

# **Io Therapeutics Phase II Clinical Stage and Preclinical Retinoid Compounds for Treatment of Cancers**

**Presentation for BIO International Convention  
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**Io Therapeutics, Inc.  
Martin E. Sanders, M.D.  
Chairman and CEO**

# **lo Therapeutics**

## **Cancer Treatments Pipeline**

- **IRX4204: Phase II Clinical Stage Selective RXR Agonist for Her2+ Breast Cancer, and Other Solid Tumors**
- **IRX5183: Phase II Clinical Stage RAR $\alpha$  Agonist for Multiple Myeloma and AML**
- **RAR $\gamma$  Agonists for Triple Negative Breast Cancer and Non-Small Cell Lung Cancer**

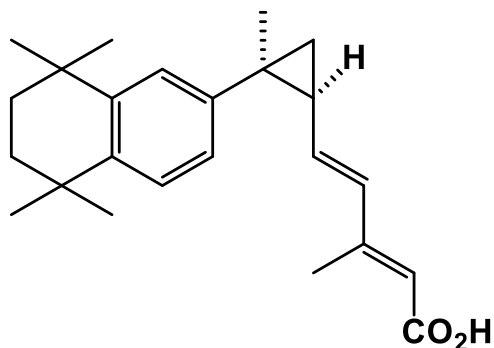
# **IRX4204**

**A Phase II Clinical Stage Selective RXR  
Agonist for Her2+ Breast Cancer, and  
Other Solid Tumors**

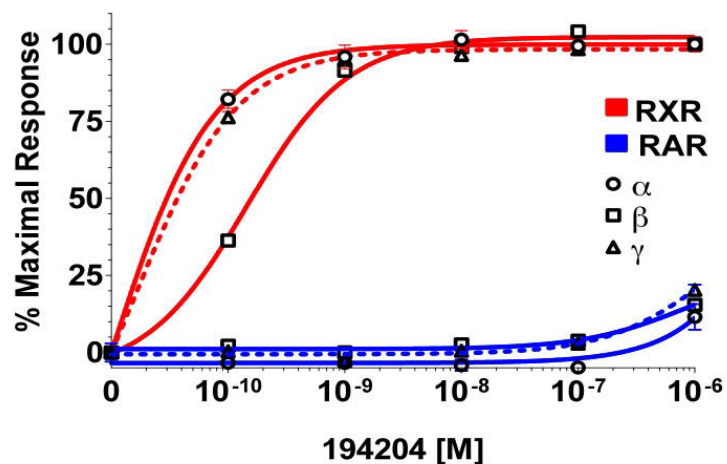
# IRX4204 Summary

- IRX4204 is a potent, and highly selective RXR agonist with demonstrated safety and anti cancer activities in preclinical and phases I and II clinical studies.
- 100 patients have been treated with IRX4204, including 85 with various cancers and 15 with early-stage Parkinson's disease under US INDs.
- IRX4204 has been safe and well tolerated with up to 20 months of treatment in humans.
- Oral PK in humans is consistent with once per day dosing.
- Common side effects include dose related suppression of TSH with resultant hypothyroidism, mild to moderate increased triglycerides, and transient mild to moderate reversible leukopenia.
- Open label phase I and IIA clinical trials in cancers and Parkinson's disease support clinical safety and efficacy.
- Preclinical data demonstrate synergy of therapeutic effects of IRX4204 plus anti-Her2 mab trastuzumab; HER2 tyrosine kinase inhibitors; or paclitaxel in HER2+ breast cancer.
- Preclinical data demonstrate therapeutic activity on trastuzumab resistant, and HER2 tyrosine kinase resistant HER2+ breast cancers.
- IRX4204 has been shown to be brain penetrant, with potential use in the treatment of brain metastasis in HER2+ breast cancer.

# IRX4204: A Phase II Clinical Stage RXR Specific Agonist for the Treatment of Cancers

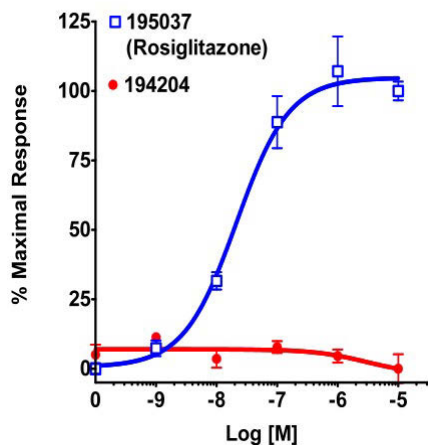


## IRX4204 – A Potent RXR Homodimer Agonist with no RAR Activity at nM Concentrations

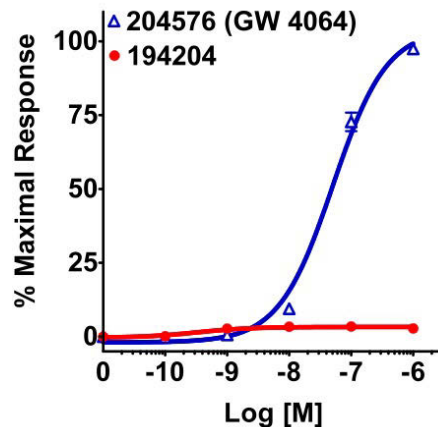


# IRX4204 is highly selective for RXR

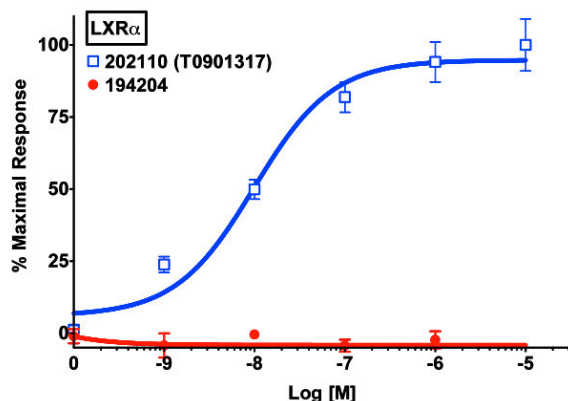
## It does not transactivate PPAR $\gamma$ , FXR, or LXR



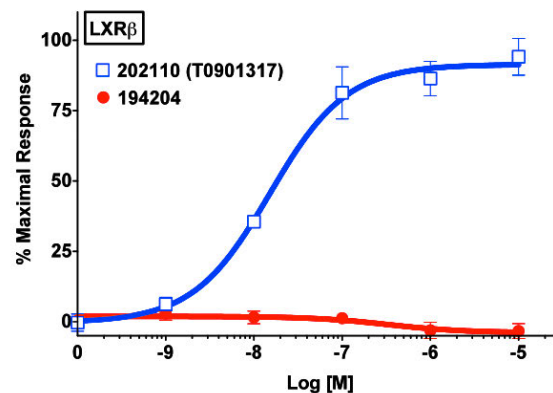
PPAR $\gamma$ /RXR



FXR/RXR



LXR/RXR



LXR/RXR

# IRX4204 is More Potent and More Selective than Bexarotene (The Only Currently FDA Approved RXR Agonist)

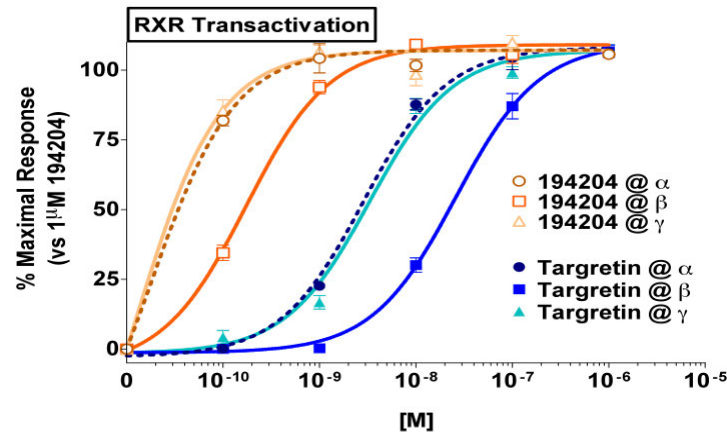
## Bexarotene

- Bexarotene is a non-selective, less potent RXR agonist – approved by FDA for T-Cell lymphoma
- Bexarotene transactivates RXRs, RARs, PPAR $\gamma$ , and LXRs
- Bexarotene is more toxic in humans than IRX4204 (rashes, greater lipid elevations)

## IRX4204

- IRX4204 is a highly selective RXR agonist, 100x more potent than bexarotene
- IRX4204 is specific for RXRs; not active at RARs, PPAR $\gamma$ , and LXRs
- IRX4204 was well tolerated in 100 humans in Phase I/II clinical trials; less cutaneous rash and less lipid elevations than bexarotene

### IRX4204 is >100 Fold More Potent Than Targretin (Bexarotene) in Transactivation of RXR Homodimers



## IRX4204 Pharmacology in Cancer Models

- Dose dependent inhibition of proliferation of breast (especially HER2+), NSCLC, SCLC, prostate, colon, pancreatic, cervical, lymphoma, leukemia, melanoma, glioblastoma, and multiple types of sarcomas.
- Effective in *in vivo* cell line xenograft models of breast (HER2+), lung, and prostate cancers.
- **Synergistic inhibition of HER2+ breast cancer proliferation *in vitro*** with trastuzumab, neratinib, lapatinib, tucatinib, and paclitaxel.
- Inhibits proliferation *in vitro* of some **trastuzumab or HER2 TKI resistant HER2+ breast cancers**.
- Effective in *in vivo* models of breast (HER2+) and lung cancer prevention.
- Induces apoptosis in HER2+ breast cancer cells.



