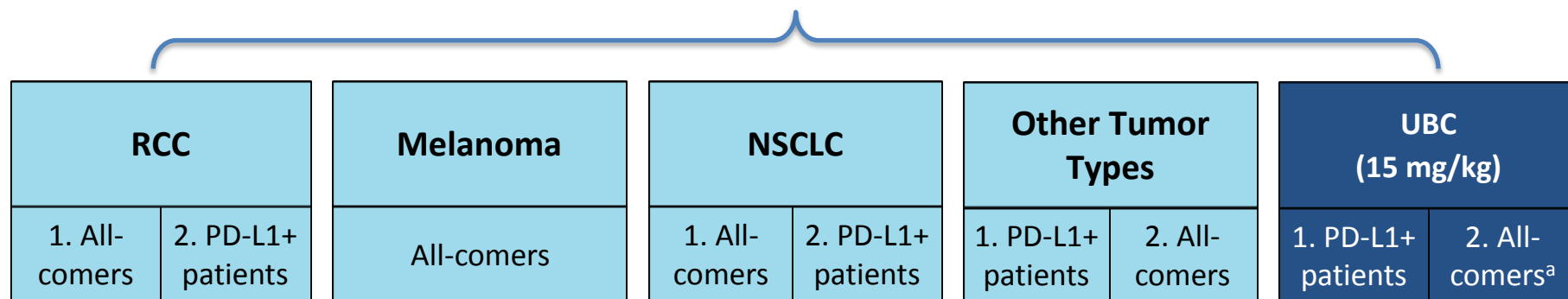
Metastatic renal cell carcinoma monotherapy (phase 1a) & combination with Avastin

Combination with Avastin +/- chemo (FOLFOX) in advanced solid tumors (phase 1b)

Clinical activity in metastatic urothelial bladder cancer (phase 1 update)

MPDL3280A Phase Ia

Phase Ia Expansion Ongoing



MPDL3280A administered by IV q3w for up to 16 cycles

Key Eligibility Criteria

*Measurable disease per RECIST v1.1
ECOG PS 0 or 1*

^a Primarily recruited PD-L1–negative patients.

MPDL3280A: Treatment-Related AEs

Safety-evaluable population with UBC in Phase I expansion

| Patients With UBC N = 74 | All Grade n (%) | Grade 3-4 ^a n (%) |
|-----------------------------|--------------------|---------------------------------|
| All | 48 (65%) | 4 (5%) |
| Fatigue | 11 (15%) | 0 |
| Decreased appetite | 9 (12%) | 0 |
| Nausea | 8 (11%) | 0 |
| Pruritus | 7 (9%) | 0 |
| Pyrexia | 7 (9%) | 0 |
| Asthenia | 5 (7%) | 1 (1%) |
| Chills | 3 (4%) | 0 |
| Dry skin | 3 (4%) | 0 |
| Influenza-like illness | 3 (4%) | 0 |
| Lethargy | 3 (4%) | 0 |
| Rash | 3 (4%) | 0 |

- Median treatment duration 95 days (5.5 cycles)
- MPDL3280A well tolerated in patients with UBC
 - No discontinuations due to treatment-related AEs
 - No investigator-assessed immune-related toxicities reported as of the clinical cutoff
- MPDL3280A not observed to be associated with renal toxicity
- No treatment-related grade 5 AEs

^a Additional treatment-related grade 3/4 AEs: One patient experienced an increase in alanine aminotransferase (grade 3), aspartate aminotransferase (grade 3) and gamma-glutamyltransferase (grade 4). Two additional patients (one each) experienced either thrombocytopenia (grade 3) or decreased blood phosphorus (grade 3). Clinical data cutoff was April 21, 2014.

Includes events occurring in ≥ 3 patients.

MPDL3280A: Summary of ORR in UBC

Efficacy-evaluable population with UBC in Phase I expansion

| PD-L1 IHC (IC) | ORR, Best Response % (95% CI) | PD-L1+ vs PD-L1– ORR, Best Response % (95% CI) |
|----------------|----------------------------------|--|
| IHC 3 (n = 10) | 60% (27, 85) | 52% (34, 69) |
| IHC 2 (n = 23) | 48% (27, 68) | |
| IHC 1 (n = 24) | 17% (6, 37) | 14% (6, 28) |
| IHC 0 (n = 12) | 8% (0, 35) | |

- 3 CRs (1 IHC 2, 2 IHC 3)
- Median follow-up was 6 months (range, 1+ to 12) for PD-L1+ patients and 4 months (range, 1+ to 7) for PD-L1– patients

Investigator-assessed ORRs (unconfirmed) per RECIST v1.1.

1 patient with unknown IHC status not included in table.