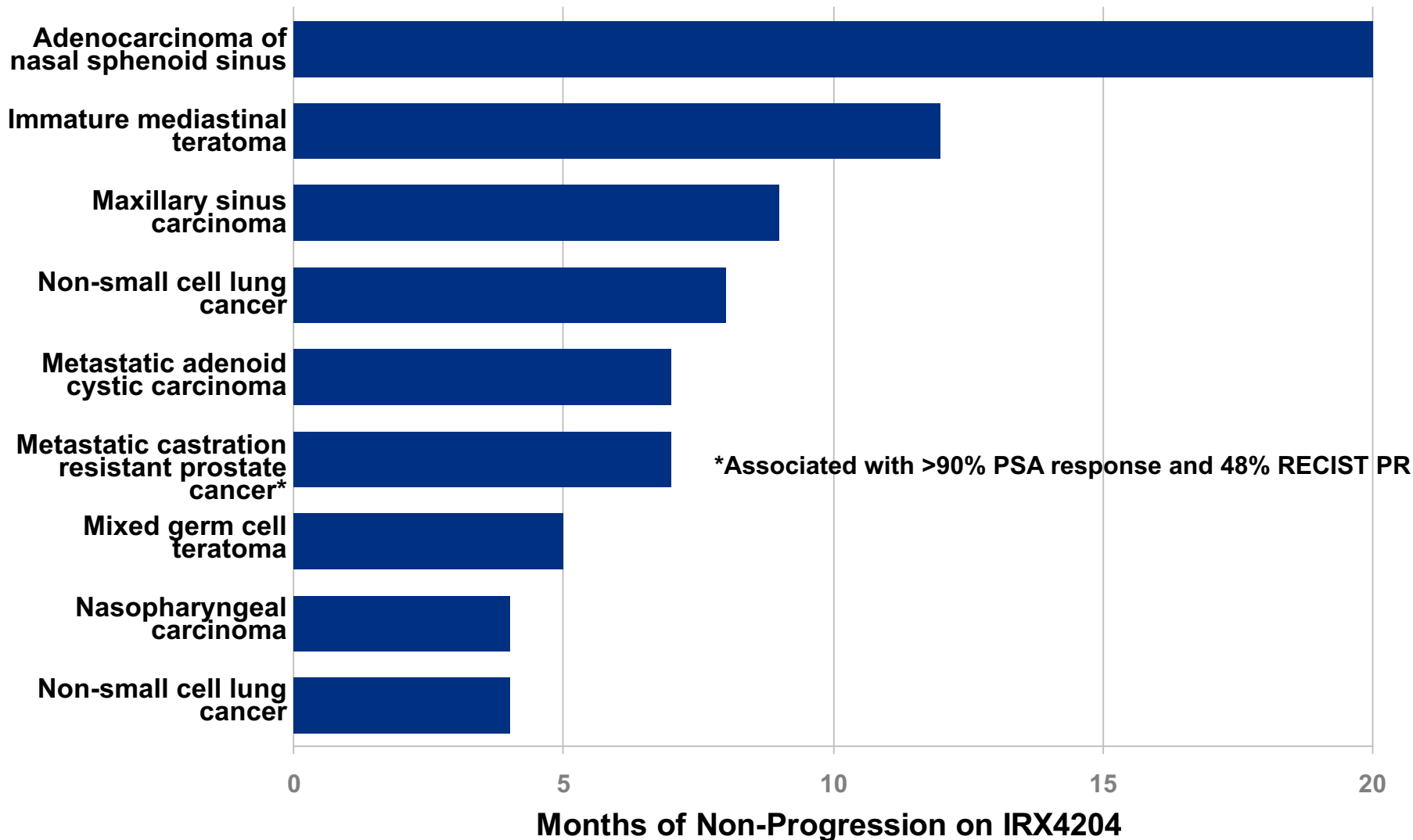
# Patients Treated with IRX4204 To Date

Study/Site	# of Patients
Phase I study, various solid tumors	18
Phase II NSCLC, USC	6
Phase II NSCLC, Dartmouth	5
Phase II Mesothelioma, USC	6
Ph II Castration Resistant Prostate, UCLA/consortium	37
Ph II NSCLC + erlotinib, Dartmouth	10
Compassionate use, adenoid cystic carcinoma	3
Phase I Parkinson's Disease	15
<b>Total</b>	<b>100</b>

# Phase I/II Study of IRX4204 in Refractory Malignancies

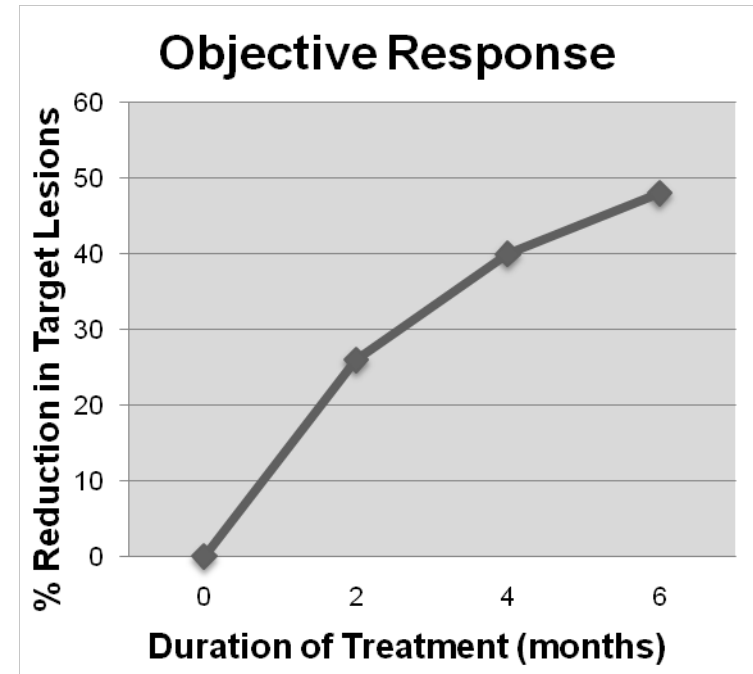
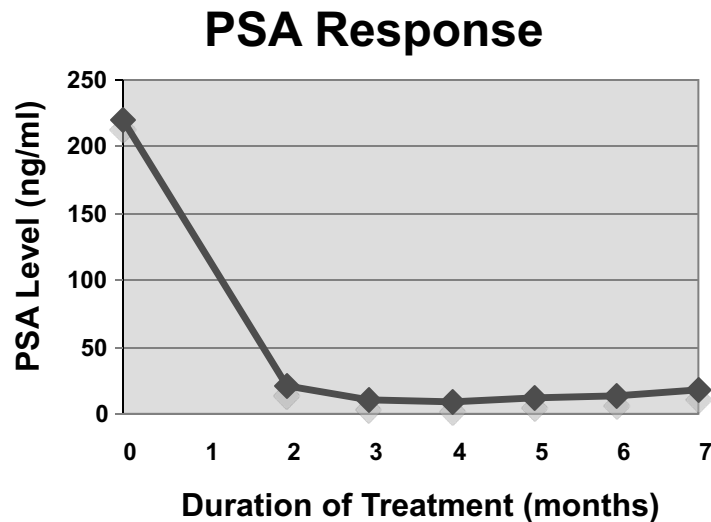
- Multi-center, open-label study of once-daily oral IRX4204 in patients with refractory malignancies
  - Dose groups of 3, 6, 12 and 24 mg/m<sup>2</sup>
  - Treatment for a minimum of 4 weeks, with longer treatment possible for patients with disease stabilization
- Enrolled 18 patients with progressive solid tumors
- No serious adverse events considered possibly or probably related to study drug
- Adverse events included triglyceride elevation and hypothyroidism, both types of events treatable

# 50% of Patients in Phase I Study had Non-Progression for $\geq 4$ Months



# PSA and Objective Response in Phase I Prostate Cancer Patient

- 73 year old patient with advanced, metastatic disease, post-castration, taxane-resistant, failed multiple prior therapies.
- Received 7 months of treatment with IRX4204
- Patient had a rapid, dramatic, and durable PSA response.



- Concurrent with biochemical response, patient experienced a ~50% objective response (RECIST)