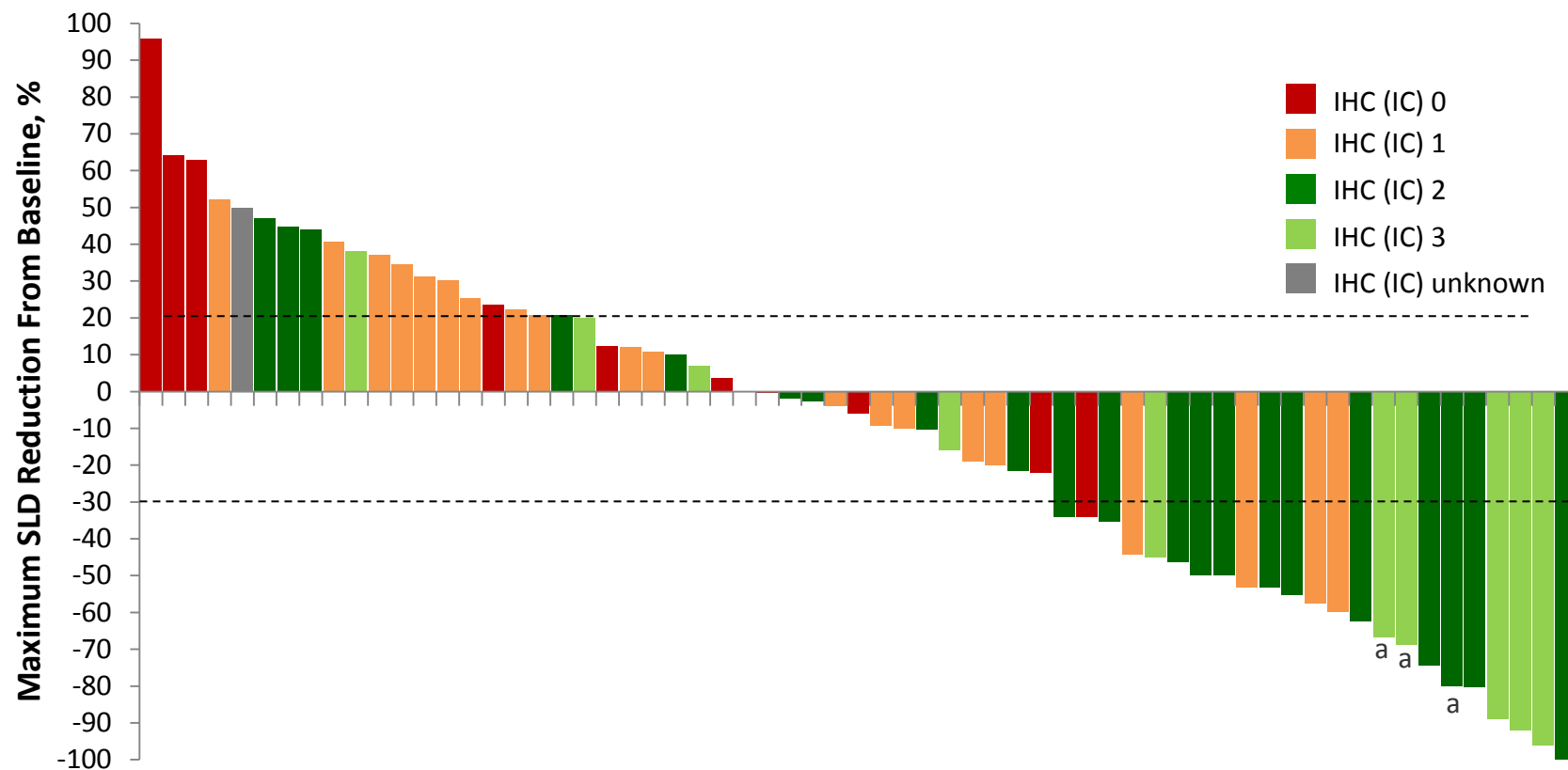
PD-L1+: IHC (IC) 2/3; PD-L1–: IHC (IC) 0/1.

Patients dosed by Jan 27, 2014 (≥ 12-wk follow-up) with measurable disease at baseline. Clinical data cutoff was Apr 21, 2014.

Bellmunt J et al., 26-30 September 2014, Madrid, Spain

MPDL3280A: Summary of ORR in UBC

Efficacy-evaluable population with UBC in Phase I expansion



^a Patients with complete responses. Patients with a CR had < 100% reduction of the target lesions due to lymph node target lesions. All lymph nodes returned to normal size per RECIST v1.1.

IC; tumor-infiltrating immune cells.

Responses are investigator assessed (unconfirmed). 7 patients are not included due to no post-baseline tumor assessments.

PD-L1+: IHC (IC) 2/3; PD-L1-: IHC (IC) 0/1.

Patients dosed by Jan 27, 2014 (≥ 12-wk follow-up) with measurable disease at baseline. Clinical data cutoff was Apr 21, 2014.

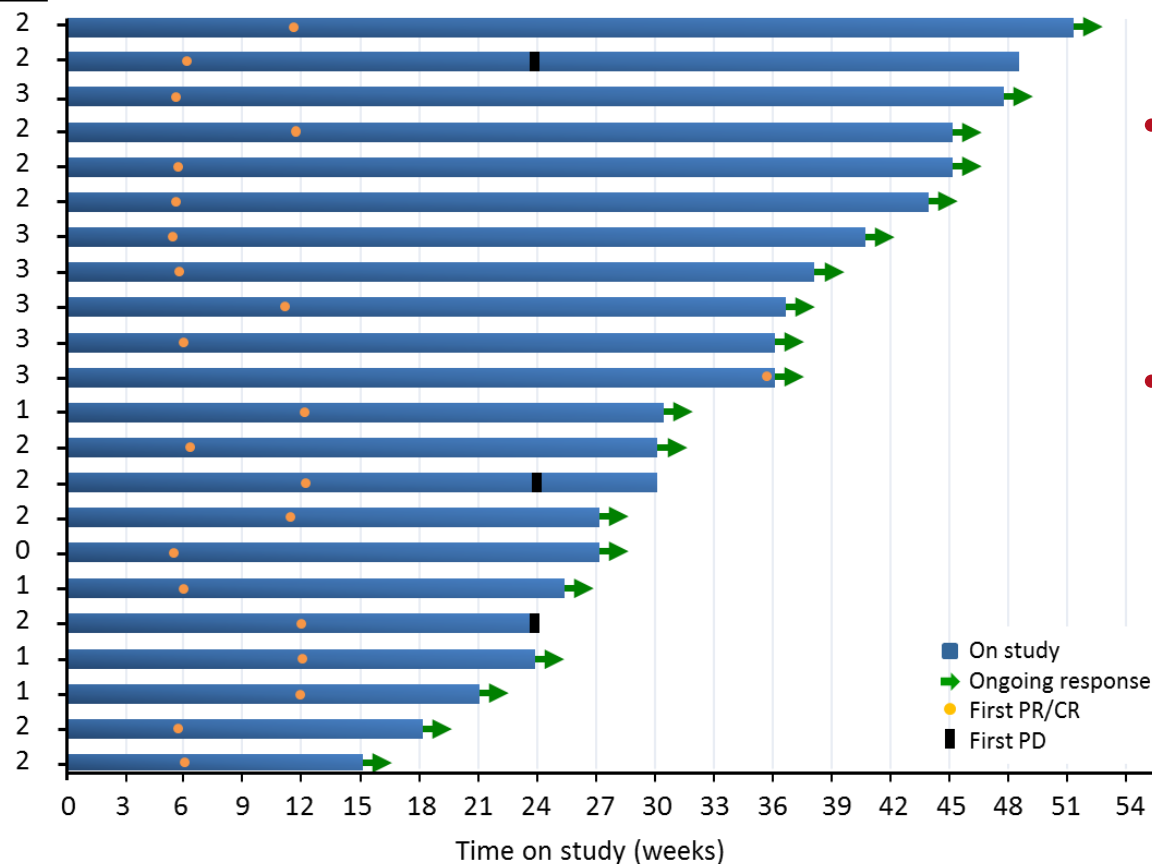
Bellmunt J et al., 26-30 September 2014, Madrid, Spain

MPDL3280A: Duration on Study, Treatment and Response in Responding Patients

Efficacy-evaluable population with UBC in Phase I expansion

PD-L1

IHC^a



- 19 of 22 responding patients had ongoing responses at the time of data cutoff
- Median duration of response has not yet been reached
 - PD-L1+ patients (n = 17): range, 0.1+ to 42+ weeks
 - PD-L1– patients (n = 5): range, 6+ to 19+ weeks

^a IHC 3, 2, 1, 0: $\geq 10\%$, $< 10\%$ and $\geq 5\%$, $< 5\%$ and $\geq 1\%$ and $< 1\%$ tumor-infiltrating immune cells positive for PD-L1, respectively.

Investigator-assessed ORRs (unconfirmed) per RECIST v1.1. Arrow indicates the status of no PD or no death only and has no implication on the timing.

Patients dosed by Jan 27, 2014 (≥ 12 -wk follow-up) with measurable disease at baseline. Clinical data cutoff was Apr 21, 2014.