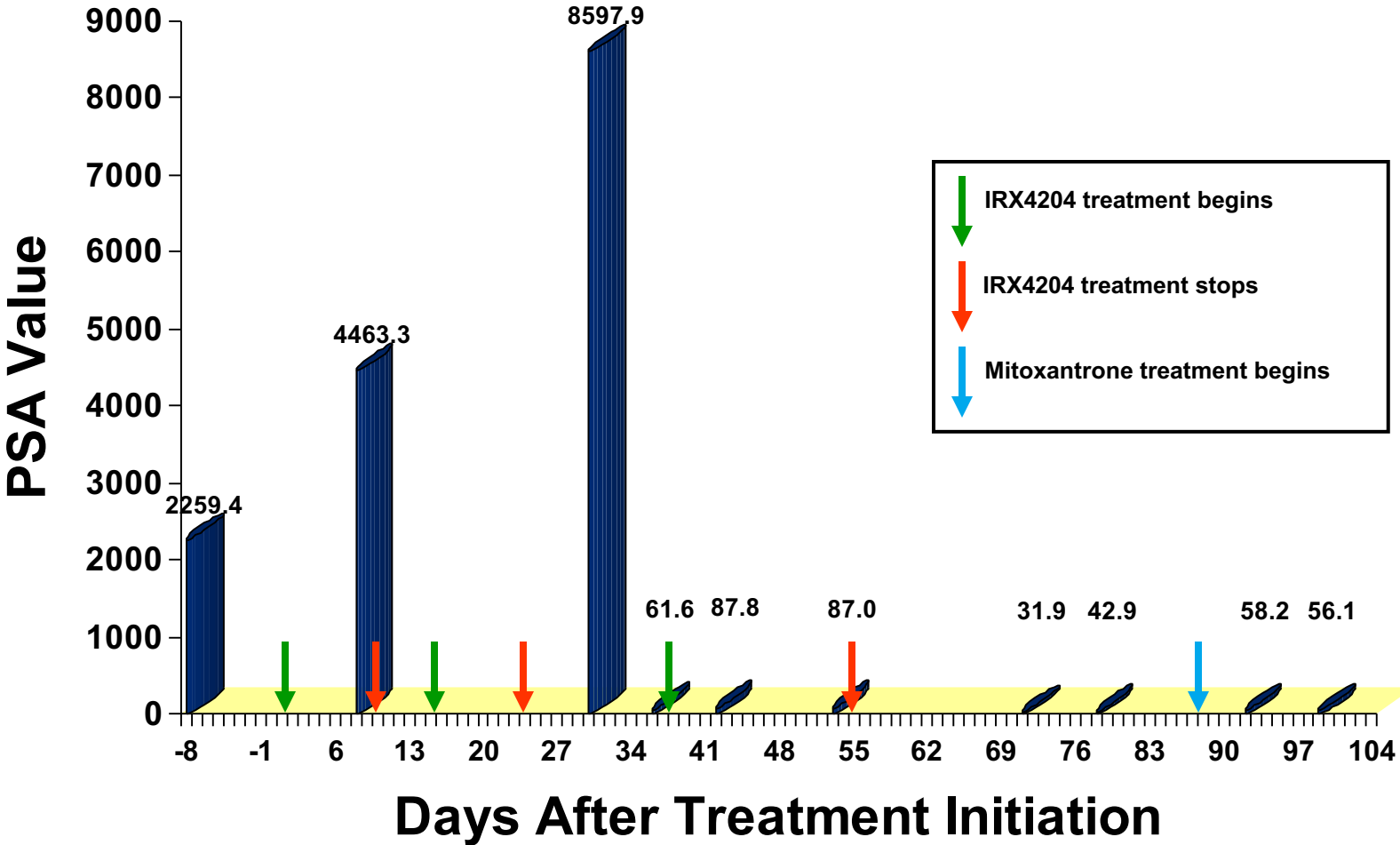
## Phase IIA Castration Resistant Prostate Cancer Clinical Trial

- 37 patients with progressive castration resistant prostate cancer were enrolled in this open label uncontrolled clinical trial and treated with IRX4204 at 20 mg/day. Continued hormonal therapy was allowed.
- Primary objective was assessment of safety. Efficacy outcomes were collected.
- IRX4204 was generally safe and well tolerated for up to 540 days. Drug related adverse events included increased lipids and hypothyroidism.
- “Clinical Benefit” was prospectively defined as greater than two cycles (56 days) without observed progression. The study was prospectively defined to be positive if 6 of 37 patients were treated for at least 56 days without progression.
- 19 of the 37 patients were treated for more than 56 days without progression.
- One patient with baseline PSA of 2259 experienced rapid tumor lysis (peak PSA of 8598) associated with serious coagulopathy, followed by sustained PSA values of 88 or less.
- One additional patient experienced a low magnitude 50% decrease in PSA while being treated for 540 days without progression. No other patients experienced a 50% drop in PSA.

# IRX4204: Clinical Development Status

- 100 patients have been treated with IRX4204, including 85 with various cancers, and 15 with early Parkinson's disease.
- IRX4204 was safe and well-tolerated for up to 20 months of continuous oral treatment over a range of doses.
- PK in humans is consistent with once per day oral dosing.
- Common side effects include dose related reversible suppression of TSH with resultant treatable hypothyroidism; mild to moderate reversible increased triglycerides; and mild to moderate reversible leukopenia.
- Open label uncontrolled phase I and II clinical trials in cancers and Parkinson's disease support clinical safety, efficacy, and effective doses.
- Synthesis of GMP clinical trial drug supply API is completed.  
Manufacture of drug and placebo capsules for Phase II trials completed.
- Planning phase II clinical trials in Her2+ breast cancer and NSCLC.

# PSA Response in Phase IIA Prostate Cancer Patient

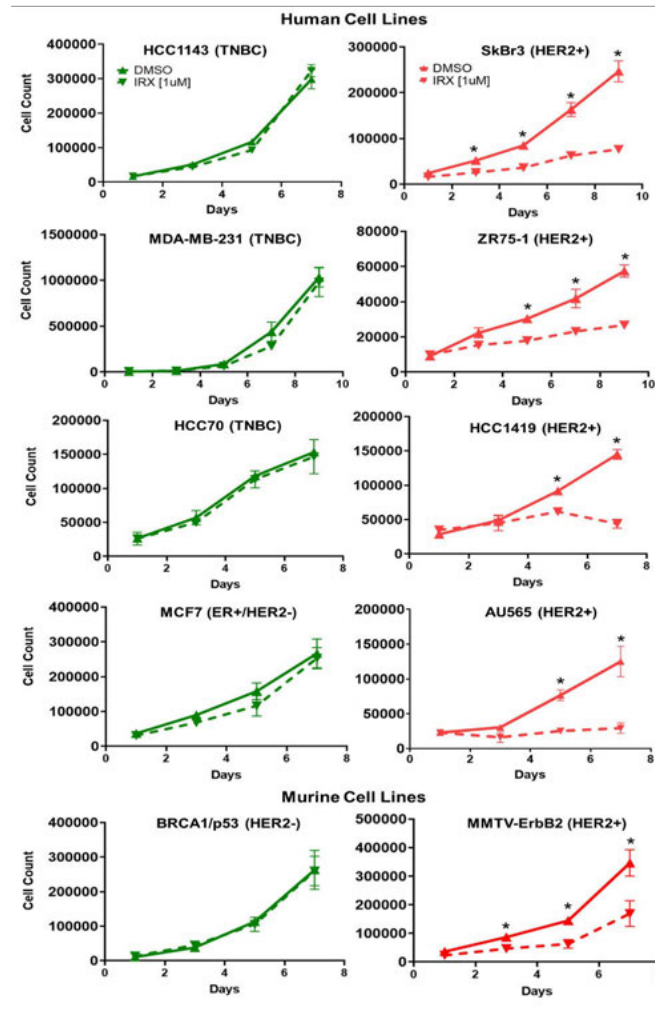


# IRX4204: Product Development Status

- INDs for IRX4204 for treatment of cancers and Parkinson's disease;
- GLP 6-month rat, 9-month dog toxicology completed; dose related ocular cataracts noted in rats and dogs; milder findings than in bexarotene toxicology (which also showed ocular cataracts)
- PK in rats, dogs and humans consistent with once daily oral dosing
- Brain penetrance demonstrated in rodents and humans
- Panlabs binding assays on panel of diverse CNS receptors negative
- hERG binding assay negative
- GLP gene toxicology panel negative
- GLP *in vivo* safety pharmacology panel (CNS, CV, Resp) negative
- GMP manufacturing completed on multi-kg scale; producing API with chemical and chiral purity 99+% without requiring a terminal chromatographic purification step
- Multi-year compound stability demonstrated
- Formulated in oral capsules for Phase II clinical trials
- Can be formulated for intravenous, inhaled nose to brain, inhaled lung, dermal, and ocular administration



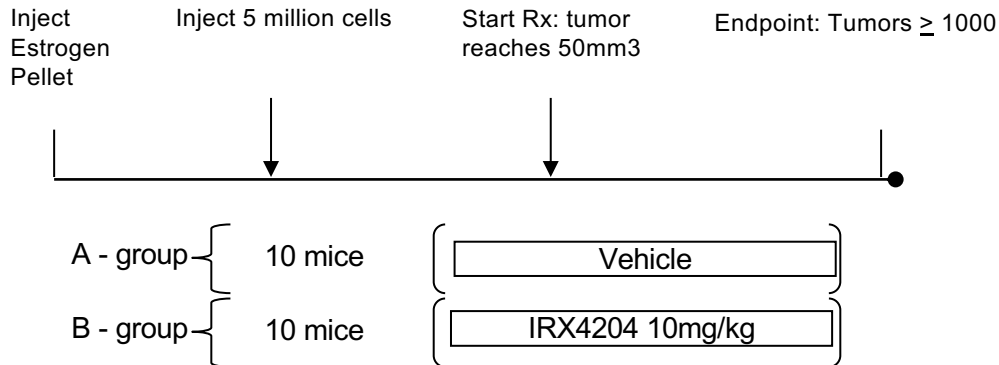
# IRX4204 Inhibits Tumor Growth *in Vitro* in Most HER2+ Breast Cancers, but Not in Most HER2- Breast Cancers



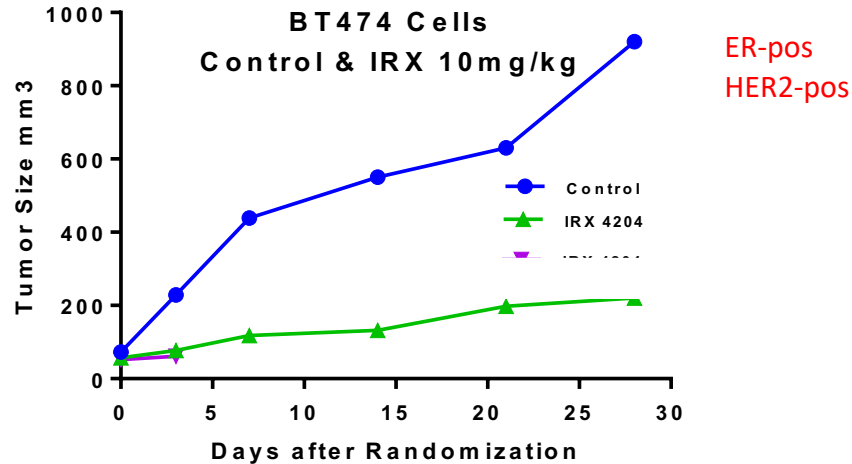
Data from PH Brown, MD, PhD; A Mazumdar, PhD and Cassandra Moyer, PhD; MD Anderson Cancer Center