Bellmunt J et al., 26-30 September 2014, Madrid, Spain

MPDL3280A: Summary of Progression Free Survival

Efficacy-evaluable population with UBC in Phase I expansion

| PD-L1 IHC (IC) | Median PFS (range), weeks | PD-L1+ vs PD-L1– Median PFS (range), weeks |
|----------------|------------------------------|--|
| IHC 3 (n = 10) | Not reached (5 to 48+) | 24 (5 to 50+) |
| IHC 2 (n = 23) | 24 (5 to 50+) | |
| IHC 1 (n = 24) | 11 (0.1+ to 30+) | 8 (0.1+ to 30+) |
| IHC 0 (n = 12) | 7 (5 to 24+) | |

- Median PFS appears to be associated with PD-L1 expression

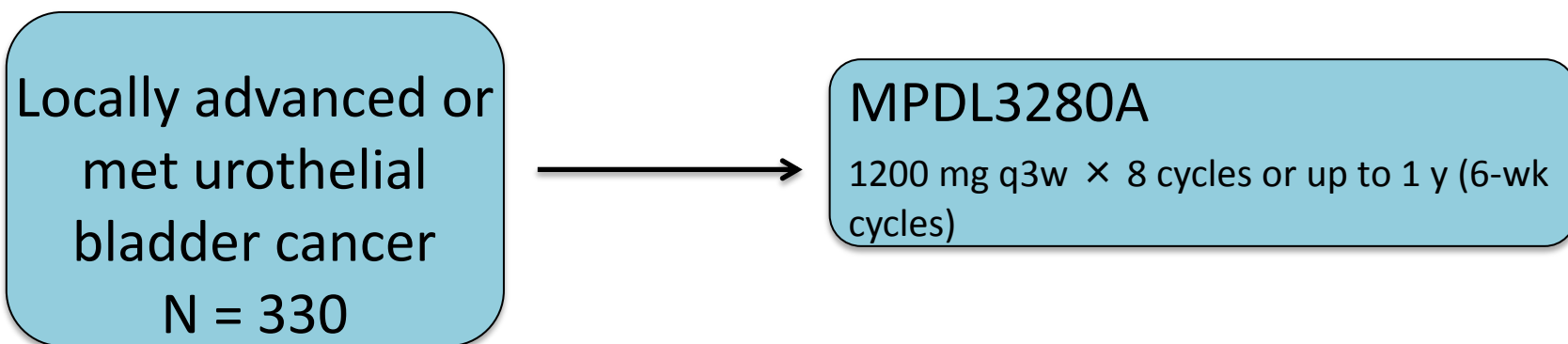
Investigator-assessed PFS per RECIST v1.1.

PD-L1+: IHC (IC) 2/3; PD-L1–: IHC (IC) 0/1.

Patients dosed by Jan 27, 2014 (≥ 12-wk follow-up) with measurable disease at baseline. Clinical data cutoff was Apr 21, 2014.

Bellmunt J et al., 26-30 September 2014, Madrid, Spain

Study GO29293 MPDL3280A: Phase II Trial in mUBC (NCT02108652)



- Key objectives: ORR, DoR, PFS per RECIST v1.1, OS, safety
- 2 cohorts recruiting
 - cohort 1: treatment naive and cisplatin-ineligible, N=30
 - cohort 2: 2nd line patients who progressed on platinum-containing treatment, N=300

MPDL3280A: Conclusions in UBC

- MPDL3280A had high ORR of 52% observed in mostly platinum-pretreated IHC 2/3 patients with metastatic UBC
 - ORR of 14% observed in IHC 0/1 patients
 - Rapid responses seen
 - 19 of 22 responding patients had ongoing responses at the time of data cutoff
 - Median PFS was 24 weeks in IHC 2/3 patients and 8 weeks in IHC 0/1 patients
- MPDL3280A was well tolerated
 - Only 5% of patients experienced Grade 3/4 treatment-related AEs
 - There were no grade 5 treatment-related AEs
 - Renal toxicity has not been observed in MPDL3280A-treated patients to date
- On-treatment plasma tumor burden markers, but not baseline markers, associated with response
- Additional studies of MPDL3280A in UBC are planned and ongoing (including NCT02108652)

Roche ESMO 2014: Summary

- ***Colorectal cancer:***

- Avastin, the only drug with proven survival benefit in 1st and 2nd line, and across multiple lines (TML), irrespective of biomarker status

- ***Breast cancer:***

- Perjeta unprecedented overall survival benefit in Her2-positive breast cancer
- Avastin: continued commitment to improving outcomes for people with HER2-negative metastatic breast cancer

- ***Melanoma:***

- Cobimetinib plus Zelboraf offers strong profile in a market with rapidly changing treatment options

- ***Cancer immunotherapy (aPDL1):*** Committed to making a difference

- Bladder cancer: strong set of data in monotherapy
- Renal cancer: early promising efficacy in mono and in combo with Avastin
- CRC: good safety profile in combination with Avastin and chemo backbone

Doing now what patients need next