# Effect of IRX4204 Monotherapy Treatment on BT474 (ER+ / HER2+) Tumor Growth in *In Vivo*

## Treatment Schema:



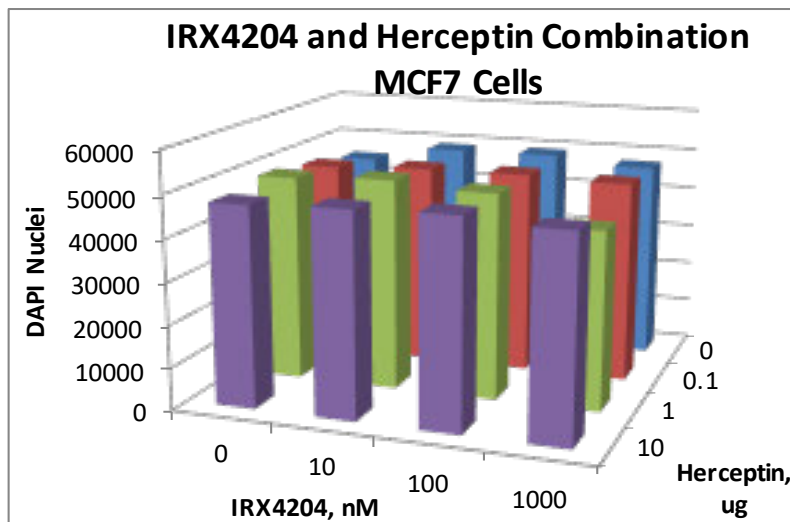
## Results:



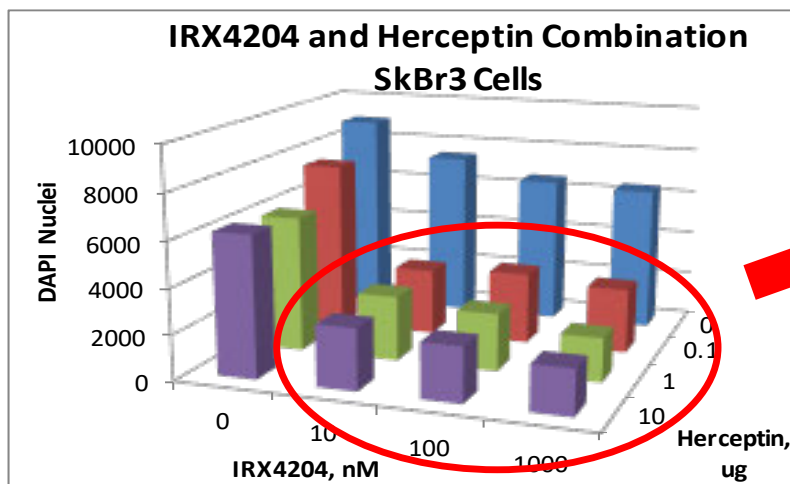
Data from P Brown, MD, PhD  
MD Anderson Cancer Center

# IRX4204 plus Trastuzumab (anti-HER2 Mab) Have Synergistic Inhibitory Effects on Human HER2+ Breast Cancer Growth *in Vitro*

MCF7  
ER-pos / HER2-neg



SkBR3 cells  
ER-neg / HER2-pos

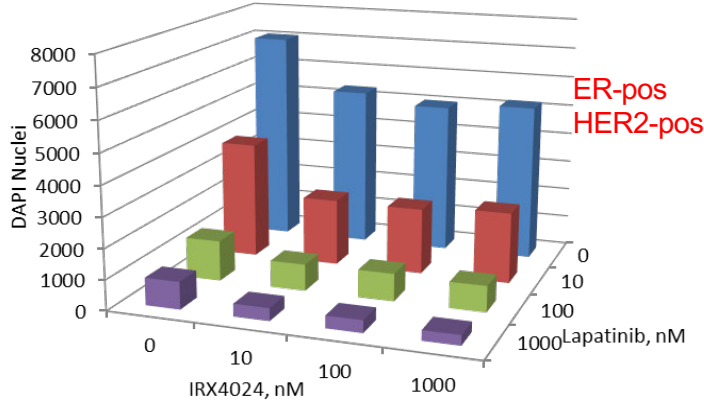


**Synergistic  
Activity !**

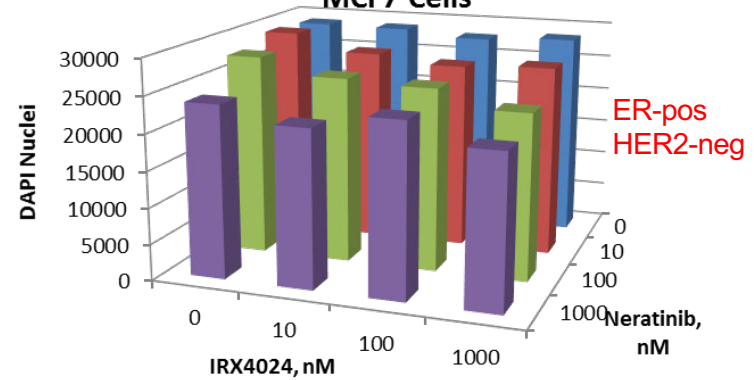
Data from P Brown, MD, PhD  
MD Anderson Cancer Center

# Combination Therapy for HER+: IRX4204 plus Small Molecule TKI Inhibitors Lapatinib and Neratinib Have Synergistic Effects

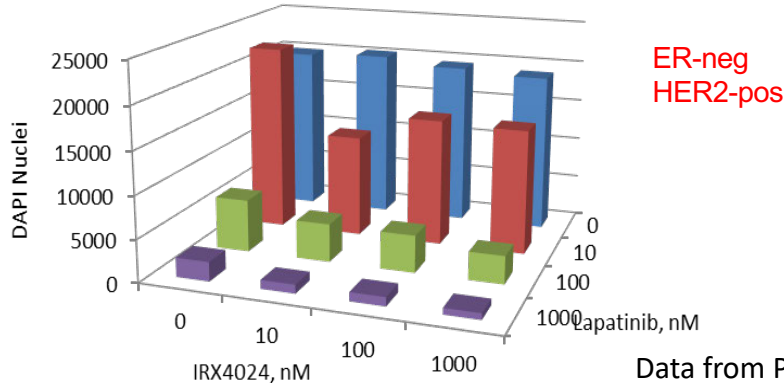
IRX4204 and Lapatinib Combination  
MDA-361 Cells



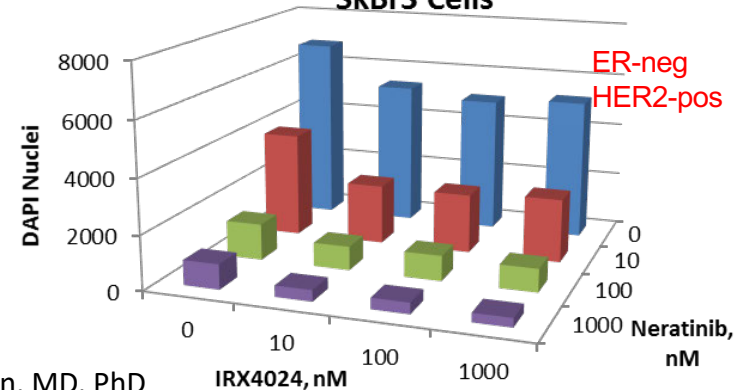
IRX4204 and Neratinib Combination  
MCF7 Cells



IRX4204 and Lapatinib Combination  
SkBr3 Cells

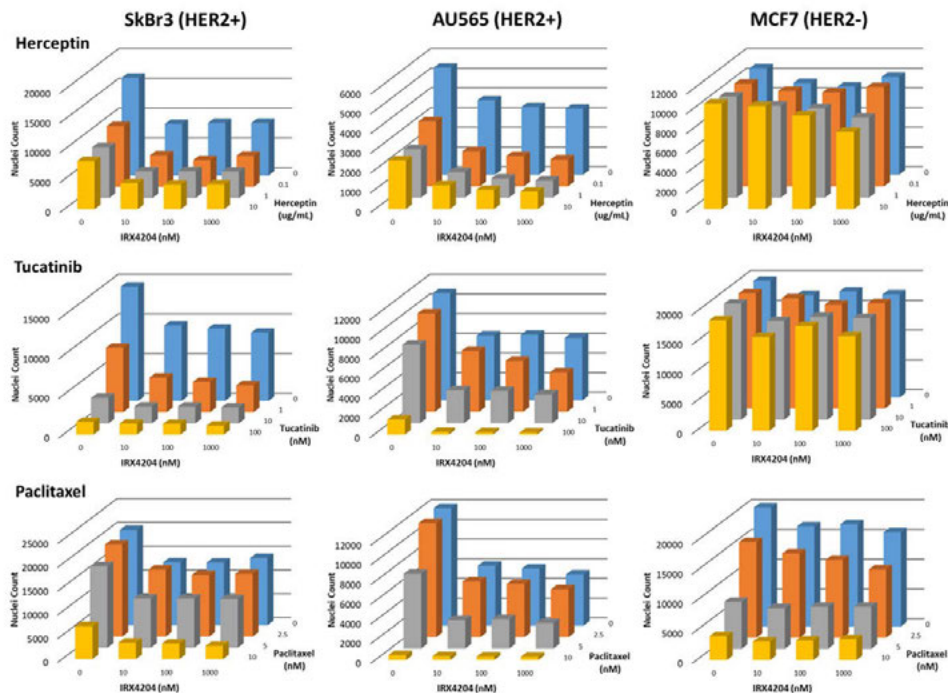


IRX4204 and Neratinib Combination  
SkBr3 Cells

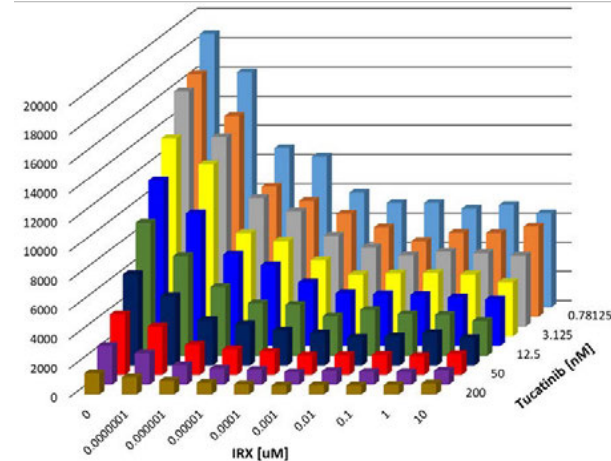


Data from P Brown, MD, PhD  
MD Anderson Cancer Center

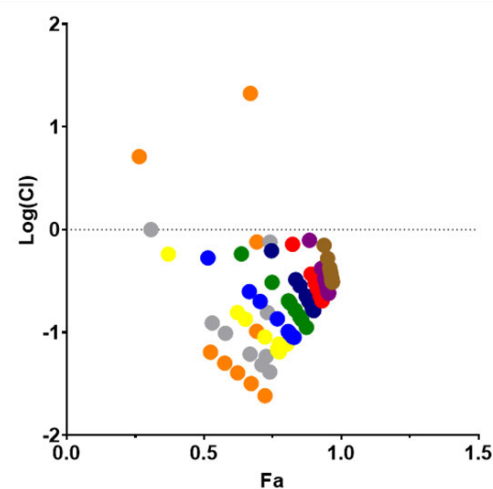
# IRX4204 has Synergistic Inhibitory Effects with Tucatinib on Human HER2+ Breast Cancer Cells *in Vitro*



SkBr3 IRX + Tucatinib Combination



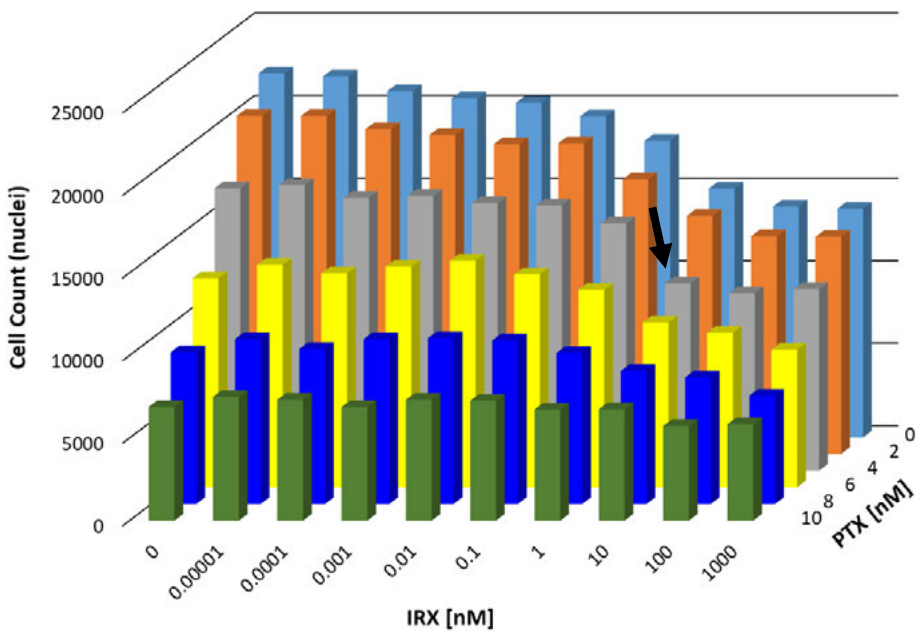
Combination Index Plot



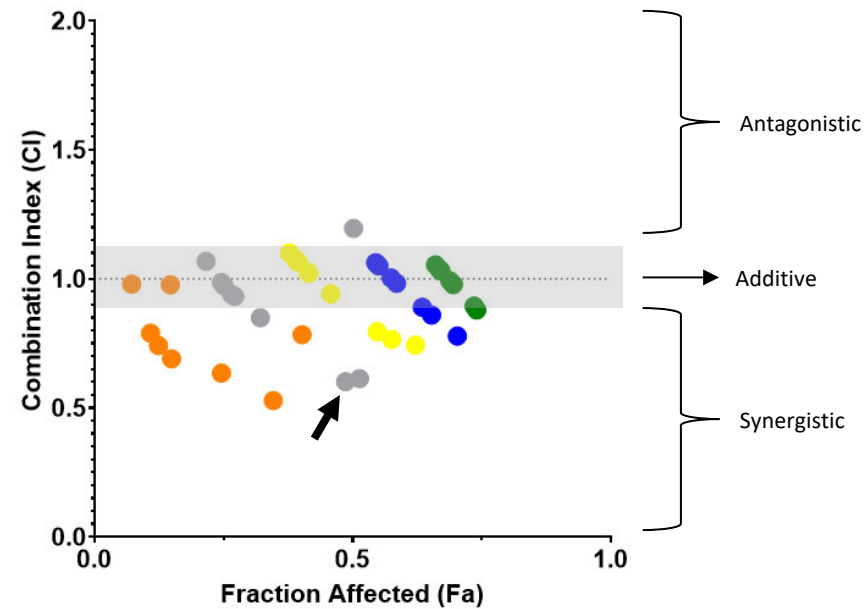
Data from P Brown, MD, PhD; A Mazumdar, PhD; and Cassandra Moyer, PhD; MD Anderson Cancer Center

# IRX4204 has Synergistic Inhibitory Effects with Paclitaxel on HER2+ Human SkBr3 Breast Cancer Cells *in Vitro*

SkBr3 IRX4204-Paclitaxel Combination



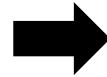
IRX4204+Paclitaxel CI Plot in SkBr3(HER2+)



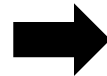
Data from P Brown, MD, PhD; A Mazumdar, and Cassandra Moyer, PhD;  
MD Anderson Cancer Center

# IRX4204 Monotherapy Prevents Development of Her2+ Breast Cancer in MMTV-ErbB2 Mouse Model; and Induces Apoptosis of Mammary Cells

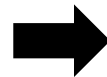
Prevents ER-neg / HER2-pos BC in MMTV-ErbB2 mice (Dose: 20 mg/ kg in feed)



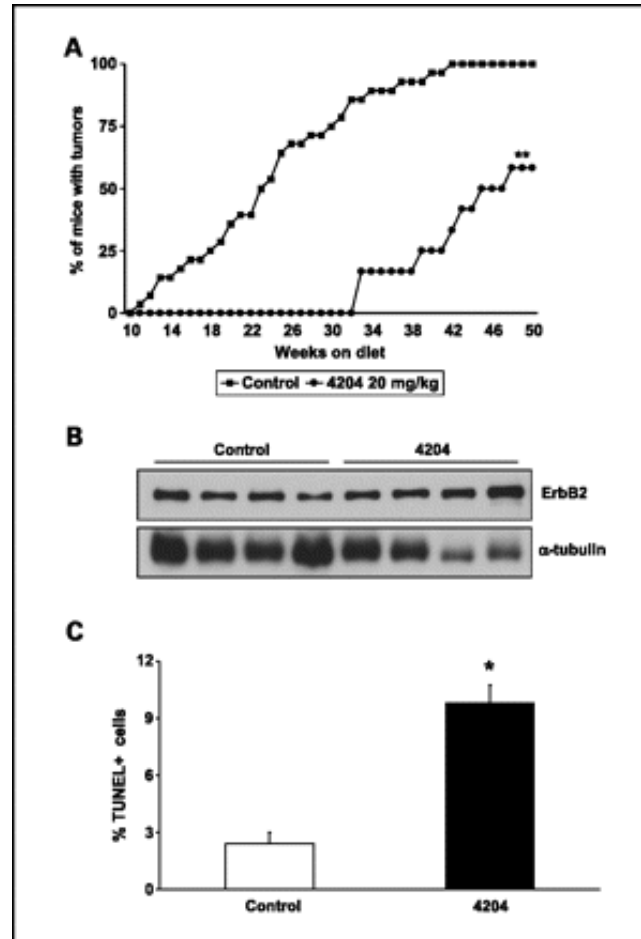
NRX194204 treatment does not affect the ErbB2 transgene expression



NRX194204 treatment induces apoptosis of mammary cells



Liby et al. Clin Cancer Res, 2007  
Dartmouth School of Medicine



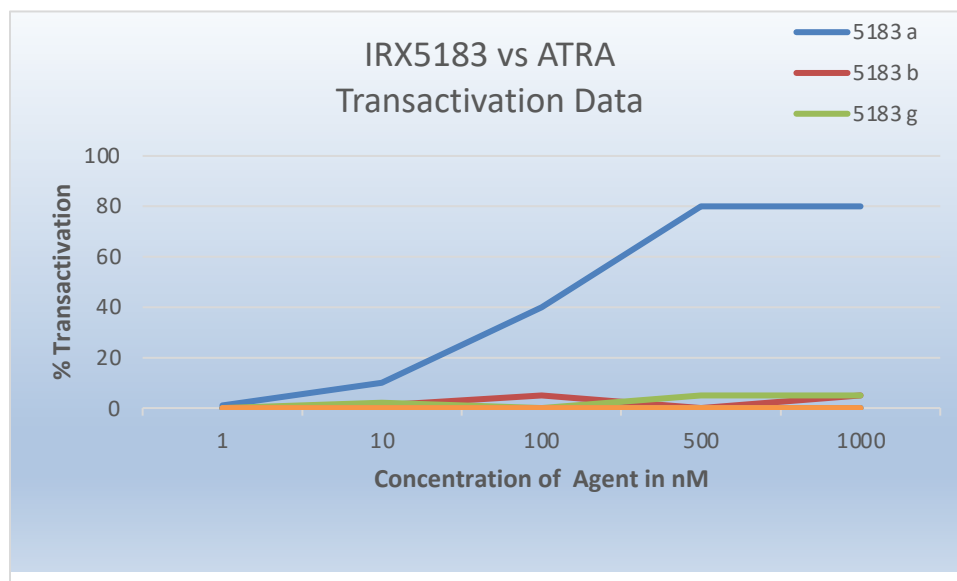
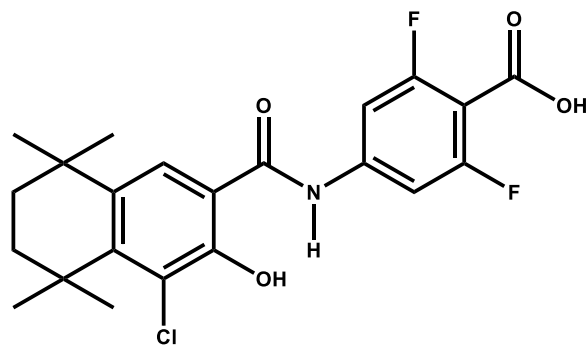
**IRX5183**

**A Phase II Clinical Stage**

**RAR $\alpha$  Selective Agonist for the Treatment  
of Multiple Myeloma and AML**



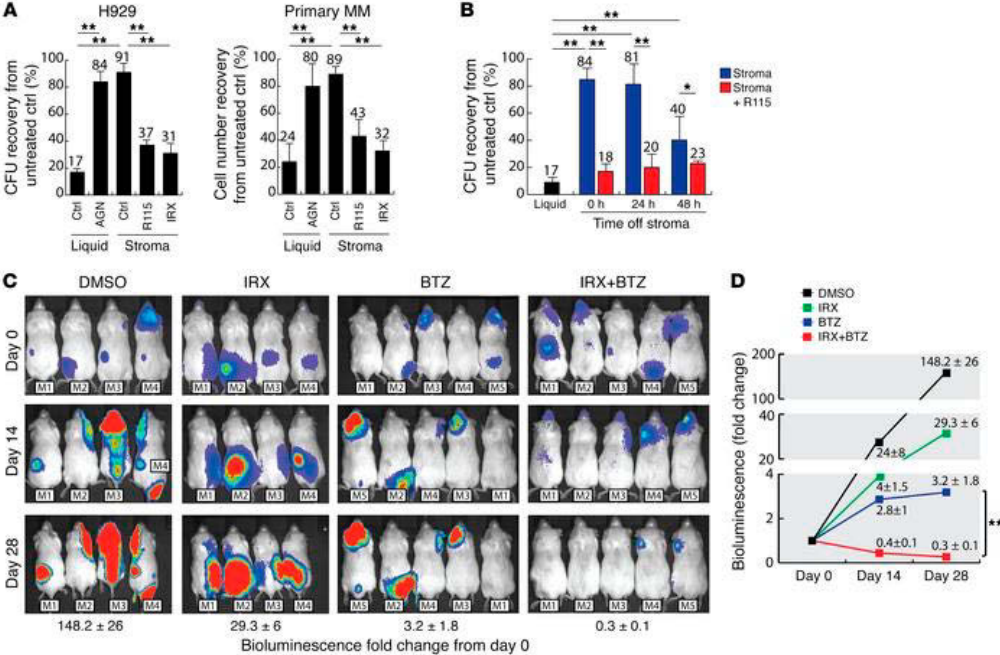
# IRX5183 is a Highly Selective RAR $\alpha$ Agonist with no RAR $\beta$ or $\gamma$ Activity at $\mu$ M Concentrations



## Patients Treated to Date with IRX5183

- Phase I Trial in Patients with solid tumors 15 Patients
- Phase I Trial in Patients with Lymphoma or Multiple Myeloma with G-CSF for Peripheral Blood Progenitor Cell Mobilization 8 Patients
- Phase I Monotherapy Trial in Patients with AML 11 Patients
- Compassionate Treatment of APL 2 Patients
- **Total = 36 Patients**
- IRX5183 was generally safe and well tolerated for up to 112 days of treatment.
- Drug related adverse events included elevations of triglycerides and possibly low-grade elevation of liver enzymes.
- IRX5183 induces AML leukemic blast maturation *in vivo* in humans.
- **One AML patient treated with IRX5183 monotherapy achieved a morphological complete remission with incomplete hematologic recovery (CRi).**
- Four of eleven AML patients (36%) had stable disease or better while receiving IRX5183.

# IRX5183 Increases Bortezomib (BTZ) Sensitivity of the Multiple Myeloma (MM) cell line H929 and Primary CD138 MM Cells in Various Retinoid-low and -high Conditions; and is Effective in a Xenograft Model of Human MM

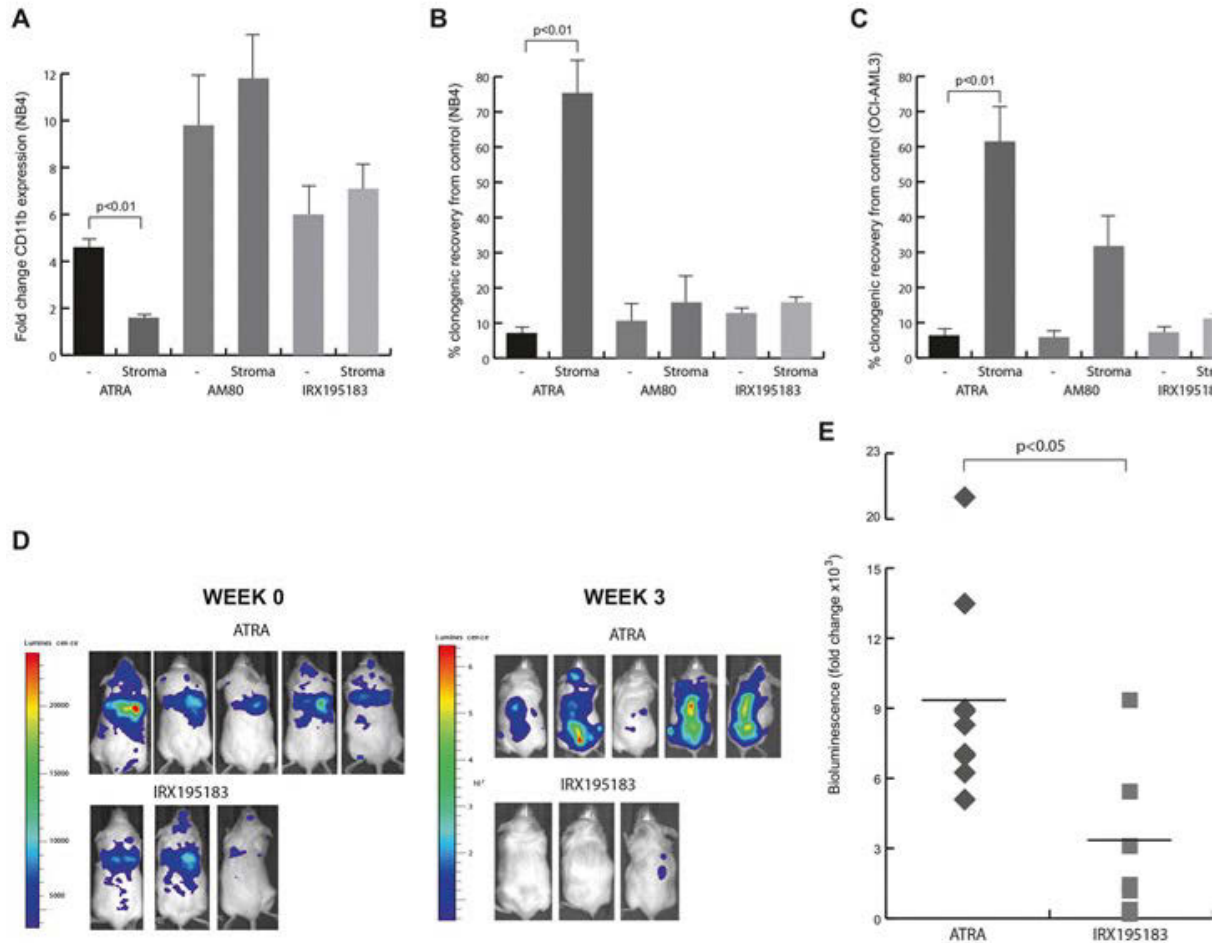


(A) Clonogenic recovery (CFU) of H929 cells or cellular recovery of primary CD138<sup>+</sup> MM cells from 3 different patient samples. (B) Clonogenic recovery of H929 cells treated with BTZ (2.5 nM). (C) Bioluminescent images of systemic MM xenografts. Following engraftment of H929 Luc<sup>+</sup> cells, mice were treated with IRX (n = 4), BTZ (n = 5), or a combination of both (n = 5) for 4 weeks. (D) Fold change in bioluminescence from day 0.

J Clin Invest 2016; DOI: 10.1172/JCI88152

Data from G Ghiaur Laboratory  
Johns Hopkins School of Medicine

# Effects of CYP26 Resistant RAR $\alpha$ Selective Agonist Compound IRX5183 on Differentiation of AML Cells in Stroma Co-culture and in Xenograft AML Model



**A-C:** Fold change CD11b expression (A), and clonogenic recovery (B) of NB4 cells as well as clonogenic recovery of OCI-AML3 cells (C), treated with various retinoids in the presence or absence of mesenchymal stroma. **D:** Tumor burden by bioluminescence activity of xenograft mice transplanted with OCI-AML3-luciferase and treated with ATRA or IRX5183 (10 mg/Kg) for 3 weeks. **E:** Quantitative analysis of data presented in (D). Horizontal lines represent mean of bioluminescence fold change from D0 or treatment. Squares and diamonds represent individual mice.

Leukemia, 2020; DOI: [10.1038/s41375-020-0790-4](https://doi.org/10.1038/s41375-020-0790-4)

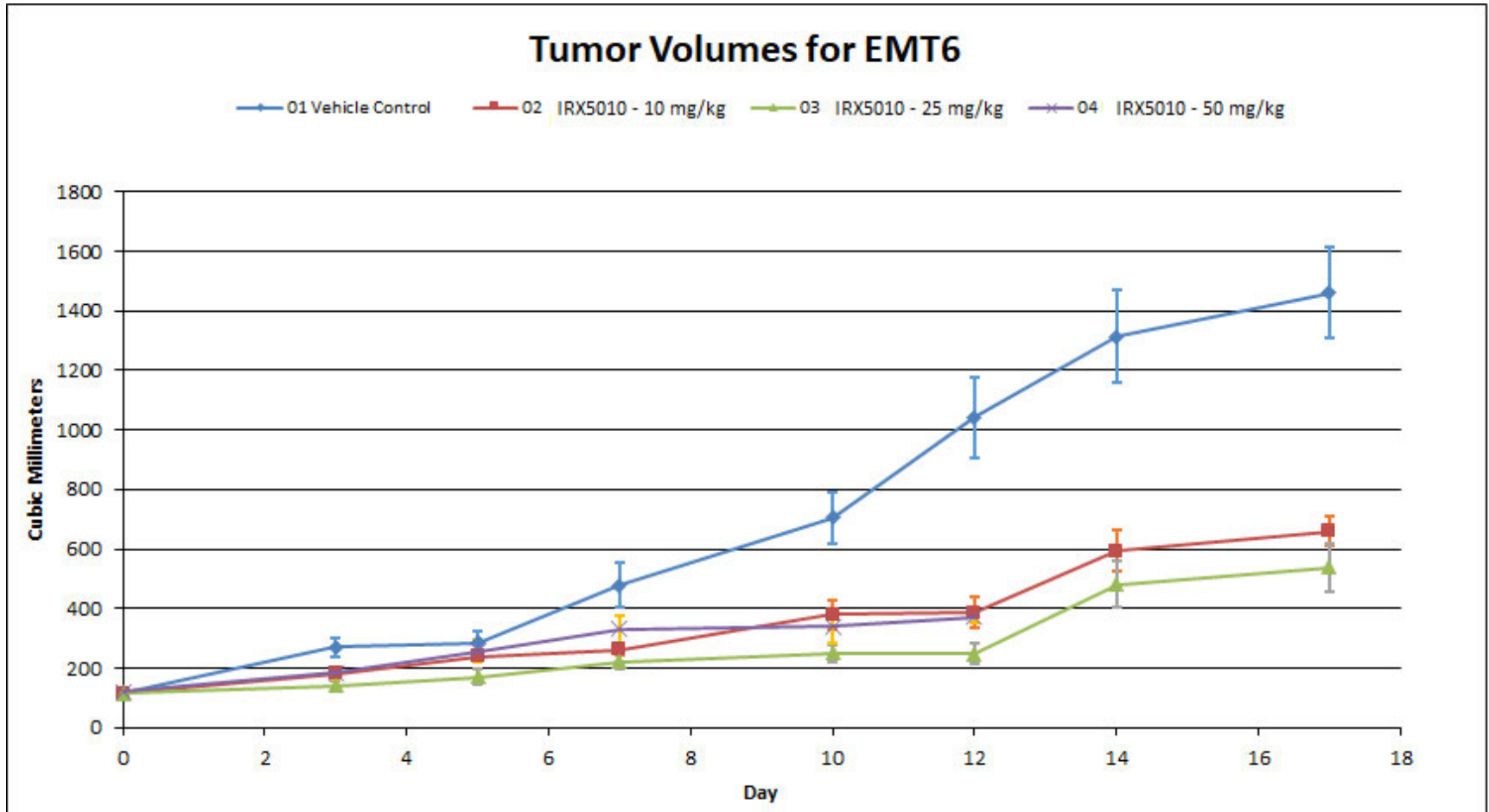
Data from G Ghiaur Laboratory  
Johns Hopkins School of Medicine

# Selective RAR $\gamma$ Agonists

## Drug Discovery and Preclinical Development

- **Io Therapeutics has discovered RAR $\gamma$  agonist compounds which are effective as monotherapies in syngeneic mouse models of triple negative breast cancer and non-small cell lung cancers.**
- **These RAR $\gamma$  agonists promote tumor infiltrating T-lymphocytes which inhibit tumor growth in the in vivo models. The RAR $\gamma$  agonists compounds have minimal direct in vitro activity on growth of cancer cells.**
- **RAR $\gamma$  agonism has combination effects in vivo on NSCLC growth with anti-PD-L1 checkpoint inhibitor.**

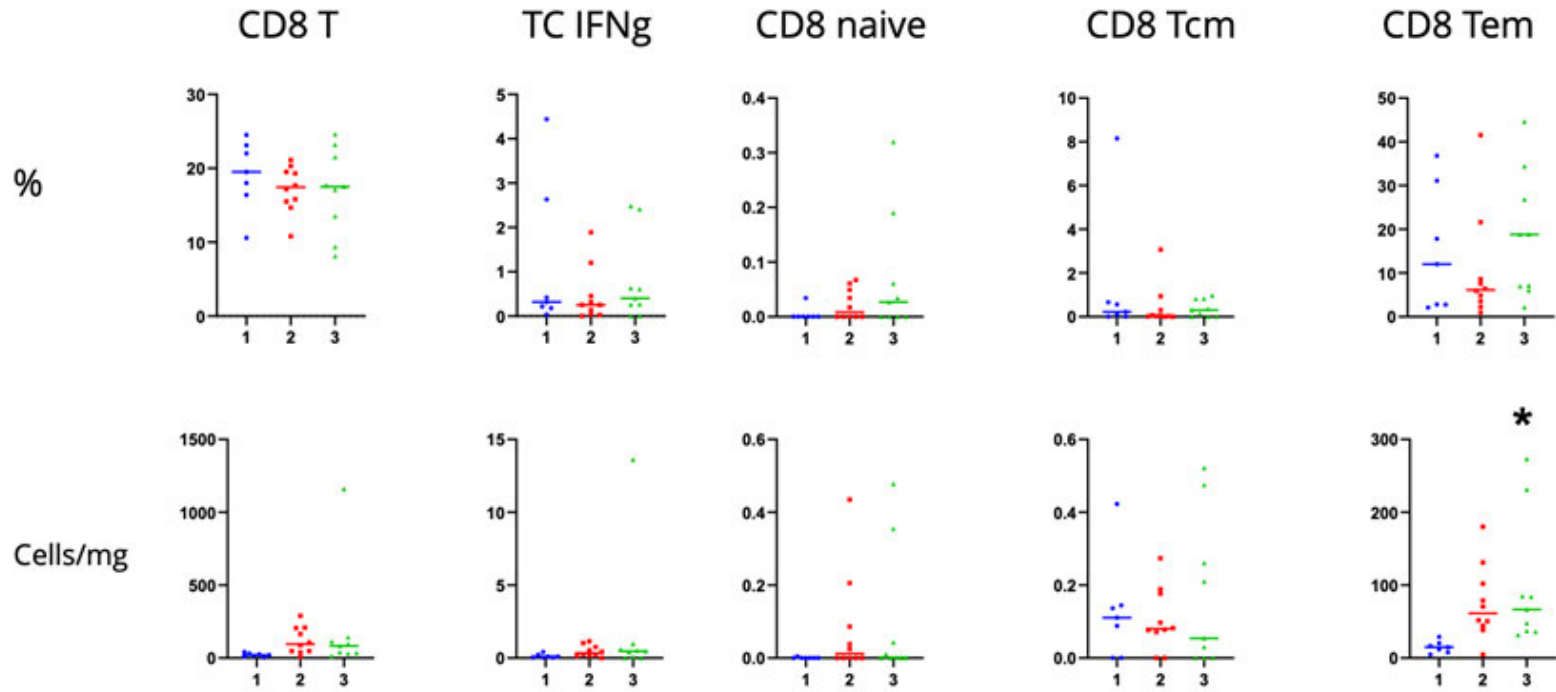
# IRX5010: a Highly Selective RAR $\gamma$ Agonist Compound Inhibits In Vivo Tumor Growth of EMT-6 Triple Negative Breast Cancer in Syngeneic Mouse Model



Data from Champions Oncology, Inc.

# IRX5010: a Highly Selective RAR $\gamma$ Agonist Compound Induces Effector Memory Tumor Infiltrating Lymphocytes in EMT-6 Triple Negative Breast Cancer in Syngeneic Model

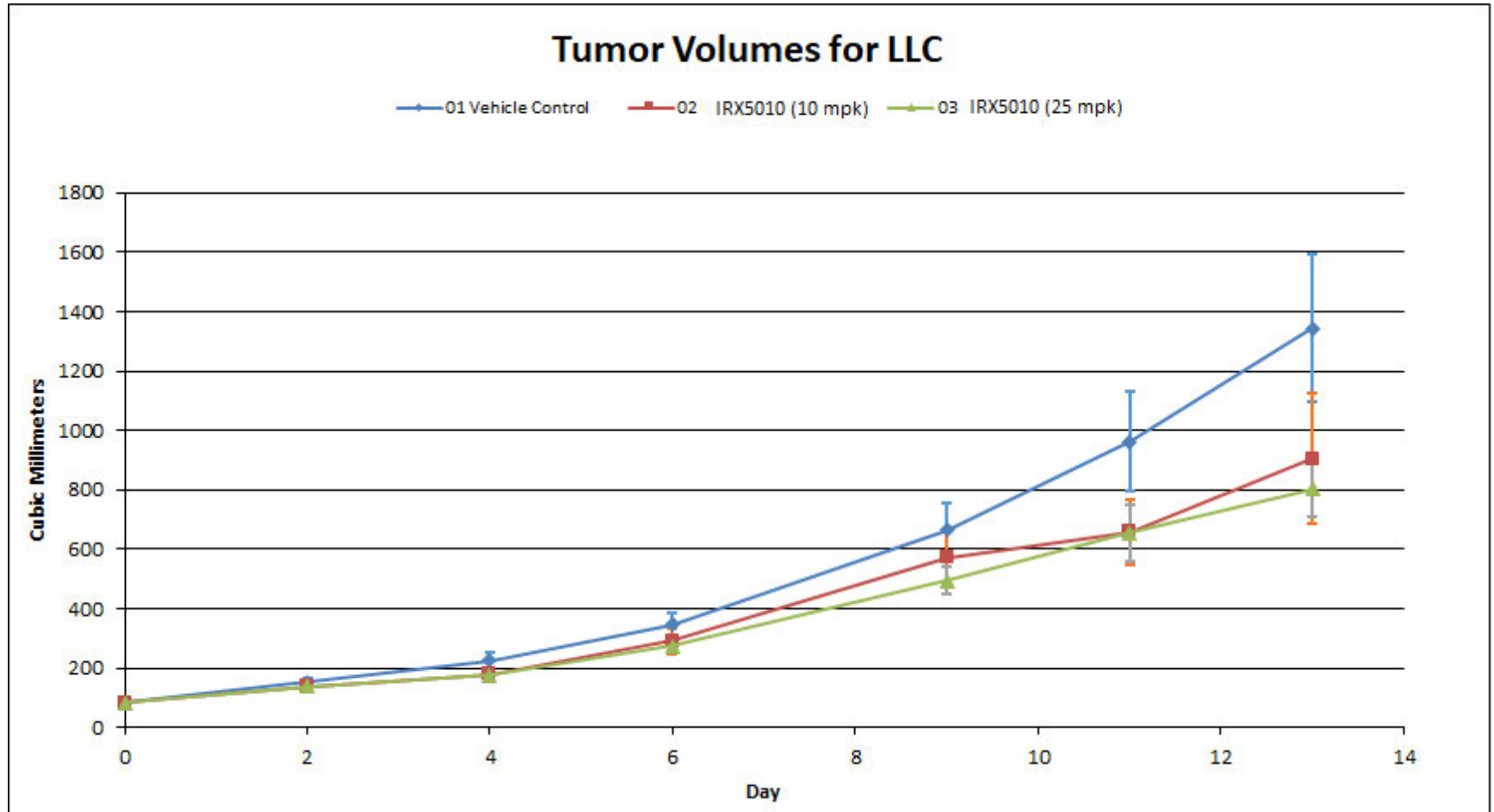
● Vehicle Control   
 ● IRX5010 (10 mpk)   
 ● IRX5010 (25 mpk)



CD8 Tem = CD8 T effector memory (CD8+ CD44+ CD62L-)

Data from Champions Oncology, Inc.

# IRX5010: a Highly Selective RAR $\gamma$ Agonist Compound Inhibits In Vivo Tumor Growth of Lewis Lung Cancer in Syngeneic Mouse Model

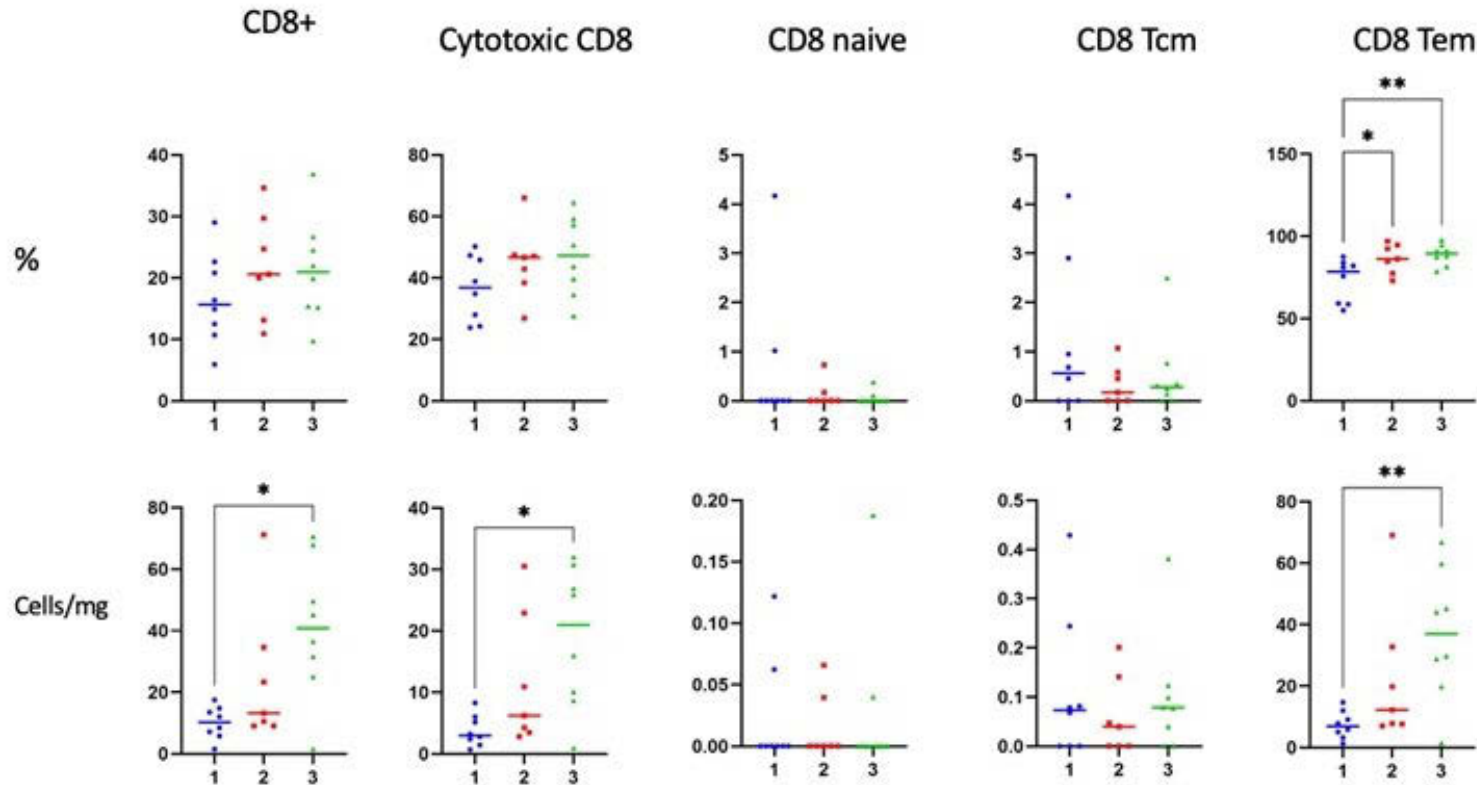


Data from Champions Oncology, Inc.



# IRX5010, a Highly Selective RAR $\gamma$ Agonist Compound Induces Effector Memory Tumor Infiltrating Lymphocytes in Syngeneic Lewis Lung Cancer Model

○ Vehicle Control    ● IRX5010 10mg/kg    ● IRX5010 25mg/kg



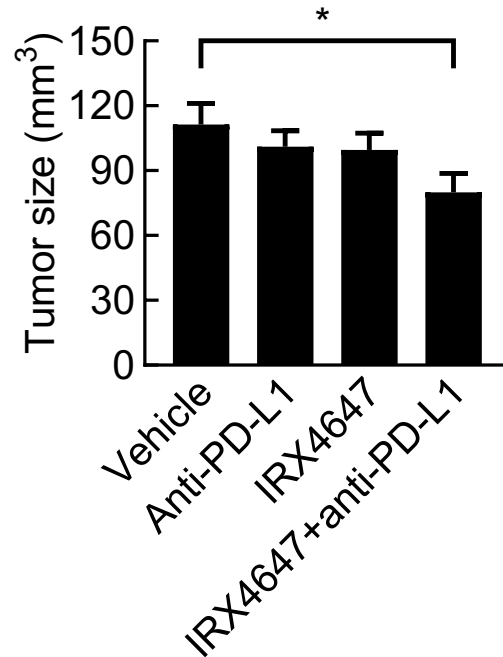
Cytotoxic CD8 = CD8+ IFN $\gamma$ +

CD8 Tem = (CD8 T effector memory) CD8+ CD44+ CD62L-

Data from Champions Oncology, Inc.

# Combined RAR $\gamma$ Agonist and Anti-PD-L1 Treatment Reduced Non-small Cell Lung Cancer Growth

344SQ cell injection  
(129/sv male mice)



Treatment day 14

Data from E Dmitrovsky, G Wei, X Lui  
Frederick National Laboratory for Cancer Research

# Collaborators and Acknowledgements

Powel Brown, MD, PhD; Cassandra Moyers, PhD  
MD Anderson Cancer Research Center  
RXR agonist IRX4204 in preclinical Her2+ breast cancer studies

Ethan Dmitrovsky, MD; Gina Wei, Xi Lui  
Frederick National Laboratory for Cancer Research  
RAR $\gamma$  agonist in preclinical in vitro and in vivo studies of non-small cell lung cancers and combination studies with checkpoint inhibitor

Gabriel Ghiaur, MD; Christian Gocke, MD, PhD; Richard Jones, MD  
Johns Hopkins School of Medicine  
RAR $\alpha$  agonist IRX5183 in clinical and preclinical studies of multiple myeloma and AML

Mary Topalovski, PhD; and colleagues at Champions Oncology, Inc.  
RAR $\gamma$  agonist in preclinical in vitro and in vivo studies of triple negative breast and non-small cell lung cancers